Green Supply Chain Management in the Pharmaceutical Sector: An Investigation in the UK context

By

Md Mostain Belal

M00575628

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

Business School

Middlesex University

January, 2021

Middlesex University Research Degree

Candidate Declaration form

Student details

Student name:	Md Mostain Belal
Student number:	M00575628
Thesis Title:	**Green Supply Chain Management in the Pharmaceutical Sector: An Investigation in the UK context**
Degree for which thesis is submitted	PhD

Candidate Declaration

1 Research Integrity

I declare that the work presented is wholly my own, unless clarified as part of the submission.

2 Material submitted for another award

either	*I declare that no material contained in the thesis has been used in any other submission for an academic award
or	*I declare that the following material contained in the thesis formed part of a submission for the award of ……Not Applicable……(state awarding body and list the material below)

*delete as appropriate

3 Research Ethics

I confirm that the research submitted has been subject to ethical review and has not deviated from the terms of ethical approval given by the Research Ethics Committee.

Ethics ID number:……3386…… (this can be found in the MORE system or in your ethics approval letter)

Statement by the Student

Signature of Student: 	Date: 03/01/2021

Abstract

The key focus of this thesis is to explore Green Supply Chain Management concepts (e.g., green practices, green drivers, green barriers and green performance measures) in the pharmaceutical sector. It considers a synthesized understanding of Green Supply Chain Management practices in terms of *Materials, Energy* and *Toxicity.* This synthesized framework is used as a baseline to explore related green concepts and sub-concepts in the pharmaceutical sector.

Today's global environment has undergone a massive transformation from what it was in the last century. This transformation has translated into numerous disastrous events ranging from extreme climates, unprecedented levels of ocean pollution from plastic wastes, pesticides, drugs and other chemicals, scarcity of fresh drinking water, increased levels of tropical disease due to warmer weather, biodiversity loss leading to natural ecosystem disruptions, and many more. Whilst industrial manufacturing operations are traditionally understood to be a significant contributor to environmental pollution, pharmaceutical operations have recently been paid a considerable amount of attention by governments, regulators, NGOs, water companies, and consumers due to the presence of pharmaceuticals in the water and food cycles. Though this issue was raised many years ago, for instance, in 1976 when the river fish in England were contaminated with birth control pills, it has recently been paid significant scientific and business attention due to the issue of anti-microbial resistance. Antibiotics and painkillers are continuously being deposited into the environment and are accelerating the risk of growing microbial resistance and, hence, the future of humankind is under significant threat of illness and death from antibiotics no longer working. This is just one side of a coin of the environmental impact of pharma operations. The other side is contributing to the environmental footprint due to the pharma supply chain consuming significant amounts of energy, water, non-renewable raw materials, toxic substance etc. Therefore, an innovative management system is urgent to deal with these issues as they pose a significant threat to a company's bottom line, as well as to wider community.

An innovative management system, such as the Green Supply Chain Management (GSCM) approach, has emerged in the supply chain and operations management domain to deal with these environmental issues. The GSCM approach considers the environmental impact in each node of a product or service supply chain. The key concepts of GSCM are: green practice, green drivers, green barriers, and green performance. Though some green practices, such as

green design, green manufacturing, green purchasing, green distribution, reverse logistics and remanufacturing, are widely investigated in diversified sectors, these concepts are still not clear in the pharma sector, especially in the elemental level in terms of *Materials, Energy* and *Toxicity*. Whilst there is huge scope for applying these green concepts in pharma, there is no single study that has focused on this. Supply chain stakeholders' level environmental analysis is crucial for pharma, and GSCM could be fertile ground for this, as pharma drug discovery, design and development, manufacturing, distribution, and use-and-disposal phases have significant affinity with environment pollution. Due to operating in a highly regulated environment and having a discovery nature of business with highly complex supply chain and stakeholder interdependence, and having an uncompromising level of attention to quality, safety and efficacy in each stage of drug production, the pharma supply chain is different from other industries. Therefore, a separate investigation is urgently required to understand the scope of GSCM in the pharma sector.

Due to the exploratory nature of the investigation, a qualitative methodology was adopted. Qualitative multi method was used for data triangulation. Using a purposive sampling strategy, 47 interviews were conducted among the managers/senior managers across upstream and downstream pharma stakeholders. The contents of 112 environmental / sustainability related reports were also analysed to collect data. The data analysis was done using both Excel database and NVIVO Pro 12 software.

Regarding the findings, many green concepts / indicators were identified, justified, and validated with empirical evidence to enrich the concept of GSCM in the pharma sector. Significant sub green design aspects were identified under materials, energy, and toxicity practice. These included design process to use greener substances, design process to increase materials efficiency, design process for energy efficiency, and design process to reduce air and water toxicity. The significant green manufacturing concepts included run continuous manufacturing, solvent recycling, waste converting to beneficiary use, and conduct eco-pharmacovigilance. Furthermore, the significant green use-and-disposal aspects included medical intervention projects (Medicine Usage Reviews, New Medicine Service), rationale prescribing, digitising prescribing and the repeat dispensing process, drug take back and drug incineration. In general, Innovative pharma are at the forefront for adopting green practices followed by bio pharma and generic pharma. Across the industry, energy related practices were predominantly and frequently used rather than materials and toxicity related practices. Costs efficiency and internal environmental commitment were the key green drivers for the

innovative companies. Cost of production, bureaucratic regulatory approval of post-marketing process change, and meeting stringent quality and efficacy specification of products were key barriers for generic pharma. Operational and sophisticated engineering difficulties were predominantly felt by bio pharma in adopting green operations. Significant performance measures used by the innovative pharma included Process Mass Intensity, Amount of hazardous waste produced, Scope 1 and Scope 2 emission measures. The performance measures achieved significant results: huge solvent related costs savings due to recovery; huge energy, water savings due to energy and water kaizen projects. These were mostly achieved by innovative pharma when compared with generic and bio pharma.

The new model of GSCM for pharma equipped with sub green indicators under materials, energy and toxicity is a significant contribution to both theory and practice. This model will undoubtedly influence practitioners' green decision making in the context. The findings (e.g., bureacratic regulatory approval of post marketing process change) are also expected to influence related policy and regulations. This study also advances the core organizational theories such as EMT, DOI and RBV through unique observation of pharma operations linking the green strategy of firms.

Acknowledgements

This work is full of lively emotions! My PhD journey has been an amazing experience. The journey has given me an opportunity to experience how to learn. Most importantly, the journey has significantly increased my thirst for learning. This is because some 'ignition engines' were continuously triggering in me throughout my PhD journey. My primary supervisor *Dr Vinaya Shukla* was one such engine who has continuously triggered me to reach my goal. The work would have been uncompleted without his continuous guidance, constructive feedback and support. I must also acknowledge my second supervisor *Dr Costas Priporas* for his motivation and suggestions to improve the work. I am also grateful to *Dr Arvind Upadhyay* for his guidance and pastoral support during hard times.

I am also grateful to the Middlesex Research Degrees Office for providing excellent admin support throughout the journey. I would also like to thank those who have taken care of the PhD Research Room. I really enjoyed reading and using my desk in the office.

I must acknowledge those pharma organizations, pharmacies, hospitals, care-homes, local councils, water companies, waste vendors who have provided me exciting information and knowledge for my thesis. I am also grateful to all of my participants, especially medicinal scientists, process chemists, GPs and pharmacy managers who have shown high appreciation of my work and shared their expertise to contribute to my project.

Finally, my family has played a significant role to this journey. My father, Mohatab Uddin, who has sacrificed his own life to build strong ground for me to be here today is always a source of limitless motivation. I lost my father when I started my PhD journey. I must be in debt to my mother, Nilifar Banu, for her unconditional love, nurturing, caring and fostering. I must acknowledge my brother, Mostofa Kamal, and sisters, Mahbuba Parvin, Makshuda Pervin and Mahbuba Pervin who have encouraged me throughout, especially my brother who has supported me a lot.

Last but not the least, I wish to acknowledge my wife, Munira Makshud, whose contribution throughout this journey cannot be expressed in words due to her selfless support and sacrifice. She is an intelligent pharmacist with experience of working in upstream pharma R&D, manufacturing and in the downstream pharmacy service. I have learned a lot from her throughout my PhD journey.

Table of Contents

List of figures

List of Tables

Acronyms

GSCM	Green Supply Chain Management
GSCM-PMs	Green Supply Chain Management Performances Measures
DTP	Direct to Pharmacy Model
GMP	Good Manufacturing Practice
GDP	Good Distribution Practice
GLP	Good Laboratory Practice
PIE	Pharmaceuticals in the Environment
AMR	Antimicrobial Resistance
PSC	Pharmaceutical Supply Chain
MURs	Medicine Usage Reviews
NMS	New Medicine Service
CCGs	Clinical Commissioning Group
FDA	Food and Drug Administration
EMA	European Medicine Agency
MHRA	Medicines and Healthcare Products Regulatory Agency
PNEC	Predicted No Environmental Concentration
PEC	Predicted Environmental Concentration
COD	Chemical Oxygen Demand
BOD	Biological Oxygen Demand
API	Active Pharmaceuticals Ingredients
PMI	Process Mass Intensity
QbD	Quality by Design
GHG	Greenhouse Gas Emission
VOCs	Volatile Organic Compounds
ODS	Ozone Depleting Substances
CFC	Chlorofluorocarbons
EHS	Environmental Health and Safety
GPs	General Practitioners
NHS	National Health Service
OTC	Over the Counter
EA	Environmental Agency
CIP	Chemical Investigation Program
NICE	The National Institute for Health and Care Excellence
UKWIR	UK Water Industry Research
GHG	Greenhouse Gas

Chapter One: Introduction

This chapter presents the background and motivation of this study. It introduces the key environmental issues in the context and the status of green approaches to dealing with those issues. It also provides the key research aims and objectives of the study and introduces the research context in which the research was carried out. Lastly, it provides the structure of the thesis.

1.1 Environmental degradation – the scale of the issue

The global environment is under serious threat due to the unprecedented levels of global warming, air pollution, water pollution, soil pollution, loss of bio diversity, and unsustainable natural resource depletion that has occurred across the globe (WCS, 1980; WECD, 1987 and OECD, 2012; EEA, 2016). Global greenhouse gas emission has increased by 78% from 1970 to 2011 (EPA, 2020). It especially originates from fossil fuel combustion and industrial processes. Emissions will continue to grow over the coming decades and beyond (EPA, 2020). Climate change due to increased levels of greenhouse gas emission has become a pressing issue around the world. Scientific evidence suggests that significant change in climate is predominantly caused by human activities (IPCC, 2013a; IPCC, 2019). It was also warned that the entire world will be inundated within the next forty-five years if corrective actions are not taken immediately to reduce carbon emissions (WECD, 1987). Even if emissions of carbon dioxide are stopped today, most aspects of climate change will persist for many centuries. This shows a multi-century climate change commitment created by past, present and future emissions of carbon dioxide (IPCC, 2013b). Howver, global energy sources will still predominantly be non-renewable sources, such as oil and natural gas, committing to continued energy related carbon emission (OECD, 2012). So, it is high time now to become more proactive in daily economic activities to deal with carbon emission and climate change to leave a safer space for the next generation of people.

Water, another important element of life in the earth, is also continuously being polluted around the globe due mainly to the flow of untreated, contaminated wastewater into the water cycle. More than 80% of global wastewater is released to the environment untreated (UN Environment, 2019). By 2050, more than 2.4 billion people across the globe will be deprived of fresh drinking water (OECD, 2012). Globally, water contamination is predominantly attributed to the extensive amount of hazardous chemical exposure from industrial production

of pesticides, heavy metals, pharmaceuticals, construction materials, foods, toys, jewelleries, textiles, and other related consumer products (OECD, 2012). So, the production management of daily consumer goods must be redesigned to reduce water contamination.

Continuous depletion of natural resources (e.g., oil, natural gas and fresh water) for meeting unprecedented levels of growing global demand for varieties of consumer products has become one of the pressing concerns. Over the last four decades, the global extraction of natural resources from eco systems and mines has grown exponentially. For instance, the annual global extraction of materials has grown from 27 billion tons in 1970 to 92 billion tons in 2017 (UNEP, 2019). Figure 1.1 shows how global extraction of natural resources is increasing. As seen in the fig. 1.1, the demand for biomass has increased from 9.1 to 24.1 billion tons, demand for fossil fuels has increased from 6.2 billion tons to 15 billion tons, and demand for metal ores (iron, aluminium, copper and other non-ferrous metal) has increased from 2.6 billion tons to 9.1 billion tons within the same period (UNEP, 2019). This global level of natural resources extraction will continue to rise to meet global food, energy, and water demand. However, this unsustainable consumption trend of natural resources will collapse the food, water, and energy supply soon, if no sustainable alternative is adopted.

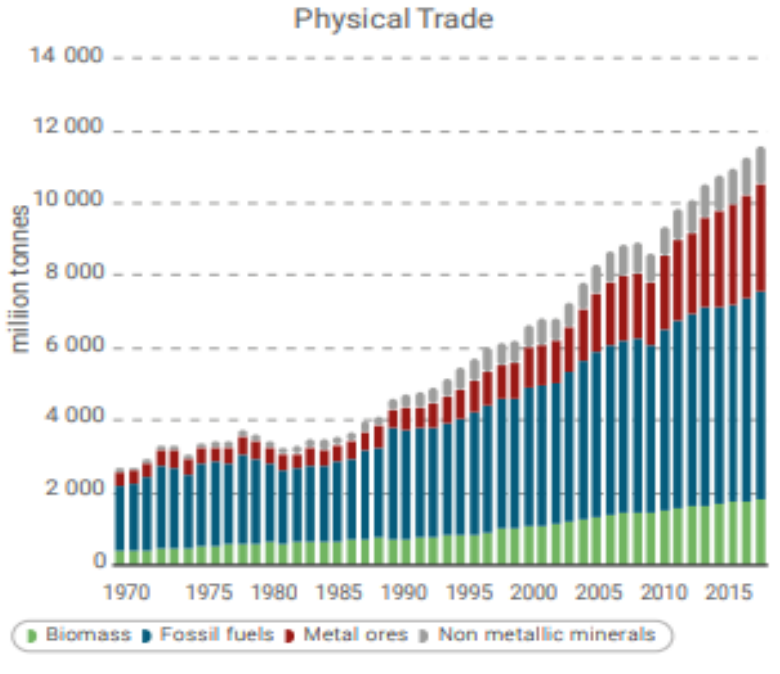


Figure 1.1 Global consumption trends of natural resources (biomass, fossil fuel, metal ores & non-metallic mineral) between 1970 – 2017 (Source: UNEP, 2019).

The global environmental impact of climate change, air emission, water pollution, and hazardous chemical exposure has remained a serious threat for global human health (WHO, 2010). For instance, climate change is expected to cause 250,000 additional deaths per year between 2030 and 2050 (WHO, 2018). Contaminated water is expected to cause 485,000 deaths per year (WHO, 2019). Chemical exposure from heavy metals, pesticides, solvents, paints, detergents, carbon monoxide, and drugs is also expected to cause 193,000 deaths annually across the globe (WHO, 2016). Drug pollution alone is expected to kill around 700,000 people globally each year through antimicrobial resistance growth (The Telegraph, 2018).

Given such significant impact of environmental degradation on human and natural health, urgent attention is required by government, businesses, and NGOs to address these issues. To address such global scales of the problem, it is becoming essential for each individual industrial sector to take the lead and responsibility to assess the scale of the issue, and redesign business operations accordingly. For instance, the pharmaceutical sector has recently been identified as a significant source of environmental pollution globally.

1.2 Environmental degradation – Pharma context

Process related industries like chemical and pharmaceutical related production have recently been viewed as among the top ten polluting industries in the world due to their bulk production, demand and huge amount of industrial wastewater discharge (Nag, 2020). The pharma production volume in Europe alone has been significantly increased in the last decade; for instance, the production volume has more than doubled (€258,000 million) in 2017 from the base year of 2000 (€127,504 million) (EFPIA, 2018). This growing trend of pharma production has become a new concern for environmental degradation (Clark et al., 2010; Kummerer, 2009).

The environmental relevance of pharma operations is twofold. Firstly, the protection of natural environments in terms of energy, water, waste, and raw materials consumed in the operations; and secondly, the protection of pharmaceutical products or drugs when they are in the environment. The second issue, which is known as ‘Pharmaceuticals in the Environment’ or PIE, has become one of the crucial challenges for the pharma industry and related researchers, practitioners and policy makers due to shown potential negative environmental and related economic loss (Clark et al., 2010; Kummerer, 2009). Pharmaceuticals may enter into the environment in three ways (see fig. 1.2): via patient excretion (88%), via

inappropriate disposal (10%) (e.g., disposal of unused/expired drugs via household bins or sinks) and via industrial wastewater discharge (2%) (AstraZeneca, 2017).

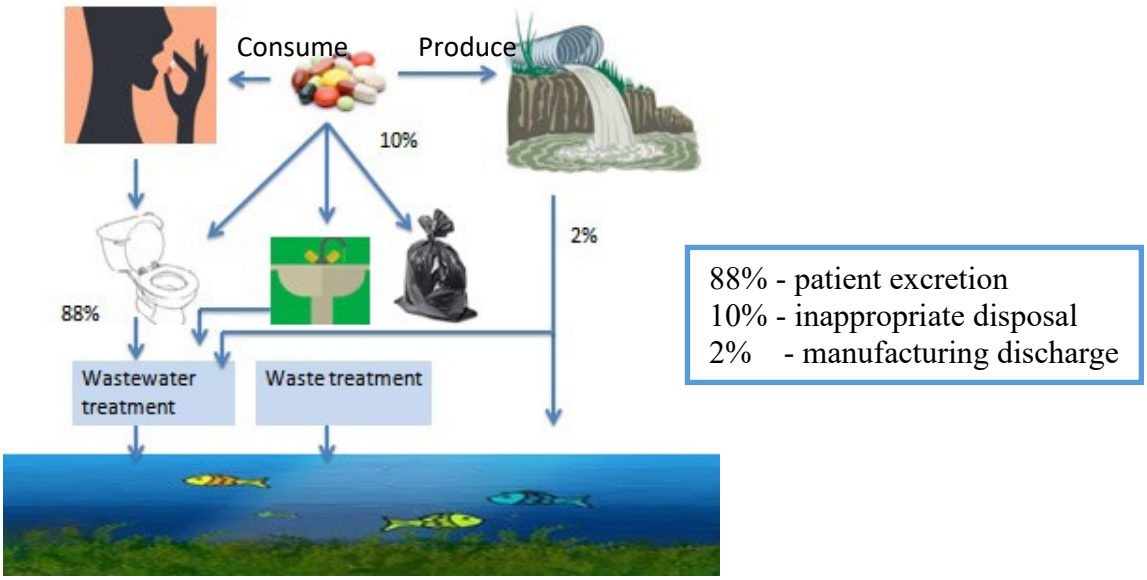


Figure 1.2 Sources of how drugs may enter the environment (Source: Researcher)

The presence of human pharmaceuticals in the water cycle, particularly drinking water, is now well established across the globe (Kummerer, 2009; Gotz and Deffner, 2010). Humans are unintentionally exposed to very low concentrations of medicinal products via daily intakes of drinking water, leaf crops, root crops, fishes, dairy products, and meats (Mudgal et al., 2013). There has been growing concern among citizens about pharmaceutical residues in water and food supply since the identification of the presence of hormonal products in British rivers in 1976 (Bound and Voulvoulis, 2005; Sumpter, 2010; Xie and Breen, 2012). Drug contaminated drinking water can be a threat for pregnancy because the unborn baby/foetus may receive toxic drug substances (drugs that are designed to kill dividing cells, for example) (Sumpter, 2010). Hence, it has been warned that detrimental effects may happen if the transfer of drug substances occurs within the water and food chain.

Just as biodiversity loss and ecosystem disruption (e.g., dichlofenac poisoning of millions of vultures in India, and feminisation of fish in British rivers) have already been evidenced due to PIE (Bound and Voulvoulis, 2005; Sumpter, 2010), antimicrobial/ antibiotic resistance (AMR) growth has become a new global threat for humankind (Daughton, 2003). This is because when drugs (especially antibiotic) continuously deposit in the environment, they work against the natural bacteria and grow resistant to that antibiotic. AMR is expected to

cause 700,000 deaths globally each year with 25,000 deaths each year in the EU alone (HCWH Europe, 2016). AMR related global death is also expected to reach 10 million by 2050, which is more than the combined number of cancer (8.2 million deaths), diabetes (1.5 million deaths) and road accident (1.2 million) related deaths globally (HCWH Europe, 2016; Johnson & Johnson, 2017).

In addition to the environmental impact of finished drug products, the protection of the natural environment and natural resources is also under serious threat due to the consumption of considerable amounts of raw materials and energy during pharma operations (Clark et al., 2010). For instance, more than 90% of pharma raw materials (e.g., organic chemicals) in current use are derived from petroleum-based feedstock, which are finite and non-renewable (Clark et al., 2010). The industry is also a large consumer of fresh water (Massoud, 2015). The pharmaceutical manufacturing process has traditionally been identified as one of the biggest waste producers in the history of process industry, where a typical pharma manufacturing process induces more than 25 to 100 kg of wastes per kg of final product produced (Slater et al., 2010; Roschangar et al., 2017). The industry has also projected 15 billion kg of overall annual drug manufacturing waste (Roschangar, 2018). Use of solvents as raw materials in the pharma process is contributing to a 40% increase of the VOC (GHG emission contributor) in the atmosphere (Perez-Vega et al., 2013).

The negative environmental consequences of pharma operations are also associated with significant economic loss. For instance, AMR could cost the global economy more than $100 trillion between 2014 and 2050 (Johnson and Johnson, 2017). It could cost the EU economy 1.5 billion euro annually (HCWH Europe, 2016). Unused prescription medicines, due to ineffective drug prescribing and dispensing management, and drug non-adherence, costs NHS UK £300 million per year (NHS Waste Management Campaign, 2017). Apart from the costs of raw materials, water and energy, the drug manufacturing wastes related disposal costs the industry 50 billion US dollars annually (Roschangar, 2018).

Given such unprecedented levels of environmental and economic impacts of drug production, use and disposal, a systematic and innovative management process is urgently required to deal with it. Historically, there have been many such varieties of management systems such as green product design (Dewberry, 1996; Tian, et al., 2014), internal environmental management (Darnall, 2020), green product manufacturing (Srivastava, 2007; Li et al., 2010), pollution prevention, recycling, remanufacturing (Rusinco, 2007), environmental purchasing

(Min and Gale, 1997). However, the pharma industry will require more innovative, integrated and supply chain level attention to address such environmental issues. GSCM has emerged as such an innovative integrated management system to deal with environmental issues.

1.3 Responses to the scale of environmental issues – A GSCM view

Realizing the unprecedented level of global environmental degradation, researchers and practitioners have started incorporating environmental issues into the supply chain level, which is known as GSCM (Darnal and Kim, 2012; Govindan, 2014a; Li et al., 2015). GSCM predominantly assesses each phase (e.g., design, manufacture and disposal) of a supply chain to identify the scope of environmental improvement (Srivastava, 2007; Zhu et al., 2012; Verma et al., 2018). The key aim is to integrate extensive levels of green practices to reduce environmental degradation (Tseng et al., 2019). It also identifies related drivers and barriers to evaluate the effectiveness of each green practice adopted. The concept of GSCM is receiving significant attention from practitioners and policy makers across diversified sectors such as automotive (Azevedo et al., 2012), general manufacturing (Hajmohammad et al., 2013), electronic (Hsu and Hu, 2008), textile (Wu et al., 2012), package printing (Vachon and Klassen, 2008), electrical (Lee et al., 2012), iron and steel (Zhang, 2012) and chemical (Zhu et al., 2010). This is because both practitioners and policy makers have recognized the win-win cases of economic outputs and environmental sustainability achievements from applying GSCM concepts (Sangwan and choudhary, 2017).

Whilst it is crucial to understand green practices, drivers, barriers and performance measures for greening any sector, stakeholder-wise GSCM assessment within a supply chain has also been paid significant attention recently (Drohomeretski et al., 2014; Balasubramanian and Shukla, 2017). This is because the overall effective green efforts ultimately depend on the individual stakeholder-level green adoption capability. So, it is important to understand how each stakeholder could play a role within a product/project supply chain to achieve green-related goals. The influences of green practices, drivers, barriers, and performance measures differ across the sectors due to the involvement of unique product/process and diversified stakeholder goals (Zhu et al. 2013; Balasubramanian and Shukla, 2017). For instance, some traditional green concepts, such as green design, green manufacturing, recycling, reusing and reverse logistics applied in discrete industries, may not be clear in the process industries. It is especially the case when the supply chain is complex and different from traditional supply chains, such as the drug / pharmaceutical supply chain where safety, efficacy and quality of

product in each stage is paramount. Therefore, individual sector wide GSCM assessment is becoming significantly important to contribute to addressing the wider global environmental issues, as well as to achieving wider sustainable development goals.

1.3.1 GSCM in Pharma sector

Intuitively, like other sectors, the pharma sector could also benefit from adopting GSCM. As a result of the devastating environmental background of pharma operations, the sector urgently requires a thorough green assessment at the supply chain stakeholder level for effective environmental protection (Clark et al., 2010; Sumpter et al., 2010). A pharma supply chain consists of diversified stakeholders, such as drug innovators (who discover, design, patent and develop drugs), manufacturers, distributors, pharmacy, hospitals, clinics, care homes, doctors, patients, waste vendors and wastewater treatment. In general, the supply chain starts with drug discovery, designing and development followed by marketing authorization (regulatory approval), manufacturing, distribution, and use-and-disposal. So, the concept of GSCM, such as green practices (e.g., green design, green manufacturing and green distribution), could readily be applied in each phase of the drug supply chain to curb those environmental impacts. Adoption of related green practices could significantly improve the materials, energy, toxicity, carbon emission and wastes footprint across the drug supply chain (Clark et al., 2010). For instance a drug could be designed in such a manner that it uses fewer materials, less energy and induces less toxicity during production through applying the concept of green design (Clark et al., 2010; Bullock and Walls, 2013). This could also induce significant cost savings. Similarly, the concept of green manufacturing and end-of-life management could significantly control the discharge of drug concentration into the water cycle to deal with PIE issues. Complex drug discovery, development and manufacturing processes, in line with complex interactions among the stakeholders across the supply chain to serve the end consumer, is also a fertile field in which to explore green related practices, drivers and barriers to understand the green needs. Additionally, because of the innovative nature of pharma business operations, the adoption of GSCM concepts will not only be a best fit for the sector to increase competitive advantages further, but also be able to advance the related concepts of GSCM for the entire process industry.

Unfortunately, despite such potential benefits of applying GSCM, very little is known about the scopes of GSCM in pharma sector. The detailed concepts of GSCM have remained undiscovered; to date, there are no studies published on the scopes of green supply chain

management in the pharma sector that cover relevant supply chain stakeholders. None of the previous studies have attempted to consider green supply chain management related practices, drivers, barriers, and performance measures to address PIE, and other materials, energy and toxicity related pressing environmental issues in the pharma sector. There are a number of theoretical assumptions published in pharma related journals, conference proceedings, books etc. For instance, use of chemicals with lower environmental impact in the early drug design and development phase (Boltic et al., 2013); drug design process for reducing raw material consumption during the manufacturing phase (Dunn, 2013); co-operation among employees (e.g., between chemist/scientist and engineer) for developing greener drug processes (Clark et al., 2010); safe disposal of drugs (Vollmer, 2010); and green supply chain risks (Kumar et al., 2019). These fragmented green assumptions do not make fully clear how, what, and why pharma companies could consider these practices. As each pharma product / process is locked into related regulations and needs to adhere to safety, quality and efficacy in each stage of supply chain, so, it is vital to understand the scopes of GSCM applications including related challenges they could face in such dynamic environments. However, related knowledge is yet to be explored. Therefore, the concepts of green related practices, drivers, barriers and performance are new for pharma, and are yet to be identified.

As the motivation for drugs supply chain is different from other traditional products, the existing green practices borrowed from other sectors could work as a guiding principle only, but not a complete solution. Also, how and to what extent these green practices could be adopted across the key supply chain stakeholders, such as innovative pharma (who are mainly involved in new drug innovation and production), generic pharma (who mainly produce off patent drugs) and bio pharma (who mainly use biological sources as raw material for producing drug). It was also unknown how the downstream stakeholders (pharmacy/GPs/Hospitals/Care homes/ Clinics) ensure effective and efficient drug prescribing, dispensing, consumption and disposal of unused drugs to reduce unnecessary drug wastes and related environmental contamination. So, the characteristics of green practices, drivers, barriers, and performance across these stakeholders are not known and this requires a new investigation for clarification. This limited understanding could mislead both practitioners and policy makers when undertaking related decisions or enactments.

Both the generic GSCM literature and the limited green related literature in pharma have highlighted why it is worth exploring GSCM scopes in pharma. It is unequivocally true that

whilst the assessment of key GSCM approaches (such as green practice, green drivers, green barriers and green performance) are crucial for greening a particular sector (Clark et al., 2010; Zhu et al., 2013), the pharma sector is identified as a fertile area of research for cultivating GSCM approaches. The importance and related knowledge gaps are also stressed and outlined by the recent researchers in both the generic GSCM field, such as the studies of Kumar et al. (2019) and Veleva et al. (2003), and in pharma supply chain field, such as the studies of Weraikat et al. (2016) and Singh et al. (2016). Growing global demand for pharma production and increased levels of ageing populations across the globe (EEA, 2012), (e.g., by 2050 more than 1.7 billion people will live to age 60 or above in the developing regions; WPA, 2017), has become an unprecedented environmental concern because of the considerable amounts of pollution and related economic losses from pharma operations globally. Therefore, a new investigation of GSCM in the pharma sector is crucial and timely. Addressing the aforementioned theoretical gaps and practical implications, this thesis has mainly attempted to answer the following four research questions:

RQ1. What are the green practices implemented by individual pharma sector stakeholders and what is the extent of their implementation?

RQ2. What are the drivers faced by individual pharma sector stakeholders for adopting green practices and what is their perceived importance?

RQ3. What are the barriers faced by individual pharma sector stakeholders for adopting green practices and what is their perceived importance?

RQ4. What are the green performance measures (in terms of environmental and economic) used and related (environmental and economic) benefits captured by individual pharma sector stakeholders and what is their perceived importance?

While related research questions are identified, it is further worth justifying whether a separate investigation to understand the scope of GSCM in the pharma sector is needed. The next section presents the unique features of the pharma sector where GSCM could behave differently, and justifies the need for a new investigation into the sector.

1.3.2 Unique features of Pharma – a need for new investigation

The pharma supply chain is unique in many ways. It raises more questions than answers on whether and how existing GSCM concepts (e.g., practices, drivers, barriers, and

performance) borrowed from other industries could be applicable to pharma. Table 1.1 below precisely presents key arguments to demonstrate why we need a separate investigation to explore the concepts of GSCM in the pharma sector.

Table 1.1 Key reasons why there is a need for a separate investigation on GSCM in Pharma

Key pharma supply chain characteristics	**Implication to green practice**
Value of the final product: Life Vs Death	If the finished product (a drug) does not reach its final destination (consumer patients) at the right time, with the right quality, safety and efficacy, with the right quantity and in the right place, the consequence may be the difference between life and death for the final consumer: the patient (Nusim, 2005). This typical supply chain atmosphere, where both product and process are critically scrutinized by the regulators for safety, quality and efficacy, makes it unique from products and processes from other industries where the end quality or speed deviation may not directly link with consumers' life and death. So, the scope of green practices adoption is generally assumed to be highly selective and sensitive in nature, as safety, quality and efficacy are the key priority rather than any other consideration. So, the trade-off between 'the adoption of green practices into this sensitive drug supply chain' and 'related economic and environmental benefit' could be different from other industries.
Nature of product / process design	Compared to other sectors, the pharma R&D process involves a series of chemicals discovery and clinical development, which makes it more challenging with a highly unpredictable success rate relative to the amount of investment and resources used (Sing et al., 2016). Therefore, the R&D could be reluctant to experiment green at this stage. So, the consideration of green aspects in the early drug design and development phase is more likely accidental than experimental (Kummerer, 2010; Leder, 2015). As the process design of a drug depends on scientific discovery, the question is when and how green aspects could be incorporated into process design: before discovery, during discovery or after discovery? To the best of our knowledge, nothing is known on how green practices behave in such an inventive product / process design environment. Though apparently the scope of green in this context seems to be limited and challenging, it requires an investigation to understand the green phenomenon in pharma process / product design.

Key pharma supply chain characteristics	Implication to green practice
Longer product development timeline (10 to 15 years) Vs limited product patent life	Compared to other sectors' R&D processes, longer product and process development (normally 10 to 15 years) of drugs is assumed to be a fertile land for successful green design innovation diffusion across the pharma sector. As application of green practices in any sector in general is not an overnight process, it requires sufficient understanding of different product / process operational parameters (e.g., cost, product integrity, efficacy, flexibility) during the product / process R&D phase. With their business being about the 'discovery' of new products, companies patent their potential drugs early in the development pipeline. However, the limited patent life (15 to 20 years from the early patent date) for exclusive sales rights of each new drug leads companies to reduce the development time line. Consequently, it would reduce the scopes of green innovation. Therefore, it would be interesting to investigate whether and how different green practices can be adopted in such longer development timelines in a limited patent environment, and to see whether such longer development timelines are really a favourable condition for green adoption.
Stringent regulation on each stage of supply chain	As pharma products' integrity and efficacy can be a matter of life and death, stringent regulations are essential. That is why design, development, manufacturing, packaging, distribution, use, and disposal are locked into specific regulations for the marketing authorization of drug products. Any post-marketing related changes in the process / product will require new investment to regain costly regulatory approval (Ding, 2018). So, there is less scope for continuous product / process improvement – which is a hostile environment for adopting green. There would therefore be less motivation for stakeholders to apply green. In particular, there would be significant impact on generic pharma (off patent producers) taking green practices on board, as they are based on a short-term, profit-making philosophy, but unfortunately, they are dominated in the entire drug industry. Therefore, it would be interesting to see how GSC behaves in such a stringent regulatory environment.
Nature of consumerism	Compared to other sectors, the end consumers do not have any control over choosing the finished product (a drug). The end consumers depend on the physicians / doctors to purchase a product. So, demand for a greener product (drug) may not be generated from end consumers, rather it could be generated from the manufacturers and/or other external environmental bodies. For instance, consumers apply significant pressure to reduce plastic waste, as they directly purchase and experience plastic products. So, it is important to know whether and how end consumers' pressure for green pharma products exists. Thus, generic consumer

Key pharma supply chain characteristics	Implication to green practice
	pressure for green products in pharma may not be translated from the end consumer but it would be translated through a complex pharma consumerism where the producers, regulators, doctors, pharmacists and end consumers' collaborative actions and perceptions are key.
Value of product return	Compared to other sectors, there is no salvage value of the recycled and/or returned pharma products (drugs). So, the zero-salvage value of returned medications could not motivate the producers, distributors, or related other stakeholders to participate in reverse logistics (Xie and Breen, 2012; Weraikat et al., 2016). Therefore, other academic researchers and practitioners have also emphasised the fact that pharmaceuticals are quite different from other commodities (Savage et al., 2006; Xie and Breen, 2012; Weraikat et al., 2016), which means a separate investigation is required to understand the scopes of green manufacturing and/or recycling practices.
Nature of business: Limited patent	Compared to other sectors, pharma product sales are capped into a limited patent life of around 15 to 20 years from discovery and a significant amount of investment is required, around half a billion to one billion dollars (Taylor, 2016). The patent is obtained during the development of the drug when it shows potential outcomes to manipulate the disease. So, the innovative pharma companies always rush and try to reduce the development timeline in order to launch the new drug into the market as quickly as possible to cover the investment, as the patent time starts ticking. Hence, there is a ''just in time'' mentality in pharmaceutical drug development (Perez-Vega et al., 2013). This patent limitation may not motivate the sector to invest in green technologies. So, it is important to understand whether and how GSC behaves in this kind of constrained business climate. On the other hand, once the patent expires the drug becomes generic, and there is fierce competition among the generic pharma to become the first to produce the generic version of the off-patent drug. This is because the first generic pharma will enjoy 6 months of sales exclusivity. So again, the time limitation for making money could be the key factor rather than investigating environmental process development in the generic versions of drugs. After six months, cost focus becomes the key strategy for generic pharma. So, the nature of green design and manufacturing practices could be negatively influenced by these key pharma business factors which still need to be understood.
Improved product quality may decrease	Drug products are made to be stable to heat, light, oxidation, acid, bases etc under all reasonable manufacturing, storage and use conditions (Veleva and Jr, 2016).

Key pharma supply chain characteristics	Implication to green practice
environmental quality	But these physical stability properties of drug substances may decrease the degradability of drugs when they enter water cycle, hence drugs deposits into the environment. To the best of my knowledge I have not seen this green dilemma in any other sector. Therefore, the pharma sector must balance safety standards while improving its environmental impact (*Roberson, 2016)* So, it is important to understand whether and/or how this dilemma could be reduced for increasing environmental degradability of drug substances without hampering product stability.

1.4 Research Aims and Objectives

Given the significance of greening the pharma operations in line with the related knowledge gaps in the literature, this research aims to explore the concepts of GSCM in the pharma sector considering the key supply chain stakeholders involved. Therefore, the key research objectives are as follows:

I. To explore key green practices adopted by the key stakeholders in the pharma sector.
II. To identify key green drivers and barriers faced by the key stakeholders in the pharma sector.
III. To develop a green performance measure model for the pharma sector.
IV. To comprehend the actual benefits (in terms of environmental and cost/economic) from applying green practices in the pharma sector.

1.5 **Research Settings**

The study has chosen the United Kingdom to explore the scope of GSCM approaches in the pharma sector. The UK pharmaceutical sector plays an important role in the UK economy. Britain is one of the world's largest exporters of pharmaceuticals by value (IBIS, 2018a). The UK pharmaceutical preparations (e.g., vaccines, various medicines and biotech pharmaceuticals) sector is placed in an important position in both the global pharmaceutical market and the UK economy (IBIS, 2018b). During 2018 the pharmaceutical preparation industry was projected to rise by 3.5% to £14.9 billion, due to domestic demand by leveraging £641.4m profit (IBIS, 2018b). The growing demand for drug production is also

expected to be driven by the ageing population, as the proportion of the population aged over 65 is expected to increase in the coming years (IBIS, 2018b; EEA, 2012). However, the growing economic activities are also a concern for environmental emissions. Especially as part of the UK's voluntary CO2 emission reduction by 80% by 2050 from the base year of 1990 in the Kyoto Protocol agreement (Kyoto Protocol, 1998), the chemical and pharmaceutical sectors are under significant pressure to meet the goal. In addition, UK pharmaceutical manufacturers are under tremendous pressure from their investors and stakeholders to combat the issue of PIE and AMR (AstraZeneca, 2017). For instance, the UK government has published a 20 years vision and 5 year national action plan for aiming to control the issue of AMR by 2040, and pharmaceutical supply chain stakeholders are being scrutinised for drug (antibiotic) production, use and disposal (UK Department of Social and Health Care, 2019).

The presence of world leading pharmaceuticals innovators and producers, such as AstraZeneca, GSK, Novartis, Pfizer, in the UK context has provided a perfect learning hub for green innovation. More specifically, there are many pharma companies in the UK who are actively engaged in learning and implementation of green innovation, green chemistry, and green engineering as part of the American Chemistry of Society, Green Chemistry Institute (ACS GCI) Pharmaceutical Round Table. ACS GCI is the world's largest scientific society which aims to encourage innovation and the integration of green chemistry and green engineering in the pharmaceutical industry. It has been sought as one of the most significant sources of learning, training, researching, developing, and implementing green practices by collaboration with the companies. So, learning from this kind of green idol would be key. These green leaders are also experienced in industry regulations and committed to corporate responsibility to improve environmental performance for the wider community. Additionally, building a GSCM model from a developed green culture could be very useful and could be applied to many underdeveloped and/or developing regions where green pharma has not yet been considered. Therefore, the UK is identified as an appropriate context for this study.

1.6 Theoretical and practical contribution of the thesis

With regards to theoretical contribution, this study has not only advanced the existing GSCM related literature in pharma sector but also advanced the core management theories such as EMT (Ecological Modernization Theory), DOI (Diffusion of Innovation) and RBV (Resource Based View). To the best of the researcher's knowledge, this is the first study which has

provided a comprehensive GSCM model for pharma sector. The model is not only unique for pharma sector but also a unique contribution to the existing body of wider GSCM related knowledge. This is because none of the previous study has considered MET (Materials, Energy & Toxicity) led green model underpinned by the application of Green Chemistry principle for pharma sector considering key supply chain stakeholders. The study has significantly enriched the existing understanding on Green practices which are critical to deal with environmental degradation in the context. For instance, increase biodegradability of a process considering bio-based process design, AI based drug discovery to dematerialize the process, nano technology-based drug formulation for materials reduction, apply quality by design concepts, PMI based process design, design and develop combined drugs, design and develop manufacturing process by installing and validating energy efficient equipment system (e.g., reaction vessel), design and develop drug process to reduce air toxicity, and digitise the drug dispensing process for drug waste reduction . The study has also advanced the existing green related knowledge through identifying some unique green drivers such as F-gas related regulation, ERA related regulation, REACH, drug takeback legislation, cost savings from solvent recycling, cost savings from medical intervention (e.g., MUR), cost savings from drug recycling, top management commitment, and stakeholder pressure etc. The new green model has also included some key green barriers which were unknown (and/or unclear) in the existing literature, for instance, complex marketing authorization process of green drug, high costs and investments for green process, lack of greening culture, lack of standardization in equipment and process, time to market, lack of green related data, uncontrolled drug wastes from high concerned patient groups, lack of performance measures of patient interventions scheme (e.g., MUR), lack of regulatory guidance on environmental consideration in prescribing, and contradictory regulatory guidance for disposing unused/expired drugs. Related green performance measures (e.g., reduction of scope 1, 2 GHG emission, reduction of VOCs/ODS, amount of energy generated onsite, amount of energy saved from conservation and process efficiency improvements, toxicity measures of wastes etc) and the actual performance induced (e.g., costs/environmental savings from recycling projects, cost/environmental savings from energy efficiency programs, costs/environmental savings from toxicity measures, cost saving from drug recycling etc) across the key stakeholders were never discussed in the existing green related pharma literature. This is how the new model built upon green practices, green drivers, green barriers, and green performance measures has significantly advanced the existing green related knowledge in pharma sector.

The study has advanced EMT theory through explaining how politics of pollution or political modernization is being formed in such a complex and discovery nature of pharma business where safety, efficacy and quality are the key prior to forming a typical environmental policy in the context. To the best of the researcher knowledge this is the first study to understand the political modernization of drug supply chain. The study findings indicate that environmental governance related decision making in pharma moves from deterministic to stochastic mode due to involve a degree of uncertainties from drug discovery and early production to final consumptions. Given such important advancement within the EMT theory, environmental governance is identified one of the fundamental drivers for sustainability across the sectors. The degree of drug production (discovery-led) and consumption and its influence on natural environment leads to a crucial dilemma between 'saving human life' versus 'saving environmental life'. The theory has also been advanced through explaining how voluntary environmental policy making in such dilemma has led the companies for technological breakthrough (e.g., cleaner production or adoption of green chemistry principles). Such environmental dilemma and related technological breakthrough for environmental benefits were unknown before. The study has also advanced the DOI (Diffusion of Innovation) theory through explaining how green innovations diffuse across highly complex, expensive, and regulated pharma stakeholders. The scopes of diffusion of green innovations within an uncertain discovery nature of business (including stringent regulations) where the implication of unsafe and inefficacy of product lies between 'life' and 'death' of the end consumers. The study has also advanced the RBV theory through demonstrating how non-discrete production process (e.g., API production) can also achieve competitive advantages by harnessing internal resources like green chemistry led knowledge and innovation, green collaboration for process development etc.

With regards to practical contribution, the study has developed a new green supply chain model considering all key stakeholders involved. The new green model will undoubtedly improve the relevant practitioners' understanding on what green practices to consider in which condition based on the related green drivers and barriers. To the best of the researcher's knowledge this is the first study that has offered stakeholder wise green practices, drivers, barriers, and performances. Such extensive and stakeholder wise green model was never known for pharma. The model is expected to influence those conservative operations and manufacturing managers as well as upstream medicinal and process chemist to adopt green with a degree of confidence due to the relevant extensive empirical evidence in

the study. It also aims to influence the downstream players (e.g., pharmacy, GPs, hospitals) to consider performance measures for undertaking any forms of medical intervention. The study is also expected to influence the related policy makers and marketing authorizers of drugs such as MHRA, EMA and FDA. For instance, drug producers could be incentivised for promoting green drugs production, and especially the generic producers could be encouraged to promote more green practices through streamlining the validation of those drug processes aimed for green production. This will have a significant positive environmental impact in the context as most existing drug portfolios is still generic due to market demand. Similarly, EMC could be further upgraded to include the clear direction of selecting eco-friendly alternative drugs without compromising the quality of patient health. The study also aims to influence the relevant stakeholders to create more green partnerships to deal with PIE and other MET related environmental issues. For instance, the study findings are expected to clarify the individual role of department of health, local councils, and local environmental agency or DEFRA in the drug wastes reduction.

1.7 Structure of the thesis

Structure of the Thesis		
No	**Chapter Heading**	**Focus**
Chapter One	Introduction	Highlights the key practical and theoretical issues underpinning the thesis; also, clearly states the key aims, objectives and research questions and sub research questions.
Chapter Two	Literature Review	Conducts extensive, structured, and synthesized literature reviews in two separate streams; one in the general GSCM stream of knowledge, the other is in the green related literature in the pharma sector. It justifies the related research gaps/research questions. It provides a strong foundation for this thesis to build an appropriate research methodology.
Chapter Three	Methodology	It justifies the researcher's philosophical stance upon which the thesis is built. It provides a detailed explanation of what, why and how a particular research tool or method, data analysis technique is used.
Chapter Four	Findings on Green	Presents and analyses the findings related to green practices and sub green practices undertaken by both upstream and downstream

	Practices	pharma supply chain stakeholders
Chapter Five	Findings on Green Drivers	Presents and analyses the findings related to green drivers faced by both upstream and downstream supply chain stakeholders prior to implementing green practices.
Chapter Six	Findings on Green Barriers	Presents and analyses the findings related to green barriers faced by both upstream and downstream supply chain stakeholders prior to implementing green practices.
Chapter Seven	Findings on Green Performance	Presents and analyses the findings related to green performance measures used by both upstream and downstream pharma supply chain stakeholders prior to measuring the performance (in terms of environmental and economic) of green practices implemented.
Chapter Eight	Analysis and Discussion	Reflects on the findings (including significant one) and discusses them referring to the previous literature and demonstrates the key areas of contribution
Chapter Nine	Implication & Conclusion	Reflects on the practical and theoretical implications of the research; related research limitations and future research directions

Chapter Two: Literature Review

Whilst the previous chapter outlined the importance and practical relevance of this study, this chapter identifies and justifies the related research gaps through synthesizing the existing literature in the field. Each research question is formulated based on not only the gaps in the literature but also on related ambiguities, disagreements, omission of empirical evidence, and inconsistencies in practical relevancies of the proposed theories/practices etc through critical review of the existing literature. This systematic approach by the researcher has accentuated the investigation to its utmost validity and acceptability in practice. It starts with the background of general environmental sustainability to understand the practical relevancy of the thesis. Then it synthesizes the existing knowledge on generic GSCM concepts to create a suitable framework to explore existing green related knowledge in the pharma sector.

2.1 Environmental Sustainability

One of the simplistic understandings of 'environmental sustainability' is to conserve and maintain the natural environment in such a way that there is an equilibrium position between 'the rate of exploitation of natural resources' and 'the rate of meeting human demands for today and tomorrow' (WCS, 1980; WECD, 1987; Brandenburg et al., 2014). Unfortunately, the growing 'pattern of human needs' with a limited 'pattern of natural resources' on the planet is becoming a new dynamic due to disequilibrium practice between these two different patterns (Tseng et al., 2013; UN Environment, 2019). This disequilibrium practice leads the planet to endangerment having already damaged the biosphere, and caused deforestation, desertification, ozone layer depletion and inundation among many more natural disasters (IPCC, 2013a ; IPCC, 2018). People and planet are two inseparable components. People oriented social construction has been sustaining natural environmental construction since the creation of the planet. This sustainability becomes weak and sometimes vulnerable when humans use more natural resources to meet social demand or to develop its social construction rather than preservation for natural balance (Mebratu, 1998). It was also assumed in history that some ancient societies were distinct from the planet due to environmental catastrophes caused by manmade pollution.

The concept of environmental sustainability is clearer and more scientific when it is viewed through the lens of ecosystem and ecology. Since the creation of the universe, humankind is

continuously interacting within a system of the natural environment consisting of both living (e.g., plants, animals and organisms) and non-living (e.g., air, sun /atmosphere, water and soil/land) components. This system is termed as ecosystem. The interconnectivity between humankind and ecosystem is termed as ecology (Mebratu, 1998). The production and consumption mechanisms in the natural ecosystem are self-regulated and self-governed by nature, and continue their function without interruption, which is important for all kinds of life in the earth. A healthy ecosystem is a prerequisite for humans to live in it. However, this natural ecosystem may become interrupted and not sustained if the elements of the ecosystem are polluted and/or over consumed due to anthropogenic activities. For instance, increased energy production may lead to potential environmental pollution and ecosystem degradation (Chen, 2016). Similarly, exhaustive irrigation may cause a drought and lead to lifeless species in that area of the ecosystem. Or, environmental loading of toxic chemicals could potentially affect life in the water. Ecology demonstrates the two ways of connectivity between the human and natural environment (or ecosystem) – which means impact in one dimension will have an impact on the other.

Inspired by the mechanism of the natural ecosystem, the concept of industrial ecology, which is considered as one of the key grounds of today's environmental sustainability, has emerged (Jelinski et al., 1992; Erkman, 1997). Industrial ecology follows the principle of the natural ecosystem. While an equilibrium production and consumption is maintained without generating any wastes in the natural ecosystem, a manmade industrial ecosystem could follow the same by turning from a linear production system to a more closed and/or cyclic system to become more sustained using fewer raw materials and eliminating waste. Therefore, the concept of 'environmental sustainability' can be further defined as the degree of adaptation of industrial ecology in a production system by mimicking the natural ecosystem for reducing/eliminating the wastes and conserving resources. This is how the degree of coherency between industrial ecology and natural ecosystem for a particular context represents the degree of environmental sustainability for that context (Jelniski et al., 1992; Malbatru, 1998; Zhu et al., 2012).

However, the concept of environmental sustainability is predominantly context specific due to the involvement of new technology, engineering, economics, sociology, politics, biology, physical science, and natural science (Nunes, 2011). This concept is increasingly found in the literature of economics, business, and management since 1990 (Linton et al., 2007). For instance, in the business context, specifically in the manufacturing context, environmental

sustainability may be achieved by designing product and process considering environmental criteria, use of minimal packaging, low energy and resource use, reuse/reprocessing of by-products, non-linear system and environmental efficiency (Sarkis, 2001; Srivastava, 2007). Even though the key focus in attaining environmental sustainability is the consideration of more environmental activities in the firm, the final decision on environmental investment is influenced by the other two dimensions of sustainability: economic and social (Seuring and Muller, 2008; Seuring, et al., 2008; Koberg and Longoni, 2019; Brandenburg et al., 2014). To broaden the understanding of the concept, a chronological definition of environmental sustainability is presented in Table 2.1.

Table 2.1: Chronological definition of Environmental Sustainability (Source: Previous literature)

Authors	**Key features in Environmental Sustainability definition**
WCS (1980)	Conservation of living and non-living natural resources through controlled production and consumption. Conservation of living resources is the prerequisite for sustainable development.
WECD (1987)	Environmental sustainability can be achieved by meeting the present generation needs without compromising the ability of future generations to meet their own needs
Erkman (1997)	Mimicking the natural ecosystem - the distribution of the material, energy and information flow in the industrial ecosystem will be such that the final waste or by-products will be consumed by another industry.
Jelinski et al (1992)	Moving from linear production system to more closed loop and/or cyclic manufacturing system to gain environmental sustainability.
Mebratu (1998)	It is important to focus on both living (biotic) and non-living (abiotic) elements for attaining environmental sustainability.
Sarkis (2001)	Design for environment, usage of minimal packaging, low energy and resources usages, non-linear system could be some of the prescriptive management systems for the manufacturing context to achieve environmental sustainability.
Morelli (2011)	Environmental sustainability is a condition of balance, resilience, and interconnectedness that allows human society to satisfy its needs while neither exceeding the capacity of its supporting ecosystem to continue to regenerate the service necessary to meet those needs nor by our actions diminishing biological diversity.
Laurent and	Environmental sustainability can be measured by the input /output rule, such as we

Owsianiak (2017)	should deplete non-renewables at the rate at which renewable substitutes are developed.

Regardless of different interpretations in the different contexts, the basic interest of environmental sustainability is seen as long-term maintenance of businesses / manufacturing without hampering the elements of the natural ecosystem, either locally or globally. Precisely, pharma industry's long-term sustainability could be determined through conserving both living (e.g., avoid drug poising of biota/aquatic species) and non-living (e.g., reduce water usages from manufacturing, saves energy, reduce toxic by-products etc) natural resources. In doing such, the Industrial Symbiosis (IS) or the elimination of by-products and wastes from the drug manufacturing through waste conversion process (e.g., waste to energy conversion) could perfectly mimic the natural ecosystem process for long term sustainability as per Erkman (1997)'s view on sustainability. Hence, pharma's zero waste philosophy underpins the input and output functions of natural ecosystem. At the same time, pharma could significantly increase its environmental sustainability through designing and discovering new way of producing drugs aiming to reduce raw materials and energy consumption across its supply chain in line with Sarkis (2001)'s sustainability view. Therefore, Erkman (1997) and Sarkis (2001) definitions of sustainability are adopted for this research as they are highly relevant to greening pharma operations.

However, to fulfil and sharpen the background of environmental sustainability in pharma, it is urgent to understand the key drivers and the importance of considering environmental sustainability. The next section has attempted to clarify these.

2.2 Implication of Environmental Sustainability in the light of environmental pollution

Whilst is clear that unsustainable usage of natural resources could break the relationship between humankind and the ecosystem, leading to a lifeless planet. The continuous depletion of both living and non-living natural resources due to the unprecedented level of human needs is the key driver of environmental sustainability (WCS, 1980, WECD, 1987). The global population was projected to increase from eight to fourteen billion by the twenty first century (WECD, 1987). This means feeding and accommodating double the amount of people within the same planet which has had fixed volume, capability and capacity since its creation. This increased amount of population drives increased amounts of basic need for

food, shelter, clothes, sanitation, health and many more products and services exploiting limited resources in nature. Therefore, it is time to rethink how efficiently those natural resources could be used and conserved to accommodate and feed people generation after generation.

There are two main types of natural resources: renewable – these materials naturally grow, become bio degraded and then re-grow; and non-renewable – these materials are finite materials in nature which do not grow and may become depleted if used extensively (Choudhury, 2017). Renewable resources include plants, animals and microorganisms. Most of the living elements in the ecosystem are renewable. Non-renewable resources include oil, natural gas, coal, different metals and drinking water. If the renewability and non-renewability aspects of these natural resources are not considered during production and consumption, the society grounded on an ecosystem will not sustain. However, the earth has undergone a dramatic change due to continuous disruption of the natural ecosystem in its different parts. This is as a result of anthropogenic activities such as excessive use of naturally extracted raw materials, over utilization of land and urbanization, producing toxic and non-toxic wastes from inefficient industrial production systems and through modification of extracted natural elements, over industrialization etc (WECD, 1987, Beamon, 1999).

Therefore, precedented and unprecedented levels of environmental issues in the past, current and future centuries have encouraged today's humankind to consider environmental sustainability for a safer planet to live in. The key environmental issues that drive environmental sustainability are global warming, deforestation, overpopulation, ozone layer depletion, climate change, pollution, industrial and household waste, loss of biodiversity, natural resource depletion, waste disposal, ocean acidification, water pollution, public health issues, water scarcity, and soil degradation (OECD, 2012). A brief account of each key environmental issue is presented in the next section.

- ✓ ***Depletion of non-renewable materials***

Faster rates of consumption of non-renewable materials (e.g., coal, oil, natural gas, uranium etc) due to increased levels of demand for different products has become one of the critical environmental issues. Oil remains the world's leading fuel, accounting for 32.9 % of total global energy consumption (World Energy Council, 2016). Unsustainable consumption together with limited reserves of oil, natural gas, fresh ground water, heavy metal elements etc are of great concern in today's science and business, as it takes more than centuries to

replenish these resources in nature. Continuous extraction of these raw materials as feedstock for numerous industries (e.g., petroleum for the chemical industry and palladium metal for the pharma industry), and production of numerous products demanded globally, has led the next generation to danger. It is crucial to manage these materials sustainably, as the increased demand for energy and necessity of production of raw materials is of prime concern across the globe.

- ✓ ***Biodiversity loss***

Continuous extinction of natural species, natural forests, natural lakes and natural habitats due to climate change, toxic wastes, infrastructure development, industrial expansion, urbanization, exhaustive usages of species for special production (e.g., use of species in drug developments and production) etc have led to the significant loss of local biodiversity across the globe. Industrial toxicity has significantly affected the local air, water, and soil, which eventually has become unsuitable for different types of species within the local ecosystem. Local biodiversity loss significantly disrupts local ecosystems. Species abundance is expected to decrease a further 10% by 2050 and the primary forests (which are rich in biodiversity) are projected to shrink by 13% due to anthropogenic activities (OECD, 2012).

- ✓ ***Climate change: Energy related greenhouse gas emission***

The level and severity of environmental pollution reported in some influential reports, such as WCS (1980), WECD (1987) and OECD (2012), indicates the inability of humans and other living organisms in the earth to fit in this planet in the near future. For instance, scientific evidence suggests that significant change in climate is predominantly because of human activities (IPCC, 2013b). Observations of the atmosphere, land, oceans, and cryosphere are the most compelling evidence of climate change. Evidence has also shown that greenhouse gases such as carbon dioxide, methane, and nitrous oxide have increased over the last few centuries. The ocean absorbs the emitted anthropogenic carbon dioxide, causing ocean acidification (Cubasch et al., 2013). Thus, the accumulation of greenhouse gases in the atmosphere leads to the risk of a more than 2-degree Celsius temperature rise (IPCC, 2013b). Even if emissions of carbon dioxide are stopped today, most aspects of climate change will persist for many centuries. This has led to a multi-century climate change commitment created by past, present and future emissions of carbon dioxide (IPCC, 2013a). It is also a warning that if the way business is conducted and the way the humans are leading their lives continues, the entire world will be inundated within the next forty five years (WECD, 1987).

The key source of greenhouse gas emission is from the usage of energy, which has induced a 70% growth of carbon dioxide emission (OECD, 2012). As non-renewable sources of energy are still dominating the global energy market, with a slight (10%) increase in renewables source of energy, the scarcity of energy supply is a confirmed reality soon. Hence, it is crucial to explore more options for energy efficiency, and sustainable or renewable sources of energy. Due to unprecedented levels of economic activity across the globe, atmospheric greenhouse gases could reach almost 685 parts per million. As a result, the global temperature is projected to increase between three degrees Celsius and six degrees Celsius by the end of this century (OECD, 2012). This increased level of world temperature can lead to numerous disasters such as extreme weather from heat waves, floods, and hurricanes, and can be the biggest driver of biodiversity loss (WCS, 1980, OECD, 2012, IPCC, 2013a). Also, the excessive burning of fossil fuel leads to acid rain which may destroy the local ecosystem. Ocean acidity has increased by 30 percent and it is expected to reach 150% in the near future, which will significantly impact on aquatic life, as well as those human populations (more than a billion today) who are dependent on sea food as their primary source of protein (PMEL Carbon Program, 2018; EPA, 2018).

- ✓ ***Air pollution***

Air pollution due to aggressive urbanization, industrial production, globalization and frequent movement of people and raw materials across the globe has hampered public health and increased pulmonary disease and related deaths across the globe annually. For instance, the number of premature deaths globally linked to airborne particulate matter is projected to more than double to 3.6 million a year (OECD, 2012). Particulates that take the form of soot (deep black powder due to incomplete combustion) emitted by diesel engines may have carcinogenic effects. These particulates also lead to respiratory and cardiovascular problems. It has been estimated that in the UK, PM10 pollution causes the premature deaths of 12000 to 24000 people annually (Rogers, 2007). Emissions from ships (e.g., SOx, NOx) can adversely affect coastal populations and ecosystems. It has been reported that around the world there are approximately 60,000 ‘premature mortalities’ each year primarily because of the inhalation of ship-related PM emissions (Corbett et al., 2007). It has also been predicted by the European Commission that total emissions of SOx and NOx from international shipping will exceed those of land-based sources of these gases by around 2015 to 2020 (McKinnon et al. 2010). Volatile Organic Compounds (VOCs) constitute another air pollutant originating from organic chemical substances such as Benzene. Many household goods (e.g., paints,

varnishes, cosmetics, degreasers, cleaners, disinfectants) are also made of organic chemicals. Hence, these goods can also emit VOCs during manufacturing, distribution, and usage. 70% of atmospheric VOCs in Europe are induced from petrol vehicles (Environmental Protection UK, 2019). So, industrial operations must be optimized to manage and/or eliminate toxic air emission from the process.

- ✓ ***Ozone layer depletion***

Due to continuous usage of Chlorofluorocarbon (CFCs), a component of greenhouse gases, in consumer products (e.g., aerosol spray, refrigerants and solvents), it is being released into the atmosphere during the production and product usage stages. This gas is attributed as depleting the ozone layer, which protects humans from the exposure of toxic / harmful ultraviolet radiation from the sun. Therefore, sustainable strategies, such as elimination or reduced use of CFCs, alternative technologies are urgently required across industries.

- ✓ ***Water pollution***

According to an OECD report (2012), due to population growth, urbanization, and industrial production, a large proportion of the world's population will continue to lack access to safe and clean drinking water (OECD, 2012). The report also projected that more that 40% of the world's population will be living in water stress areas and will be deprived of fresh drinking water by 2050. The most prevalent water quality problem across the globe is eutrophication – a result of high-nutrient loads such as phosphorus and nitrogen from agricultural runoff, domestic sewage, industrial effluent etc, as well as with emerging water quality concerns due to the loading of personal care products and pharmaceuticals such as birth control pills, painkillers and antibiotics (UNDESA, 2014). Over 80% of global wastewater is released into environment without adequate treatment (UN Water, 2017). It is also reported that unsafe water kills more people each year than war and all other forms of violence (UNDESA, 2014). In 2004, around 1.6 million deaths were reported due to unsafe water supply and associated exposure to pathogenic micro-organisms (OECD, 2012). Global water shortages and food shortages are also expected to occur due to the unprecedented level of increase in water demand by manufacturing (+400%), thermal electricity generation (+140%) and domestic use (+130%) (OECD, 2012). The depletion of ground water for irrigation will be another concern soon. This background clearly shows the urgency of undertaking sustainable water management control for efficient usage of water, such as reduced usage, reuse, recycling, and source control from the loading of chemicals and pharmaceuticals.

- ✓ ***Waste (Hazardous and/or non-hazardous)***

Continuous waste disposition from construction, packaging, electrical and electronic equipment, vehicle and oily wastes, healthcare and pharmaceutical waste, and household waste are of great environmental concern, as the inappropriate disposal and/or inappropriate segregation of these wastes could potentially damage the quality of the environment by polluting water, soils and air (DEFRA, 2018).

Global waste generation is estimated to rise to 3.4 billion tonnes from the current trend of 2.01 billion tonnes per year by 2025 (World Bank, 2018). OECD countries generate around half of global waste per year. It is estimated that two to three billion people, often in the least developed countries, still lack access to regular waste collection and /or controlled disposal services for municipal solid wastes (ISWA, 2018).

Due to the special requirements of products and process (e.g. chromium in leather production, chlorinated dyes in textiles, benzene in pharmaceutical production) lots of hazardous/toxic waste is continuously being produced from process industries across the globe. It is reported that more than 200 million people around the globe are at risk of exposure to toxic waste (Parameswaran, 2013).

Humans can also be exposed to chemicals from consuming water or food contaminated with chemicals from agricultural and industrial processes (e.g., pesticides, heavy metals and pharmaceuticals). This exposure can also be via ingestion, inhalation, or skin contact with chemicals emitted from construction materials or indoor products, toys, jewellery, textiles, food containers, or consumer products (OECD, 2012). For instance, phthalates (which are used as plasticizers to plastics to increase their flexibility, transparency, durability, and longevity) can be exposed via products ranging from adhesives and glues, electronics, packaging, children's toys, modelling clays, waxes, paints, printing inks and coatings, pharmaceuticals, medical devices, food products, and textiles.

There is also a growing concern about chemicals or mixtures of chemicals (e.g. birth control pills) which may have endocrine-disrupting properties carried by the water and food cycle to humans. It is reported that the burden of disease related to exposure to hazardous chemicals is significant worldwide, especially in those contexts where good chemical safety measures have not yet been put in place. Therefore, sustainable management of chemicals is continuously becoming important. Most importantly, sustainable waste management, such as

waste reduction strategies, source reduction, appropriate waste segregation, reuse, recycling, converting energy from waste, will be of great interest in the coming years.

Concisely, all these environmental impacts can predominantly be viewed and categorized into three key areas: ***materials related, energy related and toxicity related***. Table 2.2 has presented materials, energy and toxicity related environmental impact. The table has also highlighted those key factors which determine the related environmental impact. A brief background on each of these areas is also presented in the next section.

Table 2.2 Categorization of key environmental impact based on materials, energy, and toxicity (Source: Researcher)

Key Focus	Key environmental impact	Key determinants of environmental impacts
Materials related	Depletion of renewable and non-renewable materials (excluding energy source), Wastes (exclude hazardous) generation	• Amount (less/more) of materials used • Types of materials (non-toxic/reusable/recyclable) used • Methods of use/application
Energy related	Climate change: Energy related greenhouse gas emission; depletion of non-renewable materials	• Amount of product / process based (e.g., heating / cooling) energy requirements • Amount of plant-based energy requirements • Sources of energy (e.g., renewable / non-renewable) used
Toxicity related	Air pollution (exclude energy related GHG emission), Ozone layer depletion, water pollution, Hazardous chemical exposure, biodiversity loss, Hazardous Waste,	• Types of by-products or wastes • Methods of disposal used

Materials related: Physical (e.g. strength, size, hardness), chemical (e.g. toxic, non-toxic, flammable, immiscible) and biological properties (e.g., biodegradability) of materials determines the severity of environmental impact. The greater use of materials to produce a product leads to the greater use of energy, and this generates more waste. Faster rates of

depletion of non-renewable materials (e.g., coal, oil, natural gas, uranium) for producing chemical raw materials (e.g., petrochemicals) is one of the potential environmental threats. Depending on the composition of materials, manufacturers decide what disposal method should be used to treat waste materials. If a product contains non-toxic materials and most of its waste (non-hazardous) can be recovered via reuse or recycling, they pose minimal environmental concern. However, if a product contains toxic materials, recycling or other types of recovery become difficult. Hence, this increases the use of virgin materials. Even if the product is recyclable, it would require significant amounts of energy and other raw materials. Additionally, how a particular material is applied (e.g. under mild temperature and pressure / under high temperature and pressure) also has an impact on energy requirements, amount of materials use and toxicity (e.g., toxic air emission). This is how materials themselves are interrelated to toxicity and energy.

Energy related: Energy related carbon emissions and the related climate impact are largely dependent on the sources of energy used and the amount of energy required for a process / product and/or for a plant. Use of non-renewable sources (e.g. coal, oil, natural gas) of energy is one the most significant sources of carbon emission compared to renewable sources of energy (e.g. solar panel, wind turbine, waste to energy or biomass). As the predominant sources of energy are non-renewable, non-renewable materials have been extensively depleting. In addition, types of manufacturing equipment used in a process also determines the amount of energy consumption.

Toxicity related (air/water/soil): A product (and/or process) may pose a toxic effect via air pollution, water pollution and soil pollution depending on several key factors: firstly, the types of wastes produced, such as toxic byproducts with / without scope of recovery. Secondly, how the product (and/or process) is being managed or maintained across its lifecycle, for instance, incorrect ways of storage, distribution, use or disposal, produce toxic by-products, and use of toxic raw materials; and thirdly, effectiveness and efficiency of disposal methods used to reduce toxicity from wastes. It is important to note here that non-toxic waste with high recyclable properties (e.g., general corrugated packaging wastes) is of lowest concern for environmental toxicity. However, the level of recyclability or toxicity also depends on how the packaging is used to hold the products' integrity. For instance, if the product is chemically active and contaminates the packaging system, the recyclability of that packaging is reduced. It not only increases the use of virgin materials, but also poses a risk to the environment through landfilling of the non-recyclable parts of the packaging. Even non-

toxic packaging may be a source of toxic air pollution. For instance, corrugated packaging for food containers (e.g. a pizza box) may not be recycled completely due to food contamination. So, some contaminated parts with greases/oils are left for incineration, which may cause carbon monoxide emission to the air. Therefore, though in general non-hazardous wastes do not pose significant environmental pollution, they may still be an environmental concern depending on the availability, scope, ability, condition, and resources required to treat the wastes. So, apparently, the available disposal method in hand is one of the important determinants for toxicity measures.

A brief account of current and future environmental degradation clearly demonstrates why it has become so important for organisations to rethink their economic activities. The concept of environmental sustainability is particularly gaining attraction by the process industries that consume extensive amounts of naturally extracted feed stocks, consume extensive amounts of energy, and induce toxic wastes. Even though sustainable development has been discussed as interdependency between economy and ecology (WCS, 1980; Brundtland, 1987; Mebratu, 1998) for decades, environmental sustainability, economic growth and globalization are still the subject of debate. The debate however has entered the operation and supply chain level within the organizations due to the engagement of multiple suppliers, customers, contractors, sub-contractors, manufacturers, 3PLs providers, and emerging models of outsourcing. Additionally, supply chain activities are traditionally identified as a significant source of environmental degradation (e.g., GHG emission) specifically in the process industries (Paksoy, 2011). Managing the environment by reducing environmental degradation (e.g., greenhouse gas emission and pollution) has led companies to redesign their supply chains (Amemba et al., 2013; Suryanto et al., 2018).

Hence, environmental sustainability must be understood and incorporated into the supply chain level within an organization to hit the main target of environmental sustainability. Realizing the significance of environmental sustainability in the supply chain level, the last three decades have experienced a paradigm shift from traditional supply chain and business operations to greener operation across the industries by incorporating recycling, reusing, remanufacturing, waste reduction etc (Carter and Rogers, 2008; Lintukangas et al., 2013; Ashby et al., 2012).

Thus, companies have started practising environmental sustainability in the supply chain level which is known as Green supply chain management (GSCM) (Sarkis, 2003; Zhu et al., 2012). Significant environmental benefits can be achieved while the concept of environmental sustainability is applied across the supply chain stakeholders rather than being considered in isolation (Beamon, 1999; Zhu et al., 2012; CanKaya and Sezen, 2019). For instance, a product or process can be designed in such a way that the possible environmental impact across the lifecycle can be considered at the design stage and then followed up in manufacturing and distribution all the way through to the final use and disposal. The importance of considering environmental sustainability in the supply chain level is evident when an attempt to reduce carbon emission is considered across the supply chain of a product; for instance consider scope 1, scope 2 and scope 3 emission to achieve not only a short-term carbon offset target but also to attain environmental sustainability (Plambeck, 2012).

Studies such as CanKaya and Sezen (2019), Gupta and Palsule-Desai (2011), Green et al., (2012) etc strongly suggest that environmental consideration in the supply chain level may potentially conserve natural environment. Thus the environmental sustainability dimension in supply chain management studies has evolved through different themes of operational management, such as reverse logistics (Mishra, et al., 2012; Srivastava 2008), remanufacturing (Zhu et al., 2014; Yalabik et al., 2014), green supply chain management (Zhu et al., 2007a, Wu et al., 2012; Tseng et al., 2019), lean production (Kainuma and Tawara, 2006) and closed loop supply chain (Zhu et al., 2008; Quariguasi, et al., 2010). Sometimes all of these themes are together or separately considered as GSCM, which has been paid increased attention recently and the concept is being widely accepted both in the industries and organizations (Lee et al., 2012; Green et al., 2012). The next section discusses the key concepts of GSCM in detail.

2.3 Green Supply Chain Management

Incorporation of environmental concerns into traditional supply chain management to attain environmental sustainability (or both economic and environmental) is the most simplified and straightforward understanding of GSCM in the literature (Beamon, 1999; Zhu and Sarkis, 2004; Vachon, 2007; Tseng et al., 2019). Whilst the traditional supply chain focuses on quality, speed, dependability, flexibility, and cost (Christopher, 2000), today's supply chain has added green or 'environmental sustainability' requirement into it (Dubey et al., 2017).

The influential 'green' component has been added to every node of supply chain operations (e.g. product design, materials sourcing, manufacturing, distribution, as well as end of life management of the product after its useful life) to make a bridge between supply chain management and the natural environment (Srivastava, 2007). Realizing the win-win cases from applying the concepts of GSCM, academic researchers, industrial managers, manufacturing companies, government and non-government organizations across the globe have paid an unprecedented level of attention to it to deal with environmental degradation (Handfield et al., 1997; Bansal and Roth, 2000; Wu et al., 2012; Kumar et al., 2012; Mutingi, 2013; Zhu et al., 2013; Verma et al., 2018; Dubey et al., 2017).

Historically, many important but fragmented environmentally friendly operational concepts emerged between the early 70's and 90's; for instance, Ayres and Kneese's '*Material Balance View'* in 1969, Stern et al's '*Process Chain Evaluation Model'* in 1973, and Jelinski et al's '*Industrial Ecology'* in 1992. The '*Material Balance View'* argues that residuals can be recycled and returned back into the productive system instead of discharging into the environment. It also entails that the throughput of new materials is maintained at a given level of production and consumption, so that the technical efficiency of energy conversion and material utilization increases (Ayres and Kneese, 1969). The key message of the '*Process Chain Evaluation Model'* was to choose an alternative manufacturing process which was proved to be the least environmentally harmful and the most economical (Stern et al., 1973). '*Industrial Ecology'* proposes that manmade industrial products and processes should be mimicking the dynamics of the 'natural ecosystem' where there is no loss of materials and energy.

Whilst these earlier environmental concepts collectively shaped a strong view of environmentally responsible operations in the manufacturing industries, it was assumed that the concept of GSCM, or integrating environmental concerns into supply chain management, was first introduced in 1996 by the Manufacture Research Consortium (MRC) at Michigan State University. The National Scientific Fund (NSF) in the USA provided $400,000 financial aid to the MRC to conduct a research project named "*Environmental Responsible Manufacture*" (Xu et al., 2012). Since then the concept of GSCM has been evolving and has undergone a paradigm shift, from non-environmental supply chain to environmental supply chain, in particular due to the supply chain revolution in the 1990s (Nune, 2011).

Interestingly, though the GSCM definition and concepts have been enriched dramatically from the 90s to date, the concept has been very diverse, fragmented and multifaceted in nature due to the involvement of dynamic product, process, technologies, and business contexts (Ahy and Searcy, 2013; Dubey et al., 2017).

However, the concept of GSCM is sometimes interchangeably used as SSCM (Sustainable supply chain management) or ESCM (Environmental Supply Chain Management) due to having an almost similar and closer focus (Kumar et al., 2012; Ahi and Searcy, 2013; Mutingi, 2013). It is however evident that SSCM deals with the social, environmental, and economic dimensions of sustainability equally, whereas GSCM predominantly deals with the environmental dimension of the triple bottom line, and rarely with both the economic and the environmental. Hence, GSCM, which is the key focus of this study, is assumed as a subset of SSCM rather than an interchangeable meaning between the two terminologies (Fortes, 2009; Gupta and Palsule-Desai, 2011; Ahi and Searcy, 2013).

While searching for a structured understanding of the key concepts of GSCM, the concept has predominantly been viewed through four distinct perspectives. For instance, *green practices / environmental activities and strategies for application in particular industries* (Eltayeb et al., 2011; Albino et al., 2012; Lee et al., 2012; Abdel-Baset et al., 2019); *green drivers / motivations and influence factors of GSCM* (Zhu and Geng, 2013; Wu et al., 2012; Dubey et al., 2015); *green barriers / operational challenges for implementing particular green practices in particular contexts* (Muduli et al., 2013; Govindan et al., 2014b; Luthra et al., 2015) and *green performance / evaluation of green practices applied in particular contexts* (Xu et al., 2012; Perotti et al., 2012; Green et al., 2012; Zhu et al., 2013; Li, 2014; Tuni et al., 2018). The subsequent sections discuss each of these concepts in detail.

2.3.1 Green Practices

Green practices are defined as those environmental activities and/or strategies which are implemented by organisations to deal with environmental degradation originating from the organisations' operational and supply chain activities (Vachon, 2007; Xu et al., 2012; Scur and Barbosa, 2017). An organization's green supply chain practices entail internalizing by integrating its environmental management activities (collaboration) with other organizations in the supply chain or externalizing environmental management (monitoring) in the supply chain by employing market-based mechanisms having the aim to improve the overall environmental performance of the organization (Vachon and Klassen, 2006; Younis et al.,

2016). Selection and evaluation of an operational and /or strategic green practice in a given context is the key to the GSCM decision process, as it involves the ultimate success or failure of the green investment (Xu et al., 2012; Lee et al., 2012; Zu et al., 2013).

The extent and types of green practices for environmental protection largely vary across industries due to diversified business functions with dynamic product and process requirements which induce different levels of environmental impact (Zhu and Sarkis, 2006; Zhu et al., 2012; Suryanto et al., 2018). Therefore, different environmental activities have been sought in the different stages of the supply chain (Beamon, 1999; Toke et al., 2010). In line with key supply chain stages, the previous literature has predominantly focused on five strategic level green practices: green design, green manufacturing, green purchasing, green distribution and green use-and-disposal or end-of-life management (Srivastava, 2007). Each supply chain stage's green practice predominantly considers three environmental implications: materials, energy, and toxicity. Hence, each of the green practices can be sub-categorized as materials related, energy related and toxicity related. Exploring key environmental implications in terms of materials, energy, and toxicity under each stage of the supply chain also resembles a life-cycle analysis (Beamon, 1999).

Life cycle analysis (LCA) evaluates the key environmental impacts (e.g., materials related, energy related and toxicity related) of a product or a process across each stage of its life cycle from raw materials extraction to use, disposal and recovery (Beamon, 1999; Srivastava, 2007). LCA is evidently embedded into the green supply chain, as environmental burdens are not limited to a single company to manage independently (Seuring, 2004; Maditati et al., 2018). Rather, they also depend on the operational activities undertaken by the other stakeholder companies involved in the life cycle.

Figure 2.1 Life cycle environmental impact of supply chain stages (adapted from Beamon, 1999; Seuring, 2004; Srivastava, 2007; Bullock and Walsh, 2013)

Life cycle environmental impact assessment, in terms of materials, energy and toxicity (see fig. 2.1), provides a product and/or process manager (or engineer) with a grounded understanding of how a product or process should be designed and managed across its entire life cycle to minimize environmental impact. Hence, LCA is becoming an effective methodology to assess the environmental impact of a product or process across diversified industries from chemical and pharma to automotive and electronic (Beamon, 1999; Hsu and Hu, 2008; Soete et al., 2017).

However, being the key determinants for environmental performance, material, energy and toxicity related green practices take a holistic environmental perspective in any functional level of a supply chain (Srivasta, 2007; Zhu and Sarkis, 2007; Zu et al, 2012; Xu et al., 2012). For instance, materials focused green practices alone (e.g., less use of virgin materials) cannot provide a rigorous green design strategy for a product or process, as it lacks the toxic profile of the product / process, including the related energy requirements. Also, the green design of a product not only deals with climate change by looking for an option to reduce carbon emission, but also the green design may lead to increased biodegradability after the end of life of the product by looking for the option to reduce / eliminate toxic material from the product (Srivastava, 2007; Walsh and Bullock, 2013). Hence, it is vitally important to understand the trade-off and win-win proposition for each green practice (and sub level practices) prior to making a final decision of investment in them (Handfield, 1997; Vachon and Klassen, 2006).

Table 2.3 gives an overview, based on the previous GSCM literature, of how each functional level green supply chain stage can consider material, energy and toxicity related green activities to address related environmental impacts. As materials, energy and toxicity impacts are interrelated, it is important to clarify what impact is considered under which practices throughout this thesis in order to avoid confusion. For instance, materials related practices predominantly consider both materials related wastes and materials related energy emission. Energy related practices (in the design and manufacturing stage) consider process based (and/or plant based) energy emission. Toxicity related practices consider air (excluding energy related carbon emission) toxicity and water toxicity.

Table 2.3 Green practices and sub practice matrix (Sources: previous GSCM studies across diversified sectors)

	Material related	Energy related	Toxicity related
Green Design	• Less materials input (Bullock and Walsh, 2013; Vanalle et al., 2017) • Increase greener materials input (Donnelly et al., 2006) • Use recycled and/or renewable sourced packaging materials (Donnelly et al, 2006; Zailani et al., 2012) • Consider flexible process design (Deutz et al., 2013) • Consider process automation (Bag et al., 2018) • Consider green collaboration for process design (Chin et al., 2015)	• Choose alternative process design that consumes least energy (Zhang et al., 2004) • Design process with energy efficient equipment system (Deutz et al., 2013)	• Design to reduce overall toxicity (air & water) of a process (Rusinko, 2007) • Design to increase overall biodegradability of a process to reduce water toxicity (Walsh and Bullock, 2013)
Green Purchasing	• Consider product/materials content requirement (e.g., recycled/reusable materials) (Toke et al., 2010; Vanalle et al., 2017)	• Consider energy efficiency certification (e.g., Energy start, EMAS) of suppliers (Blome et al., 2014)	• Consider product/material content restriction (e.g., lead free, CFC free) (Eltayeb et al., 2011)

		• Local sourcing (Toke et al., 2010)	
Green Manufacturing	• Run continuous mode of manufacturing (Zhang et al., 2004) • Recycle and reuse materials (exclude packaging) (Govindan et al., 2015) • Consider lean operations for materials efficiency (Plambec, 2012; Hsu et al., 2016)	• Run process / plant by renewable energy sources (Ellram et al., 2008) • Consider process / plant energy efficiency management programs (Hajmohammad et al., 2013)	• Pollution Prevention: monitor and control materials toxicity (product stewardship) (Rusinko, 2007) • Responsible waste management (e.g., zero landfills) ((Rusinko, 2007)
Green Distribution	• Reduce secondary packaging wastes (McKinnon and Edward, 2010; Cankaya and Sezen, 2018) • Reduce product wastes through effective storage & handling (e.g., meet storage protocol such as temperature) (McKinnon and Edward, 2010)	• Choose transport that consumes less fuel (Cullinane and Edward, 2010; Cankaya and Sezen, 2018) • Choose transport that runs by alternative fuel (e.g., bio-based fuel, electric) (McKinnon et al., 2010)	• Choose transport that emits low level of toxic air emission (e.g., NOx, SOx, PM etc) (Dekker et al., 2011) • Responsible management of contaminated toxic packaging / product wastes (Beamon, 1999)
Green Use-and-Disposal	• Reduce product wastes through effective and efficient use (Scur and Barbosa, 2017)	• Effective and efficient use of products to reduce energy consumption (Beamon, 1999) • Choose least energy consumptive disposal (Lee and Tansel, 2012)	• Consider safe and responsible disposal of end-of-life products (Beamon, 1999; Srivastava, 2007)

The next section discusses each key green practice, including relevant sub green practices focused on materials, energy and toxicity related practices and activities, to provide a basic understanding on how each functional level supply chain stakeholder can achieve related environmental benefits. This baseline understanding is key to explore the scope of green supply chain management in any new sector like pharma.

2.3.1.1 Green design

Green Design is a systematic design process of a particular product or material where the designers are responsible to investigate and synthesize new technological possibilities to reduce the environmental burden during the life span of that particular product or material (Dewberry, 1996; Tian, et al., 2014). A number of terms exist in the literature for describing environmentally responsible design, for example, Green Design, Design for Environment, Life Cycle Design, Eco Design and Sustainable Design. The aim of different design aspects is similar: to reduce environmental impact, but in different levels (Dewberry, 1996;Wu, et al., 2012; Tseng et al., 2013; Tseng et al., 2019).

The core perspective of greener design is ‘product based’ and ‘process based’ (Dewberry, 1996). The product-based perspective of green design deals with materials, energy, and toxicity improvement for individual products where the expected functionality of the product is not compromised. The process-based assumption seeks to implement an innovative manufacturing process design through which each product achieves the desired level of positive environmental impact in terms of materials, energy, and toxicity. The process based aspect of green design is however more stringent towards a sustainable design approach due to the consideration of the trade-off between green aspiration and key manufacturing related aspects, such as product volume, quality, safety and equipment (Dewberry, 1996; Beamon, 1999).

Green process designs have emerged from the concept of industrial ecology (IE). One of the focuses of IE is change in the production process to prevent toxic pollution, as well as improve efficiency of production (O’Rourke et al, 1996). Under IE, the manufacturing process must be designed in such a way that all necessary environmental pollution parameters (e.g., emissions and wastes) are considered during design phase (Sroufe, 2003).

The design decision also largely depends on the procurement, production, distribution, and use and disposal phases in the lifecycle of a product. Hence, the function of the product,

process or service is defined and the raw materials, supplies, energy sources and process chemicals are selected at the early stage of product design or process design in order to lock the environmental influence (Eltayeb, et al., 2011). Additionally, another important green design factor is whether a product/process is going to be designed from scratch or redesigned from an existing product/process for a better environmental footprint. The scopes of green design in terms of operational challenges, such as time, costs and related technical difficulties, vary depending on the two different phases of green design. For instance, redesign (e.g., incorporating recycling feature) into an existing manufacturing process is more viable (operationally) than those with a completely new process design.

The importance of implementing Green design, especially in manufacturing firms, has been continuously evidenced in the literature due to observing both economic and environmental benefits (Zhu, et al., 2008; Eltayeb, et al., 2011; Laosirihongthong, et al., 2013). If green credentials are not considered in the design phase, companies could pay a significant amount of disposal costs or related environmental penalties (Srivastava, 2007), and consequently this may impact on brand image and loss of market share (Chen et al., 2016). Therefore, a synthesis of previous GSCM-related literature is done to identify what and how materials, energy and toxicity related sub green practices are considered during the design and development phase (see Table 2.3). A brief description of them is presented below:

- ✓ ***Material related***

Products and/or processes are designed in such a way that the products and/or process consume fewer materials in the production phase as well as in the design and development (R&D operations) phase. This concept is also known as 'Dematerialisation' (Walsh and Bullock, 2013). The amount and types of materials selection in the early design phase also have direct impact on the amount of related energy requirements during the production, consumption, packaging, and distribution phases. So, this green design predominantly aims to reduce material input (and related energy) in any phase of a product life-cycle (Beamon, 1999; Sarkis, 2003; Gopalakrishnan, 2012; Ahy and Searcy, 2013; Walsh and Bullock, 2013; Vanalle et al., 2017). As increases and/or decreases in materials consumption also increase and/or decrease the amount of related energy consumption, this design practice also considers materials-related energy consumption.

This is one of the fundamental practices for any organization to get on the ladder of environmental sustainability, as this practice directly deals with key environmental issues –

depletion of natural resources, climate change potential, cumulative energy demand (as materials usages and energy requirements are interrelated), water consumption and waste generation (Beamon, 1999; Bullock and Walsh, 2013). At the same time, it offers cost savings opportunities, for instance, reducing raw material costs, materials-related energy costs, transportation costs, and disposal costs (Sarkis, 2003; Bullock and Walsh, 2013). It is viewed as an in process, relatively proactive set of measures that can be taken by the organizations. Table 2.3 presents materials related key green activities that are explained below.

Consider recycled and renewable sourced packaging materials in the early design of a product decreases the usage of virgin materials (and related energy) significantly. In the electrical and electronic industry, for instance, electronic components and packaging are designed using renewable and recycled sourced materials for reducing the usage of virgin materials and the related energy requirements (Donnelly et al, 2006). Similar evidence is gained from the textile industry that considers recycled cotton in the garment design and considers recycled content (e.g. recycled polyester, recycled polyamide etc) in packaging (Shen, 2014). Manufacturing firms in Malaysia have also considered these design aspects and gained significant positive cost savings (Zailani et al., 2012).

Product packaging can be categorized as primary, secondary, and tertiary. Primary packaging is in direct surface contact with a product while secondary and tertiary packaging are extra layers of packaging to further protect the safety and quality of the product depending on the storage condition and transportation used. While this design consideration is predominant and less complex in the packaging related design, considering this aspect in product design largely depends on the quality, safety, and technical complexities of the product. For instance, when the design of a product (e.g., a drug) is largely dependent on a series of materials discovery processes (i.e., what materials should be selected is not certain unless the product functionality is confirmed), considering recycled and renewable content in the initial design phase in this scenario is comparatively difficult and sometimes impossible compared to other products, such as designing a microwave. Similarly, the design decision on recycling a plastic product (made of different grades of plastic materials) is also not so straightforward due to the engineering difficulty (e.g., dismantling and identifying new mixing materials) within the process design (Gupta, 1994). However, when the production process of that product is well known, as time passes, the process/product could be redesigned through

optimization. Hence, the consideration of recycling for those products (e.g., drugs) become less cumbersome during the manufacturing phase.

Increased use of greener materials in the product / process design has significantly reduced the usage of materials and related energy requirements. It is important to note here that, though apparently reducing or eliminating toxic / hazardous materials from the process may improve the overall environmental toxicity of the process, a proven greener material also has the promise to reduce materials waste, related energy and toxicity at the same time. An electronic company, Lucen Technologies, for instance, has redesigned one of its hardware products using an alternative greener material and a new body construction, which eventually reduces the volume of the product by one-third. This redesign approach consumes fewer raw materials during both the product developmental stage (R&D operations) and the manufacturing stage, and reduces materials-related energy consumption by 15 to 25% (Donnelly et al., 2006). It also reduces packaging during distribution.

Products can also be designed with such a material, so the final product uses less energy during storage. For instance, products which require less cold storage will save energy. Manufacturers have also been sought to reduce the amount of packaging wastes from the production line by considering this green practice in the early design phase. For instance, *minimizing the amount of packaging materials* by replacing corrugated boxes with shrink wrap in the shipping industry (Zsidisin & Siferd, 2001). If the design considers less raw materials input, it also reduces the energy requirements. For instance, when book publishers use 80 gsm paper rather than 100 gsm paper for producing books, the amount of energy reduction in the production and distribution phase will reduce (Bullock and Walsh, 2013). Thus, the amount of energy reduction in the production and distribution phase depends on input raw materials efficiency.

Consider flexibility in process design is another important design criterion which may help manufacturers to reduce further materials waste and related energy requirements. Designing a green product is an iterative process of determining the likely shape, materials, production process and production specifications (e.g., time, temperature and throughput) for the product (Deutz et al., 2013). As quality, functionality and environmental requirements are continuously balanced for improved green design, a flexible design approach is urgently needed to reduce unexpected materials waste. Therefore, it is important to work closely with external regulators and internal design teams to devise a flexible design approach. This is

because some regulatory bodies (e.g., in chemicals and pharma) may restrict this flexibility due to product safety and quality issues.

Consider automation in manufacturing process design is becoming another important process design criterion to reduce materials waste and the related energy requirements. For instance, printing companies in the UK have designed a printing process with a built in automatic cleaning process to reduce unnecessary cleaning materials in the manual process, which eventually has optimized the overall manufacturing process (Walsh and Bullock, 2013). Similarly, the virtualization of the manufacturing process using industry 4.0 technologies in the early process design phase has enabled companies to optimize their manufacturing processes. For instance, real time signals from processes promises the avoidance of unnecessary wastes (Bag et al., 2018).

Green or environmental collaboration is also an important green design credential for overall environmental footprint. A product or process is designed based on a two-way feedback (environmental impact related) between suppliers and customers to optimize the existing design of the product or process. This collaboration can be intra (e.g., between R&D and manufacturing within same organization) or inter organizational (when R&D and manufacturers are two separate organizations, for example). For instance, downstream customers (e.g., manufacturers) give environmental feedback on the production process to upstream R&D suppliers to improve existing process design (Chin et al., 2015).

- ✓ ***Energy related***

The manufacturing process of a product is designed in such a way so that the overall manufacturing process of the product consumes less energy (in terms of coal, gas and electricity) during production. The scope of this design practice is limited to reduce energy requirements for a manufacturing process, as materials / product related energy is covered under 'materials related' practice above. So, this practice predominantly considers the impact of energy related carbon emissions and conserves non-renewable energy sources. Table 2.3 shows two key energy related design practices.

Under this design practice, companies *choose alternative process design which shows least energy consumption during production*, for instance, selecting a process design which runs the operations at normal room temperature and pressure, rather than controlled temperature and pressure, to reduce overall process energy consumption (Zhang et al., 2004). Another

example in a book publishing company in the UK shows that the production process has designed a waterless printing process over water-based process, which reduces overall process energy consumption (Walsh and Bullock, 2013). Also, the *manufacturing process can be designed with energy efficient machineries, equipment, lighting, and digital technologies* to reduce overall energy consumption from the production process (Gopalakrishnan, 2012). Choosing a specific type of equipment/machine plays a crucial role in calculating process energy demand. For instance, consumer electronics component producers in the UK have considered energy savings equipment installed in the manufacturing process design to reduce energy consumption from the manufacturing process/plant (Deutz et al., 2013).

- ✓ ***Toxicity related***

The product or process is designed in such a way that it induces lower amounts (or phase out) of toxic emission into air and water from R&D, production, distribution, use and end-of-life management. So, the key environmental consideration here is air toxicity and water toxicity. Here, air toxicity excludes energy-related carbon emission but considers other process-related greenhouse gas emission such as VOCs and CFC. Table 2.3 shows two key toxicity related design practices to curb air and water toxicity.

Process can be designed to reduce overall toxicity to air and water. For instance, reducing or eliminating toxic / hazardous materials input is one of the key toxicity-related design decisions to reduce overall process toxicity. An example of this in the printing industry, is when the printing process (a chemical process) can be designed with alternative ink (e.g., non-organic solvents) in order to reduce VOCs emissions significantly from the mass production process, which ultimately impacts climate change (Walsh and Bullock, 2013). Similarly, electronic companies in Thailand have replaced 'lead' (a hazardous substance) with lower impact 'silver', 'copper', 'gold' etc in their product design (Ninlawan et al., 2010). Toxicity related green design also improves product quality. For instance, when scientists at Raytheon redesigned their process to eliminate chlorofluorocarbons (CFCs) used in cleaning printed circuit boards, the new process improved the product quality (Rusinko, 2007) as well as air toxicity.

If product design (not process) considers toxic/hazardous materials, waste disposal becomes difficult, costly, energy consumptive and raw materials exhaustive. Hence, the level of toxicity of a product has also an indirect material and energy relevancy. For instance, Alcatel-

Lucent, a French/American based global telecommunication equipment company, has eliminated all potential hazardous materials by considering substitution of materials while designing equipment. This design approach has reduced 28% of the environmental footprint (in terms of materials, energy and toxicity) across the whole life cycle of the product (Zhu and Liu, 2010).

Process can be designed to increase overall biodegradability to reduce water toxicity. For instance, considering biodegradable substances in the early design phase of a product/process is a promising toxicity related green design approach which aims to reduce water toxicity. So, the products can be degraded over time when they enter the environment after the end of useful life, rather than persisting for longer to pollute like plastics (Srivastava, 2007; Bullock and Walsh, 2013). Another example from printing companies in the UK is the introduction of vegetable-based ink (a comparatively biodegradable process) instead of organic chemicals based printing processes to increase environmental biodegradability of wastes and thus reduce water toxicity of the new printing process (Bullock and Walsh, 2013).

2.3.1.2 Green Purchasing (GP)

Procurement or Purchasing involves functions such as vendor selection, material selection, outsourcing, negotiation, buying, delivery scheduling, inventory, and materials management (Toke, et al., 2010). The consideration of sustainability issues on the traditional purchasing criteria of cost, quality, and delivery has induced an unprecedented level of anxiety for purchasers. The purchased green materials reduce environmental impacts, improve energy efficiency, limit toxic byproducts, and contain recycled contents. Even though there are some factors (e.g., management support, organizational capabilities) hindering the adoption of GP in practice, its performances are positive in multiple directions. For example, GP increases product performance by reducing waste and using more recycled materials (Liu et al., 2017). It also reduces the cost of purchasing (Salam, 2011; Eltayeb, et al., 2011). Green purchasing can also be viewed from a material, energy, and toxicity perspective:

- ✓ **Material related**

The purchasing function is done in such a way that there is less use of materials (e.g., packaging materials or other raw materials) across the life cycle of a process and/or product. For instance, the specification should contain the recyclability and/or reusability of purchased materials or products (Toke et al., 2010; Liu et al., 2017). The manufacturing firm should

only negotiate with those vendors who could participate in product recycling, reusing or disassembling activities (Blome et al., 2014). The focal manufacturing firms should only outsource to those suppliers who are dedicated to reducing packaging waste across the life cycle of the product/process. The commitment of active involvement of the material suppliers in product/process design as part of negotiation is also a key purchasing parameter for reducing materials waste.

- ✓ **Energy related**

The purchasing function is done by considering energy reduction across the life cycle of a product or process, for instance, seeking suppliers with low energy consumption (Blome et al., 2014), considering only those suppliers who are willing to participate and go through the EMS certification system, including energy reduction targets, and seeking local sourcing. Suppliers are required to have a recognized EMS certificate, such as British Standard 7750 (BS 7750), ISO 14001 or the European Union eco-management and audit scheme (EMAS). The focal manufacturing companies consider only those suppliers who practically provide with on demand energy management evaluation and are willing to participate in regular energy auditing schemes to determine the level of compliance with environmental compliance set by the focal manufacturers (Toke et al., 2010; Eltayeb et al., 2011). The purchasing function also considers ***Energy Start***: a joint program of the US Environmental Protection Agency and the US department of Energy that deals with the energy performance of a range of products (Ho, et al., 2010).

- ✓ **Toxicity focus**

The purchasing function is carried out by considering the environmental toxicity of the products or materials purchased across the life cycle. For instance, the manufacturers specify in the spec sheet that the purchased raw materials / products should not contain environmentally undesirable attributes such as lead, CFCs, or plastic foam in packaging materials (Eltayeb et al., 2011). As part of negotiation the suppliers are asked to commit to the goal of hazardous waste reduction.

2.3.1.3 Green Manufacturing

Green manufacturing (GM) is a systematic and innovative manufacturing process by which environmental impacts such as wastes (toxic/non-toxic), air pollution, water pollution or other environmental parameters are controlled and reduced during the manufacturing of a

specific product. Manufacturing operation is generally attributed to significant environmental degradation (e.g., carbon emission, toxic wastes, toxic air emission, water stress) in the supply chain due to usage of considerable amounts of raw materials, water, energy, and inducing related wastes (Rusinko, 2007; Srivastava, 2007). Most of the environmental degradations may occur in this stage. So, environmental consideration in manufacturing could significantly reduce environmental burden and save costs (Sroufe, 2003; Hajmohammad et al., 2013; Rehman and Srivastava, 2016; Govindan et al., 2015).

Though the existing literature has attempted to address the application of GM in different directions, three fundamental sub green practices: material reduction related, energy reduction related, and toxicity reduction related are predominant. A brief discussion on each is given below:

- ✓ ***Material related***

A product/process is run and controlled during manufacturing in such a way so that there is less or minimum levels of materials usages. Table 2.3 shows four key green practices that have helped companies to make a process green. Choosing a particular mode of manufacturing (batch/continuous) has a high relevance on the environmental footprint. R*unning continuous mode of manufacturing* induces a positive environmental footprint. For instance, the commercial production process of a chemical raw material (called 'chromium') has been shifted from multi-stage batch process to continuous process. It significantly reduces raw materials input due to avoiding multiple reaction stages. The required temperature for the process has also reduced from 1200 degrees Celsius to 300 degrees Celsius (Zhang et al., 2004).

Reuse and recycling of materials (exclude packaging) during manufacturing process has significantly reduced materials waste and reduced the requirements of virgin materials (Sroufe, 2003; Srivastava, 2007; Rushinko, 2007). For instance, Govindan et al (2015) have identified the three best green manufacturing (GM) sub practices for Indian rubber industries for material reduction in the process. These best GM practices are reducing, reusing, and recycling. Manufacturers also seek the opportunity to reduce raw materials (including water) consumption in the production process as part of their *continuous improvement or lean programs*. They also consider using renewable raw materials, as well as process optimization by applying lean, JIT and TQM projects (Plambec, 2012).

- ✓ ***Energy related***

A process (and/or plant) is run in such a way that there is less consumption of energy. It comprises two factors: the way of producing the goods and the energy supply to the production plants. Recovering energy from the process and use of *renewable sources of energy* (e.g., wind turbine) help manufacturers to reduce overall process or plant level energy consumption (Ellram et al., 2008). Process optimization plays a crucial role in reducing energy consumption during manufacturing. *Process and/or plant wide energy efficiency program* (e.g., lean activity, process optimization tool etc) is one of the key approaches to reducing overall process / plant energy. The process optimization can be either primary types (e.g., change the manufacturing process completely) or secondary types (e.g., replace energy efficient equipment and reduce water consumption). The primary type process optimization will influence process design change. The secondary type process optimization is like lean operations, i.e. focus on energy loss across the process, and improving machines /tools/ equipment efficiency and effectiveness.

- ✓ ***Toxicity related***

The manufacturing process is run and controlled in such a way that there are reduced toxic emissions to air, water, and soil. *Responsible waste management*, *product stewardship* (or green product management, or extended producer responsibility) and use of pollution control parameters (e.g., amount of hazardous waste induced) are the key to reducing toxicity from the manufacturing process (Rusinko, 2007; Srivastava, 2007). *Responsible waste management* ensures the correct and most eco-friendly action taken to process and/or reprocess the hazardous wastes from the manufacturing process so there is less environmental impact, for instance, reducing toxic solid waste, reducing toxic emissions, recycling toxic wastewater, diverting toxic solid waste from landfill, recycling products (not incineration), and recycling toxic solid waste (not incineration) (Srivastava, 2007). Product stewardsip ensures that the producers continuously observe, monitor, and assess the degree of toxicity to air, water, and soil across the life cycle of their products to take appropriate measures to tackle pollution. Pollution control parameters (e.g., air emission permit and wastewater discharge limit) ensure that the manufacturing processes do not exceed the permitted discharge limit.

2.3.1.4 Green Distribution

In general, the green distribution process entails environmental consideration such as energy sources, emissions and wastes into transportation, storage, and warehousing, and retailing of goods for achieving environmental sustainability. While searching the relevant research papers, it became apparent that green distribution related aspects are broadly covered under the green logistics literature and they are interchangeably used.

Freight transportation has a significant impact on the environment, generating roughly eight percent of energy related CO_2 emissions worldwide (McKinnon, 2010a) and accounts for the main source of NOx, So_2 and PM (particulate matter). Relevant strategic and operational environmental practices could help to mitigate these problems. It was reported by the Tata Strategic Management Group (2014) that lighting, HVAC system and material handling equipment are the largest energy users in warehouse operations.

Whilst different aspects of green distribution or logistics have been incorporated to understand the complexities of relevant operations under environmental issues, specifically energy use, freight emissions and related wastes, the green related practices in the distribution can also be identified under three core areas: materials reduction, energy reduction, and toxicity reduction.

- ✓ ***Material related***

Goods or products are stored, transported, and retailed in such a way that there is less use of materials, especially packaging materials, throughout the distribution process. For instance, the packaging requirements for storage and transportation could be reduced by customizing and optimizing the pack shape, dimensions, and stackability (McKinnon and Edward, 2010). *Reduce, and reuse* could also be followed in warehouse packaging for reducing ecological impact (Tata Strategic Management Group, 2014). *Reduce* involves using light weight, less toxic and thin packaging material, eliminating excess/unnecessary packaging and bulk packaging in primary distribution. *Reuse* involves reusing packaging materials which result in the reduction in packaging inventory and improved warehouse utilization. Product *storage requirements* (e.g., time, temperature, light sensitivity etc) are also maintained throughout distribution to reduce unexpected product waste.

- ✓ ***Energy related***

Goods or products are stored, transported, and retailed in such a way that there is less use of energy (especially due to excessive packaging and mode of transportation used) throughout the distribution process. Use of energy efficient packaging materials and the most energy efficient transport types are the key. For instance, modal shifting from road freight to rail and water are evidenced based on the assessment of energy consumption and atmospheric emission from different modes of freight transport (Cullinane and Edward, 2010).

Efficient utilization of vehicles could potentially reduce energy consumption. McKinnon and Edwards (2010) have outlined several measures to improve vehicle utilization. The measures are: tonne-kilometres per vehicle per annum, weight–based loading factor, space-utilization/vehicle fill and empty running. It is suggested that after unloading goods at a particular warehouse, a truck can be used to transport goods of some other manufacturers (or suppliers) located in the warehouse's vicinity and thereby overcoming the challenge of empty truck returns and the related energy loss (Tata Strategic Management Group, 2014).

Warehousing operations consume significant amounts of energy. According to Gazeley's (a property developer) sustainability report, between 65 to 90 per cent of energy is consumed in a warehouse during ongoing operational activity through power for heat, ventilation, and air conditioning (HVAC), lighting, and equipment (Marchant, 2010). Major scope for improving energy efficiency in warehouses is temperature control, lighting, and equipment handling. Efficient temperature control in different locations, such as in storage areas, loading bays, picking areas, despatch areas, would save significant amounts of energy. It was reported that a 1 degree decrease in internal warehouse temperature can lead up to 10% energy consumption savings (Marchant, 2010; Tata Strategic Management Group, 2014). The use of energy efficient lighting systems in warehouses is another option. For instance, fluorescent lights provide the same amount of light but with lower energy consumption (up to 50% less compared to traditional fittings) at a cost effective price (Tata Strategic Management Group, 2014). Under an energy management scheme, green building, efficient lighting and refrigeration systems and green energy are predominant. Also, the *use of alternative fuels* such as electric, CNG and LNG reduces dependency on non-renewable sources of energy.

- ✓ ***Toxicity related***

Choose transport that emits low level of toxic air emission (e.g., NOx, SOx, and PM). Goods or products are stored, transported, and retailed in such a way that there is less toxicity to air and water, especially from hazardous products waste (or hazardous product contaminated packaging waste) / spillages throughout the distribution process.. For instance, switching mode of transportation from air to sea reduces air toxicity, as air freight emits significant amounts of SOx, while rail and water modes do not differ much in SOx emission (Dekker et al., 2011). Retail leaders such as ASDA and TESCO have switched their transport from road freight to rail and water. This results in a significant reduction to air toxicity. It is reported that TESCO uses rail between the Midlands and central Scotland, saving more than 7 million road kilometres per annum and leading to around 6000 fewer tonnes of CO_2 being emitted each year (Woodburn and Whitening, 2010). Similarly, the pharmaceutical leader, AstraZeneca, has introduced the new Air2Sea project in its Swedish operation in 2015 and established sea freight in 13 countries (AstraZeneca, 2015). This modal shift to sea has achieved a massive 97% CO_2 savings compared with air transport.

Reducing hazardous product (e.g., drugs, agro chemicals etc) contaminated packaging wastes during transportation and/or storage, and *responsibly managing those wastes* reduces water toxicity. The use of plastic pallets over wooden pallets for some kinds of time and temperature sensitive products (e.g., drugs and foods) are safer and produce fewer toxic wastes due to having less possibility of microbial contamination (Hardisty, 2011).

2.3.1.5 Green Use-and-disposal

The concept of green use-and-disposal focuses on understanding the environmental impact of ‘usage of a particular product over its life span’ and ‘ the disposal options chosen at the end of its useful life’, so it can be taken as proactive measures to protect environmental damage (Beamon, 1999; Srivastava, 2007). It is important to note that the concept of ‘use-and-disposal’, ‘end of life management’ and ‘producer’s extended responsibility’ are similar and could be used interchangeably (Beamon, 1999; Srivastava, 2007; Gupta and Palsule-Desai, 2011).

The inappropriate use and disposal of products are significantly damaging the environment by polluting air, water, and land. For instance, inappropriate methods of disposal could contaminate land with heavy metals such as arsenic, cadmium and lead, oils and tars, chemical substances and preparations like solvents, gases, asbestos and radioactive

substances (DEFRA, 2018). This can significantly harm people, property, or protected species and pollute surface and ground water. Capturing this phase under green supply chain management could significantly reduce landfill contamination and save environmental penalty costs, as it induces profit by reducing the amount of wastes (Zhu et al., 2008) and processing the wastes for beneficial use (Srivastava, 2007; Azevedo et al., 2011). The key sub green practices can be categorised as below:

- ✓ ***Material (finished goods wastes) related***

The finished goods are used / applied in such an effective and efficient way that there is minimum waste. Improper usage of finished products or materials, especially those products which are time and temperature sensitive losing potency, safety, and efficacy, such as drugs, could induce significant negative environmental footprints. This practice ensures *efficient use of the finished goods through reuse and optimum and effective usage of goods* to reduce unnecessary product wastes (Beamon, 1999; Scur and Barbosa, 2017). The key stakeholders involved in a product supply chain play a crucial role for effective and efficient usage of finished goods. Individual stakeholder-led initiatives could involve reusing and reducing related lean activities based on product types.

- ✓ **Energy related**

The finished goods are used and disposed of in such an effective and efficient way that there is less requirement of energy. For instance, the way electronic appliances or equipment are handled and used has an impact on energy consumption. Additionally, the process of final used and/or unused disposals, such as wastewater treatment, incinerations and landfills, require significant amounts of energy depending on the amount, categories, and state of the disposal wastes (Azevedo et al. 2011). The waste management could select the most energy efficient method of disposals. But the amount of energy savings largely depends on the types of products / materials being disposed. For instance, though recycling and landfills are the two disposal options for disposing the household water-using appliances, recycling consumes more energy than landfills (Lee and Tansel, 2012). It is also possible to regenerate energy from wastes processing plants.

- ✓ **Toxicity related**

The finished products are used and disposed of in such a way that there is less toxicity to air, water, and soil. For example, ineffective and inefficient application of solvents in car coating

/ painting can increase air toxicity (e.g., VOC emission). The water cycle could also become toxic while irresponsible and unsafe methods of disposal are used, such as landfilling electronic wastes, plastic wastes, unused drugs, instead of recycling or other environmentally friendly ways of processing.

So, the suppliers, producers, distributors, end users and other related key stakeholders' responsible behaviour could potentially reduce this toxicity. Though incineration and landfill are common practices, they are highly dependent on types of products / materials (e.g., degree of toxicity, hazardous and non-hazardous) to be disposed of. For instance, landfill emits more greenhouse gas (0.117 kgCO2e) per kg of materials than recycling (0.098kgCO2e) (McDougal et al., 2001) in the case of residential water-using appliances. In another instance, disposal of wooden boxes through municipal incineration contributes minimum amounts of CO2e greenhouse gas, whereas plastics packages have high impact (Accorsi et al. 2014). Emission was also lower in the case of landfill due to the slow process of the releasing of pollutants. Negative environmental impacts (air emissions) were estimated in the case of recycling either wooden or plastic packages. Product take-back programmes, which actually originated from the ERP (Extended Producer Responsibility) legislation (Beamon,1999; Qu et al., 2013), are also an effective practice to reduce environmental toxicity, for instance, a well-defined and structured collection system for collecting electronic wastes for appropriate disposal. Nowadays almost every European country requires their manufacturers to take back their used products and dispose of them properly without negative effects to the environment (Gaussin et al., 2013). However, choosing a disposal option (incineration/landfill) is complex, involving multifactorial decision making, as the trade-off between cost effectiveness and environmental effectiveness is not always justifiable.

While up to now a clear foundation of green practices and related sub practices has provided a grounding to understand and imagine the scope of greening activities in any new sector, like pharma, knowledge on the related motivations and challenges could be more fruitful to better realize the big picture of the application of green activities in the sector. Table 2.4 presents a summary of the key drivers and barriers across different industries. These drivers and barriers provide us a base line for investigating the related facts in the pharma industry. The subsequent sections discuss the key drivers and barriers of green practices implementation.

Table 2.4: Key green drivers and barriers (source: previous GSCM literature)

Green Drivers				**Green Barriers**			
Regulatory	**Business benefits: Cost savings**	**Top management commitment**	**Market: Stakeholder pressure (exclude govt.)**	**Complex marketing authorization of green products/process**	**Financial: High investment & cost**	**Cultural issues**	**Operational challenges**
REACH (Registration, Evaluation and Authorization of Chemicals): force companies to design / produce low impact chemical product (Zhu et al., 2008; Shi et al., 2012; Gopalakrishnan et al., 2012;Tseng et al., 2013) **F-gas related**	**Cost savings from green manufacturing process:** companies are driven by the raw materials-related costs savings via recovery practice (Gupta, 1994; Wong et al., 2012) **Cost savings from reverse logistics:** companies are	**Internal environmental target:** departmental operations managers are forced to achieve company's internal environmental goals and targets such as zero landfill (Berry and Rondinelli, 1998; Harvani et al., 2005) **Community well-being & corporate responsibility:** companies felt responsible and	**Demand for green product/process by downstream customers:** upstream suppliers are forced to comply with downstream customers' green specification (Wong et al., 2012) **Increased end consumers' ecological thinking and knowledge:**	Bureaucratic approval process of green product by related approval body (Porter & Ven Der Linde, 1995; Walker et al., 2008; Li et al., 2015) Lack of clear guidance for green product approval (Li et al., 2015)	High cost of green product (Walker et al., 2008) High cost of environmental programs (Rao and Holt, 2005) Uneconomical recycling (Rao and Holt, 2005)	Lack of green mindset among employees (Govindan et al., 2015)	Engineering & Technological challenge: related equipment and engineering incompatibility / shortcomings for executing green operations such as remanufacturing, reusing, recycling etc (Zhu & Geng, 2013; Govindan et al., 2014b; Li et al., 2015)

Green Drivers				Green Barriers			
Regulatory	**Business benefits: Cost savings**	**Top management commitment**	**Market: Stakeholder pressure (exclude govt.)**	**Complex marketing authorization of green products/process**	**Financial: High investment & cost**	**Cultural issues**	**Operational challenges**
regulation: force companies to reduce or replace f-gas (e.g., CFC, HFC etc) related materials from the product /process (e.g., CFC free inhaler) (Garnett, 2007) **RoHS** (Restriction of Hazardous Substances): force companies to avoid hazardous substances (e.g., lead) in electrical product	driven by the salvage value of returned products (Rao and Holt, 2005; Eltayeb et al., 2010) **Cost savings from operational efficiency (via green practice):** companies are driven by lean /CI (e.g., energy efficiency program) related cost savings (Rao	accountable for managing environmental impact of their product manufactured (Gupta, 1994; Walker et al., 2008) **Incentives and awards for green innovation:** employees motivated to innovate green products/process **(**Graci and Dodds, 2008)	increased green awareness drives companies to shift from resources exhaustive to lean and green production (Ball and Craig, 2010) **Primary stakeholders encourage environmental strategy**: Due Business owner's / shareholder's / investor's pressure		Uneconomical re-use (Rao and Holt, 2005)		Time constraint (Li et al., 2015) Lack of green related data & information (Walker et al., 2008) Lack of environmental education and training (walket et al., 2008)

Green Drivers				Green Barriers			
Regulatory	**Business benefits: Cost savings**	**Top management commitment**	**Market: Stakeholder pressure (exclude govt.)**	**Complex marketing authorization of green products/process**	**Financial: High investment & cost**	**Cultural issues**	**Operational challenges**
design and manufacturing **(**Tseng et al., 2013) **WEEE** (Waste electrical and electronic Equipment): force companies to adopt recovery practice via product take back **(**Zhu et al., 2008;Tseng et at., 2013)	and Holt, 2005) **Cost savings from waste conversion:** companies are driven by generating profit from converting waste to beneficial use such as waste to energy or waste to fertilizers (Gupta, 1994; Porter & Ven Der Linde, 1995)		for green (Walker et al., 2008) **High green pressure for high profiled companies**: High profile companies are forced to adopt green (Walker et al., 2012)				

Green Drivers				Green Barriers			
Regulatory	**Business benefits: Cost savings**	**Top management commitment**	**Market: Stakeholder pressure (exclude govt.)**	**Complex marketing authorization of green products/process**	**Financial: High investment & cost**	**Cultural issues**	**Operational challenges**
Product take-back legislation: force companies to adopt recovery (e.g., recycling, repair, reuse, remanufacturing) practices via mandatory collection of end-of-life used products from customer zone (Esenduran et al., 2012).							

2.3.2 Green Drivers

Green supply chain management drivers are those key success factors that influence the relevant stakeholders in the supply chain to adopt green practices over time (Zhu and Sarkis, 2004; Zhu et al., 2007; Zhu et al., 2013; Maditati et al., 2018). A green driver advocates why and how a particular green practice has been adopted in any context (Gopalakrishnan, 2012; Zhu et al., 2013). The study of green drivers is not only important to understand the key green practice adoption mechanisms in a particular sector but also to understand the trade-offs between green investment and organizational performance (Murphy and Gouldson, 2000; Zhu et al., 2012; Green et al., 2012).

Additionally, the rate of green practices adoption is predominantly dependent on the intensity of a driver (e.g., WEEE regulations) perceived by the organizations (Zhu et al., 2013). Whilst it is clear that the rate of adoption of different green practices varies across different sectors (Zhu et al, 2008; Wu et al., 2012; Zhu and Geng, 2013), it is crucial to understand the related drivers in the details that eventually force them to implement a particular green practice. Understanding the intensity of different drivers for a similar sector or for diversified sectors may provide business managers with new opportunities for increasing competitive advantages by adopting green practices. Specifically, stakeholder-wide separate driver identification with their intensity across the supply chain will help managers to rank them in terms of the most important GSCM practices adoption, such as eco design and green manufacturing. The intensity of drivers is also important for policy makers to rectify policy or related policy development accordingly for achieving a greener society (Wu et al., 2012). The adoption behaviour of a particular green practice over the time will help the laggards or early adopters to make green decisions considering their resources and capabilities. So, it is important in any context (either with a voluntary approach or a regulatory approach) to understand the key drivers for attaining environmental sustainability.

Table 2.4 presents a summary of the key drivers across different industries. These drivers provide us a base line for investigating the related facts in pharma industry. As seen in the table, four types of green drivers are identified as the key determinants for successful green implementation across different sectors. They are: ***Regulatory*** – e.g., regulations such as WEEE, REACH, RoHS etc (Tseng et al., 2013); ***Business benefits*** – e.g., cost savings from

greening; ***Top management commitment*** – e.g., setting internal emission target; and ***Stakeholders pressure*** – e.g., market / consumer pressure (depending on social legitimacy or social cohesion), consumer green awareness, consumer ethical beliefs and ecological thinking (Carter et al., 2000; Ball and Craig, 2010; Sarkis, 2011). The subsequent sections discuss the key drivers of green practices implementation.

2.3.2.1 Regulatory

Regulatory pressure is exerted from powerful institutions, such as government bodies. Regulation-related government fines can be imposed on companies. As seen in Table 2.4 there are five key regulatory drivers that predominate across different industries. Highly toxic or hazardous chemicals contained materials or products pose significant negative environmental and human health impacts. REACH (Registration, Evaluation, Authorization and Restriction of Chemicals) regulation is one of the related regulatory drivers enacted by the EU. This regulation forces companies to reduce highly toxic or hazardous chemicals (e.g., benzene) use in their products or process (Shi et al., 2012; Gopalakrishnan et al., 2012; Tseng et al., 2013). For instance, British Aerospace Systems (BAe) has reduced its negative environmental impact driven by REACH (Gopalakrishnan et al., 2012). Thus, companies that use raw (chemical) materials would probably increase their capabilities and resources by looking for alternative (green) chemicals in response to REACH regulation.

Fluorinated greenhouse gases (termed as F-gas), such as CFC and HFC, pose negative impacts on climate change, as they are ozone depleting substances. These gases are normally emitted from refrigeration, air conditioning and heat pump applications in both domestic and industrial scales. They are also emitted from some chemical processes through equipment installation. F-gases are also emitted from some products during their usage phase, such as aerosol products. F-gas-related regulations drive companies to consider F-gas-related impact in the early product/process design phase to produce F-gas free products (e.g., CFC free inhaler). The regulation also forces companies to reduce/eliminate those F-gases and use lower climate impact substances during the manufacturing process. For instance, driven by f-gas regulation, UK food manufacturers have started replacing CFC/HFCs with hydrocarbons as a refrigerant (Garnett, 2007). Though there are several types of F-gas-related regulations in existance (e.g., ODS regulation EC 1005/2009, and Fluorocarbons Recovery and Destruction Law), the key motivation of all F-gas related regulations is either use F-gas alternative (or reduce usages) or increase appliance/equipment efficiency to reduce emissions.

Companies across diversified industries (especially electrical) are now forced by industry specific regulatory bodies to collect end-of-life discarded products from the customer zone for safe disposal (Esenduran et al., 2012). This is known as product take-back legislation. For instance, China has implemented and practised a product take-back (of end-of-life discarded products) scheme in manufacturing based companies due to WEEE (Waste Electrical and Electronic Equipment; product take back scheme) regulation (Zhu et al., 2013). RoHS (Restriction of Hazardous substance) is also a closely related regulation with WEEE. RoHS has restricted the use of hazardous materials (e.g., lead) in electronic products. Both WEEE and RoHS have forced Chinese electrical manufacturers to adopt recovery practices.

To gain competitive advantages, the organizations try to equip themselves with the necessary resources to increase their capabilities to implement innovative organizational practices to overcome those external regulatory pressures (Sarkis, 2011; Zhu et al., 2013). Regulation is seen as one of the main drivers of environmental reform and the development and application of innovative technologies that enhance industrial competitiveness (Murphy and Gouldson, 2000; Zhu, et al., 2012; Green et al., 2012).

2.3.2.2 Business benefits: cost savings

Cost savings from applying green technology or green operation is one of the key determinants for green revolution across diversified industries. As managers are continuously under pressure to achieve cost efficiency without compromising quality and service, cost savings from green operations are becoming lucrative for operations managers to explore green operations. As seen in Table 2.4, companies from diversified sectors have predominantly been driven by those four sub factors under business benefits. For instance, by adopting green manufacturing processes (e.g., replacing mode of manufacturing, built-in recycling etc), managers can save costs through reducing energy consumption, reducing the raw materials usages via recycling and reducing activities, reducing the cost of waste treatment and disposal, and avoiding environmental related fines (Zhu and Sarkis, 2004; Rao and Holt, 2005; Srivastava, 2007). One of the pharma manufacturing sites of 3M in the USA, for example, has replaced solvent based (e.g., organic chemicals) medicine coating with water-based process. This change in the production process has resulted in savings of US$180k by eliminating the need for pollution control equipment installation in the process (Gupta, 1994). Similarly, Renolds Metals, known as largest aluminium company in the US, has replaced solvent-based ink with water-based in their packaging plant, which has resulted

in a 65% emission reduction and saved US$30m in production equipment (Gupta, 1994). Re-engineering manufacturing processes for recycling also brings significant amounts of materials savings. For instance, recycling in the manufacturing process has helped 'Catalyst Semiconductor Inc' to reduce consumption of fossil fuel by 46% between 2002 and 2005, which has resulted in savings of $13 million. Given such cost effectiveness as a driving force, even in some non-regulated markets, firms are applying materials recovery practices, in terms of recycling, just for cost efficiency (Zhu et al, 2008). However, the payback period of such recovery practice in the manufacturing phase largely varies across sectors.

Companies have also saved costs from the reverse logistics function through reducing the cost of materials and packaging, as they use recycled or reuse materials instead of virgin materials (Eltayeb et al., 2010). Companies have also been able to reduce operational costs through better utilization of natural resources, improved process efficiency and higher productivity (Rao and Holt, 2005). For instance, The Holiday Inn in British Columbia has installed a sensor based automatic energy control system which has saved approximately $16,000 in energy related costs annually through saving 28% of its energy consumption, and the payback period was only 14 months (Graci and Dodds, 2008).

Green supply chain innovation has enabled manufacturers to exploit wastes as an opportunity and resource rather than merely a waste. Converting wastes into many facets of beneficial usages is increasingly becoming a central business strategy across many industries (Rao and Holt, 2005). Reprocessing wastes to beneficial use brings business benefits in several ways: a) reducing disposal costs, b) reducing raw materials purchasing costs (if recycled wastes are used as direct raw materials for the same process or different processes in the same plant, or used in some other purposes such as cleaning within the same plant), c) generating energy from wastes, and d) selling recycled products to other industries for usable input materials. For instance, Rexham Corporation, a well-known packaging compnay, has installed a new recycling technology (e.g., distillation unit) investing $16,000 to recover waste solvent (e.g., n-propyl alcohol) from the manufacturing process. This has enabled the company to recover 85% of its waste solvents, which eventually reduces purchasing costs of virgin solvents ($15,000 per year) for the site and reduces the disposal costs by $22,800 (Gupta, 1994). Another photo-processing company has adopted a new recycling technology (electrolytic deposition process) that recovers silver from the rinse water (or wastewater) in film-processing equipment to sell it to a small recycler company. By removing silver from the process, the process becomes non-hazardous and can be disposed to the sewer without

additional treatment. Thus, it reduces disposal costs (Gupta, 1994). The process was also capable of burning the used films and recovering silver from the ash. So, the ash also becomes non-hazardous and does not require high cost of disposal. This new advanced process pays back in less than two years.

2.3.2.3 Top Management commitment

Top management's proactive planning, strong vision, philosophy towards operations, rigid support for employee development and effective implementation of plans are a few of the important pillars of top management commitments (TMC). TMC has been a strong enabler of green practice adoption across diversified industries through providing strategic and financial support, new process implementation, use of decision support systems, effective corporate environmental communication and building strong internal environmental management systems (Hervani et al., 2005; Walker et al., 2008; Balon et al., 2016). As seen in Table 2.4, TMC drives green practices through: setting up internal environmental targets, adressing community wellbeing and corporate responsibility, and providing incentives and awards for green innovation.

Strong commitment, guidance, and strategic direction from the top management for achieving environmental targets (e.g., reducing CO2 emission by 90%) force the firms to adopt green related activities and technologies. All successful companies declare clear environmental goals and targets. For instance, a Canadian based telecommunication MNC named NORTEL had set up clear environmental targets (e.g., 50% solid waste reduction, 30% reduction in paper purchase; 10% improvement in energy efficiency) for the years 1993 to 2000 (Berry and Rondinelli, 1998). Top management commitment for resource allocations to achieve this environmental target was significant for adopting related green activities or green technologies (e.g., green production). Proactive planning taken by the top management to adopt green practice (e.g., green packaging design) goes beyond dealing with regulatory aspects and is committed to building a strong supplier relationship for green practice adoption. The ultimate environmental performance as well as related financial performance gained from adopting green practices is largely dependent on the extent of top management commitment towards green innovation (Li, 2014). For instance, some big pharma companies' (e.g., AstraZeneca and Pfizer) departmental ambition is to achieve zero waste to landfill as the top management has committed to implementing more stringent voluntary environmental standards to stay in line with the global environment.

Community wellbeing and corporate responsibility have become another important aspect of TMC. Top management's strategic vision towards products and process now looks beyond sales and profits and has started to realize their responsibility to understand how product and process affect the local community. For instance, a McKinsey survey report states that 90% of CEOs and top executives have considered environmental challenges as one of the critical business issues in the recent century and 83% have indicated responsibility for the products they manufacture (Gupta, 1994). Driven by corporate responsibility and community wellbeing, the Electroment, a well-known electronic equipment manufacturer, became one of the first global businesses to obtain a single, global ISO 14001 certification for its worldwide manufacturing operations (Walker et al., 2008). Underpinned by community wellbeing and corporate responsibility, it was also pointed out by one of the South African textile companies that interest and willingness of the top management to recycle textile waste was a stronger driving force than regulations and/or cost-saving initiatives (Larney and Aardt, 2004).

Incentives and awards to promote green practices have become another important top management commitment as they play a crucial role to motivate employees to innovate green technologies or green process and systems to increase environmental benefit (Graci and Dodds, 2008). The incentives and awards can be from both external (government / private / NGOs) and internal (R&D investment, departmental awards / departmental non-monetary recognition etc) sources in the relevant industry. Top management leadership motivates employees (via divisional and/or departmental operations managers) to attract both sources of incentives and recognition awards for innovating new green solutions within organizations. For instance, the Indonesian hotel industry has been motivated by external incentives and internal recognition awards to provide a wide range of green improvements such as increasing waste recycling rates by 80% and decreasing energy consumption by 21% (Setiawati and Sitorus, 2016).

2.3.2.4 Market: Stakeholder Pressure

This pressure is due to market/consumer demand for environmentally friendly products. It also represents the social legitimacy where companies may prepare themselves to conform to the legitimized social norms (Sarkis, 2011). A firm may desire to improve the appropriateness of its actions within an established set of regulations, norms, values, or beliefs for showing perfections and pro-activity (Suchman, 1995). The interaction between

final consumer and downstream markets is entirely based on social cohesion. When a particular social norm or trend, such as the essence of an eco-friendly product, is being established, this social norm directly impacts on manufacturers' production process. As seen in Table 2.4, those fours aspects, under market drivers, are repeatedly highlighted across different industries.

Firms have realized that their operations are under pressure to consider proactive environmental measures to satisfy diversified stakeholders' expectations. In particular, downstream business customers have exerted tremendous force to go green (Berry and Rondinelli, 1998), as 87% of customers would accuse the upstream suppliers of environmental negligence (Wong et al., 2012). Thus, the social norms for green products in the downstream may influence upstream stakeholders to adopt green practices. Consumer awareness for green products has been increased in the developed countries. For instance, 75% of U.S. customers consider environmental criteria prior to purchasing and 80% of consumers were willing to pay a premium for environmentally friendly products (Carter et al., 2000). The normative isomorphic driver has transformed the traditional non-environmental focused society to an ethical society based on the ethical beliefs and ecological thinking of the downstream consumers (Ball and Craig, 2010). Hence, consumers' strong ethical beliefs and ecological thinking lead organizations towards adopting environmental management practices to conform to this emergent social belief. This is also evidenced in the developing countries, such as China, where organizations (e.g., Chinese manufacturers) are implementing environmental practices for serving foreign customers, such as IBM and Xerox (Zhu et al., 2011). The market for green products has also been driven by globalization and joint ventures, which have provided ample opportunities for local companies to adopt green practices in line with foreign partners (Christmann and Taylor, 2001; Zhu et al., 2012). High profiled private companies are also under tremendous pressure and scrutinized from different internal (e.g., shareholder and investors) and external stakeholders (e.g., NGOs and industry alliances) to address environmental issues (climate change, water pollution etc) originating from suppliers' operations (Walker et al., 2008).

Whilst it is clear how and why green practices are being adopted in the organization, it could be similarly important, especially for a new sector, to enrich our knowledge on the key challenges for implementing a green practice. Hence, the next section is focused on green barriers.

2.3.3 Green Barriers

Green barriers are those factors that demotivate and hinder the relevant stakeholders in the supply chain to implement green practices (Zhu et al., 2007). As each green practice adoption is dependent on the relative advantage, compatibility, complexity, trialability and observability within a particular context , understanding the intensity of relevant challenges or barriers (e.g., lack of capital, lack of skills etc) are important for successful adoption of green practices (Rogers, 1995; Chan et al., 2018). Due to those barriers being in place, companies may not be able to implement green practices despite having tremendous institutional pressures. So, it is important to understand the relevant barriers prior to implementing GSCM practices. Specifically, stakeholder-wide separate barrier identification and their intensity across the supply chain will help the managers not only to rank them in order but also may increase resources and capabilities accordingly to deal with the barriers of the most important GSCM practices such as eco design and green manufacturing.

While reviewing the related literature, the key green barriers that are identified are: complexity in market authorization of green products / process (Li et al., 2015), high investment and costs (Rao and Holt, 2005), cultural issues (Govindan et al., 2014b) and operational challenges (Zhu & Geng, 2013; Muduli et al., 2013). Table 2.4 has outlined these barriers and related sub barriers. They are briefly described below:

2.3.3.1 Complex marketing authorization of green product / process

Burdensome quality standard settings (unnecessary validation, verification, certification etc), unrealistic costs and timelines for authorizing a green product or process change potentially hinder the organizations from going green (Porter & Ven Der Linde, 1995; Walker et al., 2008; Li et al., 2015). The bureaucracy of authorizing a new green product becomes more difficult when it comes to highly regulated industries such as chemicals or drugs (Matus et al., 2012). For instance, Taiwanese chemical companies from iron and steel making, paper mill and pulping, and petrochemicals producers have evidently felt that relevant regulatory bodies take too long to assess the impact of newly developed green products for market authorization (Li et al., 2015). This also incurs significant costs. Therefore, the companies have proposed the relevant regulatory body for shorter and smoother authorization procedures for developing and implementing green technology. Also, complex validation, verification and certification processes in the carbon offsetting process have become a barrier

to greening the economy (Milne and Mahanty, 2019). Lack of clear regulatory guidance for green product development and the marketing approval process may lead companies to become more reluctant to implement green practices. For instance, the process industries, like chemical in general, are still far from implementing GSCM practices compared to other discrete industries, like automotive, due to the lack of clear regulatory guidance for green product or process development and clear market authorization requirements (Zhu et al., 2007; Zhu et al., 2013; Matus et al., 2013). This is how companies' ecological responses may become weaker when there is significant complexity in the marketing authorization of green products.

2.3.3.2 Financil barrier: High investment and costs

Installation of green technology or green manufacturing process, including costly green raw materials and costly disposal, requires significant amounts of financial investment which has a direct impact on production cost, and does not motivate companies to go green. For instance, auto component manufacturing industries are struggling to meet the high cost for disposing their hazardous wastes (Mathiyazhagan et al., 2013). As sometimes the entire manufacturing processes need to be replaced with a new manufacturing plant (e.g., production of a typical chemical with recovery facility), the financial model for it is not always justifiable, for instance, the return on investment is longer and not satisfactory (Porter and Ven Der Linde, 1995). Therefore, the trade-off between costs and related environmental programs such as recycling, reuse, remanufacturing is not always so straightforward. So, the green adopters are not always convinced. Additionally, and more importantly, if there is low market demand for green products, companies become sceptical about taking this financial risk. Companies may also face a lack of funding for R&D activities for designing and developing an eco-friendly product or process. Therefore, sector specific understanding and managing this green barrier is crucial for organizations.

2.3.3.3 Cultural issues

Employees are at the heart of innovating new green technology. Therefore, a lack of their green mindset, such as employees' personal awareness and responsibility on environmental protection, employees' personal obligation to the companies environmental policies and procedures, employee involvement and communication between employees and operations management for green innovations/projects is a significant barrier (Li and Hamblin, 2016). For instance, this barrier has impeded Chinese manufacturers to develop and implement a

cleaner production process due to conservative mindsets on developing a green production process, such as fear of losing profit and fear of losing operational control (Li and Hamblin, 2016). Lazuras et al (2011) has also identified that lack of employee's mindset especially lack of employee involvement in green decisions is one of the key internal green barriers. However, it lacks empirical evidence in the pharma context to understand why and how such employee involvement is important for creating a green culture.

2.3.3.4 Operational challenges

Factors like lack of time, lack of green related data, information gaps / information asymmetry, lack of appropriate performance measures, lack of knowledge on green technology, a complex manufacturing process, stringent quality requirements, unavailability of green materials, complex reverse logistics systems become barriers for companies to adopt green. As seen in Table 2.4, technology and related engineering inefficiencies and/or incompatibility is one of the key barriers to adopting green. Engineering specifications for green technology, such as energy efficient equipment system in the production process, cleaner production for energy, water and materials in industrial manufacturing, heat recovery systems from the manufacturing process and incineration process, are crucial for successful green production (Li et al., 2015). Not meeting the engineering requirements for these green technologies has been identified as one of the crucial green barriers in manufacturing industries (Zhu & Geng, 2013; Govindan et al., 2014b; Li et al., 2015).

While most of the operational tasks involve cost reduction with reduced cycle time to accelerate market launch, investing extra time on green innovation has become another crucial barrier in the industry (Li et al., 2015). For instance, longer waiting time was the key barrier to installing renewable energy sources in Taiwan during the set up of an eco-industrial park. The majority of the time (e.g., more than eight months in France) is consumed by complete related procedures and waiting to receive the industrial permit (Li et al., 2015).

Lack of green related data and information is another key green barrier across industries. For instance, manufacturers fail to incorporate green design in their initial product design due to the lack of life cycle inventory data (Slater et al., 2010). Additionally, companies are reluctant to share environmental related data and information due to the fear of exposing weaknesses or giving competitive advantages to another company (Walker et al., 2008). When there is inconsistent flow of information (also known as information asymmetry) within a supply chain, the entire supply chain is disrupted and collapsed. To relate this with

GSCM, information asymmetry occurs when the suppliers hold more information about their green products, process, and environmental performance than their customers (Delmas and Montiel, 2009; Sarkis et al., 2011). This typical information asymmetry or lack of green related data may impede the adoption of GSCM practices in the downstream customers due to the supplier firms' inability to communicate their environmental performance to their customers (Delmas and Montiel, 2009).

Lack of environmental education and training among employees is another crucial barrier to adopting green practice in firms. Environmental illiteracy is one of the key reasons for managers showing a conservative mindset towards green operations (Walker et al., 2008). While raw material sourcing is the key to greening manufacturing operations, many purchasing managers have failed to consider green credentials in their materials sourcing due to the lack of green related understanding (Walker et al., 2008). In regards to this shortcoming in pharma, for instance, it was outlined in an interview with Johnson and Johnson conducted by Pharmatech that the supply chain stakeholders may first need to be educated about environmental sourcing, and that has an upfront potential to impact interest level and commitment (Arnum, 2009).

As these operational factors are directly associated with the success or failure of a product or service supply chain, it is crucial to study those factors in each sector (especially highly regulated sectors like pharma) separately to understand the wider scope of green adoption. The operational factors are crucial as firms can induce competitive advantages by harnessing their internal resources that are valuable, rare, imperfectly imitable, and non-substitutable, such as the green design or green process design of a product (Sarkis et al, 2011). Companies develop dynamic capabilities and resources to discover new green technology that supports the value, rarity, inimitability, and non-substitutability aspects of the resource-based view (Carter and Carter, 1998). Hence, the lack of dynamic capabilities and internal resources may impede the firms from adopting green practices (Gonzalez-Torre et al., 2010; Zhu and Geng, 2013). For instance, the lack of organizational learning leading to the lack of knowledge and skills on green practices such as EMS or Eco-design may be the barrier to adopting GSCM (Govindan et al., 2014b).

While the key green drivers and barriers are known, it is vital to understand the related KPIs to evaluate the effectiveness of the green practices applied as well as to evaluate whether

firms are able to address related drivers and barriers in the same line. The next section presents related green performance measures.

2.3.4 Green Performance measures

Performance measure is one of the key success factors of green supply chain operations (Beamon, 1998; Hervani et al., 2005). Green supply chain performance measures (GSCM-PMs) are not only required for internal control and external reporting purposes, but also play an important role in planning, design, implementation and monitoring of the system from strategic, operational and tactical levels of management (Hervani et al., 2005). Many companies have not succeeded in maximizing their supply chain's potential because they have often failed to develop the performance measures and metrics needed to fully integrate their supply chain to maximize effectiveness and efficiency (Gunasekaran et al., 2004).

Green performance measures are highly context specific and there is lack of agreement on how performance should be measured in the GSCM context (Ahi and Searcy, 2015). For instance, Ahi and Searcy (2015) have identified a total of 2555 unique metrics where the majority of the metrics were used once only. It has been suggested that selecting appropriate performance measures for supply chain analysis is particularly critical, since the system of interest is generally large and complex (Beamon, 1999). There is growing importance in measuring overall performance of the entire supply chain, considering balanced metrics (financial and non-financial), inclusiveness, universality, measurability, and consistency (Beamon, 1998: 1999; Hervani et al., 2005). However, as seen in Table 2.5, there are two types of performance measures: strategic level and operational level. Table 2.5 also shows how each level of measures are being considered. Under operational level measures, two types of performance measures are predominant: environmental performance measures and economic performance measures. They are briefly discussed below.

Table 2.5 GSCM performance measures (sources: previous GSCM literature)

Strategic level performance measures	**Operational level Performance measures**

Carbon reduction target: strategic planning includes firm level carbon reduction goal (e.g., reduce 80% carbon emission by 2020 from the base line of 2010) voluntarily (Kazancoglu et al., 2018) **Energy reduction target**: strategic planning sets firm level energy reduction target (e.g., process energy reduction by 30%) yearly basis, which is translated into different departments across the operations (Kazancoglu et al., 2018) **Water reduction target**: strategic planning sets firm level water reduction target yearly basis (e.g., '20% water reduction in manufacturing process'), which is translated into different departments across the operations (Larney and Aardt, 2004) **Waste reduction target**: strategic planning sets firm level waste (hazardous/non-hazardous) reduction target yearly basis (e.g., 'zero waste to landfill') which is translated into different departments across the operations (Rausch and Powell, 1997).	**Environmental performance measures** **GHG emission related**: measures elemental emissions (e.g., co, co2, CFC, VOC etc) either originating directly from the plant/process (scope 1) or from purchased energy (scope 2) or from supply chain (scope 3); (Plambec, 2012) **Energy efficiency related**: measures plant base / process base energy efficiency such as amount of energy consumed or amount of energy saved or amount of renewable energy used etc by a process/plant (Shi et al., 2012) **Raw Materials efficiency related**: measures the amount of raw materials consumed or amount of water consumption reduced, or amount of packaging materials consumption reduced etc by the plant / process (Harvani et al., 2005; Eltayeb et al., 2011) **Waste efficiency related**: measures the amount of waste by-products (hazardous/non-hazardous) produced or amount of wastes reuse/recycled/remanufactured/ land-filled / incinerated etc from the manufacturing process / plant (Eltayeb et al., 2011; Zhu et al., 2013).	**Economic performance measures** **ROI of green project** (Perotti et al., 2012; Green et al., 2012; Ahi and Searcy, 2013) **Amount of cost savings from green operations** (e.g., cost effectiveness of adopting recycling) (Zhu et al., 2013; Ahi and Searcy, 2013) **Cost of green production:** (e.g., cost of green raw materials, technology, energy etc) (Zhu et al., 2012; Laosirihongthong et al., 2013; Ahi and Searcy, 2013)

2.3.4.1 Strategic level green performance measures

Companies have dramatically changed the way they used to capture traditional loss/profit, delivery, quality and speed-based performance in the last few decades. Companies have started considering environmental oriented KPIs (e.g., carbon, energy, water and waste) into their core business strategies due to stringent regulatory pressure, increased level of corporate responsibilities of production, consumer pressure and related economic gain and competitive advantage (Harvani et al., 2005; Zhu et al., 2008). Given the importance of tackling global warming from operations, companies are becoming desperate to include carbon emission reduction related goals into their corporate strategy. For instance, a cement production plant which emits approximately 900 kg of CO2 per ton of cement production (equivalent to 5 -7% of all global CO2 emission) has proactively considered carbon emission reduction targets into their core strategic planning (Kazancoglu et al., 2018). For instance, Nokia was one of the first 100 companies in the world in 2017 to commit to reduce carbon emissions in line with the Paris climate accord (Nokia, 2019). Companies also consider energy efficiency in their strategic planning due to the usage of non-renewable sources of energy and materials (Plambec et al., 2012). Similarly, companies set water and waste reduction goals and departmental targets to reduce waste related water and land toxicity. For instance, companies involved in water intensive manufacturing processes, such as dairy processing and textile processing, have strictly set their water reduction goal into their strategic planning (Rausch and Powell, 1997; Larney and Aardt, 2004). Dell has a 5-year responsible water risk mitigation plan from all its production sites to reach the strategic goal of reducing water usage by 20% in water-stressed regions (Dell, 2020). Similarly, P&G (Procter and Gamble) has considered a goal of 'zero waste to landfill' into its core business strategy by 2020 (Whitehouse, 2018).

2.3.4.2 Operational level green performance measures

Departmental managers are accountable to monitor and assess the performance of green practices applied. As seen in Table 2.5, operational level green performance measures are considered as environment-related and economic-related performance.

Environmental performance measures: These measures are typically used to assess the performance of green practices, for instance, assessing the outcome of a newly installed energy efficient production system in terms of 'amount of energy savings' from the production line, 'amount of CO2 emission', 'amount of hazardous discharge', 'amount of raw

materials used', 'amount of packaging wastes', 'amount of recycling' from the production process etc.

The appropriate measures are crucial for controlling and achieving corporate level environmental targets. Some of the measures are widely used across the industries, such as reduction of air emission; reduction of wastewater; reduction of solid wastes; decrease of consumption of hazardous/harmful/toxic materials; frequency of environmental accidents and amount of recycled materials used in a process etc (Zhu et al., 2005; Zhu et al., 2008). As shown in Table 2.5, all these performance measures can be categorized into four areas: GHG emission related, energy efficiency related, materials efficiency related, and waste efficiency related. The measuring scope of each of these categories is limited to process, product or plant based on the data availability and compatibility of related technologies used for measuring (Hervani et al., 2005).

GHG emission related measures considers three different types of measures: scope 1, scope 2 and scope 3. Scope 1 emission is related to those carbon emissions that emit directly from operations, whereas scope 2 is an indirect emission source (e.g., purchase of electric supply) and scope 3 is the indirect emission induced from the supply chain of the product (Plambec et al., 2012). While scope 1, 2 and 3 provides a comprehensive assessment, scope 1 and 2 are significant for assessing plant / process wide emission performance. For instance, IBM uses the scope 1 measure to assess the amount of carbon emission from its operational activities such as use of refrigerants in cooling systems and use of chemicals for research and manufacturing activities, and scope 2 considers its energy consumptions.

Energy efficiency related measures are used to assess how effectively and efficiently manufacturing operations and related technologies use energy sources. Potential energy loss from the manufacturing process is identified and rectified using this measure. It may also measure and compare different energy sources (e.g., onsite produced green energy, purchased electricity, coal and gas) in terms of efficiency (Shi et al., 2012). It may be applied to the entire plant or process or it can be product-based, assessment based on the measurement viability.

Raw materials efficiency related measures are used to assess how effectively, and efficiently raw materials are used in the manufacturing process. It measures the amount of materials used in the process or amount of total materials used to produce a product. The measure also entails the amount of recycled / reused / remanufactured materials used (Eltayeb et al., 2011).

Dynamic design characteristics for product or process development require special attention and employ assessment of toxicity of product, components or the material characteristics, for instance, amount of hazardous / non-hazardous materials used in the process/plant (Rao and Holt, 2005; Hervani et al., 2005).

Waste efficiency related measures are used to assess how effectively and efficiently wastes byproducts from the manufacturing plant (hazardous / non-hazardous) are reduced, managed and processed. For instance, the amount of hazardous / non-hazardous wastes produced, amount of wastes recovered in terms of reuse, recycling, and remanufacturing (Eltayeb et al., 2011).

There is enormous evidence and a win-win situation of environmental performance from applying green practices across different industries. For instance, a leading pharmaceutical and chemical company has recently reported saving 200,000 metric tons of chemical wastes and 3 million tons of CO2 emissions between 2007 – 2020 just by moving from traditional raw materials (e.g., solvent) to greener ones (Pfizer, 2020). Also, Apple Inc has recently reduced 69% energy usage from one of its products (11-inch iPad Pro) by applying green design concepts (Apple, 2019). One of the giant construction companies, Vinci, has reduced energy consumption by 20% from 40% by developing greener process such as the 'Tempera warm mix process' (Vinci, 2018). Another top sports retailer, Adidas, has recently been able to reduce water usage by 22% in their material processing phase by considering the concept of material reduction (Addidas, 2017). These industries have also seen a significant trade-off with economic gain.

Economic performance measures: These measures are used to assess the economic/cost related outcomes from applying green practices - for instance, assessing the 'return on investment' from installing recycling plant, considering that appropriate economic measures are significantly important to assess the trade-off between green practice adoption and economic performance. As seen in Table 2.5, the most dominant economic metrics are cost saving from green operations, cost of green production and ROI - return on investment (Ahi and Searcy, 2013). However, a set of sub metrics was widely used in terms of achieving economic performance (Positive economic: decrease of cost for materials purchasing; decrease of cost for energy consumption; decrease of fee for waste treatment; decrease of fee for waste discharge; Negative Economic: increase in investment; increase in operational cost; increase in training costs; increased cost of purchasing environmentally friendly materials)

(Zhu and Sarkis, 2004; Zhu and Sarkis, 2007; Perotti et al., 2012; Laosirihongthong et al., 2013; Zhu et al., 2013).

GSCMP is a well-established symbol for good business sense and higher profits (Srivastava, 2007; Mutingi, 2013). For instance, Molina-Azorín, et al. (2009) have examined 32 studies quantitatively to find out the impact of GSCM on financial performance. Even though the results are mixed, the majority of studies show a positive impact of environment on financial performance. Kumar et al. (2012) has applied a model in two case studies, Coca-Cola and Apple, for improving supply chain sustainability practices. The results of this study demonstrate that the new supply chain model that eliminates waste throughout the supply chain will yield more profits. Cost savings from reuse, recycling and reduced usage of materials and energy are also evidenced across the sectors. For instance, one of the top pharma companies has reported that it has reduced its disposal costs by managing wastes responsibly, such as it has converted 98% of its wastes into beneficial uses (AstraZeneca, 2018). One of the giant computer technology companies, Dell, in 2018, saved disposal costs through reducing 6.9 million cubic meters of wastewater and saved over 1.38 million cubic meters of freshwater by installing a water recycling process.

While key GSCM concepts are known in diversified contexts, it is now crucial to understand how those concepts are underpinned and enriched by the background management theories. For instance, how diffusion of innovation theory and ecological modernization theory have enriched our understanding of the adoption of green practices in a particular context. The next section highlights those key theories that shape the concept of GSCM.

2.3.5 Theoretical foundation of GSCM

Theoretical underpinning is crucial to clarify the key concepts of GSCM (Alexander et al., 2018; Dubey et al., 2016). Theoretical lenses undoubtedly enrich and validate the practical observation of green practices adoption in a particular context (Toubolic and Walker, 2015). For instance, understanding the adoption mechanism of a particular green practice in a particular context is not so straightforward, due to the involvement of multifaceted complex aspects (e.g., systems of systems, social cohesion, science and technology, power and interest of stakeholders), unless underpinned by relevant management and organizational theories.

There must be a philosophical stance and worldview behind every phenomenon like the GSCM concept, which is important to outline prior to creating new knowledge in the field. A

sound philosophical stance/theory could potentially create new knowledge and enrich our existing understanding on different aspects of green practices, drivers, barriers, performance, and their interrelationships. The use of theories in the GSCM adoption process would enrich the underlying knowledge on the relationship between adoption of a particular green practice and organizational behaviour. This extended understanding would help managers to be more proactive to deal with relevant barriers. It would also help policy makers to reform environmental policy. Moreover, the theoretical foundation of GSCM is critically important to supporting the application of GSCM in a new organizational context such as pharmaceuticals.

Therefore, this section aims to review the existing theory of GSCM to identify what theories could best fit to underpin the key GSCM findings in the pharmaceutical sector. It will also enrich some of the existing theories by carrying out an in-depth investigation of the application of GSCM concept in a new context. After an extensive review of the existing literature, including the identification of more than fifteen theories, nine theories have been applied widely to explain the key concept of GSCM. These theories are briefly outlined in Table 2.6.

Table 2.6 Relevant theories of GSCM

Theory	Key focus	Relevance to GSCM	Studies that suggested/indicated/applied these theories in GSCM/SCM
Ecological Modernization Theory	Industrial development and environmental protection are achieved through technological breakthrough. Encourages firms for innovation and diffusion of new technologies through appropriate policy implementing by the governments.	GSCM practices (e.g., eco design) are new innovations due to the continuous expansion of ecological modernization. Both organizational and technological integrations are needed to implement GSCM innovation in practice. Environmental policies may significantly promote greener production process.	Murphy & Gouldson, (2000); Sarkis et al., (2011); Zhu, et al., (2012); Er, et al., (2012)
Information theory (information asymmetry and signalling theory)	Uninterrupted and clear flow of information is crucial to maintain supply chain and end consumer satisfaction. An information asymmetry occurs when upstream suppliers hold more information than downstream customers. This information asymmetry leads mistrusts and unreliable relationships among the supply chain stakeholders.	A successful implementation of green practice (e, g., green design) in any context will require co-ordination among stakeholders in terms of green related data and information sharing. For instance, an upstream R&D product engineer must know what difficulties are faced by the downstream waste vendor to dispose the product.	Delmas and Montiel, (2009); Sarkis et al., (2011)
Institutional theory	Companies adopt new organizational practices due to three	Regulation-related government fines can drive	Zhu, et al., (2011); Sarkis, et

Theory	Key focus	Relevance to GSCM	Studies that suggested/indicated/applied these theories in GSCM/SCM
(DiMaggio and Powell, 1983)	key external pressures. For instance, coercive pressures exerted by government institution (e.g., fines, trade barriers etc) influences companies to adopt related changes. Normative pressures exerted by consumers' ethical belief and ecological thinking also influences firms to adopt related changes. Mimetic pressures exerted by mimicking the organizational best practices from the successful companies in the same sector also influences firms to adopt related changes.	companies to adopt green practices. For instance, REACH and WEEE regulations drive eco design practice. Market/consumers demand for environment friendly products (e.g., product with lower carbon footprint) drive firms to adopt related green practices. Firms in developing countries mimic green design practices from developed country for competitive advantages.	al., (2011); Zhu, et al., 2013.
Resource Based View (RBV)	Firms develop dynamic capabilities and resources to achieve competitive advantages. To be competitive, firms must focus on developing a product/process/organizational resource which is rare, non-substituTable, non-imiTable, and valuable.	Lack of dynamic capabilities and internal resources may impede the firms to adopt green practices. For instance, the lack of organizational learning leading to the lack of knowledge and skills on green practices such as EMS or Eco-design may be the barrier to adopting GSCM.	Barney, (1991); Gonzalez-Torre et al., (2010); Sarkis et al, (2011); Zhu and Geng, (2013)
Resource Dependence Theory (RDT)	Firms strengthen dynamic capabilities and resources through accessing another partner company's resources by means of collaboration. Firms are not fully self-sufficient rather they need to depend on each other for sustainable development.	Inter-organizational relationship is essential for managing the internal and external co-ordinations for successful implementation of GSCM practices. Lack of collaboration or the lack of weak inter-organizational relationships could impede the	Carter and Rogers (2008); Sarkis et al., (2011); Lee et al. (2012); Touboulic and Walker (2015)

Theory	Key focus	Relevance to GSCM	Studies that suggested/indicated/applied these theories in GSCM/SCM
		implementation of a particular green practice such as green sourcing.	
Social Network Theory (SNT)	Organizational performance is the function of social relationships between organizations or individuals in an organization. Density and centrality are the key determinants of social relationships.	Firms improve inter-relationships to execute a green practice successfully. For instance, subsidiary firm pays close attention to the focal firm's green activities to adopt them. While firms with densed operational locations across the globe, it feels significant external pressure to adopt green.	Sarkis et al., 2011. Touboulic and Walker (2015)
Stakeholder Theory (ST)	Firms satisfy the needs and expectation for both internal and external stakeholders involved in a supply chain. An organizational practice is adopted by the influence of both external and internal stakeholders.	Both internal and external cooperation between stakeholders are crucial for developing a sustainable supply chain. Identifying stakeholder wise environmental responsibility and related barriers is the key to adopt green practices across the supply chain.	Zhu et al. (2008a); Sarkis et al., (2011).
Complexity theory	A firm is composed of a heterogenous or diversified environmental factors such as suppliers, customers, regulators etc. The integration of these diversified actors within a supply chain makes it a complex system of interaction. As the degree	Green practice implementation can be a challenge due to evaluate and understand the complex nature of integration between diversified supply chain actors. For instance, for a successful product return program	Sarkis et al. (2011). Touboulic and Walker (2015)

Theory	Key focus	Relevance to GSCM	Studies that suggested/indicated/applied these theories in GSCM/SCM
	of complexity increases, firms struggle to plan and predict the right course of organization action.	a complex array of customers, suppliers, manufacturers, regulators, and other related players are interacted within such a complex system for product and related information sharing purposes.	
Diffusion of Innovation	A process by which an innovation is communicated through channels, over time among the members of a social system (Rogers, 1995). Innovation is diffused into four different dimensions: the innovation, communication channels, time, and the social system. The innovation involves relative advantage, compatibility, complexity, trialability and observability (Rogers, 1995).	The initiation stage of GSCM involves creating awareness of upcoming change among the members of channels due to regulatory pressure. After persuasion of management it leads to eventual adoption, which involves commitment of resource efficiency to improve productivity and environmental performance.	Murphy & Gouldson, 2000; Sarkis et al., 2011 Zhu, et al., 2012

While the key concepts of GSCM – practices, drivers, barriers and performance with theoretical underpinning are absorbed, the range and scopes of the application of GSCM in a new industry, especially in Pharma sector, being the interest of this thesis, needs to be understood. Hence, it is necessary to understand thoroughly the Pharmaceutical supply chain, including its key functional supply chain stages, key stakeholders, and the key specialities. The next section endeavours to outline these features.

2.4 Pharmaceutical Supply Chain

The Pharmaceutical Supply Chain (PSC) is defined as the integration of all activities associated with the flow and transformation of drugs from raw materials to the end user through primary and secondary manufacturing, wholesale distributors or third party distributors and retail pharmacies, as well as through improved supply chain relationships to achieve a sustainable competitive advantage (Uthayakumar and Priyan, 2013; Asamoah et al., 2011). The definitions of the pharma supply chain in the literature are similar but with a slightly different views. A chronological definition of PSC is presented in Table 2.7 below to understand its breadth in different contexts.

Table 2.7 Key definitions of Pharmaceutical Supply Chain

Authors	PSC Definition
Settanni et al., 2017	PSC is a socio-technical system that integrates and aligns firms from raw materials supplier to the end consumer in enabling the achievement of improved health status through providing medicines provision.
Jaberidoost et al., (2015)	PSC contains all procedures, information, resources, and players such as suppliers, manufacturers, intermediaries, third-party service providers, logistics activities, merchandising and sales activities, finance, and information technology.
Asamoah et al., (2011)	PSC is a medium through which prescription medicines are delivered to patients. The medicines are produced in manufacturing sites which are then transferred through wholesale distributor and retail pharmacies; subject to price negotiation and processed through quality and utilization management screen; dispensed by pharmacies and ultimately delivered to and taken by the patients.
Shah (2004)	A typical PSC will consist of one or more of the following nodes: a) primary manufacturing (possibly including contractor sites), b) secondary manufacturing (possibly including contractor sites), c) market warehouses/distribution centres, d) wholesalers and e)

	retailers and hospitals.

Medicines supply is one of the major priorities across the globe. Inefficiencies and ineffective supplies of medicines could pose potential threat to human health (Jaberidoost et al., 2015). The pharmaceutical supply chain has been sought as one area of the healthcare system which is highly sensitive to quality and efficacy – which ultimately has a crucial influence on patient outcomes (Chircu et al., 2014). Interruption in any phase of the supply chain, such as if manufacturing problems arise, if cold chains are interrupted, containers are damaged or sensitive medication is shaken during storage or transport, can have serious consequences, including patients becoming sick or even death (Chircu et al., 2014). Therefore, it is important to understand the key functions of a pharmaceutical supply chain in line with environmental implications. The subsequent sections explain the key functional areas of a pharmaceutical supply chain including key supply chain stakeholders followed by the environmental implication of each supply chain stage.

2.4.1 Pharmaceutical supply chain - Key stages, players, and environmental implications

The key functional stages in a pharmaceutical supply chain are Drug design & Development, Manufacturing, Distribution, and Use-and-Disposal. A brief account of each stage is described in the subsequent section. Additionally, a detailed account on each functional stage is presented in Appendix 3(a), 3(b) and 3(c). Figure 2.2 depicts the key stages of the pharma supply chain. It also shows the key stakeholders involved in the supply chain. It also highlights how each functional stage is related to environmental degradation in terms of materials, energy, and toxicity.

Figure 2.2 Key functional stage (including key players) in drug supply chain (Source: Researcher)

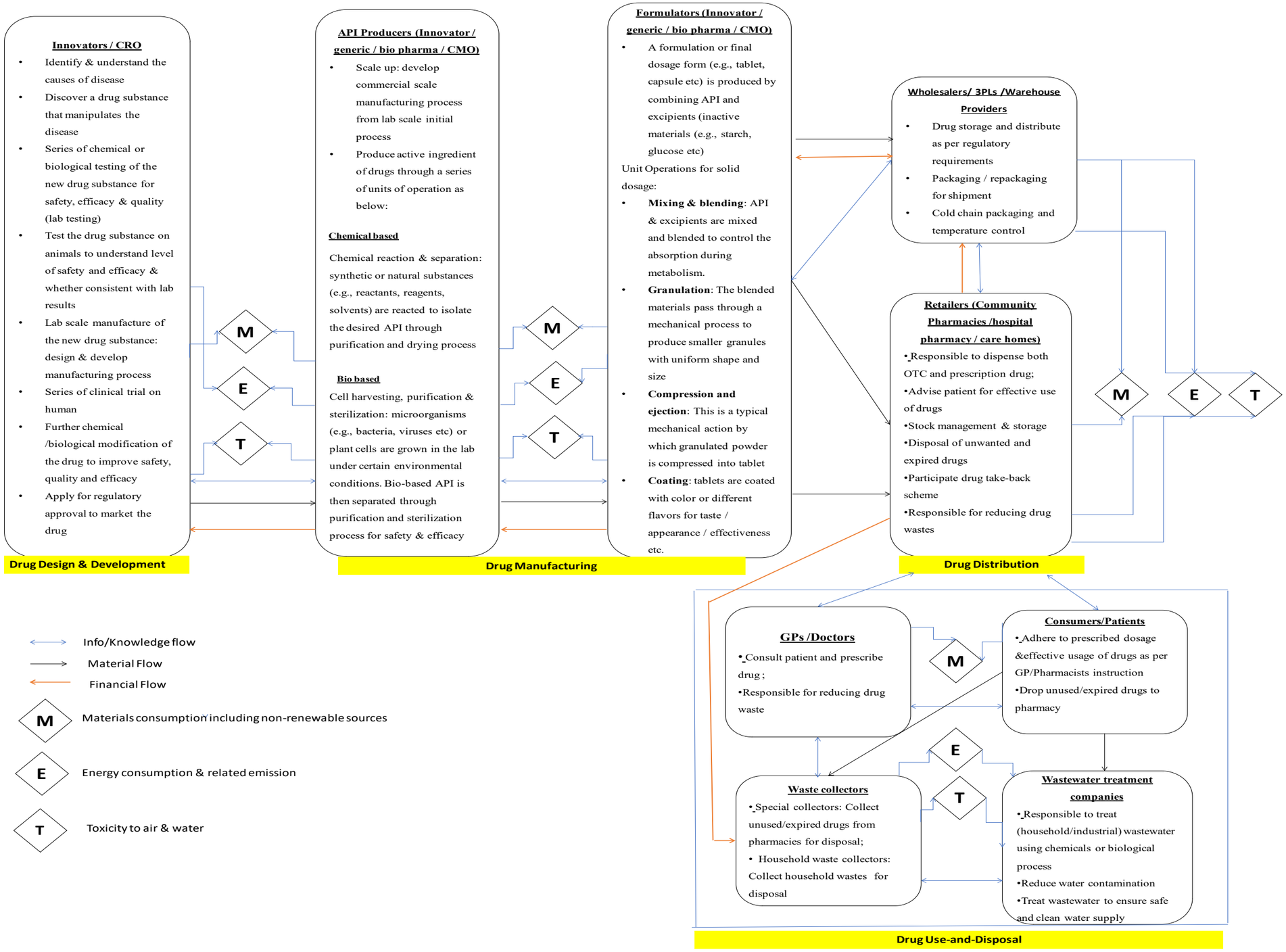

Innovators / CRO
Identify & understand the causes of disease
Discover a drug substance that manipulates the disease
Series of chemical or biological testing of the new drug substance for safety, efficacy & quality (lab testing)
Test the drug substance on animals to understand level of safety and efficacy & whether consistent with lab results
Lab scale manufacture of the new drug substance: design & develop manufacturing process
Series of clinical trial on human
Further chemical /biological modification of the drug to improve safety, quality and efficacy
Apply for regulatory approval to market the drug
Drug Design & Development
API Producers (Innovator / generic / bio pharma / CMO)
Scale up: develop commercial scale manufacturing process from lab scale initial process
Produce active ingredient of drugs through a series of units of operation as below:
Chemical based
Chemical reaction & separation: synthetic or natural substances (e.g., reactants, reagents, solvents) are reacted to isolate the desired API through purification and drying process
Bio based
Cell harvesting, purification & sterilization: microorganisms (e.g., bacteria, viruses etc) or plant cells are grown in the lab under certain environmental conditions. Bio-based API is then separated through purification and sterilization process for safety & efficacy
Drug Manufacturing
Formulators (Innovator / generic / bio pharma / CMO)
A formulation or final dosage form (e.g., tablet, capsule etc) is produced by combining API and excipients (inactive materials (e.g., starch, glucose etc)
Unit Operations for solid dosage:
Mixing & blending: API & excipients are mixed and blended to control the absorption during metabolism.
Granulation: The blended materials pass through a mechanical process to produce smaller granules with uniform shape and size
Compression and ejection: This is a typical mechanical action by which granulated powder is compressed into tablet
Coating: tablets are coated with color or different flavors for taste / appearance / effectiveness etc.
Wholesalers/ 3PLs /Warehouse Providers
Drug storage and distribute as per regulatory requirements
Packaging / repackaging for shipment
Cold chain packaging and temperature control
Retailers (Community Pharmacies /hospital pharmacy / care homes)
•Responsible to dispense both OTC and prescription drug;
•Advise patient for effective use of drugs
•Stock management & storage
•Disposal of unwanted and expired drugs
•Participate drug take-back scheme
•Responsible for reducing drug wastes
Drug Distribution
GPs /Doctors
•Consult patient and prescribe drug ;
•Responsible for reducing drug waste
Consumers/Patients
•Adhere to prescribed dosage &effective usage of drugs as per GP/Pharmacists instruction
•Drop unused/expired drugs to pharmacy
Waste collectors
•Special collectors: Collect unused/expired drugs from pharmacies for disposal;
• Household waste collectors: Collect household wastes for disposal
Wastewater treatment companies
•Responsible to treat (household/industrial) wastewater using chemicals or biological process
•Reduce water contamination
•Treat wastewater to ensure safe and clean water supply
Drug Use-and-Disposal
M
E
T
Info/Knowledge flow
Material Flow
Financial Flow
M Materials consumption including non-renewable sources
E Energy consumption & related emission
T Toxicity to air & water

Table 2.8 Key supply chain players / stakeholders: key features and their key importance to deal with environmental issues (Sources: Clark et al., 2010; Vollmer, 2010; Kummerer et al., 2010; Rees, 2011)

Supply chain players / Stakeholders	Key features	Key importance to deal with environmental issues
Innovators / innovative pharma	They discover, develop, patent, produce, and market new drugs through regulatory approval. They also redesign existing drug products for improved quality, safety, and efficacy. They enjoy exclusive sales right (monopoly) until patent expires (normally 15 to 20 years). Cost of products is high due to higher invest on R&D.	Their nature of activity (e.g., discovery and innovation) is a promising field for green innovation (e.g., greener process design). They are under tremendous ethical and corporate pressure to maintain energy, water, and toxic emission. Felt significant corporate and regulatory pressure to deal with PIE. They initiate and invest on environmental projects.
Generic Pharma	They produce off patent drugs (called generic drug) which must show similar safety, quality, and efficacy as like patented one. Cost of production is low as there is no discovery related R&D activity. Higher product demand due to low cost and availability. Competition is high due to comparatively easy entry to market. The first generic producer (of any off-patent drugs) enjoys exclusive sales right for first six months.	High volume of production due to high global demand. Hence, exhaustive resources consumptions (e.g., raw materials, energy, and water) and big waste producers. Tremendous pressure from investors, shareholders, and customers to reduce environmental loading of drugs. Less motivation of initiating environmental related projects unless there is potential financial gain.
Bio Pharma	They produce drugs using biologically sourced raw materials and applying biotechnology. Less use of chemicals in process. Very	Very less chemical based operations and more biological operations. Likely to increase environmental

Supply chain players / Stakeholders	Key features	Key importance to deal with environmental issues
	complex instrumentation and engineering requirements. They also discover and develop new drug. Discovery success rate of biologic drug is twice than chemical-based drug (Otto et al., 2013).	biodegradability of drugs due to use bio-based materials, though it is still debated, as they are extensive user of water and energy for synthesizing complex bio-based substances
CRO (Contract Research Organization)	They subcontract some part of drug discovery and developmental works from innovators or other bio pharma. They rely on CRO either due to lower the cost or due to the lack of relevant resources.	Their environmental decision is dependent on the focal company who give the contract.
CMO (Contract Manufacturing organization)	Produce either key intermediates, active ingredients (AI) or even final products or packaging by providing outsourcing services to innovators or generic companies	Their environmental decision is dependent on the focal company who give the contract. Materials selection, manufacturing process uses, and wastewater management process are governed, supervised, and developed in line with outsourcers' policy guidance
Wholesalers/3PLs providers	Procure, storage and distribute drugs to the retailers. Wholesalers take the ownership of the products. Sometimes wholesalers/3PLs act as only service (storage and transportation) providers but do not	Their operations are prone to drug wastes due to the failure of cold chain and temperature excursion. Significant amount of varieties packaging requirements and concern for related

Supply chain players / Stakeholders	Key features	Key importance to deal with environmental issues
	own the ownership of the products	packaging wastes.
GPs/ Doctors	Identify disease through medical interventions and then prescribe medicines for patients. Advise patients for effective use of drugs	Their prescribing decision, advise and medical interventions influences consumers' drug consumption habit, which eventually determine degree of drug adherence by patients
Retailers (e.g., Community Pharmacies, hospitals pharmacies & care homes)	Dispense drug to the patients as per the prescriptions. Communicate with prescribers, patients, and suppliers (wholesalers) for efficient dispensing of drugs to the final consumers.	Their operations influence consumers' decision on usages and disposal of drugs. Ineffective and inefficient drug dispensing (including patient intervention) influences level of drug adherence.
Consumer	Take medication as per the dosage instructed by the doctors. Feedback to doctors and/or pharmacists.	Their knowledge and awareness on general diseases influences buying OTC drugs. Ineffective and inefficient use of prescription / OTC drugs leads to drug nonadherence.
Waste collectors / Waste management	Collect expired/unused/unwanted drug wastes from pharmacy, hospital, care homes, and local community either to hand over to	Their disposal decision from waste collection to final disposal via segregation of drug wastes is influenced by the

Supply chain players / Stakeholders	Key features	Key importance to deal with environmental issues
companies	another waste handler to dispose or to dispose itself as per regulatory guidance.	types of wastes (hazardous/non-hazardous) handled and types of contracts / negotiation between waste vendors .
Wastewater treatment companies	Receive and treat both industrial wastewater and household wastewater before releasing into the environment.	Types of technology available to detect and treat pharmaceuticals in the receiving wastewater
Regulators	They regulate each operational area: R&D, manufacture, distributes and use-and-disposal. Give marketing authorization of drugs produced. Any significant changes made in the manufacturing process of existing drugs will further need for regulatory authorization.	Pharma regulators (e.g., FDA, EMA) are more concerned about safety, quality, and efficacy of drugs than environmental improvement.

2.4.1.1 Key supply chain stakeholders and features

As seen in figure 2.2, the key pharma supply chain stakeholders are innovators, generic pharma, bio pharma, CRO (contract research Organization), CMO (Contract Manufacturing Organization); distributors: wholesalers / 3LPs, GPs/Doctors; retailers: community Pharmacies, hospital pharmacy, care homes; waste management companies; wastewater treatment companies; and pharma regulators. However, innovators, generic and bio pharma play a crucial role in the pharma supply chain for drug design, development, and commercial manufacturing. Table 2.8 shows a brief overview of each pharma stakeholder and their importance in influencing pharma environmental footprints. The subsequent section provides a detailed account of each of the stakeholder.

Innovators / Innovative Pharma:

They are also known as innovative pharma or big pharma. So, the terms 'innovator' or 'innovative pharma' or 'big pharma' are interchangeably used throughout this thesis. These entities can be either the large research-development based multinationals (mainly branded manufacturers) with multiple manufacturing sites in different locations (Shah, 2004). Their investment decisions are crucial due to complex, time consuming (10 to 15 years) and very expensive ($500 – $1 billion) and risky investments due to the discovery nature of drug design and development (Clark et al., 2010). The investment decision is dependent on multiple factors, for instance, to consider the extent of current medical needs, availability of current therapy, novel approaches to the management of the disease and commercial opportunities.

They play a crucial role in the initial drug design and the selection of raw materials and relevant chemical process design, as the same design is then scaled up for commercial manufacturing (Clark et al., 2016). It is important to note here that once a process for producing a drug is approved by the regulator (e.g., FDA – Food and Drug Administration), it must be followed by all types of producers at all times for the purpose of consistent quality, safety and efficacy of drugs (Clark et al., 2010). Any modification to the process after regulatory approval must be re-approved by the regulators. In doing so the producers must again go through a complex time consuming and expensive regulatory approval process (Clark et al., 2010).

A drug is produced by combining two substances: active ingredients (called API) and inactive ingredients (called excipient). Though innovators predominantly develop and produce innovative drugs (new API), they also sometimes produce generic drugs (off patent API) using their separate facility (Catalano, 2005). The innovators also supply a wide range of generic versions of API to generic producers across the globe for generic drug production. For efficient and effective therapeutic value, the innovators share technical knowledge continuously with second tier manufacturers (called formulators who use API and excipient to produce drugs), research and development teams and raw materials suppliers (Asamoah, 2011). Innovators are also responsible for scaling up the API manufacturing process developed by third party contract research organizations (who are normally subcontracted to complete some developmental works) for commercial success. As innovators are extensive users of raw materials (e.g., water, organic chemicals, solvents, reagents and excipients) and varieties equipment, packaging and machineries in the facilities, they are responsible for reducing manufacturing emission (Slater et al., 2010). So, they play a crucial role in determining the reaction condition, selecting relevant raw materials (e.g., solvents, reagents, or other chemicals), processing byproducts, and managing wastes disposal. Being large and high-profile companies, they are continuously seeking innovation to optimize the manufacturing process and have shown more responsible business operations than other entities in the sector (Slater et al., 2010).

Generic Manufacturers:

They are one of the dominant players in the sector and meet most of the demands across the globe for generic versions of drug products (Catalano, 2005). They contribute to the global economy significantly while supplying low price medicines to consumers. For example, generic manufacturers in the United Kingdom account for more than 90% of the total UK market by volume (Deloitte, 2014). This introduces competition in the market to bring more affordable drugs to the NHS and consequently the NHS now saves more than £13 billion annually (BGMA, 2020).

Though they are responsible for producing varieties of final dosage form (tablets, capsules, liquid syrup etc) by mimicking the same quality, safety and efficacy of the original patented drugs, they also produce generic versions of API (Slater et al., 2010). As their production process involves several unit operations (see fig. 2.2) for different dosage forms, they play

key roles in managing related raw materials usages, energy control, inventory, quality, process control and process emission, and waste management (Slater et al., 2010).

Bio pharma:

The demand for bio-based drugs has significantly increasing due to increased levels of effectiveness and efficacy to manipulate disease. The market for bio-based drugs has doubled in the past ten years (McBeath, 2012). Currently there are 1500 bio-based drugs undergoing clinical trials (Otto et al., 2013). It is estimated that the average growth of biologics (or bio-based drugs) production will be 15% per year and this growth exceeds the rest of the pharmaceuticals industry (Castiaux, 2010). This is due to the fact that there are many bio based drugs whose patent have already expired and bio pharma are taking the lead to produce biosimilar (i.e., off patent bio-based drugs) drugs due to high demand. However, the bio-based drugs are costly due to higher development costs, higher costs of installing complex manufacturing equipment and related engineering, and higher cost of raw materials. From an environmental perspective, though bio pharma consumes fewer amounts of chemicals in manufacturing operations, they consume significant amounts of water, energy and other related resources to synthesize the key active ingredient, or API, from complex biobased substances. The operations also show longer process duration with lower yields. Additionally, some bio-based API synthesis (e.g., peptide) are highly complex and consume significant amounts of hazardous chemical raw materials (e.g., solvents and reagents) in their production (Clark et al., 2010).

Contract Manufacturers:

The role of contract manufacturers is also becoming significant in the pharmaceutical business due to the perceived operational excellence. As seen in Table 2.8, these manufacturers do not have their own product portfolio, but produce either key intermediates, active ingredients (AI) or even final products or packaging by providing outsourcing services to other innovators or generic pharma companies (Shah, 2004). They also play an active role in determining raw materials, manufacturing process, operational control, wastewater management etc, though most of the time the manufacturing specification comes from a focal company that is subcontracted.

However, manufacturing capacity management is predominant for these firms rather than input materials (Boulaksil and Fransoo, 2010). For example, a generic manufacturer can

supply its API to a contract manufacturer for producing final dosage form. So, the contract manufacturer produces the final product accordingly and sends them back to the outsourcer's packaging plant for final packaging. Similarly, if the contract manufacturers do not have specific packaging capacity, the contract manufacturers can also outsource their packaging through another CMO to outsource packaging work and directly deliver to the main outsourcer.

Contract Research Organizations (CRO):

They play a crucial role in the early drug development process through providing full or some part of the research process (pre-clinical discovery, clinical trial works etc) to the main innovators / big pharma. For instance, it is estimated that 40 - 45% of clinical works are currently being outsourced by the innovators, and this is expected to increase by 60% in future (Buvailo, 2020). Though sometimes CROs conduct clinical studies for them, the outsourcers are responsible for investing in new drug design and development including clinical studies. CROs do not share the risks of failure in the drug development pipeline; hence the investment for CROs is risk free. CROs also sometimes develop a new manufacturing process (lab scale) for innovators or other pharma manufacturers. The lab scale process is then scaled up by the outsourcers. From the environmental perspective of their operation, the majority of operations involve clinical trial with less environmental implications. Some discovery activities could pose a negative environmental footprint due to weak guidance and governance from focal/sponsor companies, but these case are very unlikely.

Wholesalers / 3PLs / Warehouse Providers:

Based on different business arrangements, they can either act as only appointed logistics providers by the manufacturers, or they can act as independent primary wholesalers for the retailers. Regardless of the engagement, these entities are responsible for storage, handling, packaging, repackaging, and transporting of drugs to their customers (Rees, 2011). They continuously ensure optimum temperature and humidity throughout the storage period. They are also responsible for maintaining the quality and efficacy of drugs during transportation either using normal transport packaging or using cold chain packaging (special packaging for time and temperature sensitive pharmaceutical products) (Vaisala, 2010). Maintaining temperature inside the warehouse and during transportation is always critical for these entities (Vaisala, 2012). They also ensure the correct selection of pallet racking and the layout for

efficient operations. In terms of environmental relevancy, their operations pose significant amounts of transport related carbon emission, packaging materials-related energy and wastes, and temperature excursion related (cold chain) product wastes.

Retail Pharmacies / Hospitals / Care homes:

Retail pharmacies, either chains or independents, hospital pharmacies and care homes, purchase drugs from wholesalers and sometimes from the manufacturers directly (PSNC, 2017). These retailers play an important role especially in generating demand both for generic and over-the-counter products through interacting with physicians/GPs or patients. The technical knowledge flow is maintained between pharmacists and physicians/GPs on a daily basis, which may also have a great impact on generating demand for products (Rees, 2011). Repeat prescriptions (for long term medication) from these stakeholders can be another major source of demand (deterministic). Retailers also work closely with both wholesale distributors and manufacturers for smooth inventories and product recalls management when necessary. Community pharmacists, previously known as chemists, are part of the NHS (National Health Service) family, and play a crucial role in managing patient medicines via reliable and responsible communication with patients. It is estimated that everyday about 1.6 million people visits a pharmacy in England (PSNC, 2017). They play a key role in reducing drug wastes in the customer zone. They are also responsible for ensuring the safe disposal of unused/expired/unwanted drugs in the customer zone.

Consumers / Patients:

The role of consumers or patients in the pharmaceutical supply chain is also significant due to the degree of adherence or non-adherence to the prescribed drugs (Volmer, 2010). The level of awareness about a drug and/or disease influences the OTC drug sales. The nature and belief towards a particular disease and/or lifestyles may influence the level of consumption of drugs. Consumers can also be influenced by drug marketing and advertising which can lead to increased OTC drug sales. They also play a key role in determining how they are going to dispose of their unused/expired drugs. The amount of drug consumption and related wastes also rely on the statistics of elderly people (who are the key users of drugs) in different geographical areas. Patients are unknowingly contributing to environmental toxicity via excretion. They also contribute to several types of drug wastes such as: drug non-adherence or non-compliance, intentional non-compliance/unintentional non-compliance and non-preventable wastes (e.g., changes in therapy before the completing existing dosage).

GPs / Doctors:

The roles of GPs/doctors in the pharmaceutical supply chain are paramount. They are the main sources of inducing demand for prescription drugs (Volmer, 2010). So, their prescribing practices (knowledge and experience about drugs, frequent changes in therapies, alternative therapy, etc) not only influence health costs but also induce drug wastes. Under the UK healthcare context, the smooth flow of information between GPs, pharmacists, and patients are the key to the best medication management by shaping patient's effective drug usage behaviour.

Waste Collectors:

These entities can be either specialist waste collectors (e.g., clinical waste vendor) or normal household waste collectors (e.g., household general waste collection by local councils). The special waste collectors collect drug wastes (unused and/or expired drugs) from the retail pharmacies for controlled disposal for a credit paid by pharmacies (who later on are reimbursed by the manufacturers or local National Health Service) (Volmer, 2010). These special waste collectors also collect drug waste from distributor warehouses, manufacturers, hospitals, clinics, and care homes for safe disposal of drugs wastes. The general waste collectors collect household wastes and take them to the sorting facility and then dispose of them either via landfill or incineration, or sometimes send them to wastewater treatment plants (PSNC, 2017). Most of these waste collectors are governed by local councils. As the patients throw unused/expired drugs in the household waste knowingly or unknowingly, waste collectors and/or local councils have an important role to play (PSNC, 2017). Waste collectors also play a crucial role for segregating and managing unused drug wastes (both toxic and non-toxic) from households and retailers or manufacturers. That is why they are highly relevant to green pharmacy supply chain management.

Wastewater treatment companies:

They are responsible for purifying the received wastewater either from industry and/or from household sewerage prior to pouring them into river water. As drug substances may enter into the water cycle via sewerage systems due to the inappropriate disposal via toilet/sink and due to normal human metabolism/excretion (Taylor, 2010), wastewater treatment companies may play a key role in dealing with them by increasing awareness or applying advanced waste treatment technology. They also ensure that correct measures are taken to identify the drug

substances or API in the received wastewater and treat them with the latest analytical technology. Traditionally, Chemicals (e.g., alum, ferric chloride and/or synthetic polymer) are added with the effluent, which results in larger particles. The bigger particles are then filtered out as a thick precipitation which is known as sewage sludge. The residual liquid is then disinfected, often with chlorine in the United States and ozonation (a kind of chemical reaction in the presence of oxygen) in Europe (Kallaos et al., 2007). They are nowadays responsible for protecting API from pouring into river water. As the sewage sludge is normally used as fertilizer, the end wastewater treatment companies play an important role in avoiding contamination via this type of fertilizer. Their end of pipe action to protect from API entering into the water system is significantly important, as it is highly unlikely for the redesign of the existing drugs (which are already in the markets – around 3000 types) to reduce their water contamination especially through human excretion.

Pharma Regulators

The pharmaceutical industry is considered as the most highly regulated industry worldwide. Regulators' rules, guidelines, regulations, and laws must be followed by the producers, distributors and other related entities involved. The requirements for regulations drive from information asymmetry between the pharmaceutical producers on one side and consumers and medical practitioners on the other (Brhlikova *et al.*, 2007). Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP), Good Clinical Practice, Good Distribution Practice etc, are the key regulatory guidelines in pharma. GMP is one of the crucial guidelines followed by drug manufacturers across the globe. A brief description of GMP and other related regulatory guidelines is presented in the subsequent sections.

- **Good Manufacturing Practice (GMP) Guidelines:**

In the 1960s, the World Health Organization (WHO) prepared its first version of Good Manufacturing Practices for the Pharmaceutical industry (Bellm, 2015). GMP has been defined by the WHO as:

"[...] that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization." (WHO, 2007, p-17)

The WHO's guidelines have been adapted by individual countries (e.g., US FDA-GMP, EU-GMP) and regions (e.g., the areas of ASEAN and Mercosur) over time (Bellm, 2015). The

GMP has also been acknowledged by other international organizations such as The Pharmaceutical Inspection Convention (PIC[1]), International Conference on Harmonization (ICH[2]) and International Standard of Organization (ISO) (Narhi and Nordstrom, 2008). Several regulatory bodies are involved in harmonizing the guidelines over the life cycle of pharmaceutical products (see Table 2.9). The key focus of each of the guidelines and their environmental relevancy are presented in Table 2.10. Also, a detailed description of each is presented in appendix 4 for interested readers.

Table 2.9 Pharmaceutical regulatory guidelines across lifecycle. Adapted from Brhlikova *et al.*, (2007)

Drug Lifecycle	Guidelines	WHO	ICH	EU	UK	US
Drug discovery	Good Laboratory Practice	×	×	×	×	×
Clinical Trials (Phase 123)	Good Clinical Practice		×	×	×	×
Manufacturing	Good Manufacturing Practice	×	×	×	×	×
Distribution	Good Distribution Practice	×	×	×	×	×
Post-marketing surveillance	Pharmacovigilance	×	×	×	×	×

The enforcement of GMPs rests on individual states. So, in the USA, the responsibility is with the FDA; in the EU, with national regulatory agency (e.g., MHRA in the UK); in Australia

[1] PIC was established in 1970 by the EU free trade area (EFTA). Its main goal was to harmonize the GMP requirements and promotion of mutual recognition of inspections and uniformity of inspection systems (Narhi and Nordstrom, 2008).

[2] ICH was established in 1990. Its main aim is to improve the efficiency of the drug development process and the registration of new drug products in its member countries through harmonization of national guidelines. The member countries are EU, Japan and USA. ICH published the guidelines of APIs production (Narhi and Nordstrom, 2008).

Table 2.10 Key regulatory guidelines and their environmental relevancy (Sources: Brhlikova *et al.*, 2007; Clark et al., 2010; MHRA, 2015; Bellm, 2015)

Drug Life cycle	Guidelines	WHO	ICH	EU	UK	US	Key focus	Key Environmental relevancy
Drug discovery and development	Good laboratory practice	✔	✔	✔	✔	✔	To assess the safety of new chemicals to humans, animals and the environment by validating related SOPs (standard operating procedure) and Quality assurance	*Study environmental fate (i.e., rate of biodegradation of the new chemical substance) and environmental toxicology (i.e., determine the toxic effects of the new chemicals on aquatic and terrestrial organism)*
	Good Clinical Practice		✔	✔	✔	✔	To ensure that designing, conducting, recording, & reporting of clinical trials follow a set of ethical and scientific quality requirement	Guidance does not lead to any significant environmental relevance
Drug Manufacturing	Good Manufacturing Practice	✔	✔	✔	✔	✔	Ensure that medicines supplied in the market meet high standard of safety, quality, and efficacy by controlling and validating key manufacturing process including related starting raw material and process equipment. A well-defined quality system, quality control & validating system are the keys.	*written policies, procedures, protocols for 'environmental monitoring' (as part of documentation required to produce)*
Drug Distribution	Good Distribution Practice	✔	✔	✔	✔	✔	Ensure that drugs are handled, stored, and transported as per marketing authorization or product specification.	Guidance does not lead to any significant environmental relevance
Post-marketing surveillance	Good Pharmacovigilance Practice	✔	✔	✔	✔	✔	Ensure the continuous safety, quality, and efficacy of the marketed drugs over times by developing a process that records authentic, legible, accurate, consistent, and verifiable side effects or adverse reaction to the marketed drugs reported by the users.	Guidance does not lead to any significant environmental relevance

with the Therapeutic Goods Administration; in India, with the ministry of Health (Brhlikova *et al.*, 2007). Interested readers can see details on each area of regulation in Appendix 4.

MHRA and GMP:

In 2002, the Medicine Control Agency and the Medical Device Agency were merged to form the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK. It is responsible for regulating all medicines and medical devices in the UK by ensuring they work and are acceptably safe (MHRA, 2015). The United Kingdom follows EU guidance on Good Manufacturing Practice.

EU Guidance on GMP: The figure 2.3 below shows how EU guidance on GMP covers two broad spectrums of pharmaceutical products manufacturing.

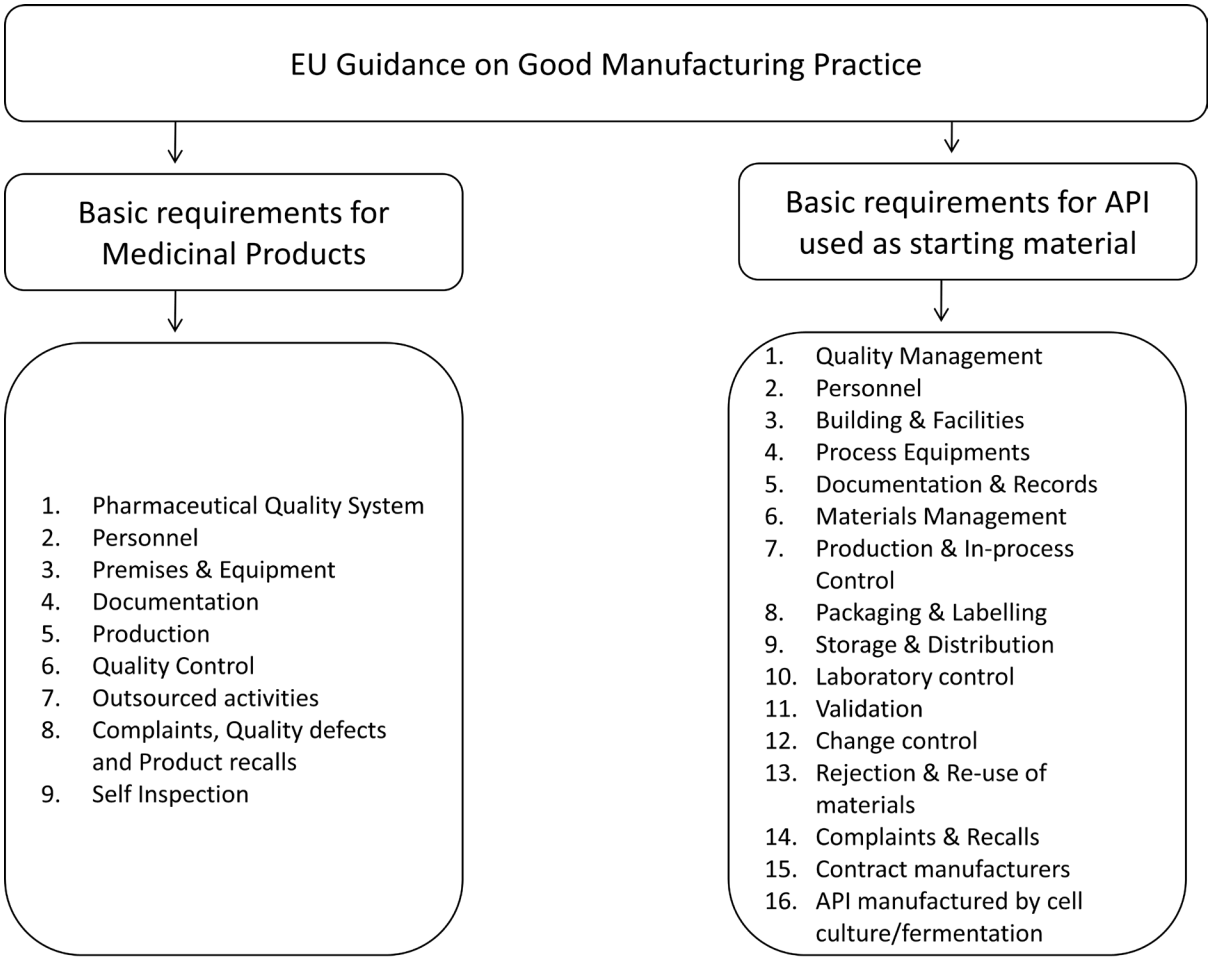


Figure 2.3: EU guidance on Good Manufacturing Practice (Source: MHRA, 2015)

As per the MHRA GMP guidance (2015), it is important to highlight that to be granted the marketing authorization for a drug product, companies must follow the minutes of GMP

regulations throughout the manufacturing process. A small deviation in quality or safety in between batches is not acceptable. As part of GMP regulations, companies must take responsibility to monitor quality, safety, and efficacy even after getting the product to the market – which is known as pharmacovigilance. It is also important to note that any changes to the process of drug manufacturing (e.g., changes in any raw material and equipment) must be approved by the regulatory body (e.g., FDA in USA and EMA in EU) prior to producing the upgraded version of of the drug product. Similarly, as per good laboratory practice, it ensures the chemical testing and safety of chemicals used in the pre-clinical design and discovery activities. It also ensures the uniformity, consistency, reliability, reproducibility, and integrity of chemicals (MHRA, 2015). Good distribution guidance ensures that the safety and quality of products are maintained across the movement of products using appropriate handling equipment and in correct warehousing and/or vehicle temperature to maintain the product integrity (MHRA, 2015).

While the discussion up to now provide us with a background on the key roles played by each stakeholder in the drug supply chain and their preliminary relevancy to environmental degradation, it is now important to clarify the key operations involved in each functional stage of the supply chain, and to demonstrate the necessity of adopting green in each functional stage. The subsequent sections will cover this.

2.4.1.2 Drug 'design and Development' and the importance of adopting green practices

A drug is defined as any substance that brings about a change in biologic function through its chemical action (Katzung et al., 2012). Drugs are an indispensable part of modern life. They are exceptional products which are invented and developed through multi-talented efforts for saving lives or improving human life-expectancy. A pharmaceutical supply chain starts with innovations and discovery activities (Taylor, 2016). The entire discovery process from a disease to a final drug can be divided into two major tasks – 'Drug Design and discovery' (Pre-clinical activity) and 'Drug Development' (clinical trial). Figures 2.3 and 2.4 show the overall steps in the drug design and development process. The key operational activities involved in each step are also presented in Table 2.11. The table also demonstrates the potential environmental implications of those activities. Interested readers are also referred to

appendix 3(a) for a detailed account of each stage. It is also important to highlight here that the drug design and development phase is also known as R&D. So, they are interchangeably used in the thesis.

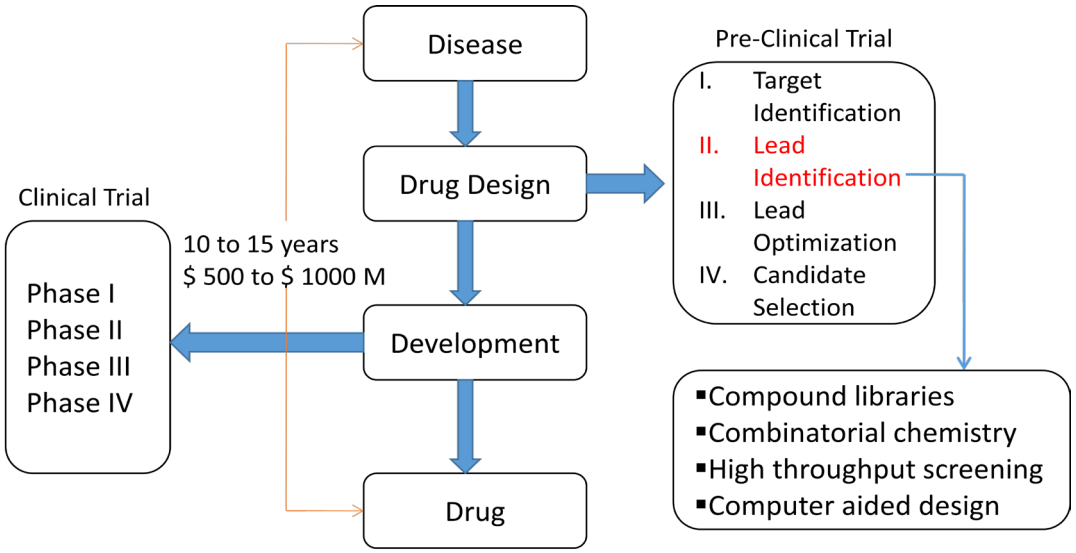


Figure: 2.4 Overview of drug design and development process

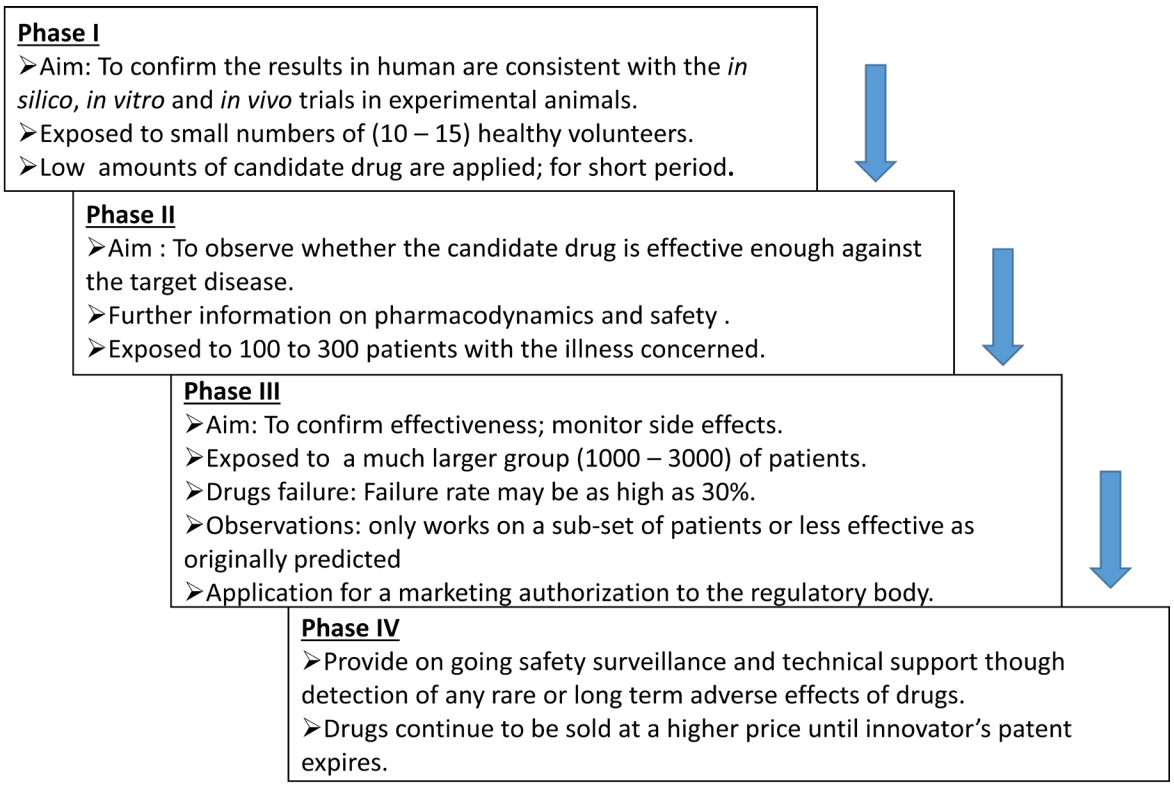


Figure 2.5 Overview of drug development process (clinical Trial); adapted from Taylor (2016)

Table 2.11 Key R&D activities and related potential environmental implication during drug design and development stage (Sources: Clark et al., 2010; Hughes et al., 2011; Solon, 2012; PhRMA, 2015; Taylor, 2016; Smiciklas and Sljivic-Ivanovic, 2016; Bountra et al., 2017; Poleto et al., 2018; ; Pharma Intelligence, 2019).

Supply chain stages	Key activities	Players involved	Potential Environmental Implications
Drug Design & Development	**Understanding the Disease**: Identify the biological cell in human body that causes disease. Conduct series of chemical and biological test using varieties of organic solvents (Target Identification) (ND*)	Innovator (or, innovative pharma), Contract Research Organization (CRO)	Continuously increased trend of drug discovery activities in R&D pipelines in the recent years, rising in almost 50% in 2019 from 2013, is prone to increase toxicity, resources uses and energy wastes: **<u>Toxicity to air</u>** • VOC emission from organic solvents application, contributing to increased greenhouse gas emission. • Use of flammable organic solvents (e.g., Benzene, Ethanol, Methanol etc) contributing to atmospheric emission. **<u>Toxicity to water</u>** • Use of Chlorinated solvents (e.g., methylene chloride, Chloroform used in chemical testing), which are persistent to the environment and increase toxicity • Use of Radioactive Chemicals (RC) in lead identification phase to assess the effectiveness of the prospective drug substance. RC is hazardous, and it reduces the fertility of the land, increase water toxicity. • Some chemicals compound (e.g., aromatic nitro group, aromatic amines etc) used to test the chemical properties of the prospective drug substance. These chemical compounds produce toxic by-products. • Use of corrosive chemicals (e.g., acids – hydrochloric acid, sulphuric acids, nitric acid, etc); bases - ammonium
	Discover the drug substance: Discover a suitable chemical (or biological) substance that manipulates the disease through continuous testing of wide array of chemicals (which are taken from a stored chemical library). Continue test until few numbers (e.g., 10 to 15) of new chemical (or biological) substances show potential manipulating effect of the disease (Lead compound Identification) (ND).		
	Testing the drug substance (a): Use automation (e.g., HTS – High Throughput Screening) to accelerate chemicals testing process in both target identification and lead identification (ND). Test is done using different sizes of micro titter plates containing solvents.		
	Testing the drug substance (b): Improve efficacy of selected chemical substances through chemical modification to reduce number of potential chemical substances to 3 – 4 (Lead optimization) (ND). This modification involves further		

Supply chain stages	Key activities	Players involved	Potential Environmental Implications
	chemical testing with solvents.		hydroxide, potassium hydroxide; increase environmental toxicity • Promising toxicity: 'Chemicals' are still predominant starting raw materials than bio source; For instance, in 2019, number of chemical-based drug was 8285 whereas bio based was 2041 in developmental pipelines globally (Pharma Intelligence, 2019). **Spent energy:** • Use of automation (e.g., HTS -High Throughput Screening) • Controlled heat and temperature (HVAC) • Refrigerated compound libraries • Separation and purification technique used (called chromatography) during lead testing. • Energy uses: Holding inventory of chemicals for longer time (6-7 yrs.) under controlled temperature (PhRMA, 2015) **Spent Materials** • Extensive use of microtiter plastic plates and test-tubes. • Plastics auxiliary equipment in HTS (e.g., liquid handlers) • Related Resource wastes due to higher rate of (more than 90%) clinical failure (Bountra et al., 2017) • Accelerates resource wastes while duplication of discovery efforts made for a same disease by several research organizations • Typically, in the industry, a single R&D project might screen 200 000 to $>10^6$ chemical compounds initially in the lead identification phase (Hughes et al., 2011). In 2019, there are 16181 different R&D projects across the globe (Pharma Intelligence, 2019). If the success rate is less than 10% (Bountra et al., 2017), we can imagine the severity of resources wastes and related environmental implication
	Testing the drug substance (c): Further testing the selected chemical substance to see whether it can manipulate the disease through a series of trial on animals (ND)		
	Testing the drug substances (d): Modify and further assess the ability of the new drug substances to interact with biological cells using chemical analysis (Candidate drug selection (ND)		
	Making the drug: Design and develop a manufacturing process for the first time to produce a very small scale of the selected chemical substance for clinical trial (ND)		
	Clinical Trial: (see fig. 2.4) Further assess the safety, efficacy, and effectiveness of selected chemical substance through three phases of trials on human (Clinical trial) (ND) Phase One: Conduct trial on 20 -100 health volunteer; Phase two: Conduct trial on 100 – 500 patients with the disease; Phase three: 1000 – 5000 patients; Phase four: ongoing monitoring of the drugs for safety and side effects after market launch		
	Design and develop drugs from bio based starting materials (ND)	Bio Pharma, CRO	
	Design and develop manufacturing process applying biotechnology (ND)		

Supply chain stages	Key activities	Players involved	Potential Environmental Implications
	Partnering and R&D collaboration for successful new drug development (ND)		during pharma design, discovery, and developmental process. • R&D activities in generic companies are expected to induce much lower environmental footprint than innovative and bio pharma. Because it does not involve any discovery process and related exhaustive chemical testing. However, formulation development incurs lots of energy and materials wastes
	Lesser use of chemicals in new drug development (ND)		
	Redesign / modify manufacturing process (either API or formulation) of existing drug products in the market for the purpose of materials and energy optimization without compromising safety, efficacy, and effectiveness of the products (ED**)	Generic Pharma, CRO	
	Design and develop drug manufacturing process (mostly formulation) to achieve exactly similar safety, quality, efficacy, and effectiveness of the innovative drug which is off patent (ED)		
	ND: New Drug* *ED**: Existing Drug*		

As seen in Table 2.11, in line with figure 2.4, once companies strategically decide which disease they are going to consider developing a drug for, the scientist and medicinal chemist start hunting for a new drug substance that could show potential efficacy to manipulate the disease. Once the lead drug substance is discovered and shows a minimum efficacy after a series of lab testing, the substance is then patented. This normally happens within three to four years in the discovery and developmental timeline (Taylor, 2016). The patent normally lasts between 15 to 20 years. It then goes under further modification based on continuous chemical and biological testing. This is an iterative process until the new substance shows an optimum effect on the disease for which it is designed to treat. After showing a satisfactory level of effectiveness in lab testing, it then undergoes four stages of clinical trial (see fig. 2.5). The new drug substance is continuously modified based on the safety, efficacy and effectiveness data gathered from the clinical studies. Once it shows successful manipulation of the disease with lower side effects and with a high level of safety and efficacy, the company then applies for marketing authorization of the new drug to the relevant regulatory bodies, such as FDA in the USA and EMA in Europe. Once the drug is approved, it is ready to manufacture and the innovator enjoys exclusive sales rights until the patent expires.

However, companies may also focus on redesigning existing drug products (i.e., off patent drugs) for improving further efficacy, safety and reduced side effects. In doing so, companies may slightly modify the existing API rather than innovating a new drug substance. In that case, they will also need to apply for a new marketing authorization licence from the regulatory body. Drug design and development related activities are crucially important for the pharma industry due to the complexity, uncertainty and challenges in the discovery process, having risky high investment (between 500 million to a billion Dollar per drug) and a long developmental phase (between 10 to 15 years) (Reese, 2011; Taylor, 2016). For instance, the recent drug R&D trends and facts (see Table 2.12) have shown that the cost of drug development has doubled in the last ten years while the clinical success rate is still low. Hence, resources used during the R&D phase are critical for pharma.

Table 2.12 Key facts and figures of drug R&D (Sources: Takebe et al., 2018; FDA, 2019; EvaluatePharma, 2019; Pharma Intelligence, 2019)

Year	No of R&D projects in pipelines in the last five years	R&D spends in the last five years ($ billions)	No of new drugs approved by FDA in the last five years	Drug discovery success rate globally between 1991 -2010 (in average)	Key challenges
2019	16181	213	48	Preclinical – 31.8% Clinical Phase 1-75.1% Clinical Phase 2- 50% Clinical phase 3- 58.6% New drug submission to approval – 87.5%	-High R&D costs (almost double in the last 10 years from $129 bn in 2010 to $213 bn in 2019 globally (EvaluatePharma, 2019) -Increase pressure for lower pricing. -lower rate of clinical success
2018	15267	207	62		
2017	14872	202	55		
2016	13718	196	48		
2015	12300	189	37		

The importance of green consideration during this phase is paramount due to the unprecedented level of environmental concerns in the drug design and development process. As seen in Table 2.11, the entire environmental implication during the drug R&D phase can be categorized into materials related, energy related and toxicity related.

Materials related

As seen in Table 2.11, drug discovery and development is a material exhaustive process due to the nature of discovery and unpredictable outcomes from a wide range of chemical testing possibilities. For instance, there can be as many as ~10^{62} possible chemical testings in the universe (Triggle, 2010). It is evidenced that on average, 1 to 2 of every 10,000 substances synthesised will successfully pass all stages of development required to become a marketable medicine (EFPIA, 2018). Also, the inefficient process of chemical substances synthesis and chemicals management during the drug discovery and development process may consume more energy and incur wastes. Complex multi-step designed chemical reactions exponentially increase wastes during the manufacturing phase. For instance, a complex multi-stage reaction process can typically require more than 100 tonnes of material for every one tonne of active pharmaceutical ingredient (API) produced (Srai et al., 2015); so, if materials

consumption reduction criteria are not considered in the early design phase it will have significant material impact on the manufacturing phase. Therefore, materials related design practice in the early drug design and development phase is crucial. For instance, a drug process can be designed with such greener substances which may significantly reduce the requirement of raw chemicals during the manufacturing phase. It could also reduce materials related energy. Also, the discovery process can be designed with advanced automation to reduce the dependency on chemicals-based raw materials usage for testing purposes. Drug formulation can be designed in such a manner so there will be fewer requirements for raw chemicals and packaging materials.

Energy related

As seen in Table 2.11, drug R&D is an energy exhaustive process and carries significant environmental implications. It is also reported that the majority (60%) of a pharma manufacturing facility's carbon footprint contribution is from HVAC system operations and is linked to process duration (D'Aquila et al., 2017). The R&D laboratory consumes significant amounts of energy for air treatment, temperature control, electricity and heating and cooling (Mongiardo and Bobrow, 2005; Dondero and Palmer, 2012). Also, drug discovery centres, including scientific laboratories in large pharmaceutical companies or government scientific/ academic institutions, where potential drug molecules are screened and developed, are comparatively large facilities and equipped with multifaceted equipment and machines. They are extensive energy consumers due to maintaining specific conditions (temperature, pressure, air density etc) continuously. Also, thousands to millions of chemical substances are screened during the drug discovery process using plastic plates, and using energy extensive screening machines, using solvents, reagents, water etc (Comley, 2006). Given such energy impact, it is important for pharma to consider energy related green practices during R&D operations. For instance, a drug process can be designed and developed with energy efficient equipment systems. Also, it could be possible to choose an alternative drug process design which requires the least energy to produce.

Toxicity related

As demonstrated in Table 2.11, the drug R&D process is significantly responsible for both air and water toxicity. It is further reported that demand for the usages of hazardous chemicals in R&D is increasing due to the emerging complexity in processing of new chemical based drug molecules in drug development pipelines (Moscrop, 2018). Additionally, in the R&D

laboratory, a common manufacturing process step, the chromatographic purification method, has a high environmental impact, since it typically involves large quantities of harmful or toxic solvents running at high flow rates (Biotage, 2018). According to Biotage (2018), "chemistry, by its very nature, involves the use of chemicals that can be harmful, toxic and potentially damaging to the environment, which means that drug discovery currently has a large and expensive environmental footprint".

Though the environmental impact of the pharmaceutical industry in general, and its products in particular, were not considered to be significant until the end of last century, work is now undertaken in the R&D process in two specific areas – 'sustainable drug production' and 'understanding the impact of the use of new pharmaceutical on environment' (Taylor, 2016).

Sustainable and green designed pharmaceuticals are not only driven by the concerns of increased levels of GHG emission, extensive use of raw materials and energy, and solid and liquid wastes, but also it is becoming a centre of attraction for the innovators to deal with unprecedented levels of the environmental contamination of drugs – which is widely known as PIE (Pharmaceuticals In Environment) in the industry (Clark et al., 2010). PIE has become an area of interest for academic researchers, practitioners, and other relevant stakeholders. Though the significant negative impact of PIE on humankind is still a matter of ongoing research and debate, the negative impact on biodiversity and the natural ecosystem is significant (Volmer et al., 2010). Therefore, pharmaceutical companies are becoming highly committed to tackling these unprecedented environmental issues and are considering producing as many green and sustainable pharmaceuticals as possible. Hence, it is vitally important for pharma companies, especially the innovators, to consider toxicity-related green design practices in the early design phase. For instance, a drug process can be designed with biodegradable materials and/or eliminate uses of toxic chemicals, which not only green the R&D phase but also reduce toxic wastes significantly during the manufacturing phase. A drug process can also be designed in such a manner that there is less toxicity to air, such as designing CFC free inhalers, so there is less air emission impact during the usage phase.

In a nutshell, considering green aspects in the initial drug design and development phase is crucial for reducing environmental impact in the commercial stage. Eco-friendly process design at this stage will reap both environmental and cost benefit in the commercial production stage, whereas an inefficient process design that uses more energy, toxic materials, solvents, producing more byproducts, will eventually have a higher negative

impact and incur costs. Additionally and more importantly, consideration of green credentials in drug design will determine whether it is going to be deposited into the environment via the water and food cycles after use, or whether it is going to degrade over time while the drug is in the environment. Hence, it is important to identify the key green practices employed across the sector.

2.4.1.3 Drug Manufacturing and the importance of adopting green practices

A drug contains two key ingredients: API and excipient. The API is a chemical or biochemical ingredient which has a therapeutic effect, whilst the excipients (such as water, lactose, starch, sugar, colouring etc) have no therapeutic effect but are necessary to ensure the final dosage form acts as intended (Plumb, 2005). As a drug is composed of two substances (API + Excipient), manufacturing is a two-stage process which involves production of Active Pharmaceutical Ingredients (API) and formulation. The entire drug manufacturing process and key stages involved are shown in fig. 2.6. Key activities of each unit operation in the process and related environmental implications are also highlighted in Table 2.13. Interested readers can also refer to Appendix 3(b) for a detailed account of drug manufacturing peocess.

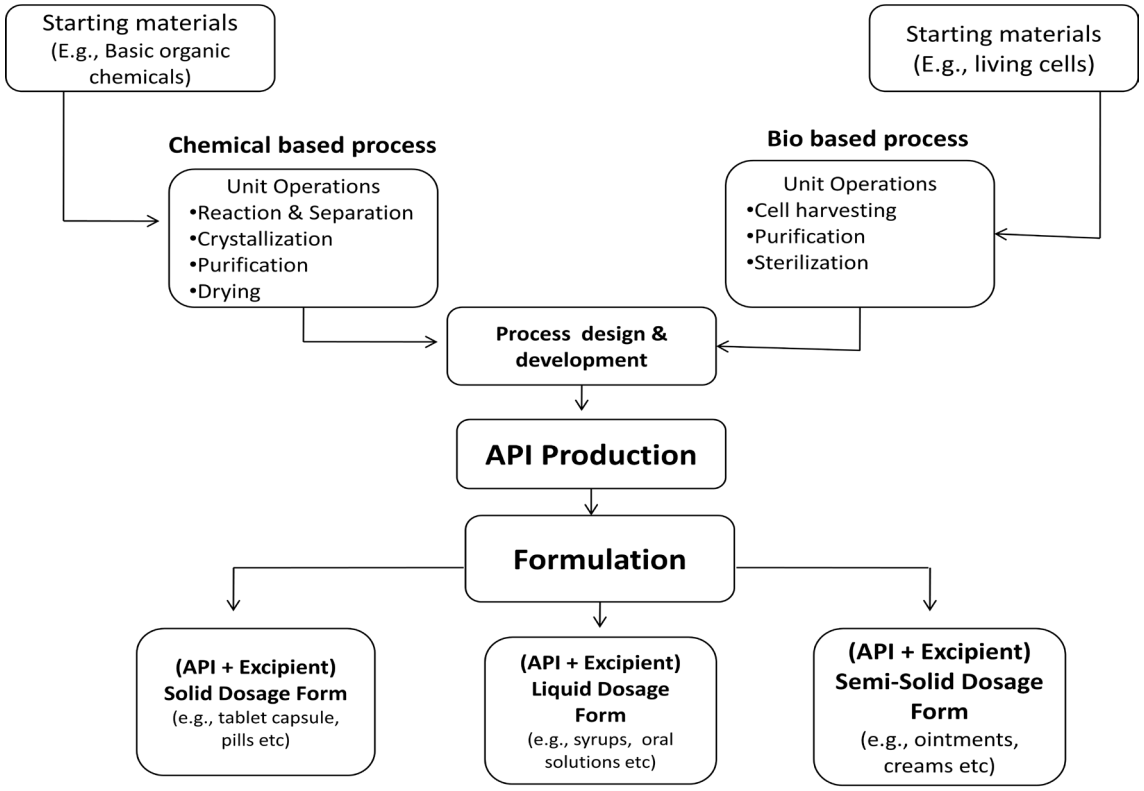


Figure: 2.6 Overview of Pharmaceutical manufacturing process (Source: Adapted from Gad, 200; Slater et al., 2010; Clark et al., 2010)

Table 2.13 Drug manufacturing related key activities and related potential environmental implication during manufacturing stage (Sources: Rosas, 2005; Christina et al., 2006; Slater et al., 2010; Clark et al., 2010; Pratyusha et al., 2012; Perez-Vega et al., 2013; Tait et al., 2017; Jaseem et al., 2017)

Supply chain stages	Key activities	Players involved	Potential Environmental Implications
Drug Manufacturing	**API production** API or active pharmaceutical ingredients are the key chemical or biological substances which have therapeutic effect and manipulate disease. **Chemical synthesis-based API Production** • **Chemical reaction & separation:** synthetic or natural substances (e.g., reactants*, reagents**, solvents***) are reacted to isolate the desired API • **Crystallization**: purify the isolated substances by removing liquids • **Purification/Recrystallization:** further purify the isolated substances to enhance effectiveness and efficacy of the final products (API) • **Drying:** vaporize and remove all types of liquids from the intermediate products • **Packaging:** pack and ship API to formulation plants **Biosynthesis based API production** • **Cell harvesting:** Microorganism (e.g., bacteria, viruses, algae, fungi, protozoa etc) or cells or small	API producers: Innovator (or, innovative pharma), Generic Pharma, & CMO	**Toxicity to air** • Fire and explosion hazards may arise during solvent extractions • Almost each operation emits VOCs; Solvents are accountable for 40% increase of the GHG emission (e.g., anthropogenic VOCs) (Perez-Vega et al., 2013) • Produce toxic solvent vapors and potent drugs as airborne dusts • **Use of Carcinogenic solvents**: e.g. benzene, 1,2 dichloroethane. • **Use of Ozone depleting** solvents e.g. Carbon tetrachloride • **Photochemical smog**: e.g., use of chlorinated solvent **Toxicity to water** • Solvents are predominantly used in reaction, separation, purification, washing/cleaning of equipment. Solvents can be organic (carbon contained) or inorganic (does not contain carbon); 56% of materials used for API manufacturing are organic solvents. Organic solvents can be volatile, toxic, and corrosive. Organic solvents produce residual impurities or by-products • Produce complex wastes from chemical synthesis of hazardous solvents, e.g., chlorinated solvents increase water toxicity • Generate acids, bases, aqueous or solvent liquors, cyanides

Supply chain stages	Key activities	Players involved	Potential Environmental Implications
	plants can grow up in solid, liquid, or semi-solid medium in a predefined environmental condition. Then the grown cells are harvested or separated from the medium which can be analysed, and biobased chemicals (API) can be extracted from it. • **Purification:** Unwanted debris (organic wastes after a cell dies or dead cells) from the grown cells are removed using salt solution or other chemical solution • **Sterilization:** The purified solution is sterilized to remove any possible microbial (e.g., viruses, bacteria etc) contaminants. It can be done either by physical methods (e.g., heat, radiation, ultrasound or high temperature and pressure, etc) or chemical method using different chemical solutions.		and metal wastes in liquid or slurry form. • Washing: Washing of reaction tank can lead to highly erratic discharges which potentially contaminate surface water and ground water; Use of cleaning materials / chemicals which later leaks into the effluent • Trace amounts of raw materials, solvents and by-products may be present in the wastewater from crystallizations and wash layers from extractions and equipment cleaning. These waste waters are high in organic matter (BOD, COD and TSS) which is detrimental for aquatic life **<u>Energy spent</u>** • Heating and Cooling: Extensive energy is required for a specific step in synthesis in batch operation • Re-crystallization: Required excess amount of energy for further purification • Facility: Heating Ventilation Air Conditioning (HVAC), warehousing and adequate lighting facility consume huge energy; Energy consumption from HVAC is significant as Pharma industry consumes 65% energy for HAVAC system running (Christina et al., 2006) • Reaction (catalytic process): the catalytic process involves high-pressure and high temperature reaction (e.g., hydrogenation) which is high energy-consumptive • Energy extensive process of production of industrial graded water (e.g., potable water, purified water, highly purified water, water for injection) • Non-renewable source of energy is also predominant in the industry (AstraZeneca, 2017).

Supply chain stages	Key activities	Players involved	Potential Environmental Implications
			<u>Spent Materials</u> • More than 90% of pharma raw materials (e.g., organic chemicals) in current use are derived from petroleum-based feedstock, which are finite and non-renewable (Clark et al., 2010; Roig and Touraud, 2010) • Biopharma process (cell harvesting) consumes significant amount of water • In a typical batch manufacturing process in the pharmaceutical industry, solvent use can account for as much as 80 to 90% of the total mass in the process (Slater et al., 2010) • Solvents usages in API manufacturing are associated with about 60% of the overall energy use and 50% of greenhouse gas (GHG) emissions (Dunn, 2012; Slater et al., 2010) • Materials related Energy consumption: consume higher energy to treat wasted solvents, e.g., high energy of decomposition of nitromethane • Water use: uses varieties industrial graded water (e.g., poTable water, purified water, highly purified water, water for injection) which are resource exhaustive; most of them are used in cooling, mixing, cleaning equipment, chemical/bio-synthesis.
	<u>Formulation of chemical-based API (Solid dosages form)</u> • **Stability testing** of Excipients and API • **Mixing & blending**: Chemical based API &	Innovator (or, innovative pharma), Generic	**<u>Toxicity to air</u>** • High levels of solvent vapours occurred during compounding, granulating and Tablet coating; and dusts are occurred during drying, milling and blending.

Supply chain stages	Key activities	Players involved	Potential Environmental Implications
	excipients are mixed and blended. It controls the absorption during metabolism. Excipients are inert materials that do not have any therapeutic effect but increase the stability of the final drug / give taste and colour etc. • **Granulation**: The blended materials pass through a mechanical process to produce smaller granules with uniform shape and size • **Compression and ejection**: This are a typical mechanical action by which granulated powder is compressed into Tablet • **Coating**: Tablets are coated with colour or different flavours for taste / appearance / effectiveness etc. • **Quality control**: Testing each production batch for its safety, efficacy, and effectiveness. It involves usages of wide variety of chemicals to test the physical, biological, and chemical properties of drugs. **Formulation of bio-based API** Most of the API is used for parental use / injection or in liquid form. • API is first examined for its chemical, biological safety and effectiveness and stability. • Then API is mixed with excipients. The key excipients materials used are: buffer solution (e.g., acidic or basic solution) and preservatives (e.g., m - cresol, phenol, parabens, thimerosal, sorbic acid, potassium sorbate, benzoic acid, chlorocresol, and benzalkonium chloride),	pharma, CMO	• Generate atmospheric and fugitive dust emissions (during drying, milling & blending operations) • Solvents used during wet granulation, compounding and Tablet coating produce VOCs and hazardous air pollutants to the atmosphere. • Emits co2 from using time and temperature sensitive packaging materials **Toxicity to water** • A typical pharma manufacturing process produces more than 25 to 100 kg of wastes by-products in per kg of final product produced (Roschangar et al., 2017; Slater et al., 2010), most of them are toxic in nature. • Generates solid and liquid wastes during cleaning and sterilization, and from leaks and spills and rejected products. • API contained wastewater is high in organic matters (COD, BOD and TSS) which affects aquatic life; Some APIs are toxin and health hazards • Organic Solvents are used in blending, Tablet coating and cleaning stage **Spent Energy** • High energy consumption from heavy machineries used in granulation, compression, and coating • Wet Granulation: This technique consumes high energy as drying is necessary once the wet granulation process is complete (Schneider, 2008) • Huge energy consumption from HVAC system • Some APIs' melting point is too high and require more **thermal energy** to dissolve with excipients

Supply chain stages	Key activities	Players involved	Potential Environmental Implications
	Reactant**- a type of chemical or biological substance (can be in a form of solid/liquid/gas) that takes part in a reaction and is consumed during chemical reaction to produce a product.* ***Reagent**-** *a typical chemical or biological substance (can be in a form of solid/liquid/gas) that is used to cause a chemical reaction or is used to detect the presence of another type of chemical elements present in the reaction* ***Solvent*-** *predominantly a typical liquid substance that is used to dissolve other substances in a chemical reaction.*		• Some excipients' melting point is too high and require more **thermal energy** to dissolve **<u>Spent Materials</u>** • Consume non-renewable feedstock • Materials wastes from quality failure • Packaging wastes • Materials wastes from: Drug-Excipient interactions, Excipient-Excipient interactions, Package-Excipient interactions • Packaging materials used: glass, paper, aluminium foil, plastics, stainless steel, lead, active/passive packaging materials for TTSPPs etc. • Some packaging materials may interact with drugs; some packaging materials may induce microbial growth and contaminates drugs; trace of aluminium foil end up with landfill

As seen in Table 2.13, in line with figure 2.6, a drug is produced by combining API with excipient through a series of chemical and mechanical operations. It is done in two stages. Firstly, an API is produced through synthesizing chemical or biological substances. Then the API is shipped to a formulation plant to carry out the final formulation (or mixing API with excipients) through a series of mechanical operations. The API production process is a more raw materials exhaustive process than formulation. This is because the API production process involves the chemical or biological synthesis process, which uses varieties of chemicals and other raw materials. The key raw materials used in API production are water, excipients, reactants, reagents, and solvents. Solvent (56%) and water (32%) consumptions are huge compared to other chemical raw materials such as reagent (5%) (Rogers and Jensen, 2019). As seen in Table 2.13, biobased API production is less chemicals consumptive than a chemical based one. However, consumption of varieties of industrial graded water (e.g., purified water) is significantly higher in the case of biobased API production than a chemical based one.

In the case of formulation, the key raw materials are APIs, excipients, solvents, and different types of packaging materials (glass, paper, aluminium foil, plastics, stainless steel etc). There are three layers of pharma packaging: primary, secondary, and tertiary. Primary packaging: direct contact with the dosage form (e.g., blister pack), secondary packaging: protecting primary package (e.g., boxes, cartons), tertiary packaging: bulk handling/shipping (e.g., barrel or container). Aluminium foil is one of the most popular forms of primary packaging materials used in pharma. Excipients play a crucial role in forming the drugs. They are chemical substances (natural / synthetic source) and sometimes the excipient constitutes about 50% of the drug composition. It protects, supports, or enhances the stability of the drugs, meaning that it supports biological function in the body, as well as protects the drug from physical damage (reduce sensitivity to light, air etc). APIs and excipients are mixed to formulate different forms of drug products, such as solid tablets, liquid syrup or capsules depending on need. However, it is apparently clear from the background of drug operations that the types and quantity of raw materials usages, and related potential energy, waste and toxicity, are prone to environmental degradation. The upward trend of global drug manufacturing and demand for related raw materials, such as the global demand for API - $198.8 billion by 2022 (Bajpai, 2018), solvent - $3.8 billion by the end of 2024 (ResearchNester, 2020), excipient - $7.7 billion by 2022 (Walker, 2017) and packaging - more than $80 billion by 2020 (PR Newswire, 2015), has become crucial for the industry to

adopt an innovative manufacturing process for resources optimization through employing materials, energy and toxicity reduction related green practices. Also, as seen in Table 2.13, the entire environmental implication of drug manufacturing operations can be viewed from a materials, energy, and toxicity perspective.

Materials related

As seen in Table 2.13, drug manufacturing is crucially sensitive to its environmental footprint, as it involves a huge amount of varieties of raw materials (e.g., solvents, APIs, excipients and reagents reactants) consumption and related energy investments (Rees, 2011). The amount of solid and liquid wastes produced from API and formulation plants are comparatively large and use a considerable amount of raw materials (e.g., organic solvents) to reprocess them. In addition, the exhaustive usage of some natural non-renewable metal elements is also becoming a serious threat for the pharma and chemical based industries for next generation chemical production (RSC, 2018). For instance, at present, 85% of chemical products worldwide are produced via a method that uses metal elements where most of these metals are estimated to last for another 100 years; some of them are even estimated to be deployed in the next 50 years (RSC, 2018). So, renewability practice in pharma manufacturing is of paramount importance. The industry is also large consumer of fresh water (Massoud, 2015). Given such materials impact on pharma operations, related green practices adoption is crucially important. For instance, the industry could benefit from changing their manufacturing processes from batch to continuous to reduce the requirements of raw materials in the process and improve related energy efficiency. Also, the manufacturers could adopt solvent reuse and recycling in the process to reduce usages of virgin solvents. They could also consider related lean practices such as reducing water consumption, reducing packaging materials and using digital technologies to dematerialize the process.

Energy related

As seen in Table 2.13, during the API manufacturing process, some of the operational units require significant amounts of energy such as in heating and cooling, or the in (re-) crystallization phase (Rosas, 2005; Slater et al., 2010). Also, some typical (catalytic) reaction processes involve high pressure and high temperature requirements which are expensive and high energy consumptive (Challener, 2016). Both API and formulation manufacturing facilities require HVAC (Heating Ventilation Air Conditioning) in the warehousing (and

R&D laboratories) area to continuously control the temperature, which contributes significantly to energy emissions (Mongiardo and Bobrow, (2005). Also, during tablet manufacturing, the room is kept at a controlled temperature and humidity to enable successful tableting (Taylor, 2010). Given such energy implications in pharma operations (see Table 2.13), manufacturers could adopt energy related green practices, such as considering energy efficient equipment systems and technologies, and considering energy management programs (e.g., energy related kaizen projects) across the manufacturing process to reduce energy consumption by the manufacturing plants.

Toxicity related

In line with the pharma toxicity impact indicated in Table 2.13, most of the API unit operations produce solvent byproducts and/or some other intermediate products or precipitation, which may cause environmental concerns. For instance, byproducts produced from the application of some key solvents (e.g., benzene, dichloroethane) in API production are carcinogens, toxic and environmentally hazardous (Tait, 2017). Also, many pharmaceutical chemicals have been identified as hazardous and have an adverse impact on human health. For instance, the chlorinated solvents used in chemical synthesis have a negative impact on human health (Braal, 2009); the use of substances such as rhodium as a catalyst in the pharmaceutical process is considered as toxic. The washing of reaction tanks during API production can lead to highly erratic discharges that contaminate surface and drinking water (Larsson, 2014). Toxic effluent from the industry may interrupt the local ecosystem due to the increase in chemical concentration and decrease in oxygen levels for the aquatic living organism (Chaudhari and Patil, 2012). Decreasing numbers of typical river fish dying from chemical exposure will undoubtedly destroy aquatic ecosystems. For instance, in Oslo, river fish were killed due to phosphoric acid discharged from API plants (Larsson, 2014).

Industrial catastrophe is also evident in the Indian context, where the API concentration in the releasing water was higher than those found in the blood of patients taking medicine (Larsson, 2014). For instance, the concentration of ciprofloxacin (a broad-spectrum antibiotic) was as high as 31mg/L, which is one million times greater than the levels that are regularly found in treated municipal sewage effluents (Larsson, 2014). Similarly, another plant in China reported 51ng/L, which is also considerably greater than the concentrations found in sewage effluents and clearly high enough to destroy reproduction in aquatic

vertebrates. The continuous deposition of antibiotics grows the resistance to the drug working against microbials or bacteria – which is termed as AMR (Anti-Microbial Resistance), which is also becoming a global environmental and health threat (AstraZeneca, 2017). Due to the extensive exposure of antibiotics into the environment, microbial or bacterial resistance has been developing in nature and consequently, the antibiotic no longer works against these bacteria or other microorganisms – which means there will be a threat of death for millions of people across the globe (AstraZeneca, 2018). For instance, it is estimated that around 10 million people will die from AMR by 2050, which would be more than cancer (estimated 8.2 million), diabetes (1.5 million) and road accidents (1.2 million) (HCWH Europe, 2016).

Additionally, as indicated in Table 2.13, the pharmaceutical manufacturing process has been identified as one of the biggest sources of VOC (Volatile Organic Compounds) – a hazardous air pollutant (Perez-Vega et al., 2013; Pharmaceutical Manufacturing, 2015). VOCs are a wide variety of hydrocarbon-containing chemicals and they are numerous, varied, and ubiquitous. The risks associated with VOCs are aggravated by the fact that hazardous concentrations are usually very low and the health issues they can cause can be accumulative and slow to develop (Pharmaceutical Manufacturing, 2015). Hence, the release of VOCs from industrial processes not only poses a direct potential hazard to human health, but their release also has more widespread environmentally damaging consequences, including their carbon footprint. Therefore, greening the pharmaceutical manufacturing process is continuously receiving attention by every level of stakeholders. Additionally, due to the extensive use of refrigerants, chlorinated / fluorinated solvents and CFCs / HFCs based propellant (inhaler) products, the pharma industry also poses a potential risk to contributing ozone layer depletion. Though from a chemical stability point of view (during production), CFCs are relatively safe and non-toxic for drug use, they are responsible for their potential to damage the environment (Noakes, 1995).

In response to such drastic levels of toxicity in the pharma process, manufacturers could adopt toxicity reduction related green practices, such as preventing the process from toxic release to air (e.g., VOCs), monitoring and controlling API discharge from the process and considering responsible waste management (e.g., waste to recovery – waste to energy, waste to fertilizer, zero landfill etc). These green practices could potentially reduce the toxicity levels in both air and water.

It is clear that the pharma manufacturing process has undoubtedly contributed to the global scale of environmental pollution and is expected to continue doing so in the near future due to the increase in global demand for drugs and lifestyle products (Taylor, 2010; Clark, 2010). Additionally, the ageing population across the globe is increasing, especially in the UK and EU context. This increment in life expectancy would induce huge pharma production related pollution. Therefore, identifying, understanding, and applying the relevant green practices in the pharma manufacturing process is becoming crucial.

2.4.1.4 Drug Distribution and importance of adopting green practices

The manufactured drugs are transported from the production plant to final consumers via some strategic distribution channels which are decided based on the combination of two factors – drug distribution based on sales and marketing strategy, and drug distribution based on operational activity. In pharmaceutical distribution, there are three core operational areas – transportation, warehousing, and retailing, which may have direct impact on product quality, efficacy, delivery, and the environment. Materials movement, storage and transportation are the daily parts of operational decisions among the key players. Table 2.14 presents the key distribution activities and related environmental implications. Interested readers can see appendix 3(c) for details of each aspect of distribution to understand the environmental relevancy.

Table 2.14 Key distribution activities and related potential environmental implication during distribution phase (Sources: Corbett et al., 2007; Rees, 2011; Clark et al., 2010; McKinnon et al., 2010).

Supply chain stages	Key activities	Players involved	Potential Environmental Implications
Drug Distribution	• Drug storage and distribute as per regulatory requirements • Packaging / repackaging for shipment • Cold chain packaging and temperature control	Wholesalers/ 3PLs /Warehouse Providers	**Toxicity to air** • Atmospheric Pollution: GHG emission- CO2, CH4, NOx, HFC, PFC and HF6 • Dry ice used as phase change materials in TTSPPs emits CO2 • Heavy vehicles used in pharmaceutical transportation (either by focal company or 3LPs) emit comparatively more CO2 due to consuming more energy • Emissions from ships (e.g., SOx, NOx) can adversely affect coastal populations and ecosystems. It has been reported that around the world there are approximately 60, 000 'premature mortalities' each year primarily because of the inhalation of ship-related PM emissions (Corbett et al., 2007) **Toxicity to water** • Acid rain due to use of sulphur contained fuel in shipping • Use of polystyrene packaging materials which is not biodegradable and emits significant CO2 while incinerated • Wooden pallet contamination and related drug wastes due to the use of a chemical, tribromophenol (TBF) as wood preservatives; Recalled 191,000 bottles of Pfizer's cholesterol-lowering drug, Lipitor due to wooden pallet contamination; related costs and environmental loss are huge. **Spent Energy** • Uninterrupted power supply for the equipment of TTSPPs storage (e.g., refrigerators, freezers, building management system, heating, ventilation, and air conditioning (HVAC) system, compressors, air-handling units, monitoring systems, alarms, and related computer equipment) • Cold chain transportation consumes significant amount of energy due to use refrigerated vehicles and cold packaging materials (Castiaux, 2010).

Whilst sales and marketing aspects predominantly focus on cost and quality, operational aspects of pharmaceutical distribution mainly focus on safety, efficacy, delivery time and the environment above cost and quality. However, taking decision on each of the core operational areas could be significantly influenced based on whether they deal with the conventional product chain, where products are not sensitive to temperature and moisture, or cold chain management, where products are highly sensitive to temperature and moisture. In the conventional product chain, storage and transportation do not require any stringent arrangement such as cold packaging, temperature, and moisture monitoring devices, whereas the cold chain product requires them. Special cold chain packaging materials, related storage and transportation are extremely energy and packaging consumptive. Temperature excursion in the distribution process also incurs toxicity. Hence, storage, transportation and retailing operations are highly related to materials, energy, and toxicity.

Materials related

As indicated in Table 2.14, the main freight-based wastes of pharmaceutical products are from air cargo, where 80% of excursions occur among all flight transport (Lennane, 2014). Cold chain transportation may also induce related packaging wastes such as wastes originating from wood pallets. Cold chain transportation has also contributed to these atmospheric emissions due to using cooling packaging materials such as dry ice. Additionally, returned and recalled TTSPPs may induce further co2 emission (as they require further handling, transportation and storage) and waste. Also, a lot of packaging and repackaging (tertiary packaging) are involved in the pharmaceutical warehouse operations, especially in picking and dispatch. It involves using thousands of plastic totes and other cardboard cartons.Consequently,it has been suggested that reducing, reusing, and recycling strategies could be followed in warehouse packaging operations to reduce ecological impact.

Energy related

It has been reported that the TTSPPs (Time and Temperature Sensitive Pharmaceutical Products) are rapidly increasing, and most shipments of biologics are transported via cold chain (Castiaux, 2010). Cold chain transportation consumes a significant amount of energy due to the use of refrigerated vehicles and cold packaging materials (Castiaux, 2010). The uninterrupted power supply for the equipment of TTSPP storage (e.g., refrigerators, freezers, building management system, heating, ventilation, air-conditioning -HVAC systems, compressors, air-handling units, monitoring systems, alarms and related computer equipment)

consume significant amounts of energy (WHO, 2011). Given such energy impact during cold chain distribution, distributors could adopt related green practices such as green transportation systems, which actually consider clean mode of transportation, intermodal transport, use of alternative fuel, efficient vehicle utilization, use automation and technology to avoid temperature excursion.

Toxicity related

Pharmaceutical distributors are continuously being confronted about tackling atmospheric emission and wastes induced from their distribution operations (McKinnon, 2010). Conventional freight transport (depending on the types of fuel used) emits different types of GHG emissions such as carbon dioxide (CO2), Methane (CH4), Nitrous Oxide (NOx), Hydrofluorocarbons (HFC), Perfluorocarbons (PFC) and Sulphur Hexafluoride (HF6) (Cullinane and Edwards, 2010). It has also been predicted by the European Commission that total emissions of SOx and NOx from international shipping will exceed those of land-based sources of these gases by around 2015 – 2020 (McKinnon et al. 2010). To address these issues, distributors could adopt green and clean transportation, efficient vehicle utilization including co-loading, use of alternative fuel etc. Either in cold chain transportation or in warehouse storage, the use of wooden pallets may contaminate the products and incur medicine wastes. However, inappropriate management of plastic pallets, such as end of life management without recycling, could have a negative impact on the environment.

Similar concerns can be raised for wooden pallets used in warehousing. Wooden pallet hazards and related medicine waste in the pharmaceutical supply chain is now well established. This was due to the use of a chemical called tribromophenol (TBF) as a wood preservative during pallet manufacturing. For instance, in 2010 Johnson and Johnson recalled 128,000 bottles of tainted Tylenol 8-hour capsules, Motrin and other over-the-counter drugs, after consumers complained of feeling sick from an unusual odour and more severe cases reporting nausea, vomiting and diarrhoea (Hardisty, 2011). In the same year, Pfizer recalled 191,000 bottles of its cholesterol-lowering drug, Lipitor due to wooden pallet contamination (Hardisty, 2011). This is how toxicity is increased during distribution operations.

So, pharmaceutical distribution operations (transportation, warehousing, and retailing) have a significant negative impact on the natural environment, ranging from global level atmospheric emission to local ecosystem disruptions. Realizing this level of environmental

degradation, it is urgently required to discover a number of green distribution practices in the pharmaceutical industry

2.4.1.5 Drug Use-and-disposal and importance of adopting green practices

Drugs are prescribed by the doctors or physicians. Pharmacists dispense the prescribed drugs to the patients. Patients are advised by both doctors and pharmacists how the prescribed drugs should be taken for best effectiveness. Patients take drugs as per their direction. However, drug usages are generally determined by two different strategic sources: prescription drugs and self-medication choice from OTC drugs. Self-medication choice from OTC drugs can be influenced by pharmaceutical marketing communications, or consumers' previous experiences and medical knowledge, whilst prescription-only medicines are prescribed by the GP doctors/nurses/authorised pharmacists based on diagnosis of the patients (Volmer, 2010). Table 2.15 also presents related key activities undertaken by each of the relevant stakeholders and the related environmental implications.

Table 2.15 Key drug use-and-disposal activities and related potential environmental implication during use-and-disposal phase (Sources: Bound et al. 2006; Kummerer, 2009; Clark et al., 2010; Vollmer, 2010; Castensson and Ekedahl, 2010; Mudgal et al., 2013; Vellinga et al. 2014)

Supply chain stages	Key activities	Players involved	Environmental Implications
Drug use-and-Disposal	**Prescribing: GPs / Physicians** • Consult patient and prescribe drug; • Responsible for reducing drug waste **Dispensing: Pharmacists** • Dispense both OTC and prescription drug; • Advise patient for effective use of drugs • Stock management & storage • Disposal of unwanted and expired drugs • Participate drug take-back scheme • Responsible for reducing drug wastes **Usages: Patients / Consumers** • Adhere to prescribed dosage &effective usage of drugs as per GP/Pharmacists instruction • Drop unused/expired drugs to pharmacy **Disposal: Waste collectors** • Special collectors: Collect unused/expired drugs from retail pharmacies for disposal. • General Household waste collectors: Collect household wastes for disposal **Disposal: Wastewater treatment** • Treat (household/industrial) wastewater using chemicals or biological process • Reduce water contamination • Treat wastewater to ensure safe and clean water supply	Pharmacists, GPs, Patients, waste management companies & wastewater treatment companies	**Materials (finished drugs products) Impact** • More than 50% of drugs prescribed globally are wasted (WHO, 2003; Mudgal et al., 2013). • Unused /unwanted / expired drugs accumulate due to ineffective and inefficient prescribing, dispensing & consumption **Energy Impact** • Constant requirements of cold storage • Temperature excursion and related energy loss • High energy requirements for drug incineration **Water toxicity** • Inappropriate disposal of unused / expired drugs contaminates water cycle; almost 75% of UK inhabitants still uses inappropriate methods of drug disposal (Bound et al. 2006) • Inappropriate usage (e.g., irregular use / not completing dosage etc) of drugs may increase the tendency of water contamination through unnecessary human excretion • Globally 160 different API were detected in the surface and ground water, where the concentration level exceeds the safety threshold (0.1mg/L or 0.01 µg/L) for aquatic organism (Kummerer, 2009).

As seen in Table 2.15, drug use-and-disposal activities also have environmental implications in three areas: materials (finished drug wastes) related, energy related and toxicity related.

Materials (finished drug wastes) related

Drug wastes have become a serious global threat both environmentally and economically (Vellinga et al., 2014; Castensson and Ekedahl, 2010; Vollmer, 2010). The Department of Health reported that unused medicines cost the NHS around £300 million every year, with an estimated £110 million worth of medicine returned to pharmacies, £90 million worth of unused prescriptions being stored in homes and £50 million worth of medicines disposed of by Care Homes (PSNC, 2018). This cost will be amplified hugely when new government spending will be required to protect environmental disasters due to the continuous loading of pharmaceutical substances into the water cycle.

However, as indicated in Table 2.15, inefficiencies and ineffectiveness in drug prescribing, dispensing and usage may lead to potential medicine wastes and related environmental degradation (Clark et al., 2010; Vollmer, 2010). Drug usages behaviour by patients, prescribers' prescribing practices and pharmacists' dispensing practices determine the number of unused drugs accumulated in patients' hands. While drug wastes originated by the manufacturers, pharmacies, hospitals or GPs are disposed of according to the regulatory guidelines or healthcare waste management guidelines (e.g., HTM – Health Technical Memorandum in the UK), wastes generated by the patients at home are of greater concern. People dispose of their unused and/or expired medication via three main routes: household garbage, toilet/sink and via pharmacies (Kumerer, 2009; Volmer, 2010). Incineration of unused drugs through pharmacies is the most preferred option.

Under the precautionary principle of drug usage (Start, 2008), any leftover or unused and expired drugs in households are assumed to be unsafe and are prone to environmental contamination (Vollmer, 2010). As the leftover unused drugs in households may not be controlled under the correct environmental requirements (e.g., temperature) for reuse and are always intend to be discarded, researchers have categorized them as dangerous, harmful, hazardous, special waste or problematic waste (Castensson and Ekedahl, 2010; Vollmer, 2010; Vellinga et al., 2014). Medication changes during therapy and drug non-adherence are the key reasons for unwanted drug wastes. The key reasons for the accumulation of unused or expired drugs are presented in Table 2.16 below.

Table 2.16 Factors of accumulation of unused or expired drugs (Ruhoy and Daughton, 2008 ; Braund et al., 2009; HDMA report, 2009; Vollmer, 2010; Castensson and Ekedahl, 2010; Vellinga et al. 2014).

a. Therapy is succeeded before all tablets are taken.
b. The product's expiry date is passed.
c. The patients stop the therapy due to side effects.
d. Patients are not happy with the existing therapy and they may decide to obtain drug therapy elsewhere (from a different pharmacy, clinic).
e. Patient non-compliance: medication is not being taken according to the prescriptions; for instance, there is a higher incidence of non-compliance for clinical depression and for drugs that are prescribed for long-term treatment of a chronic disorder.
f. Patients are moved to a generic equivalent due to low costs.
g. Frequent alteration of dosages of existing drugs by the prescribers.
h. Over-prescribing practices by the prescribers.
i. Bulk packaging of certain OTC drugs in quantities that cannot be consumed before expiry.

Irresponsible drug use-and-disposal behaviours and related wastes have now become a global issue. Recent research has shown that almost 80 to 90% of the people surveyed in different countries around the globe have had left over medicines in their homes. For instance, key statistics of drug usage behaviour and disposal behaviours, presented in Table 2.17 and Table 2.18 respectively, give a comprehensive picture of the issue. The number of leftover drugs is also directly correlated with economic loss, as well as negative environmental impact when the unused drugs are discarded via the sink/toilet and/or with household garbage (Vellinga et al., 2014).

Table 2.17 Summary of studies focused on Drug Use and Disposal Behaviours

Study	Country	Methodology	Key findings
Teni et al. 2017	North-western Ethiopia	Survey	44.2% (of 771 household surveyed) stored medicines for various reasons apart from the intended use prescribed by the physicians. Of the total 553 medicines stored, 53.3% was in use by the person originally intended for, 5.4% was in use by another person, 25.1% was kept for future use and 16.1% was kept with no purpose.

Table 2.17 Summary of studies focused on Drug Use and Disposal Behaviours			
Study	Country	Methodology	Key findings
Vellinga et al. 2014	Ireland	Survey	Nearly 90% of the respondents have unused medicines at homes. 80% of the respondents have non-prescription medicines at home and females were more likely to have over the counter medicines at home compared to males. Astoundingly, 57% of them kept medicines for future use and 20% of them did not want to waste the leftover medicines. 16% were involved in sharing the left-over prescription medicines with another person. Disposal preferences are via toilet and with garbage.
Abahussain et al. 2006	Kuwait	Survey	Almost all respondents (95.7%) reported that they had left over medicines. Dominant disposal preference is with household garbage.
Braund et al. 2009	New Zealand	Survey	Majority of the respondents have unwanted medicines in their house, and it was mostly because the medical condition was improved or dissolved. Dominant disposal preference is via sink/toilet.
Persson et al. 2009	Sweden	Survey	The left-over medicines were comparatively lower (30%) in Sweden. Dominant disposal preference is return to pharmacy.
Bound et al, 2006	UK	Survey	Around half of the respondents (52.8%) finish their medication (no left-over medicines) and 30.7% of respondents keep their medicines until expiry. Dominant disposal preference is with household garbage.

Table: 2.18 Drug disposal behaviours among the household consumers.				
Country	Disposal preferences (% of population in each study)			**Reference**
	Via Toilet/Sink (non-eco-friendly)	With Garbage (non-eco-friendly)	Return to pharmacy (eco-friendly)	
Germany	16% (Tablet) 43% (Liquid drugs)			Vollmer, 2010
Sweden		3%	43%	Persson et al. 2009

Table: 2.18 Drug disposal behaviours among the household consumers.				
Country	Disposal preferences (% of population in each study)			**Reference**
	Via Toilet/Sink (non-eco-friendly)	With Garbage (non-eco-friendly)	Return to pharmacy (eco-friendly)	
UK	11.5%	63.2%	21.8%	Bound et al. 2006
USA	35%			Glassmeyer et al. 2009
	55%		2%	McCullah et al, 2012
Pittsburgh	35%	54%	1.4%	Kuspis and Krenzelok, 1996
Kuwait	41%	73%		Abahussain et al. 2012
	11.2%	76.5%	54%	Abahussain et al. 2006
New Zealand	55% Liquid drugs 19.4% Tablets	24% Liquid drugs 51% Tablets	17% Liquid 24% Tablet	Braund et al., 2009
Ireland	43%	51%		Vellinga et al. 2014
Southern California	28%	45.2%	5.9%	Kotchen et al. 2009
Santa Barbara	45%	28%		Kallaos et al. 2007

The key conclusion that can be drawn from the findings and statistics presented in Table 2.17 and Table 2.18 is that current drug usage and disposal behaviour needs to be transformed into eco-friendly practices to reduce drugs waste for safer human health and natural environment. Not only the consumers but also pharmacies, GPs and Government Health Authority could play a significant role in this transformation process. For instance, the relevant stakeholders could consider some lean activities, such as reducing patient non adherence through effective and efficient patient care management, ensuring rationale prescribing practices, reuse of patient medicines where applicable and safe, encouraging alternatives to medicines such as

exercise and lifestyle changes, ensuring effective and efficient drug dispensing through the application of digital technology and promoting other related medicine waste optimization programs.

Energy related

As indicated in Table 2.15, time and temperature sensitive drugs require constant cold storage to maintain the quality, safety, and efficacy of drugs during their entire shelf-life. Hence, a significant amount of energy is consumed due to running continuous refrigeration systems. A typical pharmacy refrigerator consumes 1kw per day (24 hours) (Bell, 2017). The total number of retail pharmacies in the UK is approximately 15000 (PSNC, 2017). So, if each pharmacy uses at least three refrigerators on average, the daily cold storage related energy consumption would be 45000 Kw. The unit energy consumption would be more significant if the refrigerators in hospital pharmacies are also considered. However, this energy consumption could be reduced using energy efficient refrigeration systems and related maintenance activities. As high temperature incineration (burning of waste) is the most preferred way of disposing drug wastes, an incineration plant is highly energy consumptive. A significant amount of heat (or thermal energy) is lost during the incineration process. However, this lost energy can be reused to produce electricity, which could improve the overall energy efficiency of the incineration process.

Toxicity related

Drug substances may enter the water cycle via normal patient excretion (or metabolism), or via inappropriate disposal (e.g., toilet/sink/garbage) or via the manufacturing process (Vollmer, 2010). More than 88% of the environmental concentration of drugs is due to patient usages via the normal excretion process, 10% from inappropriate disposal of unused/expired drugs and 2% from manufacturing plants (AstraZeneca, 2017). However, water pollution from inappropriate disposal is more prone due to the direct contamination of the unmetabolized API of the drug substance. The environmental sensitivity of an API is also dependent on whether it is being excreted in an unmetabolized form or a partially metabolized form (Kumerer, 2009). So, the extent of API excretion is one of the environmental toxicity determinants (Bound and Voulvoulis, 2005). Some classes of drugs (e.g., atenolol) are identified as the biggest sources of human excretion over other classes (e.g., Ibuprofen). Table 2.19 presents some examples of such classes of drugs and their excretion rate.

Table 2.19 Excretion rate of Unchanged API for selected pharmaceuticals. (Adapted from: Bound and Voulvoulis, 2005)		
Drug	Therapeutic class	Parent compound excreted (%)
Ibuprofen	Painkiller	10
Paracetamol	Painkiller	4
Amoxycillin	Antibacterial	60
Erythromycin	Antibacterial	25
Sulfamethoxazole	Antibacterial	15
Atenolol	Beta Blocker	90
Metoprolol	Beta Blocker	10
Carbamazepine	Antiepileptic	3
Felbamate	Antiepileptic	40 – 50
Cetirizine	Antiepileptic	50
Bezafibrate	Lipid regulator	50

The presence of human pharmaceuticals in the water cycle, particularly drinking water, is now well established across the globe (Kummerer, 2009; Gotz and Deffner, 2010). This issue is well-known in the pharma sector as PIE (Pharmaceuticals in the Environment). Humans are unintentionally exposed to very low concentrations of medicinal products via daily intakes of drinking water, leaf crops, root crops, fishes, dairy products, and meats (Mudgal et al., 2013). PIE has historically affected the environment and aquatic life through increasing the toxicity of water. For instance, it contaminates fish and enters the food cycle. Table 2.20 below highlights some key environmental incidence, facts, and related impacts of PIE.

Table: 2.20 PIE incidence and Environmental Impact			
Year & Place of Incidence;	**Pharmaceuticals**	**Environmental Impact**	**References**
2014; Germany	Metformin – the most widely prescribed antidiabetic drug	Found in drinking water, at concentrations exceeding environmental safety levels. The researchers concluded that the drug is likely distributed over a large fraction of the world's potable water sources and oceans	Trautwein et al., 2014
1976; South-East England	Contraceptive pill: Ethinylestradiol (EE2)	Feminisation of male fish in the river	Sumpter, 2010
2004; South East Asia	Diclofenac	Biodiversity Impact: all 3 species of vultures are almost distinct in this part of the world due to acute poisoning of oriental vultures	Sumpter, 2010

USA; 2009	Drugs	Drugs have been detected in 41 million Americans' drinking water from disposing the unused/expired drugs in the domestic rubbish or wastewater	Xie and Breen, 2012
USA; 2014	Drugs	Found evidence of 32 pharmaceuticals and personal care products in the water and 30 in the lake's sediment. Fourteen of these were measured at concentrations considered to be of medium or high risk to the ecosystem	Blair et al., 2013
UK: 2004	Contraceptive pills: Ethinylestradiol (EE2)	86% of male fish sampled at 51 sites around the country were intersex	Nawrat, 2018

Although many researchers argue that human pharmaceutical contaminated drinking water may not be harmful due to the low concentration of pharmaceuticals (Kummerer, 2001), the variety of ongoing new chemicals used in pharmaceutical production and the long term consumption of different levels of concentration of these chemicals in drinking water is still a matter of concern (Kummerer, 2001; Sumpter, 2010). Additionally, it is assumed that human pharmaceutical contaminated drinking water can be a threat to pregnancy because the unborn baby/foetus may receive toxic drugs (drugs that are designed to kill diving cells, for example) (Sumpter, 2010). Hence, warnings have been made that detrimental effects may arise if the transfer of compounds occurs within the water and food chain. The increased levels of environmental loading of drugs is also prone to AMR and the related human health impact.

Given such significant environmental impact, toxicity related green drug use-and-disposal practices could be a way forward to tackle this. For instance, the related stakeholder could ensure safe and responsible disposal of drugs through effective and efficient collection of unwanted drugs from customer zones. Also, they could ensure rationale prescribing, such as considering the excretion profile of a drug during prescription whenever possible and exploring whether alternative drugs are available. Close co-operation between drug-prescribers, drug-dispensers and drug-users is crucial in dealing with such an environmental catastrophe. The waste management companies and wastewater treatment companies could also play a crucial but reactive role for dealing with this toxicity, as the proactive option, i.e. redesigning existing drugs in the market for lower toxicity through the use of more biodegradable substances, is highly unlikely in the near future (Clark et al., 2010). This is because there are nearly 3000 APIs already on the market across the globe, and redesigning those APIs means looking for innovation, new discovery, and new investment for new

regulatory authorization. Therefore, downstream waste management and wastewater companies have a crucial role to play through a number of innovative end of pipe technologies and appropriate waste segregation. For instance, the wastewater treatment process could involve monitoring, detecting, and limiting discharge through innovative water treatment technologies.

Briefly, the practical relevancy and importance of using green practices in the drug use-and-disposal phase is clear. Firstly, there is increasing recognition amongst the UK health service providers and prescribers of the growing amount and cost of prescribed medicines that are unused or wasted (Jesson et al., 2005). Secondly, there has been growing concern among citizens about pharmaceutical residues in the water and food supply since the identification of the presence of hormonal products in British rivers in 1976 (Sumpter, 2010; Bound and Voulvoulis, 2005; Xie and Breen, 2012). Thirdly, the economic loss incurred from unused drugs was evidenced and realized, when the 'dump' (Dispose of Unwanted Medicines and Pills) campaign (collected unused drugs from patients) recovered GBP 37 million worth of unused drugs in 1996 (Abahussain et al., 2006). It was also reported that in the UK the national pharmaceutical associations (NPA) estimated the annual value of wasted dispensed drugs at £37.6 million, compared with a total expenditure on drugs in 2002 of £6.8 billion (Jesson et al., 2005). Therefore, pharmaceutical companies both upstream and downstream are being confronted about tackling these unprecedented environmental issues and are considering producing as much green and sustainable pharmaceuticals as possible.

2.5 Scope of GSCM in Pharma: previous studies and related research gaps

A systematic and synthesized literature review of previous green/environmental management related studies in the pharmaceutical sector has been conducted. Underpinning Srivastava's (2007) core concept of GSCM, Green Pharmaceutical Supply Chain Management (GPSCM) is assumed to be the combined efforts of 'Green Drug Design and development' + 'Green Drug Manufacturing' + 'Green drug Purchasing' + 'Green Drug Distribution' + 'Green Drug use-and-Disposal. This road map provides systematic investigation of existing knowledge and identifies the relevant knowledge gaps in the pharma sector in terms of key GSCM concepts such as green practices, green drivers, green barriers, and green performance. These knowledge gaps have led to important research questions for this thesis.

2.5.1 Current understanding on Green Practices in Pharma

While reviewing the existing literature, it is observed and understood to the best of the researcher's knowledge that there is not a single study that has focused on understanding green related practices across the pharma supply chain. Though some fragmented and disjointed attempts (e.g., solvent recycling, replacing chemical substances with more environmental ones, green process design, use of green packaging materials, and less water use in the process) were found in the existing literature, most of them lack empirical evidence. Being a highly diversified supply chain with diverse stakeholder motivations, the existing green ideas are dispersed into different areas of pharmaceutical science and engineering. Therefore, the current understanding lacks supply chain-wide green coordination.

However, the existing review with limited empirical evidence indicates that pharmaceuticals design and manufacturing operations are predominantly underpinned by the concept of 'Green Chemistry'. Green Chemistry is a set of twelve principles (see Table 2.21) that focus on how to make a greener chemical process, chemical product or chemical reaction, resulting in minimising the environmental impact by using less raw materials, eliminating wastes and avoiding the use of toxic solvents (Sheldon, 2010; RSC, 2019). Under the environmental operations management perspective, the twelve principles of green chemistry (which are derived on the basis of both chemical reaction theory and operations) predominantly share **M - Materials, E - Energy** and **T- Toxicity efficiency** (or MET). That is why the subsequent sections in the thesis interchangeably uses the concepts of 'MET' and 'green chemistry'.

Table 2.21 Operationalizing the principle of green chemistry (Anastas and Kirchhoff, 2000; Clark et al., 2010) in terms of Materials, Energy and Toxicity.

Green Chemistry Principles	Material Reduction	Energy Reduction	Toxicity Reduction	
			Air	Water
P1: *Waste prevention*		✔	✔	✔
P2: *Yield efficiency*	✔			
P3: *Less Hazardous Chemical synthesis*		✔	✔	✔

Green Chemistry Principles	Material Reduction	Energy Reduction	Toxicity Reduction	
			Air	Water
P4: *Designing safer chemical*				✔
P5: *Use of safer chemicals*		✔	✔	✔
P6: *Design for energy efficiency*		✔		
P7: *Use of renewable feedstock*	✔			✔
P8: *Reduce by-products formation*	✔			
P9: *Catalytic reaction*	✔			
P10: *Design for degradation*				✔
P11: *Real-time analysis for pollution prevention*			✔	✔
P12: *Inherently safer chemistry for accidental prevention*			✔	✔

The subsequent sections explore and simplify the materials, energy and toxicity related green concepts in the pharma sector, and identify and justify green related knowledge gaps in the selected areas of the supply chain. This approach will help the researcher to identify what green aspects/concepts are required for greening the pharmaceutical supply chain. The subsequent sections present green related research gaps in the drug design and development, manufacturing, purchasing, distribution, and use-and-disposal phases. A critical account for each case is presented in the subsequent sections.

2.5.1.1 Current understanding on green drug design and development practices

The concept of green drug design and development considers the environmental impact (e.g., energy, toxic emission and raw materials exploitation) of each key functional stage of the drug supply chain (e.g., design and development, manufacturing and use-and-disposal) in the early drug discoveries and developmental phase (Kummerer, 2009; Clark et al., 2010).

Prior to analysing in details of the related green design aspect, it is mandatory to understand the key aims and objectives of the drug design and development process, either for new drugs or existing off patent drugs, and related activities involved in both bio-based and chemical based drugs. The fundamental difference between these two types is that bio-based drugs are originated and processed from biological sources (e.g., living cell, enzymes) whilst chemical based drugs are produced by a series of chemical synthesis. Another key difference is that the equipment arrangement and engineering in bio-based production is more complex than chemical based small molecule drugs, which is one of the grounds for the different requirements of the amounts of raw materials, waters, energy etc. It is also important to highlight here that the scopes and extent of design or R&D activities are not always similar among the key industry players: Innovative Pharma, generic pharma, and biopharma. So, their key R&D focus and related activities are presented in the Table 2.22(a) to understand better their environmental practice adoption, while Table 2.22(b) summarise the previous literature that focuses on green drug design and development related practices in terms of materials, energy and toxicity.

Table 2.22a: Key R&D objectives and related characteristics across pharma industry			
Key R&D objectives and related characteristics	Innovative Pharma	Generic Pharma	Bio Pharma
Comparatively huge investment on discovering and developing an innovative drug substances (either chemical based or biobased) to a disease of interest	√		
Design innovative route of chemical synthesis or bio synthesis from the scratch	√		√
Design drug formulation (API + Excipient in solid, liquid, injection etc)	√	√	√
Design dosage form and innovative delivery system	√		√
Redesign / modify existing route of chemical synthesis process and/or formulation of existing drug products in the market for the purpose of optimization without compromising safety, efficacy and effectiveness of the products	√	√	
Sufficient amount of investment opportunities and capacities and capabilities to redesign / modify existing process.	√		
Establish exactly similar safety, quality, efficacy and effectiveness of the innovative drug which is off patent and ready for generic verson;		√	
Redesign / modify existing formulation process (and/or API synthesis process) of existing drug products in the market for the purpose of producing second generation / third generation / fourth generation of drugs	√	√	
Comparatively more focused on speed, flexibility and a desire for value creation for patients, healthcare providers and customers worldwide		√	
Produce products with low price in short development-time;		√	
Developing an innovative drug molecules (bio-based predominantly rather than chemical) to a disease of interest;			√
Design innovative route of biological synthesis or bio synthesis from the scratch using biotechnologies	√		√
Partnering and R&D collaboration is the key for successful NPD	√		√
Comparatively complicated equipment deign than traditional chemical based			√
Lesser use of chemicals in the process			√
Most of the R&D laboratory involves continuous heating and cooling	√		√

Table 2.22 b Review of green drug design & development related literature on the pharmaceutical sector

Study	Country	Methodology	Key focus	Stakeholders involved	Key green consideraiton in drug design										Key green design impact consideraiton in functional areas		
					Design manufacturing process to use green substances	Design and develop drug discovery process to reduce testing related materials	Design and develop manufacturing process for flexibility in quality	Design packaging for material efficiency	Design combined drug for material efficiency	Design and develop manufacturing process for least energy consumption	Design & develop manufacturing process for alternative process & validate energy efficient equipment system	Design & develop manufacturing process to reduce water toxicity	Design & develop manufacturing process to reduce air toxicity	**Design impact in use-&-disposal**	**Design impact in R&D**	**Design impact in manufacturing**
					Materials					**Energy**		**Toxicity**					
Leder et al., 2015	.....	Literature review	Green process design practice	Innovators								√		**Practices:** consider biodegradability in lead identification; consider biodegradability in lead optimization; benign by design concept used;	None	None
Sumpter, 2010	.....	Literature Review (Book Chapter)	Drug process redesign for green	Innovators								√		**Practice**: redesigning existing drugs for improved biodegradability	**Practice**: Consider Toxicity reduction by replacing with green substance	**Practice**: Consider Toxicity reduction by replacing with green substance
Kummerer, 2010	.....	Literature Review (Book Chapter)	Green process design practice	Innovators								√		**Practices**: consider biodegradability in the lead identification and lead optimization stage through slight modification of the drug molecules (e.g.,	None	None
Challener, 2016	.....	Literature Review	Green Process design	Innovators	√					√		√		**Practices**: design process to use bio based catalyst (e.g., Enzyme);	**Practice**: Consider Toxicity reduction by replacing with green substance	**Practice**: Consider Toxicity reduction by replacing with green substance

Study	Country	Methodology	Key focus	Stakeholders involved	Key green consideraiton in drug design									Key green design impact consideraiton in functional areas		
					Design manufacturing process to use green substances	Design and develop drug discovery process to reduce testing related materials	Design and develop manufacturing process for flexibility in quality	Design packaging for material efficiency	Design combined drug for material efficiency	Design and develop manufacturing process for least energy consumption by evaluating alternative process	Design & develop manufacturing process to install & validate energy efficient equipment system	Design & develop manufacturing process to reduce water toxicity	Design & develop manufacturing process to reduce air toxicity	**Design impact in use-&-disposal**	**Design impact in R&D**	**Design impact in manufacturing**
					Materials					**Energy**		**Toxicity**				
Boltic et al., 2013	Serbia	Case study	Green process design practice	Generic Manufacturer (formulation)				√						**None**	None	**Practice:** Consider Toxicity Reduction: use of green (aqueous /water based) solvent replacing with toxic (organic) solvents; **Performance:** Expected Positive environmental performance
Clark et al, 2010	.....	Literature Review (Book Chapter)	Green process design practice	Innovators		√				√				None	**Practice:** early coordinaion between medicinal chemist and process chemists for successful green design; usage of HTS, focused library, design software	**Practice:** evaluate and compare process energy
Ding, 2018	.....	Literature review	Drug process redesign for green	Innovators					√					**Practice**: design combined drug formulations (e.g., combine multiples APIs)	None	**Practice:** design combined drug formulations (e.g., combine multiples APIs)

In reviewing the previous works in the Table 2.22 (b), it is evident that there *is a lack of empirical research on green drug design and development, as the majority of the existing studies are literature review based*. The key focus of the existing studies can be broadly seen from two perspectives: MET practices for designing new drug processes and MET practices for redesigning existing drug processes for an improved environmental footprint. *Comparatively less focus is given to redesigning aspects of the existing drugs*, though the existing drug products (off patent generic) meet the majority of demand across the globe, leaving a significant, negative environmental footprint. Moreover, these studies only outline the green drug design and development specifications for innovators and do not consider other important supply chain stakeholders, such as generic pharma and bio pharma. As a result, *the contribution of each individual stakeholder during this phase is not known, and the extent and types of related green practices undertaken by each of the stakeholders are also not known*.

While trying to understand Materials, Energy and Toxicity related green design practices, the majority of the studies (e.g., Sumpter, 2010; Kummerer, 2010; Leder et al., 2015) focus on developing a theoretical understanding of how to improve environmental biodegradability of drugs through developing more bio-based drug processes for reducing water toxicity. *Still, this biodegradable drug process development is debated due to the lack of empirical evidence on toxicity-related drug design and development practices in the sector* (Clark et al, 2010). *There is also limited understanding of design impact consideration in each functional area prior to initiating design activity*. Very few studies have considered the design impact in the three key functional areas (design and development, manufacturing, and use-and-disposal) in the early designing phase. Therefore, a new empirical study is required to fill all these gaps. The following sections provide a detailed account of each area of Materials, Energy and Toxicity related design practices and the related knowledge gaps.

Design for material reduction

As seen in Table 2.22 b, the existing literature indicates five key green design aspects to dematerialize not only the R&D process but also the manufacturing and disposal phase. For instance, materials reduction could be achieved during the drug discovery process (especially in the lead identification and lead optimization stage by *designing and developing the discovery process in such a way so that it reduces the usages of chemical raw materials for laboratory testing purposes*. For instance, screening the focused library, rather than the entire

compound library, could significantly reduce the uses of raw materials (cells, microtiter plates, reagents, disposal plastic tips, etc) (Clark et al., 2010). Using computer software to identify the 3D structure of a drug target (e.g., a protein) could help medicinal chemists to find an appropriate lead compound. The use of a virtual compound library combined with the 3D view of the initial target site could increase the confidence in the medicinal chemists for using a focused library (Sundgren, 2004). So, this material reduction approach reduces the number of compounds screened in the lead identification and therefore reduces the use of relevant resources. *Unfortunately, the scope of these assumptions still needs to be verified empirically. Additionally, it is still not well understood how to conduct an exhaustive chemicals screening process while increasing materials efficiency during drug discovery.*

As the scientists in lead identification are responsible for screening and testing compounds to find leading drug candidates for further development, Tucker (2006) has advocated the application of high throughput screening (HTS). The process of HTS has been very promising and successful in identifying potential lead compounds whilst using less material, producing less waste and saving time. Clark et al (2010) have also mentioned the usages of HTS for reducing the drug discovery timeline. *However, it is still a matter of research to establish the viability and scopes of these material reduction opportunities during the drug discovery and development phases using these technologies or some other emerging technologies.*

It is also important to highlight that the initial lab scale process (as part of developmental process) could be designed in such a way so that the commercial manufacturing could save raw materials such as solvents, reagents and excipients. It could also be possible that the size and weight of the drugs could have been reduced by using nano materials and improving strength and effectiveness while using lower dosages – consequently the manufacturers could save huge amounts of packaging materials and costs. *However, it is not known whether this design decision in the early stage of drug process design is currently being considered or not; if considered, we do not know to what extent, and the possible barriers to doing it are also not known. We also do not know the related stakeholders' roles here.*

It is also possible *that a drug manufacturing process could have been designed and developed in such a way, so it uses greener substances such as biocatalysts*. Biocatalysts are bio-based substances that effectively and efficiently accelerate the reaction throughput and reduce the need for further raw materials for completing a chemical reaction. The substances

also reduce byproduct formation during the reaction process. They also reduce materials related energy for typical chemical reactions. Under the concept of Material reduction, it is remarkable that the concept of biocatalysts is only covered by a small number of studies, such a generic review by Challener (2016) and the study by Sheldon (2010). Unfortunately, these studies have not been able to clarify the scope of viability and acceptability of designing a drug process with bio-based catalysts (by both innovative and generic pharma) and their possible implications on commercial manufacturing. *Those studies also lack practical evidence. In addition, the current level of consideration of bio-based catalyst in the early process design phase is not known. It is also not clear in the existing literature how bio-based catalysts actually improve materials, energy and toxicity at the same time*. Furthermore, *it is not known how this design decision is currently being taken by different pharma stakeholders (e.g., innovative pharma, generic and bio pharma) and, whether this is the case for only new drug design or whether it can be applied on redesigning existing drug processes.*

A flexible design approach could be another important design criterion for pharma R&D for reducing materials usages. It is possible that quality variations (between batches) may occur during mass production due to the variations in the starting raw materials (e.g., API sourced from different vendors) or due to the variation in reaction parameters such as throughput time, reaction temperature and pressure. Therefore, this could lead to significant amounts of product wastes due to not conforming to quality standards. As the pharma process is locked into a predetermined validation process approved by the regulatory body for marketing authorization, it would be very difficult to revalidate a process with new process requirements while the product is already in the market.

It is also important to note here that the level of green design practice is not always significant due to the imbalanced understanding between environmental issues and design space (e.g., different variables of product/process design) for a particular product or material or service (Dewberry, 1996; Deutz, et al., 2013). The design space for a pharma process initially is very limited but as time passes, the manufacturers learn more about the process requirements. Therefore, the design space becomes more visible and it requires redesigning the existing process by considering related design variables (e.g., reaction time and raw material variability reaction speed). Therefore, a flexible design approach which could consider all related variables in the initial design or re-(design) of a process could be more effective to avoid unnecessary product recall or quality-related materials wastes during the manufacturing phase. *However, the scope of reducing materials wastes from commercial*

manufacturing operations through adopting a flexible design approach is still not well understood. The extent and scope of this practice between innovative pharma and generic pharma is also not known. Though apparently it could benefit both innovative pharma and generic pharma, materials savings from generic pharma would be significantly high. However, it is still merely a subjective matter and requires empirical evidence to demonstrate whether and how it is being adopted.

Designing the pharma packaging (primary / secondary / tertiary) system in such a way so that there is less usage of raw materials and related energy reduction. For instance, the packaging systems may use renewable materials or reusable/recyclable materials, considering the life cycle impact of packaging (Ding, 2018). Though there are few LCA related studies conducted in the big pharma sector (Raju et al., 2016; Soete et al., 2017; Chaturvedi et al., 2017), they predominantly focus on process development and do not capture the viability, capability and entire scope of conducting LCA across the pharma industry to deal with packaging related environmental issues. A life cycle based environmental impact analysis for a particular packaging system could be useful to manage packaging wastes in the later stage of the life cycle (Jimenez-Gonzalez, 2000). *However, the scope of LCA and related other green packaging design activities in the early design phase is not well understood yet. Additionally, it is also important to investigate how and to what extent different stakeholders (e.g., innovators, generic, and bio pharma) consider these green design activities.*

Designing drugs with multiple active ingredients into one instead of separate drug design with a single active ingredient could also reduce raw materials usages significantly (Ding, 2018). *However, the scope, extent and possibility of this design aspect still requires practical evidence across different stakeholders. Though apparently this design aspect could potentially be effective for generic versions of the existing drug design process rather than new drug design due to the complexity of the discovery process of a new drug, this assumption still requires confirmation.*

Design for Energy Reduction

As seen in Table 2.22 b, two key approaches are identified to save process or plant level energy. *Though two studies (Challener, 2016; Clark et al., 2010) highlight materials related energy saving (covered in the material related section), none of the studies demonstrate process / plant level non-material-based energy savings. Designing and developing a new manufacturing process or re-designing an existing manufacturing process to improve energy*

savings through installing energy efficient equipment system across the industry could be one of the key green design approaches. This is because drug discovery centres, including scientific laboratories in large pharmaceutical companies (and/or R&D facilities in generic and bio pharma companies), where the potential process of a drug substance is designed and developed, are comparatively large facilities and equipped with multifaceted and complex equipment and machines. They consume huge amounts of energy to maintain specific conditions (e.g., temperature, pressure and air density) continuously. Appropriate efficiency control and measures are essential in handling materials and process equipment. *However, it is still not established in the existing literature whether there is any such kind of energy efficiency practice currently being considered across the industry and, if so, to what extent. It is also not known if there is any kind of measure currently being developed to achieve energy efficiency within new process design and development. It is also not known whether energy efficiency practice is being considered for new drug development, or for re-designing the existing drug manufacturing process, or in both cases. The extent of consideration of this green practice across different pharma players (e.g., big pharma, generic pharma, and bio pharma) is also not known.*

Though Clark et al. (2010) and Slater et al. (2010) assumed that greener process could have been designed and developed using less energy, *there is still a lack of empirical evidence to discover what and how it could be achieved*. Additionally, *there could be some other relevant green practices that could have been used for achieving energy efficiency in the drug design and development phase which are still not known*. For instance, the *least energy consumptive process could be designed based on the assessment of energy input and output of a process*. While it takes time to understand the key process parameters over time, this design aspect could be applied only for re-designing the existing process where the process has already been critically understood. But *it remains unconfirmed whether this could be the case for new drug process design, or in re-designing existing drug process.* Therefore, further investigation is required to understand the scope and extent of energy efficiency practices in the early process design of a new drug substance.

Design for toxicity reduction

As seen in Table 2.22 b, two key approaches are highlighted for dealing with water and air toxicity. For reducing water toxicity, a drug can be made of greener substances and use more bio-based substances, so it can be degraded when it goes into the environment. So, a drug

process can be designed for using eco-friendly raw materials (e.g., API, solvents, reagents, excipients or other chemicals) and replace high impact substances, for instance, avoiding chlorinated chemicals and replacing them with less toxic ones for greater environmental performance. In particular, to detoxify the process during mass production, it is important to *use less toxic and non-hazardous raw materials and use the greener solvent* in the process (Watson, 2012). So, the toxicity consideration in the early design phase is critical. However, the *concept of detoxification or reduced toxicity in the diversified pharma manufacturing environment is not well explored. For instance, the various toxicity reductions-related green aspects in innovative pharma or in generic API or generic formulation are not known.* The concept of green solvent selection, for instance, is still an issue and involves multifaceted aspects during manufacturing and is highly company specific (Clark et al., 2010; Perez-Vega et al. 2013). The current state of understanding of green solvent selection is highly scattered and it is not confirmed if there are any standard guidelines for selecting a greener solvent. It is also not known whether and to what extent a solvent guide is being currently used by the different types of manufactures.

Using a similar concept, drug substances can be selected and optimized in such a way so that the final API can be easily recyclable (of unused-disposed drug) and easily degradable or disassembled into metabolites (that are not harmful for environment) in the environment after excretion (Kummerer, 2009). So, this approach can be used in both lead identification and lead optimization in the drug design stages.

Such a design approach is called bio-based drug design or biologics, which could potentially be biodegraded in the environment. Biologics is an innovation for greener pharmaceuticals-known as biopharmaceuticals. Biologics are mainly biologically sourced substances (e.g., protein based) which are replacing traditional chemical drugs (Clark et al., 2010). Taylor (2010) has advocated for biopharmaceuticals which may have minimal or no adverse impact on the ecosystem, as they are specially designed to interact only with a diseased human receptor. In addition, Holzer (2010) demonstrated that protein-based APIs are supposed to be readily degradable and do not therefore accumulate in the environment. *But the data that allow for a generalisation of these assumptions are missing. However, the researcher has also identified that the protein-based active ingredients are too large and complex to be synthesised by conventional chemical techniques (Clark et al., 2010). So, the extent of viability of biopharmaceutical production may be still a matter of environmental concern, which we do not know clearly.*

Whilst biodegradability (design for biological degradability of drugs inside the body) practices are advised in the literature, such as a study by Clark et al. (2010), Kummerer (2009), Leder et al. (2015) has highlighted that consideration of environmental biodegradability in drug design is very complex and sometimes impossible, as the stability of the drug needs to be considered first for efficacy. They have also mentioned that even if any drug is developed with environmentally biodegradable property it happens by chance rather than an intentional effort during drug design and developmental phase. Taylor (2010) has also argued that increasing environmental biodegradability of drugs is sometimes the opposite principle of increasing bioavailability or stability of a drug molecule within the human body. Therefore, *it is still not clear whether R&D based innovative companies are currently considering this aspect or not; if yes, then the extent of this practice and the level of complexity of this practice should be also investigated. Also, it is not known whether this is an issue with designing and developing new drugs or redesigning existing ones. The views of different stakeholders on this green design aspect are also not known.*

Sumpter (2010) has indicated that pharmaceutical companies need to think about the environmental stability of a compound early in the drug design process (i.e. 10 or more years before a successful drug reaches the market). He has provided an example of fluorine containing drugs, such as *Prozac, Lipitor* and *Ciprobay*, which are known as 'Blockbusters'. Although the carbon-fluorine bond provides an increased bioavailability of the pharmaceutical for patients, it is a major disadvantage for the environment because it is designed to be resistant to degradation. So, in the lead identification and optimization process, fluorine (or other halogens atom) could be replaced with greener substances.

However, though the literature suggests considering the environmental stability data of drug compounds early in the design phase (Sumpter, 2010), the concern is the unavailability of environmental impact data for the compounds that are being continuously discovered for developing new APIs. *It is not clear that whether or to what extent medicinal chemists consider this aspect prior to developing the new API.* Additionally*, it is also not clear if this type of consideration would be a challenge for the R&D and drug discovery based companies, as the efficacy of the drug would be a serious issue whilst selecting the greener drug substance.* In order to reduce toxicity, modification of chemical structure for achieving the biodegradability of drugs is also suggested (Kummerer, 2010) but *it is not clear in the existing literature whether this type of structural modification is practically possible while*

considering the efficacy of the drug substance. This is how the knowledge domain under 'designing bio-based drug' or designing for biodegradability of drug is still unclear.

There is also a huge knowledge gap when trying to understand the individual stakeholder's contribution to green drug design, either for new drug development or existing drugs in the market. It is also not known what could happen with the existing drugs which are already in the market. As the downstream players (such as manufacturers, wastewater treatment plants, and waste management companies) and external bodies (such as regulators and environmental groups) are continuously monitoring the environmental impact of the existing APIs with the advent of advanced analytical measures, it is possible that more PBT data are becoming available to redesign existing drugs. *Unfortunately, the current literature has rarely focused on the aspect of the redesigning possibility of existing drugs in the market*.

It is also important to highlight that the concept of degradability could be used not only in the drug chemicals, but also in the packaging materials and chemical equipment in the lab, so the related wastes produced in the later stage of the supply chain could be degraded, as all the packaging materials and process equipment are selected in the early design stage. This will ultimately reduce environmental impact in these stages of the supply chain. *However, this kind of design impact consideration is not known.*

For reducing air toxicity during operations, drug processes can be designed in such a way so that there is lower usage or elimination of CFCs. Currently the pharma companies' R&D use extensive amounts of chlorinated solvents in product and/or process design, such as usage of CFC-based inhalers and chlorinated equipment in solvent separation technique (e.g., the chromatography process). All these activities could potentially incur significant amounts of volatile organic compounds (VOCs) which are responsible for depleting ozone layer depletion via atmospheric pollution. The production and consumption of CFC-based inhalers are significantly increasing. For instance, one of the leading pharmas has reported that Scope 3 GHG emissions from product usage has increased from 99 kilotons in 2014 to 124 kilotons in 2015 due to growing production volumes of the inhaler (Novartis, 2017). Though from the chemical stability point of view CFCs are relatively safe and non-toxic, they are also responsible for their potential to damage the environment (Noakes, 1995).

However, despite this potential environmental consequence, it is not known how the pharma companies deal with the unprecedented level of VOCs emitting into the atmosphere. Furthermore, the extent of employing those green activities or practices across the sector is

not yet known. So, this knowledge is urgently required to understand what green design aspects are currently employed by the pharma companies to tackle the toxicity to air, especially in the case of inhaler / aerosol-based drug products.

In a nutshell, the concept of green drug design and development is still not fully understood in the existing literature. Although the concept of green design is widely demonstrated (Dewberry, 1996; Zhu and Sarkis, 2007; Eltayeb et al., 2011; Bullock and Walsh, 2013; Tian, et al., 2014) across the industries in different products, none of them focus on drug design. Additionally, the consideration of the key concept of green chemistry (or MET) in the design phase has rarely been explored in the environmental operations management research. As the motivation for the drugs supply chain is different from traditional products, the existing green design practices could be working as a guiding principle only, but not a complete solution. So, the concept of green design in the drug design, discovery and development process is new under GSCM and in the operations literature, and it requires a new investigation for clarity. Also, it could be possible that some of the materials reduction, toxicity reduction and energy reduction related practices could be applied to other related industries such as textile, leather, cosmetics and pesticides. Therefore, it is crucial to understand the scope of MET in drug design and development in detail. Hence the first sub research question appears:

RQ1.1 what green design practices are implemented by individual pharma sector stakeholders and what is the extent of their implementation?

Whilst the key design aspects are understood, it is apparently clear that the manufacturing phase will enjoy efficiency in materials, energy, and toxicity by following those design aspects. However, the dimensions of pharma manufacturing are very complex, and it depends on multifaceted factors from day to day plant operations (API, formulation, and packaging) to final wastes disposals through the involvement of diverse stakeholder interaction. Additionally, streamlining actual mass manufacturing processes is not controlled by early design aspects but it can be controlled by adopting related lean practices, for example. Hence, some green aspects in the initial drug design and development phase may not be effective enough to green the pharm supply chain. Therefore, it is important to have a clear picture on how to green pharm manufacturing operations. The next section presents the existing green manufacturing attempts and related knowledge gaps.

2.5.1.2 Current understanding on green drug manufacturing practices

The concept of green manufacturing of drug products entails the consideration of the environmental impact of API and formulation activities to avoid excessive materials usage, energy usage, non-renewable raw materials usages, toxic materials usages etc, throughout the manufacturing operations (Clark et al., 2010). Table 2.23 summarise the previous literature that focuses on green manufacturing related practices in terms of materials, energy, and toxicity.

Table 2.23 Review of green drug manufacturing related literature on the pharmaceutical sector

Study	Country	Methodology	Key focus	Stakeholders involved	Key green manufacturing practices considered									Key green impact consideration in functional areas	
					Run continuous mode of manufacturing	Recycle and reuse of solvents	Consider lean operations for material reduction	Consider green collaboration for material efficiency	Energy efficient equipments system & technology	Energy management program	Greener chemical application & management process	Product stewardship (Eco-pharmacovigilence)	Responsible waste Management	Green practices	Green practice impact on use-and-disposal
					Material				**Energy**		**Toxicity**				
Taylor, 2010	.....	Literature review	Pollution prevention: Solvent reusing and recycling,	Innovator (R&D, API manufacturers)		√					√		√	**Practices:** develop advanced system to select eco friendly solvent and reagents; reusing and recycling of solvents; use of aqueous cleaning system (green) in the formulation companies (for equipment cleaning purposes)	Toxicity reduciton
Clark et al., 2010	.....	Literature review	Greener Solvent selection guide	Innovator		√					√		√	**Practices**: use of catalysis, reduction in the number of synthetic steps (telescoping), waste minimization; employ energy efficient methods, avoiding hazardous chemicals, reduction in resource consumptions.	Toxicity reduciton
Challener, 2016	.....	Literature Review	Material, Energy, Toxicity	Innovator										**Practices**: reduce traditional (chemical based) metal catalyst; increase bio based catalyst (e.g., Enzyme);	Toxicity reduciton
Sheldon, 2010	.....	Literature review	Material, toxicity, energy focus	Innovator (R&D, API Manufacturers)							√			**Practices:** reduce use of raw materials; reducing reaction stages; replace greener solvent with traditional organic solvents such as chlorinated and aromatic hydrocarbon;	Toxicity reduciton

Table 2.23 Review of green drug manufacturing related literature on the pharmaceutical sector (cont')

Study	Country	Methodology	Key focus	Stakeholders involved	Key green manufacturing practices considered									Key green impact consideration in functional areas	
					Run continuous mode of manufacturing	Recycle and reuse of solvents	Consider lean operations for material reduction	Consider green collaboration for material efficiency	Energy efficient equipments system & technology	Energy management program	Greener chemical application & management process	Product stewardship (Eco-pharmacovigilence)	Responsible waste Management	Green practices	Green practice impact on use-and-disposal
					Material				**Energy**		**Toxicity**				
Slater et al., 2010	.....	Literature review	Material reduction, Toxicity reduction, pollution prevention	Innovator (R&D, API Manufacturers)	√	√	√		√					**Practices**: use of solvent selection guide; optimize the reaction stage; solid state chemistry and continuous reactor are recommended for reducing solvent use; advise solvent reuse and recycling;	Toxicity reduciton
Perez-Vega et al., 2013	.....	Literature review	Green and sustainable solvent selection	Innovator (R&D, API Manufacturers), Waste Management companies	√	√		√			√			**Practices:** cooperation practice among the relevant stakeholders [e.g., synthetic chemists, process chemical engineers, disposal contractors (or waste management companies), and suppliers] prior to selecting a solvent in the early stage of API process development; solvent reusing; solvent recycling, catalyst use and continuous operation.	Toxicity reduciton
Plumb, 2005	.....	Literature review	Energy reduction; material reduction;	Innovator (API manufacturers and formulators)	√									**Practices**: use continuous manufacturing process;	Less co2 emission; toxicity reduction
Mollan and Lodaya, 2004	.....	Literature review	Energy. Material Reduction	Manufacturers (APIs and formulators)	√									**Practices**: advocate for continuous manufacturing process; use of PAT (Process Analytical Technology) guidance for reducing process wastes;	Less co2 emission; toxicity reduction

Table 2.23 Review of green drug manufacturing related literature on the pharmaceutical sector (cont')

Study	Country	Methodology	Key focus	Stakeholders involved	Key green manufacturing practices considered									Key green impact consideration in functional areas	
					Run continuous mode of manufacturing	Recycle and reuse of solvents	Consider lean operations for material reduction	Consider green collaboration for material efficiency	Energy efficient equipments system & technology	Energy management program	Greener chemical application & management process	Product stewardship (Eco-pharmacovigilance)	Responsible waste Management	Green practices	Green practice impact on use-and-disposal
					Material				**Energy**		**Toxicity**				
Teunter et al., 2003	Germany	Case study	Pollution Prevention; Responsible waste management	API manufacturers		√								**Practices:** by product recycling; reusing and recovery of solvents; less purity solvents sometimes are used as fuel and impure recycled solvent goes to incineration;	Less toxicity; Low air emission
Raju et al., 2016	India	Literature Review	LCA	Formulators								√		**Practices:** life cycle analysis model (gate to gate) for a pharmaceutical formulated dosage form considering environmental impact;	Less toxicity; Less air emission; Less energy
Soete et al., 2017	Europe	Literature review, stakeholder survey, expert interview, roundtable discussion	Green Chemistry metrics and LCA	Private organization, makers, NGOs, academic research institution, hospital, pharmacies, patient, GPs								√		**Practices**: less use of material, energy; reduce toxicity; use of bioprocess; continuous process;separation and reaction technology, recycling, optimization, quality by design;	None
Chaturvedi et al., 2017	India	Literature Review	Green Chemistry, LCA	Manufacturer (API)								√		**Practices**: less material, less energy, apply LCA	Less air emission; less toxicity

Table 2.23 Review of green drug manufacturing related literature on the pharmaceutical sector (cont')

Study	Country	Methodology	Key focus	Stakeholders involved	Key green manufacturing practices considered									Key green impact consideration in functional areas	
					Run continuous mode of manufacturing	Recycle and reuse of solvents	Consider lean operations for material reduction	Consider green collaboration for material efficiency	Energy efficient equipments system & technology	Energy management program	Greener chemical application & management process	Product stewardship (Eco-pharmacovigilence)	Responsible waste Management	Green practices	Green practice impact on use-and-disposal
					Material				**Energy**		**Toxicity**				
Schneider et al., 2010	.....	Examine sustainability report	Pharma sustainability	Manufacturers			√							**Practices**: Less energy, less material, less toxicity; Eco-intensity ratio, LCA, Lean, Six Sigma	Less toxicity
Watson, 2012	Global	Survey	Application Green Chemistry	Manufacturers	√						√		√	**Practices**: Use of green solvent, water based solvent, continuous process/flow chemistry/micro reactor, catalysis, bio catalysis, avoid highly toxic reagent, consider environmental footprint of raw materials,	Less air emission; less toxicity

As seen in Table 2.23, under the methodology column there *is a lack of empirical research on green drug manufacturing,* as the majority of the existing studies are literature review based. Only one study used a case study, another one used a survey and another one used reports, but the rest are literature review based. The complex nature of the manufacturing process and related green adoption requires empirical evidence. While reviewing the key research focus, it is shown that the application of green chemistry (or MET practice) is the central the focus during the manufacturing phase. Few of the reviews also highlight LCA related practices. Under the stakeholder column, there *is a lack of understanding on the role of generic and bio pharma manufacturers in greening the manufacturing process, as there is no study that focuses on their role.*

While reviewing key green manufacturing practices in terms of materials, energy and toxicity efficiency, the related green concepts are narrowed, scattered, and dispersed into different dimensions and lack complete understanding on each area of focus. For instance, under materials efficiency practices, few studies highlight continuous manufacturing; a few of them suggest solvent reuse and recycling requirements in the process; and very few of them highlight lean practices, and green collaboration for materials efficiency. *These limited and fragmented green focuses have not been able to demonstrate the scope of a holistic view of achieving materials efficiencies during API production or the formulation stage*. Similarly, under energy and toxicity, *the current level of understanding on related green approaches is missing supporting evidence*. It is also evident that the majority of MET-related green practices will have resulted in reducing air and water toxicity during the use and disposal phase, though the related concepts are still required to understand this in detail.

In addition, as seen in Table 2.23, the majority of the literature has predominantly discussed the scopes of green practices in the upstream API production and neglected the formulation process, while there is also a considerable number of environmental burdens in the formulation stage, due to extensive use of cleaning agents, solvents, binders or tablet coating, equipment etc. Though the majority of the studies indicated the concept of MET (Taylor, 2010; Clark et al., 2010; Slater et al., 2010; Velva and Jr, 2017), *none of the studies have demonstrated how the key concept of MET can be applied by relevant stakeholders, especially generic and bio pharma manufacturers. It is assumed that MET could have been adopted in varying levels among the stakeholders, which are yet to be explored in detail.* Therefore, a successful implementation of MET in drug manufacturing will require understanding related key indicators and variables to operationalize them under a controlled

management system. The subsequent section explores material, energy and toxicity related green practices and relevant limitations and knowledge gaps in detail to justify the need for this investigation.

Material Reduction

As seen in Table 2.23, four key green approaches (continuous manufacturing process, solvent recycling, lean practice, and green coordination) were specifiedfor material reduction during drug manufacturing. *For instance, material recovery (especially solvents) in terms of recycling and reusing* is important for pharma manufacturers in order to reduce hazardous wastes and save related energy and virgin materials (Perez-Vega et al. 2013). Recycling and reusing practices are comparatively new in the pharmaceutical industry compared to other industries. It is reported that less than 50% of solvent is reused and recycled (Perez-Vega et al. 2013). Efficient solvent recycling and reusing systems have been sought that are economically profitable and environmentally sustainable (Teunter et al., 2003). Used solvent that cannot be recycled must be disposed of as wastes effluent discharge or incineration, which will increase the negative environmental impact and associated costs. Successful recycling depends on recycling methods. It is reported that distillation (a method of solvent recycling) is used for approximately 95% of all solvent separation processes (Slater et al., 2010). However, the author has also outlined that this method of recycling generates wastes, such as releasing GHGs and high energy requirements. But Teunter et al. (2003) have advocated the distillation process for solvent recycling, as the process recovers high purity solvent and requires fewer raw materials (e.g., solvent). Hence, *the limited empirical based research has not been able to resolve these ambiguities relating to the solvent reusing and recycling process.*

The byproducts from the process could be used as raw materials or as raw materials substitution in other processes. The cooling water could be recirculated. The equipment wash-down waters and other process waters (such as leakage from pump seals) could be used as makeup solutions for subsequent batches (WBG, 1998). *However, the scopes of these recovery practices undertaken by diversified stakeholders are not known. For instance, it is not known whether innovator and generic are considering similar approaches to recovering solvents or other raw materials from the process.* However, like the recycling process in the innovator sector, the generic industry could also recycle solvents using the distillation process, or other methods which are not clear in the existing literature. Though there is little

indication of on-site recycling practices in the innovators'API facilities (Schefer, 2017), *it is not known whether an on-site recycling process in the generic formulation industry could be viable in terms of environmental as well as economic benefit.*

On the other hand, it needs to be justified for the entire industry whether on-site solvent recycling and recovery process would be viable. Though it has been reported that on-site recycling and recovering process is safer and eco-friendly and the payback period is less than two years, the majority of companies still rely on off-site recovery and disposal processes which are not safe as well as not being environmental friendly (Schafer, 2017). *However, this requires further investigations to understand current levels of on-site or off-site solvent recovery and the motivations for choosing these options.*

Therefore, using the current level of understanding, it is not feasible to claim solvent recycling and reuse as management practices for achieving green manufacturing attributes. As recycling and reusing practice are comparatively new in the pharmaceutical industry compared to other industries, little is known about it (Perez-Vega et al. 2013). Only one study (Teunter et al., 2003) shows that efficient solvent recycling and reusing systems induce economic profitability and environmental sustainability in an innovator's API production company. *Therefore, using the current level of understanding, it is not feasible to claim solvent recycling and recovery as the management practices for achieving green manufacturing attributes in pharma. The scope is also unknown in the case of generic and bio pharma.*

As seen in Table 2.23, lean practice is indicated as another green manufacturing practice under materials reduction. *Considering lean operations is significantly important* for each new or existing drug manufacturing process for not only reducing machine throughput for energy savings, but also for gaining cost efficiency and manufacturing effectiveness (Slater et al., 2010). This effectiveness and efficiency in the manufacturing process could significantly reduce process wastes. Though lean operations could significantly reduce solvent wastes (Slater et al., 2010), the extent and *scope of the lean operations process (by applying lean practices) across diversified stakeholders (in case of both API and formulation manufacturing environment) is not well understood.* For instance, it is not known how bio pharma and generic pharma streamline their process compared to innovators. Additionally, *there could be some optimization programs like six sigma, lean or continuous improvement projects for reducing their individual manufacturing wastes and increasing profitability,*

which still need to be identified and confirmed via empirical evidence. Though some other important concepts are also assumed to be effective for green manufacturing, such as efficient inventory management, efficient production and quality control, substitution and greener packaging, these concepts are underestimated in the current literature.

Process energy and material wastes also largely depend on the process calibration efficiency and effectiveness. Reducing faulty calibration may be a good practice. Faulty calibration of the analytical equipment may incur production loss and reduction in product quality, increasing wastages and loss of energy. *However, little is known about equipment calibration-related lean practice.* So, inappropriate calibration in full scale manufacturing can be a huge source of low yield, high energy, and solvent wastes. Most of the consequences originating from the lack of proper calibration of process equipments are reduction in product quality yield, increased unexpected byproducts, longer cycle time, inability to reproduce key properties such as colour, size, or crystal structure etc. Obviously, inappropriate and/or wrong calibration of equipment would induce considerable amounts of wastes due to either faulty products or lower quality yields. So, it is important to understand the scale up and calibration strategy adopted to reduce materials wastes and related energy. *It is not known how the calibration issues are resolved through lean operations. The current focuses do not pay attention to explaining the scope of calibration issues and their associated environmental and economic loss.*

Water reduction could be another important lean operation. Water is one of the most widely used natural resources in the pharma manufacturing process, especially in the API production process and biopharma production. This green aspect has paramount importance for the pharma industry due to the global issue of scarcity of safe drinking water.

Inefficient equipment choice in the formulation process could yield substantial amounts of wastes. In the formulation industry, right equipment choice for a particular unit operation is important to avoid energy loss and unnecessary wastes. The formulation industry also need to think about the quality and efficacy of the drug. For instance, in the tablet manufacturing process, wet granulation is a well known process. However, the wet granulation process consumes more energy and produces more waste than dry granulation. The reason is that wet granulators use liquid solvent. However, in the current literature, it is not clear whether companies select equipment considering the environmental footprint. Therefore*, it is important to investigate what different kinds of lean approaches are currently being taken*

across the industry. It could also be beneficial to know the extent of lean application across different types of pharma stakeholders, such as innovative pharma, generic pharma, and bio pharma.

As seen in Table 2.23, running continuous modes of manufacturing is one of the key green manufacturing practices under materials reduction. Moving towards continuous manufacturing from traditional batch process is another important focus for improving environmental footprint. Studies have advocated that a continuous manufacturing process has a positive environmental impact over batch operation (Plumb, 2005; Mollan and Lodaya, 2004; Slater et al., 2010, Watson, 2012; Perez-Vega et al., 2013). Batch operation requires more energy, more solvent for cleaning equipment in between batches and hence more wastes. There is huge scope for continuous manufacturing in API synthesis. For instance, Hydrogenation (a type of reaction that uses catalysts to accelerate throughput) is a frequently used reaction in bulk pharmaceutical and fine chemical synthesis that can be efficiently run in a continuous fashion. Similarly, continuous crystallizers (where crystallization of intermediate drug substances happens during API production), as opposed to batch crystallizers, have the built in flexibility to control temperature, rate of saturation (of solids), crystal growth and all the other process parameters that influence crystal size (of drug substance) distribution (Mollan and Lodaya, 2004). Compared to batch operation, continuous process is simple and well understood. Continuous process provides good yield over the batch process mainly because of improvements in temperature control and mass transfer. Continuous process reduces waste, energy and hence cost (Plumb, 2005).

However, due to equipment flexibility and invariable demand for pharmaceutical products, traditional batch manufacturing is assumed to be fruitful. Apparently, at the same time it would require infrastructural change to move to continuous. It is also outlined that the unit operations approach is beneficial because a complex, many-step process can be separated and better understood as a series of simpler activities (unit operations) that are more easily interpreted (Agalloco and Desantis, 2005).

Although the majority of researchers (Plumb, 2005; Mollan and Lodaya, 2004; Slater et al., 2010, Perez-Vega et al., 2013) have identified potential benefits for shifting towards continuous, some disagreements (regulatory barriers, ease of operation for highly complex multi-faceted reaction process etc) cannot be ignored. Therefore, a separate study is required

to establish the absolute viability of this shifting in the case of both API production and formulation across the key industry players such as innovative, generic and bio pharma.

In a few cases, recent trends have sought to move from traditional batch manufacturing to continuous manufacturing in the formulation process as well. For instance, continuous coating in the production of solid-dosage forms reduces energy consumption and yields quality product (Siew, 2015). Continuous operations with dedicated equipment facilities will reduce the amount of cleaning operations and related solvent wastes in the formulation process. *However, the trade-off between 'staying focused on batch manufacturing' and 'moving towards a continuous manufacturing process' is still a matter of further research. Additionally, it is still not clear to what extent it will be viable for companies to move from batch to continuous process, and it is also not known how continuous process is becoming beneficial for them, both economically and environmentally across different stakeholders. For instance, the scopes and extent of continuous manufacturing among innovators or generic or bio pharma is still not known.*

Under a continuous manufacturing process, there is also significant scope for reducing materials-related energy. For instance, the *application of built-in web-based technologies or digital technologies* within the pharma equipment system could also reduce significant amounts of materials-related energy. It is apparent that manufacturers could proactively take some prevention measures from incurring any wastes and accidental damage related energy loss during and prior to manufacturing. For instance, inappropriate equipment calibration and scale up prior to large scale batch manufacturing could have a significant impact on the final quality of products and related wastes incurred and direct energy loss due to the variation of relevant manufacturing parameters such as throughput time, stability, purity and uniformity. Manufacturers could use PAT (Process Analytical Technology) to continuously monitor the process parameters to prevent accidental damage related energy loss of a batch (Slater et al., 2010). Similarly, there could be other green practices and programs which are still not known. So, manufacturers could adopt some tactical, operational and/or strategic practices to prevent these kinds of unexpected wastes related energy loss induced from the process. So, the scope of related digital technologies, such as usage of PAT in different pharma manufacturing environments, especially during continuous manufacturing phase, will need to be investigated.

As seen in Table 2.23, *collaboration for materials efficiency* is another important approach to dematerialize the pharma manufacturing process. For instance, it is possible that upstream medicinal chemists and process chemists may collaborate with downstream chemical engineers, waste disposal companies or waste contractors for effective usage of solvents, reagents, APIs etc, through sharing related knowledge and information (Parez-Vega et al., 2013). *However, the detailed scope and nature of this collaboration for green manufacturing practice is still not clear. It would also be interesting to see the scope and extent of this green collaboration across different pharma stakeholders – innovative pharma, generic pharma, and bio pharma.*

Energy Reduction

As seen in Table 2.23, two key approaches, energy efficiency equipment system installation and energy management program, are identified to improve energy efficiency during manufacturing. *Several energy efficient equipment systems, such as HVAC system, ventilation recovery system, LED lighting, insulation technology and renewable sources of energy for fuelling the process, could have been used in pharma operations.* However, the understanding of these energy efficient equipment systems installation in API facilities or formulation facilities or within key pharma stakeholders (innovative, generic and bio pharma) is not clear. For instance, it is not known what kind of energy efficiency equipment systems are currently being used across the stakeholders and the extent and scope of installing of the different types of energy efficiency systems to improve process or site based energy efficiency. There is no such detailed empirical evidence for pharma to learn from those process based/site based energy efficiency systems and the related environmental and economic benefits.

Considering different energy management programs such as energy monitoring programs and energy related lean operations are applied to save energy in day-to-day pharma manufacturing operations. This is because pharma manufacturing process parameters (throughput, temperature, pressure, key quality deviation facts during tablet manufacturing etc) are well understood as time passes from the initiation of the new process and they can be controlled accordingly. For instance, it is possible that pharma manufacturers could take appropriate action to reduce product wastes related energy through identifying the root causes of quality failure or quality variations in the process. It may also be possible that the operations could employ energy savings programs such as detection of leakages across the

process equipment systems to reduce consumption of overall process energy. *However, the existing literature does not hold sufficient information on related energy management programs (e.g., lean energy approaches or energy kaizen) undertaken by either innovators or generic or bio pharma to learn from.*

Toxicity Reduction

As seen in Table 2.23, three key green approaches were determined, such as effective chemical management, product stewardship and responsible waste (hazardous) management. These concepts for pharma are comparatively new compared to other industries. Though Clark et al (2010) have indicated the importance of considering the impact of drugs on the environment even after use and disposal, the concept of drug stewardship or extended producer responsibility for pharma is not well known in the literature. To detoxify the operations, it is also important to understand the extent of green programs such as the green chemistry principle and related awareness among the employees to make the right decisions while using raw materials and other resources in the manufacturing process. *There could be some other related green practices to detoxify the process, such as sustainable chemical management and site specific guidance for environmental risk assessment for a particular chemical applied, which still need to be explored*. Therefore, an investigation is required to understand how a greener chemical application and management process works in the pharma manufacturing environment.

A responsible waste (hazardous) management process is also crucial for pharma manufacturers. Pharma companies need to deal with an abundance of predicted and unpredicted/unavoidable process waste after it is being produced. Like other non-discrete industries, pharma companies could also maintain their process wastes responsibly. The pharma production process is known as a most polluted production process among other discrete industries through producing more than 25 to 100 kg of wastes per kg of products produced (Sheldon, 2010). Hence, it is crucial to have a well-managed process in place to avoid environmental degradation, as well as avoiding related penalty costs due to non-adherence to waste regulations. *However, there is no study that demonstrates what is meant by responsible waste management for pharma manufacturing stakeholders (innovators/generic/bio pharma), and how and to what extent the pharma stakeholders deal with their process wastes responsibly. Additionally, it is not known how pharma*

manufacturers coordinate with other internal and external stakeholders to deal with the issues of PIE and AMR while managing process wastes. Therefore, it is important to investigate the key indicators of Responsible Pharma Waste Management which could be used as a model for other developing and under developing countries' pharma companies.

Continuous monitoring and control of environmental toxicity of existing and new drugs substances are crucial for pharma manufacturers due to the ongoing issues of PIE and AMR. The concept of producer extended responsibility or product stewardship (sometimes called green product management, but known in pharma as 'eco-pharmacovigilance') is attributed as one of the core concepts under green manufacturing practice (Rusinko, 2007). *However, this concept is not well explored, especially in the case of pharmaceuticals product management*. The product stewardship concept has been sought as more strategic than pollution control and pollution prevention. Product stewardship extends the boundary of a green approach from internal stakeholders to external suppliers and other stakeholders. *But little is known about how key stakeholders (or innovators, generic and bio) play a role in eco-pharmacovigilance programs, for instance, whether and how they monitor and control the toxicity levels of their products. It is also not clear how innovators, generic or bio pharma actually monitor the environmental loading of APIs (or related chemicals by products) to deal with PIE and AMR issues.*

Managing pharmaceutical products from production to final use and disposal is becoming crucial for not only product safety, efficacy, and quality but also for protecting the environment. This is because the issue of PIE is an ongoing alarm for pharma manufacturers. The evidence of pharmaceutical products in the environment is obvious around the world; and its impact on the aquatic environment (Bound and Voulvoulis, 2005; Sumpter, 2010) as well as predicted impact on humans (Kummerer, 2001; Mudgal et al., 2013) are also evident. The issue of AMR (Antimicrobial Resistance) due to the continuous emission of the APIs of antibiotics into the environment also raises global health concerns (AstraZeneca, 2017). In addition to inappropriate prescribing, dispensing, and use, the emissions from manufacturing plants are attributed to the deposition of antibiotics in the environment that causes ineffectiveness and reduce efficacy in dealing with bacterial infectious diseases in humans; it also resists natural bacteria growth in the environment and water leading to a lifeless atmosphere for the aquatic family.

For instance, in the Indian context the concentration of ciprofloxacin (a broad spectrum antibiotic) was found to be as high as 31mg/L, which is one million times greater than the levels that are regularly found in treated municipal sewage effluents (Larsson, 2014). Similarly, a Chinese plant reported 51ng/L, which is also considerably greater that the concentrations found in sewage effluents and clearly high enough to disturb reproduction in aquatic vertebrates. Therefore, taking product responsibility for the pharma manufacturers, especially for the R&D based pharma, has been extended from pharmacovigilance to eco pharmacovigilance (Taylor, 2010). So, managing drugs from production to final disposal has become a serious concern for pharma manufacturers.

Under product stewardship or green product management practice, LCA is a well-known tool to identify and deal with environmental impacts throughout the life cycle of a product. Though there are to date a few attempts to analyse LCA (Raju et al., 2016; Soete et al., 2017; Chaturvedi et al., 2017), they do not capture the viability, capacity and entire scope of conducting LCA across the pharma industry to deal with environmental issues. Rather, they limit the scope of the environmental impact to only either formulation or API production or packaging (rare). This is only because of the lack of related life cycle inventory data. However, there could be some other important product stewardship programs, such as environmental risk assessment and continuous monitoring of the fate of pharmaceutical products after post marketing, which is also termed as eco pharmacovigilance. *Unfortunately, none of these aspects or related other programs are amplified in the existing literature. Therefore, there is an urgent need for a new investigation to identify the core indicators of drug stewardship or green drug management to deal with water toxicity and the related global issues of PIE and AMR.*

It is not clear in the literature that how pharmaceutical companies in general will adopt MET principles as a new management practice during API production or the formulation phase. For instance, it is not clear whether there will be any standard workup procedure to be followed by the synthetic chemist for material reduction practice or energy reduction practice or toxicity reduction practice etc. It is also not known how MET can be considered in the API production and formulation for existing products (~3000 API) in the market. As a result, a simplified MET management approach is required to benefit the entire industry. So, next, it is necessary to understand how efficiently each of the green manufacturing practices in the MET model can be incorporated into the tactical, operational, and strategic levels of management in the industry. Prior to doing this, it is mandatory to develop a set of indictors

for this new model of MET for the pharmaceutical sector to deal with the environmental impacts of its operations. Being an extensive user of a diversified range of chemicals and their derivatives, the pharma sector could benefit from implementing this new model of MET by reducing cost and increasing efficiency. There is also significant managerial interest in attaining environmental sustainability in the pharma sector due to the unprecedented environmental impact of drug chemicals. Additionally, a MET led green model in any sector could improve environmental performance of any wasteful manufacturing process, though related elemental level practice could be slightly different based on the product/process. So, this MET led green manufacturing will also add new dimension in the existing GSCM literature.

In a nut shell, while there are a few studies demonstrating overall sustainability issues in pharma, there is a lack of detailed knowledge of the elemental level green practices such as materials, energy and toxicity reduction related green practices across different types of manufacturers (e.g., innovator, generic, bio pharma). It is also not known how effective and efficient those elemental green practices are. Furthermore, it is not clear which green practices are predominant in the pharma sector and to what extent. Though there are some green inventions in other sectors, because of having unique product & process requirements with stringent regulatory requirements, the pharma sector would require thorough investigation to establish whether those similar green principles could be applicable to pharma or if it requires a different focus in the green chemistry principle.In particular, the differences in the green practices in Primary manufacturing (API synthesis) and Secondary manufacturing (Formulation) are not known. Therefore, the relevant ambiguities need to urgently be discovered. Therefore, the second green practices related sub research question:

RQ1.2 what green manufacturing practices are implemented by individual pharma sector stakeholders and what is the extent of their implementation?

2.5.1.3 Current understanding on green procurement

The role of procurement in the pharmaceutical industry is undoubtedly attracting significant attention from stakeholders due to its direct impact on a company's bottom line. It is reported that procurement represents more than fifty percent of total costs in the pharmaceutical industry (Polterauer, 2012). As quality, cost and efficacy have been the main norms in the pharmaceutical industry, the environmental impact of pharmaceutical procurements has been overlooked. Energy related emission and waste generation are the two main concerns due to

unsystematic, inefficient, low quality procurements of materials and/or raw materials in the industry. The disposal costs of generated wastes are increasing (Slater et al., 2010).

Extensive pharmaceutical procurements are also contributing to adverse climate change due to increased levels of CO2 emissions. For instance, the procurement operations of the NHS in the UK were reported to be one of the biggest sources of CO2 emissions (60% of all other sources) in 2004 (Clark et al., 2010). The report further interpreted that pharmaceutical procurement contributed approximately the same carbon footprint as the entire NHS energy requirements for heating, hot water, electricity consumption, and cooling, and more than all travel undertaken on behalf of the NHS. Inefficient and inappropriate decision-making on some core procurement activities, such as preparing raw materials specification, standardization of items/categories, negotiation and agreement, outsourcing decisions and making vs buying decisions, could lead to environmental degradation such as GHG emissions and relevant waste generation. This environmental degradation is much more serious because of the recent tendency of outsourcing in the industry to focus on cost effectiveness and operational flexibility (Rees, 2011; Zhang, 2011).

While attempting to explore the existing knowledge on different green approaches in pharmaceutical procurement, the evidence is almost non-existent. Only two studies (Ombaka, 2009; Chris I et al., 2010) have been identified which provide a narrowed focus on operational aspects of procurement practices. Additionally, the studies do not reflect the entire industry procurement system, as they are limited to retailers (e.g., hospital purchasing) and generic manufacturers. Though there are some theoretical understandings about the operational perspective of pharmaceutical procurement (WHO, 2000; WHO, 2002; Catalano, 2005; Ombaka, 2009; Rees, 2011; Zhang, 2011), none of them are empirical and they do not highlight the environmental perspectives of procurements. Hence, a systematic road map is required to investigate the green procurement practices in the pharmaceutical industry.

However, the concept of green purchasing, on the other hand, has become a well-established phenomenon in other industries such as automotive, electrical and chemical (Zhu and Sarkis, 2007; Zhu et al., 2007a; Toke et al., 2010; Eltayeb et al., 2011) to improve their environmental as well as economic performance. The concept of green purchasing borrowed from other related manufacturing industries (such as chemical) could be a road map for investigating the green purchasing practices in the pharmaceutical industry. For instance, the concept of green specification practice has been outlined in many green purchasing studies in

related industries (Zhu & Sarkis, 2007; Toke et al. 2010; Ho et al. 2010; Eltayeb et al. 2011). Pharmaceutical stakeholders could consider environmental criteria (recycled/reuse item, LCA assessment of API etc) as product content requirements under this practice.

Similarly, they could highlight product content restrictions (e.g., exclusion of halogenated molecules during synthesis, not to use lead, or CFC in the tertiary packaging in formulation plants) as part of green specification (Eltayeb et al., 2011). They could also incorporate green labelling under green specification practice. However, due to the lack of relevant empirical studies in the field, it is still unknown what environmental credentials are being considered in their specification list. The pharmaceutical industry could also be interested in developing green suppliers by cooperation with its suppliers, mutual investment in green technology (e.g., investing on green chemistry), and rewarding suppliers.

Though the concept of green supplier development has been highlighted in other related industries (Zhu & Sarkis, 2007; Zhu et al. 2007a; Laosirihongthong et al., 2013; Blome et al. 2014; Weele and Tubergen, 2017), this concept is yet to be discovered in the pharmaceutical industry. Pharmaceutical companies could also benefit from implementing environmental monitoring and evaluation practices with their suppliers. Environmental monitoring and evaluation have become another well-established green practice in the chemical and allied industries (Zhu and Sarkis, 2007; Toke et al., 2010; Eltayeb et al., 2011). However, it is still a matter of investigation to establish whether and/or how pharmaceutical stakeholders evaluate their supplier's environmental performance. There is also huge scope for improving internal operational efficiency in relation to pharmaceutical procurement (e.g., simplification of purchasing lists, making vs buying decisions etc), which leads to reduced wastes and emissions. Though Ombaka (2009) has provided a set of operational practices, an investigation is still required to establish whether these operational efficiencies are worthy in terms of both environmental and economic improvement. Additionally, these operational aspects would need to be extended to other stakeholders in the supply chain as well.

However, understanding of those related green purchasing practices through a separate investigation is not as important as design and manufacturing. This is due to the fact that though the pharmaceutical supply chain behaves in considerably different ways compared to other discrete industry supply chains, its purchasing functions across the chain could fundamentally follow the similar green purchasing principles applied (e.g., green supplier management, supplier environmental audit and green product specifications) in other

industries. A wide range of related studies have already been published, and interested readers can always refer to the studies of *Zhu & Sarkis, (2007); Zhu et al. (2007); Toke et al. (2010); Eltayeb et al. (2011); Ho et al. (2010); Blome et al. (2014); Laosirihongthong et al., 2013; Weele and Tubergen, (2017).* Therefore, this supply chain stage is excluded from this study.

2.5.1.4 Current understanding on green distribution

Pharmaceutical distribution operations (transportation, warehousing, and retailing) have a significant negative impact on the natural environment ranging from global level atmospheric emissions to local ecosystem disruptions. Realizing such environmental impact, while searching the relevant contributions to date, little or no focus can be found on greening the pharmaceutical distribution process. For instance, only three grey literature studies have so far mentioned Cold chain management (Castiaux, 2010), Co-loading (Evans, 2009) and cold chain packaging (Catizone, n.d.). These literature review based studies do not cover all aspects of distribution, such as mode of transportation, warehousing and the retailing process.

Fortunately, some other literature and books in related sectors (or without focusing on any particular sector) have provided a grounding for understanding green logistics, such as modal choice based on energy and emission performance (*Cullinane and Edwards, 2010; Woodburn and Whiteing 2010; Leal Jr and D'Agosto, 2011; Dekker et al. 2011)*, intermodal transport (Dekker et al. 2011; Janic, 2011), selecting alternative fuels (*McKinnon et al. 2010; Cullinane and Edward, 2010),* vehicle utilization (*McKinnon and Edwards, 2010; Tata Strategic Management Group, 2014),* eco-driving (Eglese and Black, 2010; McKinnon, 2010b) and vehicle maintenance (McKinnon, 2010b), under the Green Transportation concept.

Whilst pharmaceutical transportation (either traditional or cold chain transportation) related decisions are complex and multifaceted due to maintaining GMP and GDP regulations, some of the operational aspects such as modal choice, intermodal transport, alternative fuel, packaging design, vehicle utilization and eco-driving have been stressed as improving the environmental foot print (Kam, et al. 2006; McKinnon, 2010a; Woodburn and Whiteing, 2010; Ubeda et al. 2010; Dekker et al. 2011; Leal Jr and D'Agosto, 2011). Green transportation could be achieved through focusing on these operational areas.

In pharmaceutical warehouses, energy efficiency can be achieved through efficient temperature control, efficient lighting, and efficient use of handling equipment. Maintaining an optimum level of temperature in the pharmaceutical warehouse is highly critical for product integrity as well as energy efficiency. Marchant (2010) and Tata Strategic Management Group (2014) have suggested that efficient temperature control in different locations such as in the storage area, loading bays, picking area and despatch area would save significant amounts of energy. They have also suggested some tactical operations such as using controllable thermostats (zoned / time-controlled thermostat) and HVLS (High Volume Low Speed) fans to regulate warehouse temperature. The types of data loggers (manual data downloading / GPS enabled real time monitoring) and temperature monitoring devices that are being used for continuous monitoring are also important. For instance, YaoPharma has replaced the manual data logger with an internet based real time monitoring system for quick, accurate and better operational efficiency (Vaisala, 2013). This approach could help reduce wastes and the related disposal costs. However, it is not clear what strategies or tactical operations are being taken by the pharmaceutical warehouses for controlling temperature.

Each of these green concepts has raised many questions for the researcher prior to adopting them in pharmaceutical distribution. For instance, it is not known what environmental criteria are being incorporated by the pharmaceutical 3PLs providers prior to choosing a particular vehicle (vans/truck). It is also not known whether intermodal transportation system could be adopted by the pharmaceutical 3PLs providers due to handling complex configured products such as time and temperature sensitive products. It is also not known whether the co-loading is a viable option for them. It is still confusing whether the active or passive packaging materials could be used for achieving green credentials. It is also not known how they ensure temperature control in the case of cold chain management. It is also not clear whether the pharmaceutical distributors use plastic pallets over wooden ones due to the ongoing issues of product contaminations. It is also assumed that there could be some other important practices, drivers and barriers which are missing.

However, understanding these green related scopes through conducting a separate study are not as important as drug design, manufacturing, and disposal. This is because there is a considerable amount of literature that demonstrates green transportation systems which can be applied to both conventional and cold chain transportation in the pharma sector, assuming no to minimal differences between the greening efforts of pharma and other sectors, such as perishable goods. Interested readers can always refer to green logistics (*Cullinane and*

Edwards, 2010; Woodburn and Whiteing 2010; Leal Jr and D'Agosto, 2011; Dekker et al. 2011), intermodal transport (Dekker et al. 2011; Janic, 2011), selecting alternative fuels (*McKinnon et al. 2010; Cullinane and Edward, 2010),* vehicle utilization (*McKinnon and Edwards, 2010; Tata Strategic Management Group, 2014),* eco-driving (Eglese and Black, 2010; McKinnon, 2010b), vehicle maintenance (McKinnon, 2010b). Similarly, the key green concepts for energy reduction in warehouse and retailing phase in other temperature controlled perishable products (e.g., food, vegetables etc) sector can be applied in the pharma sector assuming no to minimal variation (Woodburn and Whiteing, 2010).

2.5.1.5 Current understanding on green drug use-and-disposal

The concept of green drug use-and-disposal is to consider the environmental impact of drug usages and disposal activities to avoid air, water, and land contamination of drug residues (Vollmer, 2010; Clark et al., 2010). For instance, safe disposal practices and effective usages of drugs could significantly reduce these environmental burdens (Kummerer, 2009; Vollmer, 2010).Whilst the production of green API and bio based drugs have started but are not yet common, the priority remains to ensure reducing drug wastes and safe disposal methods for expired and unused pharmaceuticals (Vollmer, 2010; Gotz and Deffner, 2010). Table 2.24 summarises green drug use-and-disposal related studies.

Table 2.24 Review of green drug use-and-disposal related literature on the pharmaceutical sector

Study	Country	Methodology	Key focus	Stakeholders involved	Key green drug use-and-disposal practices considered						Key Findings / Related sub-Green practices
					Consider lean operations for optimized prescribing, dispensing and usages	Consider digital technologies for optimized prescribing, dispensing and usages	Consider lean operations for energy efficiency	Energy recovery from drug incineration process	Safe and responsible disposal management of unused and expired drugs	Consider greener wastewater treatment options	
					Material		**Energy**		**Toxicity**		
Latif et al., 2013	UK	Observations	Patinet medication review	Pharmacy	√						Practice: MUR; Performance: Realization of perceived benefits (e.g., patients adherence, drug management, understand the doses, side effect etc) of MUR is little.
McDonald et al., 2010	UK	Observations	Patinet medication review	Pharmacy	√						challenges for pharmacists to deal with MUR services. For instance: increased professional responsibility, pressure on checking prescription and managing delivery etc.
Mackridge & Marriott, 2007	UK	Survey	Drug reuse / recycling	Pharmacy / Hospital	√						Practices: reusing unused drugs collected via pharmacies;
Ruhoy & Daughton, 2008	.....	Literature Review	Drug reuse / recycling	None	√						Practice: Pollution prevention practice: Unit dosing; Trial package; Patient monitoring; Practice of concordance; Drug recycling (donation);

Table 2.24 Review of green drug use-and-disposal related literature on the pharmaceutical sector (Con't)

Study	Country	Methodology	Key focus	Stakeholders involved	Key green drug use-and-disposal practices considered						Key Findings / Related sub-Green practices
					Consider lean operations for optimized prescribing, dispensing and usages	Consider digital technologies for optimized prescribing, dispensing and usages	Consider lean operations for energy efficiency	Energy recovery from drug incineration process	Safe and responsible disposal management of unused and expired drugs	Consider greener wastewater treatment options	
					Material		**Energy**		**Toxicity**		
Gotz and Deffner, 2010	Germany	Survey	Alternative therapy to reduce drug use	None	√						Practices: Behaviour-modification strategy composed of: a) environmental classification of drugs, b) awareness program for doctor and pharmacists, c) alternative therapy, and d) safe disposal practice
Daughton, 2014	.....	Literature Review	Green prescribing	GP/Doctors	√						Practices: Eco-directed sustainable prescribing: dose reduction (where possible); and select drug based on excretion profiles of an API;
Castensson and Ekedahl, 2010	-------	Literature review	Sustainable drug use	None	√				√		Practices: Trial package, Sustainable drug use; Consistent guidance is still not available for safe disposal; Sewerage and garbage is still common practice;
Mudgal et al., 2013	Europe	Literature review	Safe disposal of unwanted drugs	Wastewater, policy maker					√	√	Over consumption of drugs; Lack of env. Data; weak legislation; over prescribing; high cost of new technology; over consumption of drugs; lack of publicly available toxicity data;
Glassmeyer, et al., 2009	USA	Literature review	Safe disposal of unwanted drugs	None					√		Practices: Disposal awareness program; Drug recycling, Collection program (mail back, return to pharmacy); 'Consumer awareness program'

Table 2.24 Review of green drug use-and-disposal related literature on the pharmaceutical sector (Con't)

Study	Country	Methodology	Key focus	Stakeholders involved	Key green drug use-and-disposal practices considered						Key Findings / Related sub-Green practices
					Consider lean operations for optimized prescribing, dispensing and usages	Consider digital technologies for optimized prescribing, dispensing and usages	Consider lean operations for energy efficiency	Energy recovery from drug incineration process	Safe and responsible disposal management of unused and expired drugs	Consider greener wastewater treatment options	
					Material		**Energy**		**Toxicity**		
Vollmer, 2010	Europe	Survey	Safe disposal of unwanted drugs	Pharmacy					√		Practices: Disposal awareness program; Take-back scheme; Return schemes via pharmacies; Take-back legislation (coercive force); Weak Legislation
Breen & Xie, 2010	UK	Literature Review	Safe disposal of unwanted drugs	Pharmacy	√				√		Practices: Reverse logistics, MUR, consumer awareness program, drug take-back; manage inventory with supplier; select suppler with high environmental compliance; repeat prescription; patient reminder for medication return; classification, storage, segregation, destruction, disposal; use recyclable package;
Kotchen et al., 2009	USA: Southern California	Survey	Safe disposal of unwanted drugs	None					√		Practices: take-back location, collection events, awareness program; Increase awareness of PIE, people are willing to pay a surcharge for disposal program;Performance: There is positive financial benefit of establishing drug disposal program (e.g., take-back location, collection events, awareness program).
Schiff et al., 2011	--------	Review article	Safe disposal of unwanted drugs	Noe					√		Practice: Alternative therapy; rely on underlying cause not just treat symptoms; increase knowledge by applying few limited drugs; avoid frequent switching without clear evidence; learn new drugs from unbiased sources; avoid prescribing (where possible) newly marketed drug; consider hypertension patients' non adherence

Table 2.24 Review of green drug use-and-disposal related literature on the pharmaceutical sector (Con't)

Study	Country	Methodology	Key focus	Stakeholders involved	Key green drug use-and-disposal practices considered						Key Findings / Related sub-Green practices
					Consider lean operations for optimized prescribing, dispensing and usages	Consider digital technologies for optimized prescribing, dispensing and usages	Consider lean operations for energy efficiency	Energy recovery from drug incineration process	Safe and responsible disposal management of unused and expired drugs	Consider greener wastewater treatment options	
					Material		**Energy**		**Toxicity**		
Doughton and Ruhoy, 2013	.....	Literature Review	Green prescribing	GP/Doctors					√		Practices: Lower dose prescribing (whenever possible); consider excretion profile of a drug, consider lowest effective dose; select dose when consider - route of administration, pharmacokinetic profile, organoleptic (taste and odor) properties, quantity dispensed, polypharmacy, health status, age, gender etc)
Latif et al., 2011	UK	Observations	Patinet medication review	Pharmacy	√						Practice: Medicines User Review (MUR) Service; Performance: Improved patient adherence leading to personal drug management may reduce unused drug wastes
Thach et al 2013	Texas	Survey	Safe disposal of unwanted drugs	None					√		Driver (expected): Customer pressure (for drug take-back program); Both users and non-users support the program; Customers highly appreciate this program even if it incurs extra costs for services.
Peterson and Anderson, 2002	Canada	Survey	Trial package of drugs	None					√		Practice: trial package prescription; Driver (expected): Customer pressure (for drug take-back program) ; Performance: Trial prescriptions were acceptable to patients and, if focused on specific medications, could reduce the direct cost of drug wastage

As seen in Table 2.24, it is clear that drug use-and-disposal related green practices are predominantly researched within developed countries (e.g., UK, USA, Canada, Europe) and there is a lack of studies in under developing countries. Geographical context plays a key role in determining related green practices, as drug demand, marketing, prescribing, and dispensing related regulations are different across the globe. Countries with loose regulation to drug use and disposal are prone to the issue of PIE and AMR. Surveys, observation, and literature reviews are the key methodologies used. While reviewing the key focus of the studies, it is evident that safe disposal of unused/expired/unwanted drugs has been paid the most attention. *Few studies have highlighted optimizing the drug prescribing and dispensing process to reduce drug wastes. Under stakeholder focus, pharmacies are considered as key dispensers while the role of other pharmacies in hospitals / care homes in dealing with drug waste reduction is missing. Additionally, some other key downstream stakeholders, such as Doctors/GPs, local councils /clinical waste collectors/waste management companies and waste treatment companies, are rarely considered. Hence, their key role in optimized drug prescribing and dispensing process is not clear*.

Under materials related green practices, it is clearly seen in Table 2.24 that prescribing and dispensing optimization (through related lean practice) have been paid more attention than any other practice. Though there is huge scope for adopting digital technologies (Breen et al. 2010) in optimizing prescribing and dispensing process, *there is no study that has focused on understanding how digital technologies have optimized the prescribing and dispensing process to reduce unnecessary drug wastes in the consumer zone*. *Similarly, energy related green practices during the drug use-and-disposal phase are not known*. *Though a few studies have focused on identifying relevant practices (for drug waste reduction and/or safe disposal options) they are theoretic rather than empirical in nature.* Few researchers have recently started to outline a wide range of actions for responsible drug disposal, and some eco-friendly practices to reduce drug waste reduction (Vollmer, 2010; Castensson and Ekedahl, 2010; Gotz and Deffner, 2010) as part of the goal of creating sustainable pharmacy (Clark et al., 2010).

For instance, some fragmented lean activities to reduce drug wastes such as raising awareness of issues through drug collection programs (Kotchen et al., 2009; Gotz and Deffner, 2010), rationale prescribing (KNAPPE, 2008; Start, 2008), drug take back schemes (Vollmer, 2010; Castensson and Ekedahl, 2010) and medicine Use Reviews (Latif et al., 2011) have been suggested. Under responsible drug disposal practices, drug recycling (Pomerantz, 2004),

landfill/incineration, and advanced technology have been suggested. *However, the current level of understanding on each of these practices is still inadequate due to the lack of relevant empirical investigations (Vollmer, 2010; Gotz and Deffner, 2010). For instance, the level of implementation of this practice is still unknown. The perceived benefits and effectiveness of these practices are not completely clear. Moreover, there could be some other environmentally friendly practices/concepts involved in drug use-and-disposal operations which are yet to be discovered. Although the concept of green use-and-disposal practice has been somewhat covered in the GSCM literature (Beamon, 1999; Srivastava, 2007), the scope of understanding of green use-and-disposal practice in the chemical and pharmaceutical industries is still narrow (Beamon, 1999; Srivastava, 2007; Azevedo, 2011). More specifically, in the UK pharmaceutical sector, it is new.*

Additionally, the majority of survey-based studies are focused on identifying consumers' disposal behaviour rather than focusing on eco-friendly use-and-disposal practices. Also, the environmental input from individual stakeholder for reducing the negative impact of drugs use-and-disposal is missing. *Although existing studies have indicated two streams of practices – drug waste reduction related (including reduced human excretion) and responsible disposal related - they still lack complete understanding and require separate empirical investigation for clarification.*

From the green or environmental perspective, the existing review of literature could also be reviewed from the lens of MET. The subsequent section discusses each of them to present current knowledge and justify relevant research gaps.

Material Reduction

As use-and-disposal does not involve any production, so the 'material' refers here to 'the finished drug products' (e.g., tablets, capsules, etc) rather than the 'raw materials required producing the drug'. Therefore, the concept of materials reduction in this section is translated as 'effective and efficient usages of finished products (drugs)' to reduce unnecessary product (drugs) wastes.

Considering lean operations for optimized drug dispensing and usages could be one of the key green aspects for material reduction or drug waste reduction in the use-and-disposal phase of drugs products. The individual stakeholders such as pharmacists, GPs, care homes and hospitals (wards) could play a crucial role for optimized drug dispensing and usages.

Effective and efficient drug dispensing is one of the crucial functions in the downstream drug supply chain. Inefficient dispensing activities could induce drug wastes as well as inappropriate drug disposal among consumers, which also incur related costs. Therefore, related lean activities are essential during dispensing. For instance, pharmacists could play a crucial role to reduce unexpected drug wastes by evaluating patients' medication usage habits (where applicable). MURs are such a special service provided by the pharmacies where the pharmacist consults with patients to discuss whether they use the medicine as prescribed, whether they know the medicine's purpose, whether they are faced with any adverse/side effect (Latif et al., 2011). Although the scope of MURs is significant in terms of reducing the unwanted medicines wastes, some operational inefficiency has been reported while conducting interviews among the UK community pharmacists (McDonald et al., 2010).

For instance, it has been reported that when pharmacists are conducting MURs, opportunities for other activities such as patient counselling as the last stage in the dispensing process are reduced (McDonald et al, 2010). Whilst pharmacists are normally overcrowded and highly committed to the dispensing process, there seems to be poor integration of the MURs service into their routine workload (Latif et al., 2011). The author is also concerned about the format of the MUR form used to collect information from patients. However, *it is not clear from the pharmacists what types of questionnaire (open ended or close ended or mixed) could be more effective*. On the other hand, GPs think that pharmacists do not conduct MURs properly (Personal communication with an NHS Consultant). Therefore, *it is important to understand more about the effectiveness of this service from both pharmacists' and doctors' perspectives. Although GPs consider this service as highly effective in improving drug non-adherence and reducing related unwanted drug wastes, perceived benefits of MURs are still unknown. It is also not clear whether the MURs service reduces drug wastes. So, further investigation is needed to justify the rationale of the MURs service for reducing drug wastes. Additionally, there could be some similar pharmacy services such as NMS (New Medicine Services) which have not yet been explored in terms of reducing drug wastes. Additionally, there could be some other lean activities taken by pharmacists (e.g., reducing dispensing errors, stock management etc) which still need to be explored.*

Reuse and recycling of unused drugs could be another lean approach. Although researchers have investigated the scopes of recycling of drugs i.e. re-distribution of unused/unexpired drugs and testing and confirmation for re-use (Mackridge & Marriott, 2007; Ruhoy and Daughton, 2008), *it is still not known whether such practices exist in the UK context. If so,*

what are the operational procedures to carry them out and the related barriers? Therefore, these options still lack clarity in terms of operational procedure and practical acceptability. Hence a further investigation is required to see the viability and acceptability of drug recycling practice. However, there could be some other green approaches taken by pharmacies which are still not known.

Rationale prescribing practice by GPs for optimized drug usage could be another important lean approach for reducing materials or drug wastes, for instance, considering alternative therapies or drug substitution where necessary. However, it has been suggested that the amount of medications prescribed could be reduced via the choice of active substance (e.g., drug substitution) or alternative therapies (exercise, physical therapy, diet, etc), reducing dispensed drug quantities (especially amounts suitable for short-term trials/ trial packages)and reducing unnecessary repeat prescriptions (Gotz and Deffner , 2010; Daughton, 2014). *As the efficacy and safety of patients is the top priority, an investigation is needed to find out whether and how these practices are currently being considered or whether they could be considered in the future.*

The concept of trial package (or trial prescription) by GPs could be another important lean practice for reducing drug wastes (Ruhoy & Daughton, 2008; Castensson and Ekedahl, 2010). The idea of a trial package (or trial prescription) is to prescribe a limited number of drugs for a short period for long-term treatments such as depression. It is suggested that trial prescriptions and increased monitoring of patients not only reduce drug wastes (or unwanted drugs) but also improve health outcomes and physician-patient relationships (Ruhoy and Daughton, 2008). This concept is already being used both in Sweden and Canada, and is highly recommended (Castensson and Ekedahl, 2010). It is reported that the value of the wastage avoided was roughly Can$ 5.50 per trial initiated (Paterson and Anderson, 2002). As the changes of medication by doctors has been evidenced as one of the dominant reasons for accumulating unwanted medicines (Braybrook et al, 1999; Abahussain et al., 2006), so trial packages could be one of the solutions to tackle this problem. *However, it is still not known whether this program is being considered in the UK; and to what extent it is being considered and its perceived benefits. The conditions under which trial prescription programs are feasible for pharmacists and drug plans are also not known (Paterson and Anderson, 2002). Apart from GPs, care homes and hospital (wards) could also adopt some lean initiatives, which still need to be investigated.*

Considering digital technologies could be another important approach to reduce materials (or drug) wastes in the use-and-disposal phase. For instance, the applications of electronic prescribing systems could reduce unnecessary repeat prescription dispensing through a common digitised communication platform where prescribers (GPs/doctors) and dispensers (pharmacists) could share similar demand and supply of prescription information for optimised dispensing operations. *However, the related digital technologies and their impact on drug waste reduction is still a matter of further investigation. It is not known what kinds of digital technologies are currently being used, and how the key downstream stakeholders (GPs, Pharmacists, and patients) are currently considering these technologies and why.*

Energy Reduction

This energy efficiency gaining is only related to how drugs are stored, dispensed, used, and disposed. For instance, pharmacy premises could *apply some energy related lean activities* such as usage of energy efficient cold storage, effective and efficient control of temperature during cold storage, reduction / reuse / recycling of tertiary packaging etc. Temperature deviation could damage drugs (specially, those of TTPPs – Time & Temperature sensitive Pharmaceuticals Products) significantly. *So, it is vital to understand how pharmacies manage TTPPs and what types of temperature control they follow and whether they are energy efficient. There could be some other related lean measures currently being taken which still need to be explored.*

Selection of an energy efficient drug disposal could be another important lean approach. For instance, when it comes to local councils (or local pharmacies) to decide which clinical waste vendor should be selected to dispose unused/expired drugs could be based on their energy efficient disposal process as part of waste contracts. *However, it is still not known whether these stakeholders really consider this lean aspect as part of their contract. Additionally, it is also not known what the clinical waste management companies do in terms of choosing energy efficient disposal options and the related drivers and barriers. Similarly, it is also not known whether and how the wastewater treatment companies consider energy efficiency while treating the receiving wastewater either from the pharma industry and/or households. If it is industry wastewater streams, energy must be a big factor in the treatment*. The energy factor is also becoming a big concern for treating normal household wastewater, as the issue of PIE is escalating day by day. Hence, it is important to further investigate the related energy efficiency measures taken by these stakeholders.

Toxicity Reduction

Safe and responsible disposal management of unused and/or expired drugs could be the key to reduce water contamination of drugs and reduce related AMR concerns. The downstream players – pharmacies, hospitals, care homes, waste management companies (especially clinical waste vendors) and/or local councils play a crucial role in this safe and responsible disposal management. For instance, pharmacies ensure effective and efficient collection of unused/expired drugs from patients for safe disposal through the pharmacy take back program.

Though the United Kingdom has defined a legal obligation of pharmacies to participate in a take-back program, the return pattern and related economic and environmental benefits still need to be investigated. Although there is an increased pattern to participate in the take-back program, the literature has also pointed out the lack of proper return or reverse distribution related infrastructure for the take-back scheme (KNAPPE, 2008). *However, it is not known whether and how the other pharmacies in the UK are dealing with related operational inefficiency in relation to drug take back programs. It is also not clear in the literature how the performance of this scheme is measured. It is also reported that the quantitative information on the efficiency of the collection schemes is missing in the current domain of knowledge (Mudgal et al., 2013).*

Increasing public awareness for safe disposal of unused / expired drugs through managing a number of awareness programs could be another approach. This approach explains how downstream stakeholders such as GPs, pharmacists, patients, local councils, local clinical commissioning groups and waste management companies could undertake a combined effort to deal with PIE, drug wastes and inappropriate disposals to avoid unexpected/expected environmental loading of drugs. Increasing patient awareness on safe drug disposal could be a way forward. Although attempts have been sought in increasing awareness among consumers for safe disposal (Glassmeyer et al., 2009; Vollmer, 2010), none of the previous studies have focused on identifying awareness programs for doctors, pharmacists and other individual stakeholders for managing the safe disposal of drugs. *It is not known what specific awareness programs (e.g., training, medical journals etc) are currently being introduced for the safe disposal of drugs; what is the level of adoption of this practice and what is the perceived benefit of implementing it.* Though some high profile companies like AstraZeneca have been continuously increasing the awareness (about the concentration of pharmaceuticals

residue in water) among its downstream players through ongoing scientific research (e.g., environmental risk assessment programs), the roles of R&D companies and manufacturers in increasing awareness among the downstream players (e.g., GPs, pharmacies) is still not completely clear.

Though it has been reported that the awareness/communication campaigns involve substantial costs and resources (Kummerer. 2009; Gotz and Deffener, 2010; Mudgal et al., 2013), *little is known about the types of awareness/education programs and their related performance. The majority of existing studies focus on the importance of having a particular awareness/education program rather than outlining the operations aspects of the programs themsleves.*

However, there could be some other source control measures which are still not known. For instance, as the easiest and cheapest option of disposal, landfill is the prime disposal option in the UK (Butt, et al., 2008; Defra, 2017). So, if general waste contains unused drugs, the negative environmental consequence is obvious due to leaching. *It is also unknown how the waste management companies in the UK decide to go for incineration or landfill. The landfill gas could probably be collected for energy production.* However, further investigation is required to clarify all these assumptions.

Additionally, and more importantly*, the roles of each relevant stakeholder for the management of safe drug disposal, which are still not known, are crucial to investigate*. For instance, it is still not known what kind of eco-friendly disposal options are currently being taken by the clinical waste management companies or what kinds of related decisions are being taken by the local councils to manage drug contaminated household wastes and/or collected clinical wastes from households.

Considering eco-friendly wastewater treatment options could be another key approach to detoxify the water cycle from drug contamination. There could be a variety of sources of incoming wastewater to water treatment companies, such as wastewater from the pharma industry, from hospital / clinics, from care homes, and from household patients. Each of these sources of stakeholders plays a crucial role in deciding and selecting a particular disposal option leading to no to low environmental contamination of drugs. *Unfortunately, the role of each stakeholder on this aspect is still not known. For instance, it is still not known what measures are currently being taken by the wastewater treatment companies in the UK to deal with pharmaceutical contamination. Though it is suggested that there is no single technology*

that fits for removing all pharmaceutical compounds in the wastewater (Kummerer, 2009), it is still not known what specific approach or methods are currently being used by the UK wastewater treatment companies when considering pharmaceutical residues in the wastewater. The existing literature on how the WWT (Waste Water Treatment) companies make their decisions for choosing a particular technology is aimed at removing the concentration of pharmaceutical residues from the wastewater. There could be some other greener options for managing wastewater which are not known.

The discussion till now is a clear reflection of the lack of understanding about green drug design practice. The current level of theoretical understanding will not motivate the relevant stakeholders to create innovative supply chain management practices to tackle the unprecedented environmental burdens profitably. Extensive understanding on all possible green practices undertaken by each downstream stakeholder in the supply chain is mandatory for a paradigm shift of greening the pharmaceutical sector. This stakeholder focus is essential for not only improving the overall greenness but also to enrich the scope of life cycle inventory data for effective and consistent green operation in future. This is because the underdeveloped life cycle inventory in the pharmaceutical sector is attributed as one of the important barriers to greening (Slater et al., 2010). Additionally, and more particularly, no attempt has viewed this problem from a green supply chain perspective to deal with drug use-and-disposal. Therefore, there is an urgent need to formulate an empirical investigation to understand this green phenomenon. This leads us to the green practice related third sub research question:

RQ1.3 what green use-and-disposal practices are implemented by individual pharma sector stakeholders and what is the extent of their implementation?

Once the key green practices being employed are understood, it is also crucial to understand the key motivations behind green practice adoption or why the relevant stakeholders are willing to invest resources on developing green processes and green product management. Hence, the next section presents green drivers in pharma.

2.6 Current understanding of green drivers

Drivers of green practices are the key to identifying the possible scopes of new innovations as well as the emerging demand for green/environmental operations in a particular sector (Zhu and Sarkis, 2004; Zhu et al., 2007). Understanding the key drivers or antecedents of each

green practice adopted by the upstream R&D and manufacturers and the downstream pharmacies, GPs, Hospitals, waste management companies etc, is essential for practitioners and policymakers, as well as researchers for greening the entire pharmaceutical sector by prioritizing each green practice. This understanding will guide stakeholders towards where the focus should be in a supply chain. Understanding the magnitude of each driver for each pharmaceutical stakeholder is also urgent for effective use of resources and justification of green investment.

Whilst it is crucial to identify and understand the extent of each relevant green driver for practitioners, policy makers and researchers for greening the pharma manufacturing process, there is a dearth of research that provides this typical understanding. Though a few pharma related studies, such as Clark et al. (2010) and Sumpter (2010), have indicated a few drivers (e.g., regulations and customer pressure), they are not clear about what and how key regulations or customer pressures drive different pharma stakeholders (especially, generic, bio pharma, and innovators) to go green. As a result, a combination of those indications within general GSCM related drivers are investigated from a pharma perspective. Hence, the subsequent section presents key green drivers for the pharma industry and the related research gaps in the four key areas: regulatory, business benefits: cost savings, top management commitment, and market: stakeholder pressure due to their utmost importance in general and for the pharma industry. A critical account for each case is presented in the subsequent section.

2.6.1 Regulatory

The pharma industry is one of the most regulated sectors across the globe (Geijo, 2000). Each stage in pharma operations from lab-based drug discovery to final market, distribution and disposal through stringent manufacturing process involves stringent scrutinization. Even within similar manufacturing processes, different batches are validated individually for marketing authorization. This is because a slight deviation of product integrity may significantly reduce product effectiveness and efficacy, which can eventually lead to either life or death of a patient. As a result, the regulatory influences in pharma for greening could be significantly different from other sectors like automotive, electrical equipment, computer, textile, or the construction industry. Given such a stringent regulatory environment where safety, efficacy and quality are more important than anything else, it remains a valid question whether and how green innovations are being driven in such a sensitive environment.

Apparently, regulations could be one of the key drivers for pharma to adopt green practices across the pharma supply chain. Although *upstream pharmaceutical operations (R&D and manufacturing)* are assumed as highly regulated by good manufacturing practice (GMP) (Clark et al., 2010), the GMP guide does not seem to drive companies to implement green technology in general. It is assumed that some regulatory *drivers such as ERA (Environmental Risk Assessment)* of new drug substances prior to approving marketing authorization of drugs could drive the innovative pharma companies to consider greener chemical or biological substances as starting materials to design and develop new drugs. It may also drive the manufacturers to adopt greener and responsible wastewater management (e.g., continuous monitoring and control of API discharge from the manufacturing plant) practices across the industry. *However, there is no previous study that demonstrates the scope of this driver on how and to what extent the innovators, generic or bio pharma are currently being motivated to adopt those green related practices into their operations.*

Though it is apparent that high throughput screening (HTS), focused library, artificial intelligence (e.g., 3D manipulation of target proteins), and green chemistry may help medicinal chemists to discover more target-based drug molecules within a short period of time, *it is still a matter of research to understand whether these green activities in the R&D phase are driven by ERA.*

Unfortunately, there is no existing study that has empirically confirmed and has explained the scope and extent of this driver in pharma. This driver could bring rudimental change in the industry from non-green operations to greener operations across the supply chain, as this will have a direct impact on other related dependant suppliers and/or third-party outsourcers/contractors in the chain.

In addition, some other regulatory factors such as F-gas related regulation, REACH regulation, Industrial Emission Directive (IED) and waste legislation could influence pharma companies to adopt green practices and activities which are still subject to exploration. For instance, *while REACH regulation as a green driver is understood in other industries (Sarkis et al., 2011; Zhu et al., 2013), the scope of this green driver in pharma still not known*. This is due to the fact that while *REACH regulation* restricts the registration, authorization and usages of chemicals in the chemicals and related industries, some of the restriction has been lifted for innovative drug manufacturers to facilitate the discovery of new medicines. However, as at the same time pharma operations require many other auxiliary and

intermediate chemicals, the *REACH* could have been a huge implication for pharma – *which is yet to be known*. So, it is vital to explore how and to what extent *REACH* could drive pharma towards green practice adoption. Similarly, F-gas related regulation could have significant implications for pharma, especially for some products such as inhalers products - *which still needs to be clarified.*

For adopting green practices in the downstream use-and-disposal phase, though take-back legislation (Vollmer, 2010) is assumed to be one of the key drivers for safe and responsible use-and-disposal of drugs, whether and how this driver actually drives the downstream pharma stakeholders is still to be explored (e.g., Pharmacies, GPs, Clinics etc) for the eco-friendly management of drugs usages and disposal of unused / expired drugs. Also, the concept of the driver is still highly theoretical and requires empirical evidence to establish the scope and intensity of this regulatory driver.

There could be other regulatory drivers (e.g., CQC regulation) which still need to be investigated to establish if green practices are being driven across the downstream stakeholders (GPs/physicians, pharmacies, clinic etc) due to this driver. Though CQC (Care Quality Commission) regulation (a part of the Health & Social Care Act 2008) aims to monitor, inspect and regulate health and social care services (e.g., drug dispensing, drug use and disposal management) to make sure they meet fundamental standards of quality and safety throughput the process, *it is not known whether, how and to what extent this regulation could drive the downstream stakeholders to adopt green practices such as drug waste reduction.* This is because it is crucial that CQC standards in medicine management are followed in pharmacies, care homes and hospitals.

2.6.2 Business benefits: cost savings

The nature of pharma operations is highly diverse across the sector. While innovators pursue being the first to discover, develop and market innovative drugs through investing huge amounts of money (around one billion dollar for a new drug) (Taylor, 2010) and take outrageous investment risks considering the low rate of product success (less than 10%), generic firms' key motivation is to cut costs and just to adhere to regulation for safety, efficacy and quality. Bio pharma production is still a huge and costly process in comparison to other chemical-based process. Bio pharma is also hunting for cost reduction scopes especially for bio similar drug products to increase market demand. As a result, cost savings from green innovation could be highly attractive for pharma. But the question is how green

innovations could bring their operational costs down. For instance, though cost savings from recovery practice are well understood in other sectors (construction, automotive, textile, electronic etc), *it is still a fertile area in pharma to understand the scope of cost savings from recovery practices such as cost savings from solvent recycling.*

Though it is assumed that adopting green practices in the upstream pharma operations could bring significant cost savings, the related evidence is still very limited and not clear. For instance, it is suggested that the high cost of solvents and their treatment can be a large driving force for pharmaceutical companies to come up with innovative green solutions to reduce solvent use and wastes (Slater et al., 2010). However*, this assumption will require further validation and justification in pharma companies*. This is because *the trade-off between 'installation of recycling / reusing process and equipment in the plants' and 'the return on investment and /or payback period' still is not clear.* Additionally, *it is also not known how this cost saving would actually work across different stakeholders, let say, how and to what extent this would drive the generic manufacturers to go green or similar queries for bio based and innovative pharma companies. Therefore, it is important to clarify what key aspects of costs savings are practical and what key green practices are being driven by each stakeholder.*

In addition, the downstream pharma operations could also financially benefit from adopting green related activities. For instance, though pharmacies can be financially motivated to conduct MURs, as the government pays £28 per MUR completed by a pharmacy, the scope and extent of this financial motivation is still not known. It is assumed that the trade-off between 'MURs and related documentation process' and 'financial gain' in the downstream pharmacies still not known. The continued increasing of healthcare costs across the globe could be another driver for adopting effective and efficient measures to reduce drug wastes. However, there is still the need to establish some empirical evidence on this aspect.

2.6.3 Top management commitment

The influence of top management commitment, as seen in other industries (Zhu et al., 2008; Darnall and Kim, 2012; Li et al., 2015), could be one of the key drivers for adopting green practices in the upstream pharma operations. For instance, though strong internal environmental targets and overall environmental goals (zero waste to landfills; lower limit of API discharge from the manufacturing effluents etc) from the top management could significantly reduce related environmental footprints, the driver is still not known in pharma.

As pharma operations are highly dominated by regulations and confined by the safety, efficacy and quality of drug products, it would be interesting to see how related internal environmental commitment or targets could really influence pharma manufacturers and R&D companies to perform in such a complex pharma environment. It could be some other forms of top management commitments, such as community wellbeing and corporate responsibility, which is sometimes termed as good business sense, or incentives and awards commitment for green adoption, which are yet to be explored in pharma. Though it is assumed that patient safety and wellbeing is the key to managing the drugs usage and disposal process effectively and efficiently (Clark et al., 2010), the scope of this driver in pharma still needs to be investigated for empirical evidence.

2.6.4 Market: stakeholder pressure

The pharma supply chain is formed of complex internal and external stakeholders. Compared to other sectors' supply chains, pharma stakeholders are highly sensitive to maintaining relationships, reliability, and responsiveness (Narayana et al., 2014). This sensitivity to reliability and interrelationships is due to stringent regulation across the supply chain. How pharma stakeholders may react to a particular environmental issue (e.g., PIE) and its impact on the wider community can be one of the key drivers to go green. Hence, it is important to identify those stakeholder pressures to better understand the market for green pharma products. Astoundingly, *there is a dearth of research on understanding such drivers in pharma*. Only Sumpter's (2010) study has mentioned 'customer pressure' as a driver of green drug-design. *But it is not clear how this pressure could drive drug R&D or innovative big pharmaceutical companies to consider green components in the drug design phase. For instance, it is not known which hierarchy of customers in the supply chain are responsible for this driver.*

Obviously, like other products, drug design specification is not dependent on or considered by the downstream players, rather it depends on the human disease target and relevant efficacy and quality. Also, the process of drug discovery is very uncertain, as it is a challenging task to establish a drug from lab to actual patient. So, customer cooperation for design specification, as explained in Xie and Breen (2012), is not consistent with drug design. Therefore, *there is an urgent need to identify those specific stakeholder groups to understand how and why they create pressure for green drugs*.

However, there is a possibility of indirect influence from these downstream customers for green drug design, such as the issue of PIE. *But further investigation is required to see how these downstream customers play a role in considering environmental aspects in the drug design process*. PIE issues are increasingly becoming a burning concern among all levels of customers in the pharmaceutical supply chain.

For instance, major suppliers to the NHS are currently facing pressure for greener API (Clark et al., 2010). Though the current research did not find any significant damage to human health due to PIE, there is increasing concern about drug contaminated drinking water (and its longer term impact both on human and animals) which should not be accepted (Sumpter, 2010). The impact of PIE, on the other hand, is significant and detrimental to the aquatic environment. However, *it is still a matter of research to understand how downstream customer pressure drives green drug design*.

Due to the lack of relevant empirical investigation, it is still not clear whether and how customer pressures drive downstream stakeholders to implement green related disposal practices. It is also not known which stakeholders will be influenced most by this pressure. To understand the adoption mechanism of green use-and-disposal practices, it is also important to investigate the impact of this driver on the level of adoption of green use-and-disposal practice.

It is also possible that companies (both upstream and downstream) could be concerned about their brand image and reputation and hence adopt related management and control measures to reduce API discharge into the environment. For instance, API discharge became a greater concern after drug contaminated water was found in 41 million Americans' drinking water from disposing unused/expired drugs in domestic rubbish or wastewater (Xie and Breen, 2012). However, it is still not known whether and how the reputation and image of the pharma companies are currently related to API discharge management in the pharma industry, whilst the trade-off between company image/reputation, and profitability in general, is well known. Therefore, it is important to identify the scope of this driver (company reputation) in the pharma context.

In summary, the current level of understanding about green drivers is not sufficient to justify the adoption mechanism of a particular green practice in the use and disposal phase of the pharmaceutical supply chain. The current state of knowledge is not enough to understand the emerging demand of overall green drug use and disposal operations in the pharmaceutical

sector. Compared to other discrete industries, final consumers' preference to choose a pharmaceutical product (e.g., drug) is negligible in general. So, it is urgent to explore all relevant drivers so that policymakers and managers can become confident about applying relevant policies and practices accordingly.

This leads to the second research question and sub questions:

RQ2. What are the drivers faced by individual pharma sector stakeholders for adopting green practices and what is their perceived importance?

RQ2.1 what are the drivers faced by upstream pharma sector stakeholders for adopting green design and green manufacturing practices and what is their perceived importance?

RQ2.2 what are the drivers faced by downstream pharma sector stakeholders for adopting green use-and-disposal practices and what is their perceived importance?

Once related green drivers are known, it is important to understand the related barriers as well to increase the capability and capacity of the companies to deal with those barriers for successful implementation of green practices.

2.7 Current understanding of green barriers for pharma sector

To implement green practices in the pharmaceutical sector, it is crucial to identify the green related barriers (Clark et al., 2010). Understanding of the barriers will help individual stakeholders, such as R&D companies, primary manufacturers, formulators, distributors, GPs, pharmacists, NHS regulatory bodies, consumers, waste management companies and wastewater treatment plants, to prepare themselves with the necessary capabilities and resources to successfully deal with each barrier and adopt green practices. Unfortunately, there is a dearth of research on understanding the key green barriers in pharma. Only one study, Kumar (2019), has focused on identifying the key green supply chain risks in the Indian pharma context. It identifies 26 different risks in seven areas: operational, supply, product recovery, financial, government and organizational, and environmental. However, it lacks detailed focus on drug design and development, manufacturing, and use-and-disposal. For instance, under operational risk, the green technology related issue only entails cold chain management rather than extending the understanding of drug design and manufacturing operations. Additionally, it only focuses on quality issues of supplied raw materials but has not focused on actual quality deviation issues during the manufacturing phase. Therefore,

separate work is needed to understand related green barriers in detail for pharma. The subsequent section discusses key barriers in pharma.

2.7.1 Complex marketing authorization of green product/process

Developing a green process requires extra time and costs, while time to market is crucial for the innovator to launch the product quickly and start recovering the huge investments made (Taylor, 2016). Understanding process through gathering process related info (e.g., safety, quality, throughput, stability) over time provides a space to streamline it. So, it is not merely the use of greener substances to start with, rather it takes significant amount of time to understand the process better for quality, safety, and efficacy (Plumb, 2005). Therefore, it is more likely for companies to redesign the existing processes of the drugs which have already been in the market for many years and the manufacturers are in a good position to evaluate process quality variations etc. However, redesigning the existing process is not so straightforward and it requires further quality validation and regulatory approval to market it. The complexity in producing validation documentation is dependent on the level of process change (e.g., changing mode of manufacturing / change of raw materials).

Stringent pharma regulations are maintained in each operational life cycle to ensure product quality, safety, and efficacy. For instance, GMP (Good Manufacturing Practice) scrutinises each stage of the drug manufacturing process and it requires specific validation for each manufacturing process development. This stringent, complex validation and regulatory approval process for getting marketing authorization of those redesigned drug processes is assumed to be one of the key barriers for pharma to considering green operations (Plumb, 2005; Slater et al., 2010). *However, there is no empirical evidence to establish such a barrier. For instance, little is known about what regulatory barriers the pharma manufacturers could face while changing their existing process for solvent recycling or solvent recovery or changing the manufacturing process from batch to continuous or similar operations for environmental benefits. Therefore, it is important to understand this barrier through a new study, particularly to see how the stringent regulations impede the upstream pharma companies from implementing green design and manufacturing practices.*

2.7.2 Lack of clear guidance to the downstream stakeholders for effective drug use-and-disposal

The lack of regulatory guidance on environmental considerations for downstream stakeholders could be the key barrier to implementing related green practices. For instance, whilst PIE and AMR have become unprecedented environmental concerns for pharma, there is still no clear guidance for the key downstream stakeholders (e.g., GPs / Pharmacists) to take any reactive measures such as restricted or controlled prescribing of those drugs whose concentration have been found in abundance in the water cycle. *There could be similar sorts of shortcomings in other aspects of regulatory guidance as barriers to consider environmentally friendly practice – which are still subjects to be investigated.* Hence, it is important to make further enquiries into how and to what extent these regulatory shortcomings could impact on the adoption of particularly green use-and-disposal related practices.

2.7.3 Financial barrier: High investment and cost

Pharma process development employs sophisticated and costly technologies and equipment systems, which require skilled handling and regular maintenance. Generally, it is assumed that green technology such as artificial intelligence (e.g., HTS, chemoinformatics, bio-informatics), green chemistry realted technology (e.g., installation of solvent recovery process, changing process from batch to continuous, PAT) and sourcing green raw materials, require significant amounts of financial investments (Velva and Jr, 2017; Slater et al., 2010). Regarding the investment in sourcing green raw materials, though the biomass-derived (renewable source) chemicals identified may be a building block for green drug design, they are not commercially available and suffer both purity and cost issues (Clark et al., 2010). *The trade-off between these extensive financial investments and environmental gains are still limited and widely unknown in the pharma context (Start, 2008). It is not clear whether and how and to what extent different companies (innovative, generic and bio pharma) can face this barrier to implementing green practices. It is still not known whether and how related financial investments and cost saving strategies are currently being considered, particularly for developing green drug design and manufacturing*.

2.7.4 Cultural issues

While employees' green mind set plays a crucial role in greening, the pharma industry supply chain employs a wide variety of people ranging from medicinal chemists, scientists, process chemists, process engineers, formulation designers, and formulation engineers to downstream GPs, pharmacists, waste vendors, and wastewater treatment companies. Lack of top managements' and operations mangers' general mindset on environmental responsibility, or green mindset, could be another key barrier for pharma to go green. For instance, operations managers could be resistant to, or full of fear of, changing their manufacturing process due to the involvement of risky and costly regulatory validation processes (Slater et al., 2010) – which ultimately shapes a culture, putting it in a weak position to deal with other related environmental degradations. Furthermore, there could be some negative perceptions on implementing green practices, such as quality deviation due to the use of recycled / recovered solvents in the process, or fear of losing safety, quality and efficacy focus while adopting greener approaches into the conventional way of operations. *However, unfortunately, though this is one of the crucial barriers for pharma to identify, the scope of understanding this barrier is limited.* Therefore, whilst the green mindset of companies could easily embrace green practice, it is important to understand how the companies are being impeded to consider green practice due to the lack of this cultural shift.

Lack of the green mindset could also affect downstream players. Although it is evidenced that people who are environmentally concerned are more likely to return their unused medicines to the local pharmacy or collection point (Abahussain et al., 2006), it is not clear whether those people are concerned about PIE issues particularly or if they simply participate in the take-back scheme as part of being a good citizen. It is also not clear whether GPs/pharmacies implement drug take-back schemes merely for regulatory reasons or other cultural reasons such as being well-aware of the environmental facts of PIE and AMR. Though the literature has identified the *lack of awareness as a barrier,* it did not focus on the impact of this barrier on green use-and-disposal practices adoption. So, it requires further investigation to see how and to what extent the lack of awareness could influence green use-and-disposal practices as well as the diffusion process parameters of these practices.

2.7.5 Operational Challenges

Compared to other process industries, pharma operation is highly complex with a two stage manufacturing process (API and formulation). Both API production and formulations are

highly dependent on each other in terms of considering materials, energy, and toxicity. The green uptake for the upstream manufacturing process is also dependent on green related data/info from downstream players. A lack of relevant environmental data could potentially hinder the adoption of green practices in the upstream pharma companies. More specifically the PBT (Persistence, Bioaccumulation and Toxicity) data for a particular API or new chemical is vital to undertake a decision on whether and how to control its application (Clark, 2010). *Unfortunately, there is still a significant lack of PBT data (Clark et al., 2010) which could be used by the R&D companies and manufacturers to consider alternative strategies.* At the same time, *there is limited understanding on how the lack of PBT affects the companies in undertaking greener operations.*

Time to market is assumed as another critical operational barrier to considering green activities in the drug design and development phase, either for new drugs and/or existing drugs in the market. Due to the nature of business, the innovative companies could probably focus more on how quickly to bring the drug to the market for gaining competitive advantages for a longer period of time - for 20 years for monopoly sales right, while the typical developmental timeline is 10 to 12 years (Taylor, 2016). Therefore, the companies' key focus is reducing the timeline and just meeting the key quality, safety and efficacy measures required by the regulators. This typical time-focused atmosphere may not lead to the exercising of green practices and the companies may fear being distracting from their focus on the quality, safety, and efficacy of the new product. *However, understanding of the scope of this barrier in pharma is still very limited.*

Time is also crucial for downstream players, especially during prescribing and dispensing. It could be a barrier under *the lack of management control over drug waste reduction*. Both prescribers and dispensers are under acute pressure to maintain related administration tasks for safe and effective use of drugs within a constrained time frame (McDonalad et al., 2010; Latif et al., 2011). Therefore, the constrained time for these operations could result in ineffective drug use and disposal leading to drug mismanagement and the related wastes. *However, the scope of this barrier still needs to be investigated to establish how time is a barrier for downstream stakeholders. There could be some other management control-related barriers linked to drug waste reduction, such as lack of communication between prescribers, dispensers and patients, or patient non-adherence related issues (Vollmer, 2010; Clark et al., 2010), or patient access to MURs etc – which still need to be explored to have a concrete understanding on the management control related barriers.*

After careful synthesising of the existing literature, it is *clearly evident that there is a lack of understanding of the barriers to adopting green practices in both the upstream and downstream supply chain*. It is important to highlight here that the few relevant barriers are mostly predictive in the literature rather than empirical evidence oriented. The predictive list of barriers is not exhaustive, and it is also possible that companies could face some other barriers to implementing green practices, which are not known. Considering the partial understanding and some ambiguities, an empirical investigation is required to understand the relevant barriers in detail so that these barriers could be mitigated for successful implementation of green practices in the pharmaceutical sector. Hence, below a key research question and sub-questions are formulated for investigation:

RQ3. What are the barriers faced by individual pharma sector stakeholders for adopting green practices and what is their perceived importance?

RQ3.1 what are the barriers faced by upstream pharma sector stakeholders for adopting green design and green manufacturing practices and what is their perceived importance?

RQ3.2 what are the barriers faced by downstream pharma sector stakeholders for adopting green use-and-disposal practices and what is their perceived importance?

Once green related practices, drivers and barriers are understood, it is now important to focus on understanding how related green practices induce both environmental and financial benefits for companies. The financial benefits from adopting green practices could be the key focus for stakeholders across the industry to embrace the green culture. Hence, the next section presents green related performance measures and performance impact and related knowledge gaps.

2.8 Current understanding on green performance measures and related benefits in the upstream pharma sector

Performance measures of green practices are crucial for green investment decisions. Inappropriate and/or inefficient performance measures could lead to the wrong green decision. The rate of environmental performance, for instance, amount of energy and water saving per unit of product produced, is also linked to short and/or long-term cost savings or

economic performance. Companies may not succeed in gaining environmental sustainability if the measures lack *inclusiveness* (measurement of all pertinent aspects), *universality* (allowing for comparison under various operating conditions), *measurability* (data required are measurable), and *consistency* (measures consistent with organization goals) (Beamon, 1999). Therefore, detailed performance measures and actual performance must be understood for successful green practice implementation within a particular context, especially for pharma which consists of diverse stakeholders' interests, and related measures can be complex and misleading. Pharma performance measures can be investigated two ways: strategic level measures and operational level measures.

Strategic Level measures: As pharma industries, especially the big innovators, have felt the necessity to improve their environmental footprint significantly due to ongoing global environmental sustainability pressure (Veleva et al., 2003), they have started taking environmental goals into consideration in their corporate level strategy (Schneider et al., 2010). Strategic targets for reducing carbon, energy, water, and waste are predominant across the industry (Schneider et al., 2010). *However, there is a lack of detailed understanding on how companies in different pharma sectors (innovative/generic/bio) consider these high-level environmental goals and objectives.*

Operational level measures: Operational level green performance measures are the key for pharma, as upstream drug design and manufacturing (API synthesis and formulation) are extensively materials and energy exhaustive processes. A simple measure of the 'amount of raw materials used for a process' could significantly reduce the materials wastes and related cost. Unfortunately, *there are no studies in the literature that focus on identifying performance measures taken by different stakeholders for measuring related green design and manufacturing operations.* Only one study by Boltic (2013) has indicated positive environmental performance by redesigning process but *it did not explain what measures were considered - for instance, how the level of toxicity, level of materials and level of energy were measured to differentiate the performance between the new redesigned process and the previous version.* It is crucial that R&D and manufacturing operations consider the right indicators to measure each green design and manufacturing practice to understand the actual performance induced from the process. The application of MET in the design and manufacturing phase will increase if the related performance measures and actual performance are clearly understood.

When reviewing the previous pharma related research, it is also clearly evident that no single study has precisely aimed at identifying green performance measures from the supply chain perspective. However, a few studies (e.g., Roschangar et al., 2017; Henderson et al., 2010; Jimenez-Gonzalez, 2011) have focused on developing some green chemistry related metrics (e.g., Process Mass Intensity or PMI, Green Aspiration Level or GAL, E factor, atom economy) for measuring environmental performance for a specific process, and they are designed only for API manufacturers; while green measures for formulators are yet to be investigated. *Additionally, the level of practice and the extent of harmonization of these metrics across the supply chain are as yet unknown. Other important environmental measures, such as biodegradability of drug molecules, reduced use of toxic substances, GHG emission levels in scope 1,2, and 3, BOD (Biological Oxygen demand), COD (Chemical Oxygen Demand) and TSS (Total Suspended Solid) level (these measures are important to understand the life in the aquatic system) could have been relevant but are missing in the existing literature. It is also not understood how efficiently companies could measure the greenness of a process to manage and control each aspect of MET throughout the manufacturing process.* Furthermore, *it is not known what key metrics are predominating in the industry and their related challenges and benefits.*

Under environmental measures, GHG emission related, energy efficiency related, raw materials efficiency related, and waste efficiency related would be the key measures considering the nature of pharma operations. Though pharma companies are continuously monitoring GHG emission from their operations (Schneider et al., 2010), *it is still not clear how different pharma stakeholders are measuring elemental levels carbon emission such as scope 1, scope 2, VOCs etc and how they would rank them in order to manage them.* Similarly, though there is indication of energy efficiency practice, *it is still not known what relevant measures are used to evaluate those efficiency practices.* Due to having complex API synthesis processes, companies may struggle to measure those parameters (GHG emission, energy efficiency, wastes efficiency etc) for each process. But *it is still not clear what kind of practices cannot be evaluated on a process level and why.*

However, though some existing common measures (e.g., waste reduction, GHG emission, amount of raw materials use, amount of water use and amount of energy use) borrowed from other related industries could be useful, *due to the lack of empirical research, the measurability, consistency, universality, inclusiveness and overall practical acceptability of existing plan /process level measures are not advocated for the pharmaceutical supply chain.*

As every supply chain is unique due to having some special characteristics, the requirements of context-based matrix development are of enormous importance. On the other hand, *the lack of context-based metrics is highlighted in a recent study by Ahi and Searcy (2015). So, there is an urgent need for formulating a new investigation for developing a set of GSCM-PMs for the pharmaceutical industry.* The lack of agreement on how performance should be measured is not only addressed in the pharmaceutical context (Henderson et al., 2010; Roschangar et al., 2017) but it has also been highlighted in the general GSCM literature such as Ahi and Searcy's (2015) study.

Merely understanding and/or identifying the performance measures is not enough to assess and/or implement a particular green practice; rather it would require knowing the actual benefits/performance from each green practice adopted. The evidence of actual performance is becoming increasingly urgent for practitioners, policymakers, and academic researchers prior to greening the pharmaceutical supply chain (Teunter et al., 2003; Clark et al., 2010; Henderson et al., 2010). Unfortunately, none of the existing studies in the reviews has predominantly focused on understanding actual green performance from adopting a particular green practice. *However, there is a small indication of addressing actual performance in studies by Teunter et al. (2003) and Slater et al. (2010).* For instance, it is evident in a German pharmaceutical company (Schering AG) that pharmaceutical byproduct recycling and solvent reuse leads to annual savings of approximately DM 25 million, which was about 8.5% of the total production cost (Teunter et al., 2003). Similarly, it is crucial to understand the actual performance level from implementing each green practice by each stakeholder. This level of understanding will eventually help the practitioners to implement green practices with increased levels of confidence. While understanding that the perceptual performance is predominant in the other GSCM related studies (Zhu and Sarkis, 2007; Eltayeb et al., 2011; Green et al., 2012), the actual performance captured from adopting green practices is rare, especially in pharma sector.

In summary, *there is a dearth of knowledge about green measures (both environmental and economic) and the actual performance (both environmental and economic) generated from each green practice adopted by the individual pharmaceutical stakeholder.* So, it is essential to understand the holistic view on performance measures in the upstream pharma sector.

2.9 Current understanding on performance measures and related benefits in the downstream pharma sector

Identifying performance measures and documenting actual performance from applying green practices would be undoubtedly crucial for dealing with the unprecedented levels of PIE and AMR concerns. While reviewing the existing literature, it is clear that none of the previous studies has focused on this performance aspect, apart from only a few that have documented actual performance from applying green practices, such as studies by Peterson and Anderson, (2002); Kotchen et al. (2009); and Latif et al. (2013). But these are not sufficient and exhaustive in the sense that they do not cover the entire spectrum of issues, for instance, it is not yet known how much has been improved so far from the MUR service, or how the benefit is documented, or what measures are being taken to quantify the benefit of MUR service. Similarly, how the impact of eco prescribing practice could be quantified; how the impact of drug take back program could be measured; or holistically how drug waste reduction is calculated in pharmacies, hospitals or in GP settings etc are still a matter of new investigation.

Therefore, based on the related research gaps identified, the final set of research questions have been formulated as below:

RQ4. What are the green performance measures (in terms of environmental and economic) used, and related (environmental and economic) benefits captured by individual pharma sector stakeholders and what is their perceived importance?

RQ4.1 what green performance measures (in terms of environmental and economic) are used, and related (environmental and economic) benefits captured by upstream pharma sector stakeholders and what is their perceived importance?

RQ4.1 what green performance measures (in terms of environmental and economic) are used, and related (environmental and economic) benefits captured by downstream pharma sector stakeholders and what is their perceived importance?

2.10 Theoretical discussion and opportunities for further development

Whilst reviewing related theoretical foundation of GSCM in section 2.3.5, EMT (Ecological Modernization Theory), DOI (Diffusion of Innovation) and RBV (Resource Based View) are more relevant and significantly important for advancing GSCM related concepts in pharma. The relevancy and related knowledge gaps for each of the theories are outlined in the subsequent sections.

EMT (Ecological Modernization Theory): The level of environmental protection during continuous industrial development is predominantly dependant on political influences, technological discovery, and social cohesion for greener transformation in any context examined (Terryn, 2010; Ewing, 2017). It is unclear how environmental policy reform influences stringent industrial operations where product integrity, safety and efficacy can not be compromised by any means. More importantly, environmental reforms become significantly complex when increased environmental biodegradability of drug works against biological biodegradability. Science and technological innovation could be one of the significant reactions into such environmental policy reform (Andersen and Massa, 2000). Whilst green pharma operation is viewed, to some extent, as a precautionary principle (e.g., to deal with PIE), implementation of such precautionary principle relies heavily on science and technological development. Though multi-stakeholder involvement should be the key in implementing such precautionary principle in reality, the related scope is still unknown in existing EMT view. Such unique understanding (e.g., how different actors play a role to exert a new policy and innovate new process technology accordingly for long term sustainability) will undoubtedly advance the existing concept of environmental reform, as one of the core concepts of EMT.

While the political modernization in terms of environmental reforms and related policy through environmental regulations (e.g., WEEE) has widely been known in other related discrete industry (e.g., textile, computer, automotive, construction etc), little is known in the case of non-discrete sector such as pharma, especially the scopes and related drivers and barriers of reforming environmental policy. Hence, it aims to advance the core aspect of EMT. Continuous vigilance of products (drugs) while they are in the environment to deal with PIE could be another unique environmental reform since the inception of EMT. This is because though curative and preventative nature of environmental reforms are common in the core of EMT, the understanding on how precautionary led principles (e.g., green chemistry led green pharma to deal with PIE) influence both public and private institutions to reform environment is still needed to advance (Mol, 2010).

It is also important to note here that the EMT is debated from two core perspectives: a school of thought which predominantly urge for rudimental changes within socio-economic structure to attain environmental sustainability; another school of thought is against it and reaffirm the firms that environmental reform can be adapted in an ongoing basis rather than a radical social or political-economic change (York et al., 2010). This study is expected to contribute

to this debate to further advance the EMT. For instance, it is assumed that multinationals pharma companies and governments are acting in their own self-interest for long term survival by placing ecological concern (e.g., materials, energy, toxicity) in centre stage, which aims to focus on ongoing environmental degradation (e.g., PIE) but create a ground for long term sustainability. This is how green pharma observation is expected to contribute to the existing debate of EMT to advance the theory within broader context.

Though EMT was viewed through materials and financial flow (Mol, 2010), green cooperation among multi stakeholders through analysing the scopes of such flow is still not clear. Additionally, though institutional pressure for adopting such green cooperation or related technological adoption were evidenced (e.g., Zhu et al., 2012; Murphy and Gouldson, 2000), there is dearth of knowledge to understand the scopes of voluntary environmental reform (e.g., ERA prior to approval of pharma products) to enrich EMT. Why and how voluntary environmental reform is becoming the key to attain long term environmental sustainability through incremental socio-economic changes (e.g., promote solvent recycling) (but induce rudimental environmental and economic change) is significantly important to understand. This study is expected to advance this understanding through empirical observations.

***DOI (Diffusion of Innovation)*:** DOI theory suggests that an innovation is communicated through particular channels, over time, among the members of a social system (Rogers, 1995). GSCM practices are regarded as environmental innovation which is communicated across diversified sectors over the last three decades across the supply chain for successful diffusion of green practices (Zhu, et al., 2012; Murphy and Gouldson, 2000). DOI theory also suggests that the rate of adoption of each innovation is dependent on relative advantage, compatibility, complexity, trialability and observability (Rogers, 1995). It also ranks the adopters as early adopter, follower, and laggards.

While it was known that early green adopters gain more business and environmental benefits than late adopters / laggards in the discrete industry (e.g., electronic manufacturers, automotive, construction) (Zhu et al., 2012; Balasubramanian and Shukla, 2017), however, it was not clear how such adoption benefits work out in the non-discrete industry like pharma where the process entirely dependent on the invention of new molecules rather than following a deterministic path. Additionally, due to the raw materials variation (e.g., variation on API quality in terms of solubility, biological degradability, or variation in excipients quality)

across the different pharma manufacturers (e.g., innovative, generic, bio pharma), the success of green adoption and related benefits is not entirely dependent on the time / stages of adoption (e.g., early/late etc). Rather it predominantly depends on the success of discovery and invention process applied to identify a new drug manufacturing process. The drivers of such diffusion of innovation (e.g., MET related innovations) in an inventive business environment is also not clear. Such unique understandings in a unique context (e.g., pharma) will undoubtedly advance the existing knowledge of DOI.

Understanding green adoption mechanism and related benefits through diffusion of green knowledge across different stages of innovation in diversified sectors is the central to advance the DOI theory (Rogers, 2003; Sarkis et al., 2011). The diffusion process of green related knowledge and information in pharma is predominantly a collaborative approach which dependent on multi stakeholder involvement including multi-talented efforts for successful green adoption. Such diffusion of green innovation is not known yet to further advance DOI theory. Additionally, understanding the adoption of green innovations and related characteristics (e.g., relative advantages, compatibility, complexity, trialability) in a discovery led business environment where key business success depends on the successful discovery of a drug would advance the existing DOI knowledge. It is also rarely addressed in DOI, especially under green supply chain domain, that why green innovation is rejected still having green related knowledge and appropriate persuasion in some context like pharma.

RBV (Resource Based View): RBV theory suggests that firms can induce competitive advantages by harnessing their internal resources that are valuable, rare, imperfectly imitable, and non-substitutable, such as green design or green process design of a particular product (Sarkis et al, 2011; Barney, 1991). As per the theory, companies develop dynamic capabilities and resources to design new green innovation that supports the value, rarity, inimitability, and non-substitutability aspects of the RBV (Carter and Carter, 1998; Sarkis et al., 2011). Hence, the lack of dynamic capabilities and internal resources may impede the firms from adopting particular green practices (Gonzalez-Torre et al., 2010; Zhu and Geng, 2013). For instance, the lack of organizational learning leading to the lack of knowledge and skills on green practices, such as EMS or Eco-design, may be the barrier to adopting GSCM (Sarkis et al., 2011; Govindan et al., 2014). However, it is assumed that some contexts like pharma may not adopt green still having internal capabilities and resources. Exploring and understanding such cases could significantly advance the existing view of RBV.

From the RBV view, the scope of some key green innovations (e.g., recycling, reusing etc) are well understood through developing unique capabilities to create competitive advantages, especially in the discrete industry such as automotive, electronic, furniture, toys, smart phones, household appliances etc (Azevedo et al., 2012; Hajmohammad et al., 2013; Scur and Barbosa, 2017). However, the application of RBV in the non-discrete industry, especially in the inventive business environment like pharma, is still underdeveloped. For instance, the scopes of dynamic capabilities and related competitive advantages gained from solvent recycling would further advance the RBV view. It would be also interested to explore the RBV view while some products such as drugs do not induce any salvage value from adopting green practice such as recycling (Xie and Breen, 2012). It is also rarely known in the RBV lens why and how companies increase internal capabilities to adopt such green practice. The existing RBV view also does not explain why and how to develop dynamic capabilities in the firms where green innovations counteract with safety, quality, and efficacy of some products manufacturing such as drugs. This is how the study is expected to advance the RBV view, to some extent, through analysing empirical evidence.

2.11 Conceptual model of the study

Given the background of existing GSCM knowledge in general and particularly in pharma a conceptual model (fig. 2.7) is formulated. Green chemistry led MET related practices adoption in pharma could predominantly be driven by regulatory, cost savings, top management commitment and stakeholder pressure to exert both environmental and economic performance measures. At the same time, however, such MET related green practices adoption could be hindered due to complex marketing authorization process of green drug process, high investment and costs, cultural issues, and related unique operational challenges to maintain safety, quality, and efficacy concurrently.

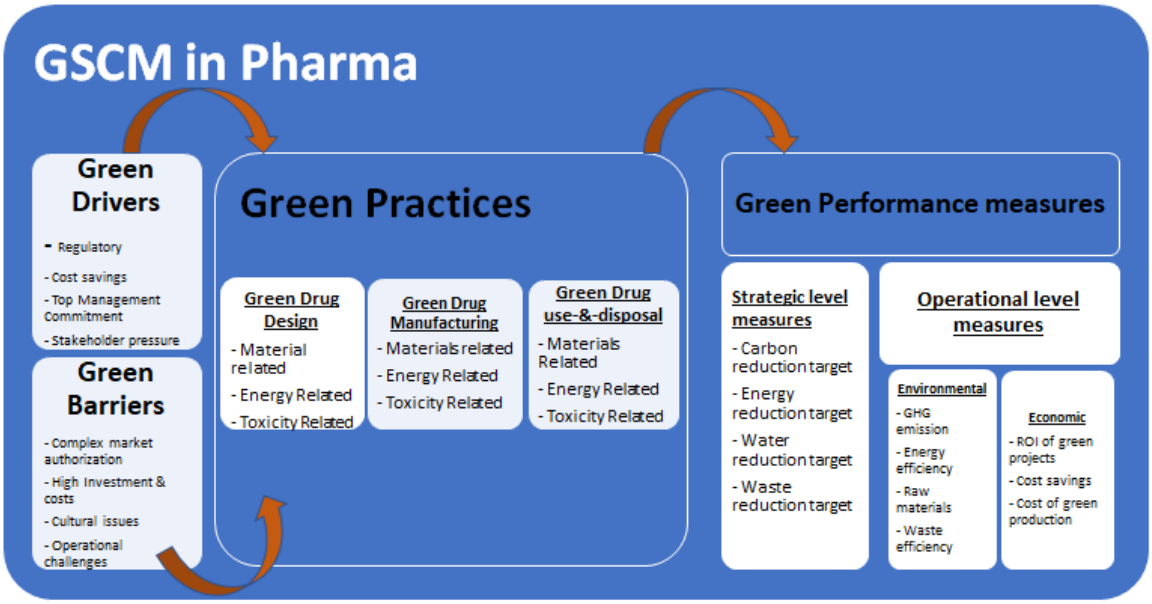


Figure 2.7 Conceptual model of the study

2.11 Chapter Summary

This chapter began with the general discussion of business sustainability to establish the rationality of green business sense. Then the discussion turned to green supply chain management and its related concepts. Green supply chain management practices were explored through the concepts of materials, energy, and toxicity for creating a MET framework to apply to a new context like pharma. Key stakeholders in the pharmaceutical supply chain were also outlined. Then a thorough critical review of the existing literature in the pharmaceutical sector, in conjunction with GSCM studies in other related sectors, was carried out. A synthesized literature review has helped the researcher to identify the research gaps and to formulate some demanding and interesting research questions. To answer these research questions a detailed research design and methodology needs to be outlined. The next chapter presents the detailed methodology for this investigation.

Chapter Three: Methodology

This chapter outlines the philosophical stance of the thesis including a brief background on the philosophy of science and management research. The justification of the methodological choice has been made in the light of the current research paradigm of GSCM studies. The data collection method, sampling technique and data analysis method are also presented and justified.

3.1 Philosophy of Science and Management Research

The philosophy of science deals with the complicated nature of scientific enquiry. It involves discovery, justification, and falsification of a particular phenomenon through the application of scientific methods. It articulates metaphysical, epistemological, and ethical issues related to the practice in different branches of science, such as biology and physics (Kitcher, 2013).

The philosophy of science is fundamentally concerned with two dimensions: the theory of knowledge and metaphysics of science: laws of nature, natural kinds, and explanation of phenomena (Shand, 2003). This branch of science has developed its axioms, theories, methodological strategies, and investigation methods to contribute to the knowledge generation process. Four assumptions have evolved based on the philosophy of science: ontology, epistemology, axiology, and methodology. These assumptions have a profound effect on the quality of management research design (Easterby-Smith et al., 2001). With different sociological persuasions, these assumptions are followed consequentially to each other; that is, the view of ontology affects epistemological consideration which, in turn, decides the methodological choice (Holden & Lynch, 2004).

Ontology focuses on the nature of reality or the nature of knowledge. It is the picture of worldview. Worldview is the starting point of investigation for a scientific problem. Sociological researchers use this method to acquire knowledge, either being objective or subjective by clarifying and arguing the worldview (Solem, 2003).

Following the ontological assumptions, epistemology confirms and explains how the researchers understand reality and communicate this to other people. It deals with the

groundwork of knowledge, which involves reasoning process, guarantees of truth, proofs, axioms of validity or any other logic underlying a methodology. It is also referred to as theory of knowledge which can be created by introducing a new theory (inductive theory building process) or modification of old theory (deductive theory testing process) (Solem, 2003).

Axiology is another assumption in the philosophy of science. The Greek word 'axios' means "worthy" and 'logos' means science. It studies judgements about values. This branch of philosophy ensures the credibility of research (Flowers, 2009). It is like 'value theory' and 'meta-ethics'. Value theory attempts to understand how, why and to what extent persons svalue things (person/idea/object or anything else). Ethics is focused on moral goods rather than natural goods (Flowers, 2009).

The final assumption is the methodology which is the researcher's tool-kit; it represents all the techniques available to social scientists to investigate phenomena. Consideration of ontology, epistemology, and human nature from the point of the subjective-objective dimension for a particular phenomenon is referred to as a building block for methodological choice (Burrell and Morgan, 1979). All these philosophical assumptions can lead the researcher to choose either qualitative or quantitative methods. The mixed approach-combination of qualitative and quantitative method can also be used based on the research questions to be answered. As seen in figure 3.1, the philosophical proposition for any investigation broadly depends on objective and/or subjective views of the proposed study (Burrel and Morgan, 1979).

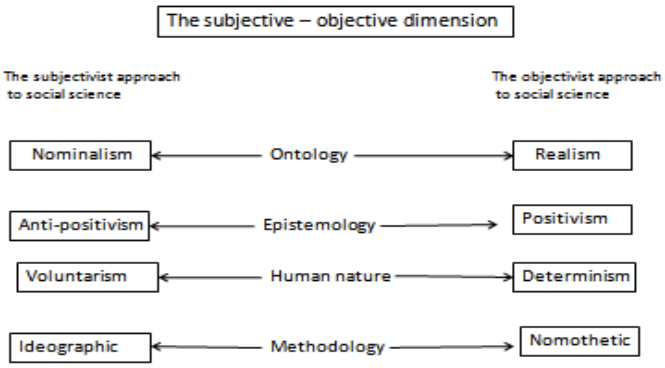


Fig: 3.1 A scheme for analyzing Philosophical assumptions (adapted from Burrell & Morgan, 1979)

Under the two polarized perspective- subjective and objective dimensions, each of the philosophical assumptions is composed of two extreme sides (see fig 3.1). The ontological knowledge of world view and reality can be described from two polarized views: nominalism- no real structure of social world exists and realism- the social world has an existence which is as hard and concrete as the natural world. Epistemological assumption is composed of positivism and anti-positivism or interpretivism. The positivists seek to explain and predict different factors in the social world by searching for regularities and causal relationship among those factors. New insights are added to the existing stock of knowledge by verification and falsification of proposed hypotheses. Interpretivists, on the other hand, seek to understand the phenomena rather than verification. Likewise, the objective view argues that the nature of humans (e.g. human activities) can be completely determined by the situation or environment, which is termed as determinism; whereas when the same nature of humans becomes completely autonomous, the philosophy changes into voluntarism. The debate on methodological philosophy continues through two broad philosophies: ideographic- subjective analysis of the investigations and use of qualitative techniques to generate insights; and nomothetic- occupied with scientific tests and use of quantitative technique for data analysis (Burrell & Morgan, 1979).

3.2 Research Paradigm of GSCM studies

Even though it can be confirmed from the extensive literature review that research on GSCM has contributed to the existing domain of knowledge by composing both positivism and interpretivism epistemology, positivist philosophy is predominant. Theoretically, in the last three decades researchers have developed many new policies and management practices in liaison with practitioners in the field of GSCM for gaining business sustainability. The implementation of these practices largely varies depending on the types of industries and times taken to adaptation. Being a multidisciplinary (business, engineering, mathematics, operations) subject of interests, academic researchers from different disciplines have applied different analysis techniques to test the existing theoretical knowledge related to practice and performance. Therefore, the necessity of testing (hypothetico-deductive approach) of practices in different industries in different contexts has increased over time. Hence majority of studies stand on positivist philosophy by constantly testing the theory. Precisely this hilosophical stance is used to investigate the effectiveness of different GSCM practices or to

enquiry of *what* extent to which the eco-design practice reduces environmental impacts, for instance.

It is obvious that the frequency of the theory building (inductive) approach in this field is considerably low compared to the theory testing approach. The development of theory in the social dimension of business sustainability is almost non-existent. Minorities of researchers have extended the core theory of EMT and DOI for the advancement of understanding the environmental policymaking in the supply chain of the most polluted industries like chemicals and pharma. Additionally and more importantly, the existing literature (Hsu & Hu, 2008; Green et al., 2010; Zhu et al., 2012) has sought to understand the adoption process of GSCM practices in a particular sector, paying in-depth attention to how green related drivers and barriers actually work in that sector.

Some researchers have become subjective on the understanding of organizational change due to implementing environmentally responsible manufacturing practices. These studies stress an interpretivist philosophy and are associated with qualitative methods. The investigations of *how* or *why* a particular driver or pressure (e.g., institutional pressure) accelerates the adoption of GSCMPs fall under interpretivism philosophy. Even though the research paradigm under positivists philosophy is dominant, recent academic researchers have developed and emphasized a composed philosophy combination of positivist and interpretivist epistemology to contribute to a cumulative knowledge creation process in the field.

Even though the notion of pragmatism underpinning the mix methodology within a particular phenomenon is still in debate philosophically, it has been sought as a new paradigm shift in social research (Denscombe, 2008). The pragmatic view is evidence that the process of knowledge creation may occur not only from positivism or phenomenological epistemology but also from a combination of both epistemologies. Pragmatists' observations can move from an objective dimension to a subjective dimension and the research problem can be viewed from the inter-subjectivity assumptions (Morgan, 2007).

Philosophically, the solutions to some GSCM research problems (Zhu & Sarkis, 2006; Zhu et al., 2007a; Jabbour et al., 2014) have been sought to move from the objective to the subjective dimension, and hence, connecting one particular phenomenon from generalizations (deduction) with another particular phenomenon from where it generalizes (deduction). This

kind of inference between deduction and induction in the same study has been coined as abduction inferences in the literature (Krippendorff, 2004).

Hence, the pragmatic view demonstrates abduction reasoning that moves back and forth between induction and deduction. It integrates epistemological concerns about the nature of knowledge produced and the technical concerns about the methods used to generate knowledge (Morgan, 2007). Having different layers of epistemological and ontological dimensions in relation to a particular research problem, researchers are unable to understand the problem clearly until they use mix methodology (Feilzer, 2009). Pragmatism helps researchers to find a solution to complex social phenomena when merely either one of qualitative or quantitative does not rectify the problems. Thus, it stresses the adoption of both quantitative and qualitative methodologies in the same study.

3.3 Philosophical stance of the thesis

It is obvious from the literature review that the concepts of sustainability - specifically the concepts of GSCM by means of environmental sustainability - are still not clear. GSCMPs differ from industry to industry due to the different products and processes involved, or even from one product supply chain to another (Zhu and Sarkis, 2004; Zhu et al 2007; Dubey et al., 2017). In particular, the concept of GSCM in the UK pharma industries remains undiscovered. Even though the current research paradigm has presented a set of GSCM practices, drivers, barriers and performance, those concepts are still unclear in the case of pharmaceutical operations. For instance, it is uncertain whether the existing green practices (e.g., green design, green manufacturing) are appropriate enough to fit in pharma context. The drug supply chain is significantly different from other conventional product supply. The reasons are multifaceted. For instance, the drug supply chain plays a role between patient life and death apart from the economic savings. Given the level of intellectual work involved in drug design, discovery and development and production, it works within an atmosphere of intellectual property and patents. Additionally, there are complex interactions among the stakeholders due to them having very diversified business aims and objectives, while environmental sustainability attainment becomes extremely difficult.

Therefore, understanding the adoption of green in such an uncertain, complex, and restricted environment will certainly require the development of very thorough knowledge in the field. It is also uncertain what and how green drivers and barriers influence the green practice adoption in pharma. Therefore, it is essential to explore the practical aspects of how green

supply chain management decisions are made in the pharma industry. So, to resolve related uncertainties and complexities, the researcher of the study should look at this phenomenon from subjective dimensions of philosophy.

It is important to highlight here that the aim of this study is to explore the key concepts of green practices, green drivers, green barriers, and performance measures for pharma. Based on clear understanding of each green concept in context, it also aims to develop key indicators for measuring each of the green concepts for the pharma sector. To understand the practical relevance of existing green practice, drivers, barriers and performance measures for the pharma sector, the researcher must remain in the subjective dimension on Burrell and Morgan's (1979) scheme of philosophical assumptions.

Ontologically there is lack of evidence of structured elements of green supply chain management practices, drivers, barriers and performance measures and related performance in the pharma sector to gain overall environmental sustainability. For example, the scope and viability of implementing recycling practices, either in the drug design phase, in the manufacturing phase, or in the use-and-disposal phase, is not clear in the existing body of knowledge. These unstructured ontological considerations accelerate the knowledge creation process (epistemological assumption) by understanding the underlying green practice adoption process influenced by green drivers and barriers in the pharma context. Hence the interpretivist epistemology is employed. In line with the aims of this study, it reflects that the researcher's thoughts and activities are completely determined by the unstructured data and concepts of GSCM in the pharma context. As a result, the qualitative method is required to understand and develop key indicators for each GSCM concept for the pharma sector.

Likewise, to understand how pharma companies deal with unprecedented levels of environmental pollution originating from pharma operations, it is most likely to be occupied with the subjective dimension. From the point of subjectivism, it is ontologically vague and unclear what, why and how green practices are being employed by pharma companies for better environmental and/economic performance. Epistemologically, it is vital to be anti-positivist, and analyse in detail each green practice, green driver, green barrier, and green performance measure to cope with increased level of environmental pollution. Thus, the ontological doubts initiate the knowledge creation process – by understanding relevant GSCM concepts being an independent inside analyser. Hence, qualitative discussion is

needed as the key tool for the execution of the study. This is how the bridge between qualitative methodology and philosophical assumptions is justified.

3.4 Research Design

To better understand the detailed design of the study, it is important to summarize those key supply chain stakeholders participated in the study, their key roles, relevant data collected and their contribution to this research. Table 3.1a outlines these aspects.

Table 3.1a Key supply chain stakeholders participated, their key roles, relevant data collected and their contribution to this study (Source: Researcher)

Pharma stakeholders	Key roles played in the supply chain	Key data collected	Contribution to research
Innovative pharma	Discover, design, develop, patent, produce (API, formulation), and market new drugs (chemical / bio based) through regulatory approval. Redesign existing drug products for improved quality, safety, and efficacy. Design innovative route of chemical synthesis or bio synthesis from the scratch.	- Key MET related practice / activities employed during drug discovery, design, and development to reduce materials, energy and toxicity impact in manufacturing, use-and-disposal, and drug discovery operations itself; and related drivers, barriers, performance measures;	Enriched initial green SC model through providing some significant green design practices such as design drug discovery process to reduce testing related materials, apply quality by design approach, design combined drugs where possible, Design and develop manufacturing process by installing and validating energy efficient equipment system (e.g., reaction vessel), design and develop drug process to reduce air toxicity. Provided some unique green drivers such as f-gas related regulations, ERA, corporate responsibility, green incentives & awards etc. Significant barriers: time to market, lack of green related data. Significant performance measures: PMI.
Generic pharma	Produce generic API/formulation. Develop drug manufacturing process (mostly formulation) to achieve exactly similar safety, quality, efficacy, and effectiveness of the innovative drug which is off patent (mostly chemical based).	- Key MET related practices / activities employed during drug manufacturing (API + formulation) phase; and related drivers, barriers, performance measures;	Enriched initial green SC model through providing some significant green practices, drivers, and barriers. For instance, consider lean operations significantly for reducing materials reduction. Provided some significant green barriers: complex marketing authorization of green pharma products, cultural issues, lack of demand of green API.
Bio pharma	Design and develop biobased drugs process. Produce drugs using biologically sourced raw materials	- Key MET related practices / activities employed during drug manufacturing (API + formulation) phase; and related	Enriched initial green SC model through providing some significant green practices and performance. For instance, design and develop bio-based drug process to reduce water

Pharma stakeholders	Key roles played in the supply chain	Key data collected	Contribution to research
	and applying biotechnology. Less use of chemicals in process. Very complex instrumentation and engineering requirements.	drivers, barriers, performance measures;	toxicity, adopt water reduction related lean project; significant performance measures: ROI from green project.
Pharmacy	Storage and dispense both OTC and prescription drug. Advise patient for effective use of drugs. Stock management & storage of drugs. Disposal of unwanted and expired drugs. Participate drug take-back scheme. Responsible for reducing drug wastes.	- Key MET related practices / activities employed during drug storage, dispensing, disposal of unwanted drugs; and related drivers, barriers, performance measures;	Enriched initial green SC model through providing some significant green practices, drivers, barriers, and performance measures. Provided some significant green practices such as digitize dispensing process for drug waste reduction, monitor & report prescriber's prescribing habit for effective use of drugs, responsible disposal of unused drugs. Significant green barriers: Uncontrolled drug wastes from high concerned patient groups; and Lack of performance measures of patient interventions scheme (e.g., NMS/MUR).
GPs	Consult patient and prescribe drug. Responsible for effective and efficient use of drugs.	- Key practices / activities employed to reduce drug wastes, and safe drug disposal, related drivers, barriers, and performance;	Enriched initial green SC model through providing some significant green barriers such as lack of regulatory guidance on environmental consideration in prescribing.
Hospitals	Storage, prepare and dispense drugs to patients. Dispose unused/unwanted/expired drugs.	- Key practices / activities employed to store & reduce drug wastes, & safe disposal of drugs, related drivers, barriers, and performance.	Enriched initial green SC model through providing some green practices and related performances. For instance, reuse of drugs which has not left pharmacy premises was a significant materials reduction (finished drugs) practice. Significant performance: Cost savings from drug reuse.
Care homes	Storage, prepare and dispense drugs	- Key practices / activities employed to store & reduce drug wastes, & safe	Enriched initial green SC model through providing some

Pharma stakeholders	Key roles played in the supply chain	Key data collected	Contribution to research
	to in/out-patients. Dispose unused/unwanted/expired drugs.	disposal of drugs, related drivers, barriers, and performance.	significant green practices such as drug usage optimization through MAR chart and MUR.
Waste management company	Drug waste collectors: Collect unused/expired drugs from retail pharmacies for disposal.	- Key practices / activities employed to ensure safe disposal of drugs, related drivers, barriers, and performance.	Enrich initial green SC model through providing some significant green practices such as use high temperature incineration of wasted drugs, energy recovery from drug incineration, recycle of incinerated ash.
Local council	Collect household wastes via contracted waste vendors. Sometimes collect waste drugs / clinical wastes via special contract.	- Key practices / activities employed to ensure safe disposal of household induced drug wastes, related drivers, barriers, and performance.	Enrich initial green SC model through providing some significant green barriers such as contradictory regulatory guidance for disposing unused/expired drugs.
Water company	Treat (household/industrial) wastewater using chemicals or biological process. Reduce water contamination. Treat wastewater to ensure safe and clean water supply.	- Key practices / activities employed to ensure safe treatment of wastewater (household & industrial) prior to releasing to the environment, related drivers, barriers, and performance.	Enrich initial green SC model through providing some significant green practices such as greener wastewater treatment options (e.g., monitoring concentration of API of high concern, apply advanced treatment)

Research design aims to provide detailed research plans and process on how to answer the research questions (Neuman, 2014; Saunders at al., 2016). The research design finalizes the methodology adopted in line with the research questions and philosophical stance, methods used for data collection, selecting the types of data required, sampling frame, and data analysis methods used (Creswell, 2013; Bryman, 2016; Saunders et al., 2016). Based on the research questions posed (in literature review sections), and in line with the researcher's ontological and epistemological position in the knowledge creation process from social phenomena, qualitative methodology is chosen.

A multi-method qualitative study is chosen for collecting data based on some predefined initial themes. Combining multiple methods in a single study (either quantitative or qualitative) for increased reliability and validity of the data collected is advocated by Saunders et al. (2016) and Neuman (2014). The multi-method research technique allows the researcher to answer the research question by evaluating the extent to which the research findings can be trusted, and inferences made from them (Saunders et al., 2016). The design also increases the data triangulation capacities (Yin, 2009). Additionally, the similar multi-methods qualitative approach has also been used in green supply chain related studies such as Nune (2011), Frost (2011) and Drohomeretski et al (2014). Interviews and content analysis have been used to collect the data for answering the proposed research questions. The detailed justification for using these two methods of data collection and how the data was collected is presented in the subsequent sections. To provide further justification of the research design based on the research questions posed, the literature review process is also presented in the subsequent sections. Figure 3.2 gives an outline of the research design for the study. The explanation on each phase of design is presented in the subsequent sections.

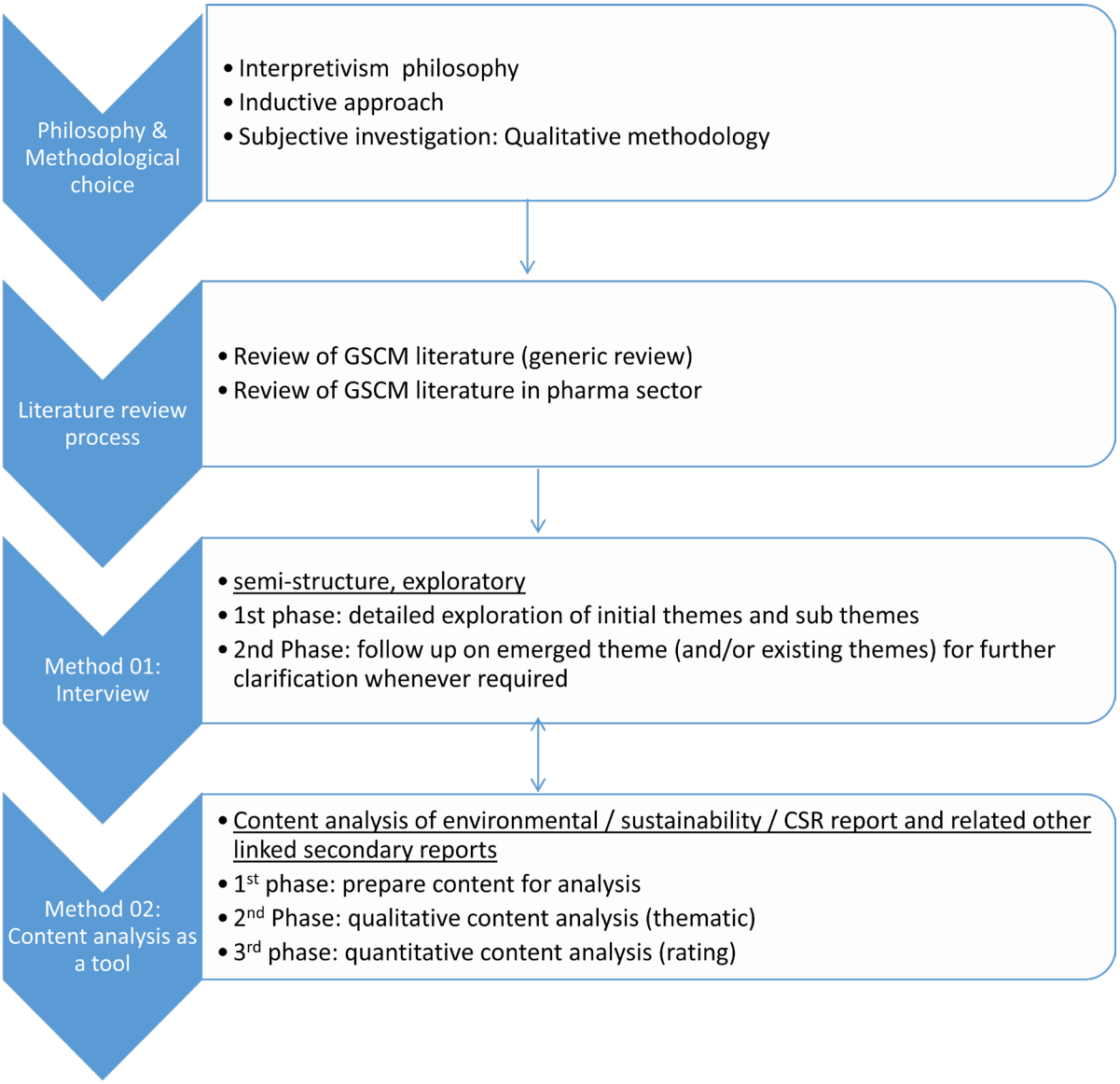


Figure 3.2: Research design of the study (source: researcher)

3.4.1 Literature Review Process

The study involved a two stage literature review process. In the first part of the literature review, a structured review of existing green supply chain studies in general was conducted to understand the current state of knowledge on the key concepts (e.g., practices, drivers, barriers, and performance measures) of GSCM. This section also refined the green practice and performance related assumptions. In addition to generic theoretical GSCM papers, this part attempted to gain relevant (practice, drivers, barriers, performance) knowledge from

diversified sectors, especially chemicals, rubbers, foods, textiles, electronics, and related manufacturing sectors. Therefore, this first part of literature review significantly underpinned the second part of literature review on how the greening process and operations would work in a new context of the pharma sector. The second part of the literature review mainly involved understanding the pharma supply chain operations and provided a detailed account on green related ambiguities under each green concept (e.g., practice, drivers, barriers, performance measures) identified from the first part of the literature review. This is how the relevant research gaps/questions were justified. As green related papers are scarce in pharma, the second part of the literature review considered varieties of sources including grey literature, such as government reports, policy statements, industrial reports, and conference proceedings across various domains of knowledge, such as management, engineering, environmental science, environmental management, pharmaceutical science and healthcare management, industrial production etc. However, papers with a highly technical focus were avoided. The 'key word search' and 'databases/journals' used in both phases of the literature review is presented in Table 3.1 below.

Table 3.1b 'Key words searches' and 'databases' used for selecting papers to review (Source: researcher)

Literature Review Phase	Key words searched	Databases / Journals
Phase One (GSCM General Focus)	Green supply chain', 'Green supply chain management', 'Sustainable supply chain', 'Environmental Supply chain', 'Green supply chain practices', 'Green supply chain management practices', 'ecological supply chan', 'Environmental sustainability', 'Green design', 'Green manufacturing', 'Green purchaisng', 'Life-cycle management of products', 'Recylcing', 'Reusing', 'Remanufacturing', 'Reverse logistics', 'Product End of life management', 'Drivers of green supply chain', 'Barriers of Green supply chain', 'DEterminnats of green supply chain', 'Success factors of green supply chain', 'Enabler and barier of Green supply chain', 'Responsible business', 'Responsible supply chain', 'Green operations', 'Green suppliers', 'Closed loop supply chain'	Google scholar, Science Direct, EBSCO, Emerald and Elsevier, Taylor and Francis, Springer and Wiley, Summon The online library, Books, Conference Papers etc. Key Journals: Journal of Operations Management, Journal of cleaner produciton, International Journal of Production Economics, Supply Chain Management: An International Journal, International Journal of Production Research, Journal of Supply Chain and Operation Management, Transportation Research Part E: Logistics and Transportation Review, European Journal of Purchasing and Supply Management,Journal of environmental management, European Journal of Operational Research, International Journal of Purchasing and Materials Management, Resources, Conservation and Recycling, Omega: the International Journal of Management Science, etc
Phase Two (Green related Pharma Focus)	Pharmaceutical supply chain', 'Green Pharmaceutical supply chain', 'Green pharma operations', 'Green supply chain in pharma', 'Pharma logistics', 'Pharmaceutical produciton', 'Drug manufacturing', 'Tablet manufactruing', 'Pharma sustainability', 'Pharma recycling', 'Pharma distribution', 'Drug design', 'Pharma regulation', 'API manufacturing', 'Drug formulation', 'Innovative pharma', 'Generic Pharma', 'Bio pharma operaitons', 'Drug reuse', 'Drug disposal', 'Pharmaceuticals in Environment', 'Pharmaceuticals Disposal', 'Pharma green practice', 'Pharma green drivers', 'Pharma Green barriers' etc.	Google scholar, Science Direct, EBSCO, Emerald and Elsevier, Taylor and Francis, Springer and Wiley, Summon The online library, Books, Conference Papers etc. Key industry Reports: Pharma Manufacturing, Pharma Logistics IQ, PharmaTech, PSNC, CCGs, WIUK, company sustainability and environmental report; Regulatory: FDA, MHRA, EMA, cGMP, WHO, UK Department of Health; Key Books: Green & Sustainable Pharmacy, Active Pharmaceutical Ingredients, Pharmaceutical Manufacturing Hand Book: Production and Process; Journal: Journal of business ethics, Journal of Managed Care Pharmacy, JOURNAL OF PHARMACY PRACTICE, Science of The Total Environment, Environmental International, Social Science & Medicine, Journal of Pain and Symptom Management, Journal of Environmental Management, etc

The first phase of literature review process involves below stages:

Stage 1: Main library databases and journals used (see Table 3.1 above)

Stage 2: Apply key words search (see Table 3.1 above)

Stage 3: Total number of related papers appeared on key journals in 2016 were more than 350

Stage 4: Apply inclusion / exclusion criteria: only those papers selected that are predominantly focus on energy, materials, and toxicity; also, chemicals related industry focus. Avoid technical papers.

Stage 5: After reviewing the title and abstract based on inclusion and exclusion criteria the total number of papers became 105. However, the list was refined and updated periodically.

Stage 6: Manual content analysis was done to understand the key themes and subthemes of GSCM. Special focus was given materials, energy, and toxicity related aspects.

In summary, after the first phase of the review, the researcher was able to conceptualise the GSCM practices through three key themes: materials, energy and toxicity. The review also enabled the researcher to understand the key drivers, barriers, and performance measures in the related field.

While the first phase of the generic literature review on GSCM provided a grounded framework to explore the related green concepts in pharma sector, the actual literature search in the second phase for pharma became more systematic and précised. The key stages involved in the second phase of the literature review are shown below:

Stage 1: Main library databases and journals used (see Table 3.1 above)

Stage 2: Apply key words search (see Table 3.1 above)

Stage 3: Total number of related papers appeared on key journals in 2016 were more than 170

Stage 4: Apply inclusion / exclusion criteria: only those papers selected that are predominantly focused on pharma sector and related green innovations; avoid highly technical papers. However, only those technical papers were considered that were necessary to develop understanding and the researcher could interpret them from an operations perspective. Due to the lack of papers on pharma, some of the papers which have partial focus of green are also considered for review. Due to the lack of green related publication, it also included book chapter, conference papers, industry reports etc (see Table 3.1 for detailed sources).

Stage 5: After reviewing the title and abstract based on inclusion and exclusion criteria the total number of papers was 82. However, the list was refined and updated periodically.

Stage 6: Manual content analysis was conducted to understand the key themes and subthemes of GSCM. Special focus was given materials, energy, and toxicity related aspects to understand related research gaps.

In summary, the second phase of the literature review has provided us with state-of-the-art knowledge on GSCM in the pharma sector. The key focus of content analysis in the second phase of the literature review was to understand materials, energy, and toxicity related practices (indicated by the initial first phase of review) under each phase of the pharma supply chain. It also focused on understanding related drivers, barriers, and performances in the context. This close content analysis helped the researcher to identify and justify related

key knowledge gaps in pharma leading to the proposed research question. Now it is important to know how data was collected to answer the proposed research questions, which is discussed in the subsequent sections.

3.4.2 Interviews

It is clear from the initial literature review that this empirical investigation of the green supply chain in the pharmaceutical context is new. As the existing literature was still unfertile in terms of understanding green practices, related drivers, barriers and performance across the pharmaceutical supply chain, an in-depth understanding was crucial to enrich the field. For instance, it required an in-depth understanding of how green process design is possible and how cost plays a key role for generic pharma to adopt green. An interview research strategy serves this purpose (Saunders et al., 2009). The investigation predominantly aimed to explore the phenomenon of emerging green practices, drivers, barriers, and performance in a new context. An interview research strategy was chosen due to the exploratory (what?) nature of the investigation (Yin, 2009). This design was also adapted to the explanatory (how? / why?) approach (Tellis, 1997). A well-designed interview also avoids radical particularism and explores the heterogeneity of approaches to understanding different barriers, drivers, practices, and perceived performances of GSCM in the chosen context (Theodorakopoulos et al., 2015). Additionally, other methods such as focus group, observations, case studies were avoided, as interview is the best method to collect customized data using either standardized and/or non-standardized forms of interventions with the respondents accordingly to achieve each research objective (Saunders et al., 2009). Though the approach was comparatively new in the proposed context, similar approaches have been used in the other industrial contexts, including pharma, while exploring the concept of the green supply chain, such as Hsu & Hu (2008) in the electronic industry, Azevedo et al. (2012) in the automobile industry, Balasubramanian and Shukla (2017) in the construction industry, and Massoud et al. (2015) in the pharma industry. Diagram 3.3 below shows an overview of interview process for the study. The subsequent section explains the types and structure of the interviews that were conducted.

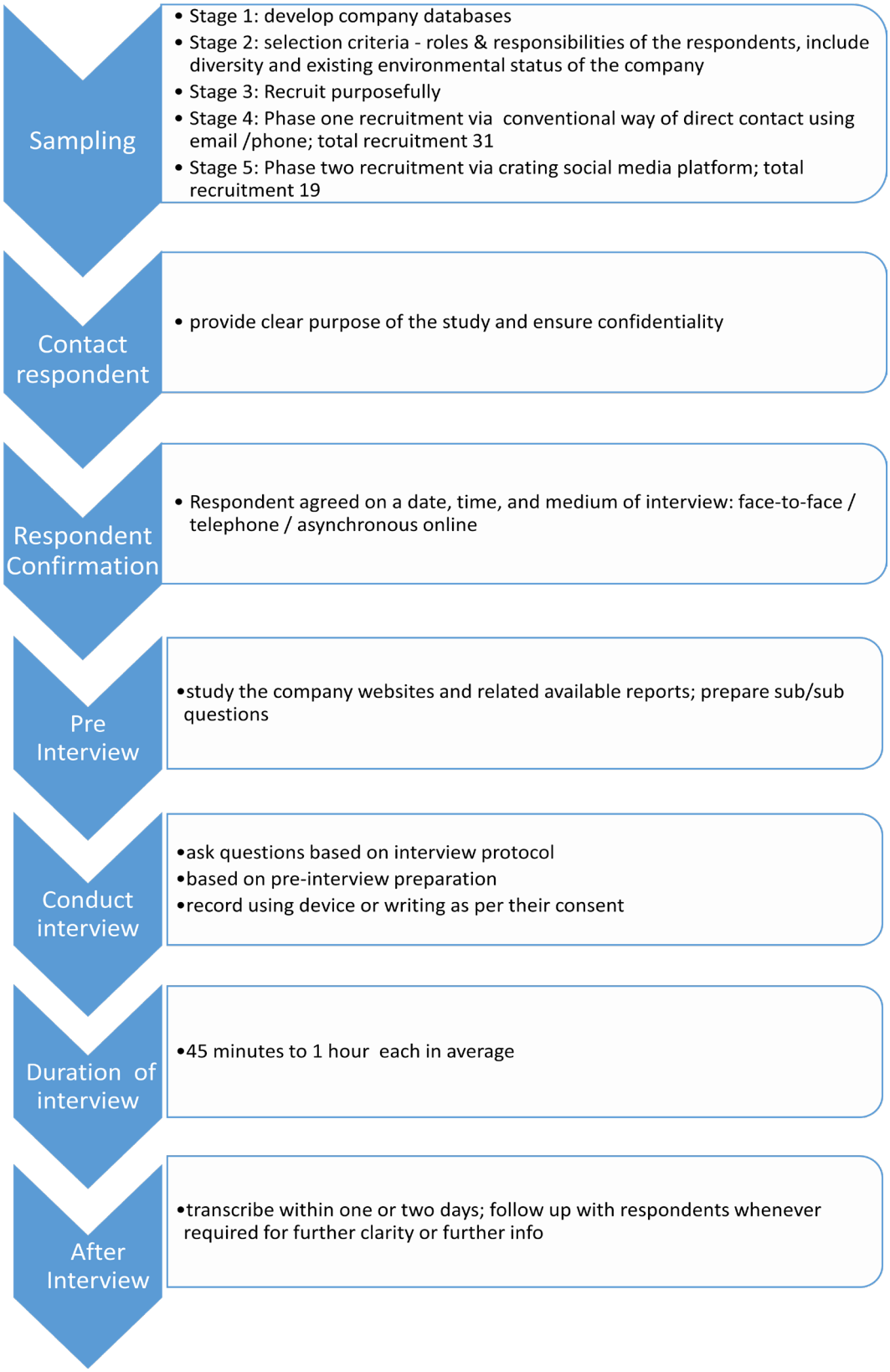


Figure 3.3 Overview of interview process in the study (source: researcher)

3.4.2.1 Sampling approach used

The main goal of this inductive reasoning-based investigation is to explore and explain the GSC phenomenon and build theory based on data provided by the diversified stakeholders within a pharmaceutical supply chain. In contrast to other non-probability sampling, purposive sampling allows the researcher to reflect on his own judgement while selecting cases/participants considering extreme cases/participants, heterogeneity (maximum variation), homogeneity (maximum similarity), critical cases/participants or typical cases/participants (Saunders et al., 2009). This type of sampling also reduces the extraneous variations by providing detailed specification of the populations (Eisenhardt, 1989). Therefore, the researcher was in a good position to select the sample respondents considering all variations (e.g., production variations between API manufacturers and Formulators; or green motivation between innovative and generic pharma) and heterogeneity (e.g., R&D activities in the new process development of a drug in an innovative environment and R&D activities in a generic environment) among different stakeholders such as innovative pharma, generic pharma, bio pharma. Due to this diversification the probability sampling (e.g., just randomly selecting a respondent from any pharma context) is not appropriate for this investigation. Controlling of extraneous variation by the selection of appropriate cases/informants (judgemental cases) could also help the researcher to define the limits for generalizing the findings. As the focus of the study was to explore and explain the key themes (e.g., green drivers, barriers, practices, performances) among the diversified pharmaceutical stakeholders, purposive sampling was a good choice (Yin, 2009). This theoretical sampling is well established and used in previous studies (Eisenhardt, 1989; Theodorakopoulos et al., 2015). A similar sampling approach is also used in the green supply chain related studies, such as Balasubramanian and Shukla (2017), Massoud et al. (2015), Nune (2011), Frost (2011) and Drohomeretski et al (2014). However, to recruit the respondents for the study, a well-defined company source was necessary. Unfortunately, the related company sources were scattered and dispersed into different branches. For instance, some voluntary organizations listed only generic companies, missing innovative ones, and vice versa. Also, some of the companies were still not categorized into innovative, generic etc based on their key characteristics. Therefore, a holistic database was required for this investigation. The next section discusses it.

3.4.2.2 Development of company database

The reason for creating the database is that there was no standard pharma company database covering all stakeholders available that could be used for this research. None of the research in the pharma sector had provided any specific source of company database in the chosen context. Additionally, prior to recruiting the interviewees for the study it was vital for the researcher to have a clear understanding of the types and total number of players across the industry. That is why this study produced a standard company database based on different scattered sources. This database will be useful and provides a new direction for future researchers in the field.

As the main focus of the study is to analyse each key stakeholder separately within the pharmaceutical supply chain, in the first stage, the researcher attempted to develop a database to categorize each stakeholder based on functional operations (R&D, API producer, Formulators, 3PLs/wholesalers, retailers, waste collectors, etc). It was done based on researching the core operational activities from the companies' annual reports, company websites, and Companies House UK. The database was also developed based on SIC (Standard Industry Classification) UK. Five different sources that are well recognized by all in the sector were used to develop this database. These sources are: ABPI (Association of British Pharmaceutical Industry), BGMA (British Generic Manufacturing Association), eMC (Electronic Medicines Compendium), Waste Management Companies and HDA (The Healthcare Distribution Association UK). The IBIS World report was also used to categorize them. The addition/reorganizing of each stakeholder company based on their core business operations were updated continuously throughout the data collection process. A detailed source of database development for each stakeholder is shown in Table 3.2.

Table 3.2 Sources used to develop company database for Pharma sector		Total number of companies identified
Stakeholder(s)	Key sources used to develop company database	
Database for upstream stakeholders		
Innovative Phaarma, Generic Pharma, Bio pharma	ABPI (Association of British Pharmaceutical Industry),	61 = (innovative pharma 16 + generic pharma 20 + bio pharma 25)
	BGMA (British Generic Manufacturing Association),	
	eMC (Electronic Medicines Compendium),	
	HDA (The Healthcare Distribution Association UK)	
	IBIS World Reports	
	PAGB (Proprietary Association of Great Britain) is the UK trade association which represents the manufacturers of branded over-the-counter medicines, self care medical devices and food supplements.	
	Dow Jones Sustainability Index Database (https://yearbook.robecosam.com/companies/#data-search*=%22astrazeneca%22]	
	GRI (Global Reporting Initiatives) Database	
Database for downstream stakeholders		
Retail Pharmacies	PSNC (Pharmaceutical Service Negotiating Committee)	14500
	NHS (https://www.nhs.uk/Services/)	
GPs	https://www.gmc-uk.org/-/media/documents/what-our-data-tells-us-about-gps_pdf-74830685.pdf	54024
CCG (Clinical Commissioning Group)	NHS (https://www.nhs.uk/Services/)	194
Hospital trusts	https://www.nhs.uk/ServiceDirectories/Pages/NHSTrustListing.aspx	223
Care homes	https://www.oscar-research.co.uk/datasheets/carehomes	21506
Waste Management Companies	ESA (Environmental Service Association) http://www.esauk.org/about/our_members/	64 (only full membership)
Local Councils	https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/491463/List_of_councils_in_England.pdf - https://www.lgiu.org.uk/local-government-facts-and-figures/	343
Wastewater treatment companies	UKWIR (https://events.ukwir.org/eng/UK-water-industry-research)	8500
	https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/69592/pb13811-waste-water-2012.pdf	

Once detailed company sources were known, a manual review was carried out on each company's operational activities described on its website, annual reports and/or environmental reports. The key operational activities that came out from the review were: drug R&D, API production, formulations, packaging, bio based production, chemical based production, logistics, distribution, contract research and development and contract manufacturing. While combining this manual review with existing pharma literature, innovative pharma, generic pharma, and bio pharma were the three key stakeholders dominating drug discovery, development, and manufacturing in the upstream sector. A total 61 upstream pharma companies in three categories (16 innovative pharma, 20 generic pharma and 25 bio pharma) were identified out of 259 different companies listed in different sources

as shown in Table 3.2. The remaining companies (259 – 61 = 198) fall under wholesale and distribution. For downstream pharma stakeholder companies, around 14500 retail pharmacies, 194 local CCGs, 64 (only full membership with the ESA association) waste management companies and 343 councils in England (not UK), and around 8500 wastewater treatment companies were identified. It is also important to note that very small numbers of CMO (Contract Manufacturing Organization) were included in the generic pharma cluster, as they follow generic pharma characteristics in most cases, so they werenot considered separately for analysis. Similarly, a few CRO (contract research organizations) were included in the R&D based innovative pharma cluster, as they follow almost the same characteristics in terms of drug design and discovery operations.

3.4.2.3 Determine key factors for respondent selection

Once the sources of all relevant pharma companies were tracked, the second stage in the recruitment process determined the key factors for recruiting the respondents. Considering the background research problems, relevant pharma stakeholders' operational activities and the existing literature review, three key factors were considered prior to recruiting an appropriate respondent who can contribute to each area of the research objectives, for instance, selecting ***managerial level employees*** in individual operational areas (e.g., operations managers in tablet manufacturing, or managerial experience in drug dispensing).

While selecting respondents, as many ***operational variations*** as possible were considered. The wider consideration of diversified operations included all relevant variations (e.g., API plant, formulations plants, packaging plants, tablet production plant, liquid production plant, chemical based production, bio based production, or community vs hospital pharmacists) across the stakeholders. However, it is important to note that in the UK context most of the innovative companies have multiple functional areas of focus (e.g., R&D and manufacturing API or Manufacturing both API and formulation and distribution).

The overall existing ***environmental status of the company*** was also another key factor prior to selecting respondents from that company. Initial subjective evaluation of environmental consideration of the company was carried out. This was done by close scanning of environmental activities/initiatives on the company website and/or sustainability reports, company's participation in the GRI (Global Reporting Initiative) process. Respondents were invited and selected from those companies which published at least two environmental

aspects out of three key areas such as carbon, energy, raw materials/finished goods usages, water, toxicity and disposal.

Consideration of these key factors improved the vicinity of the industrial sector to understanding the role of GSCM (e.g., green practices, drivers, barriers, performance, and their interactions) in the context. This diversified focus also allowed the degree of vigilance of the complex and diverse pharmaceutical supply chain in the context (Theodorakopoulos et al., 2015). To avoid the variations in institutional factors (e.g., local/national law, legislation etc), it was ensured that each stakeholder company operated within a similar context (Tsanis, 2013).

3.4.2.4 Respondent recruitment

The recruitment was done in two phases. The first phase aimed to approach the respondents in a conventional way of recruitment through direct emails / phones / mail as per company database, while the second phase employed a comparatively new recruitment process via a social media platform in order to increase the chance of recruiting relevant employees. The subsequent section discusses these two phases of recruitment.

Phase one recruitment: As per the selection criteria mentioned in section 3.4.2.3, a total 267 prospective companies were purposefully contacted directly (via email/phone/mail) using the company database created. It covered all upstream (Innovative Pharma, Generic Pharma, Bio Pharma) companies in the database and the rest were from the downstream (pharmacy, GPs, hospitals, care homes, local councils, waste management companies and wastewater treatment) companies. Each of them was given three documents: an introductory letter, participant information sheet and participant consent form. The format used for each of these documents is presented in Appendix. Only 37 respondents (out of 267) initially agreed to participate. However, out of 37, 28 interviews (26 from downstream and 2 from upstream) were finally and successfully completed, as the rest of the respondents were excluded due to various reasons such as change of mind, and not being aware of any environmental aspects reflecting their roles and responsibilities. A detailed flow diagram of how the number of respondents were recruited in phase one and two over seven months is presented in the figure 3.4 below.

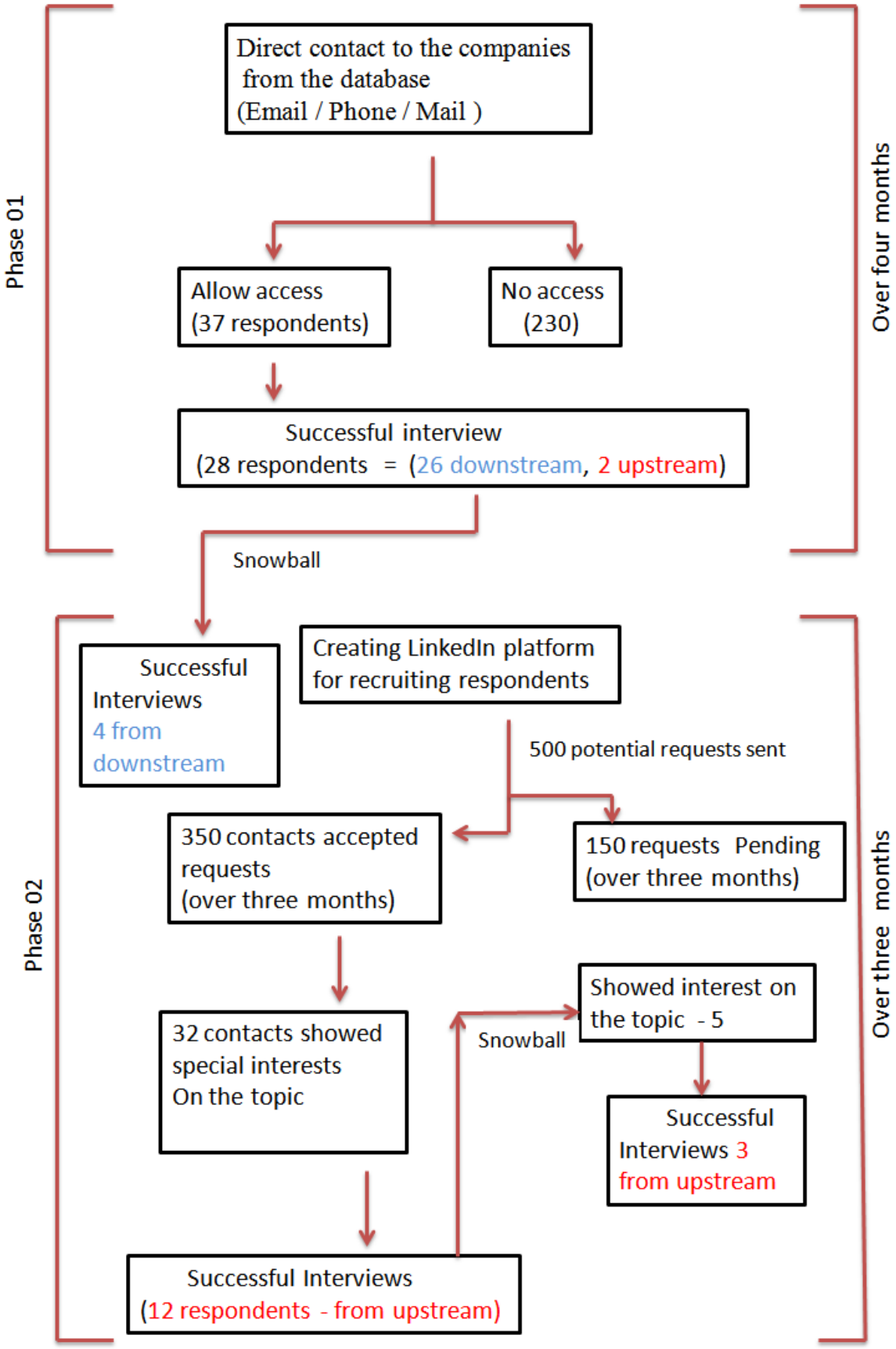


Figure 3.4 An overview of interview recruitment process in the study.

Phase Two recruitment: The key reason for this stage of recruitment was to employ a new way of recruiting respondents to increase the response rate, especially from upstream pharma companies. In the first phase only two respondents were recruited from upstream companies even though the entire universe (as per database) was contacted for selection. Additionally, after a quick analysis of the first phase interview many questions were not answered sufficiently, especially in the case of the upstream drug design and manufacturing phase, due to having a very low number of responses. Therefore, at this stage, the researcher introduced a new strategy for recruiting respondents to increase the chance of recruitment.

A social media platform, LinkedIn, was used to recruit most of the respondents from upstream pharma companies. A separate group (called 'Greening Pharmaceuticals Operations & Supply Chain') was also created on this platform to attract the relevant professionals. LinkedIn is one of the trusted and reliable professional networking websites where many of the prospective contacts from innovative, generic and bio pharma companies were found. It was much easier and effective to target the respondents by direct messaging, calling, and emailing once they approved the connection request. As Dusek et al. (2015) highlighted, ***"unlike Facebook and other more general social media, LinkedIn is a platform that connects professionals in various fields and, therefore, provides greater ability to target data collection to an appropriate social network"***

For further credibility and reliability of the recruitment process, each of the respondents was also contacted (in terms of a few exchanges) via their company's direct telephone line and/or company email.

It is also important to note here that it was also much easier to build trust and rapport once the prospective respondent was contacted and accepted the researcher's connecting request, as building trust and rapport are the key ethical aspects of collected data (Saunder et al., 2009; Creswell, 2013). Building trust and rapport was particularly important for the pharma and healthcare related sectors which are highly regulated in practice. This quick rapport and trust building opportunity via LinkedIn enabled the researcher to recruit a number of the respondents referred by the other respondents already interviewed. This referral system is known as snowball sampling where the initial respondents refer someone they know who may be eligible to be interviewed (Yin, 2009; Saunders et al., 2009). However, the priority was also given to the entire coverage of each stakeholder involved in the research. This phase enabled the researcher to recruit fifteen respondents from upstream pharma companies and

four respondents from downstream. The detailed recruitment process in phase two is shown figure 3.4 above.

3.4.2.5 Justifying the number of respondents selected for the investigation

Though there is no golden rule for selecting a specific number of respondents for a qualitative study, 'data saturation' could be a good measure for justifying the number of samples required for a particular qualitative investigation (Creswell, 2013; Neuman, 2014; Fusch and Ness, 2015). Data quality, data rich in quantity, data thick in quality, data replication etc are some of the general sub measures of the concept 'data saturation', though there is no ***one-size-fits-all*** method to reach data saturation (Tracy, 2010; Fusch and Ness, 2015).

Considering the general principal of data saturation in line with each research question, the researcher created and followed a logical process (figure 3.5) for finalizing the number of samples required for each category of stakeholder.

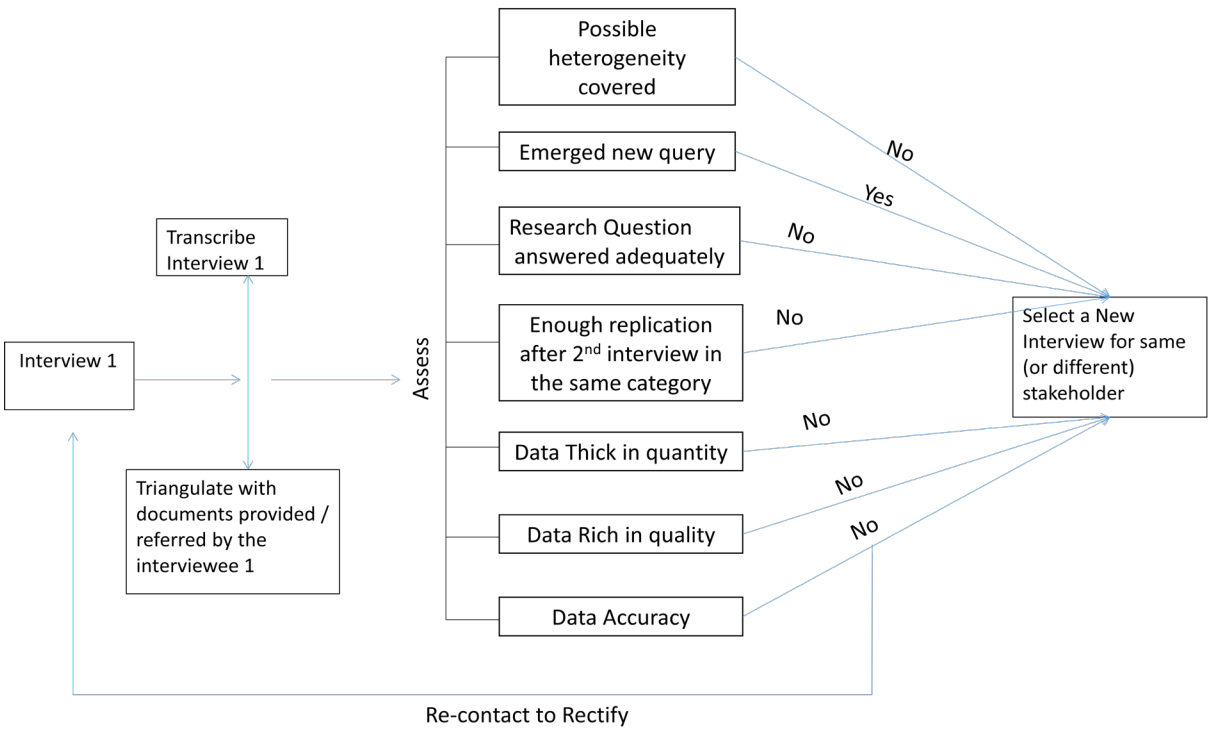


Figure 3.5 Logic and justification used for selecting number of samples (Source: Researcher)

An interweaving process was followed throughout the data collection process. Each new interview was added to the same category or a different one following the logic presented in

figure 3.5. Followed by this logical process and in line with the requirements highlighted from stage one to stage four, a total 47 respondents were finalized - 17 respondents from 10 different companies to cover upstream pharma stakeholders and a total of 30 respondents from 29 different organizations to cover downstream stakeholders. A detailed demography of respondents is presented in the subsequent section (Table 3.3 and Table 3.4).

3.4.2.6 Demography of respondents

Demography of respondents from both upstream and downstream stakeholders is the key to linking the relevancy and validity of the data collected to answer the research questions. This section presents a detailed demography of the respondents who participated in the study. For instance, table 3.3 shows the number of upstream pharma companies including different sites, the designation of each participant, types of stakeholders, key operational focus of the stakeholder company, company size, annual turnover and mode of interview used. Table 3.4 also shows the key respondents from downstream stakeholders, their key operations and mode of interview used.

Table 3.3: Demography of the respondents from upstream pharma stakeholders (Source: Researcher)

Company code	Interviewee	Type of stakeholder	Key Operational focus of the stakeholder	Size	Annual revenue (£million)	Mode of Interview
A	Senior Environmental Specialist	Innovative	R&D, Manufacturer (API + Formulation)	Large	~6510	Telephone
B - site 1	EHS Manager	Innovative	Manufacturer (Formulation: Liquid + Solid)	Large	~3439	Telephone
B - site 2	Sustainability and Utility Manager	Innovative	R&D, API manufacture (both Bio & Chemical Based plant)	Large	~6510	Telephone
B - site 3	Lab Scientist	Innovative	R&D sites	Large	~1466	Telephone
C	Senior Principal Environmental Scientist	Innovative	R&D, API manufacture (both Bio & Chemical Based plant)	Large	~3o8	Telephone

Company code	Interviewee	Type of stakeholder	Key Operational focus of the stakeholder	Size	Annual revenue (£million)	Mode of Interview
D - site 1 (R&D)	Strategic Business Development Manager	Innovative	R&D, API manufacture (both Bio & Chemical Based plant)	Large	~3o8	Telephone
D - site 2	Supply Chain and Quality Operations Executive	Innovative	Manufacturer (R&D, API + Formulation)	Large	~3438	Telephone
E - site 1	EHS Manager	Generic	Manufacturer (Generic API)	Large	~1466	Telephone
E - site 2	Manufacturing Engineer	Generic	Manufacturer (formulation site)	Large	~35	Telephone
E - site 3	Senior Supply Chain Leader	Generic	Manufacturer (formulation packaging)	Small	~10	Telephone
F - site 1	Head of Quality	Generic	Generic Formulation	Large	~35	Telephone
F -site 2	Principal Scientist	Generic	R&D sites (Generic)	Large	~3438	Telephone
G	Production Manager	Generic	Manufacturer (Liquid formulation)	Large	~3439	Telephone
H	Production Manager	Generic	Manufacturer (Sterile/Liquid)	Small	~7	Telephone
I	Senior Scientist	Bio pharma	R&D, Lab scale Manufacture (Bio based)	Mediu m	----------	Telephone
J - 1	Lab Manager	Bio pharma	R&D, Manufacture (Bio based)	Small	----------	Telephone
J -2	Quality Assurance Manager	Bio pharma	R&D, Manufacture (Bio based)	Small	----------	Telephone

Table 3.4: Demography of the respondents from downstream stakeholders (Source: Researcher)

Company code	Interviewee	Types of stakeholder	Key Operational focus of the stakeholder	Mode of Interview

Company code	Interviewee	Types of stakeholder	Key Operational focus of the stakeholder	Mode of Interview
K – store 1	Pharmacy Manager	Pharmacy (community)	Participate in MUR, NMS, drug take-back services	Telephone
K – store 2	Pharmacy Manager	Pharmacy (community)	Participate in MUR, NMS, drug take-back services	Telephone
L	Pharmacy Manager	Pharmacy (community + hospital)	Participate in MUR, NMS, drug take-back services	Telephone + face to face
M	Service Development Pharmacist	NGO (Community pharmacy)	Promote and negotiate pharmacy services with NHS	Telephone
N	Senior pharmacy technician	Pharmacy (Community + hospital)	Participating in MUR, NMS, drug take-back services	Face to face
O	GP	CCG (GP)	Participate in Nationwide drug waste reduction program, medicine optimization	Telephone
P	GP	CCG (GP)	Participate in Nationwide drug waste reduction program, medicine optimization	Telephone
Q	Senior Nurse	CCG (Hospital)	Participate in Nationwide drug waste reduction program, medicine optimization	Telephone
R	Care home Manager	Care home	Deal with drug use and disposal (aged/end of life patients)	Telephone
S	Care home manager	Care home	Deal with drug use and disposal (Dementia)	Telephone
T	Environmental Compliance Advisor	Clinical waste management	Manage industrial drug waste/clinical waste/ household waste	Telephone
U	Environment Advisor	Clinical waste management	Managing industrial drug waste/clinical waste	Telephone

Company code	Interviewee	Types of stakeholder	Key Operational focus of the stakeholder	Mode of Interview
V	Project Manager	Water company (Research based)	(Municipal & industrial) wastewater treatment development	Telephone
W	Environmental Government Manager	Water company	Municipal wastewater treatment including industrial wastewater stream	Telephone
LC – 01	Information Officer	Local council	Responsible for only waste collection; does not manage any disposal site	Asynchronous online interview (using open ended email)
LC – 02	Information Officer	Local council	Responsible for only waste collection; does not manage any disposal site	Asynchronous online interview (using open ended email)
LC – 03	Waste Contract Manager	Local council	Waste collections, Sorting site, Disposal site	Asynchronous online interview (using open ended email)
LC – 04	Information Governance Officer	Local council	Waste collections, Partial Disposal activities	Asynchronous online interview (using open ended email)
LC – 05	Corporate Services Officers	Local council	Waste collections, Full Disposal sites	Asynchronous online interview (using open ended email)
LC – 06	Head of Corporate Services	Local council	Waste Collections; No disposal sites; clinical waste collection service	Asynchronous online interview (using open ended email)
LC – 07	Technical Assistant	Local council	Waste Collection; sorting sites; full disposal services	Asynchronous online interview (using open ended email)
LC – 08	Information Access Officer	Local council	Waste collection only; does not own any disposal sites	Asynchronous online interview (using open ended email)
LC – 09	Information Governance Officer	Local council	Waste collections, Full Disposal sites	Asynchronous online interview (using open ended email)
LC – 10	Interim Assistant Director of Public Space	Local council	Clinical waste collection service; Own disposal sites	Asynchronous online interview (using open ended email)

Company code	Interviewee	Types of stakeholder	Key Operational focus of the stakeholder	Mode of Interview
LC – 11	Information Governance Officer	Local council	Does not own disposal sites but work with waste contractors	Asynchronous online interview (using open ended email)
LC – 12	FOI & Complaints Manager	Local council	Full waste collection service but another council is responsible for waste disposal	Asynchronous online interview (using open ended email)
LC – 13	Customer Feedback Manager	Local council	Waste collection; higher landfill diversion rate; rely on another council for disposal (partial)	Asynchronous online interview (using open ended email)
LC – 14	Compliance Support Manager	Local council	Waste collection; own disposal facility; waste to energy facility	Asynchronous online interview (using open ended email)
LC – 15	FOI & DPA officer	Local council	Only collection; no disposal facility; contract disposal facility	Asynchronous online interview (using open ended email)
LC – 16	Information Governance Officer	Local council	Collection of clinical wastes; no disposal facility; contract disposal facility	Asynchronous online interview (using open ended email)

3.4.2.7 Data collection process

This section explains and justifies the structure of interview (e.g., interview approaches, mode of interview to interact with respondents) used. It also explains the key data collection process, such as how interview protocol was used across different stakeholders.

Structure of the interviews

While three core interview approaches - structured, semi-structured and unstructured - are available, the best fit for each approach is predominantly dependent on the types of enquiry in hand (Bryman, 2016). For instance, if the subject of the enquiry requires exploring in depth, an unstructured interview is the most suitable. A structured interview would be the best fit if the subject is primarily involved in simple description, and explanation may be a secondary requirement (Saunders et al., 2009). A semi-structured interview was selected for this study because semi-structured interviews allow the researcher to both explain and explore the phenomenon whilst the unstructured interview only allows the exploration of the phenomenon and structured predominantly allows descriptive analysis (Saunders et al.,

2009). The matrix below (Table 3.5) also clarifies the related logic and helped with the decision to choose a semi-structured interview for the study in line with the research questions.

Table 3.5 Justification for using semi-structured interview
(Adopted from Saunders et al., 2009)

Types of Interviews	Exploratory	Descriptive	Explanatory
Structured		✔✔	✔
Semi-structured	✔		✔✔
Unstructured	✔✔		

✔✔ - more frequent

✔ - less frequent

As the investigation already had some predefined concepts (e.g., green practices, drivers, barriers and performance) and there was the intention to explore them further in detail by probing (until the clarity comes out) the respondents to get an in-depth explanation of why they implemented green practices (green drivers) and why they did not implement related green practices (green barriers) and how green practices helped them to improve environmental and economic performance (green performance and performance measures), a semi-structured interview was the best fit in this research context (Bryman, 2016; Neuman, 2014; Saunders et al., 2009). Similar semi-structured interviews are also evidenced in the green supply chain management literature, such as Balasubramanian and Shukla (2017), Massoud et al. (2015), Nune (2011), Frost (2011) and Drohomeretski et al. (2014).

Faced with some practical factors such as time constraints, cost, distance travelled, availability and flexibility of the respondents, and other related factors, a combination of face to face, telephone, online synchronous and asynchronous interviews were conducted. Though each of the options has both merits and demerits, in practice all of them are valid methods of data collection (Saunders, et al., 2009; Neuman 2014). Online synchronous were used to collect data in real time via a self-controlled chat room (e.g., facebook messenger, LinkedIn messaging etc), while asynchronous interviews were used to collect offline data such as data collected through open-ended email questionnaires (Saunders et al., 2009; Bryman and Bell, 2015). Data collected through open-ended email questionnaires using online asynchronous interviews technique was recently evidenced in the study of Priporas et al. (2017). Further detailed demography of respondents and number of interviews in each category (mode of interview) considered are shown in Table 3.3 and Table 3.4.

Data Collection:

As agreed with the respondents, a combination of face-to-face, telephone and asynchronous online interviews using open-ended email was conducted considering limited time and costs. Each respondent was asked questions in accordance with the interview protocol (see appendix 1). For instance, each respondent was asked questions under four key topics: Green / Environmental practices, Motivation / drivers of green practice adoption, Barriers / challenges for adopting green practices, and Performance captured from adopting green practices and the related performance measures used. Under each topic there was a general sequence of asking and probing questions such as 'What', 'Why' and 'How', while sometimes the respondents seemed to have forgotten some important green aspects, for instance, solvent recycling in the design phase; the respondent was probed on this occasion.

It is also important to note here that sometimes the respondents (especially downstream informants) did not understand what green practice/environmental practice or even management practice mean within his/her responsibility. But, when they were given some clues, such as drug waste management, drug waste reduction and prescribing practice, they readily understood and were able to contribute to the research questions. Sometimes interview protocol was slightly deviated to adjust to the category of respondents. For instance, slightly modified and more specific questions were asked to the respondents from local councils. See appendix 2 the interview protocol for local councils. The average interview duration was 45 minutes to 1 hour. Most of the interviews were audio recorded, and where recording was not possible, detailed notes were taken. Each recording was transcribed within one or two days. One of the transcriptions was shared with the respondents as requested. Additionally, some of the respondents were re-contacted by the phone / email / text message for further clarifications followed by the actual interviews as time passed with the data analysis. Any related reports/company documents suggested and shared by the respondents during/after interview were also used as complementary to the interview. As part of the asynchronous online interviews, a series of open-ended emails were exchanged with the respondents to obtain the answers to the research questions. This form of interview data was collected from 16 local councils. At the end of the email exchanges, the entire series of email exchanges or conversations were extracted from the email and saved as PDF files which were later saved with other interview transcriptions.

3.4.2.8 Data analysis process

Thematic content analysis techniques were used to analyse the data. It is a valid and widely used technique for qualitative information, as the researcher is able to categorize the information in different layers of meaning to sufficiently answer the research question (Krippendorff, 1980; Weber, 1990; Neuendorf, 2002). A detailed discussion of using content analysis for qualitative study is also explained in the section 3.5. The researcher used both Excel and NVIVO software to process the data prior to the final analysis. All the transcripts were uploaded to NVIVO software under three separate folders named 'Innovative Pharma', 'Generic Pharma' and 'Bio Pharma', and another folder named as 'Downstream Interviews' to upload all interview scripts related to each downstream stakeholder. An Excel database was created to organize the collected interview data under predefined themes and subthemes; so, later it was used to retrieve any relevant information for analysis purposes. A combination of both manual and software (NVIVO 12 pro) interventions provided a very effective and efficient way of interpreting each theme and subtheme and provided a valid inference from the study. This methodical approach is relatively new, as only a few researchers in the field have used this approach, e.g. Hofer et al. (2010). This study has provided further evidence of understanding the effectiveness and efficiency of applying both manual and machine intervention. A detailed analysis process is shown in figure 3.6 below.

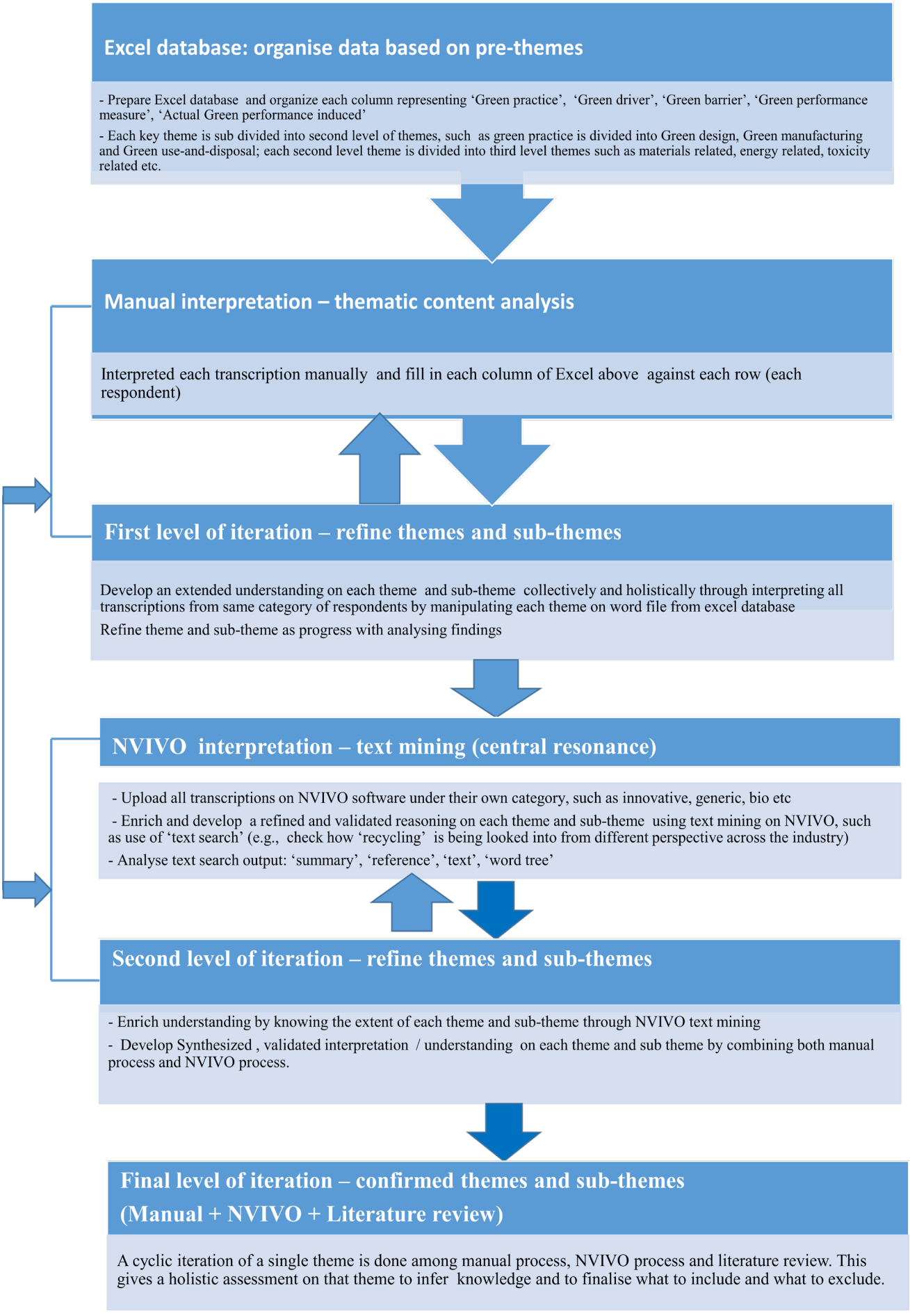

Excel database: organise data based on pre-themes
- Prepare Excel database and organize each column representing 'Green practice', 'Green driver', 'Green barrier', 'Green performance measure', 'Actual Green performance induced'
- Each key theme is sub divided into second level of themes, such as green practice is divided into Green design, Green manufacturing and Green use-and-disposal; each second level theme is divided into third level themes such as materials related, energy related, toxicity related etc.
Manual interpretation – thematic content analysis
Interpreted each transcription manually and fill in each column of Excel above against each row (each respondent)
First level of iteration – refine themes and sub-themes
Develop an extended understanding on each theme and sub-theme collectively and holistically through interpreting all transcriptions from same category of respondents by manipulating each theme on word file from excel database
Refine theme and sub-theme as progress with analysing findings
NVIVO interpretation – text mining (central resonance)
- Upload all transcriptions on NVIVO software under their own category, such as innovative, generic, bio etc
- Enrich and develop a refined and validated reasoning on each theme and sub-theme using text mining on NVIVO, such as use of 'text search' (e.g., check how 'recycling' is being looked into from different perspective across the industry)
- Analyse text search output: 'summary', 'reference', 'text', 'word tree'
Second level of iteration – refine themes and sub-themes
- Enrich understanding by knowing the extent of each theme and sub-theme through NVIVO text mining
- Develop Synthesized , validated interpretation / understanding on each theme and sub theme by combining both manual process and NVIVO process.
Final level of iteration – confirmed themes and sub-themes
(Manual + NVIVO + Literature review)
A cyclic iteration of a single theme is done among manual process, NVIVO process and literature review. This gives a holistic assessment on that theme to infer knowledge and to finalise what to include and what to exclude.

Figure 3.6 Data analysis process for the study (Source: Researcher)

Five key predetermined themes (Green Practices, Green Drivers, Green Barriers, Green Performance Captured and Green Performance Measure) were recorded in five columns in an Excel Database. Then each respondent was manipulated on each row in the same excel database. Again, based on the existing literature, several subthemes were recorded under each key theme on the Excel database. For instance, under 'Green Practices' there were three more subthemes: 'Green Design and Development Practice', 'Green Manufacturing Practices' and 'Green Use and Disposal Practices'. Again, each of these subthemes were further sub categorized based on the existing literature (e.g., MET, or green chemistry concept). For instance, under 'Green Manufacturing Practice', there were six subthemes: 'Material reduction Practice', 'Energy Reduction Practice', 'Toxicity Reduction Practice', 'Biodegradability related Practice', 'Renewability related Practice' and 'Pollution Reduction related practice'. On top of this one newer column was added named as 'other' which captured 'other /new themes' that had emerged. Next, each transcript was manually read through and the two sets of themes highlighted. The first one was matched under already defined themes/sub-themes and the second one was new was put under the 'other' tab on the Excel database. After every one/two transcription reviews and analysis, the database was updated accordingly with existing and/or any new themes or sub-themes that had emerged. This is how the process was continued from transcript number one to the final transcript analysis.

Once this round was finished, in the second phase, all data captured under the 'other' tab was extracted to further analyse it to identify newly emerged themes and related sub-themes. For instance, in this second phase of data processing, three more new key themes emerged under 'Green Manufacturing': 'Material recovery Practice', 'Product Stewardship Practice' and 'Responsible waste management Practice'. *(In this process, use of 'Text Search' under 'Query' tab in NVIVO was also useful to quickly obtain understanding about a theme/subtheme.)* So, these three key themes were added with six other key subthemes selected to understand the concept of 'Green Manufacturing Practice'. Once these three new subthemes were added into the existing Excel database, then the subthemes became 9 in total, instead of 6, to understand the concept of 'Green Manufacturing'. Then, each of the transcripts was again scanned to fill with further sub-categories of themes which were related to any of the 9 subthemes to explore the concept of 'Green Manufacturing Practice' in the pharma contexts. The process continues until any further new subcategories of themes were

identified under any of the 9 sub-themes. *In this process, use of 'Text Search' under 'Query' tab in NVIVO 12 pro version was also useful to quickly obtain an understanding about a theme/subtheme. This text search has three types of output: summary, reference, text, and word tree. These four different outputs from a single word search have enriched the researcher's interpretation capacity in the context. For instance, 'word tree' as an output was significantly useful to understand the central resonance of a particular theme and/or subthemes for articulation and make a clear inference on the themes/subthemes.*

Finally, a combination of iteration from the manual process, NVIVO process and literature review process was conducted to finalize the themes and subthemes. Once it was confirmed (after reviewing each transcript three/four times) that there were no more new themes to be included in the excel database under each of the 9 subthemes to understand the concept of 'Green Manufacturing Practice', all data captured under each of the 9 subthemes, such as 'Material reduction' related, data was extracted from the Excel database to identify the key important and common themes across the different stakeholders, which could be used as key indicators for measuring the concept of 'Material Reduction', for instance. After scanning several times, seven key themes or indicators were identified as dominant and important themes across the upstream (innovative, generic and bio) pharma companies to understand and measure the concepts of 'Material Reduction' Practice (under green manufacturing) in the pharma context. Later, each of the seven indicators was separately explained (what, how, why) based on evidence collected from the interview. This is how the analysis process continued iteratively and reorganized key subthemes (materials, energy and toxicity related) under each green practice.

NVIVO 'Text Search' was helpful to prepare this explanation quickly, as it helped the researcher to fine tune each respondent across the scripts very quickly to find out who said what, why, how, and when using relevant key words from the indicator. It is also important to note here that for best output, the researcher sometimes highlighted the option of '-with stemmed words (e.g., talking)' along with '-Exact matches (e.g., talk)' in NVIVO prior to running the 'Text Search' query. Also, using the 'word tree' as an output was tremendously helpful to infer knowledge on themes or subthemes. This quick and customized text search along with manual skim through the transcript helped the researcher to explain each indicator with valid evidence.

3.4.3 Content analysis as a data collection method

While the interview method provided a detailed grasp in each area of the research questions, a second method (e.g., content analysis) was also used to support, complement and validate the interview findings and enrich further on each area of the research questions. This second method of data collection process aimed to achieve 'Data Triangulation' which enriched the reliability and validity of the research findings (Saunders et al., 2009; Creswell, 2013). The second method helped the researcher to cover some sub areas of the research questions which were not well covered by the interviews. This is how these two methods worked as complementary for each other to answer each research question sufficiently with a greater accuracy and confidence.

Content analysis has been defined as the objective and systematic analysis of documented texts for making replicable and valid inferences from texts to the contexts of their use (Krippendorff, 1980; Weber, 1990; Neuendorf, 2002). This technique enables researchers to develop both simple formats for summarizing information or counting the frequency of statements and complex formats for analysing trends or detecting subtle differences in the intensity of statements (U.S. General Accounting Office, 1996). Objectivity, systematization, and quantification are the main distinguishing features of the content analysis approach (Bryman, 2016).

This technique is motivated by the search for those data which are too costly, no longer possible, or too obtrusive using other techniques (Krippendorf, 1980). It has also been claimed in the literature that content analysis can be used for gaining valid inferences about the creator of the text, the text itself and the audience of the message in the text (Weber, 1990).

The recorded form of contents ensures the repeatability of the study which strengthens the reliability aspect of the study (Babbie, 1995). An evidenced-based rating system is used to enhance the semantic validity (Tangpong, 2011).

Collecting data from analysing content of annual reports, environmental reports/sustainability reports has already been evidenced in the green supply chain related literature, such as Montabon et al. (2007), Hofer et al. (2010), Ahi and Searcy (2015) and Albino et al (2012). It is evidenced that content analysis technique can be used in qualitative study providing the ability of systematic analysis of rich, qualitative/textual data through multiple categorization,

which allows the researcher to convert such qualitative data into an analysable form (Wolfe et al., 1993). Qualitative content analysis allows researchers to judge multiple interpretations during extensive text analysis (Krippendorff, 1980). It enables researchers to analyse specific content both quantitatively and qualitatively to present a thematic view of the content studied, and to support theory building approaches (Spens & Covacs, 2006). In-depth qualitative content analysis in the supply chain related field is also evidenced in the literature (Morali & Searcy, 2012; Asif, et al., 2013; Turker & Altuntas, 2014). These studies intended to conduct thematic content analysis through categorization and ratings (quantitative content analysis) for understanding the extent of a theme or subtheme across the reports from companies.

It was also evidenced that supply chain researchers have used a rating technique like the Likert scale to rate the intensity of a particular environmental activity undertaken by the company. Thus, extracting survey-like data from ratings was used to analyse them quantitatively but at the same time it was helpful to enrich qualitative understanding. For instance, Montabon, et al. (2007) conducted content analysis (ratings) of corporate environmental reports for converting documentary qualitative data into quantitative data to run correlation and investigated the relationship between environmental practices and performance. Likewise, Albino, et al. (2012) adopted the content analysis technique to validate the theoretical relationship between environmental collaboration and environmental performance by using companies' environmental / sustainability reports. Another researcher (Hofer, et al., 2012) has analysed the corporate environmental reports using the content analysis technique to validate the relationship between rival firms' EM activities and focal firms' EM activities. A recent study by Brandenburg et al. (2014) used the same methodology to understand the developments and directions of sustainable supply chain management. It is therefore evidenced that the content analysis technique (both thematic and rating) in the related field is established and accepted.

It is important to note here that though the previous researchers hired human raters (who were not involved in the study but were hired and trained on how to rate) for rating each of the reports for gaining validity and reliability on each variable, this study did not consider to hire any rater. This is because, first of all, the researcher did not intend to validate any theoretical relationships where high levels of objectivity were the key, also, the researcher used both NVIVO software and a manual process to rate each report/interview script, where both processes increased the semantic validity and objectivity at the same time for justifying each rating. The previous literature also advocated increasing semantic validity and objectivity of

the rating by using both software and manual processes (Hofer at al., 2010; Albino et al., 2012). Additionally, this research was not aimed to test any hypothesis based on quantitative design, so the research should not seek an outsider (to hire any rater to rate), rather the researcher as an insider enables in-depth, subjective judgments for each rating (Creswell, 2013; Saunders et al., 2009; Krippendorff, 1980). So, the degree of objectivity obtained from applying NVIVO was enough to serve the research purposes. Also, the utmost semantic validity is dependent on the degree of expertise in that subject, where the researcher himself was the best fit as NVIVO software reduces the bias of the researcher. Also, the study not only involved one method (like content rating) used in the previous supply chain studies outlined above but it also used extensive interviews. Therefore, the rating was done by the research himself instead of hiring any rater.

3.4.3.1 Types of contents used & Preparation of the contents

Whilst the previous section provided a solid justification for choosing content analysis as a data collection method, this section explains what types of content were used to analyse the data collected. The Table 3.6 below outlines the types of reports used and their key characteristics and how the contents were processed to collect relevant data.

Table 3.6 Types and characteristics of the contents used to collect data (Source: Researcher)

Types of report & key characteristics	Report preparations for data collection
Environmental report: Environmental/sustainability/CSR, publish each year, publicly available	Save all files below into one folder for each company: ✓ Download PDF file from websites. ✓ Convert website content into PDF when PDF format is not available. Also ✓ After a quick scan of the report other linked files / websites such as special
Pharmacy service report Each pharmacy publishes their services (MUR, NMS, Drug disposal etc) on their websites. Pharmacy Services which also contain environmental related info such as drug disposal, inhaler recycling, drug take back etc.	
CCG report: STPs (Sustainable Transformation Planning) reports (named CCG report in this study) which have been published by local CCG for a five-year road map to	

Types of report & key characteristics	Report preparations for data collection
improve healthcare service quality. It was published once in 2016 and updated each year for demonstrating progress. Though it publishes plans for future actions, it also published current actions being taken to date. We consider only those parts that contain drug use and disposal related info such as drug optimization, effective prescribing etc. We also consider and add related linked reports suggested by the CCG, such as drug waste reduction campaign report etc.	environmental report or CDP report etc (suggested by the main report) also download and save (this process continue as time goes with the analysis of each report) ✓ All folders under each category and subcategory are uploaded into NVIVO Pro 12 software

The study used environmental reports/sustainability reports/GRI reports/CSR reports/CDP reports/environmental sustainability reports, or similar reports (focused on environmental discussion), published by the company within the last three to four years. The more recent reports were always the priority to analyse. Most of the upstream pharma companies (innovative, generic and bio) are very familiar withfa these reports. However, some of the downstream pharma stakeholder companies have termed these reports slightly differently. For instance, the NHS Clinical Commissioning Groups termed CCG reports 'Sustainability and Transformation Plans' (STPs). However, in this study this report is termed CCG. Though most of the retail pharmacies do not have any separate environmental or sustainability reports, they publish relevant environmental aspects, such as drug disposal, drug wastes reduction, drug take back and inhaler recycling, on their website under the 'service' tab or in the related service reports published separately. It is important to note here that any hyperlinked/linked report addressed in the main environmental/sustainability/CSR report was also analysed for enriched understanding. For instance, some innovative pharma companies have hyperlinked their environmental projects (e.g., recycling projects) which were also analysed for relevant data collection. Also, some CCG reports published drug waste reduction campaign reports in another location; these were also used with actual CCG or STP reports. Also, if any reports only published online, like on a webpage, then the whole web page was converted into PDF format into one document. It is also important to highlight here that the researcher predominantly prepared the report using the environmental information section. This is how each company report was prepared by combining both main reports and other

linked reports into one, prior to final analysis, to extract data from them to answer the research questions. All reports are publicly available. All reports were saved in the researcher's computer and each folder represented each company containing all relevant reports. Similarly, all reports were uploaded to NVIVO. Table 3.8 shows the details of reports used including sample.

It is also important to note here that the key focus in the downstream was to explore only use-and-disposal related green practices. Hence, environmental reports from local councils, waste management companies and wastewater treatment companies were not considered as they did not cover the key information on drug disposal and drug waste reduction. However, any environmental related documents provided by the informants during the interview phase were analysed as complementary. For instance, one of the respondents from wastewater treatment companies provided 3 internal research reports which were analysed to complement the interview data to present the final findings.

3.4.3.2 Sampling structure of the contents

The sampling of the contents or environmental reports/sustainability reports was easily identified from the company database created as explained in section 3.4.2.2, under *stage one* heading. The summary of the sample size is shown in Table 3.7.

Table 3.7 Breakdown of samples of the reports from each stakeholder (Source: Researcher)

	Stakeholders	Number of reports selected	Type of reports used
Upstream Pharma Stakeholders	Innovative Pharma	16	Environmental/sustainability/CSR
	Generic Pharma	20	Environmental/sustainability/CSR
	Bio Pharma	25	Environmental/sustainability/CSR
Downstream Pharma Stakeholders	Pharmacy	12	Pharmacy service reports
	NHS Clinical Commissioning Group (CCG)	42	CCG reports
Total		112	

Like interviews, a purposive sampling approach was used. The sampling approach was to take all possible reports that published environmental related information and at least cover

one or two environmental aspects, such as climate/CO2 emission or energy use or water use / material use. This approach ended up with a total of 61 environmental reports. These reports were further separated into three categories: Innovative pharma (16), Generic pharma (20) and bio pharma (25). This categorization was carried out by looking into each company's operations. For instance, if any company was only involved in producing generic formulation/packaging they fell under generic, if any company was only involved with new drug innovation and development and/or with new API production facilities, they fell under innovative company, and any company involved in producing bio based drugs only and/or partially chemicals based but bio-based predominantly fell under bio based drug. Some non-profit organizations and industrial associations, such as ABPI and BGMA (see Table 3.2), were also sometimes highlighted. Table 3.8 below shows the demography of the upstream pharmacy company reports.

Table 3.8 Demography of the upstream pharmacy company reports (Source: Researcher)

Code	Company	Key type	Size*	Key functional areas	Member of ACS GCI Pharmaceutical round Table	Ownership	Reporting intensiveness**
In-1	Pfizer	Innovative	Large	Drug Design, Manufacturing & Use-and-Disposal	Yes	Foreign	High
In-2	GSK	Innovative	Large	Drug Design, Manufacturing & Use-and-Disposal	Yes	UK Based	High
In-3	AstraZeneca	Innovative	Large	Drug Design, Manufacturing & Use-and-Disposal	Yes	UK Based	High
In-4	Eli Lilly & Company Ltd	Innovative	Small	Drug Design, Manufacturing, Distribution	Yes	Foreign	Low
In-5	Novartis UK	Innovative	Large	Drug Design, Manufacturing, Distribution, & Use-and-Disposal	Yes	Foreign	Medium
In-6	MSD (Merck Sharp & Dohme Limited UK)	Innovative	Large	Drug Design, Manufacturing	Yes	Foreign	High
In-7	Boehringer Ingelheim	Innovative	Large	Drug Design and Discovery, lab scale manufacturing, commercial manufacturing, distribution; contract manufacturer of biopharmaceuticals	Yes	Foreign	High
In-8	Janssen-cilag limited	Innovative	Large	Drug Design and Discovery, manufacturing, Distribution,	Yes	Local	High

Code	Company	Key type	Size*	Key functional areas	Member of ACS GCI Pharmaceutical round Table	Ownership	Reporting intensiveness**
In-9	Eisai limited	Innovative	Large	Drug Design and Discovery (with lab scale manufacturing)	No	Foreign	High
In-10	ALK-Abello Limited	Innovative	Small	Drug Design and Discovery, manufacturing, Distribution,	NO	Foreign	High
In-11	Sanofi UK	Innovative	Large	Discovery and development, manufacture	yes	US Based	High
In-12	Chiesi UK	Innovative	Small	Research & Development	no	UK Based	Medium
In-13	Pharmacosmos UK Ltd	Innovative	Small	R&D; Distribution	no	UK Based	Low
In-14	Lundbeck Limited	Innovative	Medium	R&D; distribution (Chemical based drug development)	no	UK Based	High
In-15	Novo Nordisk Limited	Innovative	Small	R&D and Distribution (both bio & chemical based)	yes	Denmark	High
In-16	Ferring Pharmaceuticals (UK)	Innovative	Small	R&D, Manufacture, distribution	No	French	Medium
Gn-1	Accord UK Limited	Generic	Large	Drug Design, Manufacturing & Use-and-Disposal	no	Foreign	High
Gn-2	Ipsen Ltd	Generic	Small	Drug Design, Manufacturing	yes	Foreign	High

Code	Company	Key type	Size*	Key functional areas	Member of ACS GCI Pharmaceutical round Table	Ownership	Reporting intensiveness**
				& Use-and-Disposal			
Gn-3	TEVA UK Limited	Generic	Small	Drug Design, Manufacturing & Use-and-Disposal	no	Foreign	High
Gn-4	Dr Reddys Laboratories UK (Beverly)	Generic	Large	Drug Design, Manufacturing, Distribution, & Use-and-Disposal	YEs	Foreign	Low
Gn-5	Bayer Plc UK	Generic	Small	Manufacturing	yes	Germany Based	Low
Gn-6	Aesica	Generic	Large	CDMO - Contract Development and manufacturers	No	UK Based	High
Gn-7	Baxter UK	Generic	Large	Manufacturing & Distribution	no	US Based	Low
Gn-8	Alliance Pharmaceuticals Limited	Generic	Large	Manufacture (outsourced) & Distribution	no	UK Based	Low
Gn-9	Custom Pharmaceuticals Limited	Generic	Medium	Manufacturing & Distribution (CDMO)	no	UK Based	High
Gn-10	Medreich PLC	Generic	Large	Manufacturing (formulation, CMO/CDMO)	no	Japan Based	High

Code	Company	Key type	Size*	Key functional areas	Member of ACS GCI Pharmaceutical round Table	Ownership	Reporting intensiveness**
Gn-11	Aguettant ltd	Generic	Large	R&D, Manufacture	no	French	Low
Gn-12	Advanz Pharma	Generic	Medium	R&D, Manufacture	no	Swedish	Medium
Gn-13	Egis Pharmaceuticals UK Ltd	Generic	Large	R&D, Manufacture	no	Hungary	Low
Gn-14	Mayne Pharma UK Ltd	Generic	Large	R&D, Manufacture- CMO	no	Australia	Low
Gn-15	Mylan UK	Generic	Large	R&D, Manufacture and Distribution	no	US Based	Low
Gn-16	Sandoz UK	Generic	Large	Manufacture (bio similar and generic)	no	UK Based	Low
Gn-17	Servier UK	Generic	Medium	R&D, Manufacturing	no	French	low
Gn-18	Servier CDMO	Generic	Medium	CDMO - Contract Development and manufacturers	no	French	Medium
Gn-19	Genesis Pharmaceuticals Ltd	Generic	Small	Manufacture & Distribution	no	Greek	Medium
Gn-20	Bristol Laboratories Ltd	Generic	Large	R&D, Manufacture, distribution	No	UK Based	High
B-1	Shire Pharmaceuticals Ltd	Bio Pharma	Large	Drug Design and Discovery, lab scale manufacturing	No	Foreign	High

Code	Company	Key type	Size*	Key functional areas	Member of ACS GCI Pharmaceutical round Table	Ownership	Reporting intensiveness**
	UK						
B-2	UCB pharma Ltd	Bio Pharma	Medium	Drug Design and Discovery, lab scale manufacturing	No	Foreign	Medium
B-3	Protherics UK Ltd (Part of BTG group)	Bio Pharma	Small	Drug Design and Discovery, lab scale manufacturing	No	Foreign	Low
B-4	Biocompatibles UK Ltd	Bio Pharma	Small	Drug Design and Discovery, lab scale manufacturing	No	Foreign	Low
B-5	Bristol-Myers Squibb Pharmaceuticals limited	Bio Pharma	Large	Drug Design and Discovery, lab scale manufacturing,	yes	Foreign	Low
B-6	Takeda Development Centre Europe Limited	Bio Pharma	Large	Drug Design and Discovery, lab scale manufacturing,	yes	Foreign	Low
B-7	Alexion pharma UK Ltd	Bio Pharma	Medium	Drug Design and Discovery (with lab scale manufacturing)	No	Foreign	Low
B-8	Actelion Pharmaceuticals UK	Bio Pharma	Large	Drug Design and development	No	Foreign	Low
B-9	Amgen UK & Ireland	Bio Pharma	Large	Drug Design and Discovery,	yes	Foreign	Low
B-10	Swedish Orphan Biovitrum Limited	Bio	Small	Drug Design and Discovery,	no	Foreign	Medium

Code	Company	Key type	Size*	Key functional areas	Member of ACS GCI Pharmaceutical round Table	Ownership	Reporting intensiveness**
	(SOBI)	Pharma		manufacturing, Distribution,			
B-11	Roche Products Ltd	Bio Pharma	Small	Drug Design and Discovery	YES	Foreign	High
B-12	Biogen UK	Bio Pharma	-	R&D, Manufacture	yes		High
B-13	Astex Pharmaceuticals	Bio Pharma	-	Discovery and development of drug	no	UK Based	High
B-14	Charles River UK	Bio Pharma	Large	Discovery	no	UK Based	Low
B-15	Indivior	Bio Pharma	-	Discovery and development of drug	no	UK Based	Low
B-16	Clinuvel Pharmaceuticals Limited	Bio Pharma	Large	Discovery and development, manufacture	No	Australia	Low
B-17	Sanofi Genzyme	Bio Pharma	-	Discovery and development, manufacture	No	US Based	High
B-18	Gilead Sciences	Bio Pharma	-	Discovery and development, manufacture	yes	US Based	high
B-19	Kyowa Kirin International Plc	Bio Pharma	Large	Discovery and development, manufacture	no	Japan Based	Medium

Code	Company	Key type	Size*	Key functional areas	Member of ACS GCI Pharmaceutical round Table	Ownership	Reporting intensiveness**
B-20	Silence Therapeutics	Bio Pharma		R&D	no	UK Based	high
B-21	Becton Dickinson UK Ltd (BD UK LTD)	Bio Pharma	Large	R&D, Manufacture (In the R&D focus to develop innovative products)	no	UK Based	High
B-22	Allergan Biologics Ltd	Bio Pharma	Large	R&D, Manufacture, Distribution	no	US Based	Low
B-23	Celgene UK	Bio Pharma	Large	R&D; Manufacture;	no	US Based	Low
B-24	Grifols UK Ltd	Bio Pharma	Medium	R&D, Manufacture, distribution	no	Spanish	Medium
B-25	Oxford Biomedica	Bio Pharma	Large	R&D, Manufacture,	no	UK Based	Medium

Size is determined based on employee numbers and/or annual turnover as per UK company size classification*

*Reporting intensiveness** (High/ Medium/Low); Low: consider one to two environmental factors (e.g., GHG emission) without any detailed info; Medium: Consider between one to three environmental factors with medium focus (e.g., internal target etc); High: Consider more than 3 factors with detailed information (e.g., target versus ongoing progress, internal policy etc)*

For downstream pharmacies, the researcher purposively selected 12 reports – 5 from leading community pharmacies, 4 from medium level pharmacies, and 3 from small pharmacies. This categorization was originally induced from an IBIS report from where most of the leading community pharmacies were selected. Other characteristics were also considered for report selection, such as in-depth description of services and/or wide varieties of services including drug take back, drug waste disposal, inhaler recycling etc. Though there were a wide array of community pharmacies available to select from, these 12 pharmacies in three categories also cover almost all related environmental information required for the study. It is also important to note here that the chance of operational variation from one pharmacy over another is minimal, apart from the services provided, as they are supervised and regulated by the NHS and CQC (Care Quality Commission) and standardized by PSNC (Pharmaceuticals Service Negotiating Committee). Additionally, these 12 samples also covered the MUR and NMS drug take back schemes which have environmental relevancy to drugs use and disposal. 12 samples thus aimed to provide a quick snapshot for answering the relevant research query, such as exploring the concept of drug use and disposal. It was also evidenced from a quick pilot scanning five of the reports that more than 80% of the themes were occurring again and again. Therefore, the 12 reports from pharmacies are justified.

For selecting samples from the local CCG reports, as per the research requirements, the researcher was only interested in finding drug use and disposal related info, such as drug optimization, drug waste reduction, effective and efficient prescribing etc, within the reports. This purposive approach ended up with 42 CCG reports which contained drug use and disposal and drug waste reduction related information.

3.4.3.3 Data collection process

This section explains how data were captured from the content and maintained reliability of the data used for analysis. Figure 3.7 outlines the detailed steps involved in the data collection process.

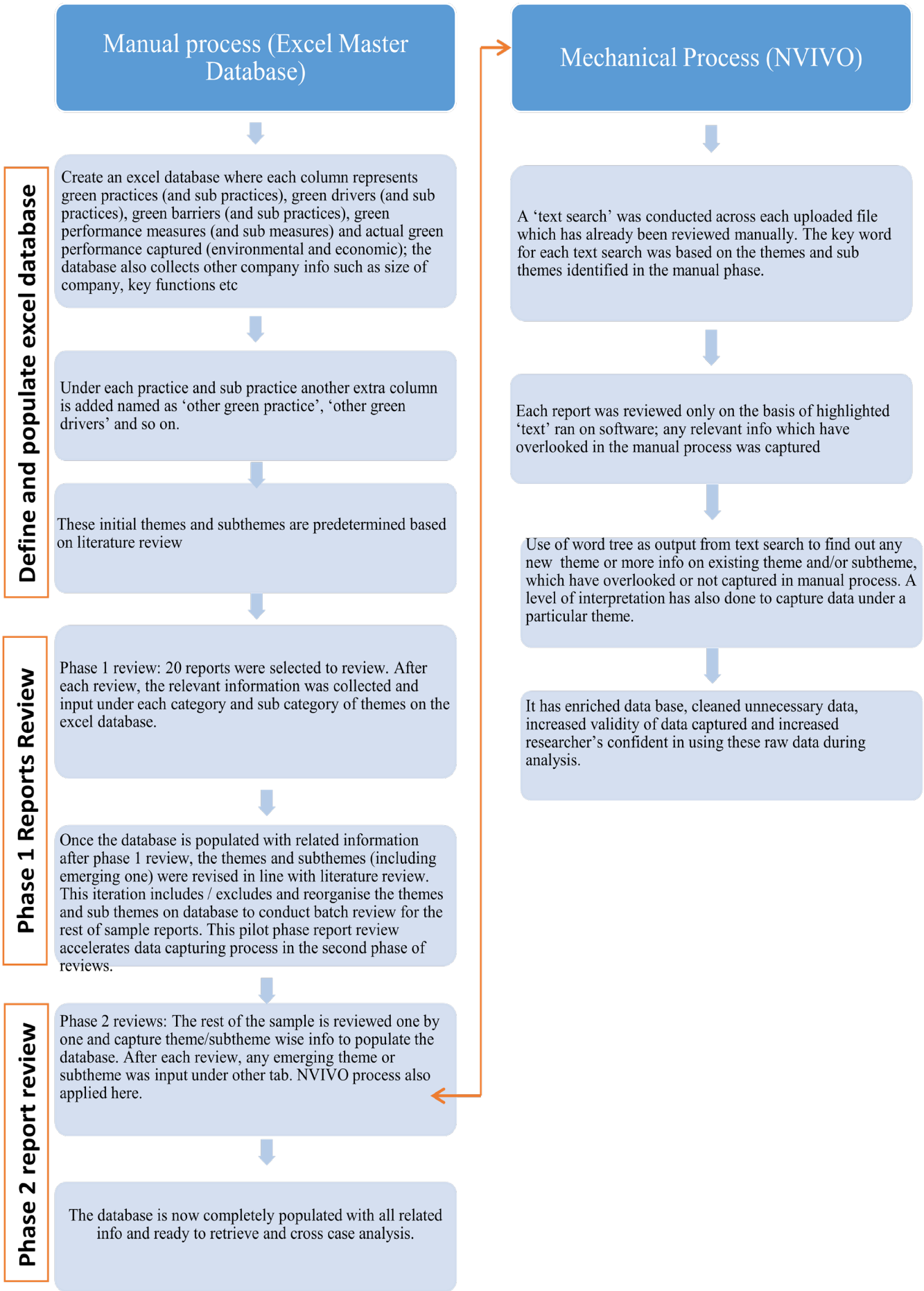

Manual process (Excel Master Database)
Mechanical Process (NVIVO)
Define and populate excel database
Create an excel database where each column represents green practices (and sub practices), green drivers (and sub practices), green barriers (and sub practices), green performance measures (and sub measures) and actual green performance captured (environmental and economic); the database also collects other company info such as size of company, key functions etc
Under each practice and sub practice another extra column is added named as 'other green practice', 'other green drivers' and so on.
These initial themes and subthemes are predetermined based on literature review
Phase 1 Reports Review
Phase 1 review: 20 reports were selected to review. After each review, the relevant information was collected and input under each category and sub category of themes on the excel database.
Once the database is populated with related information after phase 1 review, the themes and subthemes (including emerging one) were revised in line with literature review. This iteration includes / excludes and reorganise the themes and sub themes on database to conduct batch review for the rest of sample reports. This pilot phase report review accelerates data capturing process in the second phase of reviews.
Phase 2 report review
Phase 2 reviews: The rest of the sample is reviewed one by one and capture theme/subtheme wise info to populate the database. After each review, any emerging theme or subtheme was input under other tab. NVIVO process also applied here.
The database is now completely populated with all related info and ready to retrieve and cross case analysis.
A 'text search' was conducted across each uploaded file which has already been reviewed manually. The key word for each text search was based on the themes and sub themes identified in the manual phase.
Each report was reviewed only on the basis of highlighted 'text' ran on software; any relevant info which have overlooked in the manual process was captured
Use of word tree as output from text search to find out any new theme or more info on existing theme and/or subtheme, which have overlooked or not captured in manual process. A level of interpretation has also done to capture data under a particular theme.
It has enriched data base, cleaned unnecessary data, increased validity of data captured and increased researcher's confident in using these raw data during analysis.

Figure 3.7 Data collection process (Source: Researcher)

Define and populate excel database (Manual process)

An excel database was created where columns represented the initial key themes (e.g., green practices, green drivers, green barriers, green performance) and subthemes (e.g., green design, green manufacturing, green use-and-disposal) identified in the literature review, and the respected rows represent each category of stakeholder companies. Some other columns in the database also represented size of the company, types of formulations, ownership (overseas/local), key functional areas, extent of reporting, member of ACS GCI pharmaceutical round Table etc.

Phase 1 Review of reports (Manual Process)

In the first phase, 20 sample reports (4 innovative pharma, 4 generic pharma, 4 bio pharma, 2 pharmacy service reports and 6 CCG reports) were manually read through. The target was to find the matches and mismatches between two sets of subthemes: one set originating from the literature and another set of subthemes originating from the pilot scanning of the 20 reports. This initial report analysis also helped the researcher to probe during the interviews. Also, the end aim was to reorganise the themes and subthemes from this pilot review, which eventually reduced the time needed to capture data from reports in the second phase of the batch review phase. For instance, to understand the main concept of 'Green Manufacturing Practice', 6 subthemes originated from the literature and they were matched with themes captured from the 20 reports. However, 5 new subthemes, which were not matched with literature review, emerged from the pilot scanning of the reports. So, on the Excel database, 11 columns represented the 11 sub-themes (6 from the literature + 5 from pilot report scanning) under the main theme of 'Green Manufacturing Practice'. Figure 3.8 shows a partial view of the database created. Another extra column named as 'Other' was also created. If any new theme/subtheme emerged from subsequent report analysis in the second phase of review of the rest of the reports, they were stored under the 'Other' tab, which was later further analysed and refined. This initial coding based on the pilot was important for coding and sub-coding reliability as the literature highlighted that the initial coding rules should be tested with a small sample of text to reduce the ambiguity in the coding process and to enhance the coding reliability (Weber, 1990).

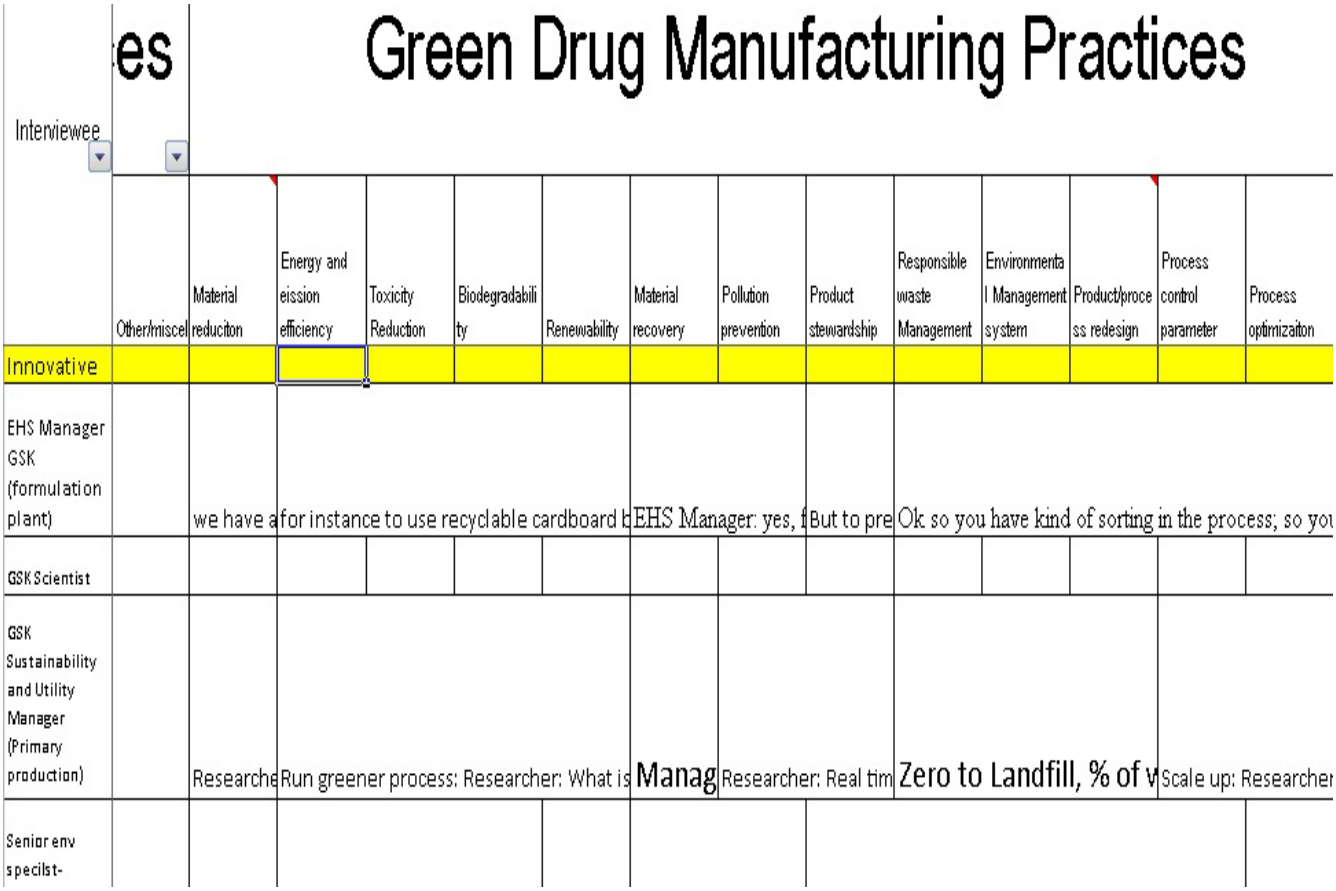


Figure 3.8 Partial View of the Excel Database used for data collection and analysis (Source: Researcher)

Phase two review of reports (Manual and mechanical process) – populating the excel database with relevant data

Once the Excel database was created the researcher used both a manual process and NVIVO software to collect the relevant information under each sub-category. In the manual process, the researcher read through the report (only environmental related sections) and captured data from the report under the relevant categories/sub-categories. For instance, any recycling and reuse related projects/activities identified in the report were captured under the sub-category of 'Recovery Practice'. 'Recovery Practice' was one of the 11 sub-categories under the main theme of 'Green Manufacturing Practice'. Once the manual process was complete, the entire report was again scanned in NVIVO software using 'Text Query Search'. The key word was generated from the manual process. The NVIVO 'Text Query' helped the researcher not only to validate the manual process, but also worked as a complementary tool for wider coverage. For instance, it was observed that some themes/subthemes which were overlooked during manual process were identified and captured using NVIVO later. This is how the process

continued to capture data from each report. It is also important to note here that while capturing data on theme or subtheme, the entire paragraphs or related paragraphs which were important, based on the researcher's subjective judgments, were captured. For instance, if a report mentioned the recycling of solvents in a particular plant, including detailed recovery projects investments, performance, any engineering difficulties etc, these were all captured for a complete understanding. This is how the data was captured on the excel database and saved under each revised and emerged theme and subtheme related to each research question. This is how the excel database was populated with the relevant data and was ready for analysis.

3.4.3.4 Data analysis process

This section explains how the data on each theme was interpreted and enriched understanding on a particular theme. Figure 3.9 shows a three-step process which was followed to retrieve and analyse data both manually and using NVIVO.

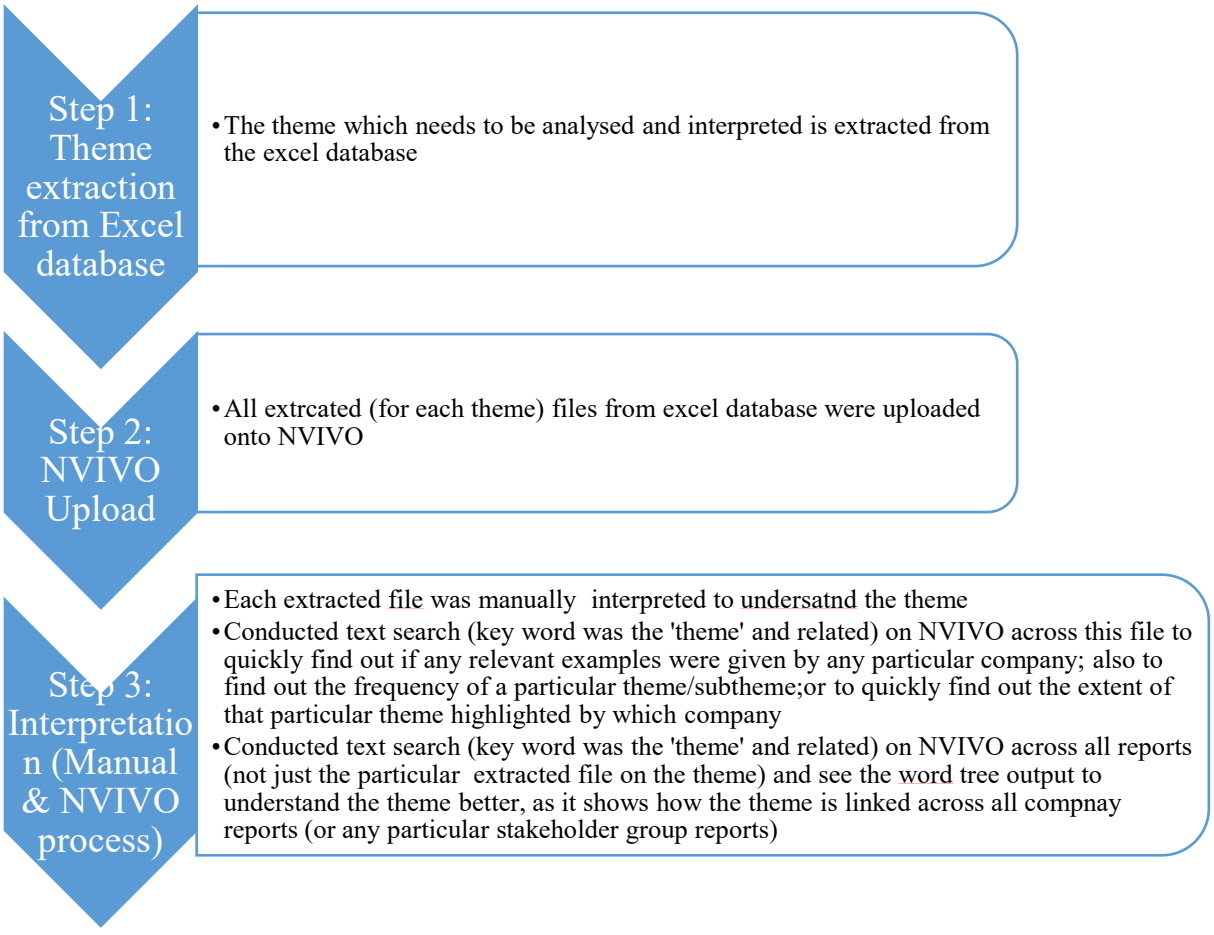


Figure 3.9 Process of data analysis (Source: Researcher)

Once the Excel database was saturated with all relevant themes and subthemes against each stakeholder company (Figure 3.8 shows a partial view of the Excel Database created), all data captured under each subtheme was exported into a single file (Figure 3.9a shows an example of an exported file from the Excel database), where it was easy to see which company report said what.

Innovative 1	Energy recovery from waste: We use food waste bins for composting and a wormery for composting of food waste from catering outlets and all other waste is used for energy recovery. Initiated chemical management program; use of recyclable packaging material; Recycle spent materials to make new products; Recover energy from waste (through combustion), where possible; the bulk of the "wastes" we generate are directly reused; However, we were able to designate 233,000 tonnes of this waste for reuse, much of it as fertilizer;
Innovative 2	maximize energy use from waste; We currently recycle approximately 80% of all nonhazardous waste and continue to maximize opportunities for reuse and recycling. The majority of solvents we used are recycled, to a large extent within our operations and partly by contractors for third-party users. Solvents that are not recycled are either used as alternative fuels or are incinerated at waste facilities that recover the energy generated from combustion. The waste solvents reused at our sites constitute recycled input materials. In 2017, Novartis recycled 21.5 million m3 of water, which is 28% of our total water use, including contact water and non-contact cooling water (verses 25.9% in 2016). management Prior to 2016, more than 8 000 tons of solvent were incin erated each year from a Novartis eye care production site in the USA. In 2017, the manufacturing site imple mented a closed loop for all solvents used. Now, the site only needs to purchase 30% of its solvents, with the rest being returned to the site after recycling.
Innovative 3	Reverse osmosis (RO) "reject water" is reused for non-potable and non-process applications such as cooling-tower feed water and fire water. In all, more than 1 million cubic meters of water are recovered, reused or recycled at our facilities, which is equivalent to 6 percent of the total water that is withdrawn. Many of our facilities employ water reuse and recovery strategies, including recirculation of water in cooling towers and condensate recovery. continously look for option to reuse and recycle; When it is not practical to reuse regenerated solvents in our own production processes, we either work with suppliers who recover the spent solvents for resale to other industries, or safely burn them as a source of energy. Any used solvents that leave our site as hazardous waste are managed at off-site facilities that are on our list of approved waste management sites.....Recovery and reuse of steam condensate and "reject water"

Figure 3.9a A partial view of exported files from database

A similar process was followed to extract each sub-theme of 'Green Manufacturing Practice' (for instance) to analyse them separately. It was then easy to find the common and important indicators across the industry by analysing those extracted files. For instance, under the subtheme of 'Material Recovery Practice' there were two key sub practices that were identified across the industries such as Recovery practice in terms of Solvent recovery and reuse; another one was Recovery practice in terms of other substances except solvents. Then each of these indicators was explained separately by providing the relevant evidence from the report analysis. For explaining each indicator, both the manual process and NVIVO were used to understand the stance of the indicator across all the industry reports. While the manual process helped to fine tune the understanding of each theme from the extracted file, NVIVO was used to see how each of the indicators (using keyword from each indicator) was making sense across all the industry reports, which eventually helped the researcher to write

in detail (e.g., what, why, how, when) about each indicator identified. It is important to note here that at this stage NVIVO helped the researcher to provide further support which was overlooked in the manual process. For instance, word tree output from the text search helped the researcher establish how a particular theme is viewed, valued, and interpreted across the industry. For instance, figure 3.10 shows how 'recycling' was interconnected across the reports, which gave the researcher further room for interpretation. The same process was applied to explore and explain each indicator identified from the reports and answered adequately each of the research questions posed. For answering the relative importance and /or intensity of each indicator, a rating approach was used for rating each company report.

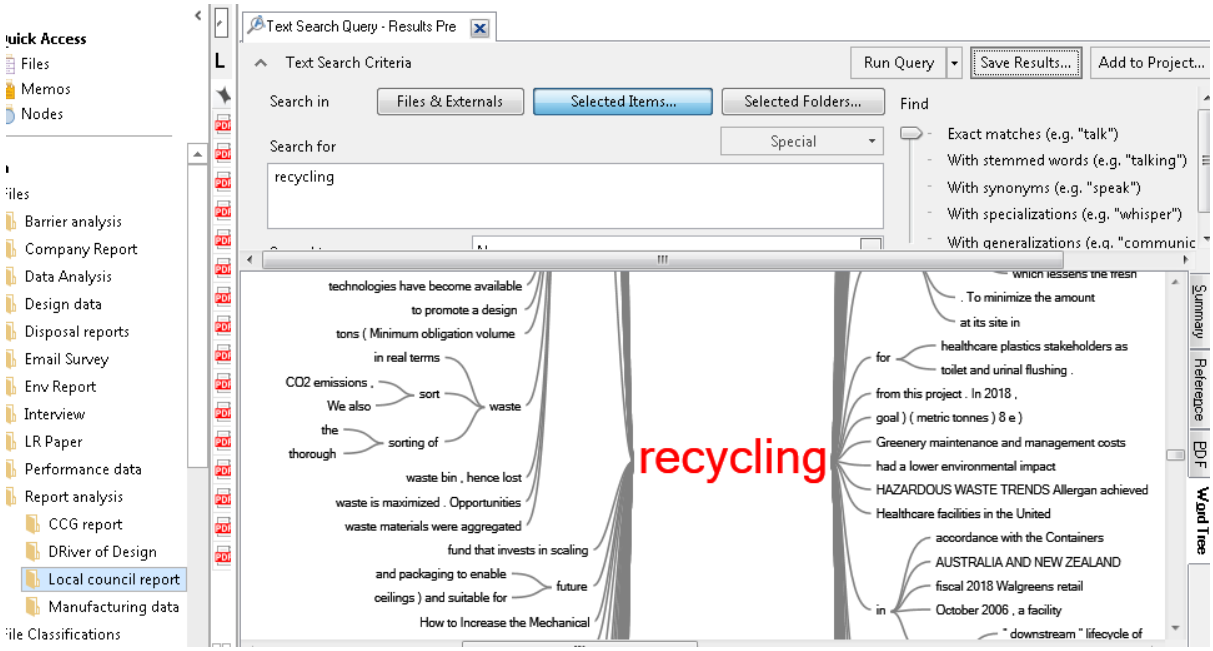


Figure 3.10 A partial view of NVIVO word search output (word tree) showing how a theme 'recycling' is interconnected across all reports.

Ratings

Rating of each theme/subtheme was carried out to understand the extent of each practice/sub practice, drivers, or barriers felt by each category of pharma companies. The relevancy and relative importance of each subtheme across the three key stakeholders (innovative/generic/bio) was rated based on a five point scale (1 = Not mentioned / no consideration; 2 = Planning to consider; 3 = Low level of consideration; 4 = Medium level of consideration; 5 = High Level of Consideration). The rate was plotted against each relevant company report. This kind of five point (Likert scale type) rating using content was also evidenced in the supply chain related literature such as Montabon et al. (2007), Hofer et al.

(2010), Albino et al.,(2012) and Brandenburg et al. (2014). Though most of the previous researchers conducted the ratings hiring human raters, this subjective rating was done based on two important criteria and the process below: (the figure 3.11 also outlines the rating process used to rate each report)

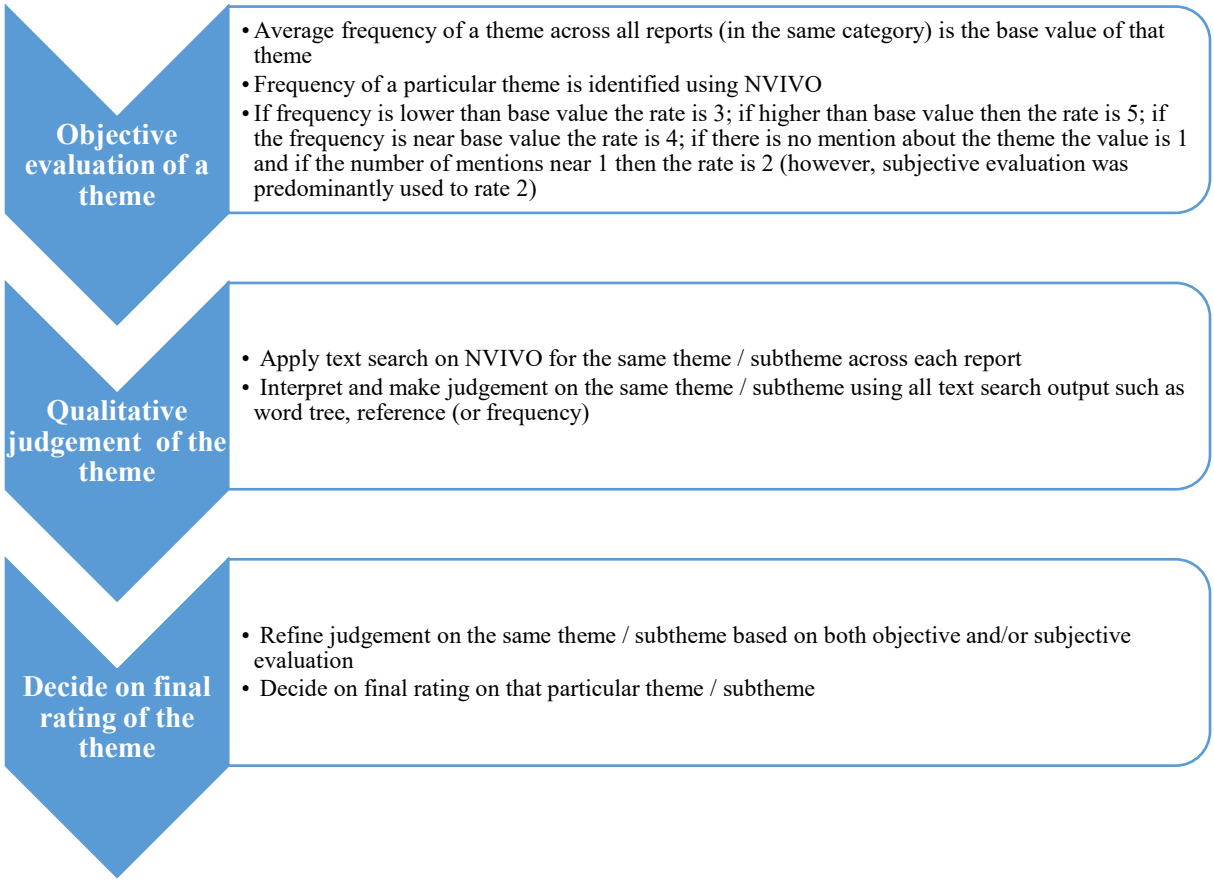


Figure 3.11 Rating process used to rate each theme and/or sub-theme identified in reports and/or interview transcripts (Source: Researcher)

I. **Objective evaluation of theme/subtheme to rate (Objective validity)** A base value was determined for each theme/subtheme to be rated. The base value was the average frequency (or industry average) of a particular theme/subtheme highlighted across all reports in the relevant category. If the frequency of a particular theme/subtheme within a report was above the base value of that particular theme/subtheme, the rate was 5; however, if it was below the base value the rate was 3; and, if the frequency was near the base value, it was rated as 4; if there was no mention the rate was 1; and if the number of mentions were far below the base value and near 1, the rate was 2. However, as the frequency/number of mentions can be misleading to rate 2, thematic understanding was predominantly taken into consideration to rate it.

The base value and other converted values were determined after conducting ratings of a few randomly selected reports prior to being applied across all reports. For instance, if we want to understand the extent of water recovery practice, we first find the base value of the word 'water' through NVIVO text search across all reports, which give frequency (or known as references in NVIVO) of 'water' for each individual company report. For instance, the average frequency found for 'water' across the innovative industry report was 27. So, any individual report that scored below 27 (e.g., 6) was rated as 3 (low level), above 27 (e.g., 57) was rated as 5, and when near 27 (e.g., 23) was rated as 4, and when near 1, it was rated as 2. This process of initial objective assessment increases the researcher's confidence to rate a particular them/subtheme.

II. **Qualitative judgments of the theme / subtheme across the report (semantic validity):** Followed by the NVIVO text search output, each frequency (or reference) of theme/subtheme was judged based on the relevant statement made within the report. Word tree output from the same text search (which was used to ascertain frequency) also helped the researcher to gain a holistic understanding of the theme/subtheme. This subjective evaluation was especially useful to rate 2. For instance, one of the innovative companies (In 09) highlighted that they had undertaken pilot research to see the viability of package materials reduction from their primary packaging system; which actually means they were still in the planning stage for implementing the material reduction practice, which actually leads to the rating 2.

This qualitative assessment of each theme/subtheme across the report helped the researcher to determine the most reasonable and justified rate for each theme/subtheme. For instance, one of the innovative companies (In – 01) was rated 3 (based on objective evaluation) in terms of water recovery practice, as the frequency of water of that company was 15 which was lower than the average value 27. However, later it was rectified as 5 since the qualitative judgement identified that the company had already initiated a longer term water recycling project and had significantly reduced water consumption across manufacturing sites. In addition, they had created the promising target of reducing freshwater consumption in the near future. This is how the researcher assessed the semantic validity (Krippendorff, 1980) of each time the word 'water' occurred across the content in NVIVO. So, the reference value helped the researcher to understand the intensity of the word 'water' used in different aspects across the content and to make a final decision on the ratings.

All ratings were done on the Excel database, which later was used to retrieve related graphs to see the extent of applying each theme/subtheme under each green practice across the sector as an example. See appendix E for a sample rating format on excel.

The 'reference value' from the NVIVO output has thus increased the semantic validity of the ratings in most of the cases and supported the 'objectivity' of the ratings decided based on frequency. This is how both 'semantic validity' and 'objectivity' were covered in this rating process, which is the fundamental requirement for a valid and reliable rating based on qualitative judgments (Krippendorff, 1980; Neuendorf, 2002; Weber, 1990).

It is also important to note here that a similar rating technique (presented above) was also followed while analysing both interviews and reports data together to get a holistic understanding on the extent of each theme and subtheme.

3.4.4 Final interpretation and analysis – data triangulation

As the key aim of this research was to explore and enrich understanding of each green practice or other theme and subtheme with the utmost accuracy, validity, reliability and completeness, interview, reports and other related secondary data were added together to view a particular theme. This led to data triangulations (Figure 3.12), which eventually enriched, completed, prioritized, and validated each theme and subtheme. This combination also helped the researcher to reorganise, refine and update each theme and subtheme holistically for complete and rigid understanding.

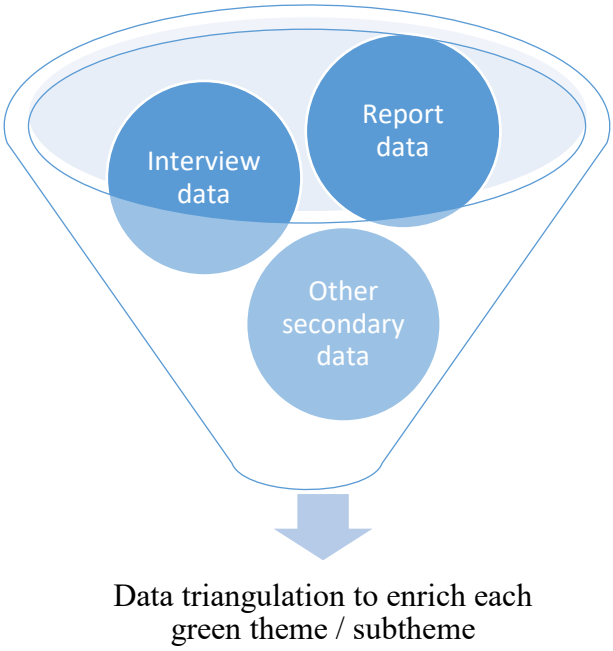


Figure 3.12 Data triangulation in the study (Source: Researcher)

The detailed steps involved in the final version of interpretation are shown in figure 3.13. The combination of this data analysis was significantly important to interpret each single theme and subtheme to obtain a holistic picture across the industry.

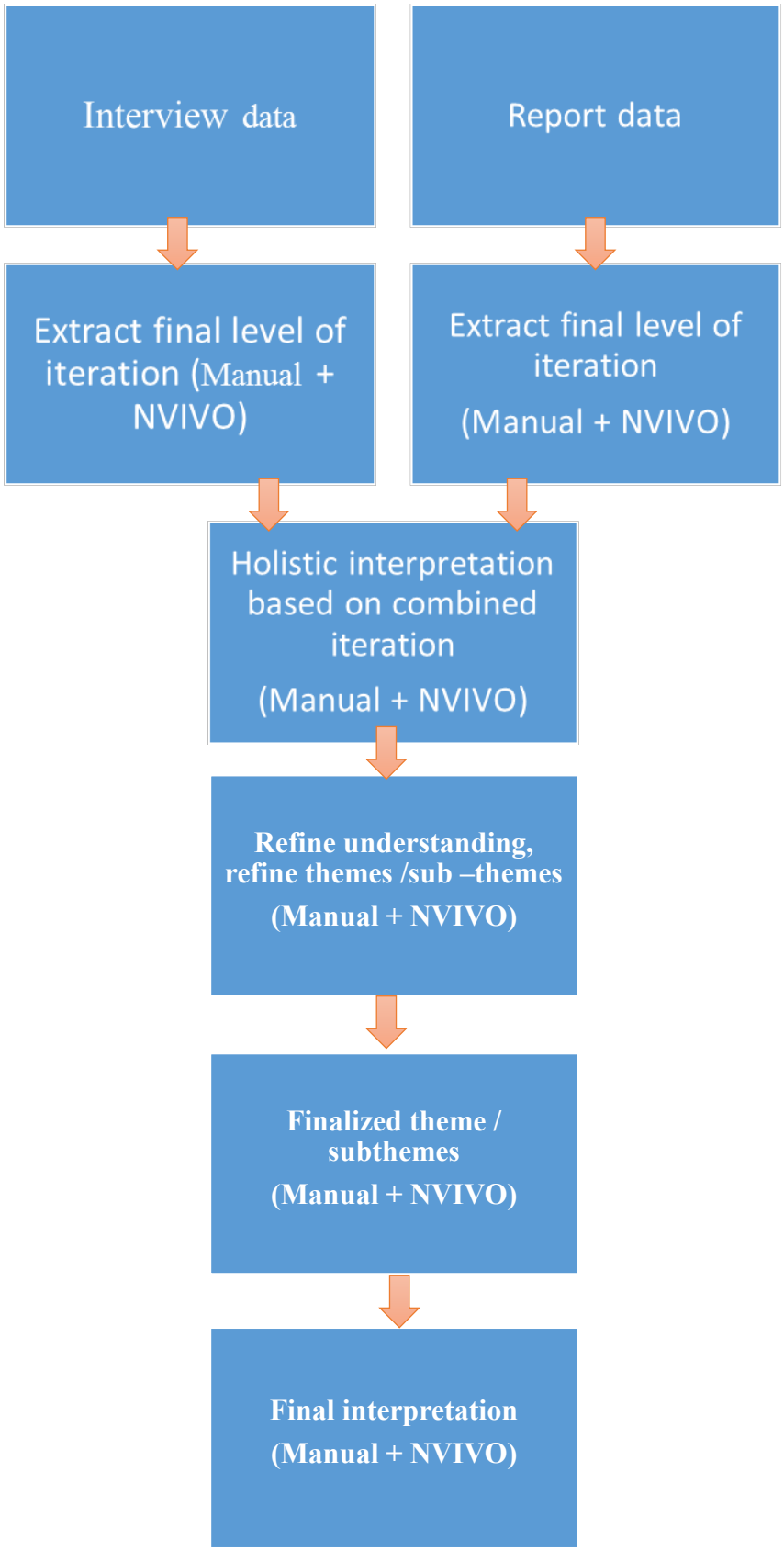


Figure 3.13 Steps involved in final version of combined data analysis and triangulation process (Source: Researcher)

While the interviews comprised a limited number of samples (though included all possible variations), many report samples were very useful to infer a conclusion on each area of research focus. Each theme was further interpreted using both a final iterated version of interview data and a final iterated version of report data. A two-way iteration cycle between interview and report was applied to refine ideas and enrich understanding on each theme/subtheme using appropriate examples in the context. Both manual interpretation and NVIVO text search output played a critical role to this final version of interpretation. This process of iteration and triangulation enabled the researcher to fit the end results into the initial theoretical MET framework. This final version of combined and holistic data analysis helped the researcher to infer and logically reorganize (through continuous addition and deletion) the relevant subthemes under the three key approaches (materials, energy, and toxicity) for each green practice.

3.5 Chapter Summary

This chapter began with the philosophical stance of the study. Driven by the interpretivism philosophy the primary objective of the study was to comprehensively answer the research questions. Hence, this chapter discussed in detail the process of data collection through interviews and content analysis of company reports. It also critically justified the methods chosen for satisfying the requirements of the interpretive phenomenon of the study. Now, it is important to evaluate the methods used through identifying the key results and findings in the next chapter. Underpinned by the methods and methodology used in this chapter, the next chapter aims to answer each research question sufficiently by integrating the findings from the interviews and reports as well as support from relevant theories and studies.

Chapter Four

Findings on Green Practices in Pharma Sector

This chapter aims to answer the first research question. Whilst the existing literature poses ambiguities and gaps in understanding different dimensions of green practices in the pharma sector, it attempts to fill these knowledge gaps with utmost clarity using both primary and secondary data. It aims to build the knowledge on pharma green practices by integrating the information from both interviews and companies' environmental reports (and/or any other appropriate related internal/external reports suggested by interviewees). It also aims to enrich the relevant knowledge on each green practice from a diversified lens of focus. Therefore, a comprehensive and wider view has been sought in each area of green practices: Green Drug-Design-and-Development, Green Drug-Manufacturing and Green Drug-use-and-disposal. The subsequent section presents each of them separately. Hence, this chapter aims to answer following research questions:

RQ1. What green practices are implemented by individual pharma sector stakeholders and what is the extent of their implementation?

RQ1.1 what green design practices are implemented by individual pharma sector stakeholders and what is the extent of their implementation?

RQ1.2 what green manufacturing practices are implemented by individual pharma sector stakeholders and what is the extent of their implementation?

RQ1.3 what green use-and-disposal practices are implemented by individual pharma sector stakeholders and what is the extent of their implementation?

4.1 Findings on Green Drug Design and Development related Practices

This section presents a detailed account on each green design and development aspect identified in the study. Though it is clear in the investigation (interviews and reports) that there is still a lack of agreement across the industry on what is meant by a green drug or what

should be considered as green drug, the investigation in general found that pharma stakeholders have predominantly considered the application of green chemistry principles, or MET practices, in the drug design and development phase. The investigation has also revealed that most of the innovative pharma has specific design objectives to apply MET practice to reduce the overall environmental footprint from the lab scale design and development process as well as from commercial scale manufacturing. In line with the previous literature, in total, ten sub green design and development related practices were identified across the industry, under MET focus. Each design aspect has been clarified and enriched through the investigation. Table 4.1 presents a summary of all sub green design practices found in the investigation. The table also shows which design aspects are currently being considered by which stakeholder and the extent of their consideration. To comprehend the findings on each sub green practice under MET, they are presented separately in the subsequent sections.

Table 4.1 Summary of the key green design and development practices and sub-practices and their extent of implementation (Source: Interviews and reports)

Green Drug Design and Development		Related sub-green practices adopted by the key stakeholders and the extent of their adoption		
Key green aspects	Sub green practices	Innovative	Generic	Bio pharma
Design for material reduction	*Design and develop manufacturing process to use greener substances*	<u>Medium to High</u> • For new drug development, most innovators have designed & developed initial process to conduct biocatalysts (e.g., enzyme-based reaction) • For redesigning existing drug process, few of the innovators have redesigned their process to reduce number of reaction stages and related byproduct formations • Redesign process to conduct chemical reaction in low temperature	<u>Planning to Low</u> • For majority, there is limited scope for redesigning existing process to conduct bio-based reaction due to the risk in regulatory approval • Few are planning to replace traditional metal-based catalysts to bio based ones for reducing byproduct formation from an existing drug process	<u>High</u> • Mostly designed and developed new process to conduct enzyme-based reaction to accelerate biochemical reaction in living organisms. • Though limited scope to redesign existing process to use enzyme technology due to safety and complex regulatory approval, some have applied it on chemical-based process.
	Design and develop drug discovery process to reduce testing	<u>High</u> • Mostly used HTS (with focused library) to identify lead drug compound • Many used 3D computer image to understand the chemical interactions	<u>Low</u> • Few of them designed R&D process to incorporate LIMS (Laboratory Information Management System) to streamline	<u>Medium</u> • Used 3D computer image to understand therapeutic target without conducting any laboratory reactions

Green Drug Design and Development		Related sub-green practices adopted by the key stakeholders and the extent of their adoption		
Key green aspects	Sub green practices	Innovative	Generic	Bio pharma
	related materials (e.g., chemicals)	• Some of them designed drug formulation to use nano materials • Used automation in R&D process for lab quality test of the key raw materials such as API, excipients etc.	R&D related materials	• Some of them designed R&D process to incorporate LIMS (Laboratory Information Management System) • Some process designs incorporated automated quality test of R&D raw materials
	Design process to consume less raw materials by applying process metric (e, g., PMI)	<u>High</u> • Majority of them designed and developed process with low PMI • Set PMI target of each process for scientists and/or chemists • Developed & enriched early process knowledge to rectify process design	<u>Not considered</u> due to risky and costly regulatory approval	<u>Not considered</u> (but under development) due to complex process equipment & engineering
	Design and develop drug manufacturing process for flexibility in quality	<u>Medium</u> • Some of them invested time to understand the process parameters and included possible quality variations in the early design related regulatory	<u>Planning</u> • Few of them are planning to consider redesigning existing process as they have plenty of process knowledge. However,	<u>Not considered</u> Difficult and challenging to enrich process knowledge in the early discovery, design, and development phase due to the nature of bio-based staring materials.

Green Drug Design and Development		Related sub-green practices adopted by the key stakeholders and the extent of their adoption		
Key green aspects	Sub green practices	Innovative	Generic	Bio pharma
	(Quality by Design)	submission • Experimented and documented stability, purity, manufacturability, and bioavailability of the drugs	costly, and time-consuming regulatory hurdles are present.	
	Design packaging for material efficiency	High • Mostly redesigned existing packaging size by increasing number of Tablets in one blister pack. • Some redesigned pack size in line with nano particle-based drug design • Few of them conducted environmental sustainability assessment (in line with stability and product integrity) of packaging materials during design phase • Designed secondary & tertiary packaging to use recycled (and/or renewable) materials • Considered life cycle impact of packaging in the early design phase	<u>Low</u> • Designed secondary & tertiary packaging to use recycled (and/or renewable) materials	<u>Planning</u> • Planning to consider sustainable primary packaging materials but only a few started considering it for tertiary packaging

Green Drug Design and Development		Related sub-green practices adopted by the key stakeholders and the extent of their adoption		
Key green aspects	Sub green practices	Innovative	Generic	Bio pharma
	Design combined drug (e.g., use multiple active substances) for material efficiency	<u>Medium to High</u> • Some innovators designed formulation which contains multiple APIs for multiple therapeutic effects.	<u>Not considered</u> Predominantly due to costly development process	<u>Not Considered</u> Predominantly due to complex manufacturing process and incompatibility of APIs within formulation
Design for Energy Reduction	*Design and develop manufacturing process for least energy consumption by evaluating alternative process*	<u>Low</u> • Few companies designed and developed process-based energy input /output metric. It used computer simulation to predict different processes with input/output energy assessment to choose from. • Assessed energy requirements for different methods of chemical separation techniques to choose most efficient process design • Assessed energy requirements for both	<u>Not Considered</u> Lack of time and cost to produce such process (or unit of a process) level data; not felt the benefit of doing so	<u>Not Considered</u> Engineering difficulty to track such unit level assessment due to have complex manufacturing process; not felt the benefit of doing so

Green Drug Design and Development		Related sub-green practices adopted by the key stakeholders and the extent of their adoption		
Key green aspects	Sub green practices	Innovative	Generic	Bio pharma
		batch and continuous process		
	Design and develop manufacturing process by installing and validating energy efficient equipment system (e.g., reaction vessel)	<u>High</u> • Mostly designed process to install and validate thermal oxidation equipment in the process, • validated heat exchangers in the process	<u>Low</u> • Few of them replaced old process equipment with new energy efficient one (especially heating and cooling process)	<u>Medium</u> • Many of them replaced traditional stainless-steel reaction vessel with 'single-use' process technology
Design for toxicity reduction	*Design and develop bio-based drug process to reduce water toxicity*	<u>High</u> • Many of them invested on developing bio-based API process • Modified lead drug compound to increase environmental degradability • Used comparatively biodegradable nanoparticles in the bio-based process • Mostly conducted ERA	<u>Low</u> • Few companies trained and guided R&D employees (e.g., formulation scientists, process chemists etc) on how to select eco-friendly solvent from in-house built solvent selection guide • Focused more on biological	<u>High</u> • Mostly designed process to use biological sourced starting materials • Used solvent selection guide to avoid (or less use) toxic chemicals usages in the process and eliminate generation of

Green Drug Design and Development		Related sub-green practices adopted by the key stakeholders and the extent of their adoption		
Key green aspects	Sub green practices	Innovative	Generic	Bio pharma
		(Environmental Risk Assessment) of new drugs • Some applied co-design strategy: e.g., design process to use a solvent whose environmental assessment is done by all stakeholders involved • Mostly considered in-house solvent guide for R&D process • Predicted toxicity level of process by using chemo-informatics and bioinformatics • Replaced DCM (dichloromethane) with water based (greener) solvent in the R&D process	degradability (or bioavailability) of drugs to maintain safety and quality rather than environmental degradability	hazardous materials as by-products.
	Design and develop drug process to reduce air toxicity	<u>Medium</u> • Some of the innovators redesigned inhaler products to replace CFC with lower global warming potential substance such as HFA (Hydrofluoroalkane)	<u>Low</u> • Few of them used VOC absorbing filter from separation process (e.g., chromatography)	<u>Low</u> • Few of them designed R&D process (especially liquid chromatography process) to use VOC absorbing filter to reduce VOC emission in the atmosphere • Also, replaced fluorocarbon containing process equipment

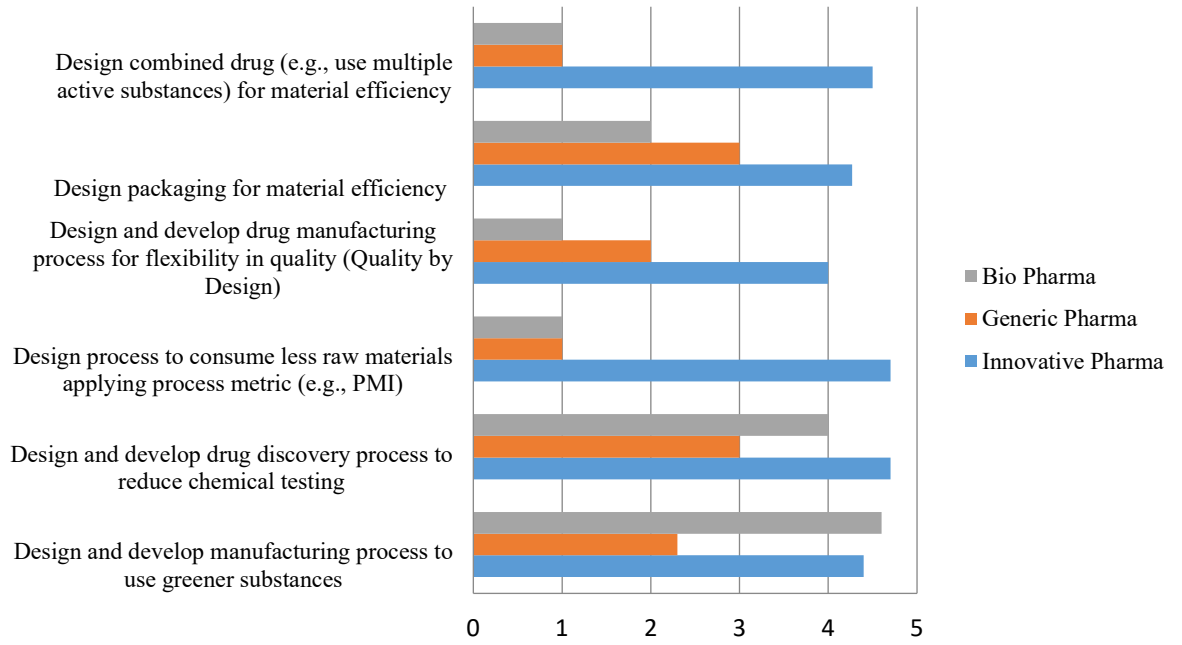
Green Drug Design and Development		Related sub-green practices adopted by the key stakeholders and the extent of their adoption		
Key green aspects	Sub green practices	Innovative	Generic	Bio pharma
				with less impact substance such as hydrofluorocarbons (HFC) and non-fluorocarbons (NON)

4.1.1 Findings on Material Reduction Related Design

As seen in Table 4.1, the investigation has identified six key sub green design practices (under material reduction) in the early drug design and development phase to reduce materials and related energy impact across the key life cycle (R&D, manufacturing and use-and-disposal) of a drug. It was also found that some design practices were relevant to new drug design and some others were relevant to the redesign of existing drugs. Hence, the scopes of related green practices and adoption levels largely vary across different stakeholders. It is remarkable that the innovative and bio pharma sectors on average are in the lead position to adopt this green aspect compared to generic sector. Figure 4.1 shows the adoption level of each sub green design practice across the key industry stakeholders. Though the rating was carried out based on the environmental report analysis, it was also supported by the findings from the interviews.

Before exploring each sub green design practice, it is important to remember that drug design is significantly different from conventional product design. This is because drug design is predominantly a discovery and development process (which involves continuous making and testing) over time rather than a rigid concept design to develop the final drug products. Hence, it predominantly involves process design aspects. The subsequent section explores first four key green design aspects. Interested readers can explore other two design aspects in appendix 6.

Figure 4.1 The extent of 'the consideration of material reduction practices in design and development phase' across the industry (based on reports)



(1 = Not mentioned / no consideration; 2 = Planning to consider; 3 = Low level of consideration; 4 = Medium level of consideration; 5 = High Level of Consideration; rating was done based on number of mentions and qualitative judgement for semantic validity of each mentions using reports)

4.1.1.1 Design and develop manufacturing process to use greener substances

As seen in Table 4.1, it was clearly evidenced in the study that majority of the innovators and bio pharma have designed the drug process to use greener substances to achieve material and related energy and toxicity reduction. This design aspect was also seen to be considered during the developing of new drugs as well as redesigning existing ones. On most occasions, the R&D managers, scientists and chemists from the key pharma stakeholders interviewed had their own interpretations of using 'greener substances'. For instance, some mentioned it as the usage of biocatalysts; or the usage of less hazardous chemicals with non-corrosive / non-radioactive characteristics; or some mentioned it as the usage of chemicals which are less organic in nature; or use of water based solvents. However, the investigation (both interviews and reports) has revealed that the use of '***Biocatalysts***' are predominant and has been paid a particular focus across the industry in order to design and develop a greener drug process.

Interestingly, while combining the findings from both interviews and reports it was clear that though a biocatalyst is predominantly applied to improve material efficiencies, it also helps (in varying extents) in reducing related energy and toxicity across the drug life cycle. But, in

most cases material and related energy efficiency showed similar importance. For instance, Table 4.2 highlights some of the key findings on the benefits gained by adopting a biocatalysts-based drug process. The table also highlights how the related benefits are reaped across different parts of the life cycle of a drug.

Table 4.2: Key benefits of biocatalyst-based drug process design across a drug life cycle (Source: Interviews and reports)

Greener Substances	**Benefits of Biocatalysts based drug process across a drug life cycle**		
	Drug Design & Development	**Drug Manufacturing**	**Disposal**
Bio catalysts (e.g., enzymes)	Reduce drug design & developmental timeline	Reduce materials consumptions (e.g., lower chemicals as input raw materials; reduce by-product formation)	Induce fewer toxic wastes. Less disposal costs
	Materials reduction (e.g., reduced usage of solvents) and related costs	Reduce (material related & process related) energy consumption and related costs	Less energy requirement to treat wastes;
	Increase renewability by replacing non-renewable metal-based catalysts	Increase renewability by replacing non-renewable metal-based catalysts	

The investigation (both interviews and reports) has clearly indicated that a biocatalysts (e.g., enzymes) based process reduces overall requirements of input raw materials. In most cases both innovative and bio pharma have highlighted that due to higher selectivity and effectiveness of a biocatalyst, the number of reaction stages and related by-products formations is reduced. Hence, the process requires fewer chemical inputs and reduces unnecessary use of chemical raw materials such as reagents, solvents, and reactants. The investigation further confirms that biocatalysts also help reduce the overall developmental

timeline, as the substance (biocatalysts) reduces the reaction time and increases the reaction throughput.

For instance, the importance attached to this green design practice can be gauged from the statements reported by one of the leading bio pharma companies, (*B-9), as* ***"… a 71 percent reduction in solvent use during the development lifecycle, a five-fold increase in throughput, and an estimated 40 percent reduction in operating time …"*** while developing a new drug called *'Parsabiv'* for the treatment of secondary hyperparathyroidism. The company has gained this result by eliminating one of five manufacturing steps designed in the process and optimized the remaining four steps through reducing related other byproducts.

The findings from reports demonstrate that the adoption levels of this green design practices significantly vary across different sub sectors (see figure 4.1). Arguably, though related process data and knowledge for existing drug process is better understood than new drugs for optimizing through this design practice, the practice is still not widely applied in the industry for the redesigning of existing drugs - as reflected in the interviews. The reason is the expensive and time-consuming regulatory approval of process change for existing drugs.

4.1.1.2 Design and develop drug discovery process to reduce chemical-based testing

The investigation (both interviews and reports) explains how the drug discovery process can be designed to apply different types of artificial intelligence (AI), automations, machine learning and other related advanced technologies to advance and accelerate the drug design and development activities to replace the requirements of actual chemical testing and related raw materials (e.g., solvents, reagents, reactants). The list of AIs and related technologies-based drug design aspects that came out from the investigation are listed on Table 4.3. It was also evidenced that the majority of the innovators and bio pharma have considered this design aspect compared to generic pharma (see figure 4.1 and Table 4.1). Evidence for some key AI and technology-based (e.g., HTS, In-silico chemical screening, and nanotechnology) drug design is discussed below. Interested readers are referred to Appendix 7 to explore some other (e.g., LIMS and quality automation) applications in details.

Table 4.3: Scopes of raw materials reduction applying key AI and related technologies during early drug discovery process (sources: Interviews and reports)

Aspects of key AI & related	Scope of raw materials reduction

technology	
HTS (High Throughput screening): Focused library	Test or screen millions of compounds at a time with utmost accuracy. Reduce raw materials requirements through focused library screening whenever possible.
In-silico chemical screening (e.g., structure-based drug design, DNA-encoded library)	Using computer program *(instead of using actual laboratory samples)* to predict how different chemicals react with target compounds using a 3D image
Nano technology	Design formulation with nano size granules or drug substances which are more effective and efficient (than traditional drug substances) in terms of binding to target site. Hence, fewer raw materials (e.g., API, excipients, solvents etc) required for producing drug.
Laboratory Information Management System (LIMS)	Streamline process raw materials across R&D labs
Automation of lab quality testing	Faster, effective, efficient quality testing lead to lower raw materials requirements

HTS (High Throughput screening): Focused library

It was evident from the investigation (both interviews and reports) that the industry, mostly innovative and bio pharma sectors, is moving from traditional (random) high throughput screening (HTS) towards more focused library screening model. The investigation has further confirmed that compared to random library screening, usage of focused library reduces the unnecessary compound testing and related resources. Many interviewees agreed and highlighted that as drug R&D aims to reduce the developmental timeline, more selective and effective screening is essential. In particular, the innovators have agreed that focused library is built upon with special and diverse groups of chemical compound collections which are more selective and effective. Hence, shorter lead time and lower usages of resources are achieved.

However, a few interviewees also warned that not all therapeutic areas have focused library, and the focused library should sometimes be used with another reference library to identify

the possible lead drug compound. For instance, one of the respondents from a leading innovative pharma (D-site 1 R&D) stressed that though focused library is a greener approach, in terms of resources reduction, the usage of focused library depends on the one existing product therapeutic area where sufficient knowledge on drug interaction (i.e., how a lead compound interact with a biological target) is available. The respondent added that not all therapeutic areas have an effective focused library that can be used; therefore, the R&D will have to use some reference library in conjunction with focused library. The key industrial trend (mostly in innovative pharma) of AI based drug design can also be understood from the comments of one of the R&D scientists (B – site 3 R&D) on the movement from randon to focused-library screening in general: "… … ***things are being streamlined to specific to avoid just stepping on the dark, we do streamline thing so that there will be a particular drug target … …"***

In-silico chemical screening (e.g., structure-based drug design, DNA-encoded library)

As per the investigation (both interviews and reports), the innovative pharma companies (as well as bio pharma) have shown greater interest in investing more in In-silico testing to get better precision and understanding of the mechanism of how the expected lead (chemical based) drug substances will react with the target and identify possible lead compounds without testing or screening actual compounds in the lab. The investigation (both interviews and reports) further reveals that this typical in-silico based understanding saves related resources (e.g., chemicals samples, micro titter plates, reagents and solvents) which are normally required in actual lab based chemical testing.

For instance, a respondent (a lab scientist) from an innovative company (B - site 3, R&D) outlined that AI and advanced technologies in the drug discovery process have significantly replaced the amount of raw materials and testing chemicals they used to deploy (though the respondent was unable to share exact figure on materials and related energy savings). The respondent further went on to say that the usages of more in-silico testing with 3D visual imaging of target substances (or proteins) have accelerated their discovery process and reduced further chemical testing.

The majority of the leading innovative pharma have planned to move from in-vivo to more in-silico compound screening, as evidenced from the interviews and reports. For instance, one of the leading innovators (In-5) reported that it is aiming to replace certain lab experiments with computer programming, for instance, to generate a DNA-encoded library

(which is mostly similar to focused library) to rapidly expand the collection of small molecules that serve as a starting point for potential chemical based new drug design.

Nano technology driven drug formulation

The investigation (both interviews and reports) reveals that a number of the leading innovative pharma has adopted nanotechnology driven drug formulation design to dematerialise the drug process. It was reported that nanotechnology uses materials less than 100 nanometres in size (nanomaterials). The investigation (both interview and reports) further reveals that drugs produced from nanomaterials can move more freely in the human body and these materials are more selective and effective for manipulating target sites efficiently than conventional medicine. Therefore, a lower strength (compared to higher strength conventional drug) of drug executes effective therapeutic value. This is how the usage of nanomaterials will significantly reduce the weight and size of the product produced. For instance, it was reported by one of the leading innovative pharma (In-06) that they have recently designed such nano technology based drug formulation, known as EMEND® (aprepitant) – a drug which is used to prevent nausea and vomiting that may be caused by surgery or cancer chemotherapy. They use nanotechnology (e.g., nanoscale milling approach) to generate very small granules for effective therapeutic value, while it gives material efficiency at the same time during mass production.

However, from this investigation it emerged that nanotechnology-based drug design is only occasionally considered in the innovative sector. None of the bio pharma and generic pharma had considered it. This is because there is less scope for developing new drugs in the generic setting. Though there is a possibility of redesigning existing formulation using nano materials, related time and regulatory costs are the key burden for the generic sector. Quality, safety, and efficacy of nano materials for bio pharma formulation are the key challenge.

4.1.1.3 Design process to consume less raw materials applying process metric (e.g., PMI)

The interviews and reports have revealed how to apply a process metric (called PMI - Process Mass Intensity) developed by the process development scientist and chemists to make a new process greener, so that both lab scale and commercial production scale can improve the materials footprint. As revealed by the study, PMI (Process Mass Intensity) actually measures the kilograms of chemical (and/or raw materials such as solvents, reagents, reactants, and

catalysts) inputs that are required for producing a kilogram of the final drug product in a single process. The majority of the interviewees agreed that as the plant wide input/output measurements are not effective enough to deal with overall materials (and related energy) reduction for a specific drug process, the consideration and assessment of process specific PMI in the early drug development phase is of great importance for pharma manufacturers for choosing most materials efficient drug process.

The investigation (both interviews and reports) further reveals that PMI based process selection (predominantly chemicals based) was considered one of the most significant green practices for increasing materials savings across the industry, especially in the case of the innovative pharma segment. The majority of the innovators investigated, through both the interviews and the reports, have developed in-house scientific teams to enrich process knowledge (on input-process-output of key materials) to provide several process centric PMI metrics. For instance, one of the leading innovative pharma respondents (C) highlighted that they had decided to select the most materials efficient process by applying the PMI metric for the last five years and had saved more than 30% in raw materials on average across their sites. However, such practice is still not common in biopharma due to the types of materials usage and their transformations across the complex equipment system and the related measurements are more complex than chemical-based processes, as expressed by a few interviewees. Though a number of other respondents (e.g., A and C) highlighted the positive implication and importance of PMI in generic pharma, none of the respondents mentioned PMI in the case of redesigning the generic drug development process. While redesigning existing drug processes (around 3000 APIs in the market) by considering PMI has huge potential for generic pharma for saving raw materials and related costs, regulatory costs are the key burdens for generic pharma to apply PMI and redesign existing drug process accordingly.

4.1.1.4 Design and develop drug manufacturing process for flexibility in quality (Quality by Design)

It was clear in the investigation of both interviews and reports that quality deviations during commercial drug manufacturing incur considerable amounts of raw materials waste and related costs. External quality failure also results in unexpected product recall and related resources wastes as reported in the study. The findings from the study identified that a built-in quality process is considered by some innovative companies during drug design and

development phase. As indicated by both interviews and reports the philosophy of this design aspect is to consider a flexible design space where all possible quality variations in relation to process parameters (e.g., reaction time, throughput, blended uniformity, purity of API, and excipient-API interactions) are experimented, understood and documented during the design and development phase of drugs, and include all those variations in the early regulatory submission. This design process is termed 'Quality by Design (QbD)'. It helps process chemists to understand the process and related critical parameters to control it.

For instance, one of the respondents, head of quality from a generic pharma (F - site 1) outlined that they have successfully adopted QbD in the early process design phase and reduced unnecessary quality testing in the mass production phase. It was also revealed in the study that excipients are one of the major sources of variability and hence they have experimented and documented the stability, purity, manufacturability and bioavailability of the drugs (under development) to avoid costly materials wastes later in the production chain. Similarly, some other respondents (e.g., one innovative pharma report, In-09 and another respondent from innovative pharma, B-site 1) also highlighted that they have considered API and excipient interaction monitoring across the developmental timeline continuously to record quality variations to dematerialize the process in the manufacturing phase (if arises due to API quality variations).

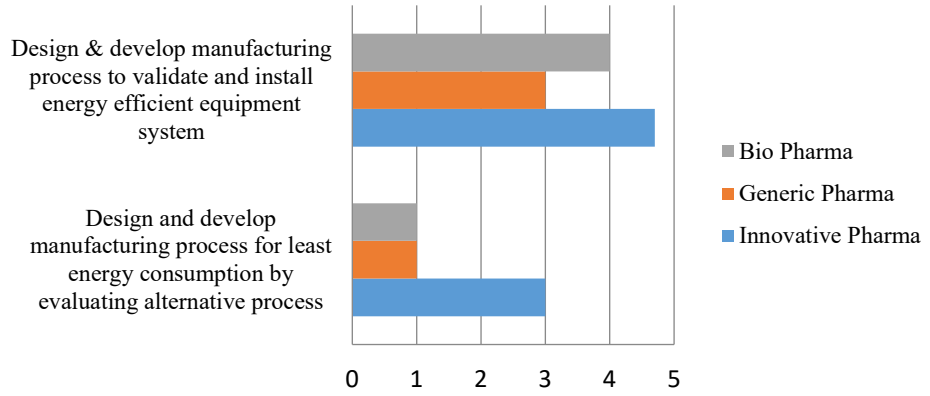
It was also revealed in the study that once the design space (DS) has been authorised by the regulator, movements within the DS are not considered a change from a regulatory point of view (no variation to be submitted). Therefore, it could be an opportunity for all pharma, especially for generic pharma companies (where making changes in a process is always a regulatory burden) to consider greener parameters in the design space. Interestingly, despite having such great potential to reduce resources, overall, the consideration of QbD in the pharma sector is still very low (see figure 4.1), and is non-existent in the generic and bio pharma sectors. The reasons could be related costs, quality, engineering and other operational issues.

4.1.2 Findings on Energy Reduction related design

As the previous section covered direct materials related energy reduction, this section mostly covers direct energy (in terms of electricity or gas) required in the process (or in a single operational stage) /plant. As seen in Table 4.1, the study reveals that the pharma industry has

adopted two key energy reduction practices during the design phase: *design and develop a manufacturing process for the least energy consumption by evaluating alternative process*; and *design and develop a manufacturing process by validating and installing an energy efficient reaction vessel*. It was also evident that both practices are applied either on developing new drug processes or re-design existing drug processes. The investigation also reveals that these design aspects have impacted positively both the 'R&D lab scale manufacturing phase for clinical development' and 'mass production phase in the life cycle' in terms of materials reduction. The subsequent section presents findings on each of the sub green practices identified. The findings show that innovative pharma and bio pharma are in average at the forefront of adopting this energy saving practice. Figure 4.2 shows the adoption level of each sub green practice across the industry. Though the ratings were made based on the analysis of the environmental report, it was also supported by the interviews.

Figure 4.2 The extent of 'the consideration of energy reduction practices in design and development phase' across pharma industry (based on reports)



(1 = Not mentioned / no consideration; 2 = Planning to consider; 3 = Low level of consideration; 4 = Medium level of consideration; 5 = High Level of Consideration; rating was done based on number of mentions and qualitative judgement for semantic validity of each mentions)

4.1.2.1 Design and develop manufacturing process for least energy consumption by evaluating alternative process

The findings from both the interviews and reports demonstrate how innovative pharma consider a detailed energy assessment during a new process design and development of a drug substance. The innovative pharma companies that participated in the investigation

revealed that they have adopted a new energy based process metric which assesses process specific (input versus output) energy to demonstrate where energy is lost, what energy might be renewable, and hence weighing different process options to choose the most energy efficient one. The study also reveals that this typical energy assessment uses computer software to predict multiple process options with energy input and output scenarios to help R&D managers to choose the efficient one. However, a few innovators also highlight that the lack of industrial benchmark data for a process or unit of a process energy consumption (e.g., heating, cooling etc) related data is the key barrier for effective computer prediction.

For instance, it was reported by one of the leading innovative pharma (In-08) companies that they have already experimented with whether crystallization or chromatography (a process step of chemical separation technique) for compound separation in the API process development is energy efficient based on this typical (input/output) energy assessment process; also, the metric in the report further examines whether distillation (a solvent recycling process) or solvent recovery is better, from an energy standpoint, for the treatment of solvent waste from the new process. It was also reported by one of the respondents (B-site 2) that their company was also comparing the energy efficiencies of continuous and batch chemical reactions within a process using the energy assessment process. Though the respondent did not know the actual savings amount from applying this process-based energy measure, he stated that the saving is significantly higher as felt by the manufacturing department. None of the biopharma and generic pharma adopted this practice due to the challenges of time, cost, quality, and complex equipment engineering involved especially in the bio process.

4.1.2.2 Design & develop manufacturing process to validate and install energy efficient equipment system

As per the investigations of both interviews and reports, this design aspect explains the scopes of exploiting different energy efficient process equipment to develop, validate and maintain an energy efficient process of a new or existing drug substance. It was revealed from the study that as R&D is responsible for validating (regulatory approval) a particular process, including the equipment system to be used in the bulk manufacturing, early decision on choosing alternative energy efficient equipment system is essential. As per the investigation, the industry has been sought to focus on two key areas:

- ✓ *Validate and install 'single use disposal reaction vessel' (also termed as 'single use technology')*
- ✓ *Validate and install energy efficient heating and cooling process-equipment.*

Detailed findings on each of this aspect are presented below:

Validate and install 'single use disposal reaction vessel' (also termed as 'single use technology')

It was evident from the investigation (both interviews and reports) that the bio pharma sector has sought to validate their bio-based drug process to use a 'disposable plastic reaction vessel', which replaces the traditional reusable 'stainless steel / glass vessel (or reactor)' where the reaction takes place. Though apparently disposable plastic reactors seem to be non-eco-friendly over reusable stainless-steel reactors, in this scenario the overall environmental benefit from validating a process with single use technology is higher than in the traditional one, as emerged from this investigation. Most of the interviewed respondents highlighted that 'single use technology' based process design saves energy via eliminating cleaning materials, purified water, sterilization, and cleaning process. This is because the traditional stainless steel-based reactor requires cleaning in-between the change overs as explained by the respondents. Some key respondents from R&D, such as a senior scientist and lab manager from the bio pharma, also stressed that traditional stainless steel reactor based design also requires frequent pre and post sterilization (and related energy) between batches to disinfect and prepare for the next batch. The key benefits of adopting 'single use technology' based process design were also highlighted in the investigation (as shown in Table 4.5 below).

Table 4.5: Key benefits of adopting 'single use technology' (Source: Interviews and reports)

- ✓ Less energy consumption
- ✓ Less requirement of cleaning materials (e.g., solvents)
- ✓ Offer flexible manufacturing (e.g., quick switching from one product to another)
- ✓ Enable continuous process, hence low energy
- ✓ Reduce operational costs: no cleaning materials, maximizing capacity
- ✓ No require for cleaning and sterilization validation in the process
- ✓ Water savings including purified water

For instance, it was outlined by one of the respondents from a bio pharma company (J – site 1) that the amount of energy savings from single use technology is more than twice than traditional stainless steel one. The similar importance of single-use equipment was also evidenced in the environmental reports, for instance, one of the bio pharma reports (B-09) highlights that ***"Single-use equipment avoids high water and energy consumptions, as cleaning and the need for copious amounts of water for injection are avoided"***

The interviews findings also revealed that single use technology is not always useful for all kind of reactions as it depends on different product and process settings. Scalability (upgrade or downgrade from lab scale during manufacturing) and leaching from plastic containers are two important challenges to deciding to adopt a single use based process, as revealed in the study.

Validate and install energy efficient heating and cooling process-equipment.

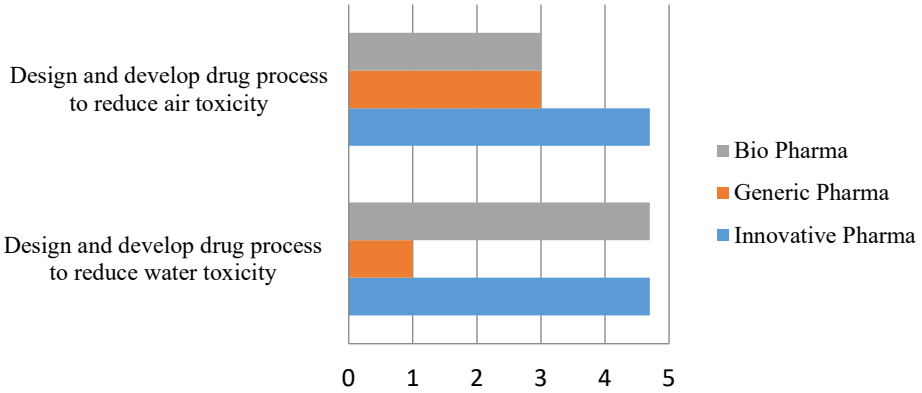
Designing energy efficient equipment systems (e.g., energy efficient heating and cooling process equipment system, testing equipment, etc) in the R&D laboratory has also been highlighted in the study. It was evidenced in the reports that the majority of the innovative Pharma companies are designing and installing energy efficient equipment (e.g., designing and validating of thermal oxidation equipment in the process, validating heat exchangers in the process etc) in the R&D lab. While only a few generic pharma reported replacing of old equipment with more energy efficient installations (e.g., energy efficient heating and cooling

equipment in the process), the majority of Biopharma reported tha they design their process to use energy efficient process technology to reduce energy emission and eco-friendly air conditioning resulting in optimum energy efficiency.

4.1.3 Findings on Toxicity Reduction related design

This section presents the findings on what and how key green aspects are currently being considered by the pharma companies to reduce toxicity across the drug life cycle. It emerged from the study that the pharma industry is currently considering two key green aspects in the design and development phase to reduce toxicity in the life cycle of a drug: firstly, *design and develop more bio based drugs to increase environmental biodegradability of drug substances to reduce potential water toxicity*; and secondly, *design and develop inhalers drugs products to reduce air toxicity during the use and disposal phase*. It was also revealed in the investigation that the first design aspect is applied for both new and existing drugs. However, the second design aspect was seen to apply to existing drugs only. As came out from the investigation, these design aspects have significant impact (in terms of air and water toxicity reduction) on the manufacturing and use-and-disposal phase of the drug life cycle across the industry. Interestingly, innovative and bio pharma are in the lead position to adopt this green aspect, rather than generic pharma. Figure 4.3 shows the adoption level of each sub green practice across the industry. Though the rating was done based on environmental report analysis, it was also supported by the interviews. The subsequent section presents each of the green aspect in detail.

Figure 4.3 The extent of 'the consideration of toxicity reduction practices in design and development phase' across pharma industry (based on reports)



(1 = Not mentioned / no consideration; 2 = Planning to consider; 3 = Low level of consideration; 4 = Medium level of consideration; 5 = High Level of Consideration; rating was done based on number of mentions and qualitative judgement for semantic validity of each mentions)

4.1.3.1 Design and develop drug process to reduce water toxicity (via increasing environmental degradability)

Findings from both interviews and reports have revealed that the pharma industry has focused on two key areas to increase biodegradability of a drug process during R&D phase. Firstly, design and develop a drug process to use bio based starting materials or biologically sourced API; and secondly, design and develop a drug process to eliminate or reduce usages of toxic chemicals (e.g., organic solvents). Table 4.6 below shows the overall view of this design aspect.

Table 4.6 Measures taken to increase environmental degradability of drugs (Source: interviews and reports)

Design and develop bio-based process

- ✓ Design and develop process to use biologically sourced starting materials or API or biodegradable nanoparticles

Design and develop drug process to eliminate or reduce toxic chemicals use

- ✓ Environmental toxicity prediction of chemicals in the early design phase
- ✓ Eliminate / reduce application of toxic chemicals (e.g., solvents)

Design and develop bio-based process: Develop bio-based process to use biologically sourced starting materials or API or biodegradable nano particles

It was evident in the findings from both the interviews and the reports that a ***bio-based drug*** is generally assumed to be comparatively more biodegradable into the environment than chemicals based ones. Most of the respondents agree that bio-based drugs are comparatively more selective and highly effective at manipulating the disease compared to chemical based drugs. Some of the respondents (especially the R&D principle scientists) also highlighted that bio based drugs have higher drug absorption by the human body and therefore there is less excretion into the environment compared to conventional chemical-based drugs. A number of the respondents also believe that even the excretion from bio-based drugs (metabolism) is

assumed to be degraded into the environment to some extent, while this is not the case for chemical-based drugs. For instance, one of the respondents from an innovative pharma (C) highlighted that more than 60% of R&D investments were related to bio-based API process development in their new product development portfolios. It was also reported by some other bio pharma companies (e.g., B -17) that biologically synthesised drugs come with a generally much better environmental degradability.

Design and develop drug process to increase environmental degradability: Environmental toxicity prediction in the early design phase

The study reveals that the majority of the leading innovative pharma and a few bio pharma involved in developing new drugs are investing in examining and predicting the environmental impact of potential drug substances which are under lab or clinical trial. The key focus of this environmental prediction is to find PBT (Persistence Bioaccumulation and Toxicity) data of the new drug substances which are still in the developmental pipeline. The majority of the respondents (especially the environmental scientists) from innovative pharma also advocated conducting such environmental assessment, as it can predict what actually could happen when a drug substance (in the forms of either metabolised or un-metabolised) enters into the environment, and how it could react with other biota in the ecosystem, and whether it could produce toxicity, and to what extent etc, so an early prediction of environmental impact assessment is significant.

It was also evidenced in the investigation (both interviews and reports) that this typical environmental prediction is done using different strategies, such as applying intelligent tool - bioinformatics and chemoinformatics for statistical prediction, or applying a co-design strategy (e.g., design a process with green solvent from insights from all relevant stakeholders), or through ERA (Environmental Risk Assessment program). The R&D scientists use intelligent tools to retrieve relevant chemical and biological data to understand the statistical prediction on a particular drug substance and its predicted interaction with another bio substance or other chemical based substances in the environment. For instance, one of the leading innovative pharma (In-03) has reported that they integrate both bioinformatics and chemoinformatics which allow them to make in-silico prediction of toxicities of the potential drug substances under investigation.

Design and develop drug process to increase environmental degradability: Design and develop drug process to eliminate / reduce application of toxic chemicals (e.g., solvents)

A design process to eliminate or reduce usage of toxic chemicals during R&D operations was found to be another approach taken across the industry, though the rate of adoption is comparatively much higher in innovative and bio pharma than generic. Most of the respondents highlighted using water-based solvents (comparatively greener solvent) whenever possible than using acid/base solvents to reduce environmental toxicity. Some of the respondents also highlighted that acid/base solvents sometimes produce toxic byproducts, and some of them are toxic in nature, and may involve costly processing to dispose of them, while this is not the case for water based solvents. Table 4.7 highlights the key chemicals which were avoided by the pharma companies in general in designing a new process, as evidenced from the investigation. The table also presents related environmental concerns that emerged from the study. Also, detailed solvent selection related findings are included in appendix 8.

Table 4.7 Key chemicals avoided in a drug process design (Source: Interviews and reports)

Examples of Key chemical class avoided from drug process	**General Environmental concern**
Substances of very high concern (SVHCs) (e.g., Benzene, Diethyl ether etc)	Chemicals classified as potentially carcinogenic, mutagenic, or toxic to the human and environment.
Chlorinated solvents (e.g., DCM-dichloromethane)	A hazardous air pollutant and suspected carcinogen
Organic solvent-based ink in packaging	Increase water toxicity; increase air toxicity via VOCs – linked to GHG emission
PRTR (Pollution Release and Transfer Register) chemical substances	Substances released as industrial wastewater which may be harmful for the environment (air/water/land) and human health

For instance, it was repeatedly reported by the innovative pharma (e.g., In-04; In-09) that they designed their drug processes to replace the usage of DCM (dichloromethane) with greener water-based solvents for cleaning R&D equipment. DCM is a hazardous air pollutant and suspected carcinogen. The importance of such design aspects was also highlighted by the majority of the innovative and bio pharma respondents. For instance, one of the respondents (C) highlighted that those drug processes which are designed to use toxic solvents in the process increase overall manufacturing costs due to the addition of special disposal costs.

This was also stressed in the innovative company reports. For instance, another innovative pharma (In-13) explained: ***"… … we work to protect and preserve the environment as part of our daily business operations e.g., by avoiding use of organic solvents and cyanide traditionally used in our industry… …"***

4.1.3.2 Design and develop drug process to reduce air toxicity

It was evident from the interviews and reports that the industry in general has redesigned their products and/or processes to address two key environmental impacts from air toxicity: ozone layer depletion and emission of VOCs. This design aspect explains the scopes of redesigning pharmaceutical products/process for combating the emission of ozone depleting substances (originating from both the design process and later lifecycle of the products, such as in the usage phase) and VOCs from the R&D process. Two key sub-green practices were identified in the study: *redesigning pharma products (e.g., CFC free inhaler)* and *redesigning equipment settings to curb VOCs from the R&D process.* The next section explains the scope of CFC free inhaler when other design aspect is included in appendix 9.

Redesign pharma products (e.g., CFC free inhalers)

The study reveals that CFC based inhaler products induce a significant amount of chlorofluorocarbon in the atmosphere during the usage phase of the products. CFC is the key substance to deplete ozone layers. It was also evident in the innovative pharma reports that ozone layer depletion impacts negatively on both human health and environment. For instance, UV rays are increased in the atmosphere, which can cause skin cancers, and UV rays also alter aquatic ecosystems and affect plant growth. It was also reported that CFC is indirectly responsible for increasing GHG emission. For instance, it was reported by one of the leading pharma companies (In -03) that Scope 3 GHG emissions from product usage has increased from 99 kilotons in 2014 to124 kilotons in 2015 and, this increment is predominately due to growing production volumes of CFC-based inhaler products.

Hence, the innovative pharma sector has redesigned the existing inhaler products to reduce usage of CFC as revealed in the investigation. For instance, it was reported by the majority of the innovative pharma (e.g., B – site 2) that they have replaced CFC with lower global warming potential substances such as HFA (Hydrofluoroalkane). Some of the respondents and reports also mentioned that a new mechanical process is also introduced while replacing CFC with liquid HFA. The new mechanical process is termed as PMDI (Pressurized Meter

Dose Inhaler). It was also evident in the investigation that the newly designed PMDI inhaler converts the liquid HFA containing products into tiny droplets (million micrometre-size droplets) like powder through tiny little nozzles under mechanical pressure, which ultimately reduces GHG impact during the usage phase of each inhaler.

For instance, it was reported by one of the innovative pharma (In - 07) that they had developed a PMDI technique-based inhaler, *called RESPIMAT,* which creates a mist of around 230 million micrometre-size droplets. They mentioned it as a technical milestone that benefits the global climate, because the liquid substances in standard devices constitutes up to 300 g CO2 equivalent per inhaler and each of which is often only used for a month. However, the report also warned that – ***"… the devices are not ideal for everyone, however, because the patient has to be able to inhale deeply so that the fine powder can enter the lungs…"*** Therefore, the company was still working towards this new design of inhaler products for reducing global emission impact.

This design aspect has predominantly been taken by most of the innovative pharma in comparison to other segments. As bio pharma were not involved in the production of any such inhaler products, the design aspect was not relevant for them. Interestingly, though it could be of great importance to generic pharma, none of the generic pharma was seen to adopt this practice. This is probably because of higher investment necessary to redesign and uncertainty in regulatory approval, which was also suggested by one of the respondents from a leading pharma (B – site 2).

4.2 Findings on Green Manufacturing Practices

Findings on this green aspect reveal key environmental activities and management practices during manufacturing of drug products in the case of both bio-based and chemical based production. The study also reveals that the importance of considering green practices during manufacturing not only reduces the manufacturing impact on the environment but also plays a crucial role for reducing environmental loadings during drug use-and-disposal phase. Whilst the green design section has provided a foundation for what and how the manufacturing operations of drug products would look like for achieving environmental goals across the industry, further empirical evidence on green practice adoption during the manufacturing phase has amplified the understanding – which has not been understood holistically and in- depth previously.

It is clearly evidenced from the investigation (both interviews and reports) that greening pharmaceutical manufacturing operations has become one of the top agendas across the pharma industry due to the unprecedented level of pressure for conserving natural resources such as energy, water and other non-renewable materials. The investigation has confirmed that the industry has already started applying green chemistry or MET related practices to an extent. Table 4.10 has summarized the relevant green practices identified for individual stakeholders in the study. The table also shows the extent of average adoption levels of each sub green practice. As seen in Table 4.10, under MET practices 9 sub green practices in total are currently being considered across the industry.

Table 4.10 Summary of the key green manufacturing related practices and sub-practices and their extent of implementation (Source: Interviews and reports)

Green Manufacturing		Related sub-green practices adopted by the key stakeholders and the extent of their adoption		
Key green aspects	Sub green practices	Innovative	Generic	Bio pharma
Material reduction	*Run continuous mode of manufacturing*	<u>High</u> • Most innovators adopt microreactors / flow reactors which contain multiples small reaction chambers where inputs (e.g., solvents) are continuously added in a smaller scale to run continuous API production • Some innovative pharma successfully aligned API and formulation into one continuous process • Most of the processes integrate PAT (Process Analytical Technologies) to optimize process parameters • Not all API processes are fit for continuous; only apply case by case • Demand for a particular product, costs, time, specific product specification, types and availability of machineries affects decision on batch to continuous	<u>Medium</u> • For some generic pharma, continuous coating and tabletting were observed • For continuous formulation, few of them set up weighing, blending, granulation, tabletting (compressing the granule into Tablet) and coating in one line where API and excipients are continuously added to blending • PAT is also integrated with to continuous tabletting process	<u>Planning</u> • A few of them adopt continuous fermentation and extraction process, majority are still in the planning stage as scale up the continuous bio process is challenging due to have complex equipment settings and quality issues.

Green Manufacturing		Related sub-green practices adopted by the key stakeholders and the extent of their adoption		
Key green aspects	Sub green practices	Innovative	Generic	Bio pharma
	Recycle and reuse solvents	<u>High</u> • Mostly recycle via onsite distillation process to extract useful chemical substances from wasted solvents (sometimes termed as wastewater) and/or intermediate wasted by-products during drug manufacturing process. • Most of them reuse the lower graded recycled solvents (which are deviated from recovery specification) for other purposes that do not require high purity solvents • In many instances, they use recovered solvents for the cleaning purposes • Mostly skilled and build capabilities to recycle organic solvents	<u>Low</u> • Predominantly planning for recycling purified distilled water from the process rather other than organic solvents due to having related equipment engineering difficulties and product quality related issues • A few of them recycle solvent from complex waste mixture (e.g., ethanol-water) in API plants to avoid incineration and converts into biologically treaTable wastes via a unique recovery system (unique distillation system) • One of them employed a cross functional team (e.g., engaging process chemists and process engineers, waste contractors etc) to examine the system of recovery	<u>Medium</u> • Some of them use recycled solvents to clean process equipment • Some of them are capable to recycle inorganic solvents (rather than organic one) • Few of them use computer simulation technique to assess the viability of solvent recovery in the process
	Consider lean operations for	<u>High</u>	<u>High</u>	<u>Medium</u>

Green Manufacturing		Related sub-green practices adopted by the key stakeholders and the extent of their adoption		
Key green aspects	Sub green practices	Innovative	Generic	Bio pharma
	materials reduction	• Water reduction: Mostly considered water efficiency targets, employees' mindset for water savings, increase production efficiency, waterless (or, mechanical) cooling system, site specific water conservation programs, and closed loop cooling system. • Mostly planned to move from paper based BPR (Batch Process Record) to paperless / electronic BPR or, eBPR. • Mostly build strong supplier relationships (internal / external) for reliable inputs such as API to reduce unnecessary QC test prior to manufacturing	• Water reduction: Few of them apply automatic wash in place (WIP). Few of them also apply a new spray technology that uses high mechanical pressure to clean-up equipment • Mostly reduce the volume of tertiary and other types of packaging materials • Some of them consider e-version of medication guide rather than paper based one • Mostly automate /digitize QC process to reduce human intervention and related error • Few of them measure equipment failure parameters such as mean time to repair a faulty equipment etc.	• Water reduction: Majority of them predominantly initiated to use waterless cooling system to save water. Some of them use closed loop cooling system (water is collected and re-circulated from the process tower) • Very few have planned to move to eBPR
	Consider green collaboration for materials	<u>Medium</u> • Some of them collaborate between upstream medicinal chemists, scientists and downstream process engineers, formulations	<u>Planning</u> • Few of them are planning to adopt different forms of communications such as 'regular	<u>Not considered</u> Very limited scope of process optimization due to complex equipment engineering and safety

Green Manufacturing		Related sub-green practices adopted by the key stakeholders and the extent of their adoption		
Key green aspects	Sub green practices	Innovative	Generic	Bio pharma
	efficiencies	managers and waste vendors to optimize process to reduce raw materials consumption. Process related data are being exchanged to improve the process efficiencies.	self-audit' / internal audit and / or external audit to collaborate internal manufacturing team with external (or, internal R&D team) process improvement experts to optimize the process for reducing inputs materials.	issues of the products (raw materials variability issues)
Energy Reduction	*Consider energy efficient technologies*	<u>High</u> • Mostly use advanced efficient heating, ventilation, and air conditioning system (e.g., HVAC): automatic scheduling HVAC and lighting system for avoiding unnecessary process cooling and/or heating • Mostly used LED lighting • Mostly used water cooling than mechanical cooling • Mostly use onsite energy generation through CHP (combined heat and power) / tri-generation (CCHP) / process heat recovery technologies / wind turbine • Some of them use leak detection technology	<u>Low</u> • Some of them use automatic tube cleaning system within production line • Few of them use energy efficient motors, compressors, and guns in packaging line • Some of them used water cooling than mechanical one • Some of them use energy efficient heating, ventilation, and air conditioning	<u>Low</u> • Few of them insulate piping and heat generating equipment • Few of them use heat recovery technology and estimate process heat waste • Some of them use onsite generated solar energy • Few of them focus on boiler efficiency; replaced steam boiler with biomass boiler • Some of them replaced old equipment with new energy efficient one

Green Manufacturing		Related sub-green practices adopted by the key stakeholders and the extent of their adoption		
Key green aspects	Sub green practices	Innovative	Generic	Bio pharma
	Consider energy management program	<u>High</u> • Mostly considered employee behavioural change related program (e.g., Zero accidental promotion) • Mostly set internal energy reduction goal / targets: set zero wastewater from process to reduce treatment related energy requirements • Mostly apply varieties of energy kaizen and CI related activities: energy assessment of a process/plant, improve chillers efficiency, gas leak detection, power savings etc • Some consider process optimization program such as 'Britest tool' to analyse process and reduce energy requirements • Introduced process innovation awards	<u>Low</u> • Few of them considered kaizen and CI programs, such as use of ultrasound measuring equipment to identify the number of leaks across the production line • Very few of them considered process optimization tool such as 'Britest tool'	<u>Medium</u> • Some of them considered CI programs to reduce/prevent faulty calibration (process calibration from lab scale to commercial scale) and related energy loss • Apply lean and six sigma methodologies to improve process efficiency • Investors are highly interested to invest on energy related lean and kaizen projects as payback period is justifiable
Toxicity reduction	*Consider greener chemical (e.g., solvent/reagents etc) management*	<u>High</u> • Mostly considered sustainable chemical management programs which motivate and train the scientist/chemists to reduce usage of hazardous solvents, reduce toxic by-products formations, use less solvents where	<u>Low</u> ▪ Some of them uses advanced technologies such as high efficiency dust collection, multi-stage filtration and recirculation system for minimizing and/or	<u>Low</u> • Some of them participate external reporting (e.g., 'Chemical Footprint Project') to assess internal chemical management process, e.g.,

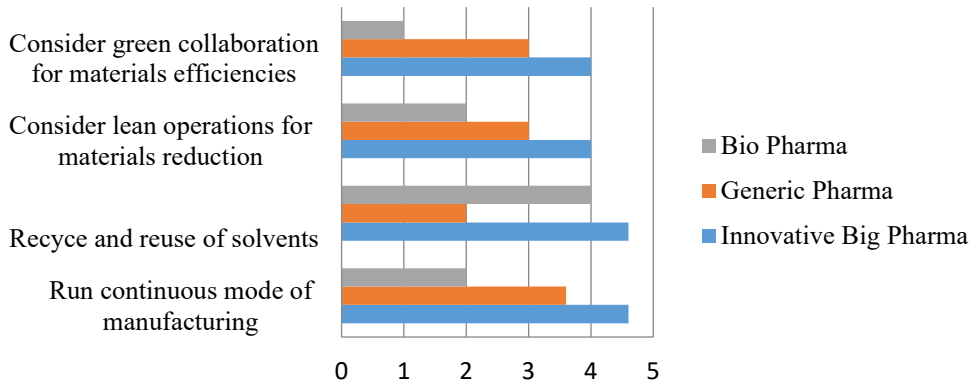
Green Manufacturing		Related sub-green practices adopted by the key stakeholders and the extent of their adoption		
Key green aspects	Sub green practices	Innovative	Generic	Bio pharma
		possible, use more water-based solvents in cleaning process, use solvents which have less probability of forming toxic by-products while enter into the aquatic system • Mostly follow equipment operating procedure to prevent VOCs emission from the process	eliminating the VOCs and/or other toxic volatile chemicals from the production process	track and trace of the chemicals of high concerns • Few of them uses risk assessments to prioritize emissions reduction efforts: routine compliance with facility leak repair, testing and record keeping requirements, replace refrigeration system with non-ODS (Ozone Depleting Substance)
	Monitor and control environmental toxicity of drug substances (eco-pharmacovigilance)	<u>High</u> • In most cases conduct ERA (Environmental Risk Assessment) of API for both new and existing drugs to understand the PBT (Persistent, Bioaccumulation and Toxicity) level of an API. Therefore, discharge level of an API into the external environment from the process is set to a safe level. • Mostly participate in PIE (or, iPIE) programs to increase understanding the impact of APIs and their by-products (metabolites) on aquatic life to set a safe	<u>Low</u> • Some of them follow site specific API discharge management guidance: e.g., equipment containment system and cleaning process to reduce the scope of API discharge into the external environment	<u>Low</u> • Few of them follow API discharge guidelines • Few of them participate PIE programs to develop environmental toxicity knowledge of bio-based API

Green Manufacturing		Related sub-green practices adopted by the key stakeholders and the extent of their adoption		
Key green aspects	Sub green practices	Innovative	Generic	Bio pharma
		discharge limit for individual process • Follow responsible antibiotic discharge guidelines		
	Consider responsible waste management for toxicity reduction	<u>High</u> • Mostly converts wastewater (hazardous and non-hazardous) into beneficial use (e.g., waste to energy, waste to fertilizers etc) • External collaboration projects to convert waste into value • High temperature incineration of hazardous waste • Consider Effluent toxicity test • Apply Hierarchy of Waste management to decide better option of treatment • Controlled management of highly hazardous waste (e.g., track records of destruction) • Pre-treatment of hazardous waste to detoxify (e.g., autoclave) • Effluent toxicity test prior to final discharge to the environment or third party	<u>Low</u> • Apply advanced wastewater purification process prior to discharge into the environment • Effluent toxicity test prior to final discharge to the environment or third party • Controlled management of highly hazardous waste (e.g., track records of destruction) • Planned wastewater recycling • Increase wastewater diversion rate applying through waste hierarchy	<u>Low</u> • Continuous review of toxic release inventory data to update wastewater discharge level • Pre-treatment of hazardous waste to detoxify (e.g., autoclave) • Effluent toxicity test prior to final discharge to the environment or third party • Process wastewater is continuously tested and purified prior to final discharge into the fresh water

4.2.1 Findings on Material Reduction related practices

Findings on this green aspect highlight the key scopes of reducing raw materials usages across the industry during the manufacturing phase. The study reveals that material efficiency is not only important to cost savings and quality assurance for pharma but also a step forward to deal with unprecedented levels of deterioration of natural resources. Four key green practices - running continuous mode of operation, solvent recycling, lean operations, and green collaboration - were identified in the study. This investigation further reveals that the scopes of these materials reduction related green practices and adoption levels significantly vary across different industrial sectors. While generic and bio pharma show this practice as almost equal in importance (between planning to low level), in most cases innovative pharma undertake this green aspect as one of the top green practices showing the adoption level between medium to high. The average intensity or extent of consideration for each sub-green practice across the pharma industry has also been captured in figure 4.4. The subsequent section presents findings and analysis on first two most important sub-green practices. Interested readers are referred to Appendix 10 to explore other two sub-green practices.

Figure 4.4 The extent of 'the consideration of material reduction practices during manufacturing' across pharma industry (based on reports)



(1 = Not mentioned / no consideration; 2 = Planning to consider; 3 = Low level of consideration; 4 = Medium level of consideration; 5 = High Level of Consideration; rating was done based on number of mentions and qualitative judgement for semantic validity of each mentions)

4.2.1.1 Run continuous mode of manufacturing

Findings on this green aspect explain the potential viability and importance of considering continuous mode of manufacturing for existing drug and/or new drug. The investigation

reveals that moving to continuous mode of manufacturing from a conventional batch process has become one of the key green manufacturing agendas across the pharma industry, regardless of the different segments, such as innovative pharma, generic pharma and bio pharma, but with a varying adoption level. The study further reveals that in some innovative pharma plants, both API production and formulation are aligned into one continuous process to produce a drug from early synthesis to final formulation such as tabletting. However, on most occasions, API production and formulation are run in a separate continuous fashion in the industry.

Continuous API production

It was revealed in the interviews and reports that in the case of continuous API production in innovative and bio pharma sector, the traditional batch reaction, separation, purification etc, are performed within a special reactor (called microreactor or flow reactor). It was further evident in the study that this microreactor or flow reactor contains multiples smaller reaction chambers where reactants or solvents are continuously added at a smaller scale to run continuous chemical reactions, separation, purifications within the reactors until a desired amount of API is produced. As per most of the interviewees, the continuous process also integrates PAT technology, which has helped the manufacturing managers to learn, control and optimize each process parameter (e.g., reaction time, throughput, temperature, pressure, blended uniformity, purity of API etc) in real time effectively and efficiently to save related solvents, waters and other raw materials, as revealed in the investigation.

For instance, it was reported by one of the innovative pharma (In -08) that if a bioprocess (e.g., fermentation process) is monitored and controlled (using PAT) key process parameters, the fermenter (the vessels where fermentation takes place) can be shut down as much as a day or two earlier than usual to save a significant amount of energy, as a biopharma plant has a dozen or two 15000 gallon vessels – so the materials, energy and cost savings are massive. This is because PAT has given them extra control for improving reaction throughput and reduces the interruption of reaction due to checking in-process quality in a continuous fashion via PAT.

However, PAT is not yet widely installed in the generic and bio pharma sector. The key role of PAT in continuous manufacturing is better understood when making a comparison between ‘process with PAT integration’ and ‘process without PAT integration’ as shown in the Table 4.11. Detailed PAT led continuous manufacturing and related findings are also

included in appendix 11a. The benefit of applying continuous process in bio pharma is also evidenced in the study. For instance, one of the leading bio pharma (B – 18) has stressed that – ***"Continuous manufacturing (e.g., flow chemistry) provides scientists with an ability to easily scale up and down, achieve significant energy and waste reductions and improve safety"***

Table 4.11: Key role of PAT in continuous manufacturing (Source: Interviews and reports)

Process with PAT integration	**Process without PAT integration**
✓ It sends signal & data on key process parameters virtually to the process operator ✓ Continuous monitoring & control of process parameters ✓ Lower risk of quality deviation: lower physical sampling ✓ Instant & quicker in-process quality test ✓ Lower risk of accidental reaction ✓ Increase operational efficiency via increased throughput, lead time ✓ Lower raw materials, energy, costs	✓ Traditional way of QC testing: samples are taken to the lab and sometimes a batch is kept in quarantine until the test result is ready; hence, slow down production ✓ No instant alert in place if any parameter is changed or behave unexpectedly ✓ Comparatively moderate risk of quality deviation ✓ Comparatively moderate risk of accidental reaction ✓ Lower operational efficiency ✓ Higher raw materials, energy, costs

Continuous formulation

The study also reveals that in case of continuous formulation, weighing, blending, granulation, tabletting (compressing the granule into Tablet) and coating are set up in one line where API and excipients are continuously added to blending. The investigation also confirms that the PAT tool is also installed within the production line to monitor and control quality of each intermediate stage. In some cases, the respondents from generic pharma operations agreed that compared to batch formulation, continuous formulations do not require cleaning in-between batches, which saves significant amounts of raw solvents and reduces related wastewater.

Adoption of the continuous formulation practice and related benefits was predominantly evidenced in the innovative and generic industries, though innovative pharma is in the

leading position to adopt it. For instance, one of the respondents from an innovative pharma (B – site 2) reported that continuous formulation reduces more than 60% of HVAC related energy. Astoundingly, though generic pharma has shown significant environmental savings from applying continuous formulation, the adoption level is still low. The significance of using this practice in the generic sector can be accessed via a few relevant examples. For instance, it was also highlighted by one of the generic pharma (Gn – 06) that their new continuous formulation design for one of their product portfolios has reduced API requirements by 80 to 90% less than that of traditional batch process and the related cost saving is 200, 000 US dollars. The report further outlined that there is less waste and yields are more than 97%.

Key benefits and challenges of continuous drug manufacturing

Key environmental benefits, operational benefits and related challenges for continuous API and formulation that came from the investigation are presented in Table 4.12.

Table 4.12 Key benefits and challenges for adopting continuous manufacturing (Source: Interviews and reports)

Mode manufacturing	**Key environmental benefits**	**Key operational benefits**	**Key challenges**
Continuous API production	✓ Reduce Hazardous by-products formation ✓ Prevent unexpected accidental chemical reaction and related health and environmental damage ✓ Saves cleaning materials and solvents ✓ Less wastes (in case of equipment failure) – so saves raw materials and related costs	✓ Safer, faster ✓ Maximize throughput ✓ Lower lobor costs ✓ Improved quality and process reliability ✓ Process parameters such as flow rate, temperature, pressures etc can easily be monitored and optimized via PAT ✓ Less complex scale up ✓ Reduce shortage of drug supply	✓ Product suitability ✓ Equipment availability ✓ Costly equipment settings ✓ Limited regulatory guidance
Continuous	✓ Lower energy related	✓ Reduce time to	✓ High initial

formulation (e.g., continuous Tabletting)	carbon footprint due to use lower production space using smaller equipment ✓ Reduce in process inventory storage and storage for by-products and testing samples ✓ Reduce in process cleaning materials ✓ Reduce wastewater ✓ Reduce API requirements	market ✓ Smooth scale up ✓ High yield	investment ✓ Regulatory burdens

The study also revealed that though continuous manufacturing has become one of the central considerations of the innovative pharma's operational strategy to go green, unfortunately not all of the manufacturing process is fully understood yet to adopt continuous. Some of the respondents also highlight here that continuous mode of manufacturing is not compatible for all processes. It is currently being considered on a case by case basis, as it involves many other important factors such as demand for a particular product, costs, time, specific product specification, types and availability of particular machineries. However, a number of other respondents also highlight that the key success factors to adopt continuous manufacturing process are multifactorial such as stability of the drug molecule, the reaction time, product safety, quality in terms of credibility and stability of the products at particular stages. For instance, one of the respondents, a *Supply Chain & Quality Operations Manager* from a leading innovative pharma (D – site 2), outlined that time and temperature sensitive drug products should be produced in batch rather than continuous. The respondent gavean example saying that "... … ***oncology products must be on batch - not in continuous; freshly prepared and send them straight way - there is strict timeline so it has to be reached to destination (to the patient) within this timeline… …"***

4.2.1.2 Recycle and reuse of solvents

Solvents are one of the key raw materials in pharma operations. Indeed, more than 80% of raw materials in pharma operation are solvents. As revealed in this study, solvents purchasing, handling, inventory and disposal are attributed as one of the key cost contributors in drug manufacturing. The study also reveals that solvent wastewater and intermediate solvent byproducts constitute one of the key environmental concerns (in terms of materials, related energy, and toxicity issues) for the manufacturers. Interviews also reveal that though initial investment in solvent recycling is high, the payback period is as low as two years. Therefore, the industry (especially innovative pharma sector) has invested in recycling of chemicals including waste solvents during the production process whenever technically feasible and financially justifiable.

Given such significant importance of solvents usage and its management in pharma industry, this investigation evidence potential savings of raw solvents and related costs by recycling and reusing solvents during the drug manufacturing phase. The study also suggests that innovative pharma is in the lead position to adopt this practice, while bio pharma shows a medium level and generic shows the lowest level of adoption. However, some key characteristics of solvent recycling and reusing (e.g., process of recovery, types of solvents, purpose of recovery etc) also differ among the stakeholders. Forms of recovery and differences among key stakeholders is discussed in the subsequent sections. Detailed findings on onsite versus off-site recycling, key benefits and challenges of recycling are also included in appendix 11b.

Recovery in terms of direct reusing

The study reveals that the solvents that come out of the recycling process are safe and reusable input as raw materials in the process if recyclers maintain the recovery specification and have early validation in place. In some other instances, when recycled solvents fall into a lower grade (in terms of purity and quality), then they can be used for other process works which do not require high purified solvent (fuel, staff training purposes etc). There is also evidence of direct reusing of solvents in the process. For instance, it was also highlighted by one of the leading innovative pharma (In – 08) that a drug called *etravirine*, which is used for HIV treatment, ***"uses direct solvent reuse in the manufacturing process, and it saw a 74.8% reduction in both solvent material and waste from manufacturing."*** Table 4.13 shows different forms of recycling that came out of the investigation.

Table 4.13 Different forms of solvent recycling (Source: Interviews and reports)

- ✓ Recycle wasted solvents and/or by-products from the process and use them for other process works which do not require high purified solvent (e.g., cleaning R&D equipment, training purposes)
- ✓ Recycle back the solvents into the next process to reuse (in this case the recyclability of the solvents is validated during early design phase)
- ✓ Recycle wasted solvents and/or by-products and then use them as fuel
- ✓ Direct solvent reuse in the process
- ✓ Recycle solvent waste mixture (e.g., ethanol-water) to avoid incineration and converts into biologically treatable wastes.

Several key differences between recycling operations among the stakeholders

Though innovative pharma is in the leading position to adopt solvent recycling practice in comparison with bio pharma and the generic sector, this investigation has observed some key differences among them. As per the findings from both interviews and reports, whilst it is difficult to recycle organic solvents, for instance, innovative pharma is at the forefront with dealing with them. For instance, one of the innovative pharma (In – 14) reported that they have refined their skills and technical capabilities to increase the recovery of organic solvents. The company has also explained "… ***In 2018, we managed to recover 76% of the most used solvents. This eliminated the need to purchase approx. 5,600 tons of solvents and consequently saved additional resources for external production, transportation and waste management"***

On the other hand, as came out in the study, generic and bio pharma companies have sought to plan predominantly for recycling purified distilled water from the process rather than organic solvents due to having related equipment engineering difficulties and product quality related issues. However, many bio pharma sought to recycle solvents to use them for other purposes than in the process or process equipment cleaning. For instance, one of the leading bio pharma (B - 2) reported that the implementation of a typical solvent recycling project has recovered 91% of its wasted solvents, which have predominantly been used as fuel to generate energy in the plant.

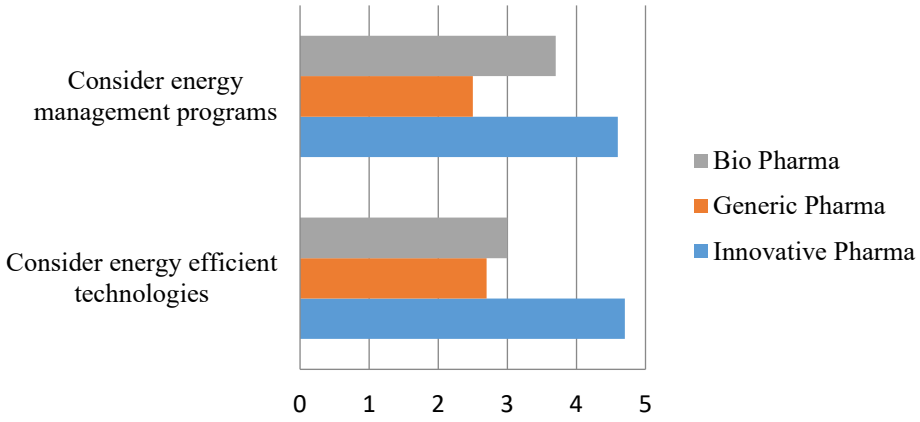
Some pharma had also sought to create interesting solvent recycling strategies such as simulation technique and co-design strategy. For instance, one of the bio pharma companies

(B – 19) applied simulation techniques by which it generates several computer models to virtually assess various operating conditions in the solvent recovery process, resulting in successful improvement in the recovery rates of solvents. One of the generic pharma (Gn – 03) has employed a cross functional team (engaging process chemists and process engineers, waste contractors etc) to examine the system of recovery of complex waste mixture (e.g., ethanol-water mixture) from an API production plant. The team later created a unique recovery system (a unique distillation system) which has been able to extract most of the water contents and other impurities from the ethanol-water mixture. It has saved 780 tons of waste which would have been sent for incineration and saved the related disposal costs.

4.2.2 Findings on Energy Reduction related practices

Findings on this green aspect reveal the key scopes of energy reduction practices during the manufacturing phase across the industry. The investigation reveals that energy reduction related operational activities and related management practices across the manufacturing plant has become one of the keys focuses for reducing environmental footprint. The investigation has identified two sub green practices (e.g., use of energy efficient technology and considering energy management programs) which have already been adopted by the industry. Compared to other sectors, innovative big pharma has been in the leading position to adopt energy reduction practices. The average intensity or extent of consideration for each sub-green practice and the scope of each practice across the pharma industry has also been captured in figure 4.5, based on published reports. The rating is also supported by the interview data. The subsequent section presents findings and analysis on each sub-green practice evidenced from interviews and/or reports.

Figure 4.5 The extent of 'the consideration of energy reduction practices during manufacturing' across pharma industry (based on reports)



(1 = Not mentioned / no consideration; 2 = Planning to consider; 3 = Low level of consideration; 4 = Medium level of consideration; 5 = High Level of Consideration; rating was done based on number of mentions and qualitative judgement for semantic validity of each mentions)

4.2.2.1 Consider energy efficient technologies

The findings from both interviews and reports reveal what, how and to what extent process and/or plant level energy efficient technologies help production managers to achieve energy efficiency throughout manufacturing operations. It came out in the study that while cooling and heating are two important key requirements for almost all pharma processes, use of energy efficient technologies within a process or plant is a great opportunity to reduce overall process and/or plant level energy consumption. This is one of the common green manufacturing practices, which has been highly considered across the pharma industry, though innovative big pharma has been the leader in adopting this practice. The investigation reveals that each company investigated mentioned at least a single energy efficient technology to reduce energy consumption. There are 22 such energy efficiency technologies that have been adopted across the industry to a varying level to reduce the energy footprint within a plant and/or process.

Table 4.18 presents those key energy efficiency technologies identified in the study. While some of the technologies (e.g., insulate piping and heat generating equipment) are not adopted or not compatible or not applicable with innovative and/or generic, they are being considered in bio pharma, and vice versa. Therefore, the blank space in the table means that either the technology is not relevant or not considered currently or not compatible with their respective operations.

Table 4.18 Key Energy efficient equipment system and technologies used (based on report analysis)	Considered by key industry players		
	Innovative Big Pharma (11)	Generic Pharma (20)	Biopharma (25)
√-Use of advanced efficient heating, ventilation and air conditioning system (e.g., HVAC) to cut down energy	√(63%)	√(15%)	√(12%)
√-Recover ventilation system to cut down electricity	√(18%)		√(4%)
√-Optimize bioler efficiency:Replace steam boiler with biomass boiler	√(18%)	√(5%)	√(12%)
√-Improve temperature regulation	√(27%)		√(4%)
√-Installation of CHP (Combined Heat & Power)	√(9%)	√(5%)	
√-installation of LED lighting	√(36%)	√(5%)	√(12%)
√-Increase onsite solar energy capacity	√(27%)	√(5%)	√(25%)
√-Consider water cooling than mechanical cooling	√(18%)	√(20%)	√(4%)
√-Install tri-generation (CCHP) technology	√(9%)		
√-Installation of heat recovery technology	√(9%)	√(10%)	√(4%)
√-Installation of onsite wind energy	√(27%)		√(4%)
√-Real-time energy consumption monitoring	√(9%)	√(5%)	
√-Installation of leak identification technology	√(9%)		√(4%)
√-Replacement of old equipment with more energy efficient installations	√(45%)		√(12%)
√-Automatic tube cleaning systems for chillers		√(10%)	
√-Insulate piping and heat generating equipment			√(4%)
√-Reduce the size of the bioreactors inside the facilities			√(4%)
√-use energy from the city's household waste incinerator, in the form of water vapour			√(4%)
√-Engineer energy-efficient prodcution process	√(45%)		√(4%)
√-Eliminate process waste heat			√(4%)
√-Optimization of standby equipment: boiler, pumps			√(4%)
√-Automation in utility management system		√(5%)	
√-Installation of energy efficient equipment, e.g., motors, compressors and energy efficient guns in packaging lines		√(5%)	

As evidenced in the interviews and reports, the majority of innovative big pharma have used ***renewable sources of energy*** (e.g., wind turbine, photovoltaic panel, CHP - combined heat, and power technology, CCHP etc) for their plants. The majority of the interviewees have installed these renewable energy technologies onsite. For instance, one of the interviewees (B – site 2) from a leading innovative pharma outlined that they are currently looking into onsite generation of low carbon and renewable activities across the plant to achieve energy

efficiency. For instance, they have also installed 10 million panels of wind turbines. Some other respondents have also highlighted that they are using onsite produced gas and electricity to run their process and they have been producing this gas and electricity from biogas generated from the onsite waste treatment plant. Some innovative pharma have also highlighted related savings. For instance, it is reported by one of the leading innovative pharma (In - 02) that one of their manufacturing sites is now generating around 30% of the site's electricity from wind turbine and saving 4,100 tonnes of CO2. Due to having cost focused strategies none of the generic pharma investigated has used wind turbines into their plants, while a small number of bio pharma have adopted them. Detailed findings on CHP, CCHP and other related technologies / strategies (e.g., retrofitting) are also included in appendix 12.

4.2.2.2 Consider energy management program

The investigation also found some key scopes of different energy management programs across the pharma industry to achieve energy efficiency across manufacturing operations. As per the interviews and reports, energy management programs play a key role in transforming a culture of inefficient energy use to efficient energy saving across a manufacturing plant. It was evidenced from the interview and report analysis that almost every innovative pharma company sought to consider at the very least an internal energy related program, while a comparatively lower number of generic and bio pharma companies were seen to be committed to such a program. Three key energy management programs were identified across the industry (see Table 4.19).

Table 4.19 Key energy management programs across the pharma industry

Key energy management program	Key stakeholder involved		
	Innovative big pharma	Generic pharma	Bio pharma
ZAP (Zero Accidental Promotion)	✓	✓	
Energy kaizen and CI programs	✓	✓	
Energy audit: Environmental assessment program for energy efficiency	✓	✓	✓

ZAP (Zero Accidental Promotion)

This program aims to shape employee's behaviour on how to become energy efficient while working with process equipment. The majority of the innovative pharma investigated mentioned these kinds of programs. Though some generic and bio pharma were seen to adopt

some fragmented (employee behavioural change related) activities (e.g., switch off equipment when it is not in use etc), they were not seen to practice any established management programs under an existing environmental management strategy. It was also revealed in the interviews that running such programs requires leadership, which was not evidenced as effective in generic and bio pharma. Hence, this practice was predominantly relevant to innovative pharma.

As per the respondents from innovative companies, under the ZAP program each process employee is provided with a working manual and a day-to-day check list to follow. Some of the respondents also highlighted that through this program each employee become more aware of energy savings, such as switching off equipment when it is idle, or effective monitoring of process parameter changes from accidental wastes etc. For instance, one of the leading innovative pharma EHS managers (B – site 1) explained that their process centric energy efficiency had increased on the previous year and the manager attributed this ZAP program as one of the reasons for this success.

Energy kaizen and CI programs

As per the interviews and reports, it was clear that all pharma companies in all sectors almost equally highlighted the importance of adopting energy kaizen and CI related activities and programs, though innovative companies were seen in the lead position to adopt them. The study reveals a wide range of such energy improvement programs and activities such as environmental assessment of each process and process equipment, looking to improve chiller efficiency, gas leak detection, power savings etc, as part of energy Kaizen and CI programs. However, the scopes and extent of these practices varied widely across the different sectors. The study also reveals that each energy kaizen project is assigned to the group leader or production manager as part of a site's energy reduction goal.

As per the findings, a wide variety of energy kaizen and related continuous improvement activities were identified in the innovative sector to achieve plant and/or process wide energy efficiency, such as zero wastewater from process, reducing faulty calibration, product specific energy efficiency measures, process optimization programs for energy efficiency (e.g., Britest tool), process innovative awards etc. For instance, one of the leading innovative pharma (in -06) highlighted that they developed an energy management strategy that seeks to achieve process energy savings through continuous improvement, for instance, automatic scheduling of HVAC and lighting system to avoid unnecessary process cooling and/or heating. Detailed findings on each kaizen and related CI initiative are also included in appendix 13.

Energy audit: Environmental assessment program for energy efficiency

It was also revealed in the reports that though companies had conducted both internal and external audits as part of their environmental performance audit, energy audits were predominantly conducted internally to achieve internal energy targets. It was also revealed that the internal energy audit was conducted by a specialized department (e.g., corporate EHS) who independently assess energy efficiency across different sites. The reports further reveal that the frequency of this audit (generally every year) largely depends on improvement objectives and any specific energy related concerns, such as significant energy wastes from hidden gas leaks. The importance of having such energy audits was equally felt by all stakeholders. The auditor assesses to what extent the site is behind/ahead of its internal energy goal and target. For instance, one of the bio pharma (B – 03) explained that ***"… each audit is accompanied by an improvement plan which the site must implement before the next audit"*** Another Senior Environmental specialist from a leading pharma (A) also stressed that energy auditing was carried out on a regular basis. The respondent further mentions that under this energy auditing system a new energy efficiency target is set after each successful audit.

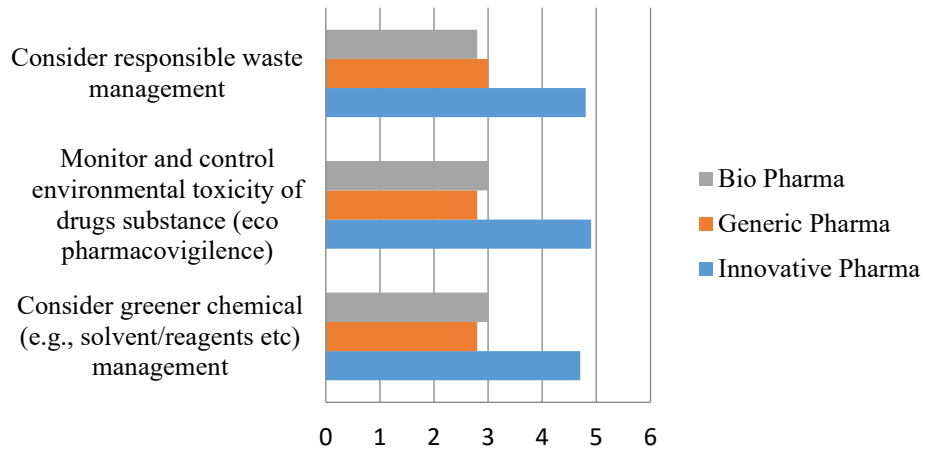
Some innovative companies also prioritised investing in internal energy auditing. For instance, a report from one of the leading innovative pharma (In – 05) outlined that energy managers use a systematic process to ensure energy considerations are given appropriate attention in all investment projects. It further highlights that "…***of existing activities, to date, all our major sites have been audited to assess energy systems and identify potential for improvement in saving energy and using renewable energy"***

As per the findings, it is important to highlight here that being more responsible stakeholders, the innovative pharma companies are, in general, leading the entire industry to become energy efficient in the case of both new and/or existing manufacturing processes. Bio-pharma companies are also increasingly considering this aspect for cost savings and reducing environmental burdens of all relevant manufacturing activities, though the scope of energy improvement here is relatively low due to safety and equipment complexity. While generic companies are predominantly satisfying the majority of the demand, the energy saving activities and programs in manufacturing process are still low.

4.2.3 Findings on Toxicity Reduction related practices

The findings on toxicity reduction related practices reveal how pharma manufacturers reduce both air and water toxicity throughout the manufacturing operations. The study also reveals that reducing or eliminating the usages of toxic substances in the manufacturing process has potentially improved the overall environmental impact of manufacturing operations. The three key sub-green practices that have been identified in the study are shown in figure 4.7. It was also revealed that all stakeholders realized the importance of considering toxicity reduction related practices, though the innovative sector was seen to be in the lead position to adopt related practices. The average intensity or extent of consideration for each sub-green practice across the pharma industry is also captured in figure 4.7 (evidence from reports). The subsequent section presents findings and analysis on each sub-green practice evidenced from interviews and/or reports.

Figure 4.7 The extent of 'toxicity reduction related green practices' across pharma industry (based on reports)



(1 = Not mentioned / no consideration; 2 = Planning to consider; 3 = Low level of consideration; 4 = Medium level of consideration; 5 = High Level of Consideration; rating was done based on number of mentions and qualitative judgement for semantic validity of each mentions)

4.2.3.1 Consider greener chemical (e.g., solvent/reagents etc) management

- ✓ **Engage in sustainable chemical management program**

Findings from the interviews and reports reveal how and to what extent pharma companies are involved in sustainability programs to manage chemical substances to avoid environmental toxicity. It was revealed that most of the innovative pharma and some bio pharma were seen to highlight that participating in sustainable chemical management programs is a way forward to effectively manage of SVHCs (Substances of Very High

Concerns) and other restricted chemicals (e.g., solvents, reagents) across pharma operations. As per both reports and interviews, none of the generic companies reported such green aspects due to having cost focused strategies and very limited scope for process innovation and the costly process of redesigning and validating existing methods of manufacturing.

The investigation identified two key chemical management programs: 'Green & Sustainable Science Program' and 'Chemical Footprint Project', which aim to the reduce environmental impact of chemicals applications. As per the investigation, one of the key focuses of these programs is to reduce water and air toxicity from chemicals applications. It was also found in the interviews and reports that, driven by these programs, companies have targeted to reduce usage of hazardous solvents, reduce toxic by-products formations, use less solvents where possible, use more water based solvents in the cleaning process, use solvents which have less probability of forming toxic byproducts when entering into the aquatic system etc.

For instance, it was reported by one of the leading innovative big pharma (In – 06) companies that it had an active 'Green & Sustainable Science Program' to re-design the drug processes to use green solvents and avoid other hazardous materials to make the process more environmentally friendly by reducing toxicity. It also followed a solvent selection guide. It was also reported that the program had enabled them to achieve their internal environmental targets, including biodegradability and toxicity of 90% of their API processes.

- ✓ **Prevent process from toxic release to air**

The investigation also identified that the pharma manufacturers take some preventative measures to manage and/or reduce possible release of toxic byproducts from the production process into the environment. There are six key approaches or preventative measures identified in the study shown in table 4.20. The blank cell in the table means that either the relevant aspect is not currently being considered or not compatible with the relevant manufacturing process.

Table 4.20 Key approaches taken to eliminate or reduce toxic release to air from the produciton process (based on report data)	Frequency of consideration by key industry players		
	Innovative Pharma	Generic Pharma	Biopharma
√-equipment operating procedure to minimize the release of the VOCs from production process	√(27%)		
√-uses new technologies (e.g., vent condenser) to curb it		√(15%)	
√-an online monitoring station for ambient air quality		√(15%)	
√-routine compliance with facility leak repair, testing and record keeping requirements, replace refrigeration system with non-ODS	√(27%)		√(8%)
√-using risk assessments to prioritize emissions reduction efforts			√(8%)
√-Apply in-house stringent standards than those required by laws			√(8%)

VOCs are predominantly originated from the use of halogenated and non-halogenated solvents in various production processes, as reported by some innovative company respondents (e.g., B – site 2). VOCs lead to photochemical ozone creation, which leads to smog and detrimental effects on health and the environment. They also contribute to GHG emission. As per the interviews and reports, the equipment operating procedure which mentions the step by step process of smooth calibration, cleaning and washing up process, green solvent selection process etc is followed to minimize the release of the VOCs from the production process of some innovative companies investigated.

However, while generic companies were seen to have a separate reaction chamber to neutralise any volatile gases to reduce their toxicity prior to releasing into the air, some bio pharma had sought to undertake precautionary measures, such as s using risk assessments, to prioritize emissions reduction efforts, and in-house stringent standards rather than those required by law. As per some reports, new technologies are used such as high efficiency dust collection, multi-stage filtration and recirculation system for minimizing and/or eliminating the VOCs and/or other toxic volatile chemicals from the production process. For instance, one of the generic companies (Gn - 04) reported that some of its API process reactors are equipped with primary and secondary condensers for managing these toxic releases to the environment. There is also an online monitoring station for ambient air quality, as reported by some other generic companies.

4.2.3.2 Monitor and control environmental toxicity of drug substances (eco pharmacovigilance)

- ✓ **Environmental Risk Assessment (ERA) of pharmaceuticals products**

Findings on toxicity reduction practices reveal how, why and to what extent pharma manufacturers conduct environmental assessment of each new drug products as part of regulatory requirements as well as some existing products of high concerns to avoid potential environmental contamination of drug substances. It emerged that realizing the crucial issue of PIE, the pharma industry extended their product management from pharmacovigilance (focus on safety, quality and efficacy) to eco pharmacovigilance (safety, quality, efficacy & environmental toxicity) in terms of ERA for both new and existing drugs.

The interviews and reports reveal that the environmental risk for a particular drug substance is assessed by the ration of 'predicted environmental concentration (PEC)' and 'predicted no effect environmental concentration (PNEC)'. 'Predicted environmental concentration' is the possible maximum concentration of a drug substance based on usages and/or consumptions, while 'predicted no effect concentration' is the lowest possible concentration of drug substances based on safety threshold (which will be safe for aquatic life) set by regulators, as explained by the respondents. It was also reported in the study that the ration of PEC and PNEC must be less than one to be safe for the aquatic environment. ERA also assesses the PBT (persistence, bioaccumulation, and toxicity) of a particular API in the aquatic environment to get a wider environmental assessment on APIs.

Though ERA is vital in the early R&D phase of new drug development as part of mandatory regulatory requirements, the priority is still safety, efficacy, quality, and successful discovery of drugs as explained in the reports and interviews. It was also revealed in the study that ERA value do not affect regulatory approval of new drugs but it is helpful for the manufacturers to keep the discharge amount of the new API as low as possible or followed by company / local water authority's limit. In addition, controlling API (more than 3000 of which already exist in the market) release from the manufacturing phase is also not negligible at all as explained by one of the respondents (C) from a leading innovative pharma. Therefore, pharma companies (predominantly large innovative ones) were undertaking several types of PIE projects for assessing the ERA of their new / existing APIs.

As reveal in the study, though ERA practice is still predominantly voluntary in nature for the manufacturing of existing drugs, majority of innovative pharma manufacturers are continuously monitoring the environmental toxicity of their APIs portfolio and setting

strategic API discharge limits from each site accordingly. For instance, another respondent from a leading innovative pharma (B – site 1) highlighted the status of their PIE program, which has helped them to identify some key environmentally hazardous substances. The respondent further explained "… ***we currently have 17 APIs classified as environmental Hazardous materials, so we assess these APIs - we assess the specific material in terms of PIE... ...”*** The respondent also confirmed that each single API is under a PIE program in terms of ERA assessment. On the other hand, another innovative pharma (C) identified four drugs only which pose environmental risks out of 130 ERA conducted. Findings on ERA / PIE related programs / projects including how to control API discharge from manufacturing sites are also included in appendix 14.

4.2.3.3 Consider responsible waste (hazardous) management

It was revealed in the investigation that the pharma process produces two streams of wastes: hazardous and non-hazardous. An example of this is wastes solvents, either produced as intermediate byproducts or as final wastewater form, from chemical-based API extraction process or from bio-based API extraction (e.g., via fermentation) process. It was also revealed in the investigation that the majority of companies across different stakeholders have treated the process wastewater including any intermediate byproducts (originating from chemicalbased process predominantly) as hazardous waste stream by means of a precautionary principle. The majority of the respondents who participated agreed that as pharma production is continuing to grow, the generation of increased levels of wastes, especially the hazardous wastes stream, is becoming a significant challenge. For instance, one of the innovative pharma (In – 03) stressed that ***“as production levels are projected to continue to grow, achieving our total 10% reduction target is a significant challenge”***

Findings on toxicity related green manufacturing practice reveal what, how and to what extent pharma manufacturers apply different environmental management approaches to deal with hazardous wastewater originating from the manufacturing process. The industry has focused on waste prevention and reduction activities, and promoting recovery practices whenever technically and economically feasible, as opposed to the end resort of landfill and incineration. However, this section will not present the findings on recovery related practices including packaging related (non-hazardous) wastes reduction as it has already been covered in other sections. It is also important to highlight here that this section does not present waste prevention related findings rather it presents managing those wastes that are already produced

in the process and within the production plants. There are 14 sub green practices or activities that have been identified. These are presented in table 4.22. The table also shows the frequencies of how many times each of the sub green practice was discussed across the environmental reports. Any empty space in the table means that either the relevant practice is not currently being considered or not compatible with the process. As observed in the study, it is also important to highlight that many of these practices (e.g., waste to energy, waste kaizen, lean waste program, hierarchy of waste management etc) were also considered for treating non-hazardous waste stream.

Table 4.22 Key green approahces undertaken for hazardous waste management from the pharma produciton process (based on report)	Frequency of consideration by key industry players		
	Innovative Pharma	Generic Pharma	Biopharma
Waste to beneficiary use (e.g., waste to energy)	√(90%)	√(5%)	√(20%)
Responsible waste-vendor management (e.g., waste audit)	√(18%)	√(5%)	√(20%)
Measure waste efficiency (e.g., waste diversion rate)	√(9%)		
Consider 'Hierarchy of Waste Management'	√(73%)	√(20%)	√(20%)
Eliminate or minimize landfills of organic hazardous waste	√(82%)	√(20%)	√(16%)
High temperature incineration of hazardous wastes	√(54%)	√(20%)	√(12%)
Comply with local and national standard for wastewater discharge	√(45%)	√(10%)	
Controlled management of highly hazardous waste (e..g., track records of destruction)	√(45%)	√(10%)	√(16%)
Monitoring and reporting wastes on regular interval	√(82%)	√(20%)	√(20%)
Continuous review of toxic release inventory data to update wastewater discharge level			√(4%)
Efficient segregation of wastes (e.g., color coding system)	√(9%)	√(5%)	√(12%)
Pre-treatment of hazardous waste to detoxify (e.g., autoclave)	√(64%)	√(20%)	√(20%)
Effluent toxicity test prior to final discharge to the environment or third party	√(64%)	√(5%)	√(12%)
Consider waste management program (e.g., waste kaizen, six sigma, lean etc)	√(82%)	√(20%)	√(16%)

As per the findings from both the interviews and the reports, once wastes are produced the production managers or dedicated waste management teams within the production plant take a decision on appropriate treatment depending on the companies' capability and capacity for waste management. As revealed in the study, the majority of innovative big pharma companies have onsite waste treatment facilities, whereas some generic and bio pharma companies rely on third party waste vendor who collect wastes from production sites and take them to their treatment sites. The investigation also reveals that all stakeholders almost

equally agreed and realized the importance of managing process wastewater (including intermediate by-products), though the scopes of and extent of adopting each practice varies across the sectors. Though the study has identified many fragmented wastes management activities across the industry (Table 4.22), three key waste management philosophies are currently predominantly leading pharma companies to managing wastes efficiently, effectively, and responsibly. They are: *waste to beneficiary use, hierarchy of waste management and Zero landfill*. Though they share some common technical elements (e.g., recycling, reusing, reducing), each of them has a slightly different motivation. Interested readers are referred to appendix 15 to explore detailed findings on each of these areas.

4.3 Findings on Green Use-and-Disposal Practices

Findings on this green aspect reveal that the key management approaches undertaken by each stakeholder involved in the downstream drug use and disposal phase to deal with PIE originated mainly from unwanted drug wastes through ineffective and inefficient drugs usages and inappropriate disposals. As the findings on disposal practices by the upstream manufacturers are covered in the previous section, the scope of this section is limited to downstream stakeholders. Whilst the initial literature review provided a systematic clue but vague understanding about the concept of 'Green Drug Use-and Disposal', a robust investigation using interviews and content analysis of CCG (Clinical Commissioning Group) reports and pharmacy service reports enabled the researcher to explore the concept rigorously in three predetermined dimensions of green aspects: Material reduction, Energy reduction and Toxicity reduction in line with the proposed research questions. It is important to note here that prior to exploring relevant green practices, it is mandatory to understand how the key stakeholders are engaged in the Drug Use-and Disposal phase within a pharmaceutical supply chain. After the investigation, a revised holistic understanding about the stakeholder involvement in Drug use-and-disposal phase is understood and is conceptualized in figure 4.8 below.

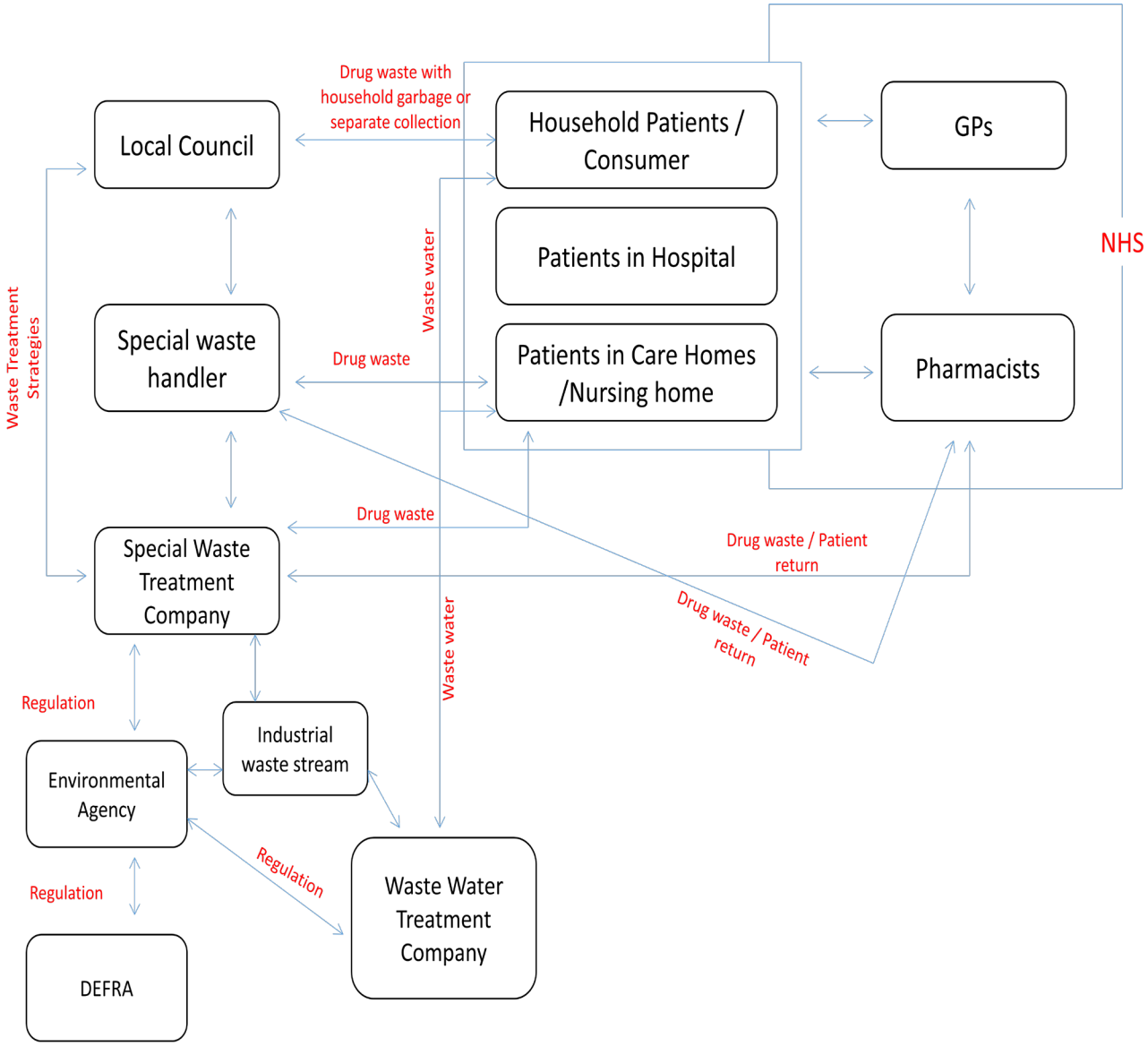


Figure 4.8 Key stakeholder involvement in Drug Use-and-Disposal Phase (source: Researcher)

As conceptualized in the study, GPs, pharmacists, patients, NHS, local councils, waste management companies (pharmaceutical waste handler/ pharmaceutical waste treatment plants), waste water treatment companies and regulatory bodies (e.g., Environmental Agency, DEFRA, Department of Health) are identified as the key players in the downstream of the pharmaceutical supply chain. As per the investigation, Green Drug use and disposal behaviour is formed based on the key characteristics of roles, responsibilities and personal behaviour attached to pharmaceutical drugs. It was revealed in the study that drug waste reduction practice has become one of the key use and disposal management practices among GPs, Pharmacists and NHS driven by cost reduction (predominantly) and general

environmental awareness, whilst waste management and waste water treatment companies are currently investing / going to invest in the near future in greener technologies for eco-friendly disposal driven by either the issue of PIE (Pharmaceuticals in The Environment) or environmental sustainability in general; or both in some circumstances. The subsequent sections present the findings in detail.

The subsequent sections have presented each of the green use-and-disposal practices: 1) Materials reduction related, 2) Energy reduction related, 3) Toxicity reduction related. Table 4.24 presents the summary of the key green and sub green practices identified in the study. The stakeholder relevancy and the degree of implementation of each practice and sub practice by the stakeholder are also presented in the Table.

Table 4.24 Summary of the key green drug use-and-disposal related practices and sub-practices and their extent of implementation (Source: Interviews and reports)

Green drug-use-and-disposal		**Key stakeholders adopted the related green practices and the extent of their adoption**					
Key green aspects	Sub green practices	Pharmacy	GPs	Hospitals (wards & pharmacy)	Care-homes	Waste management companies /Local councils	Wastewater treatment companies
Material (drug waste) reduction	Consider lean operations for optimized prescribing, dispensing and usages	<u>High</u> -Conduct medical intervention (e.g., MUR/NMS) for effective use of drugs -Blister pack reminder for older people / people with dementia -Regular patient counselling for effective use of dosage prescribed	<u>High</u> -Consider rationale prescribing: introduce trial package and follow disease alteration strategy for longer term disease -while prescribing, focus on underlying reason of the disease rather than symptoms only -Do not issue bulk supply (/over prescribe) of drugs	<u>Medium</u> - Reuse of drugs which have not left the pharmacy premises and are in good condition - Reuse the drugs brought back by the patients in hospital admission (only for the same patient who brought) - Check batch number, quality (i.e., not tempered) of the returned drug and	<u>Medium</u> - Medications in the care homes are regularly reviewed by GPs and pharmacists -Medication review project is not common to all and only determined by the local CCG budget -Regular evaluation of MAR (Medicine Administration Record) chart to optimize drug use	<u>Not relevant</u>	

Green drug-use-and-disposal		Key stakeholders adopted the related green practices and the extent of their adoption					
Key green aspects	Sub green practices	Pharmacy	GPs	Hospitals (wards & pharmacy)	Care-homes	Waste management companies /Local councils	Wastewater treatment companies
		-Monitor and report prescribers' prescribing habit	whenever appropriate -Follow antimicrobial prescribing guidelines -Prescribe alternative therapy (e.g., lifestyle related diet, exercise etc) where applicable	psychically examine them for reusability for that patient -Green Bag Scheme: encourage patient to bring back their own medication during hospital admission -My medication passport scheme: history of medication carried by the patient during hospital admission	and dispense -Periodic patient review for MUR		
	Consider digital technologies for optimized prescribing,	<u>High</u> -EPS-PT (EPS prescription tracker): online based software	<u>High</u> - EPS/eRD (Electronic Repeat Dispensing): use	<u>Not considered</u>		<u>Not relevant</u>	

Green drug-use-and-disposal		Key stakeholders adopted the related green practices and the extent of their adoption					
Key green aspects	Sub green practices	Pharmacy	GPs	Hospitals (wards & pharmacy)	Care-homes	Waste management companies /Local councils	Wastewater treatment companies
	dispensing and usages	that increases visibility of repeat prescription requests for effective dispensing -Online based Shared system software SCR (Summary Care Record): reduce unnecessary prescription / dispensing drugs using data on existing medication / clinical history of patients	electronic repeat prescription dispensing (online based shared system software) to reduce multiple prescription request from patients -Each time the pharmacists dispense a prescription it is automatically notified both GPs and pharmacists via this system -update SCR record on regular basis for effective patient care and reduce				

Green drug-use-and-disposal		Key stakeholders adopted the related green practices and the extent of their adoption					
Key green aspects	Sub green practices	Pharmacy	GPs	Hospitals (wards & pharmacy)	Care-homes	Waste management companies /Local councils	Wastewater treatment companies
			unnecessary drug dispensing				
Energy Reduction	Energy efficient refrigeration system and temperature control	<u>Low</u> - Use of energy efficient refrigerators system with CFC free refrigerant -Some uses built in insulation system with refrigerators which reduces energy consumption	Not considered as very low volume of storage	<u>Low</u> -Few of them uses 'absorption drug refrigerator' which does not use electric energy rather it uses waste heat (e.g., hot water) from an external source	<u>Low</u> - Use of energy efficient refrigerators system with CFC free refrigerant --Use manual or automatic temperature log to continuously monitor drug temperature	Not relevant	

Green drug-use-and-disposal		**Key stakeholders adopted the related green practices and the extent of their adoption**					
Key green aspects	Sub green practices	Pharmacy	GPs	Hospitals (wards & pharmacy)	Care-homes	Waste management companies /Local councils	Wastewater treatment companies
		- Use manual or automatic temperature log to continuously monitor drug temperature inside the refrigerator to reduce accidental product damage and related energy loss					
	Energy recovery from drug incineration process	Not relevant				<u>High</u> -Recover energy from high temperature (>1100ºC) drug incinerators	Not relevant

Green drug-use-and-disposal		**Key stakeholders adopted the related green practices and the extent of their adoption**					
Key green aspects	Sub green practices	Pharmacy	GPs	Hospitals (wards & pharmacy)	Care-homes	Waste management companies /Local councils	Wastewater treatment companies
Toxicity reduction	Safe and responsible disposal management of unused and expired drugs	<u>High</u> -Drugs take back: Promote unused / expired drug collection from patient zone for incineration via waste vendor --Encourage patient to bring back their unused/expired drug to nearest pharmacy for safe dispose -Follow SOPs for collecting and segregation of drug wastes	<u>Low</u> -Some GPs participate in drug take back scheme -Encourage patient to bring back their unused/expired drug to nearest pharmacy for safe dispose	<u>Medium</u> -Promote drug collection from patient via leaflet, posters, and bus adverts -Follow (SOPs) derived from the Healthcare waste Management guided by department of Health in the community pharmacies	<u>Medium</u> --Follow (SOPs) derived from the Healthcare waste Management guided by department of Health in the community pharmacies	<u>High</u> -Mostly consider high temperature incineration -Mostly recycle of incinerated ash -some councils arrange separate collection of clinical waste including household drugs (for free of charge - encourage patients via council website communication to return their unwanted	Not relevant

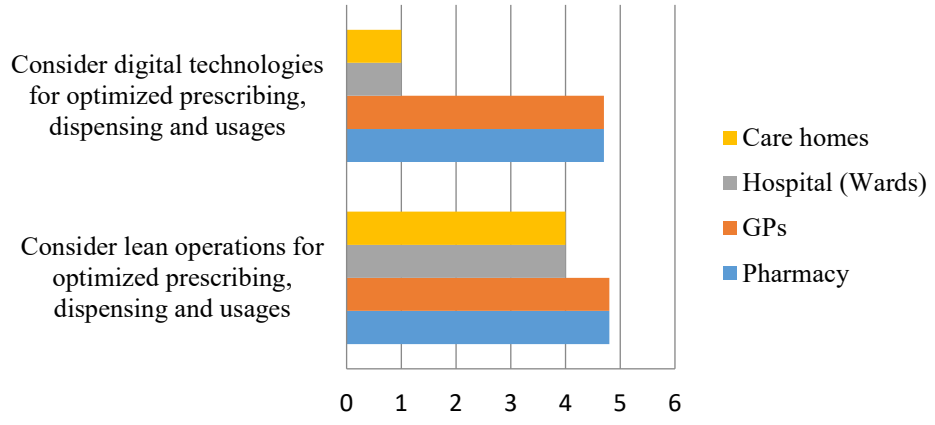
Green drug-use-and-disposal		Key stakeholders adopted the related green practices and the extent of their adoption					
Key green aspects	Sub green practices	Pharmacy	GPs	Hospitals (wards & pharmacy)	Care-homes	Waste management companies /Local councils	Wastewater treatment companies
		-Segregate drugs using correct coded bin for different categories of drugs (e.g., cytotoxic for yellow bin); special segregation of CD drugs etc.				medicines to the local pharmacy -Follow EWC (European Waste Catalogue) or use of colour code system for waste drug segregation (waste vendor)	
	Consider greener wastewater treatment options	Not relevant		Rely on local wastewater treatment plant (Wastewater of high concern:)	Rely on local wastewater treatment plant (Wastewater of high concern:)	Not relevant	<u>Planning</u> -Monitor the concentration of API of high concern (e.g., EEA, diclofenac etc) in the incoming

Green drug-use-and-disposal		Key stakeholders adopted the related green practices and the extent of their adoption					
Key green aspects	Sub green practices	Pharmacy	GPs	Hospitals (wards & pharmacy)	Care-homes	Waste management companies /Local councils	Wastewater treatment companies
							wastewater -Apply advanced wastewater treatment (e.g., advanced oxidation, activated sludge etc)

4.3.1 Findings on Materials reduction related practices

As use-and-disposal does not involve any production, so the 'material' refers here to 'the finished drug products' (e.g., tablets, capsules, etc) rather than 'raw materials required for producing the drug'. The concept of materials reduction in this section is translated as 'effective and efficient usages of finished products (drugs)' to reduce unnecessary product (drugs) wastes. As per the investigation, Pharmacists, GPs, Care homes and Hospitals (wards) are the key stakeholders who are actively involved in managing prescriptions, drug dispensing and supplies of finished drugs stocks. The investigation has identified two key green practices for effective and efficient usages of drugs: *Considering lean operations for optimized prescribing, dispensing and usages,* and *considering digital technologies for optimized prescribing, dispensing and usages.* It is also revealed in the investigation that the players adopt these lean practices for achieving both cost effectiveness and environmental benefit such as combating PIE, though cost efficiencies are predominant. Figure 4.9 shows the extent of adoption of the green practices across the downstream stakeholders. The subsequent section presents the relevant practices and sub-practices.

Figure 4.9 The extent of adoption of 'Material (drug waste)' related practices across the downstream pharma (Source: Interviews & Reports)



(1 = Not mentioned / no consideration; 2 = Planning to consider; 3 = Low level of consideration; 4 = Medium level of consideration; 5 = High Level of Consideration; rating was done based on number of mentions and qualitative judgement for semantic validity of each mentions)

4.3.1.1 Consider lean operations for optimized prescribing, dispensing and usages

The investigation reveals that each of the relevant stakeholders undertakes several types of lean activities for effective and efficient usages of drugs and reducing unnecessary drug

wastes. Table 4.25 presents those sub lean practices revealed in the study. The subsequent sections predominantly focus on most important practices such as medical intervention (e.g., MUR/NMS), rationale prescribing practice, reuse and recycle of prescription drugs, and digitization of prescription and dispensing process; however, all other related findings are included in appendix 16 for interested readers.

Table 4.25 Key Lean operations (drug wastes reduction related) identified in the downstream pharma service

Stakeholders	Key roles in supply chain	Key Lean operations
Pharmacists	Ensure right drugs are dispensed in right quantity with right quality at the right time	✓ Reduce patient non-adherence for reducing unexpected drug wastes ✓ Reduce unexpected drug wastes by evaluating patients' medication usage habit (where applicable) ✓ Ensure effective and efficient stock management ✓ Ensure effective and optimum sales of OTC drugs to reduce unnecessary stockpile
GPs	Ensure disease is diagnosed accurately and a drug is prescribed to effectively manipulate the disease	✓ Ensure rationale prescribing practice for optimized drug usage ✓ Consider drug substitution or alternative therapies (where possible)
Care homes	Ensure patient is adhered to prescribed drugs.	✓ Ensure effective and efficient usage of drugs o Adhere to the Use MAR charts o Responsive collaboration with GPs, Pharmacists, and hospitals for patient review
Hospitals (wards)	Ensure drug is available at all the time and ensure patients are adhered to prescription drugs	✓ Ensure effective and efficient usage of drugs o Reuse of drugs which have not left the pharmacy premises and are in good condition o Reuse of patient own medicines during

		hospital stay o Drug usage tracing by MAR o Consider Medicine optimization scheme: 'My medication passport'

Reduce patient non-adherence for reducing unexpected drug wastes

Given the significant importance of reducing patient non-adherence, the study reveals that the downstream stakeholders, especially pharmacies, GPs, care homes and hospital (wards), have undertaken several initiatives to reduce unnecessary stockpiling at consumer sites, for instance, patient counselling and education, blister pack reminders, and medical intervention.

Medical intervention

As revealed in the interviews, **evaluating and reviewing patients' medication usage habits** is another approach to reducing drug non-adherence. As per the reports and interviews, this is formally done by means of several types of medical interventions, such as MURs (Medicine Usages Review), NMS (New Medicines Services) and other forms of interventions. The investigation reveals that though these interventions are predominantly introduced for patient safety and drug effectiveness, they are also adopted for drug wastes reduction.

- ✓ **Medicine Usage Review (MUR)**

Almost all the interviewees have highlighted that MUR is a medical intervention which offers the scope of reducing drug non-adherence and related drug wastes by structured and/or unstructured or formal and/or informal patient engagement. It was also revealed in the pharmacy service reports that MUR is predominantly targeted at four groups of patients: Respiratory, High Risk Medicines (NSAID, Anticoagulant, Antiplatelet, Diuretic), Post-discharge, and Cardiovascular risk. As per some of the respondents, a patient is either recruited by a pharmacy or by recommendation from GPs to conduct an intervention meeting with patients to find out if there are any ongoing issues with the medication prescribed. The study found out that MUR has become an established tool for both GPs and pharmacists to understand the effectiveness of the medication and patients' drug usage behaviour. This tool has also helped healthcare professionals to identify and protect unnecessary stockpiling and non-adherence, as evidenced from the majority of pharmacy interviewees and GPs. It reveals that more than 90% of community pharmacies in England provide this MUR service. The

study also reveals a wide range of issues in relation to patients' medications taken through the MUR service (See Table 4.26).

Table 4.26 Key drug usages issues identified through MUR intervention (Source: interviews and reports)

- ✓ potential drug interaction
- ✓ potential side effects/adverse drug reaction preventing use of the medicine
- ✓ patients report not using the medicine anymore
- ✓ patients report not using the medicine in line with the directions of the prescriber
- ✓ patients report difficulty using the medicine – e.g., issue with the device
- ✓ patients report difficulty using the medicine – issue with formulation, patients report lack of efficacy,
- ✓ patients report problem with dosage regimen
- ✓ patients report unresolved concern about the medicine

It was also evident in the interviews that based on the intervening report, the pharmacists and GPs are agreed on an action plan to resolve the issue to optimize drug usages and related wastes. Some of the respondents also outlined that as MUR allows pharmacists and GPs to understand how the patients are proceeding with their medication, they can help optimize the usages, for instance, changing the dosages or early termination of dosage based on the severity of side effects etc. For instance, one of the pharmacy managers (K – store 1) stressed this topic - "***we can optimize/ reduce the full use of medication they have or whether any other implementation need to be made, to further optimize the medication they are on''*** However, it was also revealed by some pharmacy managers (e.g., L, K – store 2) that as part of the MUR the pharmacists also advise the patients about alternative therapy or a healthier life style – diet and nutrition, smoking, physical activity, alcohol, sexual health, weight management, etc which could potentially reduce drug usages by altering the disease (in some cases). It was also reported by one of the CCG reports (CCG - 25) that pharmacies have undertaken 5000 patient interventions as part of MUR service between 2011 and 2012 for showing the effective techniques for inhaler use, which has enhanced effective self-management of patients with respiratory disease. It was also important to note that a few of the pharmacy managers (e.g., L) stated that a MUR cannot be effectively implemented unless it is being effectively communicated with GPs. One of the GPs (O) also highlighted that though in a very few cases the GPs are not satisfied with the robustness of MUR reporting system by the pharmacists, most of the time pharmacists execute them effectively.

- ✓ **New Medicine Service (NMS)**

As per the interviewees, this aspect offers the scope of reducing drug non-adherence and related drug wastes by structured and/or unstructured or formal and/or informal patient engagement when the patients are prescribed with some medicines for the first time and for longer term usages. As reported in the pharmacy service reports, NMS is aimed at reviewing those patients who are prescribed new medicines for long term symptoms or long term conditions such as asthma and COPD, diabetes type 2, antiplatelet / anticoagulant therapy and hypertension.

The majority of the pharmacies interviewed provided both MUR and NMS services. As revealed in the investigation, in contrast to MUR, NMS is a stepwise follow-up system of intervening. The stages are: patient engagement, intervention and follow up. As explained by some respondents, in the engagement stage, patients are recruited for this service either via GP referral or by community pharmacists opportunistically. Initial advice on medication is given at this stage and agreed for a second review either via phone or in the pharmacy premises typically between seven and 14 days after patient engagement, as explained by some of the pharmacy managers (e.g., K – store 1) interviewed.

As revealed in the investigation, NMS has enabled the pharmacists to assess the patients' adherence to the drugs, identify problems and determine the patient's need for further information and support. A similar review is done via a further follow up review between 14 to 21 days after the intervention, which is agreed with the patient. It was also reported (M) that in the final follow up (typically in week 3 or week 4 after engagement) the service is documented as complete based on three scenarios: firstly, if patient is adhering to the prescribed drugs, the patient is exited from service; secondly, if any problem is identified (e.g., severe side effect), then pharmacist and patient are agreed on a solution, and at this point the service is documented as complete; and thirdly, if any problem is identified, referral to the GP practice for review and at this point the service will have been completed.

One of the pharmacists (K – store 1) states how they use NMS for drug usage optimization

'When a patient gets new medicine, you follow up on them for about three weeks. So, you get to know if they are going to continue it or if they are going to stop it''

As revealed in the study, being part of pharmacy service provision and as part of the NHS drug optimization agenda, the level of consideration of these services is very high. This high level of consideration is also externally verified by the relevant statistics and performance monitoring reported by the PSNC (Pharmaceuticals Service Negotiating Committee).

Ensure rationale prescribing practice for optimized drug usages

As revealed in the interviews, this is predominantly a GP-led practice by which the patients are ensured to receive safe, effective and quality medication, while at the same time GPs take effective and efficient measures to identify disease and take responsibility for prescribing the drugs in a rationale manner for optimized drug usage with effective therapeutic outcomes. The investigation has revealed that GPs and/or related prescribers focus on five key areas (see Table 4.27) to ensure rationale prescribing practice.

Table: 4.27 Key areas of focus for rationale prescribing practice to achieve optimized drug usages (Source: Interviews)

- ✓ Reduce drug usages by introducing trial package and disease alteration strategy as part of regular prescribing
- ✓ Eliminate prescribing error
- ✓ Reduce drug usage by focusing on underlying reason of the disease rather than symptoms only
- ✓ Not issuing bulk supply
- ✓ Evaluate prescription review reports
- ✓ Consider AMR while prescribing due to the outbreak of antibiotic resistance growth

- ✓ **Reuse of drugs which have not left the pharmacy premises and are in good condition**

It was revealed in the interviews and reports that scope of reusing of unused returned medication by the pharmacists is considered another rudimentary approach to dealing with unwanted environmental loading of drugs and huge healthcare costs. However, the scope of this practice is limited to certain conditions and only case by case, rather than generalised. For instance, it is practiced in hospital wards settings. For instance, one of the respondents (L) explained that they reuse only those medicines which have not left the hospital wards and the drugs brought back by patients in hospital admission are also reused.

It was also evident that the hospital pharmacists interviewed also checked batch numbers of the returned drugs and psychically examined them for reusability for that patient. Another respondent (Q) who was a senior hospital nurse, also confirmed the reuse of those unopened

and unused drugs in the hospital wards prescribed for one patient, which are then reissued for other patients. The senior nurse also mentioned that they also must maintain rigorous procedures, such as checking whether they were kept in the right temperature etc, prior to reissuing them for another patient. It was also evidenced that several hospitals trusts have adopted this practice, where they have appointed a dedicated pharmacy technicians team who regularly evaluate the quality of returned drugs prior to redispensing them. For instance, one of the hospital trusts under a local CCG (CCG – 41) reported £450K worth of drugs savings via this route.

- ✓ **Reuse of Patient own medicines during hospital stay**

The study reveals that patients are encouraged to bring their own medicines during hospital admission in order to avoid unnecessary delay of supplying medication (especially when some medicines are in low supply and only available on demand) and to avoid unnecessary reissue of drugs. This encouragement is done via a scheme named the 'green bag scheme' (which is described in detail in the subsequent section). Reuse of drugs brought into the hospital by patients is evidenced in several hospital trusts under several local clinical commissioning groups. For instance, one of the reports (CCG -07) has also confirmed the reusing of unused drugs within wards/pharmacy as the drugs are never left on the hospital premises. The report has further highlighted on this thread as – "***Patient's own drugs, brought in by the patient on admission or afterwards by a carer or relative should not be wasted if suitable for reuse"*** It further explains that the responsible person (e.g., pharmacist) on the ward checks the suitability of drugs reuse following a check list (e.g., box unopened, stored in correct temperature in case of temperature sensitive products, no sign of damage etc). A similar practice is also explained by the respondents, a senior nurse (Q) from one of the hospital trusts.

4.3.1.2 Consider digital technologies for optimized prescribing, dispensing and usages

As revealed in the study, inefficient and ineffective communications between prescribers (GPs), dispensers (Pharmacists) and users (patients) lead to less visibility of a product (drug) flow. It was explained by some of the respondents, for instance, what happens if dispensers do not get the medication changes information from the prescribers on time, or what happens if patients make multiple requests of repeat prescription to GPs/pharmacists, or what happens if pharmacists fail to track the accurate time and quantity of medications supplied to the

patients etc. As revealed in the study, in each scenario, the answer is inefficiency and drug waste. Therefore, tracking and tracing each step of a user's updated medication and related healthcare info was considered highly significant by the key stakeholders (NHS) to optimize drug dispensing and usages.

The investigation reveals that in the majority of CCGs, NHS trusts have adopted a cloud-based digital platform called EPS – Electronic Prescribing Service, eRD, EPS-PT and SCR (Summary Care Record). Table 4.31 shows the key digital technologies used and their benefits by stakeholder, as they emerged in the study. It was revealed in the reports and interviews that these typical digital interfaces are aiming to reduce drug waste significantly through minimizing prescribing errors, dispensing errors and through regulating patients. The high-level implementation of these practices is not only reflected by the GPs interviewed but also externally verified by the source of NHS Digital Report. For instance, 93% of GP practices and 99.3% pharmacies nationally have gone live with these digital practices.

Table 4.31 Key digital technologies used to optimize drug prescribing, dispensing and usages (source: Interviews and reports)

Stakeholders	Types of digital platforms	Key benefits
Pharmacists	- EPS – PT (EPS prescription tracker) - Patient Care Summary (PCS)	- minimize dispensing error (e.g., duplication of supply) - patient regulation - reduce service time - save papers and reduce related footprint - reduce operational costs
GPs	- EPS (Electronic Prescribing service) - eRD (electronic repeat dispensing);	

- ✓ **EPS: eRD and EPS-PT**

As revealed in the study, the EPS enables prescribers like GPs to send prescriptions to the pharmacy (chosen by patient) electronically. As per the CCG reports, there are two more

integrated functions of EPS: eRD (electronic repeat prescription dispensing) and EPS-PT (EPS – prescription tracker). Under this EPS- eRD system, GPs can assign repeat prescription for up to 12 months for a patient in one go. It was also evidenced in the interviews that each prescription is automatically downloaded to the nominated pharmacy site after a predefined interval (e.g., every month) set by the GPs. The second repeat prescription is only released and downloaded in the pharmacy site when the info (Dispensing Notification) on first prescription is back to the GPs site, as explained by the one of the CCG (NHS) reports.

Each time the pharmacists dispense a prescription it automatically notifies both GPs and pharmacists via thi system. Hence, both GPs and pharmacists can track any historical dispensing missing or over issued or any other anomalies as explained by one of the pharmacy managers (L). It is also important to note that staff working at prescribing or dispensing sites can track the status of a prescription by using the EPS prescription tracker (EPS-PT), as highlighted in the report. This tracking has also reduced dispensing unnecessary supplies. For instance, as per one of the respondents (O) sometimes patients used to make multiple prescription requests (via GP and/or via pharmacy) from the fear of stock running out, but this tracking system has enabled both prescribers and dispenser to control and optimize the dispensing process.

- ✓ **SCR (Summary Care Records)**

It was also evidenced in the interviews that in line with prescription records, the healthcare professionals can also check the clinical history of a patient using Summary Care whenever required. As explained by some of the respondents (e.g., N), Summary Care is a computer based digital platform where each patient's clinical and medication records are updated by the GPs. As per the respondents, health care professionals such as GPs, pharmacists, nurses, or prescribers in hospitals, or in acute departments all have access to patients' updated summary care. A patient may also request their GPs to update some extra medical info on the system if they think this will help GPs or other healthcare professionals with diagnosis and treatment. Both GPs and pharmacies have referred to this tool while talking about optimizing the prescribing and dispensing process. For instance, one of the pharmacists (L) has highlighted that they also look into the SCR in line with intervention prior to dispensing as they check whether GPs have recently changed any medication or not, or any special hospital discharge notes. If any issue or concerns are raised by the pharmacists by looking into SCR, pharmacists make enquiries with the patient's GP or consultant prior to handing out any

medication (especially repeat medication). This is how it ensures patient safety as well as reducing unnecessary drug waste.

However, another pharmacy respondent (N) explained that sometimes the patient's SCR is not updated for a while (or not at all) and meanwhile they must dispense if a patient's drug is due. The respondent made a point that there is still some ineffective synchronization in communication between departments and delay in updating (or not updating at all) SCR while patients frequently move from one department of service to another (e.g., from cardiology to ENT). The respondent has further highlighted that it is very important for pharmacists to check the updated SCR (whenever require) to identify any possible adverse drug-drug interactions prior to dispensing drugs (especially repeat prescriptions).

So, the conceptualization of all these digital platforms (as shown in figure 4.10) has provideda common communication platform for GPs, pharmacists, and patients to smooth patient care operation. The visibility among prescribers, dispensers and patients has improved considerably. This visibility has eventually reduced the chances of drugs waste and misuse as outlined by the majority of the respondents. One of the GPs (O) argued that this digital platform of EPS and eRD had significantly reduced time for patient care, prescribing and dispensing errors and eventually reduced stockpiling through controlling unnecessary reordering of repeat medication by the patient.

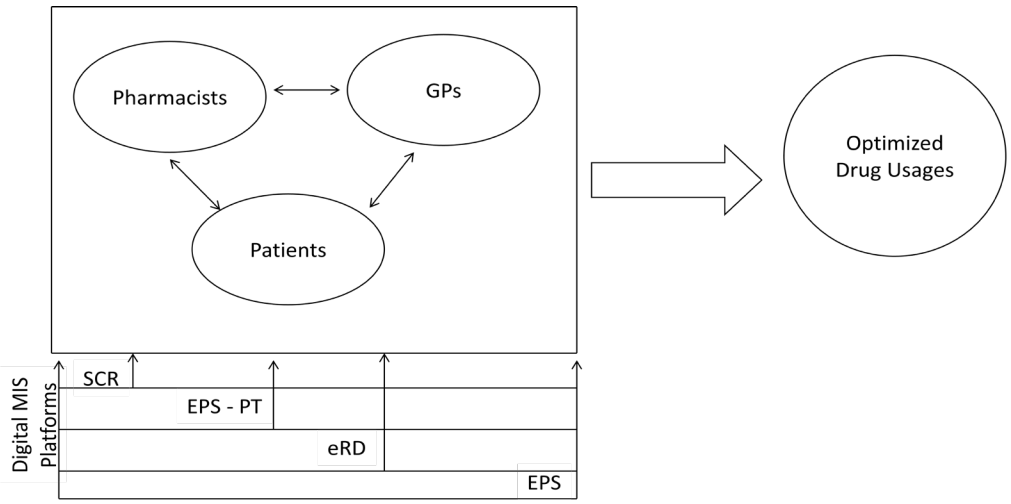
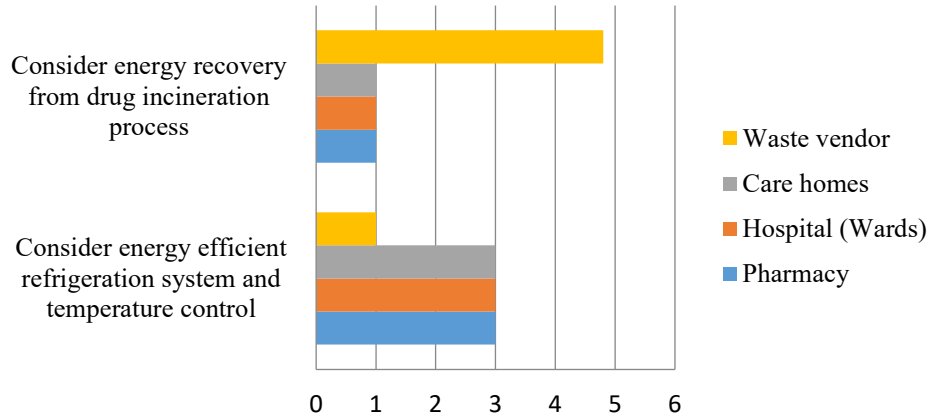


Figure 4.10 Impact of digital Information Management System on Optimized Drug Usages (source: Researcher)

4.3.2 Findings on Energy reduction related practices

The investigation reveals two key scopes of energy reduction during the drug-use-and-disposal phase: during the drug incineration process, and while dealing with temperature sensitive drug storage. Table 4.32 presents the key green practices undertaken by the relevant stakeholders as they emerged in the study. Overall, the adoption level of these green practices across the downstream stakeholders on average is between low to medium. As revealed in the study, waste vendors who run drug incineration are more concerned about energy reduction than other stakeholders. Figure 4.11 shows the average extent of adoption of each practice.

Figure 4.11The extent of adoption of 'Energy Reduction' related practices across the downstream pharma stakeholders (Source: Interview & reports)



(1 = Not mentioned / no consideration; 2 = Planning to consider; 3 = Low level of consideration; 4 = Medium level of consideration; 5 = High Level of Consideration; rating was done based on number of mentions and qualitative judgement for semantic validity of each mentions)

Table 4.32 Key energy reduction practices adopted by the downstream stakeholders (Source: Interviews and reports)

Stakeholders	Key energy efficiency aspects
Pharmacy, hospitals, and care homes	**Energy efficient refrigeration system and temperature control** **(e.g.,** Energy efficient Cold storage; Reduce drug wastes and related energy loss by effective temperature monitoring and control)
Drug waste vendors	**Energy recovery from drug incineration process** (e.g., consider lower temperature incineration whenever

Stakeholders	Key energy efficiency aspects
	possible; ensure appropriate drug packaging waste segregation in the source and related packaging management for lowering temperature for incineration plant)

- ✓ **Energy efficient refrigeration system and temperature control**

'Uninterrupted refrigeration system (24/7) for drug storage' in pharmacies, hospitals and care homes is one of the key sources of energy consumption in the drug-use-and-disposal phase. It was also evident in the interviews and reports that a wide range of drugs are temperature sensitive (e.g., injections, antibiotic liquid, ointments and creams, eye drops etc) and they are kept refrigerated between 2 and 8-degrees Celsius. The refrigerators are supplied an uninterrupted source of electricity 24/7. As per majority of the interviewees, temperature excursion at any point of time during drug storage in refrigerator destroys the potency and quality of drugs and they cannot be dispensed to the patients, which eventually induces drug wastes and related energy loss. Therefore, the majority of the pharmacies, hospitals and care homes investigated use manual or automatic temperature logs to continuously monitor drug temperature inside the refrigerator. They also use their own SOPs (standard operating procedures) to monitor drug temperature effectively and efficiently. For instance, one of the hospital respondents (Q) has outlined that they use digital temperature logger, which automatically saves the historical temperature of the drug. They also fill in daily refrigerator temperature logs.

Most of the pharmacies and hospitals investigated also reported usage of energy efficient refrigerator systems with CFC free refrigerant. Some of the hospitals were seen to use built in insulation system with refrigerators which reduces energy consumption. For instance, one of the respondents (N) stated that their pharmacy uses energy efficiency in refrigeration system installation, such as calculating how much electricity it consumes a day. Another respondent (L) also stressed that they have some refrigerators which require only a few hours (e.g., 6 to 8 hours) of electricity input to operate per day without any interruption due to the insulation system. Another type of energy efficient refrigerator called 'absorption drug refrigerator' is also used in hospitals. This typical refrigerator does not use electric energy, rather it uses waste heat (e.g., hot water) from an external source as energy to start the refrigeration

process. However, if it is not installed properly it may cause ammonia gas leaking which is a health hazard as outlined by one of the respondents (L).

- ✓ **Recover energy from drug incineration process**

As incineration is one of the safest processes of disposing unused or unwanted drugs, all pharmacies, hospitals, and care homes were seen in the study to employ licensed waste vendors to incinerate unwanted drugs. As per the respondents, most of the unused/unsold/returned drugs are incinerated in high temperature clinical incinerators to reduce environmental toxicity. However, this requires a significant amount of furnace energy, as claimed by the waste vendors who have been running drug incineration for many years. Some of the waste vendors also highlight that recovering energy from a drug incinerator is one of the energy efficient incineration processes they adopted. The majority of the waste vendors had adopted this approach. A detailed account of this process is also explained in the next section under *safe and responsible disposal management of unused and expired drugs*.

As evidenced in the study, there are two types of drug incineration processes available: low temperature (800 to 1000ºC) and high temperature (>1100ºC). High temperature incineration is carried out for highly hazardous drugs (e.g., cytotoxic) disposal only. It also depends on whether the drug wastes are well segregated prior to being put in the incinerator as explained by some of the respondents. Appropriate segregation of drug wastes plays a key role in avoiding high temperature incineration, which is both costly and energy exhaustive as suggested by most of the waste vendors investigated. For instance, one of the respondents (T) claimed that if the secondary or tertiary packaging is not removed it requires more energy to burn or it requires high temperature incineration. So, if the incineration plant does not have the facility to generating energy from incineration process it will lose the energy from the high temperature incineration process. Therefore, due to poor segregation, or not adhering to correct segregation, it incurs energy consumption. It was also reported in the study that segregation remains a big issue prior to disposal. That is why drug waste vendors regularly conduct waste audits and assess the wastes prior to incineration as explained by the respondents. A detailed account of the segregation process is also discussed in the next section under *safe and responsible disposal management of unused and expired drugs*.

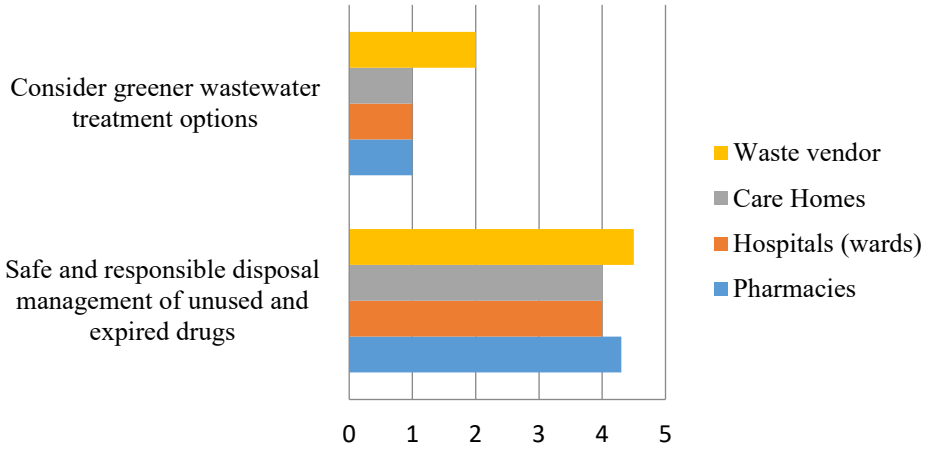
However, as highlighted in the interviews, it is also important to note here that sometimes primary packaging (or sometimes secondary packaging) is contaminated with drug chemicals (during storage and distribution) and not useful for recycling and mandatory to be sent for

high temperature incineration. So, segregation of recyclable packaging wastes from drug packages is a good practice prior to incineration. This view was also supported by another respondent from a generic pharma company (E – site 1).

4.3.3 Findings on Toxicity reduction related practices

The investigation reveals two key approaches of toxicity reduction during the drug-use-and-disposal phase: through safe and responsible management of unused and expired drugs and through consideration of greener wastewater treatment options., As the pharma use and disposal phase is regulated, most of the downstream stakeholders were seen to adopt safe and responsible management of unused / expired drugs, and the extent of adoption on average was between medium to high. The study reveals that waste vendors and pharmacies were found to be in the lead position to adopt it. However, it was also found that the scopes of the relevant sub green practices adoption and related operations were widely varied across the stakeholders. Figure 4.12 shows the average extent of adoption of each practice. The subsequent section presents the relevant findings on each sub green aspect that emerged in the study.

Figure 4.12 The extent of Energy reduciton across downstream pharma stakeholders (Source: Interview & Reports)



(1 = Not mentioned / no consideration; 2 = Planning to consider; 3 = Low level of consideration; 4 = Medium level of consideration; 5 = High Level of Consideration; rating was done based on number of mentions and qualitative judgement for semantic validity of each mentions)

4.3.3.1 **Safe and responsible disposal management of unused and expired drugs**

Given the significant importance of managing unused and/or expired drugs, each downstream stakeholder was seen to consider varieties of measurements and activities to reduce unwanted environmental loading of drugs. They are presented in Table 4.33 below.

Table 4.33 Key approaches for safe and responsible drug disposal taken by each stakeholder (Source: Interviews and reports)

Safe & responsible disposal approaches	Stakeholders			
	Pharmacies / GPs	Hospitals	Care homes	Waste vendors /local councils
Ensure effective and efficient collection of unused / expired drugs from patients for safe disposal	√			√
Ensure effective and efficient segregation management of drug wastes for safe disposal	√	√	√	√
Consider Safer and greener disposal /treatment				√

Prior to understanding the key safe and responsible drug disposal practices, it was mandatory to clarify what roles are played by each downstream stakeholder during the disposal phase. After conducting the investigation, these roles became clear. Table 4.34 presents the roles played by each downstream stakeholder

Table 4.34 Key roles played by each downstream stakeholder during drug disposal (Source: Interviews and reports)

Stakeholders	**Key role in supply chain (disposal phase)**
Pharmacy	- Participate in collecting unused/expired drugs from patients -Responsible to dispose waste via licensed waste vendor -Increase public awareness for returning unwanted drugs to pharmacy
Waste management	-collect, segregate, and treat waste in the licensed premises

Stakeholders	Key role in supply chain (disposal phase)
companies / Local councils	-responsible to track and trace wastes from point A to B
Hospital / Care homes	-Apply correct drug waste segregation process -Responsible to dispose waste via licensed waste vendor
Waste management companies / Local councils	-collect, segregate, and treat waste in the licensed premises -responsible to track and trace wastes from point A to B

The investigation reveals a responsible way of managing unwanted drugs collection and disposal. As revealed in the study, most of the downstream players were seen to ensure effective, efficient, and greener disposal of unwanted drugs following four key stages (see figure 4.13).

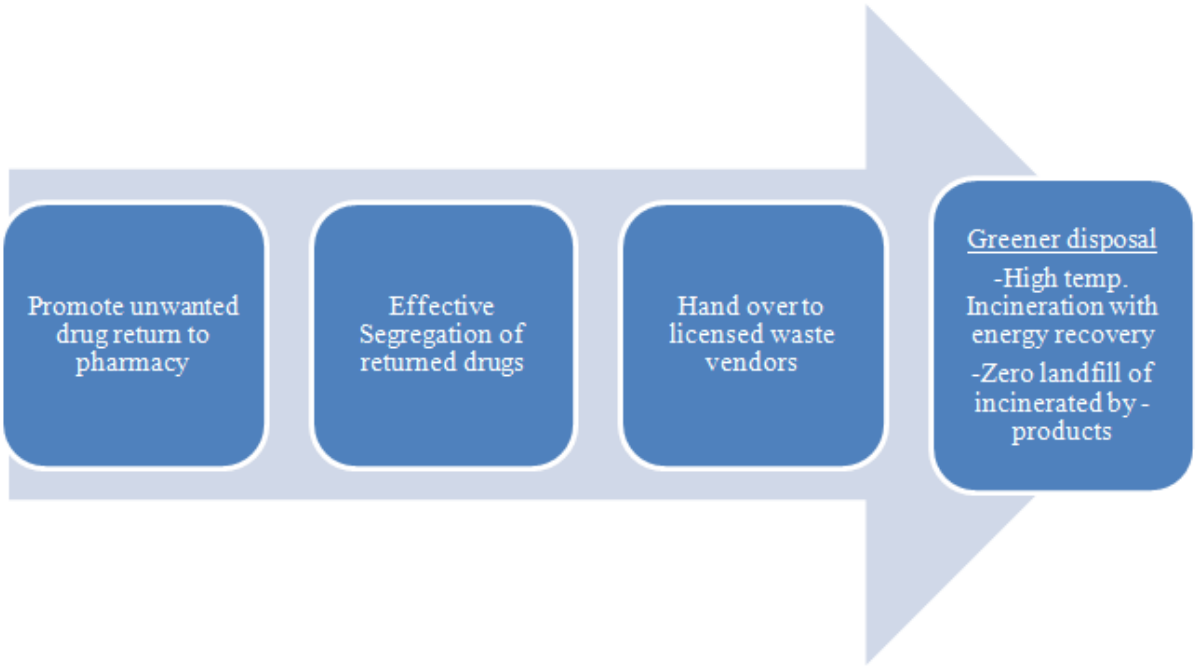


Figure 4.13 A greener road map of managing disposal of unwanted drugs
(Source: Researcher conceptualized from the findings)

The investigation reveals that different actors in the downstream use and disposal phase contribute in various ways, and in varying levels, to ensure effective and efficient collection and segregation of unused / unwanted drugs wastes from consumers or patients, to handover to registered waste vendors for treating with high temperature incineration. Appendix 17 presents in detail how each actor has acted on it as emerge in the study.

4.3.3.2 Consider greener wastewater treatment options

Given the significant impact of human excretion of drugs into the aquatic system and its emergence in the water and food cycle, it is essential for the far downstream wastewater treatment companies who predominantly deal with municipal wastewater treatments to deal with unprecedented levels of environmental loading of drug concentration via human excretion. This stream of contamination also includes inappropriate disposal of liquid drugs via the sink or toilet. Therefore, it is important to have a clear understanding on what measures have been taken so far to deal with this. Till now, as revealed in the study, the wastewater industry has focused on two key areas as below to deal with the issue of PIE:

- ✓ ***Monitoring and control APIs in wastewater***:

As per the investigation through interviews and reports, the local wastewater treatment companies are currently monitoring the concentration levels of some concerned drugs (e.g., certain painkillers, antibiotic etc) into the surface water and asses their impact on aquatic life to enrich understanding and related impact data. As per interviews, they are predominantly being motivated to do this because there is a regulatory requirement for the wastewater treatment companies to monitor a list of chemicals of potential environmental concerns. This is known as the 'surface water watch list' as part of the legislation of EU water framework directive, which requires water companies to monitor and collect environmental impact data of the listed chemicals. So, the regulators can impose further restrictions on releasing those chemicals into the surface water. See Table 4.39 below the watch list for certain APIs (human use only) guided by the water framework directive as revealed in the study.

Table 4.39 Lists of drugs whose concentration in the incoming wastewater are being monitored by the wastewater treatment plants (Source: interviews and reports)

Types of drugs for human use	Examples of APIs
Birth Control pills	*17-Alpha-ethinylestradiol (EE2);*
Antibiotics	*Amoxicillin, Ciprofloxacin, erythromycin, clarithromycin, azithromycin*
Hormonal	*17-Beta-estradiol (E2), estrone (E1)*

The study reveals that if any wastewater treatment plants identify any of the APIs from the watch lists in their incoming wastewater, they must assess the concentration level and monitor their aquatic impact. For instance, it was highlighted by one of the key respondents (W) from a wastewater company that their wastewater treatment plants have been monitoring the concentration of both EE2 and diclofenac. While another respondent (V) highlighted that their water treatment plants are currently not monitoring diclofenac, as it has already had sufficiently high-quality environmental impact data and hence removed from watch lists by European water directive. The respondent further stressed that they are now under pressure for monitoring antibiotic concentration (e.g., ciprofloxacin) due to the issue of AMR.

- ✓ ***Advanced wastewater treatment technology to reduce APIs concentration in surface water***:

As revealed in the study, a wide range of water treatment technologies have been tested to see if the drug concentrations can be reduced and/or eliminated from the incoming wastewater. It was revealed in the interviews and reports that as part of ongoing UK water industry research programs some wastewater treatment plants identified some advanced wastewater treatment technologies which have reduced the pharmaceuticals concentration in the effluent by more than 90%. For instance, it was highlighted by one of the respondents (V) that advanced oxidation (a typical chemical treatment process used to remove organic substances from the wastewater) has been able to remove more than 90% of the residues of ibuprofen, propranolol, and erythromycin from the effluent. A list of such advanced technologies (as an example) emerged in the study and is presented in Table 4.40. Table 4.41 also presents the list of some drugs whose concentration was removed by almost 90% using those advanced treatment technologies. These wastewater treatment technologies, however, are still not widely implemented (apart from a few of them such as activated sludge and membrane bioreactor which have already been adopted many plants) but they are still under consideration and are being planned for in the near future, as revealed in the study.

Table: 4.40 Examples of some advanced technologies (Source: Interviews and reports)
✓ **Advanced oxidation**: a type of chemical treatment used predominantly to remove organic substance ✓ **Activated sludge**: a mechanical and chemical

process where air/oxygen is blown into organic matters

- ✓ **Ultrafiltration / microfiltration**: a kind of nano scale filtering process to remove organic substances
- ✓ **Membrane Bioreactor**: a kind of biological filtration process to remove organic substances

Table 4.41 Advanced treatment technologies proved to remove the drug residues by more than 90% (Source: interviews and reports)

Types of drugs	Types of treatment technology applied			Effectiveness of removing drug residues
	Advanced oxidation	Activated sludge plants	Membrane bioreactor	> 90%
Ibuprofen	✓	✓	✓	
Propranolol	✓			
Diclofenac	✓			
Oestrone (E1)	✓	✓	✓	
17β oestradiol (E2)	✓	✓	✓	
17α ethinyloestradiol (EE2)	✓			

As evidenced from the interviews, though waste water companies are partially using some of the technologies, such as activated sludge, membrane bioreactor and advanced oxidation,

there is no measurement in place in general to quantify the amount of pharmaceuticals residues being released into to the environment. For instance, it was outlined by one of the respondents (W) that it is a matter of concern that many treatment facilities still do not have access to such analytical methods which can be used to detect pharmaceuticals concentration in the incoming wastewater. Therefore, the presence of pharmaceuticals in the majority of the wastewater treatment processes across the country still goes undetected as was admitted by almost all respondents.

4.4 Key contribution of the chapter

This chapter has outlined some important green practice related findings which were unknown previously in the context, and it is expected to influence the relevant practitioners and policy makers to greening pharma supply chain. For instance, the unique observation on the rate of green practices adoption across the stakeholders has clearly indicated us why the generic sector operations are becoming huge concern for achieving overall sustainability. The rate of green adoption during different supply chain (or, drug life cycle) phases (e.g., design, manufacturing and use and disposal) has also alarmed us why pharma sector should focus on design phase predominantly. Most importantly, the unique observation, of how and why design and development activities in generic operations (e.g., redesigning existing drugs) are significantly neglected, is an eye-opener observation for greening the sector. The chapter has identified some unique green design practices such as: *design and develop drug discovery process to dematerialize*; *design process to consume less raw materials by applying PMI; design and develop manufacturing process for flexibility in quality; and design and develop manufacturing process by installing and validating energy efficient equipment system (e.g., reaction vessel).* Such green design practices were never discussed before and validated empirically. The empirical evidence has clearly suggested significant environmental and related economic savings from those green design practices throughout the lifecycle of drugs. Though there were enormous concerns over adopting green during design and development phases of drugs (Clark et al., 2010; Sumpter, 2010; Taylor, 2010) due to focus on safety, quality and efficacy of drugs, the empirical evidence on each of the unique green design aspects has completely changed such myopic green mindset. Materials exhaustive, longer-period of R&D, and critically uncertain drug discovery process will undoubtedly be able to save materials and related energy through increasing in-silico practices, applying more PMI based design decision and considering possible quality variations in the early drug process validation. Such materials related design observation is unique and significantly important to

greening pharma operations. Likewise, early drug process validation with energy efficient reaction vessel (e.g., single use technology) as opposed to traditional energy consumptive vessel will significantly improve energy performance of such drug process during API manufacturing. It will have significant cumulative energy savings impact across the sector. The study has also identified a unique energy related manufacturing practices such as: *consider energy management programs (e.g., ZAP, energy kaizen, and energy audit).* Specially, some unique energy kaizen approaches such as reducing wastewater, product specific energy measure, routine leak detection of process piping system, process optimization tool (e.g., Britest tool), process calibration etc will have significant environmental and related cost savings during manufacturing phase. The chapter has also identified some unique green practices during use and disposal phase such as: *digitize prescribing and dispensing for drug wastes reduction; energy recovery from drug incineration; and reuse of drugs.* These unique green practices are significantly important to deal with PIE and related AMR impact. Effective and efficient communication among prescribers, dispensers and patients via real-time digitization process will undoubtedly reduce unnecessary drug wastes in the downstream customer zone. The unique scopes of reusing drugs (e.g., POD during hospital admission) will significantly reduce drug wastes and related costs.

4.5 Chapter Summary

This chapter has answered the first research question in the thesis. It gives a broader understanding of the scopes of green practices application in drug design and development, manufacturing, and use-and-disposal phase under three sub green areas: materials, energy, and toxicity. It also addresses how innovative pharma, generic pharma and bio pharma sectors have adopted related green practices. The findings clearly indicate that compared to other sectors, the innovative pharma sector is a green leader in reducing materials, energy and toxicity from their operations. Some design practices, such as design process to use green substances, quality by design (QbD), and design process to increase environmental biodegradability of drugs, have significant importance in reducing the environmental footprint in the manufacturing and disposal phase. In the manufacturing phase, continuous mode of manufacturing, solvent recovery and monitor and control of API discharge from the manufacturing plant have become significantly important for generic pharma, as well as for those innovative who manufacture bulk drugs to reduce environmental footprint. The scopes of green manufacturing practices in the case of both API production and formulation have

also been addressed. While the innovative and bio pharma sector in general are playing a key role in the industry through discovering, developing and/or redesigning existing drug processes for materials, energy and toxicity efficiency, the generic pharma sector is playing a pivotal role in the industry to provide low cost generic version of drugs and make them affordable to all. Therefore, the motivation of green adoption significantly varies between the sectors. The next chapter presents the findings on key motivations and related green drivers for adopting green pharma operations.

Chapter Five

Findings on Green Drivers in Pharma Sector

Whilst the previous chapter provided a detailed account of each green practice and sub practices, this chapter aims to assess key green drivers and pressures faced by the key pharma stakeholders. It also aims to focus on identifying the drivers and pressures for each key green practice – green design, green manufacturing, and green use-and-disposal. Practice-specific drivers identification is of paramount importance for the pharma sector, as it will trigger the relevant stakeholders and practitioners to identify the particular scope of implementing green practices without confusion; it will also trigger the business owners to identify the particular scopes of improving competitive advantages being a first mover over laggards. Similarly, the industry policy makers could revise their policies to help companies go green. Whilst the relevant literature still unfertile, this chapter aims to fill the related gaps by presenting and analysing the evidence from both interviews and companies' environmental reports and/or other relevant reports. It also aims to identify and present the intensity or importance of each green driver faced by different stakeholders in the industry. Therefore, this chapter predominantly aims to answer the second main research question and related two sub questions:

RQ2. What are the drivers faced by individual pharma sector stakeholders for adopting green practices and what is their perceived importance?

RQ2.1 what are the drivers faced by upstream pharma sector stakeholders for adopting green design and green manufacturing practices and what is their perceived importance?

RQ2.2 what are the drivers faced by downstream pharma sector stakeholders for adopting green use-and-disposal practices and what is their perceived importance?

5.1 Findings on key drivers faced by upstream pharma stakeholders

This section presents the key factors which drive pharma companies to undertake green related practices during early drug design and development, the API manufacturing process and/or the formulation process. It also aims to understand the extent of these drivers/pressures

faced by each stakeholder – innovative pharma, generic and bio pharma. It is clear from the previous chapter that though the overall industry is moving towards accepting and exercising most of the green practices / activities during the design and manufacturing phase (between planning stage to low), most of the innovative big pharma have taken the lead (average rating from medium to high) for greening design and manufacturing phase. So, it would be particularly important to learn from the driving force behind their adopted green practices, which could later influence the other stakeholders (especially generic pharma who produce in abundance) through a clear understanding of each driver. Also, it would be important for other followers and laggards in generic pharma to learn from those generic pharma who have successfully implemented (though comparatively lower than innovative pharma) several green practices. A total of 10 drivers have been identified in four key categories. Table 5.1 has summarized the relevant the drivers and sub-drivers identified for the individual stakeholders in the study. The average intensity or extent of each green drivers faced by key pharma stakeholders across the industry has also been captured in figure 5.1

Table 5.1: Summary of key drivers and sub-drivers faced by the upstream pharma stakeholders (Source: Interviews and reports)

Green Drivers		Key stakeholders who were influenced by the related green driver and the extent of the driver		
Key green drivers	Sub green drivers	**Innovative**	**Generic**	**Bio pharma**
Regulatory	F – gas related regulation	**<u>High</u>** -Regulator planning to impose more tax on CFC based products -Regulatory fines if exceed limits -Regulators require monitoring F-gas emission from the operations -CFC based inhalers became a parliamentary issue -Some of them driven to design CFC free inhalers -Driven to replace CFC based process equipment -Driven to adopt 'ozone depleting substance management'	**<u>Low</u>** -Driven to optimize cooling and refrigeration system to stay regulatory permit - Comparatively low scopes of use and produce F-gas related drug products (e.g., inhalers)	**<u>Low</u>** - cooling and fire extinguishing systems must stay on regulatory limit -Comparatively low scopes of use and produce F-gas related drug products (e.g., inhalers)
	Industrial Emission Directive	**<u>High</u>** -Strictly maintain the Discharge permit of VOCs / API discharge / hazardous organic chemicals	**<u>Low</u>** -Comparatively lower scopes of VOCs /organic solvents /wastewater including	**<u>Medium</u>** -Adopt advanced technology (waste hood with special absorbing filter)

Green Drivers		Key stakeholders who were influenced by the related green driver and the extent of the driver		
Key green drivers	Sub green drivers	**Innovative**	**Generic**	**Bio pharma**
	(IED)	discharge etc which is set for each process by the environmental agency - enforcement action: Warning letter (e.g., notice of violation -Require companies to have internal environmental management process or SOPs to manage discharge -Driven to invest on API detection technology to adhere to regulatory limit	API discharge as majority of them dealt with formulation rather than API production	within process to stay within regulatory permit -Driven to adopt more autoclave (pre-treat waste to reduce toxicity) technique to stay within regulatory hazardous wastewater discharge limit
	REACH regulation	**High** -Regulatory permission is required to produce or import for intermediate raw chemicals if the production / usage volume is more than 1 tonne per year -Significantly driven to adopt green chemistry practice to reduce by-product / intermediate chemicals production	**Low** -Comparatively low scopes of producing pharmaceutical intermediate products as they mostly involve formulation than API synthesis	**Low** -Comparatively Low chemicals usages: Most of the operations are predominantly based on biologically sourced raw materials than chemically driven -Driven them to regular review of SVHCs (Substance of Very concerns)
	ERA of drugs	**High**	**Low**	**Medium**

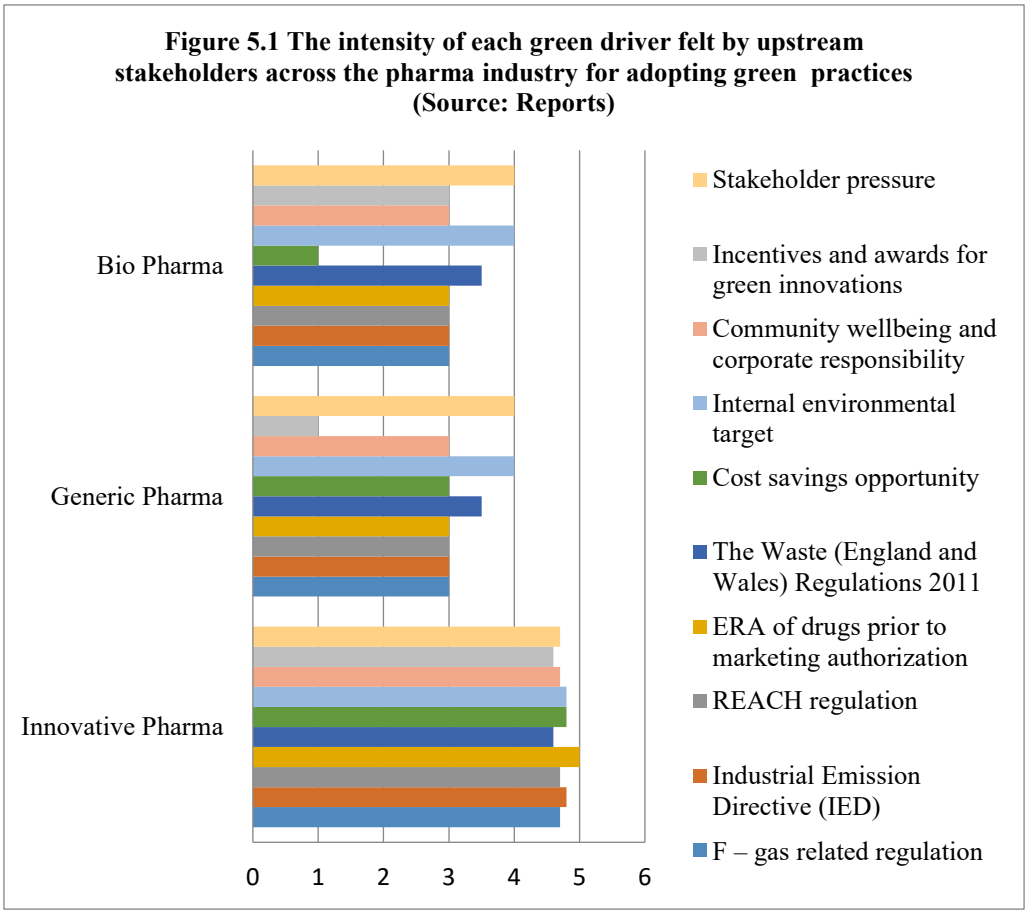
Green Drivers		Key stakeholders who were influenced by the related green driver and the extent of the driver		
Key green drivers	Sub green drivers	**Innovative**	**Generic**	**Bio pharma**
	prior to marketing authorization	-They must conduct ERA (Environmental Risk Assessment) of new drug substance as part of regulatory approval for market authorization -Driven to invest more ERA projects to develop PBT database, design more bio-based process, avoid toxic chemicals in the process etc -They must monitor, limit, and control the concentration of those APIs which already showed potential negative impact to the environment	-Generally, do not invest on new drug development -In some occasions they feel indirect pressure: pressure from focal company (normally innovators who outsourced API/formulation from some generic contract manufacturer) to monitor and control API discharge, as the focal company must ensure that the APIs with potential environmental concerns are regularly monitored, limit and controlled	-They must conduct ERA (Environmental Risk Assessment) of new drug substance as part of regulatory approval for market authorization -Driven to invest more ERA projects to develop PBT database
	The Waste (England and Wales) Regulations 2011	**High** -Penalty / warning letter if not followed the correct type of waste process -Must have internal management process to justify the scopes of hierarchy (e.g., justify why landfill has chosen over other option) -Driven to adopt more eco-friendly options to divert landfill	**Medium** -Pressure from focal company (generally innovators) to follow waste hierarchy when working as a contract manufacturer -Solvent recycling is not common as it was not economically and operationally feasible	**Medium** -Driven to adopt waste performance measures -stringent pressure to follow it for packaging related wastes

Green Drivers		Key stakeholders who were influenced by the related green driver and the extent of the driver		
Key green drivers	Sub green drivers	**Innovative**	**Generic**	**Bio pharma**
		-Driven to converts waste to beneficial use		
Business Benefits	Cost savings opportunity	**<u>High</u>** Most of them have achieved: -Significant cost savings from solvent recycling -Higher ROI from continuous manufacturing -Cost savings from energy efficient equipment installation -Cost savings from energy recovery (from waste solvents) -Cost savings from reduced use of input solvent in the process (e.g., clean equipment using process wastewater)	**<u>Low</u>** Some of them have achieved: -Cost reduction from waste diversion -Cost savings from energy efficient equipment and LED	**No direct cost savings** (However, some estimated cost saving via water reduction projects)

Green Drivers		Key stakeholders who were influenced by the related green driver and the extent of the driver		
Key green drivers	Sub green drivers	**Innovative**	**Generic**	**Bio pharma**
Top management commitment	Internal environmental target	**<u>High</u>** -Most of them have strong internal environmental commitment -Most of them have comprehensive internal environmental policy -Majority of them are member of ACS GCI pharmaceutical round Table	**<u>Medium</u>** -Some of them are strongly motivated to achieve their internal goal of Zero land fill - Some of them have internal environmental policy -Few of them are member of ACS GCI pharmaceutical roundTable	**<u>Medium</u>** -Some of them are member of ACS GCI pharmaceutical roundTable -Some of them have strong internal environmental policy -Few of them provide incentives and awards for green innovations
	Community wellbeing and corporate responsibility	**<u>High</u>** - Felt strong ethical and corporate responsibility pressure to go green -Driven to undertake many voluntary green measures (e.g., ERA for all new and existing drugs)	**<u>Low</u>** -Not felt such pressure --few number voluntary measures such as some energy efficiency activities	**<u>Low</u>** -Not felt such pressure -few number voluntary measures such as RCM (Resource Conservation Measure) – water reduction project etc
	Incentives and awards for green innovations	**<u>High</u>** -Majority of them provide employees with incentives and awards for green innovation (e.g., apply green chemistry technology)	**Not seen such incentives awards**	**<u>Low</u>** -Few of them provide incentives and awards for green innovations (e.g., apply green chemistry technology)

Green Drivers		Key stakeholders who were influenced by the related green driver and the extent of the driver		
Key green drivers	Sub green drivers	**Innovative**	**Generic**	**Bio pharma**
Market Driver	Stakeholder pressure	**<u>High</u>** -Strong Pressure from key downstream customer (e.g., NHS) for greener API (e.g., API with lower energy footprint) -strong Pressure from Internal Board of directors / Investors / top management to produce more sustainable pharma products to combat with PIE and AMR	**<u>Medium</u>** - Pressure from both internal (investors/shareholders) and external (outsourcer / NGOs like ABPI, BGMA etc) stakeholders to combat the issue of PIE / AMR.	**<u>Medium</u>** -pressure from both internal (investors/shareholders) and external (outsourcer / NGOs like ABPI) stakeholders to combat the issue of PIE / AMR.

Figure 5.1 The intensity of each green driver felt by upstream stakeholders across the pharma industry for adopting green practices (Source: Reports)



(Report ratings: 1 = Not mentioned / not driven; 2 = Beginning to drive; 3 = Low level driven; 4 = Medium level driven; 5 = High Level driven; rating was done based on number of mentions and qualitative judgement for semantic validity of each mentions)

5.1.1 Regulatory driver

Findings from the interviews and reports reveal industry wide regulations which have motivated and accelerated the adoption of green related practices during the design and manufacturing phase. The investigation highlights that these regulations play an important role to influence the key stakeholders to adopt green activities and practices. The majority of the respondents agreed that understanding of each regulatory driver and how these drivers influence green related operational decisions in pharma will also help policy makers and regulatory bodies for greening the sector. As per the findings, seven key regulations were identified as seen in Table 5.1. It was evidenced from the interviews that most of the respondents from innovative pharma were being influenced by at least one of the regulations identified for adopting green practices in the R&D and manufacturing operations, while only

a few of the generic pharma respondents and some of the bio pharma respondents had faced regulatory pressure. The average intensity or extent of each of the green drivers faced by key pharma stakeholders across the industry has also been captured in figure 5.1 (evidence from reports). The subsequent section presents findings on key sub-green driver evidenced from the interviews and/or reports.

5.1.1.1 F – gas related regulation

As revealed in the study, F-gas-related different versions of regulations such as the Montreal Protocol, Ozone Depleting Substances (ODS) Regulation (EC 1005/2009), EU Regulation 517/2014 on Fluorinated Greenhouse Gases, UK Transition Strategy for CFC-based metered dose inhalers, and Fluorocarbons Recovery and Destruction Law have also been sought as one of the key regulatory drivers for adopting related green practices or environmental activities taken by the pharma companies. As per the findings in the investigation, though known as several titles of the regulations, one common goal of these different versions of legislations is to reduce or eliminate F-gases from the design and manufacturing operations for protecting the ozone layer in the atmosphere. A detailed description of each regulation is also available online. Table 5.2 presents the key facts of this regulation in pharma as highlighted in the study.

Table: 5.2 Key highlights of F – gas related regulations in pharma (Source: Interviews and reports)

Key aspects of F – gas related regulations	
Examples of F- gases	CFC – Chlorofluorocarbons. HFC – hydrofluorocarbons. PFC - perfluorinated carbons.
Key environmental impact of F- gases	✓ Ozone layer depletion ✓ Increase global warming significantly (F-gas induced global warming is Up to 23000 times greater than CO2)
Key regulatory requirements	✓ Reduce or eliminate usage of F – gases from the process; stay within permitted limit
Key consequences for not following the regulation	✓ Monetary fines if exceeds exposure limit from manufacturing process ✓ Pharma products is still not banned from sales (e.g., inhalers) but planning to impose more tax on CFC based inhalers

Examples of green practice driven	**Green Design**: CFC free inhaler products design; use of lower impact inhaler gas such as HFA. **Green Manufacturing**: CFC free cooling / refrigeration system; Efficiency in refrigeration system (e.g., leak detection program as part of energy lean) etc

It was revealed in the interviews and reports that the regulation drives to reduce the usage of ozone depleting substance (e.g., CFC) from the pharmaceutical design, development, and production process. As per majority of the interviewees, this driver is of paramount importance for greening pharma R&D and manufacturing operations, as it not only designs CFC based inhalers products but also uses significant amounts of refrigeration and other cooling applications in the production process (e.g., API synthesis). Most importantly, as revealed in the study, this driver could significantly replace CFC-based inhalers, as the UK market for inhaler products is increasing considerably due to the treatment and management of respiratory disease such as asthma and chronic obstructive pulmonary disease.

Some of the innovative pharma companies were driven by the ozone depleting related F-gases regulations to explore alternatives to CFC and have designed and developed HFA - Hydrofluroalkane (lower ozone depleting effect than CFC) - based new inhaler products to reduce the ozone depleting effect. The findings clearly reveal that the industry (though innovative predominantly) faces more pressure than ever before to look for alternative designs to replace CFC based inhaler. This is because the issue of CFC-based inhaler production has become a parliamentary issue and reviewed by the environmental audit committee in the UK as highlighted by one of the respondents (A) from a leading innovative pharma. The respondent has further highlighted that the NHS has shown huge interest in modifying CFC-based inhalers to replace them with lower ozone depleting and greenhouse potential, as inhalers are one of the biggest sources of their carbon footprint. The intensity of the pressure can be further accentuated as highlighted by one of the environmental reports (In - 12) that – ***"… the parliamentary Environmental Audit Committee (EAC) launched its inquiry into the UK's progress on reducing fluorinated gas (F-gas) emissions, a part of which looked at the use of metered dose inhalers …"***

Interestingly, though innovative pharma companies were seen to be under more pressure than the others, generic pharma is the least likely to feel this as a crucial driver. One of the key

reasons is that it was not common to produce CFC-based products in generic pharma. However, some generic pharma still feels it as a driver to reduce use and optimization of F-gas related cooling and refrigeration systems to stay within regulatory permit (e.g., Gn - 04, Gn – 02).

5.1.1.2 Industrial Emission directive (IED)

As revealed in the study, this is an EU legislation which requires all industrial producers within the European Union member states to limit the impact of emissions from industrial production on the environment. It was revealed that this regulation aims to regulate emissions to air, water, and land, generation of wastes, use of raw materials, and energy efficiency from the production of pharmaceutical products including intermediate products produced. Table 5.3 presents the key aspects of this regulation as revealed in the study.

It was also revealed in the study that the UK environmental agency is a regulatory body responsible for regulating and protecting the UK environment sponsored by the DEFRA (Department for Environment, Food and Rural Affair). This department works with pharma industry players to set environmental discharge limits and approve local discharge permits via a particular regulation as revealed in the study. The majority of respondents from innovative big pharma have stressed that they feel pressure from the environment agency to promote green innovations in the process design to proactively manage permitted emissions in the commercial manufacturing phase. For instance, one of the respondents (B – site 2) from a leading innovative pharma highlighted that they have to maintain a discharge permit for each process set by the environmental agency and this has influenced them to take more proactive action, such as considering the discharge limits beyond the actual limit, but they also are influenced to incorporate green credentials in further upstream design and development phase of a process for the longer term. The respondent has also stressed on this thread saying – ***"we work with regulator to drive our continuous improvement".***

Table: 5.3 Key highlights of IED regulation in pharma (Source: Interviews and reports)

Key aspects of IED regulation	
Examples of industrial emissions	✓ VOCs emission to air from pharma process. ✓ APIs discharge into water. ✓ Hazardous organic chemicals discharge into water via cleaning equipment or manufacturing by products formation etc

Key environmental impact of industrial emissions	✓ Air, water, and land pollution ✓ Increase GHG emission and climate change ✓ Contaminate surface water and aquatic organism ✓ Increase AMR growth ✓ Reduce soil fertility
Key regulatory requirements	✓ Reduce harmful industrial emissions from industrial R&D and production and stay within discharge limits set by the local environmental agency through the assessment of BAT (Best available technology) installed. ✓ For solvent emission, the limit is 5% of solvent input for new process instalment and 15% of solvent input for old instalment if the plant produces more than 50 tonnes of pharmaceuticals per year
Key consequences for not following the regulation	✓ enforcement action: Warning letter (e.g., notice of violation) ✓ Planning to prohibition of manufacturing activities
Examples of green practice driven	**Green Design**: energy efficient process design; design for lower by products etc **Green Manufacturing**: install waste hood absorbers for absorbing VOCs; analytical detection, monitor and control of APIs and other organic matter into the discharge etc

Though IED regulation seems to be more relevant to the commercial manufacturing plants, it was revealed from the investigations that some proactive green initiatives, such as installation of energy efficient equipment in the early process design stage, designing less energy consumptive processes with fewer and cleaner chemicals etc, have been adopted by the innovative and bio pharma companies driven by the local environmental permit as part of IED. For instance, one of the companies (B – 08) reported installing an advanced waste hood with special absorbing filter in the process to absorb VOCs emission to reduce air toxicity driven by the IED regulation, some other bio pharma companies also adopted an autoclave process driven by the regulatory discharge limit. Evidence was also available on how companies (especially innovative ones) have become proactive to undertake green practices driven by the IED. For instance, a respondent, an EHS manager (B - site 1) from a formulation plant mentioned that they felt pressure from this directive and had implemented an internal environmental assessment of API prior to discharging the concentration into the environment. They termed this assessment EHAC (Environmental Hazard Assessment Category).

5.1.1.3 REACH regulation

It was conceptualized in the study that as per the REACH regulation, any chemical substance for production (or, export / import) is subjected to registration first with the European Chemical Agency (ECHA) for disclosing relevant specified sets of chemical properties of that substance. Then ECHA evaluates the substance for potential hazards for humans and the environment. Based on the evaluation, it also entails a list of Substances of Very High Concerns (SVHC) which are cancer causing, or endocrine disruptors, or they have harmful properties and persist in the environment for a long time and gradually build up in the environment. It was also understood that the ECHA will publish these data either through authorization for use and/or restriction of usage process based on toxicity level. However, as found in the reports, pharmaceutical finished products, API, and excipients are exempted from REACH regulation apart from the pharmaceutical intermediate products. Pharmaceuticals intermediates are considered as the building blocks for producing APIs. Every stage of API synthesis reaction produces intermediate chemical substances. Table 5.4 presents details scope of REACH in pharma as emerged in the study.

Table: 5.4 Key highlights of REACH regulation in pharma (Source: Interviews and reports)

Key aspects of REACH regulation	
Examples of SVHC (Substances of Very High Concerns)	✓ Benzene, Diethyle ether, Benzo-fluoranthene etc
Key environmental impact of SVHC	✓ carcinogenic, mutagenic, or toxic to the human and environment ✓ Toxic for production
Key regulatory requirements	✓ Any company producing (or importing) to any EU country more than 1 tonnes of intermediate pharmaceuticals per year must register the chemical properties with ECHA to evaluate and authorize it for production (or marketing), or restrict (or banned) its application.
Key consequences for not following the regulation	✓ Banned (or restrict) of the intermediate products meaning hampering the production API
Examples of green practice driven	**Green Design**: process design with Green solvents; design with bio based starting materials and less use of chemicals; design process to use biocatalysts **Green Manufacturing**: avoid of hazardous

	substances; promote solvent recycling, run continuous production etc

The study reveals that the majority of the innovative companies were driven by this regulation to reduce intermediate substance formation, applying MET or green chemistry concept. For instance, one of the innovative pharma companies (In - 07) reports that though API is excluded in the REACH regulation, the company is struggling to register the intermediate pharmaceutical substances. It was stated by the report (In - 07) that "***Companies in the pharmaceutical industry are particularly affected with regard to registering intermediates".*** Hence, this observation had driven the bio pharma company to explore green alternative chemical substances and to try to avoid SVHC substances (which were emerged as 'toxicity reduction practice during the drug design and development phase) in the early process development. For instance, one of the bio pharma (B – 01) reported that, driven by REACH, it continues to review the SVHC lists (as of 2017, 174 substances listed) to replace substances with greener ones. As per the interviews and reports, none of the generic pharma R&D process was driven by this regulation as the majority of generic R&D involves formulation design and development rather than API synthesis or initial process design of drug. Hence, there is much less scope for inducing pharmaceuticals intermediate products during generic formulation.

However, very few generic companies who produce APIs are driven by REACH in the context investigated. It was also revealed in the reports that very few of them produce generic (off patent) versions of APIs whose intermediate may have already been passed by REACH; however, only those generic APIs whose patent expired before REACH was enacted (i.e., before 2007) are subjected to REACH. But they are very few in number in the context investigated.

5.1.1.4 ERA of drugs prior to marketing authorization

It was conceptualized in the study that as per the drug regulatory authority (FDA or EMA), any company that wants to apply for marketing authorization of a newly developed drug (newly discovered or redesigned existing one) must conduct an ERA (environmental risk assessment) of the new APIs to be marketed. Hence, this driver is highly relevant to those innovators who discover and develop drugs. As revealed in the study, the early environmental impact assessment of drugs will help the regulatory body to manage and control the

unpresented issue of PIE and AMR. The key scope of this regulatory requirement is shown in Table 5.5. It was also revealed in the study that though this driver is crucially important for the pharma industry for designing and developing more eco-friendly processes for new drugs, flexible regulatory enactment due to the lack of PBT data of newly developed API has become a key challenge. Interestingly, this regulation has predominantly driven the majority of innovative pharma to adopt green practices in both the R&D and manufacturing phases.

Table: 5.5 Key highlights of ERA related regulation in pharma (Source: Interviews and reports)

Key aspects of the new regulatory requirement of ERA of drugs	
Examples of environmental risk of APIs	✓ APIs enters water cycle via huma exertion, inappropriate disposal of unused drugs and manufacturing plants
Key environmental impact of APIs contamination	✓ Antibacterial resistance growth ✓ Threats to aquatic life ✓ Threats to human life via food and water contamination of APIs
Key regulatory requirements	✓ Any company wants to apply for marketing authorization for any new drug must conduct ERA (environmental risk assessment) of the new drug to demonstrate possible environmental risks associated with the new drugs. It is evaluated in three stages. ✓ Stage 1: Pre-screening: company must provide an estimation of exposure using predicted drug consumption data ✓ Stage 2: Screening: company submits data on initial prediction of risk or PEC (predicted environmental concentration) to predict aquatic toxicology of the APIs to be marketed. The safety threshold of PEC is 0.01 micro gram per litre (µgm/L) ✓ Stage: Extended study: company provides the assessment of fate and effect of the APIs using PEC/PNEC ratio to provide PBT data
Key consequences for not following the regulation	✓ ERA assessment failure does not lead to authorization of marketing ✓ The regulator will set discharge limit / usage limit of the API based on the level of environmental risk (based on ongoing scientific data)
Examples of green practice driven	**Green Design:** design process for increased biodegradability; synthesis of API from bio-based

	substances etc **Green Manufacture**: set voluntary API safe discharge limit from the manufacturing plants

The study reveals that the majority of the innovative big pharma have been influenced by these new regulatory requirements and have taken several green measures, such as use of green solvent, avoiding using toxic chemicals in the process, designing more bio based processes and using more nano-biodegradable substances, during the design and manufacturing phase. For instance, one of the respondents (A), highlighted that they not only keep looking to develop ways to identify environmental hazard risk earlier in drug developmental phase, but they also promote greener approaches, such as using bio based substances as starting materials for API synthesis.

As revealed in the study, it is interesting that even if the companies identify some potential environmental risks, the marketing authorization will not be denied; rather the new drug product will be under continuous investigation (eco-pharmacovigilance) of environmental discharge amount and related environmental impacts. As emerged from the interviews and reports, still having such a flexible nature of regulation, majority of the leading innovative companies have become highly determined to adopt green practices (e.g., development of PBT database) voluntarily in the early drug design and development phase - so there is less environmental risk when the drugs enter into the environment. For instance, it was revealed by one of the leading innovative pharma (In – 02) that this mandatory ERA has led them to apply artificial intelligence and machine learning (e.g., chemoinformatics, bioinformatics etc) for identifying early environmental impact of a particular drug substance and relevant intermediate substances.

5.1.2 Business Benefits: Cost savings

As per the findings from both the interviews and reports, this driver explains how and to what extent pharma stakeholders are being influenced by business benefits via costs savings related forces to go green. This driver is of greater importance for companies to implement relevant green practices to increase cost efficiency. Two financial drivers were identified: cost savings and R&D investment. It was revealed that in most cases innovative pharma has been influenced more than any other sector to adopt related green practices.

5.1.2.1 Cost savings opportunity

The study reveals that pharma companies have already started slowly realizing the benefits of reaping green practices in the operations. The industry has clearly evidenced significant cost savings in the long term through applying some key green practices such as solvent recovery, MET or green chemistry adoption. Table 5.7 below presents the scopes of cost savings related drivers across the pharma sector that emerged in the study.

Table 5.7 Key cost savings drivers for green practice adoption in pharma (Source: Interviews and reports)

Examples of Key costs saving drivers
✓ Cost savings from solvent recovery ✓ Cost savings from continuous manufacturing ✓ Cost savings via operational efficiency while operational efficiency gains via green chemistry (MET) adoption ✓ Cost savings from waste diversion

- ✓ ***Cost savings from solvent recovery as driver***

The study reveals that cost savings from solvent recovery were of the key drivers for pharma to adopt related green practices in the early phase of drug process development. Given the significant costs impact of solvents, manufacturers (predominantly innovative) urge the developmental scientists and chemists to design and/or redesign drug processes for promoting solvent recovery. It was also evidenced in the study that the investment recovery or payback period is between two to six years. It was also found that though the time pressure for accelerating the R&D process is very high, considering solvent recovery in the early R&D process work is more profitable than considering it at a later stage. Hence, the majority of the respondents were in agreement about adopting solvent recovery practice in the early drug design and development phase. This is due to the fact that once the patent is granted, within five years of discovery and development, the innovative companies will still have nine to thirteen years to generate profit (considering the payback period). Though cost factors have been frequently identified throughout the conversations with most of the respondents, some

of them were also able to demonstrate how cost savings during the manufacturing phase actually has driven them to undertake green practices in the early drug R&D phase.

For instance, one of the respondents, a senior environmental specialist from a leading innovative pharma (A) explained how they are becoming financially motivated to consider solvent recovery options in the early drug design and development phase. The respondent outlined one example of solvent recovery projects that they have assessed recently. This recovery project was the extension and development of an existing process rather than a new one. The respondent further explained that the return on investment from the project was significant through massive cost savings by purchasing fewer raw materials, or ingredients and solvents, and the payback period for the project was 6 years. The respondent highlighted that though this project was driven by the company's internal environmental target, they are now becoming motivated to consider the solvent recovery process in the early drug development phase for quicker payback period and to enjoy higher return on investment until the patent expires. The respondent has further commented – ***"I guess the main driver is finance and raw materials are relatively cost effective / relatively low compared to our total income; profit margin is generally pretty high"***

As revealed in the study, apart from innovative pharma, a few generic pharma have also become motivated to adopt solvent recycling from potential cost savings opportunities, especially savings from costly disposal of solvent wastes. It was also revealed in the interviews and reports that given the significant amount of generic production volume, inability to recycle wastes solvent adds to the cost of expensive disposal, which ultimately increases the overall cost of production. For instance, one of the respondents (F – site 2) from a leading generic pharma has reported how their manufacturing process is driven by the MET (or green chemistry practices) through highlighting ***"… of course expensive disposal or the inability to recycle a solvent adds to cost but could also be viewed through a green chemistry lens"***

- ✓ ***Cost savings from continuous manufacturing as a driver***

It was also revealed in the interviews and reports that some innovative pharma companies and a few bio pharma have adopted continuous mode of manufacturing driven by the related materials and energy costs savings. As per the interviews, the expected ROI from continuous process is higher than batch. This observation has driven some innovative and a few bio pharma companies to consider continuous manufacturing process in the early process design

and development phase. For instance, one of the bio pharma companies (B – 18) has reported applying continuous API synthesis process driven by materials and energy costs savings. The company has achieved a significant amount of energy and wastes reductions through effective and efficient scale up and down of the process through effective and efficient process calibration. The company has also become motivated to adopt continuous process due to limiting the production of toxic byproducts in the process, which has ultimately reduced disposal costs of hazardous solvents. Another example reported by an innovative pharma (B – site 2) highlights that though the initial investment on adopting continuous manufacturing is high, the expected ROI is considerably more over batch by saving a considerable amount of expensive raw solvents.

- ✓ ***Cost savings via operational efficiency (by means of MET application) as a driver***

It was also revealed that pharma companies from all sectors (innovative, generic and bio) are becoming motivated to adopt more MET or green chemistry related practices to achieve operational efficiency and related costs savings. As per both the interviews and reports, increased reaction throughput, flexible scale up and increased materials and energy efficiency during manufacturing operations enable companies to save costs and promote more green practices. For instance, one of the respondents (F – site 2) from generic pharma outlined that chemical reaction becomes more selective and efficient when they use greener chemicals (e.g., bio-based substances) in the process for reducing reaction times. However, later the company realized massive environmental benefits (e.g., materials reduction, energy reduction) as well as cost saving from reduced usage of raw materials, energy saving and costly disposal. Therefore, the company is expecting to consider more green related activities in the R&D process driven by the cost effectiveness. Also, another innovative pharma (In – 06) reported that its energy efficiency efforts and operational efficiencies have resulted in significant cost savings. The report highlighted that – ***"Our efforts to reduce energy demand through energy conservation and improved operating efficiency have resulted in significant cost savings, which contributes to the company's long-term sustainability"***

It was also evidenced that few other innovative companies are expecting to adopt more green design and manufacturing related practices / projects, such as using greener (e.g., enzyme) chemicals in the process and designing processes to use less energy and raw materials, driven by cost efficiency. For instance, one of the innovative pharma (In – 01) reported such a kind of green project, which aims to save millions of tons of chemicals waste and related raw

materials costs by applying green chemistry technology or MET practices during process development. It has further reported an example drug (e.g., pregabalin) whose process has applied green chemistry related practices, and the process is estimated to save 200,000 metric tons of chemical waste and 3 million tons of carbon emission from 2007 to 2020 depending on production volume and other operational factors.

- ✓ ***Cost savings from waste diversion as a driver***

As evidenced in the interviews and reports, pharma companies have reported significant costs savings from diverting wastes into beneficiary usages. It was confirmed in the study that the majority of innovative pharma in most cases have faced this driver immensely. As revealed in the study, companies are interested in investing in waste diversions practices as they can boost significant cost savings from managing wastes responsibly and innovatively. As emerged from the interviews and reports, many innovative companies have undertaken many such innovative waste management projects such as energy from waste solvents, reuse of less purified solvent in another sector for source of energy, solvent recovery projects etc, which have brought them a significant amount of cost savings. For instance, one of the pharma companies (In – 01) reported on such a project called 'waste to clean equipment'. It was on a target to save over one million dollars in the last year. It has further reported that this project has eliminated the need for expensive high-purity solvents, such as methanol or acetone, to clean equipment. It has produced a high quality recycled solvents mixture which is used to dissolve the leftover residue inside the process equipment as part of the cleaning process.

These cost savings not only drive them to undertake relevant green projects but also this drives their API, Excipient, and other relevant raw materials suppliers to undertake green practices. For instance, one of the respondents (B – site 1) explained the fact that the API suppliers are normally responsible for paying for disposal costs if they fail to supply the product (API) specified in the contract or supply downgraded products. To avoid this disposal penalty, the suppliers also introduced relevant green activities such as internal environmental auditing or off-site solvent recycling to save costs.

There is also enormous evidence in both the interviews and reports that demonstrate how innovative pharma companies are becoming motivated to invest more on waste kaizen projects. For instance, another respondent (A), a senior environmental scientist from an innovative pharma, has also been motivated to undertake a waste kaizen project and stressed that –***"...the environmental savings are really good, we get the financial team involved, they***

are very interested because the payback periods on the projects are identified by audits tends to be … amm ... last year the payback period was two and half years"

Interestingly, generic pharma, having cost focused business strategies, were also not seen to be driven by such cost savings as the trade-off between such cost savings and the cost of regulatory approval for process change is not favourable. Such cost savings were also not seen to drive bio pharma due to the very limited scope of such recovery practice in bio pharma operations.

5.1.3 Top Management Commitment

As revealed in the study, top management commitment and related company-wide environmental strategies play a crucial role for pharma to go green. These drivers are of paramount importance for greening the pharma industry, as these drivers help persuading pharma companies to identify key internal environmental targets requirements and equip them with the necessary resources (e.g., green chemistry training for scientists and chemists) to achieve those environmental targets for the protection of natural resources and the safe use and disposal of their drug substances. There are three sub drivers (shown in Table 5.8) that have been identified in the study. The subsequent section presents the related findings.

Table 5.8 Key sub drivers of top management commitment as emerged in the study (Source: Interviews and Reports).

✓	Internal Environmental target
✓	Community wellbeing and responsibility
✓	Awards and incentives for green innovators

5.1.3.1 Internal Environmental target

Top management commitment on internal environmental targets, measures and improvement play a crucial role to foster green innovation (e.g., green chemistry applications) in the upstream design and development as well as manufacturing phase. As per the majority of the respondents, an environmental goal is set by the top management which then translates into practical implementation over time for achieving overall environmental sustainability. This strategic goal is then translated into departmental objectives. As explained by some of the

respondents, in order to achieve each environmental objective, the companies (especially the innovative ones) assess their existing capability and capacity to equip with the necessary resources (e.g., skilled chemists/technician with green chemistry skills) prior to adopting a particular green practice. For instance, one of the respondents (B – site 1) explained that the company has set a goal of achieving zero percent landfills and promoting more waste to beneficial use practices. This strategic goal was then translated into the departmental objectives such as to achieve 80% beneficial use of wastes from the formulation plants, as highlighted by the respondent. The respondent has also mentioned that to achieve this objective they have undertaken plant wide recycling, reusing and recovery projects, in line with well-defined waste kaizen projects, which have helped them to understand the current situation on waste management levels and have tried to equip themselves with all necessary resources to meet the desired levels.

5.1.3.2 Community wellbeing and corporate responsibility

The study reveals that the majority of the pharma companies have felt ethical and corporate responsibility pressure to go green. The majority of pharma companies have felt huge responsibility for the wider community to rethink how they should manage their products across the lifecycles so that there will be less chance of human and environmental exposure from their operations. The industry has incorporated ethical environmental responsibilities as a new tool of competitive advantage as revealed in the study. As per some of the respondents, corporate responsibility has driven the manufacturers to believe that medicinal products should only be used for human wellbeing, and it should not negatively affect their lives. Bearing this thinking in mind many pharma companies have undertaken both in-house and external consultation to deal with the environmental impact of the drugs products such as wastewater discharged from the manufacturing plants as revealed in the study.

As revealed in the interviews, realizing the importance of considering community wellbeing and good business sense, the majority of the innovative companies investigated have become motivated to undertake many voluntary green measures proactively. For instance, it was evidenced by one of the informants, a senior principal environmental scientist (C) from a leading innovative pharma, that the company's R&D has been driven to undertake green initiatives (e.g., enrich PBT data from ERA tests results) in the early drug design and development phase due to the pressure felt from corporate social responsibility. Interestingly, when the informant was asked whether the Environmental Risk Assessment (ERA) for each

new drug prior to marketing authorization can be a demotivating factor for them as the marketing authorization will not be denied even if the ERA test shows potential environmental concern - the respondent stressed that even if it does not stop their product authorization, they do it for social wellbeing, as their ethical principle is not to harm people and the environment from using their drug products. The respondent continued- ***"... the society has given us a greater responsibility to manage those risks to make sure the society derived the benefit from their medicines without causing any environmental harm or damage; so for us it is a motivation to do more..."***

5.1.3.3 Incentives and awards for green innovations

The study reveals that pharma industry has also become motivated by awards and incentives from both external industrial bodies and internal top management awards to innovate green technologies or related practices. It was also revealed in the study that manufacturing site managers (especially innovative) are rewarded for achieving green project goals set by top management. It has empowered them not only to undertake green projects but also, they considered this type of financial incentive as a green driver as explained by some respondents. The majority of the innovative pharma, some generic and few bio pharma have somehow reported at least one type of award for the green innovators. Table 5.9 presents some examples of related rewards that drive companies to innovate and adopt green practices. For instance, one of the leading innovative pharma (B – site 1) explained how the managers are getting motivated to innovate and adopt green technology. It has reported that each divisional manager is rewarded (monetary and holiday package) for meeting division specific absolute emission reduction targets. The target includes energy efficiency and energy saving targets (e.g., PMI target, waste / emission target etc). Similarly, another company (In – 02) stated that the green innovators were given a trophy and £1000 as part of internal rewards system for green chemistry innovation.

Table 5.9 Example of awards / incentives and related green practice driven (Source: Reports)

Name of External green innovation awards / incentives	Name of Internal green innovation awards / incentives	Reasons for awarded	Key green practice driven	Evidence
European Aluminium Foil Association (EAFA) Alufoil	None	Resource efficiency: Reduce foil consumption by 30%	Green packaging	In – 03

Name of External green innovation awards / incentives	Name of Internal green innovation awards / incentives	Reasons for awarded	Key green practice driven	Evidence
Trophy		and overall pack size by 25%;		
None	Green Chemistry awards	Reduce by product formation from 40, 000 to 29, 000 gallons	Solvent recycling and reusing	In – 01
None	Green chemistry challenge awards	71% of solvent usages reduction for a drug process (Parsabiv)	Materials & related energy reduction using green chemicals	B – 09
None	Supplier Environmental Sustainability award	Reduce packaging	Green packaging	In – 02
State environmental award		Sustainable drug production	Green chemistry	In – 01

Manager or employees who have come up with any new ideas of green innovation are also rewarded. For instance, it was reported (D – site 2) that managers coming up with and implementing the kind of employee behavioural change (e.g., turning machine or manufacturing equipment off while not using, efficiency in chemicals measurements during QC testing etc) are also rewarded. As revealed in the study, none of the generic and bio pharma considered such a driver due to the lack of green investment, comparatively lower environmental commitment, and lack of realizing such green investment.

5.1.4 Market Driver

Stakeholder pressure and company reputation are identified in the study as two market drivers for green operations in the early stage of green design and development. These drivers will not only help the pharma companies to enhance overall green operations in R&D but also improve competitive advantages.

5.1.4.1 Stakeholder pressure

This driver will have significant importance for the pharma business as failing to deal with this pressure could have huge negative impact on returns. It was evidenced from the interviews that upstream R&D operations are facing tremendous pressure from the manufacturers and the downstream customers. It was also evidenced in the interviews that pharma companies (especially the innovators) are facing pressure from downstream customers like the NHS to reduce GHG emission from the products they buy, especially inhaler products which contribute a lot to the atmosphere. For instance, one of the respondents (A) has outlined that this typical stakeholder pressure, especially from downstream customers and investors, has driven them to think of replacing CFC-based inhalers with more environmentally friendly (e.g., HFA) alternatives for lesser impact. The company's R&D is also looking for alternative options to remove fluorinated gases from the inhaler products completely. This is how the stakeholder pressure has driven the company to go for green alternatives.

As identified earlier, the issue of PIE and related AMR has become a serious public health issue. As revealed in the study, the WHO, as well as countries around the globe, are undertaking precautionary approaches to deal with AMR. It was also revealed in the reports that many government and non-government institutions have come together to invest in research and development to protect the possible environmental loading of drugs. In addition, as per interview findings, the public has become more concerned about safe water supply and people are even willing to pay more to wastewater companies for a safe water supply. It was clearly evidenced that these factors collectively have driven the companies (especially innovative ones) to develop in-house ERA teams or to get support from outside consultancies to initiate environmental assessment as early in the process development phase as possible. For instance, one of the leading innovative pharma (In – 08) has stressed on this thread that ***"Stakeholders regarding the presence of pharmaceuticals and personal care products in the environment, and work to advance society's understanding of how these products impact the environment so that we can protect environmental and human health".*** Table 5.10 also presents some key stakeholder pressures that drive pharma companies to adopt related green practices. The table also shows the significance of each pressure as conceptualized from the study.

Table: 5.10 Examples of some key stakeholder pressures that drive pharma to go green (Sources: Interviews and reports)

Stakeholders	Key pressures	Companies' key responses / green practice driven	Significance of the pressures
External Key customer: NHS	Demanding Greener API for reducing environmental footprint from its entire supply chain	-Apply green chemistry in manufacturing -Save energy in packaging & distributors	-creating new (greener) business model
Internal: Board of directors / Investors / top management	Demanding more sustainable pharma operations: combating PIE and AMR	-In house PIE program and API discharge monitoring -Responsible wastewater management	-Development and enriched PBT database which will serve next generation greener drug
Wastewater companies	Demanding safe disposal and management of existing and specially the 'watch list' drugs	-Green use-and-disposal	Lower environmental contamination from vast majority (around 3000) of existing APIs in the market

5.2 Findings on key drivers faced by downstream pharma stakeholders

This section presents the key findings on drivers (emerge in the study) which influence the downstream pharma stakeholders (e.g., pharmacy, GPs, NHS, care homes, waste management companies) who engage with effective and efficient use of drugs, drug waste reductions and appropriate disposal of unused/expired drugs. It also aims to understand the extent of these drivers/pressures faced by each stakeholder – during the drug use and disposal phase. Based on the findings from both interviews and reports, it is clear that though the overall industry-move towards a green drug design and development phase is still between planning to low stage, the reactive green practices during the drug use and disposal phase are of great importance in dealing with PIE and related AMR issues. As identified earlier, inappropriate use and disposal of drugs will accelerate PIE and AMR. So, it would be particularly important to learn from the driving force behind the green related practice adopted in the use and disposal phase, which could later influence other stakeholders through a clear understanding of each driver. A total of 3 drivers have been identified in two main

categories: regulatory and financial. Table 5.11 summarizes the details of each driver identified in the study. Figure 5.2 also shows the extent of each driver in the context.

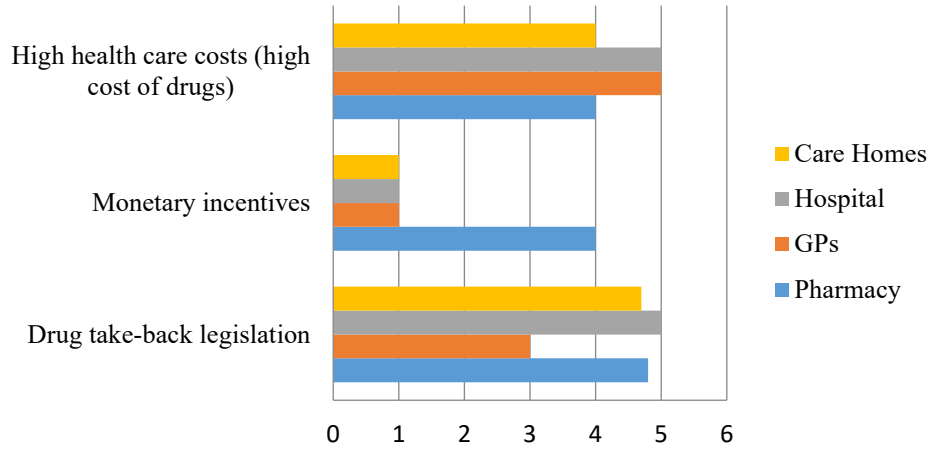
Table 5.11 Summary of key drivers felt by the downstream pharma stakeholders (Source: Interviews and Reports)

Green drivers for downstream pharma		Key drivers and sub drivers faced by the downstream pharma stakeholders and the extent of each driver felt			
Key green drivers	Sub green drivers	Pharmacy	GPs	Hospital (wards & Pharmacy)	Care Homes
Regulatory	Drug take-back legislation	**<u>High</u>** -Pharmacies must take returned drugs (unused/expired/surplus) from patients to ensure safe disposal of drugs via authorized drug waste vendors - Receive warning from independent quality body CQC -Can be banned from operating service due to breach of contract with NHS	**<u>Low</u>** -Low focus on collecting unused drugs where pharmacy is available to take drug return; However, they can also be appointed as main point to take patient return where nearest pharmacy does not have appropriate arrangement -Driven to counsel patient for safe disposal of drugs --Driven to produce patient leaflet	**<u>High</u>** -Feel strong pressure from the NHS trusts to promote patient return as many of them are internally committed to reduce drug wastes -Driven to adopt nationwide campaign to promote patient return for safe disposal of drugs -Driven to produce patient leaflet	**<u>High</u>** --Feel strong pressure from the NHS and external quality assurance (CQC) adviser to promote patient return as part of quality care provision -Responsible to arrange safe disposal of drugs via authorized waste vendor

Green drivers for downstream pharma		Key drivers and sub drivers faced by the downstream pharma stakeholders and the extent of each driver felt			
Key green drivers	Sub green drivers	Pharmacy	GPs	Hospital (wards & Pharmacy)	Care Homes
Financial	Monetary incentives	**<u>Medium</u>** -Pharmacies receive monetary incentives from NHS for each completed medical intervention (e.g., £28 per MUR) -Most of them are motivated to increase number of medical intervention (MUR/NMS) due to achieve more incentives from government	**Not relevant**		

Green drivers for downstream pharma		Key drivers and sub drivers faced by the downstream pharma stakeholders and the extent of each driver felt			
Key green drivers	Sub green drivers	Pharmacy	GPs	Hospital (wards & Pharmacy)	Care Homes
	High health care costs (high cost of drugs)	**Medium** -Pressure from NHS to reduce unnecessary drug wastes -Low level of driver as most of the pharmacists are just adhered to their own SOPs based on quality (CQC) regulation, rather to give more focus on promoting drug waste reduction campaign or any other relevant lean practice.	**High** -Pressure from NHS for effective and efficient prescribing to reduce unnecessary drug waste -Prescribing practice is monitored for optimizing under or over prescribing or wrong prescribing etc	**High** -Strong pressure for reducing healthcare costs -Drug is one of the key costs for NHS -Drug waste itself costs NHS £300 million a year -Driven to adopt trust wide lean practices (e.g., POD, waste campaign etc) to reduce costs	**Medium** -Pressure from NHS to reduce unnecessary drug wastes. -Driven to adopt more medical intervention, use of effective MAR chart etc as per CQC's guidance -Low scopes of promoting drug wastes as they just adhered to service quality standard rather than any lean scheme to reduce drug wastes to save NHS costs

Figure 5.2 The intensity of each driver felt by the downstream stakeholders (based on reports & interviews)



(CCG Report ratings: 1 = Not mentioned / not driven; 2 = Planning to drive; 3 = Low level driven; 4 = Medium level driven; 5 = High Level driven; rating was done based on number of mentions and qualitative judgement for semantic validity of each mentions)

5.2.1 Regulatory Driver

This section presents the findings on how the downstream pharma stakeholders are becoming motivated to undertake effective and efficient practices of drug usages and reducing drug wastes and inappropriate disposal of drugs driven by the relevant legislation. Understanding these drivers are of great importance in dealing with PIE and related AMR issues as well as reducing health care costs. There are two key regulatory drivers that are identified from the downstream stakeholders who are becoming influenced to undertake effective and efficient management practices for reducing drug wastes and protecting inappropriate use and disposal of drugs.

5.2.1.1 Drug take-back legislation

As revealed in the study, a drug take back regulation exists in the UK which requires pharmacies to accept retuned drugs (unused/expired/surplus) from patients or customers to ensure safe disposal of the drugs via authorized drug waste vendors. As per the interviewees, this is one of the key pharmacy care quality areas which is inspected at regular intervals by the relevant regulatory authority called CQC - care quality commission - which oversee the quality of downstream care services including drug dispensing, management and

administration in pharmacies and care homes. In general, CQC does the quality audit twice a year – one is a scheduled audit and another one is a sudden audit as explained by the pharmacy respondents. It was also highlighted by most of the pharmacy managers that not following this legislation could impose a warning for banning the pharmacy service. Because of this, most pharmacies interviewed are providing drug take back facilities to customers/patients. This in turn ensures that unused/expired surplus drugs in patients' homes are adequately and safely disposed of to avoid unexpected environmental contamination of drugs and reduce the impact of PIE and related AMR growth. Table 5.12 shows an overview of the legislation as conceptualized in the study.

Table: 5.12 Key highlights of Drug Take-back regulation in pharma (Source: Interviews and reports)

Key aspects of Drug take-back legislation	
Examples of household drug wastes	✓ Unused / expired drugs in patient home ✓ Unused and unopened (but not expired) surplus drugs in patient home
Key environmental impact of inappropriate disposal of household drug wastes	✓ Environmental contamination of drug substances lead to PIE ✓ Increase the likelihood of AMR growth ✓ Threats to aquatic life and surface water contamination
Key regulatory requirements	✓ Pharmacies must take returned drugs (unused/expired/surplus) from patients / customers to ensure safe disposal of drugs via authorized drug waste vendors. ✓ Pharmacy staff must segregate drugs into solid (including ampoule and vial), liquid and aerosols and store them in a designated area and container as per waste vendor requirement ✓ Pharmacy will only be able to accept patient return for disposal if the local NHS England and NHS Improvement team (e.g., primary care organization) has suitable arrangement for collection and disposal.

Key consequences for not following the regulation	✓ Banned from operating service due to breach of contract with NHS ✓ Receive warning from CQC
Examples of green practice driven	**Green use-and-disposal:** drug take back; effective and efficient drug prescribing

As revealed in the interviews, in light of this legislation, accepting patient return is one of the key services which is legally contracted with the NHS and promised by the pharmacies to serve the community. As per most of the pharmacy respondents, pharmacies ensure successful collection and segregation of unused / expired surplus drugs from patients for safe disposal via authorized drug incinerators. Driven by this legislation, one of the respondents (L) for example stressed that: ***"instead of patients having deal with disposing medication at home in an unsafe manner, we do request them to bring back any medication they have not used so they can be disposed of safely".*** However, remarkably, while pharmacies are bound to accept patient return, there has been a very low level of awareness among the patients about this pharmacy service. It was also evidenced and cross checked with the pharmacy professionals and GPs that very few pharmacy professionals and GPs actually regularly advise the patients and/or consumers about the drug take-back service due to the time restriction during patient service.

5.2.2 Financial Driver

The study reveals two key financial drivers which have clearly driven two key green use-and-disposal practices: patient intervention (MUR/NMS) and drug waste reduction through effective and efficient prescribing and dispensing practice. The next section explains it.

5.2.2.1 Monetary Incentives

The study reveals that the majority of the pharmacies investigated are being motivated by financial incentives for conducting MUR and NMS. Though they also feel responsible and bound to provide this service as part of key pharmacy services, most of them has predominantly highlighted monetary incentive as the key driver. This is because pharmacies receive £28 per MUR conducted with a minimum target of 400 MURs per year, while £20 - £28 is received per completed NMS depending on the percentage of target set by the

government as per the respondents. For instance, one of the pharmacy respondents (K – store 1) outlined that though they can do 2 to 3 MURs a day, they always try to conduct as much MUR per day as possible to hit the target of 400 to get more earnings. The respondent also commented on this driver saying "***…the money does the better, government wants to pay you for 400 but if at the end of year down to 200 you will only get paid for 200"***

In addition to MUR incentives, a few numbers of local CCGs have also offered monetary incentives to save repeat drugs items through generic patient interventions. For instance, one of the local CCGs (CCG – 40) highlighted that they have introduced a scheme called 'no dispensed' scheme for pharmacies which aims to intervene with the patient prior to dispensing repeat prescription and the pharmacist gets paid for this service. For instance, after patient intervention, if pharmacists find a number of items are not needed anymore, the pharmacist gets paid by £4 per drug item plus 10% of the cost of each drug item they do not dispense to the patient. Driven by this incentive, pharmacies within this area have focused more on patient intervention prior to repeat drug dispensing. A similar type of incentivised scheme but with slightly different amounts of incentives has also been applied in another local CCG (CCG – 26) where the pharmacies are offered 45% of the cost of each drug item they do not dispense to the patient.

As came out in the interviews, however, though there is an opportunity to earn via MUR and NMS, the number of cases of MURs / NMS conducted depends on some key factors such as time for patient recruitment and follow-up and interventions, and selecting the right category of patient for the scheme. For instance, one of the respondents (N) mentioned that it requires quality time (e.g., 45 min to 1 hour) for consultation with patients for both objective and subjective assessment for preparing each MUR/NMS report.

Though the category of patients under MUR scheme are known, some pharmacists have highlighted that it is crucially important to target the most vulnerable category of patient, such as patients discharged recently from hospital, to get the most benefit out of the MUR service. For instance, one of the pharmacists (L) explained that this is because medication error is a common phenomenon for those groups of patients who have recently been admitted to hospital and discharged after few days. Therefore, they have targeted post discharge patients first as they are one of the key sources of drug wastes.

5.2.2.2 High Healthcare cost (high costs of drugs)

As came out in the reports, in 2017 the UK health care cost was £197.4 billion which is 9.6% of the country's GDP. It was also reported that in 2013 the cost of medicine exceeded £15 billion, where 1 billion prescription items were dispensed in the UK community pharmacies. Cost effectiveness in drug prescribing and dispensing has become crucial need for NHS, while for example a £300 million per year loss is reported from unused prescription drugs. Given such significant cost pressure on NHS health care, the majority of CCGs or hospital trusts have implemented drug prescribing and dispensing optimization for reducing unnecessary drug wastes. For instance, driven by this cost factor, prescribers' prescribing habits are currently being monitored to identify the scope of effective and efficient prescribing as explained by the GPs interviewed. As per the GP respondents, the prescribing monitoring report has significantly reduced over the counter drugs prescriptions such as paracetamol, cetirizine and typical OTC eye drops, as well reduced other drug usages via prescribing alternative treatments such as physiotherapy or hydropool etc. The reason why drug wastes reduction occurs from limiting OTC drug prescribing is explained by another GP (P). The respondent highlighted that they have records which show that the majority of OTC drugs being prescribed are now valued, unused and not wasted.

As reveal in the study, driven by cost savings from unused drugs, many local CCGs were seen to introduce drug optimization (e.g., POD – use of patient own medicines while staying in hospital) within hospital wards. For instance, one of the CCGs (CCG -36) has introduced a new policy of dispensing for discharged patient. The CCG has audited and experimented over two weeks in a few areas of optimization such as documented number of medicine dispense stopped due to a) re-use of patient's own drugs while admitted in hospital, and b) not dispense drugs upon patient discharge as they have own drugs at home / care home / nursing home. The total savings was £14.4 K in two weeks which would otherwise have been wasted. The projected saving for the CCG is £259.6 worth of drugs waste per year. Driven by costs savings from applying the POD approach, another CCG (CCG – 25) has demonstrated £6500 of costs savings per year from only one ward. The cost savings from POD has also been reflected in one of the respondents' (Q) discussion. The cost of drugs has also driven most CCGs to participate in the nationwide medication waste reduction campaign. This is how the high cost of drugs has driven the local CCGs to reduce drug wastes nationwide as revealed in the study.

5.3 Key Contribution of the Chapter

This chapter has identified some important green drivers and related unique observations which were unknown previously in the context. The unique drivers for the upstream stakeholders identified are: regulatory: (f-gas related regulations; REACH regulations; ERA of drugs; The Waste Regulations 2011; drug take-back legislation), cost savings, top management commitment. These unique drivers and related observations are expected to influence the relevant practitioners and policy makers to greening pharma supply chain. For instance, the unique observation on the intensity of each driver across the stakeholders has clearly indicated us why the innovators are more aggressive in green adoption than others. It became also clear why some stakeholders (e.g., innovators) were driven more by a particular regulation (e.g., REACH / ERA etc) to adopt green than others (e.g., generic, bio pharma) in the context. Additionally, some other interesting and unique observations, such as how some green drivers (e.g., top management commitment / cost savings) have significantly driven innovators to adopt green than other stakeholders, and how some stakeholders (e.g., innovators) are driven to adopt a particular green practice (e.g., CFC free inhalers) than others, have significantly enriched our understanding on the green adoption mechanism in the context. Most importantly, the unique observation of how and why green related design and development activities have been placed as the top priority across the industry (e.g., driven by the ERA regulations) especially among the innovators is significant to deal with PIE and AMR issues for longer term. The enormous evidence of significant cost savings from solvent recycling / recovering related projects will undoubtedly drive the sector to adopt such early process validation to run recovery, especially the generic sector. Being cost focused the generic sector is expected to mimic or redesign many existing drug processes to gain both economic and environmental sustainability. Though drug take-back legislation was not new in the context (Clark et al., 2010; Vollmer et al., 2010), it was never known how such legislation drive the pharmacies and GPs to undertake lean activities (e.g., allocate resources to collect and dispose consumer leftover / unused drugs) to reduce drug wastes and ensure safe disposal. The evidence has also suggested that PIE issue has further accelerated drug take-back related effects. It is also significant that community wellbeing and corporate responsibility have driven the key stakeholders (especially the innovators) to initiate green activities to carb PIE impact. The chapter has also outlined two unique drivers such as monetary incentives and high healthcare costs, which have driven the downstream pharmacy retailers and local CCG. Most importantly, the monetary incentives for undertaking lean

activities (e.g., scopes of drug wastes reduction through medical intervention) identified could be a rudimental change in the downstream pharma operations to go green.

5.4 Chapter Summary

This chapter aimed to answer the second research question in this thesis on green drivers in pharma. This chapter identified key green drivers and related sub drivers for both upstream and downstream stakeholders. It also assessed the extent of each driver felt by individual stakeholder. While innovative pharma has felt more pressure to adopt green, generic and bio pharma have felt comparatively less pressure. Cost savings from green adoption has driven the innovative pharma significantly more than others. Stakeholder pressure was almost equally felt by all stakeholders though innovative was slightly higher. Similarly, in the downstream, two of the drivers - drug take back legislation and high health care costs - were almost equally influenced by all relevant stakeholders with slight deviations. These drivers are crucially important for pharma companies to understand the current situation of green operations in pharma and indicate the future requirements for the sector to go completely green. From a RBV perspective the sector must assess relevant resources, capabilities, and capacities in line with the practices and drivers known already. However, knowledge on related barriers is also crucial. Hence, next chapter presents the findings on green related barriers in pharma sector.

Chapter Six

Findings on Green Barriers in Pharma Sector

Whilst exploring the scope of green drivers across the pharma industry stakeholders, low levels of driving force for green practice implementation in many facets have made it more interesting and important to know about the relevant barriers and how these barriers actually impede the companies to implement green practices. These findings will undoubtedly help the relevant pharma stakeholders to equip themselves with all necessary resources for undertaking green practices. This will not only help the sector to attain a generic green culture but also will provide a built-in green capacity for competitive advantages. Therefore, this chapter attempts to present the findings on each barrier in as much detail as possible. Whilst the relevant literature is still unfertile, this chapter aims to fill the related gaps by presenting and analysing the evidence from both interviews and environmental reports. It also aims to identify and present the intensity or importance of each green barrier faced by different stakeholders in the industry. Therefore, this chapter predominantly aims to answer the third main research question and related two sub questions:

RQ3. What are the barriers faced by individual pharma sector stakeholders for adopting green practices and what isctheir perceived importance?

RQ3.1 what are the barriers faced by upstream pharma sector stakeholders for adopting green design and green manufacturing practices and what is their perceived importance?

RQ3.2 what are the barriers faced by downstream pharma sector stakeholders for adopting green use-and-disposal practices and what is their perceived importance?

6.1 Findings on key green barriers faced by upstream stakeholders for adopting green

This section presents the findings on those factors that impede upstream pharma stakeholders (who engage with design, development, and commercial phase manufacturing activities) from adopting green practices. It also aims to understand the extent of these barriers faced by each stakeholder – innovative pharma, generic and bio pharma - during design, development, and commercial manufacturing operations. It is clear from the previous chapter that though innovative big pharma have taken the lead for greening the upstream design, development and manufacturing phase, an overall industry-move towards accepting and exercising green practices / activities during the drug design and development phase is still in the planning stage, with a lower level of green manufacturing practices. So, it would be particularly important to learn from the challenges the companies faced prior to adopting a green practice. This could later influence the entire industry to take appropriate action in liaison with regulatory bodies and government bodies for greening the pharma industry. A total of 8 barriers have been identified in different categories in the study. Table 6.1 summarizes the key barriers identified and their relevance to the related stakeholders in the investigation. 'Complex marketing authorization process of post-marketing process changes of a drug' and 'higher investment for green process development' are the two top key barriers identified for pharma to go green.

Table 6.1 Summary of key green barriers faced by the upstream pharma stakeholders (Source: Interviews and reports)

<table>
<tr><td colspan="2">Green barriers for upstream pharma</td><td colspan="3">Key stakeholders who faced the barrier to adopt related green practices and the extent of the barrier faced</td></tr>
<tr><td>Key green barriers</td><td>Sub green barriers</td><td>Innovative</td><td>Generic</td><td>Bio pharma</td></tr>
<tr><td rowspan="3">Complex Marketing authorization of green products/process</td><td rowspan="3">Complex marketing authorization process of greener drug (redesigned off patent)</td><td colspan="2"><u>High</u>

-Companies require to obtain new marketing license if they want to streamline the existing drug process (e.g., batch to continuous, solvent recycling etc) for better environmental or any other operational improvement.

-Apply for a new marketing license for an existing drug is a costly, time consuming and uncertain process depending on the level of change</td><td rowspan="2"><u>Low</u>

-The streamlining activities for environmental benefits are rare when the product is already in the market

-assurance of safety of final products to satisfy marketing authorization is a risky investment while thinking of recycling</td></tr>
<tr><td><u>High</u>

-Companies require to obtain new marketing license if they want to streamline the existing drug process (e.g., batch to continuous, solvent recycling etc) for better environmental or any other operational improvement.

-Apply for a new marketing license for an existing drug is a costly, time consuming and uncertain process depending on the level of</td><td><u>High</u>

-confronted with difficult trade-off between product stability and environmental criteria for getting a marketing authorization

-Complex automatic cleaning validation process impedes them to adopt green manufacturing (e.g., to develop continuous</td></tr>
</table>

Green barriers for upstream pharma		Key stakeholders who faced the barrier to adopt related green practices and the extent of the barrier faced		
Key green barriers	Sub green barriers	Innovative	Generic	Bio pharma
		change - companies will again need to go through quality, safety, and efficacy testing of the new modified product/process -Typical marketing authorization in general requires more than two years and cost around couple of hundred million pound -Sometimes need to conduct costly and time-consuming clinical study for demonstrating drug efficacy if there is severe design change in the process - Need to demonstrate reproducibility of the new process including quality of intermediate products or API	/semi-continuous process) --Internal management conflict between scientific teams and quality team; internal quality validation is an initial burden. -Stringent Quality requirement for regulatory approval impeded them from redesigning a process for solvent recovery.	

Green barriers for upstream pharma		Key stakeholders who faced the barrier to adopt related green practices and the extent of the barrier faced		
Key green barriers	Sub green barriers	Innovative	Generic	Bio pharma
		- Need to generate sufficient data on process parameters to demonstrate the level of consistency with approved specification		
Financial	High investment and costs	**<u>Low</u>** -Being innovators the investment in general is significantly high and less competition. Few pharma has felt costly and time-consuming product stability tests impeded them to invest on green packaging -- Some of them felt that the ROI takes different prediction when a process is changed from batch to continuous	**<u>High</u>** -Mostly faced with potential upfront costs for any process changes while cost savings is the key strategy due to fierce competition in the market -- Mostly felt huge capital expenditure for conducting relevant product stability testing to satisfy both internal and external quality requirements for changing process from batch to continuous - Mostly felt retrofitting the equipment (for	**<u>Medium</u>** -Some of them felt expensive operational and equipment engineering requirements -However, many of them adopted low cost technology (e.g., single use technology) to reduce use of chemicals

Green barriers for upstream pharma		Key stakeholders who faced the barrier to adopt related green practices and the extent of the barrier faced		
Key green barriers	Sub green barriers	Innovative	Generic	Bio pharma
			solvent recycling) installation and validation for marketing authorization are more costlier process than initial design, hence unit price goes up -- Mostly felt the long procedure for a process change having no significant cost savings is the key issue for moving to continuous -Few felt that streamline existing process to increase biodegradability require significantly higher investment	
Cultural Issues	Lack of greening culture (Green mindset)	**<u>Low</u>** -Many of them were seen to have innovative mindset to streamline process activities to reduce usage of related resources (e.g., innovate new way of reaction and transformation of substance using MET / green chemistry principle etc)	**<u>High</u>** -Mostly blamed the sceptical behaviour of internal quality team for not adopting green practices -Mostly lacks personal responsibility towards green (e.g., not following solvent	**<u>Medium</u>** -Some of them blamed employees' personal responsibility for not to follow the best practice, e.g., follow right process of chemical measurements etc -Very few of them developed site

Green barriers for upstream pharma		Key stakeholders who faced the barrier to adopt related green practices and the extent of the barrier faced		
Key green barriers	Sub green barriers	Innovative	Generic	Bio pharma
		-Some of them felt fears of external revalidation of process change -Some felt lack of green mindset than costs -Many of them developed site specific chemicals operating procedures	guide, reluctant to segregate waste in the source etc) -Mostly felt fears of external revalidation of process change	specific chemicals operating procedures
Operational Issues	Lack of standardisation in equipment and processes	<u>High</u> -Mostly felt that a solvent recovery process is complex and unique for each process, and therefore, it cannot be replicated across the entire manufacturing sites -Some felt lack of appropriate waste standard across the sites as varieties types of wastes induced from different process	<u>High</u> -Lack of reliability of machines for running continuous manufacturing; achieving reliability is difficult due to the diversified equipment systems in different process; some machines are stand still, some are not. -some equipment for some specific products (e.g., some liquid formulation) are only validated for using manual, and	**<u>Low</u>** -Many of them were seen to adopt standardized operations such as standardized 'single use technology' for delivering varieties of end products

Green barriers for upstream pharma		Key stakeholders who faced the barrier to adopt related green practices and the extent of the barrier faced		
Key green barriers	Sub green barriers	Innovative	Generic	Bio pharma
			cannot be standardized	
	Time to market	High -Mostly felt significant pressure to reduce developmental timeline and as such less time to explore alternative green process development -Felt significant time pressure to market the products due to have limited patent for exclusive sell of the product	High -Mostly felt significant time pressure to market the products due to fierce competition of generic version. As a result, mostly are reluctant to change /modify the existing process for green credentials (low materials/energy/toxicity) as the marketing approval for this change may take more than two years in general apart from the developmental time line. By the time they are afraid of losing market share.	**Medium** -Due to produce very specialized product (e.g., vaccines) they are under serious pressure to meet the market demand as soon as possible; still they do not feel time is such big pressure to develop green process, such as, adopt single use technology, replacing old style operations
	Lack of green related data	**High** -Severely felt the lack of PBT (Persistent, Bioaccumulation, Toxicity) data of the old APIs that already in the market	**Low** -Comparatively lower focus on assessing PIE of APIs; a smaller number of PIE/AMR projects	

Green barriers for upstream pharma		Key stakeholders who faced the barrier to adopt related green practices and the extent of the barrier faced		
Key green barriers	Sub green barriers	Innovative	Generic	Bio pharma
		- Discrepancies on environmental toxicological data from different sources around the world, which has led uncertainties in decision making to deal with PIE/AMR.		
	Lack of environmental education and training	**<u>Low</u>** -Mostly have in house green chemistry team who trains up scientist, chemists, chemical engineers, and related other employees -Dedicated employee education and training for PIE and ERA such as ZAP program	**<u>High</u>** -Mostly train up employees on how to adhere to GMP/GLP/GDP purely rather than focus on green education such as green chemistry education -Low limited focus on PIE/ ERA related education and training	
Market Barriers	Lack of demand of green APIs	**<u>Low</u>** -Still not clearly understood what green measures (e.g., low energy / low materials / low PIE impact etc) the market are looking for -Key downstream customers like NHS has pressurized the innovators to produce green API	**<u>High</u>** Markets for green alternatives (e.g., API with lower energy, materials, toxicity footprint) are limited for generic pharma as low cost is the key focus and markets are not ready to pay for expensive green alternatives	**<u>Low</u>** -Still not clearly understood what green measures (e.g., low energy / low materials / low PIE impact etc) the market are looking for

6.1.1 Marketing authorization of greener products/process

This section explains the key findings on how the marketing authorization process of the redesign of an existing drug process impedes the pharma companies to undertake green practices or optimization activities in the upstream drug design, development, and manufacturing phase. It is crucial to understand these marketing authorization processes and related complex factors so that a two-way green talk can be formed between regulatory bodies and the pharma industry for a successful green transformation. This will help the companies to undertake appropriate green investment decisions. The key barrier identified is the complex and bureaucratic marketing approval process of drugs which are redesigned or optimized (of drugs which are already in the market) for better environmental performance. A detailed account of this aspect is presented below.

6.1.1.1 Complex marketing authorization process of greener drug (redesigned off patent)

Complex and lengthy marketing approval for (post marketing) process change has been identified as a well-established and dominating green barrier across the industry. This barrier was felt immensely by both innovative and generic, rather than bio pharma, as the scope of the post marketing process change in bio pharma were seen to be very rare. The study reveals that post marketing process change is not welcoming at all for the commercial manufacturers in any stakeholder company studied. This is because when a drug substance is approved by a regulatory body (e.g., FDA, MHRA, EMA) for commercial manufacturing, each step of the process of making that drug, including all relevant process equipment, solvent raw materials used and cleaning validation process, are fixed into regulation as explained by the majority of the respondents. It was also revealed in both the interviews and reports that if there is any future developmental change (which is beyond QbD principle) required in any phase of API and/or formulation process, companies will again need to go through quality, safety and efficacy testing of the new modified product/process, and will need to produce related documentation for final marketing approval, which could take more than two years or so, and will need significant amounts of investments depending on the extent of change and the extent of the impact of change on quality. For instance, one of the respondents from generic pharma (F site - 1) highlighted the key challenges of redesigning pharma packaging considering green packaging materials: ***"... if you want to change it would be expensive regulatory submission to get that change made, couple of years of stability work".***

Similarly, some other respondents also highlighted that the companies would really need to be looking at what the pharmaceutical regulatory registration process and related burdens are before they actually go down that route of process change for green credentials.

As revealed in the study, the post marketing process change, in general, can be two types: *low impact change* which does not have significant impact on product quality, safety and efficacy, and *high impact change* which may have significant impact on end product quality, safety and efficacy. The study also reveals that relevant process change (batch to continuous, replacing green solvents etc) from an environmental point of view to reduce materials, energy and toxicity fall under high impact changes, which require both internal quality validation as well as external regulatory validation for marketing authorization. For instance, the study has identified a few case examples (see Table 6.2) of such process change which have significant impact on the quality of redesigned products and require undertaking experimental data to validate the stability and reliability of the redesigned process.

For instance, one of the respondents from innovative pharma (A) outlined that once the drug is designed and gets the approval from FDA, then it's very difficult to change things, especially for the types of changes that have high impact on product quality or reproducibility. For instance, the respondent outlined that the recently proposed change to their inhaler products from CFC-based to liquid HFA-based pressurised meter dosed inhalers could take years to implement and it may cost half a billion dollars to obtain marketing approval again. The respondent has further highlighted into this thread with an example: ***"... ... if we were to trying, for examples change the propellent in the inhaler product which needs to have lower global impact we would need to go back to the regulator, then re tested against the target…"***

It was also revealed in the study that depending on the severity of change, companies may even need to conduct expensive clinical studies for demonstrating the safety and efficacy of newly modified drugs. As per most of the interviewees, once a change for improvement is identified, the producer must convince the internal quality team first by providing related chemical and / or biological lab tests (e.g., stability, pharmacokinetic, pharmacodynamics property, etc) to demonstrate the safety and efficacy of drugs, as well as rationalize the environmental benefits with cost savings. The investigation also revealed that once the internal team (consisting of regulatory, R&D scientists, process chemists, process / formulation engineers, quality managers etc) evaluates and outlines the proposed change,

they apply for regulatory approval by submitting preliminary documents showing all historical laboratory test results with proposed changes outlined.

As per some other respondents, they also need to internally validate each stage of the process, such as cleaning validation, equipment validation, reprocessing of by product validation etc, to submit for regulatory approval. Once the regulator receives the application of change, they conduct their own validation study and inspect the manufacturing site (if necessary), as explained by a few of the respondents. It was also highlighted by some of the respondents from innovative pharma that the regulator could also ask to produce further evidence (based on the type of change), for instance, bio availability testing of the newly modified drugs through clinical trials or packaging stability testing to ensure safety and efficacy. This is how a considerable back and forth exercise is done until final approval, which is a costly and time-consuming process, as revealed in the study. Table 6.2 presents some examples of key post marketing process changes for green credentials. The table also shows marketing authorization related challenges prior to adopting those green practices. It is clear in the table that the revalidation process of an existing drug is a demotivating factor for the companies to redesign the existing process of a drug in order to achieve materials, energy efficiency improvement and/or reduce toxicity in the commercial manufacturing phase. Appendix 18 presents and explains some of the case examples as emerged in the study, such as ***marketing authorization challenges to adopt continuous manufacturing into existing process, marketing authorization challenges to adopt solvent recovery into the existing process, and marketing authorization challenges to adopting green packaging.***

Table 6.2 Key regulatory challenges for post marketing process change (Source: interviews and reports)

Key post marketing process changes for environmental performance	Impact of change on existing product quality, safety, and efficacy	Key marketing authorization challenges	
		To meet Internal validation of change	To meet External regulatory (e.g., FDA, MHRA, EMA) validation of change
Solvent recycling	High	--- Costly and time-consuming	--- Costly and time-consuming

Key post marketing process changes for environmental performance	Impact of change on existing product quality, safety, and efficacy	Key marketing authorization challenges	
		To meet Internal validation of change	To meet External regulatory (e.g., FDA, MHRA, EMA) validation of change
		process to: • Agree on proposed process changes upon inter departmental agreement • Devote extra resources to outline and justify proposed process change by producing substantial amount of process knowledge • Assess the impact of proposed change --- clash and disagreements between quality assurance team and process operations to accept green related change – where quality is of paramount importance	process to: • Validate method of production, method of testing etc • Demonstrate reproducibility of the new process including quality of intermediate products or API • Generate sufficient data on process parameters to demonstrate the level of consistency with approved specification • Conduct stability tests for packaging materials • Safety and efficacy test (e.g., clinical trial if required) • Exchange (back and forth) info and data on lab and/or pilot study --- uncertainty in the types of test/study and documents required --- uncertainty in cost and time required as companies do not have upfront cost and time assessment until it is approved --- complexity in the requirements of process documents when producers and customers operate in different countries, as the change may have impact on the market it sells due to have different regulatory requirements
Batch to continuous manufacturing	High		
Replace with greener solvents	High		
Upgrade with greener packaging materials	High		

6.1.2 Financial Barrier: higher investment and costs

As revealed in the study, the higher investment requirements and related decisions for green technology have emerged as another key barrier for the pharma sector for implementing green practices. This barrier has also helped us to understand why there is less green practice adoption, especially in the generic sector, though there is proven indication of cost saving via environmental savings. It was revealed in the study that investment becomes higher predominantly due to increased cost of green production. It was also found that green investment decisions becomes weaker along with the uncertainty of process changes and regulatory approval. Understanding the related barriers ensure the appropriate remedy arrangements by the relevant stakeholders to adopt green practices. The next section presents the findings in detail to understand different scenarios of how higher investment impedes green operations.

6.1.2.1 Higher investment

The study reveals that the pharma sector (predominantly generic) is still not confident enough to invest in green technology due to the higher financial investment associated with the costly production process and investment uncertainty in the complex regulatory validation process for modified process. Almost all the generic pharma interviewed reported this barrier while a few innovative pharma (who also run generic production) also reported it. It was revealed in the study that while generic production facilities are well aware of which of their processes are resource exhaustive and require optimization and/or streamlining activities (e.g., solvent recycling), financial/cost modelling for process change is not always justifiable. This is because cost is paramount for generic production to serve its customers with a drug with lowest possible price to stay competitive in the market. So, it is important for them not only to identify the potential upfront costs for any process changes but also to be certain to an extent of the payback period for each process development. For instance, one of the respondents (C) highlighted that the financial part for a generic drug is very tight and there is little room for the generic plant to invest a couple of hundred millions of dollars to make a process change for green credentials. The respondent added : ***"… there is little to motivate because the cost, the financial model for it don't really supportive"***

The study reveals two strong such cases where high investment has impeded the generic companies to adopt green. They are presented below in detail to enrich our understanding of this green barrier.

Case example 01: Higher investment required for moving to continuous

As revealed in the interviews, the ROI makes a different prediction when a process is changed from batch to continuous. Though generic pharma companies could justify the ROI based on cost savings from less energy, less raw materials use, less water, less carbon etc, the long procedure for a process change having no significant cost savings is the key issue for moving to continuous, as explained some of the respondents. Hence, top management is not confident and convinced to invest in this type of change.

There were many such case examples that emerged in the study which helped us to understand the severity of the barrier. For instance, one of the respondents (F – site 2) from a leading generic pharma has also highlighted that changing the manufacturing process from batch to continuous involve a lot of capital expenditure for conducting relevant product stability testing to satisfy both internal and external quality requirements. Another generic pharm respondent (F – site 1) has also highlighted that converting batch to continuous by developing a bio-based process (e.g., process designed with bio catalysis) requires huge investment. The respondent further explained that biologics or bio based processes cannot be possible for everything, rather a bio based production depends on the type of disease, type of mechanism and largely depends on the capability of capital investments, as it is hugely expensive. The respondent has also given an example of a steroid injective (non-bio-based production) which costs only £50, while a similar biologic one costs £1000.

Case example 02: Higher investment requirement for solvent recycling

The study also reveals that companies (predominantly generic) have felt particularly that the process of solvent recovery is significantly expensive and they see it as an uncertain investment. Though generic pharma sees potential environmental savings from adopting solvent recovery, the nature of higher and risky investment has impeded them to adopt it, as revealed in the interviews. One of the key reasons that emerged for this higher investment is the challenges of retrofitting process equipment within the existing process design, or, alternatively, investing separately on a new plant and for new process equipment to be installed for the purpose of solvent recovery. For instance, some of the respondents (e.g., A and G) highlighted the key challenges of solvent recycling adoption on their existing manufacturing facilities. They have outlined that the payback period for a recovery project is high - 6 to 7 years, takes longer time to be implemented, takes lots of staff hours, expensive new machineries and process equipment to be retrofitted – so that is a longer term driven business.

As revealed in the study, some innovative pharma has also felt this barrier immensely as they have not explored the recycling options in the early R&D phase. It reveals that during the R&D phase, companies predominantly focus on shortening the lead time to the market to allow them achieving more return due to the limited patent of the product. This leads them to not taking any proactive green measures (or process streamlining activities) in the early design and developmental phase. Hence, when the drug goes under commercial manufacturing, they realize the production process uses lots of energy, lots of materials, lots of waters, etc and there could be scope for streamlining the process, as explained by some of the respondents.

Later, they reactively respond to streamline the process, for instance, working towards retrofitting the equipment, which is a more costly process. For instance, one of the respondents (B – site 2) outlined that though they have fixed resource investment every year for retrofitting old process equipment, the knowledge of each new process developed is limited in the initial R&D phase to identify the scope of solvent recycling in the early phase. Hence, they are confronted with expensive retrofitting in the later stage of commercial manufacturing when the impact of solvent recycling on process quality is better understood. The issue of retrofit is also highlighted in some of the company reports such as (In – 05).

So, given the cost focused environment across generic pharma operations, it was found that the cheapest technology which delivers the appropriate level of quality for the application will win out in order to stay competitive, rather than choosing expensive green pharma innovation. For instance, one of the respondents (F – site 2) also stressed the extent of this driver: ***"... ... cost is not so important until that product is realised in generic off parent form where cost is paramount as is purity. Again, cheapest tech wins regardless of green credentials... ..."***

It was also clearly evidenced in the interviews that generic pharma faced high costs for green production. Most of the respondents highlighted that green manufacturing-based products in general will be costly. Some of the generic manufacturers also highlight that if they try to buy from green processes or green suppliers (of APIs) and consider their foot print in their manufacturing – their company could do it to go completely green as a manufacturer, but the product price will become too high. For instance, a key respondent (G) from a generic pharma, who is responsible for managing a liquid formulation plant, explained that the cost also includes the revalidation or regulatory approval of the process. Another respondent (E –

site 3), a senior supply chain leader from a generic pharma, also highlighted that the revalidation of process through related lab testing costs lots of money and therefore they do not do it. The respondent added: ***"... it is very rare to change something unless you need them to; for new product, yes, there is a possibility but for the existing product no - there is huge challenge"***

6.1.3 Cultural issues

As revealed in the study, the concept of green culture within an organizational setting entails how simply having a green attitude or environmental mindset within departments encourages a green culture. It plays an important role for adopting green through developing and transforming personal environmental initiatives across the company.

6.1.3.1 Lack of employee's green mindset

The diffusion of green culture across the industry is still slow. As per some respondents, the departmental green mindsets from R&D scientists to manufacturing managers are crucial for effective implementation of MET practice. Though different operational areas (e.g., R&D, API plant, formulation site etc) across the companies demonstrate differently on how lack of personal green mindset affects overall green adoption, some of the key common challenges that came out in the study was that of 'dealing with shaping employee behaviour to go green', and 'lack of personal responsibility towards green was a key issue in the study'. That means the key challenge is that though employees across the plant keep learning and being educated on how and what to do to become efficient and effective in terms of using the resources from their own job role, it is one of the more difficult tasks to modify employees' behaviour in practice, such as segregation of wastes incorrectly, inappropriate and careless chemicals measuring (manual), not following solvent selection guides etc, as explained by a few of the respondents (e.g., G, F- site 1) in the study. Though the employees are given appropriate training for the packaging segregation process, they still make mistakes frequently as they are still reluctant to take personal responsibility for green operations such as packaging waste management as revealed in the study (e.g., E – site 1). This cultural fact was particularly highlighted by one of the respondents (J – 1) from a bio pharma that –***"… the main challenges obviously to train up the people and making them aware like how they discard waste and how to utilise the right amount of chemicals in different practices"***

It was also revealed in the interviews that some generic pharma, on the other hand, have also blamed the sceptical behaviour of the internal quality team for not adopting green practices. As per a few of the respondents, the sceptical behaviour of the quality assurance team concerning process change (e.g., batch to continuous) is one of the key barriers for the production employees to innovate and adopt green practice. The interviews also reveal that though it is critical for the quality assurance team to validate each and every single step of manufacturing in line with production specification, their sceptical mindset merely focuses on traditional internal quality validation rather than motivating the process employee towards green innovation.

For instance, one of the respondents (G) mentioned that the internal quality team always has a conservative type of mindset for not wanting to use recycled materials in the process. This kind of conservative mindset towards a greening approach is due to the stringent regulatory requirements for quality and efficacy of the products, as explained by the respondent: ***"... the challenges would be working with our quality assurance people assuring the quality of recycling or reusing solvent is high enough so we enter the process".***

The reason for this typical mindset or sceptical behaviour of the internal quality team is based on a belief – *fears of external revalidation of process change*. It was clear from the interview that a majority of (five out of seven) respondents from generic and almost half (three out of seven) of the respondents from innovative pharma have indicated the existence of this kind of fear mindset. For instance, one of the respondents from a generic pharma (G) highlighted that they inherently (by sceptical belief) do not want to take the risks of process change, as the revalidation of a retrofitted process is complex, long, and involve a series of costly testing. The fear of accepting a process change for green credentials and the reason behind this have also been stressed by a few other respondents (e.g., H). They outlined that they cannot change their manufacturing specification after regulatory approval, so there is less scope for redesigning process or formulation. One of the respondents (E – site 3) also provided a sceptical comment into this topic saying: ***"… the only way you could think about the environment is to minimize the waste - this is the only focus you could do as it would be very difficult for you to redesign process specification".***

It also emerged from the interviews that some companies (e.g., H) were struggling to bring a unified wastewater incineration process in all their sites across the globe. However, some local areas show sceptical behaviour towards waste processing such as the idea that

incineration might pollute more than landfill; furthermore, a few of them were afraid of increasing toxicity (e.g., formation of dioxin) from waste incineration.

6.1.4 Operational issues

Whether green practices adoption is operationally viable was one of the key concerns among the pharma companies regardless of innovative, generic, and bio-based production, as revealed from the investigation. Identifying and understanding these operational barriers is the key to greening the pharma sector through increasing green related resources, capacity, and capability. It will also help the regulatory bodies to become aware of the issues and reform regulatory framework to open a new avenue between regulatory bodies and pharma industries to nurture a green culture. As seen in Table 6.1, five key operational issues were identified in the study, which are presented in the subsequent sections.

As each drug process is unique in terms of producing final products (including byproducts), different types of equipment settings are required. As revealed in the study, this typical diversified need of equipment installation and raw materials requirements lead to operational inefficiencies for promoting green in the facility. There are two key challenges that are identified in the study: *lack of standardized equipment and engineering* and *lack of standardized waste kaizen.* The next section presents them.

6.1.4.1 Lack of standardized equipment and engineering

As per the findings in the interviews and reports, this barrier explains how and to what extent pharma companies have faced challenges in installing related process equipment for environmental benefits. It was revealed that companies (especially innovative and generic pharma) have faced this challenge prior to adopting solvent recovery and continuous manufacturing practice. As per the interviews, a solvent recovery process is complex and unique for each process, and therefore, it cannot be replicated across the entire manufacturing sites. Some of the respondents highlight that the process is different for every drug and the solvents involved in each process are also different. Therefore, for the engineering, the equipment settings needed to separate these solvents is different as explained by the majority of the respondents. For instance, one of the respondents (A) has highlighted that as the majority of the process equipment installation in their facility is retrofitted, it is expensive, time consuming, complex and diversified engineering work. The complexities of retrofitting

of existing process for solvent recovery was also evidenced in one of the environmental reports published by an innovative pharma (In -05).

This barrier has also been faced by some generic companies while looking for options to move to continuous manufacturing. As per the interviewees, the viability of continuous manufacturing to obtain the maximum efficiency and effectiveness out of the machineries will largely depend on the reliability of the machine. For instance, some machines do not allow standstill and if it stands still it may switch off and it may have downside problems. Some of the respondents also highlighted that routine maintenance is also a challenge for continuous manufacturing. It was also reported that energy performance from continuous process will largely depend on the reliability of the machinery. For instance, one of the respondents (G) from a liquid formulation plant was concerned about the continuity of the machine for running continuous manufacturing and highlighted that ***"... if you have quality technician and engineer they confirm you keep running; if the engineer and technician don't know if any adjustment is required but do not know why - it potentially impact the continuity of the machine"***

Additionally, it was also revealed in the study that installing automatic equipment cleaning as part of the continuous liquid formulation process is also a challenge. As per a few informants, though the automatic equipment cleaning process is eco-friendlier and more reliable than the manual one, certain products need to be validated for only manual. For instance, it was stressed by one of the respondents (G) that ***"…automatic equipment cleaning is more eco-friendly than manual but there is a validation issue you can't just use automatic for all types of products"*** However, the manual cleaning process is easier to control but taking measurement (e.g., measure 50 litres) is a challenge, and there could be some variability in measurements of solvents / chemicals which may incur lots of wastes, as explained by the respondent.

6.1.4.2 Lack of standardized waste kaizen

It was revealed in the study that whilst the waste kaizen programs are in place to continuously seek the opportunity to reduce wastes from the process, it is becoming difficult to manage the site waste due to the lack of appropriate waste standards across the sites. This barrier was felt by both generic and innovative pharma. As revealed in the interviews and reports (e.g., Gn – 10; In – 03; respondent A etc), pharma companies (especially generic and innovative) are struggling to manage process wide site wastes due to the varieties of types of wastes induced

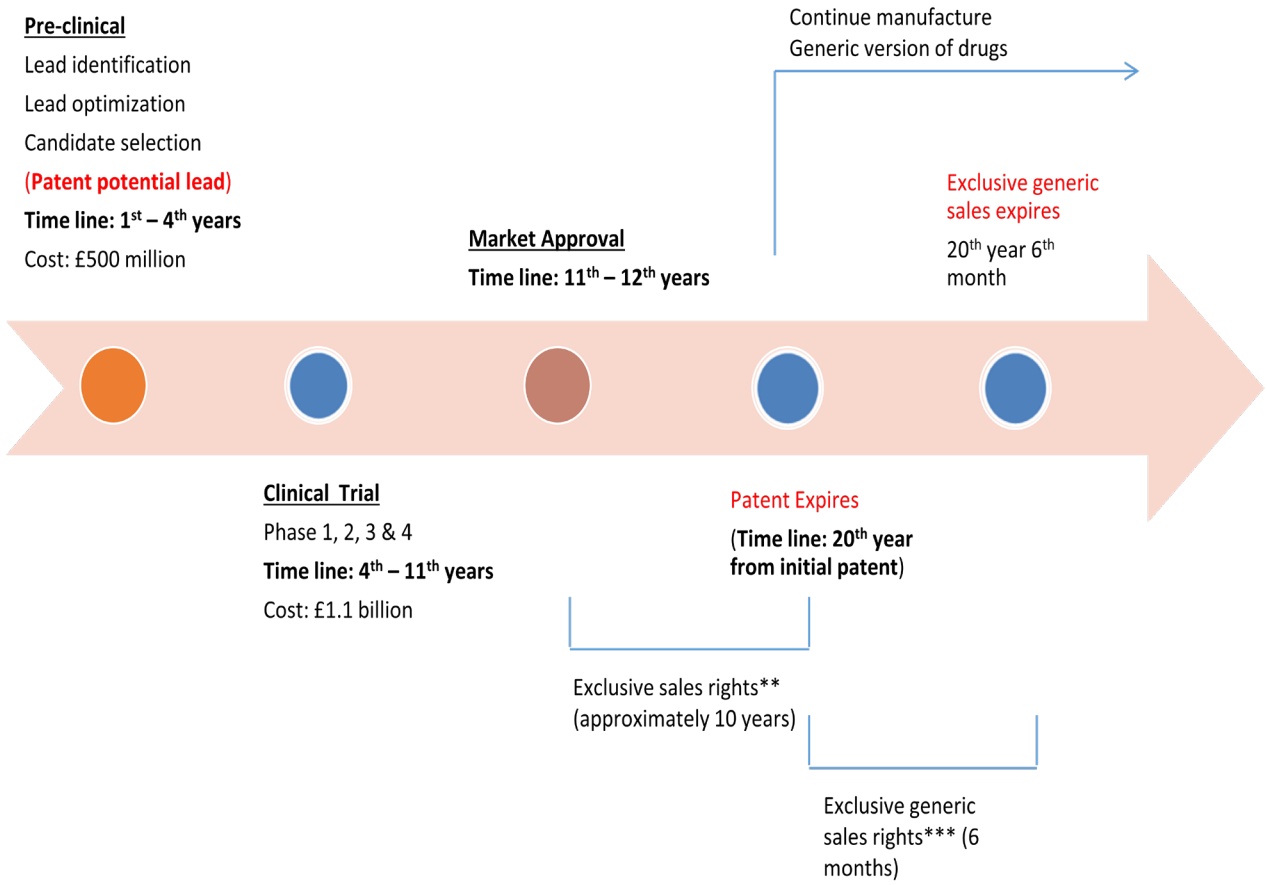
from different processes. Almost half of the (three out of seven) respondents from innovative pharma outlined this barrier. For instance, one of the respondents (A), a senior environmental scientist from a leading innovative pharma, explained that like utility measures they wanted to introduce a standardized measure for process waste efficiency across the production lines by applying waste kaizen. The respondent further went on saying that it was difficult to come up with such standardized measures for wastes within a manufacturing site, as different production lines produce different kinds of wastes. For instance, one line may be just for packaging of peel, which produces inhaler parts, and other line produce API wastes etc, which are extremely different varieties of sources of wastes. So, there is no hard or fast rule how they apply learning across the sites for a standardized kaizen like utility, as outlined by the respondent. The respondent has further added to this thread highlighting "***... waste is much more difficult challenge as utilities systems are fairly standardized no matter what kind of products you are producing ...***"

As revealed in the study, the challenge is how to measure kaizen waste within a specific production line. As per some respondents, this is due to the lack of understanding of the process specific (or even batch specific) waste data. Historically companies measure site level waste rather than specific production lines, explained by the respondents. Companies are now trying to move towards better data so they understand the specific production line and, so they can understand the volume of waste they produce and they can understand this in the production level to reduce and optimise a process. That is what they are developing. But it is quite challenging for the industry as revealed in the study.

6.1.4.3 Time to market

As seen in Table 6.1, this barrier was mostly felt by the innovative and generic pharma, where bio pharma felt it moderately. As revealed in the study and discussed before, innovative pharma companies have exclusive rights to sell a new product until the patent protection expires, which is normally twenty years. But they take normally 10 to 12 years to launch the product in the market from the early design and development phase. It was also becoming clear in the interviews and reports that when the patents expire, the first generic company who successfully produces the off-patent drug also get 6 months of exclusive sales rights. Figure 6.1 below shows the detailed timeline for a typical innovative drug development, with patented and exclusive sales rights as conceptualized from the findings. It was also clear in the report that drugs are mostly patented in the lead identification stage (2nd

– 3rd year of development) when the lead shows a potential effect to manipulate the targeted disease. Generally, a patent is given for 20 years. So, reducing the developmental timeline is crucial to launching a product as quickly as possible, as revealed in the study.



**Exclusive sales rights = (Patent expires – total drug developmental time)

***Exclusive generic sales right = First generic manufacturer will have six month exclusive sales right

Figure 6.1 Drug developmental timeline and related costs (Source: Interviews and reports)

Given such time pressure, innovative pharma always has a tendency to reduce the developmental timeline to enjoy more sales as highlighted by the majority of the respondents. Time has been sought as one of the crucial barriers for the innovative pharma companies to focus on green related practices in the early design and developmental phase, as revealed from the investigation. The majority of the respondents (five out of seven) from innovative companies highlighted this barrier. Identifying and understanding this barrier is equally important for both pharma companies and regulators to adopt more green practices in the design and developmental phase.

Real-life case examples can help us to understand how this barrier has impeded both innovative and generic pharma to adopt green practices. For instance, one of the respondents (A), a senior environmental scientist from a leading innovative pharma, explained this barrier. The respondent has faced tremendous pressure to develop the new product as quickly as possible to reduce the overall developmental time frame. The respondent has further outlined that once the drug gets marketing approval, they have to move very fast from approval to commercial scaling up to meet the demand. The respondent has also highlighted that they may have only 15 years in which they can sell their products, while they have already spent 8 to 10 years developing their product and have already spent half a billion dollars on the product.

Given that scenario, the focus is on reducing the overall developmental timeframe and, especially, reducing the time between the lab scale manufacturing process and scaling up for commercial manufacturing. Due to this time constraint there is no other intervention, such as further developing the process for solvent recovery or solvent recycling or other means of streamlining activities, which may have hampered them to hit the sales target, as the patent clock already started ticking, as revealed by some of the respondents.

It is also important to note here that respondents have also faced this barrier during developing the existing process for green credentials; for instance, they had to wait more than two years to get regulatory approval, as revealed in the interviews. For instance, another respondent (C) from a leading innovative pharma stressed that –***"... there is difficulty of ensuring low environmental footprint in the developmental phase as the pressure being on to developed the product quickly in the market".*** So, it was clear in the study that sometimes it does not lead to an opportunity to focus on solvent recovery, for example in the production process and then retrofitting, as related risks and actions day to day are more expensive.

This barrier has also been faced by generic pharma and more than half (four out of seven) respondents identified time as a crucial barrier for developing the existing process. This is because most of the process changes for green adoption require external quality validation and regulatory approval. As per a few respondents, the regulatory approval process for newly modified processes for green credentials (e.g., solvent recovery, continuous manufacturing etc) is too long. But supply of drugs to market on time is crucial as the majority (around 85%) of the drug markets demand is filled by generic drugs, as highlighted by a number of the respondents. It was further highlighted by them that there is fierce competition among generic

pharma companies to be the number one to formulate the off-patent drug successfully. For instance, one of the respondents (E – site 3) highlighted that longer waiting time (e.g., more than a year) is one of the barriers for them to decide not to redesign existing process for improved environmental performance.

Interestingly, though bio pharma is also under serious pressure to reduce the timeline to market the bio-based products, they do not feel 'time' as such big barrier as felt by other stakeholders. As per the interviews, most of the bio pharma respondents believe that if environmental measures are already in place during process development and/or operations, time is not such big factor to deliver green objectives. They have also highlighted that though time is crucial to deliver lifesaving vaccines to meet the market demand, the manufacturing process still can be standardized and streamlined from existing process, such as use of single-use technology to reduce significant amounts of chemicals usages from bio pharma operations.

6.1.4.4 Lack of green related data

As revealed in the study, it is vitally important to learn from PBT (Persistence, Bioaccumulation and Toxicity) data of the drug substances in the environment for better management of the potential negative environmental impact of a drugs substance. Lack of this PBT data has been a key barrier for most of the innovative pharma for managing the issue of PIE, though the necessity of it was felt less by generic and bio pharma due to having a low focus in PIE. For instance, it was evidenced from one of the interviews (C) with a leading innovative pharma that the lack of PBT-related data availability is one of the key barriers for making environmental decisions (e.g., API discharge limit from the manufacturing plant) on a drug substance. The respondent has further explained that if they have an interest in older generic drugs, they cannot see what data is there and they quite often end up repeating environmental toxicology studies, which would be a waste of resources, waste of animals quite often, in testing them.

It was also highlighted in the interviews that there is a shortage of environmental toxicological data for those drugs registered before 2006, though there will be long term environmental toxicological data available for those drugs registered after 2006. So, it would be very difficult to make an environmental decision based on two different data sets, as explained by one of the respondents (C). The respondent has also highlighted the discrepancies on environmental toxicological data from different sources around the world,

which has led to uncertainties in decision making. The strength of this issue can also be realized by highlighting the respondent's comments on this thread –***"... so how you can compare two very different data sets you try to make a decision on environment which is not easy; like you are comparing apple and pears".*** So, the companies are not comparing similar data sets. Likewise, it was also highlighted in the study that all the environmental fate studies they carried out on the drugs were on different sewage, and different sludge around the world, so there are lots of uncertainties when the companies try to bring some of the environmental decision data.

6.1.4.5 Lack of environmental education and training

The study reveals that green awareness still very low in general among employees due to the lack of environmental education. This barrier has predominantly been faced by the generic and bio pharma as some of the innovative pharma have adopted many voluntary initiatives to educate employees (e.g., green chemistry training) for sustainable pharma manufacturing. Assessment of this barrier will help the industry players to adopt more environmental education and supply more environmental training for increasing green awareness, which will ultimately attain a green culture across the industry.

As revealed in the study, the industry in general has predominantly focused on 'quality management' related education and training to adhere with GMP or GLP or GDP and has paid very little attention to promoting environmental education among the employees across different departments within a company. It is revealed in the study that there is ongoing environmental training, such as training on PIE and/or ERA across the industry, especially in the innovative sector. There is a significant lack of training / educational needs (especially among the generic and bio pharma sector) for improving general environmental awareness, and more importantly for increasing the knowledge of applying green chemistry principles, which has been the foundation of green pharma.

For instance, one of the respondents (B – site 1) attributed the related training and education (e.g., ZAP program) for the success of Zero API discharge from the API suppliers' plant. Similarly, another influential example can be cited here. It was reported (In – 09) that environmental education has increased green purchasing by 32.6% withing a year. As per the findings, unfortunately, this kind of approach in the generic pharma is significantly low due to the cost focus nature of business and adherence to GMP. For instance, one of the generic companies (Gn – 15) reported that they have periodic training and education for employees to

ensure they are qualified and experienced to deal with GMP requirements. There is not that kind of focus for environmental or MET education and training programs for employees to develop their green manufacturing opportunity as indicated by another respondent (E – site 1) from a generic pharma.

The study also reveals that almost half (four out of seven) of the respondents from innovative companies, a very low (two out of seven) level of respondents from generic pharma and none of the bio pharma respondents were aware of the application of green chemistry principles or MET practice in pharma development and operations. It was also evidenced from the report that generic pharma and bio pharma are still far away from adopting environmental education and training compared to innovative pharma. It is revealed from the report that more than half of the generic and almost half of the bio pharma have indicated a further need for related environmental 'education and/or training'.

6.1.5 Market Barriers

As revealed in the study, though the industry has felt a low to medium level of stakeholder pressure for overall green adoption (especially PIE related), generic pharma has particularly faced this barrier to promoting green chemistry related practices. It emerged in the interviews that while generic drug development and production is crucially under pressure due to cost and competition, green chemistry or MET practices adoption is challenging. Though to very low extent, the lack of market demand for green products has been faced by the generic pharma as one of the barriers for not promoting green practices, as revealed in the study. For instance, one of the respondents (F – site 2) highlighted that markets for green alternatives (e.g., API with lower energy, materials, toxicity footprint) are limited for generic pharma. For instance, running continuous manufacturing to save energy, raw materials and toxicity will be a very costly process for those products with lower volume and very tight specification. As per a few other respondents, however, even when the production volume is high, the process validation (external regulatory) for changing manufacturing mode is costly and time consuming, which ultimately increases the production costs. And markets are not ready to pay for expensive green alternatives.

It was also found in the interviews that the product life cycle of a generic drug is highly uncertain due to fierce cost competition and frequent development of generic versions by companies for higher quality (in terms of patient safety, efficacy, lowest side effect, effective healing etc) with lower costs. Some of the respondents also raised their concerns about

whether the customer is ready to pay extra for green alternatives. It was highlighted by one of the respondents (G), for instance, while the downstream customer like the NHS is keen to purchase green API (with main focus on carbon footprint), at the same time they are also under pressure to focus on low cost generic drugs due to constrained health care budgets. So, the market for green drugs is still volatile for the generic sector as highlighted in the interviews.

6.2 Findings on key barriers faced by downstream stakeholder for adopting green

This section presents the findings on key barriers faced by the downstream pharma stakeholders to adopt related green practices during the drug use and disposal phase. It also aims to understand the extent of these barriers faced by each stakeholder – pharmacy, GPs, hospital, and care homes during the drug use-and-disposal phase. It is clear in the study that all green efforts in the downstream use and disposal phase will potentially reduce environmental loading of drug substances from drug prescriptions, dispensing, usages and disposal options used. So, it would be particularly important to learn from the challenges the downstream stakeholders faced prior to adopting an effective management practice for appropriate prescribing, dispensing, usages and disposal of drugs. This could later on influence the entire industry to take appropriate action in liaison with regulatory bodies and government bodies for greening the pharma use-and-disposal phase for avoiding not only catastrophic environmental and human loss (e.g., PIE, AMR) but also related huge economic loss. Three key barriers have been identified under the operational and regulatory category. Table 6.3 summarize the key barriers identified and their relevance to the related stakeholders in the investigation.

Table 6.3 Summary of key barriers faced by the downstream pharma stakeholders to adopt green use and disposal practices (Source: Interviews and Reports)

Green barriers for downstream pharma		Key stakeholders who faced the barrier to adopt related green practices and the extent of the barrier faced			
Key green barriers	Sub green barriers	Pharmacy	GPs	Care homes	Local Councils /waste vendors
Operational	*Uncontrolled drug wastes from high concerned patient groups*	**<u>High</u>** - Mostly faced severe challenges to manage prescriptions, dispensing and administer for three group of patients: patient in end of life care, patient with dementia and patient with multiple morbidity - Patient in end of life care: frequent hospital admissions and lack of communication between departments induce drug wastes; lots of drug interactions and frequent prescription changes occurs which lead to unused drug wastes at the end - Severe drug non-adherence among dementia patients; gets worse if not supervised - Severe non-adherence was due to mainly actual adverse drug interactions or due to a fear of drug interaction and related side effects among the patients with multiple morbidity			Not relevant
	Lack of performance measures of patient interventions scheme (e.g., NMS/MUR)	**<u>High</u>** - Mostly concerned about the lack of performance measures from medical intervention services (e.g., MUR/NMS) which could be further developed /promoted and motivated to reduce drug wastes		Not directly felt it but similar experiences felt via community pharmacists /GPs served in care homes	Not relevant

Green barriers for downstream pharma		Key stakeholders who faced the barrier to adopt related green practices and the extent of the barrier faced			
Key green barriers	Sub green barriers	Pharmacy	GPs	Care homes	Local Councils /waste vendors
	Barriers of getting patient's consent for conducting medical intervention (e.g., MUR/NMS)	**<u>Medium</u>** -Some felt challenges to conduct MUR/NMS or similar medical interventions with house bound patients (e.g., patient in care homes / prisons) as it involves extra admin works (e.g., DBS clearance, consent from patients etc); mostly the patient not agreed to give consent to conduct such medical interventions		Not directly felt it but similar experiences felt via community pharmacists / GPs served in care homes	Not relevant
	Time constraints	High -Pharmacists under pressures to maintain routine screening prescriptions, checking formulations and dispense medicines to ensure safe use of	High -Faced time pressure to serve each patient within an allocated time, which left with no to less time to focus on routine medical interventions with the patients to	Not directly felt it but similar experiences felt via community pharmacists /GPs served in care homes	Not relevant

Green barriers for downstream pharma		Key stakeholders who faced the barrier to adopt related green practices and the extent of the barrier faced			
Key green barriers	Sub green barriers	Pharmacy	GPs	Care homes	Local Councils /waste vendors
		drugs, which left less time to conduct medical interventions to ensure effective use of drugs by patients - Time required for each MUR (thirty minutes to forty minutes) is a challenge to maintain with other administrative tasks.	check the effective use of drugs and not stockpiling by patients		
Regulatory	Lack of regulatory guidance on environmental consideration in prescribing	Not relevant as majority of pharmacy deals with dispensing with very low scope of prescribing	High -No clear guidance on NICE how to select a drug for a patient (whenever possible) for possible lower excretion rate to reduce potential environmental loading of API via patient normal excretion - no clear guidance if GPs should consider alternative (when	Not relevant	

Green barriers for downstream pharma		Key stakeholders who faced the barrier to adopt related green practices and the extent of the barrier faced			
Key green barriers	Sub green barriers	Pharmacy	GPs	Care homes	Local Councils /waste vendors
			possible) drug prescribing considering excretion profile -Patient safety and environmental criteria (e.g., excretion rate) sometimes cannot be aligned - Felt lack of proactive regulation for painkiller prescribing considering the environmental loadings of drugs (e.g., rank of drug based on environmental toxicity which has already been proven, such as birth control pill) -Felt fear of *defensive medicine (*where GP must be defended why) to prescribe alternative medicines (e.g., exercise, hydro pool, horticulture etc) to reduce		

Green barriers for downstream pharma		Key stakeholders who faced the barrier to adopt related green practices and the extent of the barrier faced			
Key green barriers	Sub green barriers	Pharmacy	GPs	Care homes	Local Councils /waste vendors
			environmental load of drugs		
	Contradictory regulatory guidance for disposing unused/expired drugs	Not relevant			**<u>Medium</u>** -Some felt unsafe drug disposal happens from contradictory regulatory guidance in the context -As per UK waste legislation general drugs (except cytotoxic and cytostatic) fall under non-hazardous waste, so there is no harm to dispose those drugs with household wastes; but drug take back legislation insists people to dispose any drugs via nearest pharmacy – hence many local councils are not motivated to take any special

Green barriers for downstream pharma		Key stakeholders who faced the barrier to adopt related green practices and the extent of the barrier faced			
Key green barriers	Sub green barriers	Pharmacy	GPs	Care homes	Local Councils /waste vendors
					collection/disposal options while collecting household waste.

6.2.1. Operational

As revealed in the study, downstream drug use-and-disposal management is still not under effective and efficient management due to the lack of management control. The next section presents the related findings in detail.

6.2.1.1 Lack of management control over drug wastes reduction

Whilst effective and efficient management control during prescribing, dispensing, and administering were seen, the study reveals that pharmacies, GPs, hospitals and care homes are still facing some circumstances where drug wastes are significantly induced due to loss of management control. Seven different such aspects identified in the study are presented in the subsequent sections.

Uncontrolled drug wastes from high concerned patient groups

The study reveals three groups of highly concerned patients whose drugs management in terms of prescribing, dispensing and consumption pattern is challenging. For instance, 'patients in end-of-life care', 'patients with dementia', and 'multiple complex morbidity'. Table 6.4 highlights some of the challenges that emerged in the study. Appendix 19 has also included the detailed evidence on each.

Table 6.4 Key challenges for managing drug dispensing and consumptions of high concerned patients (Source: Interviews and reports)

High concerned patient group	**Key management challenges**	**Stakeholders who faced the challenges**
Patient in end of life care	-frequent hospital admission -frequent change of drugs -patients move care settings -drug prescribed for complex long-term condition -patient reviews from multiple healthcare groups (e.g., community pharmacists, nurses, GPs, nutritionists etc)	Pharmacy/Care homes/GPs

High concerned patient group	Key management challenges	Stakeholders who faced the challenges
Patient with Dementia	-severely nonadherence	Pharmacy /GPs
Patient with Multiple complex morbidity (or, poly pharmacy)	-frequently change drugs due to drug interactions -severe nonadherence	Pharmacy / care homes/ GPs

6.2.1.2 Lack of performance measures (robustness of NMS/MUR report)

It was revealed in the interviews that though MUR and NMS are important tools to reduce drug wastes through regular patient interventions, there is no formal management process to measure performance of MUR/NMS in terms of drugs waste reduction. As per the pharmacy respondents, this is because there is a lack of planning and a lack of funding to capture these performance measures or a lack of understanding the value of capturing this performance in this setting. Both GPs and pharmacists have faced this barrier to drug optimization. For instance, one of the respondents (M) has highlighted that there is no exact performance measure (either qualitative / quantitative) currently being used to measure the drug waste reduction through MUR/NMS, which could have been an effective way of measuring progress to see how much has been saved in which category of drugs, and reinforce the MUR/NMS services accordingly. Another respondent (L) highlighted that though there is scope in monitoring the number of drugs that are changed or stopped (which otherwise could be wasted) per MUR to see the effectiveness of MUR/NMS, there is no such instruction or recording management from the NHS.

6.2.1.3 Barriers of getting patient's consent for conducting MUR/NMS

Some of the pharmacists and one of the GPs have faced this barrier. As patients' consent is required prior to conducting MUR and NMS, patients are not always persuaded to be recruited to this service carried out by the pharmacists. Patients also cannot be forced to be included into this service as highlighted by the respondents. As per the informants, this was seen as one of the key barriers to conducting MUR/NMS for home-based (e.g., care home) patients due to the difficulties in obtaining consent.

Some of the pharmacists interviewed have had trouble conducting MUR with housebound patients. For instance, one of the pharmacists (K – store 1) outlined that they face some extra burdens to conduct MUR for housebound patients. The respondent continued by saying that as those patients cannot come into the pharmacy premises, they must be written a formal letter to obtain their consent to be recruited into this service. The respondent highlighted that: "… ***housebound patient is more complicated because they have to do DBS check".*** Similarly, GPs raised their concerns in this case. For instance, one of the GPs (O) also raised the question: ***"So how do you do MUR when patient is housebound? That is the question. So, there are some drawbacks"***

6.2.1.4 Time constraints

Time was seen as one of the major constraints for pharmacists and GPs in conducting patient reviews such as MUR/NMS, or other similar types of regular patient interventions. The study reveals that whilst pharmacists are under pressure to complete day to day pharmacy operations from prescription screening (e.g., checking drug dosages form and dosage level, drug-drug interactions etc) to handing out medications to the patients after final checking of drugs, there is very limited time for conducting MURs/NMS on a daily basis. The majority of the pharmacists interviewed have faced this barrier. For instance, one of the pharmacists (K - store 2) stated that though there is a target of 400 MURs per year and they could achieve more for monetary incentives, the time required for each MUR (thirty minutes to forty minutes) is a challenge to maintain with other administrative tasks. For instance, one of the pharmacy managers (K – store 1) from a leading pharmacy store stressed that: ***"… the workload might not let you have the time to do it"***.

It was also revealed in the interviews that NMS is more challenging than MUR due to the need to maintain three stages of consecutive follow up with the patients, which require them to spend more time on this. For instance, one of the respondents (K – store 1) further stressed this challenge saying: ***"… Oh, the one is more challenging because it's three stages. It is too much to complete the circumstance to get paid for it. So, at times you may recruit but getting them to stick to them after one week may be a challenge"***

6.2.2 Regulatory issues

The study reveals two key regulatory barriers. The first one is the lack of regulatory guidance on environmental consideration in prescribing which is faced by the GPs, and the second one

is the contradictory regulatory guidance for disposing of unused/expired drugs faced by the waste management vendors. The subsequent section presents detailed evidence of these that emerged in the study.

6.2.2.1 Lack of regulatory guidance on environmental consideration in prescribing

Healthcare professionals, especially the GPs interviewed, strongly highlighted that there is a lack of regulatory guidance on prescribing outlining the environmental issues, such as PIE, apart from the guidance on the usages of antibiotic drugs. As per the respondents, there is no particular legislation on what to include or what not to include in prescription for environmental considerations. For instance, should the GPs limit their prescription on hormonal drugs e.g., E2/EE2 products for environmental damage? As explained by the respondents, this is particularly important because many drugs concentrations from painkiller groups and hormonal drugs (e.g., E2/EE2) are widely evidenced in the water system. Though there is clear clinical and therapeutic guidance on painkillers usage, there is lack of proactive regulation for painkiller prescribing, considering the environmental loadings of drugs, as explained by the GPs.

It was evidenced in the interviews that at present there is no clear regulatory route for using environmental concerns (e.g., regulate prescribing as per environmental concentration of drugs where possible) when prescribing a group of drugs. Hence, like antibiotic prescribing and usage practice, some other watch-list drugs (e.g., birth control pill) listed by water companies could be controlled via regulating prescribing, which could have been guided in the eMC (Electronic Medicine Compendium) guidance as explained by the GPs. For instance, one of the GPs (O) outlined that they do not have any such guidance on eMC, which they regularly follow when prescribing. The other respondent also outlined that there is lack of clear guidance on how to consider ecotoxicological aspects prior to prescribing drugs. Though the environmental classification of drugs (classify drugs based on PBT data and excretion profile of APIs) has been used in Sweden, the relevancy and practicality of the scale in the UK is still not known, as revealed in the study.

There is also the complexity of taking into consideration the excretion profile of a drug during prescribing, when the point of metabolism is the prime concern, as revealed by the GPs. As per the respondents, the higher the unmetabolized excretion rate of an API , the higher the rate of chance of environmental contamination of the API. Though eMC contains excretion profiles (% of metabolised, and % unmetabolized) of each API, there is no clear

regulatory guidance on how to consider excretion profile when prescribing considering environmental loading of API without compromising patient efficacy. Additionally, there is no clear guidance on whether GPs should consider alternative (when possible) drug prescribing considering excretion profile. This is because the decision on prescribing a drug based on its excretion profile is not straightforward because the clinical and physiological adjustment of an API with a patient is crucial, as was highlighted in the interviews. For instance, one of the respondents (O) has highlighted that ***"... ...the clinicians are interested about how these things (API) are excreting through what organs of the body".***

The severity of the challenge can also be understood using other case examples that emerged in the study. One of the respondents (P) has further outlined an example here to demonstrate the challenge of why it requires clear regulatory guidance for the prescribers. For instance, Atenolol, a drug used for lowering high blood pressure, whose parent excretion rate is 90% and metabolism takes place in the kidney; and Metoprolol, also used for lowering high blood pressure, whose parent excretion rate 10% and metabolism is in the liver; so, patients with impaired liver function may not be given Metoprolol instead of Atenolol. This is because impaired liver function does not influence the pharmacokinetics of atenolol, as explained by the respondent. Thus, the prescribers have felt the need for regulatory guidance and training on how to consider excretion profiles during prescribing so that they become more confident.

The GPs have also felt the lack of regulatory guidance on alternative therapy. As revealed in the interviews, many forms of alternative therapies are not regulated, such as acupuncture, ayurvedic etc. Additionally, no internal referral system is established for these alternative treatments, as highlighted by the respondents. Another factor that was revealed by the study was *Fear of defensive medicine,* which means GPs must be defended for deviating from normal practice and procedure. As per the respondents, defensive medicine occurs in two particular cases, either the GPs wants to avoid complaints from the patients for not deeply accepting their concerns regarding their treatment and, as such, GPs may arrange extra tests for them (which are actually not required); or undermine/avoid precautionary action (e.g., avoid expensive testing) to treat the patient. In either case, the GPs are accountable, and they must be defended. It is a fear that GPs could have been defended for prescribing alternative treatments (e.g., exercise, physiotherapy etc), instead of prescribing drugs, as outlined by one of the respondents (O). Hence, the necessity of relevant regulatory guidance is significantly important.

6.2.2.2 Contradictory regulatory guidance for disposing unused/expired drugs

It was revealed in the study that all general drugs fall under non-hazardous waste (apart from the cytotoxic and cytostatic or cancerous / radioactive drugs which fall under hazardous waste), as per the UK waste legislation. So, the public perception is that it is okay to throw drugs in the garbage rather than returning them to the pharmacy, as revealed in the study while interviewing waste vendors in the local councils. Therefore, as per the findings in the study, it remains a valid question whether drug take-back legislation (returning unused/expired drugs to pharmacy) contradicts UK waste legislation for households.

It was revealed in the interviews that the legal waste categorization and 'drug take-back' legislation is contradictory and dubious in nature, which creates confusion among the public. As per the respondents from waste vendors, patients believe that they are doing the right thing (throwing their unused drugs with household garbage), as they have been doing it for a long time and the local council always collects it and there are no issues as per waste management guidance by the government.

Interestingly, some of the local councils interviewed also think that it is okay to throw unused household drugs in the bin, as they go under waste to energy facility and they are not hazardous. For instance, one of the councils (LC - 09) has outlined that ***"Special consideration is not given to pharmaceutical waste as we have not encountered it as an issue"*** when they were asked if they have any separate special consideration for collecting and treating pharmaceutical waste (e.g., unused / expired drugs) in the household wastes streams. Similarly, another local council (LC - 14) also highlighted this: ***"There are no special arrangements in place currently. All such waste presented inside the householders residual waste bin is collected and treated as household waste"***

Therefore, some of the local councils/waste management companies interviewed also do not have any motivation to educate people for safe disposal of drugs or provide any separate collection campaign or facility for people to dispose of their drugs safely. This is due to the fact that many local councils investigated do not take the unused household drugs as hazardous wastes (as per the waste regulation) - they think it is normal to allow people to throw their drugs into the bin as long as the waste goes through the EfW (Energy from Waste) plant. However, the key motivation behind the 'drug take-back legislation' is that medicines wastes (regardless of hazardous / non-hazardous) require special treatment, such as

they must go through complete incineration at a higher temperature in a specialized drug incinerator for greater environmental benefit. This is how two related, but separate legislations have caused confusion among the local waste management providers and public about the treatment of unused/expired household drugs.

6.3 Key Contribution of the chapter

This chapter has identified some important green barriers and related unique observations which were unknown previously in the context. The unique barriers for the upstream stakeholders identified are: regulatory: *complex marketing authorization process of greener drug (redesigned off patent), cultural issues, Lack of standardization in equipment and processes, time to market, and lack of demand of green API*. These unique barriers and related observations are expected to influence the relevant practitioners and policy makers to greening pharma supply chain through advancing the understanding on each barrier to mitigate them. For instance, the unique observation on the intensity of each barrier across the stakeholders has clearly indicated us why the generic sector in general is prone to green adoption, especially due to the complex validation and marketing authorization of redesigned drugs. It is undoubtedly a unique and important observation that though generic manufacturers could save considerable amount of materials and energy through redesigning off-patent drugs, the complex and contradictory internal and external process validation have impeded them to do such post marketing process change. Operations managers' sceptical mindset and fear of losing manufacturing licensing to adopt any post marketing process change are also important observations for the policy makers to adjust the relevant policy. Such unique observation will also influence the practitioners to advance their internal capacity and scopes of continuous improvement to encourage the internal quality team for process change. Additionally, and interestingly, it became clear that why companies across the sectors were unable to standardize site wastes. The challenges of compatibilities among the different processes due to have diversified starting raw materials and process equipment have indicated the practitioners to improve capacity to measure process based wastes. Time related barrier has also indicated the relevant regulators and policy makers to find a clear trade off between 'green process developmental time line' and 'long term economic gain'. As indicated, time will still remain crucial green barrier for any stakeholder participated in the study unless the stakeholders are given any special incentives (e.g., extending the exclusive sales rights for innovators). As the formulators (especially the generic sector) have been hunting for low-cost API globally, demand for costly greener API is still low. Hence, related

government incentives and capacity of global outsourcing are important to encourage greener API production. Previous study like Clark et al (2010) and Kummerer et al (2009) have never disclosed such important observations. The chapter also identified three more unique green barriers from downstream stakeholders such as *uncontrolled drug wastes from high concerned patient groups; lack of regulatory guidance on environmental consideration in prescribing; contradictory regulatory guidance for disposing unused/expired drugs.* Uncontrolled drug wastes from certain patient groups (e.g., dementia, multimorbidity etc) has clearly indicated that why the prescribing and dispensing process for those groups must be scrutinized under well-defined and robust medication management system, where real-time medical intervention could be the key. Whilst PIE issues could be reactively mitigated via eco-friendly prescribing (e.g., consider excretion level of a drug / consider PBT data of an API etc), lack of related guidance and direction has impeded the prescribers to consider such eco-prescribing. As the existing off-patent APIs (around 3000) will be dominating the industry, such reactive green action is necessary. The unique observation on the contradictory regulatory guidance for disposing unused/expired drugs in the customer zone is significantly important for the policy makers to clarify it for the public to reduce unexpected environmental loading of drugs.

6.4 Chapter Summary

This chapter aimed to answer the third research question in the thesis. It presented key barriers faced by both upstream and downstream pharma stakeholders to adopting green practices. It outlined eight key barriers in the upstream and six key barriers in the downstream of pharma. The complex marketing authorization process of the post-marketing process change of a drug was seen as one of the key barriers to adopting green in pharma. Time consuming, expensive, and complex re-validation (internal and external) of the process stages were not seen as favourable conditions for upstream pharma (especially generic and innovative) to adopt green practices like solvent recovery and continuous process. The high costs of adopting green practices, such as retrofitting solvent recovery in the existing process, were also seen as another key barrier for upstream pharma companies, especially for generic production, where the low-cost of drugs is the key to surviving in the market. Lack of standardization in the process, time pressure to launch products, and lack of green-related data (e.g., environmental toxicity) were also seen as important. Different stakeholders were found to feel these barriers in varying degrees due to having different levels of operational capability and capacity.

On the other hand in the downstream, pharmacies, GPs and care homes felt a lack of management control in reducing drug wastes in many facets, such as uncontrolled drug wastes from high concerned patient groups, lack of performance measures of NMS/MUR, and the time it takes to intervene with patients to ensure the effective use of drugs. Contradictory regulatory guidance on general drug disposal was also seen as an important barrier for waste vendors (especially the local councils) to establish appropriate waste disposal strategy. Despite facing such green barriers, pharma stakeholders were also seen (though not too widely) to capture actual green performance through related green performance measures. The next chapter presents green performance related findings.

Chapter Seven

Findings on Green Performance measures in Pharma Sector

Whilst chapter four has provided a clear picture of what, how and to what extent the pharma industries have adopted green practices, this chapter aims to assess how the industry is performing after adopting green practices. As evidenced in chapter four, though average industry-wide green practice adoption is low, the medium to high level green practices adoption and related performance gained by the innovative pharma companies will undoubtedly motivate the other stakeholders on how to gain competitive advantages through increasing environmental performance. As the relevant environmental performance aims to induce economic performance, for instance, material reduction can save raw materials costs, solvent recovery can save on the purchasing of virgin solvents, toxicity reduction can save on disposal costs and environmental penalties due to accidental spillage, energy saving can save on utility costs, etc. Therefore, it is crucial to understand the relevant performance measures used to assess the environmental performance along with the evidence of actual performance induced. Hence, this chapter has predominantly aimed to answer the research questions below:

RQ4. What are the green performance measures (in terms of environmental and economic) used, and related (environmental and economic) benefits captured by individual pharma sector stakeholders and what is their perceived importance?

RQ4.1 what are the green performance measures (in terms of environmental and economic) used, and related (environmental and economic) benefits captured by upstream pharma sector stakeholders and what is their perceived importance?

RQ4.2 what are the green performance measures (in terms of environmental and economic) used, and related (environmental and economic) benefits captured by downstream pharma sector stakeholders and what is their perceived importance?

7.1 Findings on Performance Measures used, and related (environmental & economic) benefits captured by upstream pharma stakeholders

Performance measures are the key performance indicators for the pharma companies to assess, track, modify and manage the green practices adopted. These performance measures were seen as important to deal with the negative environmental impact of pharma operations, as well as to contribute to the wellbeing of the wider community as part of corporate responsibility. Without this measure, green investment would be in vain within pharma companies. The investigation has broadly identified two types of measures: strategic level measures and operational level measures.

7.1.1 Strategic Level Environmental Performance Measures

As revealed in the study, the strategic-level measures involve top level environmental targets and objectives, which have been translated into fragmented targets and objectives for the individual departments. It was also evident in the investigation that this high level strong environmental commitment was important to achieve year on year specific targets set by the operations. This is because top management have not only communicated related environmental targets, but also provide clear site-specific direction on how to achieve them, as revealed in the study. It was evidenced in the interviews that the majority of innovative pharma and bio pharma and a few generic pharma have set long-term environmental targets and objectives. They also conducted yearly board meetings to track progress against each target. The findings from both the interviews and reports also reveal that the pharma industry has predominantly undertaken strategic environmental targets in four key areas: carbon, energy, water, and waste reduction target. As per the reports, innovative and bio pharma are at the forefront of undertaking those targets as compared with generic, shown in figure 7.1.

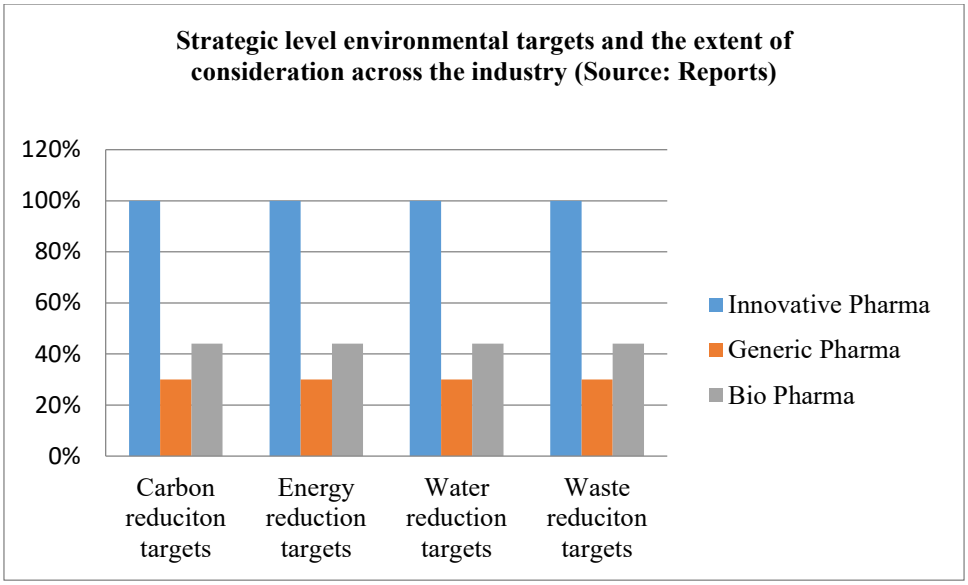


Figure: 7.1 Strategic level environmental targets and the extent of consideration across the industry (Source: Reports)

As per the interviews, the majority of the innovative pharma, a few generic and some bio pharma have received environmental targets (e.g., waste reduction targets, PMI targets, carbon reduction targets, energy targets and water targets) from their respective boards. They have also explained how their operations achieve those targets. Some examples from the investigation will help us to better understand this aspect. For instance, one of the respondents, an EHS manager (B – site 1) from a leading innovative pharma, explained that they normally receive a set of environmental targets from the board at the beginning of the year or late in the year for the next year. The respondent further elaborated that once the target is set, they set their own departmental objectives and conduct monthly meetings to check their performance against their targets. The respondent also provided an example, for instance, their department was given an objective to achieve 80% of waste to be converted to beneficial usage. So, they implemented varieties of waste kaizen projects in liaison with internal and external waste consultants, as outlined by the respondent. Additionally, there was a monthly progress meeting for tracking the performance of those waste kaizen projects in order to meet the target.

Another respondent, a sustainability and utility manager (B – site 2), also highlighted that they have a corporate target of carbon reduction, a renewable power generation target, a water reduction target, a waste reduction target, a zero to landfill target etc. The respondent

further stressed this point saying – ***"we have been working on our target for the last 10/15 years for improving carbon footprint and water impact".***

The study also evidences how companies set environmental targets for reducing toxicity levels through setting API discharge targets. As revealed in the study, the majority of the innovative companies have internal strategic plans and targets on reducing API discharge into surface water from the manufacturing plant. For instance, one of the leading innovative pharma (C) talked about their API discharge target highlighting that – ***"we have a public target of 90% compliance of our API suppliers and formulators meeting our target***". It was further explained why they do not set it at 100%. This is because quite often they have new suppliers coming in within a particular year and obviously in that year they will have to train them about the expectations on API discharge and work with them closely to make sure they work towards meeting the standard.

7.1.2 Operational Level environmental Performance Measures and related performance impact

Operational level performance measures explain how the corporate level environmental targets get translated into day-to-day environmental considerations and assessment during pharma operations. As agreed by almost all the respondents in the study, operational-level performance measures were considered as the key to achieving overall environmental sustainability in pharma. Findings from the interviews and reports have revealed four key areas of measures (e.g., GHG emission related, materials related, energy related and toxicity related) and 33 sub measures across the key industry stakeholders (innovative, generic and bio pharma). Table 7.1 summarizes the key operational measures and sub-measures and related performance impact across the industry. The table also presents the economic performance related measures and related performance. The first two columns in the table represent the measures / sub-measures and next three columns represent the performance impact and extent of impact for individual pharma stakeholders. The subsequent section briefly presents the findings on the four key areas of operational performance.

Table 7.1 Summary of key green performance measures and related performance impact across pharma sector (Source: Reports)

Green Performance Measures		**Key stakeholders used the related green measures and the extent of their improvement**		
Key green measures	**Sub green measures used**	**Innovative**	**Generic**	**Bio pharma**
GHG emission related	*Reduction of scope 1 emission*	Extent of improvement: **High** -Significant reduction in scope 1 emission in most companies; some of them also estimated significant reduction from new green process development	Extent of improvement: **Low** -Few of them has reduced considerable amount of emission from green practices. -majority of their focus still limited to tertiary packaging reduction than other chemicals raw materials used in the process/site -a few of them reported increased due to increased level of production	Extent of improvement: **Medium** -Some of them shown significant reduction. -few of them reported increased emission due to new production line /plant installations
	Reduction of scope 2 emission	Extent of improvement: **High** -Significant reduction in scope 2 emission in most companies. -Mostly due to install renewable sources of energy	Extent of improvement: **Medium** -Some of them have reduced considerable amount of emission. -majority of their focus still limited to energy efficiency (e.g., equipment /	Extent of improvement: **Medium** -Some of them shown significant reduction - lower focus on renewable source of

Green Performance Measures		**Key stakeholders used the related green measures and the extent of their improvement**		
Key green measures	**Sub green measures used**	**Innovative**	**Generic**	**Bio pharma**
		(e.g., wind turbine, CHP etc)	machine upgrading etc) than installing renewable source of energy -a few of them reported increased due to increased level of production	energy compared to innovators
	Reduction of VOC	Extent of improvement: **High** -Significant reduction in VOCs emission in most companies. -Mostly focused on reducing halogenated VOCs than non-halogenated VOCs	Extent of improvement: **Low** -Overall, no significant reduction -Very few of them use this measure	Extent of improvement: **Medium** -Significant reduction in some companies due to predominantly reducing the usages of halogenated substances
	Reduction of ODS	Extent of improvement: **High** -Significant reduction in ODS emission in most companies. -Mostly focused on phasing out ODS substances and special consideration during inhaler production	Extent of improvement: **Low** -Overall, no significant reduction -Very few of them use this measure -a few of them shows increased level of ODS emission	Extent of improvement: **High** -Significant reduction in most companies due to predominantly reducing the usages of ODS substances

Green Performance Measures		**Key stakeholders used the related green measures and the extent of their improvement**		
Key green measures	**Sub green measures used**	**Innovative**	**Generic**	**Bio pharma**
Energy related	*Total Energy use, amount of energy purchased, and total use of energy generated onsite*	Extent of improvement: **High** -Significant reduction in plant energy use in most companies. -Some of them produced significant amount of onsite energy; reduction on purchased electricity;	Extent of improvement: **Medium** -Overall a moderate level energy reduction -low level of onsite energy production	Extent of improvement: **High** -Significant reduction total energy use in most companies due to predominantly reducing through onsite energy production
	Amount of energy saved from conservation & efficiency improvements	Extent of improvement: **High** -Overall significant improvement were observed across all stakeholders -Almost all types of energy efficiency activities/projects reported successful energy savings -High level of importance were given to implement process/plant wide energy savings activities (e.g., energy kaizen projects)		

Green Performance Measures		**Key stakeholders used the related green measures and the extent of their improvement**		
Key green measures	**Sub green measures used**	**Innovative**	**Generic**	**Bio pharma**
Materials related	Reduce PMI (Process Mass Intensity)	Extent of improvement: **High** -Significant reduction of PMI reported in most companies through promoting green chemistry practice - Most of the benefits only captured in the case of chemicals-based process	Not considered due low cost focused and they do not have enough resources towards this performance measure	Not considered as bio-based process are still not well understood how/what to consider developing a similar PMI developed for chemicals-based process
	Amount of water reduction	Extent of improvement: **High** -Significant amount of water reduction reported across all stakeholder companies. -Some of them also projected high level of water reduction from the different water reduction projects -significant reduction of freshwater use -Very view companies across all sectors also highlight slight increase of water reduction due to the increase in demand on liquid production		
	Amount of raw materials (e.g. API,	Extent of improvement: **High** -Significant reduction in solvents use in most	Extent of improvement: **Medium** -Some companies showed significant	Extent of improvement: **Medium** -Some companies showed significant

Green Performance Measures		**Key stakeholders used the related green measures and the extent of their improvement**		
Key green measures	**Sub green measures used**	**Innovative**	**Generic**	**Bio pharma**
	excipient / solvent, etc) use/save/reduces	companies from applying green chemistry -Significant reduction in packaging materials use in some cases -Significant savings of excipients in few cases	reduction on tertiary packaging -Few companies showed significant solvent reductions	solvent reduction -a few companies showed significant packaging waste (tertiary) reduction
	Amount of wastes (non-hazardous) generated	Extent of improvement: **Medium** -Significantly reduced work-in-process materials from applying site specific lean projects in most cases -Though very few reported significant reduction in primary packaging, overall packaging waste (especially secondary and tertiary) were increased	Extent of improvement: **Low** -Though Work in process materials were slightly reduced through process lean activities, majority of them in general reported significant increase in tertiary packaging wastes	

Green Performance Measures		**Key stakeholders used the related green measures and the extent of their improvement**		
Key green measures	**Sub green measures used**	**Innovative**	**Generic**	**Bio pharma**
	Amount of (non-hazardous) wastes recycled/reused/incinerate/landfil	Extent of improvement: **High** -Significant increase in packaging recycling (secondary and tertiary) in most cases -Few reported significant reductions in landfill -Increased solvent incineration	Extent of improvement: **Medium** -Some reported medium level of increment in tertiary packaging recycling -Some reported to moderate increase landfill -very few reported solvent incineration -some reported waste composted (bio pharma)	
Toxicity related	Amount of Hazardous waste generated	Extent of improvement: **High** -Significant reduction in hazardous waste generated through applying green chemistry principle in most cases	Extent of improvement: **Low** -Very few cases of reporting reduction in hazardous waste generated as the scope of using green alternative in the process was less	Extent of improvement: **High** -Significant reduction in hazardous waste generated through applying green chemistry principle in most cases
	Measure toxicity level of wastes	Extent of improvement: **High** -Significantly Improved BOD and COD (mostly stayed beyond the regulatory limit) -Improved TSS (in terms of API assessment); improved API detection level (stayed beyond voluntary limit in some cases)	Extent of improvement: **Medium** -For BOD/COD, adhere to the regulatory limit in most cases -No significant improvement in TSS (in terms of API assessment)	

Green Performance Measures		**Key stakeholders used the related green measures and the extent of their improvement**		
Key green measures	**Sub green measures used**	**Innovative**	**Generic**	**Bio pharma**
	Amount of hazardous wastes converted to beneficial use (e.g., waste to energy)	Extent of improvement: **High** -Significant level of waste (both hazardous and non-hazardous) converted to energy in most cases (in sites predominantly) -More conversion from non-hazardous waste stream than hazardous waste stream	Extent of improvement: **Low** -Few cases of evidenced of waste to energy; only few reported hazardous wastes to energy production (off sites predominantly)	
	Amount of hazardous waste recycled/reuse/incinerate/landfill	Extent of improvement: **High** -Significant amount of hazardous waste were recycled in some cases -Increased level of reuse (e.g., recover lower graded solvents to use it for cleaning purposes) in many cases -Rate of incineration was decreased in many cases as overall landfill diversion rate was significantly increased	Extent of improvement: **Medium** - Overall, moderate level of reduction in landfill -Increase incineration rate in many cases -Low level of recycling	

Green Performance Measures		**Key stakeholders used the related green measures and the extent of their improvement**		
Key green measures	**Sub green measures used**	**Innovative**	**Generic**	**Bio pharma**
Economic Performance	*ROI of Green Project.* *Cost savings* (e.g., via raw material efficiencies; energy efficiency etc) *Cost of green production* (e.g., Cost of process changes, cost of single use technology etc)	Extent of improvement: **High** -Significant cost savings from solvent recovery projects in some cases -Significant cost savings from energy efficiency projects in most cases -Better ROI prediction for majority of potential solvent recovery projects (e.g., payback period 2 to 6 years) -Cost of process change (pre-marketing) is not significant -Significant reduction in hazardous solvent disposal costs in some cases	Extent of improvement: **Low** -Mostly, cost of process change (post-marketing) for green adoption is significant; or cost of green production is significantly high in most cases -Cost savings from reduced packaging in some cases. -Disposal cost savings in few cases.	Extent of improvement: **High** -Significant cost savings from water and energy efficiency projects in most cases; average payback period of water efficiency project was 2 years. -Significant cost savings from greener production (e.g., from applying single use technology) -Increased disposal costs in few cases

7.1.2.1 GHG emission related

As revealed in the study, this measure was used to assess the overall greenhouse gas emission performance from a particular pharma R&D and/or manufacturing plant. As highlighted in the study, this is one of the important measures for the pharma industry due to the unprecedented level of global institutional pressure as well the United Kingdom's voluntary commitment to the Kyoto protocol agreement to reduce its greenhouse gas emission by 80% by 2050. The importance of having such measures in place was also found in the investigation. For instance, while asking the respondents why they use these GHG emission performance measures, one of the respondents (B – site 2) from a leading innovative pharma highlighted that – ***"Campaign coming from the corporate social responsibility so we continually driving to achieve those changes like carbon footprint reduction; water reduction; risk reduction as well".*** Another respondent (B – site 1) from an innovative pharma also highlighted that GHG emission performance measures are fairly high on the green chemistry agenda.

It was also evidenced in the study that four key sub measures were predominantly used to assess overall GHG emission performance for a pharma company. The fours measures identified were scope 1 emission, scope 2 emission, VOCs consumptions and ODS emission. It is important to note here that scope 3 emission is beyond the scope of this thesis. Table 7.2 shows the relative importance of each sub measure across the industry, as identified in the reports. The relative importance of each measure covers two key important factors of performance measures: the 'extent of universality' and 'consistency of each measure' across the industry.

Table 7.2 Relative importance of each GHG emission reduction measure for each stakeholder based on frequency of each measure (based on report)

Key green performance (Environmental) measures		Innovative Pharma (16)	Generic Pharma (20)	Bio pharma (25)
GHG Emission Reduction	Reduction of scope 1 emission	100%	25%	36%
	Reduction of scope 2 emission	100%	25%	36%
	Reduction of VOCs consumption	90%	10%	24%
	Reduction of ODS (Ozone Depleting Substance) emission	90%	5%	44%
	Eco-efficiency = (Total CO2 emission/Total revenue)	9%	NM*	4%
	GHG emission intensity = (Tons of CO2 /1 employee)	NM*	5%	4%
	Total Kg of CO2 generated per production unit	NM*	NM*	8%

NM*	Not Mentioned
	- Predominant measures
	- Medium level measures
	- Low level measures

As seen in Table 7.2, three measures - reduction of scope 1 emission, reduction of scope 2 emission and reduction of ODS emission - were found to be predominant in the industry. While the first two measures were seen as highly important for innovative and generic pharma, the third measure was seen highly important for bio pharma. Appendix 20 presents the findings on key GHG emission related measures and related performance impacts captured.

Compared to innovative pharma, generic and bio pharma reported between low to medium level of scope 1 emission improvement, as revealed in the study. With regards to generic pharma, an overall low level of improvement was observed in the study, though a few of them reported significant improvement. For instance, one of the generic pharma (Gn – 04) had reduced approx. 490 tonnes of CO2 emission per annum from replacing a plastic drum with a paper fibre drum for their OTC drug portfolios. On the other hand, bio pharma was seen to improve scope 1 emission better than generic pharma. As per the reports, some bio pharma had reduced scope 1 emission considerably, while a number of them also reported increases in emission. For instance, one of the bio pharma (B – 03) had reduced approximately 3500 metric tonnes of carbon emission in 2018 from applying resource conservation measures (predominantly water reduction across the site), while another bio pharma (B – 03) reported an increase in the direct emission by 18% between 2016/17 to 2017/18 due to increased production levels and installation of some new production lines.

7.1.2.2 Material efficiency related

As revealed in the study, this measure was used to assess the performance of conducting material reduction practices / activities. This is one of the important measures to provide a holistic performance green chemistry application, as this measure is also highly interrelated with energy reduction. Table 7.7 shows related sub measures. Of them, three key sub measures - measuring PMI, the amount of water reduced in the plant/process and the amount of raw materials used in the process/plant - were predominantly used across the industry. The relative importance of each material reduction measure is also shown in Table 7.7. Appendix 21 discusses the three key sub measures and related performance impact in detail. For better

comparison and understanding, two related measures - 'Amount of wastes (non-hazardous) generated' and 'Amount of (non-hazardous) wastes recycled/reused/incinerate/landfill' - are discussed under toxicity measures, with hazardous ones, to compare.

Table 7.7 Relative importance of each material reduction measure for each stakeholder based on frequency of each measure (based on report)

	Key green performance measures	Innovative Pharma (16)	Generic Pharma (20)	Bio pharma (25)
Material Efficiency related	Reduce Process Mass Intensity (PMI)	27%	NM*	4%
	Amount of Water reduction	100%	30%	80%
	Total water usages per employee	NM*	5%	12%
	Amount of raw materials (e.g., API, excipient) use / save /recover	36%	20%	NM*
	Percentage of materials used that are recycled input materials	NM*	15%	8%
	Amount of recovering water used	NM*	30%	16%
	Amount of wastes (non-hazardous) generated	72%	NM*	4%
	Amount of (non-hazardous) wastes recycled/reused/incinerate/landfill	40%	10%	15%
	Waste Intensity = (Tons of waste produced / employee)	9%	10%	NM*
	Non-Hazardous Waste per Sales (tonnes/million sales)	NM*	30%	4%

NM* Not mentioned
- First rank
- Second rank
- Third rank

The majority of respondents from innovative pharma have strongly advocated the use of PMI, as they strongly believe that this measure has not only reduced raw materials input, but also energy and waste related costs. However, it is revealed in the study that the concept of PMI is still not widely popular in generic pharma and bio pharma. As per the majority of the respondents, they still do not have such kinds of PMI for the bio-based production process, as it is difficult to measure bio-based input rather than chemical-based input raw materials. For instance, one of the respondents (A) has outlined that they are trying to develop a PMI for bio-based production so they could control the amount of water usage. Some of the respondents have also highlighted that this kind of API for the bio-based process would be a

very efficient and effective approach for the bio pharma industry, as this industry consumes water considerably.

Given the significant potential of water footprint, the measure of water reduction has been popular across all three industry stakeholders. The majority of respondents from innovative pharma, almost half from generic pharma and two thirds of bio pharma respondents have strongly advocated measuring the amount of water consumed or reduced by means of assessing different kaizen projects. The respondents from innovative pharma and generic pharma equally highlighted that as part of kaizen projects they measure how much water they have saved from different recovery (e.g., reuse, recycling etc) activities. Driven by the measurement of water reduction, bio pharma companies have also sought to undertake proactive measures to save water, as bio pharma is one of the biggest sources of water consumption. Most of them have also reported significant improvement. For instance, one of the bio pharma (B – 09) has measured that they are expecting to save a significant amount of water (approx. 53000 cubic meters) by undertaking water efficiency projects, such as installing low flow facet aerators across its all manufacturing sites. The company has stressed this performance impact highlighting that "***we expect to save 53,000 cubic meters, equating to approximately 21 Olympic swimming pools of water per year".***

7.1.2.3 Energy efficiency related

As revealed in the study, this measure is used to assess the performance of energy related projects and activities adopted across the pharma industry. As the inefficient usage of energy not only increases utility costs but also contributes to related emissions significantly, the use of energy reduction measures have been sought as one of the top measures on the green agenda across the pharma industry. Under this measure eight sub energy measures have been identified. The importance and extent of adopting these measures are also ranked based on the report analysis (shown in Table 7.11) and it was found that the first four sub measures are predominant in the industry. It is also observed that innovative pharma is in the lead position to adopt all these measures. Appendix 22 discusses the key four sub measures and related performance impact in detail.

Table 7.11 Relative importance of each energy reduction measure for individual industry stakeholder (Evidenced from report)

Key green performance measures	Innovative Pharma	Generic Pharma	Bio pharma

		(11)	(20)	(25)
Energy Reduction	Total energy used	72%	30%	24%
	Total use of energy purchased	45%	10%	8%
	Total use of energy generated onsite	45%	10%	8%
	Amount of energy saved from conservation & efficiency improvements	36%	27%	20%
	Total electricity consumed per production unit	NM*	NM*	8%
	Total Electrical Energy per Sales (GJ/million sales)	NM*	NM*	4%
	Total Electricity usage per employee	NM*	5%	4%
	Total gas usage per employee	NM*	NM*	4%

NM* Not mentioned
- Predominant sub measures
- Medium level sub measures
- Low level sub measures

The study reveals that though companies have sought to increase onsite renewable energy generation (e.g., CHP, biomass etc) significantly, the amount of total energy consumption on average has been improved at a very slow (see Table 7.11 under appendix 22) and low amount (not so drastically) as opposed to individual energy targets. Indeed, in some cases it has increased slightly and failed to meet year on year energy targets. For instance, one of the innovative companies (In – 10) reported that their overall energy consumption increased by 4% within three years, from 2014 to 2017, due to increased production volumes.

7.1.2.4 Toxicity related

This measure is used to assess the performance of hazardous waste reduction related practices and/or activities. As revealed in the study, the majority of process wastes (e.g., wastewater) were considered and treated as hazardous waste streams across the industry. The importance of this measure is paramount, as pharma production has been identified as one of the most resources extensive and waste producing among all other entities in the pharma and chemical industries, where it produces 25 to 100 kg of wastes per kg of final drug product produced. It is reported that global pharma manufacturing wastes is expected to be 15 billion kg with associated disposal costs of 30 billion US Dollars. Therefore, taking waste reduction measures has become crucial for the pharma industry. Given such importance for waste efficiency, the industry has used a variety of types of waste measures based on types of input materials, final products, by-products etc. The study reveals eight types of waste measures which have been ranked based on the importance given by the companies in different sectors

(shown in Table 7.14). For instance, while 'amount of waste (hazardous) generated' is the key measure in innovative pharma, 'measure toxicity level of wastes' was dominant across the industry, and 'amount of wastes converted to beneficial use' was a key measure in generic and bio pharma. Appendix 23 presents the key waste measures and related performance impact in the pharma context in details.

Table 7.14 Relative importance of each waste reduction measure for individual industry stakeholder (based on report)

	Key green performance measures	Innovative Pharma (16)	Generic Pharma (20)	Bio pharma (25)
Toxicity related	Amount of wastes (Hazardous) generated	72%	NM*	4%
	Measure toxicity level of wastes (e.g., BOD/COD/TSS etc)	80%	30%	80%
	Amount of wastes (Hazardous) converted to beneficial use (e.g., waste to energy)	54%	30%	80%
	Amount of wastes (Hazardous) recycled	45%	10%	24%
	Amount of wastes (Hazardous) reused	18%	10%	8%
	Amount of wastes (Hazardous) incinerated	45%	NM*	12%
	Amount of wastes (Hazardous) land filled	54%	NM*	NM*
	Hazardous Waste per Sales (tonnes/million sales)	NM*	15%	4%

NM* Not mentioned
- First rank
- Second rank
- Third rank

As revealed in the study, both innovative and bio pharma reported significant improvement in hazardous waste reduction driven by their internal hazardous waste reduction goal. For instance, one of the innovative companies (In – 08) reported a 7.29% reduction in hazardous wastes generated within a two year period (2015 – 2017). Another bio pharma (B – 22) reported a 49% reduction in hazardous wastes in two years through applying green chemistry principles. As revealed in the study, driven by the regulatory requirements, all stakeholder companies almost equally prioritize COD /BOD measures for assessing water quality. For instance, one of the innovative companies (In – 09) reported a 14.2% increase in BOD efficiency by 2016 from the base year of 2010, meaning that the company has now improved its discharged wastewater quality, which will have lower impact on aquatic life due to having lower levels of BOD in surface water.

The study also reveals that driven by the measure – 'waste to beneficiary use', companies across the sectors have been continuously reducing their overall waste streams through

converting wastes (both hazardous and non-hazardous) into beneficial usage, though some companies have put more focus on reducing hazardous wastes through avoiding higher environmental impactful chemicals from the manufacturing process. However, regardless of hazardous or non-hazardous waste streams, the companies, especially the innovative companies, have converted wastes into beneficial usages though the ratios of conversion from hazardous and non-hazardous are slightly different in some cases. For instance, it was evidenced that one of the innovative pharma (In – 08) reported that energy recovery from hazardous wastes had decreased by 25% within two years (2015 – 2017), while energy recovery had been increased by 3.4% from non- hazardous waste stream for the same period.

7.1.3 Economic performance measures and related performance impact

As cost factor is one of the key indicators for attaining operational excellence, green operational excellence predominantly depends on the level of trade-off between environmental practice adoption and cost/economic performance. As evidenced in the study, clear trade-off between green adoption and cost savings was seen as one of the key concerns for all related stakeholders prior to making a green decision. It was revealed from the investigation that upstream stakeholders were seen to be very keen to translate the environmental benefits into monetary benefits like cost savings. It was revealed from the interviews that usage of cost or economic performance measures (prior to adopting green) in the pharma sector was widely used.

As revealed in the study, whether it was a trial or a well-established green practice, stakeholders measured cost effectiveness of each and every single green project - from very small kaizen projects to large energy optimization projects across the groups within multiples R&D and manufacturing sites. Seven cost measures were identified from the investigation, as shown in Table 7.18. The next section discusses the evidence from the three key stakeholders.

Table 7.18 Key green performance (cost/economic) measures used across the upstream pharma industry (Source: interviews and reports)

Key green performance (Cost/economic) measures
ROI of Green Project
Cost savings from raw material efficiencies
Cost savings from energy efficiencies
Cost savings from water efficiencies

Cost savings from disposal
Cost of green production (e.g., Cost of process changes, cost of single use technology etc)

Innovative pharma

Being the leaders of green adoption, innovative companies were found to use cost measures in various forms. The majority of the innovative pharma companies' respondents confirmed that the cost benefit analysis of any green project (e.g., waste kaizen project, energy kaizen project, water kaizen projects etc) was a prerequisite prior to implementing that particular green project for the longer term. As innovative pharma companies undertook different kaizen projects and each kaizen project and/or related environmental management practice involved capital investment, the cost savings from different kaizen projects through robust cost modelling for each green project was of prime interest for innovative pharma.

This cost benefit analysis or related estimation was predominantly carried out based on a preliminary pilot test. For instance, one of the respondents, a senior environmental specialist (A) from a leading innovative pharma, explained how they had used cost savings measures to assess a solvent (e.g., methanol) recovery project. This recovery project was the extension and development of an existing process rather than a new one. The respondent further explained that the return on investment from the project was significant through massive cost savings by purchasing 6% fewer raw materials, ingredients and solvents, and the payback period for the project was 6 years. This is how the cost-related measures that are highlighted here are: cost savings from raw material efficiency, ROI from green projects. As per the respondent, though similar recovery projects had already been trialled and tested in one of its manufacturing sites, the successful cost savings had encouraged the other sites to adopt this practice. For instance, similar projects helped the company's other sites to save 342 tons of equivalent solvent costs in two years. The project helped the site to recover and reuse toluene, ethylene acetate and methanol.

'Cost savings from energy efficiencies', and 'cost savings from raw material efficiencies' were also identified in a number of other cases. Some informants (e.g., B – site 2; B – site 1) from innovative pharma highlighted that they faced the driver of cost savings originating from energy and raw material efficiencies in the case of continuous manufacturing process over batch manufacturing. One of the respondents (B – site 2) indicated that the expected ROI from continuous process was higher than batch. For instance, one of the companies (In –

01) recently optimized one of its API processes to make it continuous through installing 'waste to clean equipment'. This new featured process helped the company to reuse its process waste solvents (e.g., methanol or acetone) to clean the process equipment in an automated system. This has saved over 1 million US dollars within a year. Table 7.19 also presents some key examples of related performance impact captured across the industry.

Table 7.19 Examples of key cost savings measures and related economic benefits captured across the industry (Source: reports)

Types of Cost measures	**Type of green practice applied**	**Key economic benefits captured**	**Source of evidence**
Cost savings from (water/energy/materials) efficiency	RCM (water, materials, and energy efficiency projects)	Expected Cost savings more than £1.2 million by 2018	(B – 01)
Cost savings from materials efficiency	Green Packaging: reduce packaging materials under a lean project	Cost savings up to £20,741 per annum per year	(Gn – 04)
Cost saving from continuous process	Solvent recovery: Waste to clean project:	Estimated cost saving over £765,696 last year through eliminating the need for expensive high-purity solvents, such as methanol or acetone, to clean equipment:	(In – 01)
Cost savings from energy efficiency	Energy kaizen: adopt energy efficiency programs	Annual £57,427. 26 cost savings from energy efficiency of process optimization across the manufacturing sites	(In – 04)
Cost savings from disposal	Waste diversion; energy & materials efficiency	Disposal cost has decreased by 8.6% from £2.3 million in 2017 to £2.1 million in 2018.	(Gn – 06)
Cost savings from materials and energy efficiency	RCM	estimated over £3,000,000 annual savings through 130 water and energy reduction projects	(B – 22)
Cost savings from energy efficiency	Adopt energy efficiency project	Estimated cost savings of £196,018 annually through 3800 solar panel installation which has expected to generate 3,205 MWh electricity per year. This has reduced purchase of electricity by	(In -03)

Types of Cost measures	Type of green practice applied	Key economic benefits captured	Source of evidence
		3% of its manufacturing sites.	
Cost savings from water efficiency	RCM	Estimated cost savings of £1.4 million from 30 lean projects focused on water efficiency across its four manufacturing sites. Those projects were recommended by third party auditor. Average payback period is estimated as less than two year	(B -12)
Cost savings from material and energy efficiency	Water recovery	Estimated annual savings of £700 through reprocessing of HVAC-generated condensation liquid from manufacturing plants. The project cost was £921 to implement.	(In – 01)

Note: The currency is converted to pound whenever required at the time of writing report as most of the foreign-based companies has reported cost savings on their local currency.

However, some innovative companies have raised concerns over the longer payback period for green adoption while considering the 'ROI of green project' as a measure. For instance, one of the innovative companies (A) expected a longer payback period (e.g., more than 7 years) and extra staff hours for developing greener (e.g., continuous process) process through redesigning an existing process. The measure of 'cost of production' has also taken place in this scenario and has had a profound impact on deciding to accept or reject a green project. As per some other respondents in similar cases, the cost of green production would be higher due to the fact that there is a fear of revalidation and related costs for making a change in the process, for instance, the idea of adding new equipment, or perhaps retrofitting old, inefficient lines and equipment. But this ROI prediction gets better when green adoption is considered in the early development phase, as was agreed by few other respondents. For instance, one of the companies (In -05) highlighting that ***"it is more effective to build in energy efficiency from the beginning than redesign an existing system"***

Generic pharma

It was evident in the interviews that whilst innovative pharma apply cost measures to both new and existing process development, generic pharma were seen to use this measure in the case of existing process improvement only by means of lean (packaging

materials/water/energy/solvent wastes treatments) activities. As revealed in the study, generic pharma has less incentive to redesign the existing process for major change; their cost effectiveness (via environmental practice) is limited to these traditional lean activities. It was also revealed in the study that 'cost savings from materials efficiencies', 'cost savings from energy efficiencies' and 'cost savings from disposal' were the key measures used by generic pharma. For instance, one of the companies (F site 2) projected the environmental benefits of using greener chemicals (e.g., bio-based catalyst) in the process by means of these measures. The respondent stressed that greener operations would significantly reduce the costly disposal of pharma process wastewater. For instance, one of the companies (Gn – 06) reported an 8.6% disposal costs reduction within a year. This cost benefit has predominantly been achieved by adopting greener waste treatment such as increased rate of waste diversion and energy and materials lean projects (e.g., water reduction activities). See Table 7.19 for some other relevant examples of cost performance identified in the study.

'Cost of green production' has also been highlighted in the study as a key green performance measure by generic companies. As revealed in the interviews, in many cases, the generic sector has predominantly projected the negative economic performance of green manufacturing as the cost of green manufacturing is expected to be too high due to the costs of regulatory changes of process. This is because***, "the ROI takes different prediction when a process is changed"*** as highlighted by one of the respondents (C). As per a number of respondents, though they could justify the ROI based on cost savings from less energy, less raw materials use, less water, less carbon etc, the long term procedure for a process change having no significant cost savings is the key issue for moving to green, obviously, depending on the types of product and types of process change.

Therefore, the majority of the respondents raised their concerns about the higher cost of green pharma production. For instance, one of the respondents (F – site 1) warned that the cost of green production could be 20 times higher than traditional methods of production for generic pharma. The respondent further provided an example highlighting that when the unit sales price of a traditionally manufactured (chemical based) steroid-injection is £50, the unit price for same injection produced via greener techniques (bio based) would be £1000. Similarly, another respondent (G) from a generic liquid production plant highlighted that they had carried out a cost assessment on one of the ongoing liquid products which produce toxins as byproducts. The specific risk to human health and higher costs to recycle the wastes toxin did not encourage them to recycle this typical API which is highly toxic by nature.

Bio pharma

As per the findings from both interviews and reports, bio pharma companies, being one of the extensive water users, have predominantly related cost measures such as cost savings from water efficiency. They have also captured the related economic performance. As revealed in the study, the cost savings through water efficiency have been achieved through water usage reduction and related energy savings. For instance, one of the bio pharma (B -12) was recently audited by a third-party independent auditor who proposed more than 100 different water and related energy efficiency projects. However, the company identified 30 potential projects which have shown more than 1.5 million US dollars of savings annually. Examples of some of the related economic impact are also presented in Table 7.19.

Some companies have also considered 'cost of green production' as a measure. The majority of them specifically were seen to conduct cost benefit analysis in the case of new production process. For instance, the majority of the respondents had used this measure while replacing their old styled heavy aluminium reaction tanks with single-use technology. As per other respondents and reports, it was clear that the decision of this equipment replacement is based on the overall cost of production by means of 'cost of single-use technology', 'amount of cost savings from the elimination of cleaning solvents' and 'amount of cost savings from running old aluminium reaction tank'. It was evidenced in the interviews (e.g., J – 01) that though each 'single-use bag' used for each type of drug production costs around £500, they have measured that the cost of using 'single-use technology' has benefitted them by reducing the raw materials cost such as elimination of cleaning solvents and further savings from the costs related to cleaning validation required by GMP, and the related energy costs. In addition to this, a few other respondents highlighted that though the aluminium reaction tank lasts for longer, it would increase energy and raw materials costs, as it requires significant amounts of cleaning. This is how it was revealed that 'cost of single-use technology' is a good cost/economic sub indicator to determine cost of green production in bio pharma.

7.2 Findings on Performance Measures used, and related (environmental & economic) benefits captured by downstream pharma stakeholders

7.2.1 Environmental Performance measures and related performance impact

The environmental performance measures in downstream were predominantly identified in the study to predict the possibility of potential environmental loading of drug substances into

the environment. These measures could also help stakeholders to modify and/or introduce new use-and-disposal related practices. These measures are of great importance because the drug use-and-disposal phase is attributed as the biggest source of environmental loadings of drug substance which could be translated as 49 times greater than the manufacturing phase.

However, interestingly and most importantly, most of the measures taken in the use-and-disposal phase were not predominantly driven by the environmental impacts of drugs (e.g., PIE, AMR) rather they were mainly driven by the factor of healthcare cost savings. But this is not true for some other downstream stakeholders such as local councils and waste management companies (including clinical waste vendors), who were not only driven by cost savings but also by responsibility to the environment. Two key environmental measures were identified in the downstream stakeholders to assess the use-and-disposal related practices. Table 7.20 summarizes the key measures and sub measures and related performance impact across the key downstream stakeholders.

Table 7.20 Key environmental measures taken by downstream pharma stakeholders to deal with environmental loadings of drugs (Source: Interview & Reports)

Key Measures & sub measures	Pharmacy	CCGs (Hospital)	Local Council	Waste Management companies
Materials (drug wastes) reduction related ❖ *Level of improvement in drug adherence* ❖ *Amount of (unused/expired) drugs return to pharmacy by patients (anticipated measure)* ❖ *Amount of drug saving from reuse*	✔	✔		
Toxicity related: Assess amount of waste (municipal) diversion from landfill ❖ *Rate of waste diversion from landfill* ❖ *Bottom ash testing (from drug incinerator)* Emission related: ❖ *Amount of carbon emission from drug incineration*			✔	✔

- ✓ ***Materials (Drug wastes) reduction related***

Drug non-adherence is one of the key reasons for drug wastes. More than 50% of drugs (prescribed for the treatment of longer-term disease) worldwide are wasted due to non-adherence (WHO, 2003), while the figure for UK is 30% (PSNC, 2017). It is also highly concerning that when the drug adherence rate is between 50% and 85% for the treatment of

viral infections, drug resistance is more likely to develop (WHO, 2003). Drug nonadherence (just from five therapeutic groups such as diabetes, hypertension etc only) induces a £500 million loss per year in the UK (Byrne, 2012). Therefore, measure taken to ***assess drug non-adherence levels*** are one of the key measures for the healthcare sector, as this measure indicates the likelihood of environmental loading of drugs within a given context. The subsequent sections present related findings.

- ***Level of improvement in drug adherence***

As revealed in the study, this measure is used to assess the effectiveness of MURs. The study reveals that all pharmacies who conducted MURs also recorded an anticipated improvement on drug adherence which is later on used to analyse the overall level of improvement on drug non-adherence within a given area or across the country. The extent of use of this measure is very high. For instance, one of the respondents (L) has explained that they must fill in a MUR recording form where they must mark whether a patient's drug adherence is anticipated to improve. They also have to indicate and record whether the drug adherence level is improved due to increased understanding of medicines being taken, or due to increased understanding on when and how to take medicine, or due to increased understanding of the related side effects if not adhered to. Another respondent (N) also highlighted a similar recording process and they do it on a quarterly basis and send it to the NHS prescription service department for their own analysis. Table 7.21 presents the average improvement in drug adherence from MUR in one of the community pharmacies (K – store 1 & K – store 2) from March 2019 – December 2019.

Table 7.21 Anticipated improvement of drug adherence from MUR practice within a community pharmacy between March 2019 – December 2019 (Source: Interviews)

Total No of MUR conducted in average	Medication issues identified & action taken (Yes / NO)	Patients refer to GP/other primary health care provider (Yes / NO)	Anticipate improved adherence to drugs prescribed			
			Better understanding /reinforcement of why they are using the medicine/why is it for (Yes / NO)	Better understanding /reinforcement of when/how to take the medicines (Yes / NO)	Better understanding /reinforcement of side effects and how to manage them (Yes / NO)	Better understanding / reinforcement of the condition being treated (Yes / NO)

312	Yes- 25%	Yes – 5%	Yes – 100%	Yes- 100%	Yes- 100%	Yes- 100%
	No- 75%	No- 95%	No- 0%	No- 0%	No- 0%	No- 0%

As seen in Table 7.21, overall, significant improvement in drug adherence under four key areas (e.g., why the medication, what side effects, when to take/ how to take etc) was anticipated. However, some respondents also stressed that the anticipated measures were less effective as there was no follow up under the MUR scheme. So, the measure could have been more effective if there was a follow up system. However, in terms of performance impact, the majority of the pharmacists (through their informal assessment with the patients) reported significant improvement in drug adherence. For instance, one of the respondents (L) highlighted that in more than 80% of the cases they found that patients had an improved level of adherence due to their understanding of how to take the medicines and why they were taking them through the MUR service.

- ***The amount of (unused/expired) drugs return to pharmacy by patients***

This measure was also identified in the study as another potential metric to control drug wastes. However, this metric was still under consideration and not implemented yet. It was clear in the interview that despite being identified, this important measure of the amount of patient return was not yet recorded by the relevant pharmacy professionals. But they have agreed that this could be another good indicator for drug waste reduction. For instance, one of the respondents (M) stated that though there is clear potential for capturing this kind of drug return data, the health authority (NHS) had still not paid attention to this measure. Some other respondents further explained that this could be due to the lack of planning, lack of funding to capture this performance measure or lack of understanding of the value of capturing this performance.

- ***Amount of drug savings from reuse***

As revealed in the reports, this has also been used by few hospitals as a good indicator for reducing drug wastes, though the extent of this measure is still very low and limited to some specific hospital trusts under specific local CCG. Only a few CCGs (6 out of 42) have highlighted this measure. As per the CCG reports, there are two ways of reusing drugs in hospital settings. One is via reusing patients' own drugs brought in hospital admission, and another one is re-dispensing the returned drugs from hospital wards to the hospital pharmacy. The study reveals that hospital wards can reduce a fair amount of drug wastes from reusing patients' own medicines brought from their home during the hospital stay. As per the majority of the reports, this is especially the case for those groups of patients who frequently need hospital admissions and are being prescribed long-term medication. So, it saves drug wastes as these patients bring their own medication from home to use them during their hospital stay instead of being prescribed a new supply from the hospital pharmacy. This practice is also being undertaken through a scheme called the green bag scheme as we have seen in the under practice section.

So, this measure was particularly found to be used as 'the Number of drugs saving from reuse of patient's own drug during hospital stay'. For instance, one of the respondents (Q) highlighted that they regularly monitored and recorded the quantity of drugs brought by patients from their home during hospital admission; and even if they did no bring any they recorded the reason for not bringing them. This measure has helped them to reduce unnecessary drug supply, as most of the time they used to face this issue with elderly patients who are under polypharmacy prescribing and had to redispense new packs and ultimately the patient would stockpile the amount they have at home.

As per the reports, the healthcare employees in hospitals encourage the patients to bring their own medication prior to admission as part of the Green bag scheme through communication with care homes nurses and community pharmacies. The reported savings are huge. For instance, one of the clinical commissioning groups (CCG - 25) has estimated savings of £3.6 million worth of drugs per annum on the basis of prediction that if only 40% of the patients (who are admitted annually) bring their own medication prior to hospital admission. A few of the hospital trusts have also recorded the number of drugs returned to hospital pharmacy from wards. For instance, one of the hospital trusts under a local CCG (CCG – 25) saved £100, 000 worth of medicines (unused and unopened) in a year (2011- 2012) which were returned to the hospital pharmacy to be redispensed, which would otherwise have been wasted and sent for incineration. However, the types of drugs redispensed were not recorded.

- ✓ ***Toxicity related***

Assess amount of waste (municipal) diversion from landfill

It was clear in the study that the rate of pharmacy return still very low and drug disposal via household garbage is still predominant. Hence, the ***Rate of Waste (municipal) diversion from landfills*** is one of the key measures to anticipate the toxicity level of drugs originating from the household wastes stream. Though this measure is apparently relevant to all other sectors, given the serious implication of PIE and consumers' attitude towards drug disposal, it has significant implications, especially on chemical and pharma product wastes management due to increased understanding of PIE and related environmental impacts in recent times.

That is why while the respondents from local councils and waste vendors were asked about particular assessment for drugs waste management, they all highlighted this measure (though it was not implemented by all) and claimed that as long as the waste stream is being diverted from landfill and being treated for waste to energy or incineration, there is less chance of the environmental loading of drugs and related chemicals of concern.

However, the worrying fact that emerged from the study was that a low number of cases (4 out of 16) of the councils (or related third party waste vendors) have reported waste diversion from landfill, which means still more than half of the waste management facility consider landfill for treating household wastes. For instance, a few councils, such as (LC -13), reported the landfill diversion rate as 88.5%. However, most of the waste vendors who only are responsible for clinical wastes and run clinical waste incinerators confirm a 100% landfill diversion rate and employ incineration. Additionally, it was found in the study that the few traditional waste management companies who deal with either drugs (or clinical wastes) or household wastes streams were also driven by this measure and regularly reported the rate of landfill diversion. For instance, one of the respondents (T) highlighted that both clinical and municipal waste streams were found to divert their waste to energy (more than 80%). The study also reveals that most of the waste management facilities diverted 88 - 90% waste from landfill to materials recovery and power generation. Both respondents from the waste management companies (T, U) and reports from local councils have shown that they use this measure as part of the assessment of eco performance and economic performance from waste diversion. Both respondents highlighted here that this measure will significantly reduce the environmental loading of drugs from the household wastes stream.

Bottom ash testing: As revealed in the study**,** bottom ash is the residue present in the clinical incinerator after the incineration of drugs. The study reveals that regardless of a complete or incomplete incineration process the drug incinerator produces this byproduct which may also contain hazardous substances and it is very complex to reassess the toxicity of this byproduct. Therefore, bottom ash testing is also a promising measure to control the unwanted loading of drug substances either originating from household wastes treatments or industrial drug wastes treatment (mainly from incineration).

As revealed in the interviews, the waste management companies (especially the clinical waste vendors) were seen to reassess the byproduct (or bottom ash) to understand its toxicity levels. It was also revealed that the majority of the waste vendors retreated the bottom ash either via a re-incineration process, landfill or recycling, based on the assessment of the byproducts from the bottom ash. For instance, one of the respondents (U) highlighted that they assess their bottom ash on a regular basis and most of their bottom ashes are metals and they are recycled and the parts which cannot be recycled are sent to landfill.

However, it was clear in the study that this measure was only used by clinical waste management companies to reduce the possible environmental impact from chemically contaminated waste (including drug substances) discharged into the environment, and none of the waste management companies aligned with local councils when addressing this measure from incinerated bottom ash. Therefore, it was clear in the study that there was still a fair chance of environmental contamination of drug substances even after the incineration process, though there was lesser chance of contamination in the case of clinical waste vendors compared with general waste (municipal) vendors.

- ✓ **Emission related**

Amount of carbon emission from drug incineration: This measure is particularly important when one tries to understand the greenness of a drug disposal method (e.g., incineration). As revealed in the study, though this measure is actively being taken by the clinical waste vendors who predominantly incinerate the industrial drug wastes stream (e.g., from pharmacies, and/or from manufacturers), this measure has recently been considered by some innovative companies (e.g., In – 05) to gain a rough assumption of LCA-based carbon emission of drugs. One of the respondents (T) from the waste management companies who manage both industrial and household waste treatment, including pharma wastes, confirmed that they had a continuous carbon emission monitoring system in place from the drug

incinerator. The respondent highlighted this saying ***"We have continuous machine monitoring system in the incinerators, making sure we are stayed in our permitted emission".*** This is also a promising measure to reduce the GHG emission from the drug disposal phase. However, it was clear that most of the waste vendors were predominantly seen to maintain the environmental agency permit only, rather than taking any proactive longer-term plans to reduce drug disposal related carbon emission.

7.2.2 Economic Performance measures and related performance impact

Astoundingly, though there are a number of lean measures that are currently being undertaken by the downstream players (e.g., pharmacies, CCG) for reducing drug wastes, related economic performance measures from those lean practices are still very rare and only limited to a few areas of lean practices, which are presented in Table 7.22

Table 7.22 Types of cost measures used for evaluating the effectiveness of drug waste reduction practices (Source: Interview & Reports)

Types of costs measures	Stakeholders	
	Pharmacy	CCG (Hospitals)
Cost savings from drug reuse and recycling ❖ *cost savings from reusing of POD (Patient own medication) during hospital stay* ❖ *cost savings from drug recycling from hospital wards*		✔
Cost savings from patient intervention ❖ *cost savings from medical intervention such as MUR and related other intervention*	✔	

- ✓ **Cost savings from drug reuse and recycling**

This cost saving measure was seen to apply in some hospitals under some of the local CCGs. As revealed in the study, the cost saving is predominantly measured in two cases: one is cost savings from reusing of POD (Patient own medication) during hospital stay, and the other is cost savings from drug recycling from hospital wards. As per the CCG reports and interviews with hospital nurses, in the case of cost saving from POD, cost is measured based on the

amount and types of drugs saved due to not dispensing to the patients, as they bring their own medication from their home. For instance, one of the hospitals under a local CCG (CCG - 07) reported that ***"patients bringing in and re-using their own medicines from home had reduced the Trust drugs bill by £2,400 in a single month"*** Similarly, another hospital from a local CCG (CCG – 01) also measured savings of £6500 per year from one ward alone from reusing patients' own medication. Some more relevant examples of cost savings that were found in the study are presented in Table 7.23.

Table 7.23 Examples of some key economic performance captured due to drug reuse and recycle (Source: reports)

Types of cost measures	Actual cost savings captured	Source of Evidence
Cost savings from reusing of POD (Patient own medication) during hospital stay	£14.27 saving (from general drugs) per patient per stay with average hospital stay of 7.1 days across the CCG	(CCG – 25)
	£300k saving per year from reusing of patient own medication in hospital. This is achieved from 10 wards from one hospital	(CCG – 08)
Cost savings from drug recycling from hospital wards	£100,000 savings in a year (2011 – 2012) through redispensing of returned (unused & unopened) drugs from hospital wards	(CCG – 25)
	£450K savings each year through redispensing of returned (unused & unopened) drugs from hospital wards.	(CCG – 41)

In addition to cost savings through POD, some hospitals were also seen to measure the amount of drug return to hospital pharmacy from wards for reuse. It was also clear in the interviews that those drugs were not left the pharmacy premises and kept them in right condition and the dedicated technician ensures the integrity of the drugs returned to redispense. So, the cost savings from reusing those returned drugs are significant. For instance, one of the hospital trusts under a local CCG (CCG – 41) has highlighted that they have a dedicated pharmacy technician team who regularly assess the integrity of returned (unused and unopened) drugs from wards for redispensing. The trust has stressed into this thread "***over £450k of medicines originally dispensed in the pharmacy and which have***

never left the premises, are returned to the pharmacy from wards and other clinical areas each year, representing a significant return on investment for the Trust"

- ✓ **Cost savings from patient intervention**

As revealed in the study, though there is huge scope for measuring cost savings from patient intervention, such as MUR, this measure is still not widely used across all pharmacies. As per a number of respondents, this is because the industry has recently felt the importance of quantifying the cost savings from MUR and related patient interventions. A few of the respondents also highlighted that the industry has recently realized the trade-off between investing in measuring performance of drug intervention related lean projects (e.g., MUR) and drug wastes related cost savings through adopting some pilot projects across the country. The evidence of using this measure was limited to a few (5 out of 42) local clinical commissioning areas. For instance, one of the Clinical commissioning groups (CCG – 42) reported that it had conducted 1792 MUR between 2008 and 2012. The CCG calculated total amount of costs saved on average per patient per year from MUR through using some key parameters, such as number of drugs stopped, number of drugs changed including dosage etc. This induced an average approximate saving of £122 per patient per year. Similarly, another CCG (CCG – 29) measured annual cost savings of £54000 through a review of 436 patients in care homes (targeted patients with dementia and and/or learning disabilities) in six months, where 1509 recommendations (e.g., dose optimization, medication change, monitoring etc) were made by pharmacists and of them 1209 were rectified by GPs.

Apart from MUR, some other forms of general patient intervention prior to dispensing repeat medication to the patient have also achieved significant cost savings, as evidenced in some other local clinical commissioning groups investigated. For instance, one of the CCGs (CCG – 40) outlined that this area had commissioned a local community pharmacies financial incentive for optimizing repeat dispensing through patient intervention (e.g., intervening with the patient by checking whether they needed all items in a repeat prescription) prior to dispensing repeat medicines. This project saved £37.4K in year one (2011 – 2012) and £36.8K in year two (2010 – 2011) after payment made (for financial incentives) under the scheme.

7.3 Key contribution of the Chapter

The chapter has outlined some unique environmental and economic performance measures and related observations. It also entails clear evidence of actual improvements (in terms of both economic and environmental) from applying green practices. The unique performance measures identified for upstream stakeholders are: *reduction of VOCs/ODS; amount of energy saved from conservation & efficiency improvements; amount of hazardous wastes converted to beneficial use; ROI of green projects; cost savings via materials / energy efficiency; cost of green production*. Being the first ever attempt to identify such measures and their relative importance across the individual sector, the green followers and laggards in the industry will be in a better position to benchmark their existing green attempt with this unique evidence. Consequently, it will encourage them to make more appropriate green related investments decision. VOCs/ODS related measures will significantly contribute to reduce overall carbon emission from the sector. The operationalisation evidence of such emission reduction measures from manufacturing process (especially inhaler drugs) will undoubtedly contribute towards process specific carbon reduction target. Energy conservations related measures will significantly influence the industry to adopt more RCM related green practices. Most importantly, waste conversion related measures (e.g., waste to energy) is significantly important for the sector to achieve the overall goal of zero landfilling, which eventually contribute mitigating PIE and related AMR issues. Among the economic measures, cost savings from greener production (e.g., cost savings from solvent recycling / cost savings from continuous manufacturing process etc) will be attracted by all types of stakeholders significantly to attain economically sustainable green drug production. Especially, the relevant unique evidence of higher costs savings with lower payback period is an important contribution to the sector. Such unique observation will encourage the generic sector significantly to adopt more green practices through post marketing process changes. The positive trade-off between 'materials / energy / toxicity related green practice adoption' and 'related cost savings' is an enormous motivation for the entire sector. This chapter has also identified some unique performance measures and related actual performance in the downstream such as: level of improvement in drug adherence; bottom ash testing from drug incinerator; amount of drug savings through reuse; cost savings from medical intervention; cost savings from drug recycling. This is the first ever attempt to identify such performance measures which is expected to show significant appreciation by the relevant stakeholders. These measures are expected to contribute reducing PIE impact. Significant evidence on the level of improvement in drug adherence will influence the local CCG to invest more on medical intervention projects. The unique evidence of cost savings from drug recycling /

medical intervention will not only reduce overall NHS costs but also contribute to the existing drug optimization projects.

7.4 Chapter Summary

This chapter has presented the key findings from interviews and reports to answer each research question. It has provided an in-depth understanding on green related practices, drivers, barriers, and performance measures across the sector. Empirical evidence with case examples on each aspect of green practice, drivers, barriers, and performance has helped to obtain a better understanding of the effectiveness of the current greening efforts. A wide range of green practices and sub practices were identified under the MET (Materials, Energy and Toxicity) framework in the design, manufacturing, and use-and-disposal phase. Innovative companies were identified as the green leaders across the industry, where generic and bio pharma, in general, were identified as followers in terms of green innovation.

Under green drug design and development, we have seen significant scopes of reducing materials, energy, and toxicity across the drug lifecycle. In particular, the quality by design approach and designing drug process to use greener substances in line with ERA of API were identified as two promising design aspects to reduce materials and toxicity during the manufacturing and use-and-disposal phases. Under green drug manufacturing, the study has evidenced significant materials and related energy savings from solvent recycling and continuous manufacturing process, among other green manufacturing practices. Under green drug use-and-disposal, the study has identified a wide range of drug wastes reduction related practices, such as patient intervention for optimized drug consumption, effective and efficient drug prescribing, and dispensing.

It has also presented ten sub drivers under regulatory, financial, top management commitment and market-related drivers. F-gas related regulations, IED, REACH, ERA for new drug authorization were identified as top regulatory drivers. While almost all stakeholder companies were seen to drive green related practices to deal with those regulations, innovative pharma were particularly driven to adopt green practices (e.g., solvent recycling) because of the cost savings opportunities. Internal environmental targets were seen as one of the key drivers for almost all stakeholder companies to adopt green practices, especially waste and energy related ones. Drug waste related cost savings were one of the key drivers for adopting drug waste reduction related practices in the downstream stakeholders.

It has also identified eight key factors which have impeded the upstream stakeholders to adopt green practices. More importantly, the complex marketing approval of redesigning an existing drug process was identified as one of the key barriers for pharma companies to go green. Generic pharma, in particular, were strongly affected by this barrier. The high cost of green innovation, lack of standardization in process aad limited time to market were also identified as significant factors that have clearly impeded them to implement related green practices. Uncontrolled drug wastes, lack of performance measures of patient intervention, time constraints and lack of regulatory guidance were identified as the key green barriers for downstream pharma stakeholders.

Finally, this chapter has presented key performance measures used in both upstream and downstream pharma stakeholders. In the upstream, thirty-three different environmental measures were identified under four key categories: GHG emission related, materials related, energy related and toxicity related. Significant improvement in many areas such as scope 1 and 2 emission reduction, VOCs reduction, ODS reduction, PMI, amount of hazardous waste reduction, amount of water reduction etc were achieved across the sector at varying levels. On average, Innovative pharma companies were seen to achieve more green benefits than any other stakeholders.

Whilst this chapter has provided an in-depth account of each green practice, driver, barrier, and performance, it is now important to reflect on these key findings to connect them with broader theoretical and practical knowledge. The next chapter attempts to do that.

Chapter Eight: Analysis and discussion of results

While the previous chapter provided empirical, evidence-based grounds for understanding each green practice, driver, barrier and related performance measures, this chapter reflects on the key empirical findings in the research context to enrich the insights through comparing them with the previous knowledge in the field. It also clarifies whether and how the findings presented in the previous chapter are related to the existing literature. Hence, it widens the scope of understanding on each key green area by connecting the existing literature and related theories. It also connects the findings to related theories. Furthermore, it identifies and justifies the key contributions to the field in terms of theory and practice. Table 8.1 outlines the key contribution of the study.

Table 8.1 Highlights of the key contribution of the study

Research objectives	**Key contribution**
To explore key green practices adopted by the key stakeholders in the pharma sector.	- First ever attempt to provide green chemistry (MET) led empirical GSCM practice model for pharma; stakeholder wide green practices and its adoption rate are unique. - Enriched the existing literature in generic GSCM field and green pharma supply chain field through providing a detailed and synthesized LR in GSCM practices in pharma context. Some unique green practices identified: - *design and develop manufacturing process to use greener substances;* - *design and develop drug discovery process to dematerialize*; - d*esign process to consume less raw materials by applying PMI;* - *design and develop manufacturing process for flexibility in quality;* - *Design and develop manufacturing process by installing and validating energy efficient equipment system (e.g., reaction vessel);* - *Consider energy management program;* - *Digitize prescribing and dispensing for drug wastes reduction;* - *Energy recovery from drug incineration;* - *reuse of drugs;*
To identify key green drivers and barriers faced by the key stakeholders in the	- First ever attempt to provide stakeholder wide GSCM drivers and barriers for pharma; stakeholder wide green driver and barriers intensity assessment is unique for pharma. Some unique green drivers identified: - *Regulations: (f-gas related regulations; REACH regulations; ERA of drugs; The Waste (England and Wales) Regulations 2011; drug take-*

Research objectives	Key contribution
pharma sector.	*back legislation;* - *cost savings;* - *top management commitment;* - *monetary incentives;* - *high healthcare costs.* Unique green barriers identified: - *Complex marketing authorization process of greener drug (redesigned off patent); cultural issues;* - *Lack of standardization in equipment and processes;* - *Time to market;* - *lack of demand of green API;* - *Uncontrolled drug wastes from high concerned patient groups;* - *Lack of regulatory guidance on environmental consideration in prescribing;* - *Contradictory regulatory guidance for disposing unused/expired drugs;*
To develop a green performance measure model for the pharma sector.	- First ever attempt to provide stakeholder wide GSCM performance measures model and relative importance assessment of the measures, which is unique. Unique green performance measures identified: - *Reduction of VOCs/ODS;* - *Amount of energy saved from conservation & efficiency improvements;* - *Amount of hazardous wastes converted to beneficial use;* - *ROI of green projects;* - *cost savings via materials / energy efficiency;* - *cost of green production;* - *level of improvement in drug adherence;* - *bottom ash testing from drug incinerator;* - *amount of drug savings through reuse;* - *cost savings from medical intervention;* - *cost savings from drug recycling.*
To comprehend the actual benefits (in terms of environmental and cost/economic) from applying green practices in the pharma sector.	- First ever attempt to identify stakeholder wide actual benefits (environmental / economic) from applying green practices in pharma. Some (examples of) unique benefits identified: - *Medical interventions conducted by pharmacists significantly improve (more than 95% cases) drug adherence;* - *potential cost savings from drug reuse by hospitals;* - *significant cost savings from water/energy efficiency projects by generic pharma;* - *Innovative and bio pharma reported significant improvement in hazardous waste reduction;* - *significant water reduction achieved across all upstream stakeholders;* - *PMI is continuously being lowered by the innovators only;* - Significant carbon emission reduction from redesigning inhalers products by innovators;

8.1 Analysis and discussion on Green Practices

This section reflects on the key green practices and sub practices in the study identified under drug design and development, manufacturing and use-and-disposal, and their significance to the context, practice and policy making, as well as their significance in the theoretical context. They are also supported by the existing literature.

8.1.1 Analysis and discussion on Green drug design and development

Though green design is not a new phenomenon in GSCM literature, the scope and development of green design strategies in pharma is very promising and unique. Prior to initiating this empirical investigation, the concept of green drug design and development was completely vague, disjointed and dispersed into multifaceted views. For instance, though there was an indication in the existing literature that a partial drug design and development could be possible applying the principle of green chemistry, the detailed account and industrial evidence on the scopes and detailed viability of applying green chemistry had not been presented. In addition, majority of the related green design concepts focused on technical understanding rather than looking through an operations management lens. The subsequent sections highlight the importance of the key findings and how each key finding is related to the existing literature and theories to clarify the contribution.

8.1.1.1 Design for Materials reduction

Design and develop manufacturing process to use greener substances

The related findings are significant for the industry. The investigation has provided clear evidence that biocatalysts led drug process design improves environmental footprints by reducing raw materials usages, overall process energy requirements and reduces toxic wastes byproducts. These practical benefits from adopting bio-based catalysts will undoubtedly motivate the industry, especially the generic companies, to adopt this green practice. Potential environmental and cost savings in relation to this practice can also help persuade the regulatory bodies to relax the related complexities for the approval of those existing drug processes which can be redesigned for efficiency. Additionally, speedy development (via increased throughput using biocatalysts) will be one of the crucial success factors for the investors, especially for the R&D based innovative companies, to reduce the overall drug development timeline to enjoy an extended period of monopoly of sales of the new drug

products. Therefore, the key findings in relation to this green practice are critically important for the sector.

The findings support and enrich the contribution of Challener (2016), who initially assumed that the introduction of greener or bio-based substances (e.g., biocatalysts) by replacing traditional non-bio substances (e.g., metal catalysis) could improve process materials and energy efficiency. The findings also support the study of Sheldon (2010), who highlighted that biocatalyst offers the possibility of reducing or eliminating the use of hazardous solvents and wastes as biocatalyst based reactions are carried out in water with or without organic solvents. However, neither Challener (2016) nor Sheldon (2010) provided the empirical evidence of how and why companies adopt this green practice. They also did not reveal the adoption level and how the adoption level varies across the sectors and why. This investigation has filled these gaps.

The traditional chemical reaction in the process normally uses metal catalysts extracted from non-renewable sources, whereas the biocatalysts are produced from renewable bio-based /biodegradable sources. The supply of those metal-based catalysts is also becoming costly and very uncertain. Hence, though Challener (2016) highlighted that biocatalysts also improve renewability; interestingly, the investigation did not find this as too important. The issue of metal-based catalysts which are non-renewable and finite in the nature should have been one of the main concerns. The managers did not consider these environmental benefits probably because they are unaware about this environmental impact (the scarceness of metal catalysts in nature) in general. This indicates that the operations managers must be better educated to understand the key environmental impact of the resources they are using, so they could take alternative green decisions such as promoting bio-based catalysts.

Though the application of this design aspect could have greater importance to the generic pharma due to them capturing the lion's share of the market, slow movement to adopt this practice has increased further concerns. However, the investigation indicates that the overall adoption (considering both new and existing drug process) across the industry is still not adequate for greening the entirety of pharma operations. In addition, it is still not a well-established phenomenon among the generic pharma due to the regulatory burdens, though innovative big pharma is at the forefront of designing greener reactions using bio-based substances such as enzymes and/or greener solvent than other pharma stakeholders. These findings are also in line with the study of Watson (2012). This green aspect is also in line

with the contribution of Slater et al (2010) as well, where the authors mentioned maintaining process temperature at an optimum level to reduce process energy using greener chemicals as part of green chemistry principles. However, none of the studies provided the overall scope of adoption across the innovative, generic and bio pharma sector before. They also have not considered the life cycle impact of this design aspect. It was also not known whether it differs in applying green practices in the case of new drug development and/or redesigning of the existing drug process. In particular, it was not previously known how generic pharma are facing related regulatory challenges to exploit such potential environmental and economic savings from using biocatalysts. This investigation has filled these knowledge gaps and this is how the investigation has enriched and extended the existing knowledge.

Design and develop drug discovery process that reduces chemical-based testing

The related findings are significantly important for the industry, as the drug R&D process involves a series of trial and test, which consumes a significant amount of costly materials. Also, the innovators are under considerable pressure to reduce the impact of their operations on natural resources. Whilst the drug R&D is a materials exhaustive process due to the nature of drug discovery and lower attrition rate to the discovery process, varieties of forms of In-silico designed compound screening (e.g., focused library with 3D view) have been sought as a promising design consideration for materials reduction and related costs and developmental time savings. Though the findings of HTS and 3D view of lead drug substances are in line with the previous literature of Clark et al (2010), Sundgren, (2004) and Tucker (2006), this investigation has clearly enriched our understanding on how In-silico chemical screening and related focused library (e.g., structure-based drug design, DNA-encoded library) based screening have changed the screening strategy in R&D for reducing raw materials and related costs. Those previous studies did not provide any evidence of how materials savings are actually possible from applying the non-chemical-based screening strategies. None of these studies even evidenced how and to what extent the innovative, bio and generic pharma behaved with the screening technologies.

Remarkably and arguably, compared to the other sectors, the generic companies are far behind in adopting the in-silico type testing. This is because they normally deal with developing and re-designing the existing process of drugs where their key task is not discovering new chemical compounds; rather they focus on optimizing existing process, either changing the manufacturing process or changing formulation design etc. However,

while designing a new version (sometimes called second or third generation) of generic drug process, they could adopt these in-silico type experiments to save materials.

It is also remarkable that the concept of nanotechnology driven drug design has not been discussed in the previous literature. It was not known how nano-materials would play a key role in designing new drug formulation for materials savings. Though innovative and bio pharma are currently adopting nano-materials drugs, the generic sector could also reduce input raw materials and related costs significantly by adopting nanotechnology. However, in that case they would have to redesign the formulation of existing drugs to enjoy these benefits. Whilst apparently it seems to be very profitable as well as eco-friendly in design, the entire pharma sector (especially the generic sector) could face regulatory approval related costs and time-consuming burdens. This could be the key reason for which the generic sector is still far behind in adopting this technology. Additionally, the generic sector could be motivated more to embrace this technology, when it sees the wide range of practical benefits of adopting it like LIMS integrated system – which has resulted in significant materials saving benefits across the industry. However, it is still a matter of continuous investigation for pharma companies to see the viability of nanomaterials-based drugs formulations in all therapeutics areas.

Design process to consume less raw materials applying process metric (e.g., PMI)

The investigation indicates that there are ample opportunities for pharma companies to save raw materials such as solvents, reagents, reactants and catalysts across all its new and existing product portfolio during the manufacturing phase if this design aspect is considered in the early drug development phase. As the demand for generic drugs are surging, the potential materials savings from redesigning the existing drug process applying PMI is huge. It is also important to highlight here that existing generic processes which have been in the market for many years have a significant amount of batch process data. The parameters, conditions and other related key characteristics of each existing process are also well understood. Hence, these data (e.g., materials input/output, safety, quality parameters etc) provide a strong baseline for analysing PMI for many thousands of processes, from where the most materials efficient process can be developed.

The findings are somewhat in line with Roschangar et al. (2016), Henderson et al. (2010) and Jimenez Gonzalez, (2011), where the authors have stressed on using PMI metrics in order to dematerialise the process and reduce related energy and wastes induced from production

process. However, they lack empirical evidence, which has now been found and presented. The findings have also enriched the existing understanding by showing the extent and scope of adoption of this practice industry wide.

Though the previous literature (Slater et al., 2010; Henderson et al., 2010) has identified PMI as a green chemistry metric for use in the manufacturing phase, the importance of considering this practice in the early R&D phase and its impact on the manufacturing process was not clear. Practical evidence for attributing the extent and scope of this metric in reducing the materials footprint in the early stage of drug design and development phase in innovative, biopharma and generic pharma atmosphere was not known. So, this finding has filled the existing gaps in the literature. For instance, it is clear from this investigation that PMI is predominantly used by innovative pharma, while bio pharma and generic pharma are still in their infancy for adopting this practice due to the relevant operational complexities and the regulatory, time and costs burdens.

Design and develop drug manufacturing process for flexibility in quality (Quality by Design)

This design aspect is of paramount importance for the industry as it induces significant amount of materials wastes due to quality distortion during R&D. The amount of wastes exponentially increases during mass production. Accuracy and precision in each stage of drug development is of paramount importance. Even a slight distortion in quality from one batch to another during mass production is a waste. While at the same time it is true that it takes time to understand a drug process parameter better, time to market is a crucial factor here. This is not only due to cost and competition but also to save patients' lives on time. So, time taken to analyse process parameters to understand quality variation to create a flexible design space is the key for pharma. Though the QbD concept is sought as a promising green design aspect for pharma, the adoption level is a worrying factor.

To the best of the researcher's knowledge, none of the previous literature has mentioned this green aspect. It is undoubtedly clear from the investigation that the industry could surely benefit (in terms of materials savings) from adopting QbD in the early design phase. It could potentially save a significant amount of time and costs for reapproving the process by the regulatory body - as the variations in quality are already being included in the initial regulatory approval. As QbD will require extra time and investment to acquire scientific knowledge over the developmental timeline, the industry is arguably reluctant to adopt it.

Time to market is crucial for innovative drug development and the R&D always try to accelerate the process of development for recouping the investment through generating as much revenue as possible within the limited patented period. So, apparently, putting in extra time to master the process and identify the possible quality variations may not be the key focus for pharma companies. On the other hand, being cost focused, the generic pharma may not be interested in investing in QbD.

Design packaging for materials efficiency

The findings related to packaging design are partially in line with the study of Ding (2018), where the author indicated the need for redesigning pharma packaging to reduce wastes from oversized or inappropriate packaging. Though previous research has focused on developing life cycle inventory data for analysing the environmental impact of the drug process including packaging (Raju et al., 2016; Soete et al., 2017; Chaturvedi et al., 2017), this empirical evidence suggests that the industry has predominantly adopted LCA for packaging options rather than for the drug process. The LCA of the drug process is still not a common practice. But, in the case of selecting packaging (either primary/secondary/tertiary) options they have adopted the LCA approach, though it is still limited to the innovative sector and a few bio pharma cases. This is due to the fact that the industry found it difficult to manage and incorporate lifecycle inventory data LCID) on one hand, and the willingness to invest time and money on developing a robust in-house built LCID on the other hand.

Whilst the generic sector consumes significant amounts of packaging in terms of primary, secondary, and tertiary, the greener packaging options could induce environmental and cost benefits considerably. The low level of green packaging consideration in this sector is a real concern and a surprising factor. Time and cost constraints are understandable for generic pharma but the sector could build a transparent and robust in-house LCID based on the exchange of the key information (e.g., material consumption, water usages, energy usage etc) on the existing drugs (approximately 3000 different APIs) in the market. Obviously, regulators will have to push and ease the exchange and transparency of the related key scientific data across the industry to build a sustainable pharmacy.

Though the previous literature (Clark et al., 2010) had many concerns, such as whether using recycled materials and /or re-sizing of existing packaging degrades the quality of the product and loses consistent quality requirements and stability of the products. This study has confirmed that this is not the case and pharma companies can consider recycled content in

secondary and tertiary packaging without compromising product integrity. Also, resizing is possible either by applying nano-based materials technology or resizing the packaging for reduced usages of materials, which was previously unknown.

Design combined drug (e.g., use multiples active substances) for material reduction

The findings clearly indicate that the pharma industry can save a significant amount of packaging, APIs, excipients, and other auxiliary chemicals raw materials by developing combined drugs. At the same time, it ensures drug quality, safety, and efficacy. The findings support and enrich the key literature of Ding (2018), where the author advocated producing combined drug to dematerialize. However, there was no empirical evidence to demonstrate whether the concept of designing combined drug can be seen through the lens of dematerialization. The investigation also extends the existing knowledge by providing the scopes (including related drivers and challenges) of adopting this practice across the industrial segmentation. It is important to highlight and reflect on the finding that the generic segment could save significant amounts of raw materials and related costs by redesigning the existing formulation to incorporate multiple APIs if they can afford clinical development. It also became clear that cost of redesigning combined drugs is significantly lower than cost of designing new ones, which is a great motivation for all pharma across the sector.

8.1.1.2 Design for Energy Reduction

Design and develop manufacturing process for the least energy consumption by evaluating alternative process

Regardless of new or existing drug development, process-based energy evaluation in the early phase of drug research and development can help the industry to step up to claim, tag, and sell energy efficient APIs in the market. Given the significant importance of being responsible manufacturers competing with each other, the innovative manufacturers have already incorporated the requirement of energy footprint of APIs purchasing basket lists. As heating and cooling within a pharma process consumes approximately 60% of energy, the finding is of great importance. The findings support and enrich the indication of Clark et al. (2010) and Slater et al., (2010) where they indicated a process design based on energy assessment. This investigation extends the understanding of the scope of applying process-based energy assessment across the industry. For instance, the findings clarify why process-based energy assessment in generic and bio pharma are more difficult than in innovative. The

findings also clearly indicate the requirement of urgent attention of industry leaders and regulators to come up with innovative ideas to provide more incentives for companies to promote more energy assessment-based process design. For instance, increasing patent life for developing the most energy efficient process for innovators, or reducing approval timelines for generic pharma who develop such processes.

The findings also indicate that arguably the generic pharma could not afford to invest in time and related regulatory changes costs to re-design any of its exiting drug process using such energy assessment. Similarly, the non-adoption of this typical energy assessment by the bio pharma companies indicates that the complex equipment design with the dynamic nature of bio-based process materials (e.g., high purity, contamination etc) could be a key barrier. Additionally, none of bio pharma and generic pharma is confident of considering this practice as they have not yet realized the practical benefits of applying it to date. Therefore, increasing the environmental awareness among the managers would be the key here for improvement.

Design and develop manufacturing process to validate and install energy efficient equipment system

Though the consideration of energy efficient equipment installation (apart from single use technology) in the process development was comparatively higher in the innovative companies, this practice has been hugely important to the bio-pharma companies. This is due to expanding the sector soon and it will generate environmental benefits from the replacement of more energy efficient disposable single-use reaction vessels. Additionally, the future demand for biosimilar drugs (generic version of bio-based off-patent drugs) is also increasing due to off-patent bio-based drugs. Hence, the potential of using a 'single-use technology' based drug process is promising. The lower adoption rate of single-use technology in generic pharma indicates that biosimilar drug manufacturing is still significantly low compared to innovative and bio pharma. Though there was an anticipation of achieving energy efficiency in the manufacturing phase from designing and validating initial equipment system in drug design and development phase in the initial literature review (Slater et al., 2010), combing the evidence from both interviews and reports has enriched this green aspect by providing detailed scope and the extent of this practice across the industry. In particular, the previous literature did not talk about 'single-use technology' and its potential benefits for bio-based operations. The findings also clarify why the consideration of this

design aspect is more viable for new drug designs and development than redesigning existing ones.

8.1.1.3 Design for Toxicity reduction

Design and develop bio-based drug process to reduce water toxicity

The acute pressure on upstream pharma companies to tackle the issue of PIE, biodegradable process, or somewhat similar process development to reduce water toxicity has become a key consideration across the industry. The key findings on developing bio-based drugs is significantly important for all stakeholder companies to reduce the potential issues of AMR which is expected to grow exponentially and more people are expected to die by the next decade from this drug pollution. The findings also indicate the importance of considering solvent selection guides and / or selecting raw materials by green chemistry principles. This will undoubtedly help practitioners across the industry to promote green solvent guides and green chemistry principles. It also indicates why the companies should focus on redesigning the existing process to improve its environmental degradability and why the regulatory burdens for approving such redesigned processes must be compensated or supported to achieve a wider environmental goal. Hence, the related findings could help both practitioners and policy makers to understand the trade-off between environmental goals, patient safety and efficacy of drugs. So, the role of both practitioners and policy makers has become clear throughout the related findings.

The findings on this design aspect can be supported and confirmed with several previous studies. For instance, the reduced usage of toxic chemicals (e.g., DCM) in process development among the innovative big pharma companies has also been found in the previous study of Watson (2012). It further explains that this approach also increases the environmental degradability of the drug process. The lower level of adoption of this practice was also evidenced in the study of Watson (2012). The study also confirms that pharma R&D uses water-based solvents considerably. These previous findings are in line with this study. Additionally, the findings on the usage of toxic solvent in early process development and the increases of overall manufacturing costs is also in line with the previous literature of Sumpter (2010) and Boltic et al (2013). The findings are also supported by Kumereer (2009), where the author initially indicated optimizing the drug process to use eco-friendly raw materials. The findings also support Taylor's (2010) arguments of how environmental biodegradability and patient efficacy, or biological biodegradability, works differently in many directions and

is one of the key barriers to develop bio-based drug in the early phase. Findings on the lack of environmental stability data for existing process were also in line with Sumpter (2010).

Most importantly, the study findings resolve many misconceptions and concerns on whether bio-based process can be possible across the industry and its potential environmental benefits. The scale and scopes of adopting bio-based drugs across different pharma stakeholders was not previously known. It was also not known before how innovative and bio pharma are playing a role in developing bio-based process to reduce water toxicity.

It is also remarkable that previous studies did not mention biodegradable nano particles-based drug formulation, which has a significant potential to reduce water toxicity through improving drug effectiveness and improving patients' excretion performance. However, it is still necessary to clearly identify the scopes of using this technique across the existing drug process under different therapeutic areas. Industry leaders should explore further how they could convert existing bio-based API into nano particle form for downstream formulation. We also need to know related operational challenges to overcome it and make the existing process substantially green and promote it more in the early drug development phase.

Design and develop drug process to reduce air toxicity

To the best of the researcher's knowledge none of the previous literature mentioned this green aspect. As seen, VOCs emissions from the HPLC process and CFCs from inhaler products are the two key sources of environmental footprint for pharma; this design aspect plays a crucial role to reduce the environmental burden not only in the R&D process but also in the later stage of the life cycle, such as in manufacturing phase (quality control using HPLC) and in the usage phase (using inhalers by patients). Though there is strong evidence in the investigation to consider VOCs reduction from the HPLC process, the overall adoption on average is still low across the industry. In particular, generic and bio pharma must pay more attention to revalidating their HPLC process to reduce VOCs emission. As generic pharma R&D also uses the HLPC process and other relevant developmental research for existing process development which significantly emits VOCs, it is important for them adopt this design aspect. Therefore, it is important for regulators to reconsider how the generic pharma could easily obtain this benefit from adopting it without investing lots of time and money to review both the internal (quality requirements) and external (regulatory requirements) validation process.

The findings on CFC-free and PMDI inhalers also indicate that the industry could save significantly more GHG emission (especially from type 3) if the regulatory approval process (including both internal and external validation) and related investment are reconsidered for promoting the redesign of the existing drug process.

Though the previous literature has provided a clue to applying the concept of decarbonisation (Walsh & Bullock, 2013) and VOCs reduction (by using less organic substances) (Jimenez Gonzalez, 2011) in the chemical process, the scopes and how it would have been applied in the case of pharmaceutical product design phase were not previously known. Additionally, none of the previous studies explored how a particular pharma product, such as inhalers, would have been designed for emission reduction in the early stage considering its impact in the usages phase. So, the scope of this green design aspect and its extent of application across the pharma sector have enriched the existing body of knowledge in the field.

8.1.2 Analysis and discussion on Green drug manufacturing

The study has revealed that though green design aspects have shown a promising positive environmental impact across drug life cycles, there are some operational decisions that actually develop over time and are avoided or overlooked in the early design and development phase due to various factors such as time, costs, and complex equipment settings. Hence the findings on those operational decisions during the manufacturing phase are critical for greening pharma operations. Most of the related findings have enriched our understanding significantly from the blurry view in the initial literature review. The subsequent sections have presented those key insights extracted from the related study findings and discuss them in line with the previous literature.

8.1.2.1 Materials reduction

Run continuous mode of manufacturing

It was indicated in the study that though there is a variation of implementation of this green practice across the industry due to the variability in product, process, time, demand, equipment, engineering process etc, there is huge potential for environmental savings (reduce raw materials, hazardous wastes, carbon emission and energy use), especially from converting the existing (around 3000 APIs) batch process in the market across the globe. The findings also indicate that the formulation process (especially tablets) is still not as much

continuous as API production. The engineering difficulty and top managements' traditional mindset for batch production are the key barriers for this. Lack of consistent equipment suppliers and related engineering, especially the complex scale up process from kilo lab to commercial lab are the key challenges for continuous bio pharma manufacturing operations. So, the related findings could help the practitioners to review their operations strategy accordingly.

It is important to note that though the initial literature review (Plumb, 2005; Slater et al., 2010) has indicated for the adoption of continuous manufacture in general, the previous studies did not elaborate (using empirical evidence) on how environmental savings can be achieved from both continuous API production and continuous formulation. The related environmental and economic benefits were not known before. Furthermore, the scopes of adopting continuous process (e.g., time and tempature sensitive products versus conventional tablets) across different pharma stakeholders were not known before. Therefore, related new findings have enriched the existing body of knowledge significantly.

The finding on PAT integration into continuous process also validates the concerns of Slater et al (2010) where the authors highlighted that manufacturers could use PAT (Process Analytical Technology) for continuous monitoring of the process parameters to prevent the accidental damage of a batch. The authors also had concerns whether PAT could help the industries to save significant amount of materials and energy through efficient operations. So, these understandings have enriched the existing literature. However, the extent of adopting this practice across the industry on average is still low, indicating that it requires urgent attention from industry leaders to overcome all related challenges such as reviewing the internal and external validation process of a redesigned existing process, as the key barrier to adopting PAT is complex time and cost consuming regulatory burdens. PAT related such understanding was not known before.

The finding is also in line with the literature of Plumb, (2005); Mollan and Lodaya, (2004), Slater et al., (2010), Perez-Vega et al., (2012) where they had predicted initially the positive environmental impact from adopting continuous manufacturing. But there was no empirical evidence or strong case for it so that the related policy makers or regulators or practitioners could take strategic decisions on this aspect for increasing environmental sustainability as well as cost savings. However, interestingly and remarkably, whilst the study of Plumb (2005) provided some dubious assumptions against continuous process, *for instance, batch*

process is easier than continuous to understand over time to control some specific process parameters to attain certain product qualities, the new understanding on the QbD and PAT-led continuous process (either API process and/or formulation) is that each process parameter is scrutinised and controlled proactively by using design space and PAT technology to resolve the dubious notion of continuous over batch. This is how the study contributes to the existing body of knowledge. This understanding is significantly important for practitioners to promote QbD for better environmental and economic performance.

This finding is also consistent with Plumb (2005) where it was highlighted that moving to continuous from batch would reduce energy consumption and induce less waste. The finding can also be validated with the study of Soete et al (2017) and Watson (2012). Watson (2012) also found out that the innovative big pharma companies are in the leading position to adopt continuous process.

It is also clear in the investigation that though the consideration of this green aspect is still in between planning to low level of adoption on average across the industry, the innovative pharma companies are at the forefront of adopting this practice compared with other industry players. This is because changing this manufacturing mode for a drug product is time and cost consuming, as the manufacturers would require proving to the regulatory bodies that this change will not affect by any means the quality, efficacy, and safety of the drug products. This has become a significant barrier for all companies and especially for generic pharma who normally participate in a fiercely competitive environment and cost is the key factor. This indicates that policymakers must reconsider the existing policy of approving redesigned existing process.

Recycle and reuse solvent during the manufacturing process

The related findings are important as solvent purchasing, handling, and disposing is one of the key cost contributors across the industry. The findings on the scope of solvents recycling during the pharma manufacturing process clearly indicate that there is huge potential for manufacturers to save both materials costs and related environmental footprints. It is important to highlight here that some of the findings on recovery practices are in line with the previous literature of Teunter et al (2003) and Parez-Vega et al. (2013) where the authors highlighted and indicated the potential viability of solvent recycling. Some other findings such as the recovery potential of different solvents are also in line with the study of Slater et al., (2010). However, none of them provided a detailed account of recovery practices during

pharma manufacturing, which was not feasible enough to claim solvent recycling and reuse as the management practices for achieving green manufacturing attributes across the industry. Additionally, there was only one empirical case study (Teunter et al., 2003) of recycling practice in the existing body of knowledge, which has limited understanding on the scopes of solvent recycling in the context, especially the scopes of recycling in the innovative, generic and bio pharma. For instance, it was not clear how and why different pharma stakeholders consider solvent recycling. It was also not known before how recovery differs across different processes within same production site.

The findings also clarify the confusion between Slater et al. (2010) and Teunter et al. (2003) in terms of applying the distillation (a solvent recylcing process) process for solvent recovery. Whilst Slater et al (2010) raised concerns about the environmental footprint from the distillation process, the study actually supports Teunter et al (2003)'s perception that the distillation process enables the production of high purity solvent which eventually saves significant amounts of raw solvents usages through improving materials and energy related environmental footprint.

It was also a concern whether onsite or off-site recycling practices are dominating (Schefer, 2017). Additionally, the overall extents of applying these green activities were not known. This investigation has not only filled all of these key gaps and related other gaps reflected in the literature review sections, but has also enriched existing knowledge of recovery practices across the key industrial segmentations such as innovative big pharma, bio pharma and generic pharma. For instance, it was not known before how recycling of solvents was considered in the generic and/or bio pharma environment. This investigation has attempted to identify the key similarities and key dissimilarities in terms of applying solvent recycling practices (e.g., types of solvent to recycle or process of recycling) which has enriched existing knowledge. The investigation has also clearly pointed out where to focus to develop more recycling practice across the industry. For instance, reviewing and reconsidering regulatory process for approving existing process redesigned for solvent recovery.

Consider lean operations for material reduction

The investigation is a success story for lean production. It plays a dual role: reducing materials usage and increasing cost efficiency. While the majority of the studies on other sectors have predominantly shown how lean philosophy is used for cost effectiveness, this study reveals that the pharma industry has focused on lean and green together for achieving

both cost and materials efficiency. Most importantly, the lean operations (e.g., forms of water reusing and recycling) for saving water are significantly important for pharma to reduce its water footprint and related costs. Though the previous literature of Slater et al., (2010) indicated that solvent waste reduction could be part of generic lean practice across the sector, this study reveals that in most cases solvent waste reduction was seen as a built in manufacturing approach and sometimes was practiced under special 'solvent recovery projects' rather than general lean projects in the context.

The industry can be benefitted hugely by learning and applying those detailed accounts of lean scopes identified in the proposed manufacturing areas, which ultimately have enhanced our existing operational knowledge in the area. Though the initial literature review highlighted material reduction as part of MET practices (Clark et al., 2010), none of the previous empirical studies has provided a detailed account focusing on developing water reduction practice or packaging materials reduction techniques across the pharma industry. Though Ding (2018) highlighted a narrowed aspect of packaging materials reduction, it did not provide any practical evidence and details of the scope of reducing packaging volume using digital technologies. It also did not focus on how different critical equipment parameters can be optimized to achieve lower materials footprint across the pharma plant. So, the key finding in this section has significantly contributed to the existing body of knowledge.

Consider green collaboration for materials efficiency

The related findings are significant for the pharma industry as a drug is produced through combined efforts of diversified stakeholders, whose interest and power play a crucial role for reducing related operational wastes. The study findings clearly indicate that successful green process design will require a smooth flow of data sharing (green related) and communication between upstream R&D scientists, medicinal chemists and downstream process chemists, process engineers and waste vendors. For instance, if the upstream scientists and medicinal chemists do not consider the feedback from downstream process engineers who are unable to recover solvent due to product quality issues and equipment engineering difficulty, the ultimate process design for green credentials will be in vain. Though internal and external suppliers and customers collaborations for developing green product design and manufacturing is well known in other industries like automotive, electric and construction, there was no empirical evidence or particular case studies to learn from for pharma green

operations. There was no empirical evidence to demonstrate how both internal and external pharma stakeholders can collaborate to develop a green drug manufacturing process or select a particular green solvent. This investigation has addressed these limitations.

The related finding is also somewhat in line with Parez-Vega et al (2013), where the authors highlighted that a collaboration practice among the relevant stakeholders e.g., synthetic chemists, process chemical engineers, disposal contractors (or waste management companies), and suppliers prior to selecting a solvent in the early stage of API manufacturing, could significantly reduce the solvent wastes. The finding also validates and extends Clark et al's (2010) cooperation concepts for green credentials where the authors raised concern about whether process chemists, medicinal chemists and process engineers can cooperate together to achieve green credentials of drug design and manufacturing. This collaboration practice can also be linked and explained through the information theory (Sarkis et al., (2011) as the flow of green related information and data between upstream medicinal chemists, scientists and downstream process engineers are crucial for successful green practice adoption.

8.1.2.2 Energy reduction

The key findings indicate that fuelling process from a sustainable energy source such as CHP is of paramount importance for the pharma industry to reduce energy consumption and related costs. It is important to highlight here that though some of the initial literature, such as Soete et al (2017) and Clark et al (2010), indicated less energy-based production, none of them explained what key scopes are available to optimize the manufacturing operation to reduce energy consumption. Furthermore, none of them explained the extent of usage of these practices across the industry. Therefore, the findings from this green manufacturing aspect have enriched existing knowledge and contributed new knowledge.

The study clearly indicates that as pharma companies are aggressively looking into reducing energy costs and related footprint, the success story of applying different process centric energy kaizen programs identified could significantly influence the industry to achieve their energy reduction targets. In particular, when the cost is a paramount factor, such as in the case of generic pharma, they could learn from and adopt the energy kaizen cases revealed in the study. The findings are in line with Bellm (2015), where the author highlighted the importance of applying lean for process excellence. However, the study did not consider in detail the relevant tools and energy kaizen programs (e.g., Britest tool) used for process optimization in practice, especially in terms of environmental gains.

Though the study of Clark et al (2010) highlighted developing energy efficient manufacturing, it did not cover in detail whether and what lean techniques actually can reduce energy and how this works to achieve energy efficiency in the manufacturing phase. The study also did not focus on how these measures work, and to what extent, across different industry players, i.e., innovative, generic and bio pharma sector. This is how the findings in the present study have addressed the existing knowledge gaps. The finding is also somewhat congruent with Watson (2012) where innovative big pharma was also seen as a leader for adopting energy efficiency measures. However, Watson (2012) did not cover how pharma producers can deploy process-based kaizen and lean activities to reduce energy consumption. It is also important to highlight here that the bio pharma processes have sought to be more sensitive and complex to optimize their process. Therefore, there was less opportunity to apply lean, kaizen, or six sigma approaches in bio pharma than other stakeholders.

8.1.2.3 Toxicity reduction

Consider greener chemical (e.g., solvent/reagents etc) management

The study results clearly indicate that upstream pharma employees such as process chemists, scientists and process engineers have become far more concerned about toxic chemical management than ever before. The overall industry move towards this practice was in between 'planning to consider' to 'low level', though innovative pharma was in the leading position. The findings on reducing toxicity through green chemical management and the extent of this green practice adopted are somewhat consistent with the previous literature of Watson (2012) and Veleva and Jr (2017). It is however important to note here that none of these studies outlined how chemists, scientists and engineers are engaged with different sustainable chemical management programs to manage and ensure greener chemical management and application in the process. Participating in green chemical management programs such as chemical footprint projects has not only provided chemical optimization opportunities across the pharma manufacturing plant, but also assesses their capability to manage greener application of chemicals (e.g., replacing solvents of environmental concern with greener ones).

Though the initial understanding on manufacturers' ability to detoxify the production process was limited to only technical viability of solvent selection guides (Clark et al., 2010; Perez-Vega et al. 2013), they did not explore relevant concepts of how, what and to what extent companies detoxify the production process. Though Perez-Vega et al. (2013) highlighted the

importance of combating VOCs emission from the production process via selecting green solvent in a collaborative manner, the author did not highlight the key factors such as smooth calibration, cleaning and washing up process etc, which must be looked into in detail for managing VOCs from the process. In a nutshell, none of the previous researchers attempted to provide a detailed account on the detoxification process of pharma production through empirical evidence. This research has filled these research gaps. The findings will undoubtedly help practitioners to understand the importance of regular participating chemical footprint programs and will be able to promote them across their sites.

Monitor and control environmental toxicity of drug substances (eco-pharmacovigilance)

The findings are significantly important for the industry across all relevant stakeholders, as they are under regulatory and social pressure to reduce the environmental loading of drug substances to deal with the pressing issues of AMR/PIE. The study results clearly indicate that though the design and development of toxic free APIs is still in its infancy and in planning stage across the industry, monitoring and controlling API discharge from the manufacturing process is the key. Scientific understanding of the aquatic impact of APIs and control those APIs accordingly may not be a proactive approach, but it has huge implications on managing the existing drugs (around 3000 APIs) in the market. The finding is somewhat in line with Clark et al (2010) and Kummerer (2009), who outlined that pharma manufacturers could extend their responsibility from monitoring ongoing safety and efficacy of drugs to monitor the impact of metabolised and/or un-metabolised APIs in the water cycle after patient excretion. However, they did not reveal the practical scopes and viability of this extended drug vigilance for environmental gains. This study has filled these gaps by extending their initial assumptions on protecting PIE. The finding has also empirically validated the initial assumptions of Clark et al (2010) on PIE. The attempt of ERA across the pharma industry has enriched the product stewardship concept which was completely blurry in the initial literature review. To the best of the researcher's knowledge this is the first kind of study that provides empirical evidence of how and to what extent the pharma industry has incorporated the issues of PIE into their existing pharmacovigilance programs. The findings have also supported and enriched Rusinco's (2007) green manufacturing concept, especially with regards to extending the understanding of the concept of product stewardship for managing perishable and/or time and temperature sensitive goods like drugs.

However, it is remarkable that the level of eco pharmacovigilance practice (or continuous monitoring of aquatic toxicity of APIs) is predominantly high in innovative pharma and low in both generic and bio pharma. But generic pharma has been contributing to PIE significantly due to a higher volume of production to meet demand for lower costs of drugs. It was low for bio pharma as they use fewer chemicals in the manufacturing process. The findings have also sufficiently enriched the concept of extended stewardship (or eco pharmacostewardship or eco pharmacovigilance) in the pharma context by means of regulatory guidance on ERA practice.

Interestingly, many pharma professionals who oversee the pharmacovigilance of existing drugs in the market for patient wellbeing are still not aware of ERA or they do not have any clear guidance on eco pharmacovigilance. This limited awareness is also clear because of the myopic nature of the regulatory view on ERA of drugs. For instance, if ERA fails to demonstrate the toxic free APIs, it is still under the consideration of marketing approval. But this could help mass producers to monitor and control the discharge of those APIs. This is how the concept of ERA or eco pharmacovigilance from an operations management view has been enriched. The study has also enriched the understanding on how pharma manufacturers are dealing with the increased concern of AMR through monitoring and controlling antibiotic discharge from the manufacturing process.

Consider responsible waste management for toxicity reduction

The findings have added new knowledge to how responsibly pharma companies manage their process wastes (hazardous), as the previous literature did not explore this aspect apart from solvent recycling. The findings also partially support the study of Teunter et al (2003) which indicated that solvent wastes were recycled and reused. The findings of solvent recycling also support the study of Slater et al (2010), where the author also explained how pharma process waste solvents are recycled. It has also addressed Sheldon's (2010) significant concerns about pharma wastes from the manufacturing process, and the lack of related practices. However, none of these studies provide any detailed account on the scope of process wastes management and related challenges for achieving overall environmental toxicity reduction. Additionally, previous study did not consider different types of industry players such as innovative, generic and bio pharma.

The findings clearly indicate that the concept of process 'waste to beneficiary use' in the pharma context has been sought as a rudimentary approach not only to detoxify process but

also to identify a new trade-off between waste conversion and recovery disposal investment. Applying waste hierarchy and zero landfill approaches in line with process waste recovery in the pharma context has been sought as a promising green manufacturing culture which was unknown in the previous literature. It is important to note here that zero landfill with recovery strategy has ensured pharma operation reductions in water toxicity and related AMR concerns. The extent of adopting each of the sub green practices across the key industry players has also provided a clear picture on what and to what extent innovative, generic and biopharma embrace this green aspect. Though innovative pharma has sought to adopt zero landfill predominantly, generic and bio pharma are still behind in adopting this due to operational (e.g., complex installation of equipment in bio pharma for waste recovery) and cost focused manufacturing approach (in case of generic pharma). However, zero landfill with recovery practice is far more complex in the API production plant as it induces more toxic byproducts than formulation pants.

8.1.3 Analysis and discussion on Green drug use-and-disposal

It became very clear that though green chemistry related practices are currently being practised at varying levels across the industry in the case of new drug development, the number of existing drugs (around 3000 APIs) in the market and their significant production volumes and usages still remain the biggest concern from an environmental point of view. This is because the scopes of redesigning those existing (off-patent) drugs processes for environmental savings is significantly low due to the unwillingness for the generic manufacturers and/or other manufacturers who produce off-patent drugs. Higher costs and the time-consuming revalidation process of those off-patent drugs are the key reasons. Hence, effective, and efficient use and disposal of unused or expired drugs are crucial for reducing environmental loading of drugs. The subsequent sections present the relevant insights under materials (finished drugs), energy and toxicity, respectively.

8.1.3.1 Materials (finished drug) reduction

Consider lean operations for optimized drug prescribing, dispensing and usages

Medical interventions (MUR/NMS)

MUR is of ample importance, as drug nonadherence and not understanding drug dosages incur significant drug wastes (Daughton, 2013: 2014). Though Latif et al., (2011); Latif et al., (2013); McDonald et al., (2010) outlined the concept of MUR and patient experience, none of

these studies focused on understanding the role of MUR for drug usage optimization and related waste reduction. This investigation has enriched the existing understanding of MUR in a new dimension, such as understanding the actual benefits (in terms of drug waste reduction) from applying MUR, the intensity of using MUR, and relevant drivers and barriers of implementing MUR.

The MUR related findings indicate that the majority of the community pharmacies in the UK have been providing this service for wider benefit for the local community not only for optimizing the NHS drugs budget, but also for ensuring quality of healthcare service through patient safety. The findings on the extent of high MUR practice are also in line with the secondary report (Byrene, 2012), which states that 83% (9,467) of community pharmacies are providing the service. The concept of MUR was also outlined in the study of Xie and Breen (2012) but not in detail. However, the findings of MUR can be externally verified by the study of Ruhoy and Daughton, (2008) which mentions the increased monitoring of patients; practice of concordance - actively involving patients in the treatment process, developing mutual trust with the intent of improving compliance and reducing drug non-adherence, side effects, early stopping of medication and simplifying dosage.

Whilst the existing literature was only limited to MUR intervention, this study found some other kinds of medical intervention techniques used by pharmacists, such as NMS, which has also been shown to be a drug optimizing tool in the far downstream of the service. To the best of the researcher's knowledge, none of the previous research has attempted to understand the role of these typical lean practices (e.g., MUR, NMS) for drug optimization during the use and disposal phase.

Though the concept of rationale drug use was suggested (Start, 2008; Vollmer, 2010), it was never known in the literature how pharmacists would play a role in practice to encourage people to become rationale drug users for selecting OTC drugs – which eventually reduces stockpiling and later environmental loadings.

Reuse of drugs

The study results clearly indicate that the scope of drug reuse in the context is very limited. There was vagueness in the previous literature about the reuse of drugs. This study has clarified this. Though there is an indication of reusing dispensed but unused drugs in pharmacies (Mackridge & Marriott, 2007), the scope of this practice in the research context is against regulatory advice in general, and hence, a majority of unused unopened drugs from

community pharmacies, hospitals and care homes are treated as wastes. There are three main reasons for this. Firstly, the integrity and safety of the returned unused and unopened drugs are not ensured for reuse; secondly, there is no clear regulatory guidance for reusing those returned drugs, and thirdly, even if there is an option to reuse the drugs for another patient, the related operational tasks, such as drugs physical and chemical quality inspection, would be burdensome.

So, there is a need to find the clear trade-off between the operational burdens and reuse benefits. Obviously, the reuse of most costly drugs (e.g., HIV drugs) would have been more justifiable in this case to adopt regulatory guidelines. However, there is a need to reconsider and revise the regulatory guidelines for processing patient return of unused unopened drugs when they are returned to pharmacies for disposal. However, the pharmacists have also confirmed that this practice (reuse of drugs) is only allowed for certain drugs (and unopened from the original box) in certain contexts (e.g., hospital wards/pharmacies) not for all drugs, as it is illegal to redistribute drugs once the drugs have left the pharmacy premises. When they were asked if there would be any SOP to follow for drug reusing practice, they think there could be a possibility to legitimate this practice for same patients who return them to reduce drug waste. This future assumption is somewhat consistent and supported by Mackridge and Marriott (2007).

However, it was remarkable that the scopes of drug reuse were identified in the hospital settings in two ways: reusing patients own medication during hospital stay and re-dispensing the drugs returned from hospital wards to hospital pharmacies. This finding will have a significant impact on managing drug wastes while successfully implemented in all hospitals across the country. This finding is also supported by the study of Bound and Voulvoulis, (2005) who had the same assumption. On the contrary, Ruhoy and Daughton (2008), and Pomerantz's (2004) suggestion on the redistribution of unused returned drugs (by means of donation) to other countries or within the same proximity is still not supported in the UK context. Though it was suggested by Mackridge and Marriott (2007) that with current stability testing guidance and by utilizing modern packaging techniques, including tamper evident seals and 'smart' labels that react to temperature and humidity, it would be possible to identify inappropriately stored medicines, the consideration of reusing of returned medication and related legislation has still not been changed. Thus, the study not only avoids the confusion in the existing literature whether drug recycling / reusing of patient returned

drugs is a viable option and how, and in which context, but also enriches the existing understanding about it.

Rationale prescribing

Rationale prescribing practice explains how prescribers can become more efficient and effective in their prescribing practices for achieving overall drug usage optimization through a strong establishment of reliability, relationship and responsiveness among GPs, pharmacists, and patients. This practice is of great importance as inappropriate (e.g., over and/or under prescribing) prescribing has induced drug wastes considerably (Daughton and Ruhoy, 2013; Daughton, 2014). Though the existing literature predominantly advocated for 'lowest effective dose or dose reduction (where possible)', and 'prescrib[ing] drug[s] based on excretion profiles of an API' aiming to reduce environmental loading of APIs (Daughton, 2014; Daughton and Ruhoy, 2013), the practical viability and limitations of these considerations along with a range of other sub practices have emerged to enrich the understanding of the concept of rationale prescribing practice through this empirical investigation. Additionally, whilst there was an optimistic view in the existing literature of using environmental classification of drugs during prescription (Start, 2008; Gotz & Deffner, 2010; Taylor, 2010), the inquest has clearly revealed the practical obstacles to consider such prescribing practice.

Another significant finding is that the concept of excretion profile during prescribing is not practically supported. Though some conceptual papers have repeatedly stressed it (Daughton and Ruhoy, 2013; Daughton, 2014) to reduce the environmental load of APIs, the GPs' priority is the metabolism of action or where the drug is going to be metabolised mainly in the body (either in kidneys / liver) rather than considering the amount of excretion coming out through urine or stool. For instance, a patient whose liver function is poor cannot be given a paracetamol (low excretion rate – 4% parent API) instead of Ibuprofen (comparatively higher excretion rate -10% parent API) as revealed in the study. This is because paracetamol is mainly metabolised in the liver.

It was also highlighted that drug effectiveness, efficacy, quality, and side effect profiles are of main concern for GPs to consider during prescribing. This finding has enriched empirical understanding of the concept (consider excretion profile of drug during prescribing) originated from the study of Daughton, (2014); Daughton and Ruhoy, (2013). However,

though the GPs have accepted that there could be scope to consider the excretion profile when the point of metabolism is not an issue for particular patients, there are no clear guidelines or motivation to consider this concept. It was also indicated that there would be a general fear of deviating from the main aim of treatment if they focus on the excretion profile of a drug in their prescribing practice.

It is also important to note that the eMC (electronic medicine compendium) clearly outlines the un-metabolized excretion rate of each API under the heading of 'Pharmacokinetic Properties'. When eMC outlines the pharmacokinetic properties (e.g., the rate of un-metabolized / metabolized excretion) of a particular drug, it would be possible to outline the rate of un-metabolised / metabolised excretion of other similar group of drugs in the same part of the website for a comparative analysis of un-metabolized and/or metabolized excretion rates. So, the prescribers, pharmacists or other healthcare professionals who regularly visit the eMC website for up-to-date info on each medicine could educate themselves about the variation in the excretion profile of a drug and other relevant environmental concerns. So in time, it could motivate them to prescribe lower excreted drugs for environmental reasons. However, this would require a strategic move from the upstream stakeholder, especially pharmaceutical manufacturers, to utilize the scope of this typical source control for combating PIE.

The findings of rationale prescribing practice can also be supported by the study of Schiff et al., (2011) where the author justified the rationale prescribing practice as relying on underlying cause, not just treating symptoms; increasing knowledge by applying a few limited drugs; avoiding frequent switching without clear evidence; learning about new drugs from unbiased sources; avoiding prescribing (where possible) newly marketed drugs; and considering hypertension patients' non adherence. The concept of PRR (Prescription Review Reports) as part of drug waste reduction practices was not discussed in the previous literature. Furthermore, the concept of 'Antimicrobial Stewardship' was not discussed in the previous literature as part of rationale prescribing practice or eco friendly prescribing efforts. Therefore, though the GPs interviewed believe it would be one of the best source controls to reduce antibiotics in the environment, the link between 'Antimicrobial Stewardship' programs and relevant environmental benefits is still unknown. It is important to highlight that pharmaceutical companies and wastewater treatment companies could cooperate with the department of health to extend or modify the program to include environmental fate data or ongoing scientific environmental impact data of microbial resistance in the environment to

encourage and educate healthcare professionals about the environmental consequences of drugs, more specifically antibiotics.

Trial Package

Trial package as part of effective and efficient prescription was also revealed as an efficient means of optimizing drugs usages. The study indicates that if prescribing practice includes initial experimental measures either with trial package of medicines or physical exercise or other related means to allow the patient to alter the longer terms disease, there is a greater chance to control disease and optimize drugs usages. This finding is also supported and externally validated by some existing conceptual studies - Xie and Breen (2012): assumed the use of a shorter period of prescription; Ruhoy and Daughton, (2008) and Start (2008) - trial package / unit dose. Similarly, the findings of alternative therapy up to now can also be supported by the study of Whilst Gotz and Deffner, (2010) and Schiff et al., (2011) who advocated for alternative therapies such as exercise, action sports, walking, back training, changing diet etc. However, the level of consideration in the GPs' actual prescribing practice and the related legal guidance by the governing bodies, such as NICE, was not known before.

Training and education

Training and education on drug optimization for healthcare service providers at all levels is the key to increasing self-awareness, so they can practice it in their daily responsibilities. It is interesting that the study finds that the majority of healthcare professionals (e.g., doctors, nurses, pharmacists and care home managers) have sought to be very actively responsible for their daily tasks. They put their job responsibility on top of everything else. As such, related training and education would have been effectively useful for optimizing drugs usages. Though the finding can be externally verified by the study of Kummerer (2009), where the author assumed that properly informing doctors, pharmacists and patients can contribute to a reduction of the input of APIs into the aquatic environment, the types of education programs designed for GPs and other healthcare professionals and how they are focused on reducing drug wastes by optimizing usages was not discussed. A similar case is evident in Start's (2008) study. This is because both studies were conceptual rather than empirical and did not explain in detail the educational programs for the healthcare professionals. So, the contribution of the findings in this aspect is clear. However, although the current education programs will potentially contribute to the reduction of unwanted pharmaceuticals loading in the environment, the programs still lack environmental concern of drug usages and

inappropriate disposal. This is because the key driver of these programs is cost effectiveness. So, the NHS could consider disseminating the environmental impact of drug usages and inappropriate disposal in the existing program.

The findings about the awareness campaigns have not only rudimentarily enriched the existing knowledge but have also contributed to new dimensions of knowledge. Whilst the findings of awareness programs from this study can be externally validated by the study of Vollmer (2010) and Kotchen (2009), those studies focused on increasing disposal awareness only. Some other previous studies such as Glassmeyer et al. (2009); Vollmer (2010); and Kotchen (2009) outline different types of collection events (e.g., daily, ongoing, one off, weekly, single day, by drop off facility/mail back etc) across the US rather than focusing on any kind of nationwide campaign to increase awareness for both drug waste reduction and safe disposal. Additionally, none of these studies focused on understanding the operational aspects of the campaigns or events such as the extent of implementation of the events/campaigns and the relevant drivers, barriers, and performance. However, the RUM (Return Unwanted Medicines) project governed and financed by the Australian Government, and Canadian ENVIRx disposal program sponsored by the pharmacy and pharmaceutical industry (Glassmeyer et al., (2009) are somewhat consistent with the awareness campaign in the UK.

Drug reduction campaigning is aimed not only to advise for the safe disposal of drugs but also to educate patients about how to reduce drug waste. It is also remarkable that the responsibility of the other stakeholders (especially pharmaceutical industry and/or wastewater treatment companies / local council), apart from the NHS, for initiating awareness programs in the UK context has been neglected. One of the reasons that emerged from this research is that these stakeholders have not felt any pressure (either from government / customer) or have no driver yet to deal with it. Astoundingly, the NHS has implemented the awareness campaign predominantly for cost savings rather than environmental concern. Pharmacy take back alone is not enough to increase the environmental awareness of unwanted drugs in citizens. More voluntary and private-public initiatives are required to deal with PIE. For instance, AstraZeneca has the joint working agreement with NIHR (National Institute for Health Research) to develop mobile apps of ‘My Medication Passport’ to support front line medical staff to deal with unwanted drug wastes (PMLiVE, 2013). The pharmaceutical industry must be more proactive and come forward to liaise with local pharmacies or local government environmental agencies to introduce separate collection events to raise

awareness. Though green drug design can be a rudimentary approach for future generations of drugs, the pharmaceutical industry must be reactive to this situation if the existing chemicals-based formularies dominate in the market. Though the reasons why other stakeholders (especially pharmaceutical industry) are not contributing to source control practice is partially understood in the drivers and barriers of the green drug use-and-disposal section, there still room for future research to investigate it separately.

Consider digital technologies for optimized prescribing, dispensing and usages

The study has clearly revealed that digitized prescribing and dispensing (especially repeat dispensing) systems have been a clear track and trace system of drugs movement between doctors, pharmacist, and patients. This digitization is of greater importance for the context to reduce yearly drug expenses for public health. Though the previous literature (Vollmer, 2010) has highlighted that clear and consistent communication between patients, doctors and pharmacists could play a significant role in drug optimization, it did not reveal any technological platforms for this communication process.

To the best of the researcher's knowledge, this is the first study that has discussed in detail how doctors, patients and pharmacists could optimize drug wastes using digital prescribing and dispensing management systems. However, the clear performance (in terms of drugs wastes reduction) study of the efficiency of electronic prescribing systems is still not widely done. Additionally, the summary care records are still not synchronized across the systems of sub systems for its effectiveness, for instance, a patient's care record may not be updated when the patient is admitted to another emergency care other than their usual one, or even sometimes patient care records are not updated as per the movement of patients to different care settings. Therefore, there is a system requirement of a one stop shop to further improve the effectiveness and efficiency in the care system to optimize care costs as well as drug usage optimization.

8.1.3.2 Energy reduction

Though the concept of incineration is well known in many other sectors, little is known about the drug incineration with energy recovery process and related waste segregation process and related challenges in the existing studies. One of the key differences between traditional product incineration and drug incineration in that the incineration ash from drug incinerators is assessed continuously (e.g., bottom ash testing) to reduce toxicity and continue complete

destruction to avoid landfill of incinerated ash. However, it is important to highlight here that bottom ash assessment from general waste incineration has been paid little attention, which could have been a potential threat to the environment. This is because till now most people dispose of their drugs through household garbage. So, the reluctance of bottom ash management in the general waste stream must be carefully looked at. Additionally, energy efficient refrigeration system installation and avoidance of temperature related excursion in the downstream pharmacy, hospital and care home settings have also not been discussed previously. It was also not known before how effective segregation of drug wastes plays a crucial role in energy efficiency in the final incineration phase.

8.1.3.3 Toxicity reduction

Safe disposal management of unwanted drugs is a must to tackle the unnecessary environmental loading of drugs leading to PIE and AMR. Though the previous literature (e.g., Vollmer, 2010) has highlighted different types of drug collection strategies for safe disposal of drugs, those studies did not consider a holistic view to demonstrate how downstream healthcare stakeholders (e.g., pharmacists, doctors, patients, hospital, care homes, drug waste vendor, and wastewater treatment companies) play a role to ensure effective and efficient collection of unwanted returned drugs for safe disposal. The previous studies also did not discuss the key importance of drug segregation and its process across the downstream drug supply chain stakeholders. This study has been a completely new example of an empirical case showing how each downstream pharma stakeholder has actively promoted safe disposal of drugs through word of mouth, official campaigns, continuous clinical interventions etc.

The study also indicates that there is no single technology that can be used for complete removal of pharmaceuticals residues from the effluents as of today. This finding is consistent with the previous studies of Start (2008) and Kummerer (2009). While incinerated ash from municipal household wastes normally goes through landfills, byproducts or incinerated bottom ash from the drug incinerator goes to reprocessing or recycling as metal for example.

Though these technologies have not yet been installed for treating the effluent on a large scale, the companies are planning to consider them soon depending on some further research and findings on them. However, the potential companies could start thinking of these technologies and study their individual fit and identify relevant drivers and barriers, at least to deal with those residues (presented in the table), which have commonly been found in higher

concentration in the UK waste water catchments. It is undoubtedly clear that none of the previous studies have focused and have tried to identify these kinds of greener technologies (that could be potentially useful for reducing the drug concentration in the environment) to deal with PIE issues for the waste water treatment companies.

When the overall findings on the level of green (drug use-and-disposal) practices are plotted against the waste hierarchy, the possible matrix can be produced as pictured below (see Fig.8.1). The more the practices move from disposal towards prevention, the greener the practice is. So, each stakeholder should aim to stay in the top right position in the matrix representing high level consideration of prevention practices. Though the matrix clearly shows that the majority of the practices fall in the preventive phase, some of the practices undertaken by GPs (e.g., alternative therapy, educating patient for safe disposal, opportunistic medication review) and pharmacists (e.g., increase awareness for drug take back, counselling to optimize OTC drugs) are still at a low level of consideration in their daily practice. Also, medium level prevention practices (as indicated in the matrix) taken by the waste management companies and local councils, and pharmacies would need to be further investigated to improve them. Therefore, it is clear from the matrix that there is still room to improve the low level of reuse, recycling, recovery, and disposal practices undertaken by the respective stakeholders (as shown in the matrix). However, to increase their practice, it is mandatory to understand the key drivers, barriers and related performance achieved so far from applying those practices.

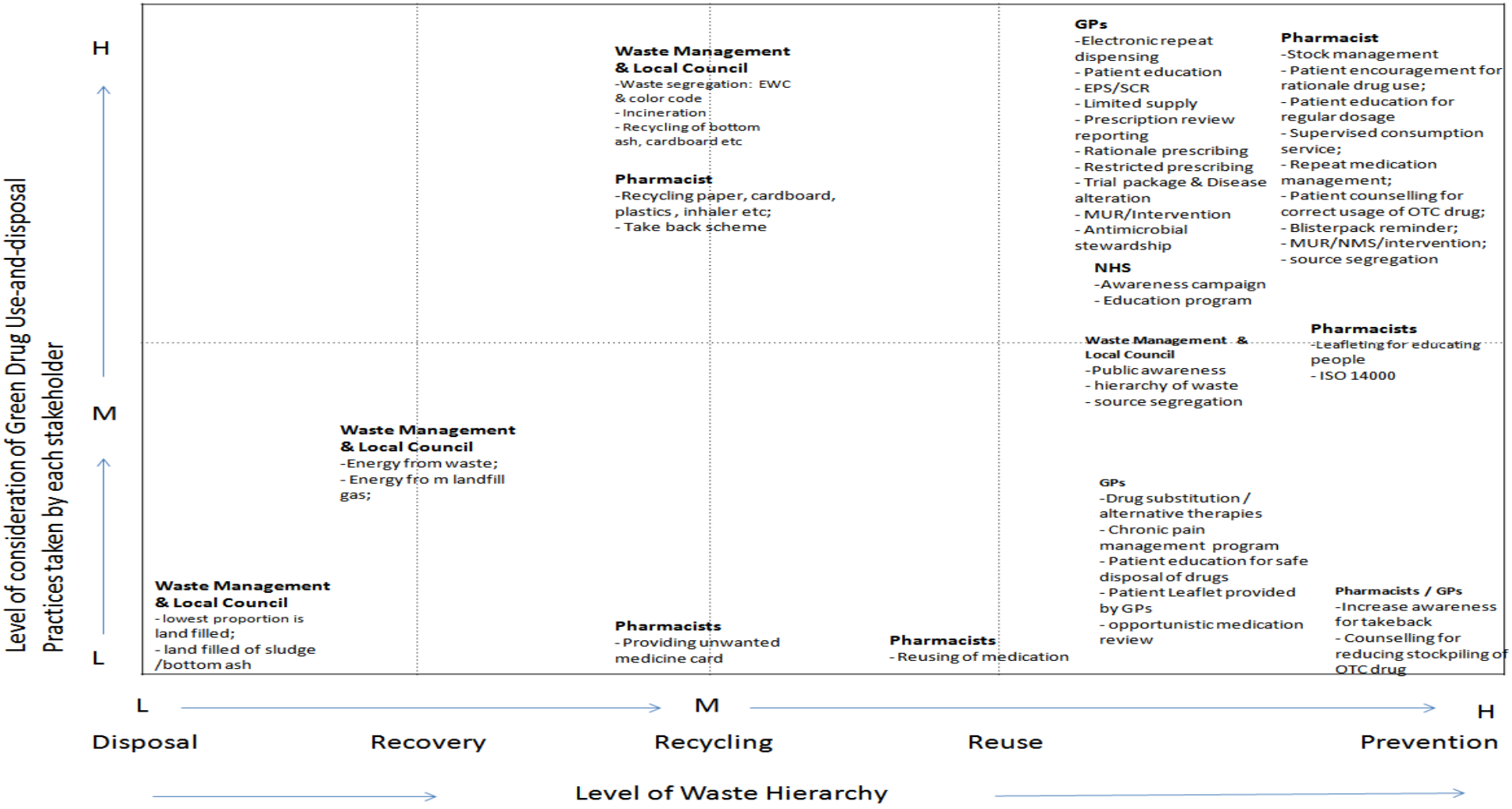


Figure 8.1 Stakeholder wise drug use-and-disposal practice matrix (Source: Interview and reports); L = Low; M = Medium; H = High

8.2 Analysis and discussion on Green Drivers

The findings on green drivers are critically important for both upstream and downstream pharma stakeholders, as they are under serious regulatory and social pressure to reduce the environmental impact of their products. Understanding those drivers could significantly help the practitioners to adopt new operational strategies to reduce drug wastes. Policymakers will also benefit from reviewing their existing policy through green drivers to impose clear policy that offers trade-off between environmental benefits and patient safety. The subsequent sections present the key insight on green drivers in the case of both upstream and downstream stakeholders.

8.2.1 Analysis and discussion on green drivers for upstream pharma stakeholders

Regulatory driver:

The study indicates that companies, especially the innovative companies, are becoming more serious about adopting MET practices to stay far beyond the regulatory limit. The generic segment pays attention mostly to the brink of regulatory limit, while almost similar steps are being taken by the bio pharma companies. F –gas related regulation, IED and REAH were identified as top key regulatory drivers for green adoption in pharma.

F – Gas related regulation: The findings indicate that this regulation has significantly changed the way inhaler drugs are produced. This transition has also led to the discovery of a new drug delivery system where the process induces F- related gas emission. Thus, the F – gas regulation has not only pressurised the companies to comply with the regulatory limit but also encourages innovation in process design. The study further indicates that innovative companies have already developed a new culture of innovation to deal with ozone depletion and related environmental consequences, for instance, upgraded cooling process and/or replacing chemicals coolant to mechanical cooling. Though there are many innovative generics in existence, they struggle for process change due to the cost-focused nature of their business. To the best of the researcher's knowledge, however, none of the previous studies has highlighted this driver in their R&D operations. Therefore, the consideration and promotion of CFC-free inhalers during R&D, and CFC-free cooling and refrigeration system during the manufacturing process driven by F – gas related regulation, is expected to enrich the existing body of knowledge in pharma green supply chain study.

IED: Though the regulation is explained in the previous study by Clark et al. (2010) in terms of air and water emissions or related toxic discharge from the production process, it is important to highlight here that how this type of regulation drives the related green practice adoption (e.g., energy efficient process design, use of less organic chemicals etc) in the pharma was not known before. It is also novel finding that innovative pharma is predominant in facing this driver in comparison with generic and bio pharma. It is remarkable that being the producers of larger volumes of drugs per year, the generic sector should have been driven more by IED compared to innovative and bio pharma to adopt green technologies. But the study shows IED has been the least important driver for generic pharma. The reasons could be two-fold. Firstly, as the generic market is highly competitive and cost-focused it does not have the capacity to invest in such new technology and secondly, weak legislation enactment - for instance, no monetary penalty for exceeding the industrial limit.

REACH: It is important to highlight here that though previous studies outlined REACH (e.g., Clark et al; 2010), none of the previous studies in the pharma sector have explored how REACH can be a key driver for adopting green practice (e.g., toxicity reduction) in the drug design and development phase. The intensity of this driver faced by the key industry stakeholders was also not known. So, these findings are expected to enrich the existing knowledge in the field. For instance, though Clark et al (2010) assumed there to be some pressure of REACH on pharma manufacturing, it did not explain how intermediate products are affected by this legislation. As a result, this investigation has provided clear evidence of how REACH has become a driving force for companies, especially the innovative companies, to implement green practices during pharma manufacturing operations. It was also assumed in the literature that REACH regulation would have no influence on green practice adoption, as API is excluded from the REACH list. The investigation has revealed that manufacturers are concerned about pharmaceutical intermediate products produced during the step wise chemical reaction process, due to REACH regulation, and adopting rudimentary approaches like green alternative chemicals use as input.

ERA: The study result indicates that the ERA has been sought as another significant move by the pharma companies to tackle the issue of PIE and AMR. It is also clear that leading innovative big pharma are being influenced more by the ERA related regulation than generic and bio pharma, as innovative pharma consider huge investment on developing new as well as (redesign) existing processes of drug substances. In addition, the high profile big innovative (e.g., AstraZeneca, Pfizer, GSK, Novartis etc) companies are driven significantly

by the ERA due to the fact that their operations are built in the strong belief of – *do it right for the first time*. That is why the ERA related regulation has driven them to invest more on green chemistry-based process design. Though the previous literature highlighted ERA requirements and focus on collecting PBT data (Clark et al., 2010), it was not known whether and to what extent ERA prior to marketing authorization of a drug could drive upstream pharma stakeholders to undertake green related design practices. Importantly, it was not known how the ERA influences three key segments of pharma: innovative, generic and bio. Furthermore, it was not known how companies behave against ERA. This investigation has revealed that ERA has led the companies to become more conservative in terms of assessing environmental risk of a newly developed / modified drug substance in the short-term as well as long-term. This has increased the existing body of knowledge on ERA and related practice drivers.

However, the trade-off between developing green chemistry-based process and research timelines still needs to be explored in detail. The reason is that innovative companies would need to rethink, as limited patents are always ticking in their drug discovery and development timeline. The relevance of this driver to generic pharma is comparatively low, as they rarely have scope (e.g., cost, and regulatory barrier) for developing /modifying new drugs compared to those of innovative companies. The importance of this driver is also comparatively lower than innovative pharma, as they use mostly biologically sourced raw materials rather than chemicals. However, it is still a matter of ongoing eco-toxicological scientific study to evidently confirm that all classes of metabolites (i.e., excreted chemicals) are not harmful when they enter the aquatic system. It is also important to note here that though there is a general belief that bio-based drugs will pose less eco-toxicological impact, there is some strong evidence that development and production of some bio-based API produce significant amount of hazardous wastes. For instance, the current study suggests that though some bio-based (e.g., peptide based API) API are highly effective therapeutic agents in the human body, their manufacture routinely involves *hazardous reagents, produces high waste-to-mass ratios, and requires solvent-intensive purification systems (In – 04).* Similar evidence was found when another bio pharma company (B – 12) was trying to produce a bio-based API (called, *antisense oligonucleotides ASOs- which are modified RNA molecules)* for treating a neurological disorder. This process is solvent exhaustive and generates hazardous, toxic waste byproducts. Therefore, future research will need to explore and identify those classes

of bio process which require more attention to MET practice. Now, to the best of the knowledge of the researcher, the extent of those types of bio-based production is unknown.

None of the previous studies provides a detailed account on different regulatory drivers and their extent across pharma industry stakeholders for adopting related green practices. This is the first study that identifies F-gas related regulations; IED, REACH and ERA are the key types of regulation that have influenced pharma companies to adopt green chemistry based practices in varying levels across the industry. This is how it has enriched the existing body of knowledge in the field. Additionally, whilst the initial pharma related literature makes some blurry assumptions on ERA, REACH, IED as green drivers (Clark et al., 2010) without any empirical evidence, this investigation has filled these gaps and enriched the existing literature. However, the overall findings are in line with previous works of Zhu and Sarkis (2007), Li (2014), Zhu et al (2005), where these authors have similarly highlighted that coercive regulatory pressure influences companies to increase environmental awareness and adopt green practices to deal with the regulations. The study findings also support the Institutional theory (DiMaggio and Powell, 1983) which suggests that regulations related government enforcement drives companies to adopt innovative practices.

Cost savings

The related findings are of great importance in the context, as companies (especially generic pharma) are still struggling to understand the trade-off between economic gain and environmental gain. Compared to other sectors (e.g., automotive, electronic etc), cost savings from green pharma operations were not well explored. It is important to note here that none of the previous studies has identified and focused on exploring this 'cost saving' concept as a driver for adopting green drug design and development. So, cost saving is contributed as a new driver in the existing body of knowledge.

It is clearly evidenced that almost half of the innovative pharma companies examined have felt cost savings as a strong direct pressure for undertaking diversified green projects, such as solvent recovery project, energy efficiency projects, waste kaizen projects or waste to energy projects etc. Though these findings are somewhat in line with Slater et al (2010) and Clark et al (2010) where the author assumed cost savings could be driving pharma companies to go green, due to the lack of evidence the concept was not justified well. None of the previous green related pharma literature has provided clear evidence on this driver. Most importantly,

none of the previous studies provide a detailed account on how cost savings occur across different segments within the industry so that they could prioritize where to focus.

While cost savings from a recycled car are well known, cost savings from solvent recycling was not yet known. Additionally, though the findings are also in line with the stream of green supply chain related literature, such as Bansal and Roth (2000), Zhu et al (2005), Li (2014), Zhu and Sarkis (2007), Zhu and Geng (2013), where cost benefits of environmental projects were discussed in detail, the fact of cost savings as competitive advantages from applying green technologies in the pharma sector was not known.

The study clearly indicates the potential cost savings from solvent recycling, continuous manufacturing, greener process development to use biocatalysts and other recovery projects such as waste to beneficial use. Therefore, this study will undoubtedly increase the confidence in practitioners to undertake more green projects by accommodating all relevant technical, engineering, and other financial related capabilities. The study also indicates that the majority of the innovative companies have invested in green project development through investing in green chemistry-based technology (or MET) and related training and development. Hence, the study findings also support the RBV theory in the research context (Sarkis, 2011), where the view demonstrates that companies must equip themselves with internal resources and capabilities to be innovative, to produce rare products and to increase competitive advantages. However, future research could potentially investigate the appropriate costing model, for example for solvent recycling, in detail, prior to adopting that green project.

Top management commitment

Internal target: Strong internal environmental targets for reducing water consumption, GHG emission, energy consumption, waste reduction, and toxicity reduction, including hazardous API discharge, became one of the key elements for green leadership in pharma. The study findings indicate that top management has a clear vision in two sides: protecting the natural environment from drug production and becoming a leader among socially responsible businesses. The study's finding also indicates that these two-sided visions have enabled the innovative pharma companies to exploit green innovations and become green leaders through proving non-imitable and rare drug products as times passes. Thus, internal environmental target based green culture follows and supports the theory of DOI (Diffusion of Innovation), where a green culture is developed through diffusing green innovation, from goals and

planning to innovation, and finally ends up with implementation (Rogers, 1995; Murphy & Gouldson, 2000).

It is clear from both sources of evidence that most of the green innovations were driven by the internal environmental goals and mostly felt by innovators compared with other sectors. This driver is somewhat in line with the previous study by Clark et al (2010) which indicated the role of top management in green adoption, but it was not clear how different elements of top management leadership (e.g., environmental target and incentivise MET based innovation) helped companies to build a green culture which eventually drives companies to continuously innovate new green technology and stay ahead in leading the green based economy. Additionally, though the previous study by Zhu and Sarkis (2005: 2007) highlighted top management commitment as an internal green practice, it is evidenced from this investigation that this practice has become a built-in green process in the innovative pharma leading to a new culture of green innovation, which has actually driven companies to undertake discrete level green practices in their manufacturing plants.

Community wellbeing and corporate responsibility: It is important to highlight here that the findings on this driver are somewhat in line with the previous study of Clark et al (2010), where the authors assumed that a high level of management on environmental issues and their risk assessment to the business from a corporate responsibility perspective, could be a major driver for implementing green design practices. However, this investigation has provided empirical evidence with a detailed account of this new driver. It was also not empirically evidenced that corporate responsibility drives the big innovative companies to conduct ERA practices in the early phase of drug development. These findings are significant for the companies to learn from in order to realize how the consideration of wider community wellbeing and corporate responsibility bring innovation to the business and improve competitive advantages.

It is clear from both evidence that innovative pharma companies have been significantly influenced by this driver to undertake relevant green practices, especially green innovations in managing waste discharge from the manufacturing plant due to the concerns of AMR and PIE. Though there was a slight indication about this driver in the study of Clark et al (2010), the concept of how community wellbeing and corporate responsibility have driven the pharma companies to adopt green practices was not clear due to the lack of empirical evidence. Therefore, it was not possible to establish this driver as a new indicator for

measuring the concept of top management commitment for promoting green in the pharma sector. It is also important to highlight here that none of the previous green supply chain related literature in the chemical related field outlined this driver and sub drivers.

Incentives: This indicates that incentives schemes (especially for R&D teams) could significantly drive the employees to generate innovative green ideas to develop a green process. Though the finding is somewhat in line with Clark et al (2010), it was not detailed or clear what kinds of incentives are given and how incentive schemes drive green innovation. Also, there was no empirical evidence to support this driver in the previous literature in the pharma sector. This study fills these gaps.

Stakeholder pressure: Though there was a slight indication about stakeholder influence on green drug production in the study of Xie and Breen (2012), the scopes of this driver were not clear. For instance, the study highlighted that the end consumer would not tolerate PIE in drinking water. However, the current study did not find any pressure about this from the end consumer. The obvious reason could be the lack of awareness among the public about PIE compared to the levels of awareness for plastics. But we found that downstream drug purchasers like the NHS have put tremendous pressure on producers to produce greener API for reducing the NHS's own carbon footprint across its supply chain. However, this finding is somewhat in line with Clark et al (2010), which also advocated for this kind of stakeholder pressure.

So, it is clear that people's perception on the ongoing issue of pharmaceuticals concentration in the water and food cycle has not driven the upstream R&D operations to become proactive to adopt relevant green activities, but the pressure is actually from another layer of customer, such as the NHS, who purchase the drugs to supply entire country. Additionally, recently the companies have also started feeling pressure from downstream wastewater treatment companies to adopt green practice (e.g., develop green or bio-based process). However, the intensity of this driver felt by other stakeholders is non-existent as innovative pharma companies are predominant investors in R&D and green decision making. Though the finding is in line with Clark et al (2010) there was no empirical evidence in the literature to show what and how R&Ds are being influenced to undertake green projects (e.g., ERA project and related API monitoring projects) driven by the downstream consumer and patients' concern.

Though the concept of this driver was somewhat in line with Clark et al (2010), due to the lack of empirical evidence, it was not so clear how eco pharmacovigilance and PIE programs

including PBT data have been developed in the pharma sector, especially and predominantly to the innovative pharma. The findings are also in line with the institutional normative driver as outlined by Zhu et al (2005), Li (2014), Wu et al (2012), Zhu and Sarkis (2007).

8.2.2 Analysis and discussion on green drivers for downstream pharma stakeholders

The study findings indicate that downstream stakeholder, especially pharmacies, have felt tremendous pressure to manage patient return for safe disposal. It has become a nationwide agenda for the safe disposal of drugs via pharmacy collection.

Drug take back legislation: Though this legislation was highlighted in the previous literature of Clark et al., (2010) and Vollmer et al (2010), it was not known how this legislation can drive the downstream pharma stakeholders, especially pharmacies and local CCGs, to undertake relevant management programs such as unwanted drug return awareness campaign. Previous studies predominantly highlighted how drugs are collected for safe disposal by various means rather than focusing on how and to what extent this legislation drives the downstream pharmacy to participate in unwanted drug collection from end users. This study has confirmed the effectiveness and efficiency of the drug take-back legislation.

This study also reveals that end consumers' perception and awareness about safe disposal of drugs has been improved due to getting the message of 'return unused drug to the nearest pharmacy for safe disposal' as part of GP consultation or pharmacy consultation, or as part of a social awareness campaign such as 'Drug waste reduction campaign'. The base of all these awareness efforts for safe disposal of unwanted drugs is the drug take back legislation. Therefore, the importance of this legislation is significant in the context.

However, it is also important to note here that not only pharmacy but also some local councils have been sought to play a key role to collect unwanted drugs from the household patient on request for safe disposal, though they are not influenced by this legislation. It is also important to highlight here that local council can also play a crucial role along with pharmacy to collect unused/expired drugs from household customers for safe disposal as the majority of end consumers still prefer to dispose of their drugs using household garbage. For instance, the household could be given a special kit/bag to put their unused / unwanted drugs for collection along with their garbage. This would increase the collection rate. So, if local GPs, pharmacies, and local councils collectively collect unused / unwanted drugs from end

consumers, the rate of collection and safe disposal will increase, which eventually will reduce the rate of unexpected environmental loading of drugs.

However, one issue for the local council (or its waste management vendor) would be that they will need to train the waste collector to inspect the unwanted drugs kits/bags prior to processing. Another issue would be the visibility and tracking of the collected household drugs as the majority of the local councils (or its waste vendor) may not have drug or clinical incinerators and would have to bypass to third party contractors to process them. This is how the study has enriched our knowledge in the context.

Another significant driver of drug optimization was the financial incentive for MUR / NMS service. The study indicates that MUR / NMS are significantly successful in terms of both patient wellbeing and drug usage optimization and waste reduction. Though Latif et al. (2011) and McDonald et al., (2010) have highlighted the operational issues for conducting MUR, such as time taken to conduct MUR, or patient recruitment for MUR etc, they did not explain how MUR or NMS can actually be used as a drug waste reduction measure and can be promoted by the existing financial arrangement provided by the government. Additionally, the previous studies have not identified if monetary incentives actually drive the pharmacy managers to undertake more MUR or reach the annual target, as they still have tight schedules for other day to day checking, dispensing and related operational tasks. This study has addressed these gaps and enriched the scope of MUR as a drug waste reduction measure in the context. Additionally, to the best of the researcher's knowledge none of the previous studies identified NMS as a similar measure to driving drug usage optimization. This also indicates that drug waste reduction could significantly be improved through incentivising the patient interventions projects across the country.

8.3 Analysis and discussion on Green Barriers

The related findings are crucial for the pharma industry to go green. This is because the study results have clearly spotted key factors such as complex marketing authorization of green drugs (redesigned off patent drug), lack of PBT data, lack of green chemistry awareness etc, which require urgent attention to reconsider them within existing operational strategies for all stakeholders involved. The related findings will significantly help the practitioners to identify their own resource needs to adopt green. The subsequent section presents related insight from both upstream stakeholders and downstream stakeholders.

8.3.1 Analysis and discussion on Green barriers felt by upstream pharma stakeholders

Complex marketing authorization process of greener drug (redesigned off patent)

Stringent quality requirement along with long waiting time for approving a modified drug process is a costly process. The study findings clearly indicate that companies could adopt more green projects from what they are doing now if the regulatory bodies (e.g., EMA, FDA) reconsider their requirements in order to promote green. For instance, if the MHRA or the FDA ask for alternative (greener) processes and allow companies more time (in terms of exclusive sales rights of the modified drugs) to deal with this changes, that could be an effective driver to go green. The faster regulatory approval of the post marketing process changes which have been modified applying green chemistry principles (or, MET) to improve environmental performance without compromising safety, quality and efficacy of the drug products would significantly reduce this barrier. This faster approval process will undoubtedly accelerate the greening process of the pharma industry by providing companies with more flexibility to process changes as part of their continuous improvement project.

More importantly the generic industry, a leading economic contributor now and in the future due to the lower cost of production, could benefit from moving towards green. Interestingly, there is very little evidence that companies have been promoting more green chemistry related practices because they receive faster regulatory responses for approving the green chemistry-based process changes. However, the exact timeframe and detailed cost benefit analysis of this process change are still not known across the industry. So, it would require further evidence to understand the scopes and impact of relaxing regulatory requirements (in terms of time, quality/ validation documentation requirements, exclusive sales right etc) for green chemistry-based process improvement.

There also could be a reformulated form of regulatory guidance (e.g., a unified cGMP) by incorporating all possible green issues across the globe, also, to reduce the discrepancies in the global regulatory requirements. Unified regulatory requirements across the globe would ensure green formulation as the formulator would have to depend on cheap API outsourcing across the globe.

The findings are also in line with previous studies by Slater et al (2010) and Plumb (2005). Though these studies assumed there to be an adverse effect of stringent pharma regulations on process improvement, the barrier of how regulatory process has impeded the companies to

go green was not clear due to the lack of empirical evidence. It was also not known whether only generic or only innovative pharma had experienced this barrier. This investigation has filled all these knowledge gaps. The findings also are somewhat in line with the previous study by Kummerer (2009) who advocated that the stringent quality requirements for a drug product for safety and efficacy work against the environmental requirement of that drug product. Similarly, this concept was established through this investigation. For instance, it was clear from the study that what is good for the environment is not always good for drug quality, safety, and efficacy. For instance, if a drug is produced for increased environmental biodegradability, it may not be a good choice for biological degradability or may not fulfil the pharmacokinetic and/or pharmacodynamics properties of drugs. This complex drug design assumption is also in line with Leder et al. (2015). It is important to note that there was also an indication of quality compliance against achieving green credentials in the study by Clark et at. (2010). However, there was no clear empirical evidence of how quality compliance for a drug product and the environmental requirements follow two different principles. The findings from this investigation have addressed these research gaps.

Higher Investment

Lack of financial investment has always been an issue for adopting green practices during the development and manufacturing phase. As aging populations and growing healthcare spending put increasing pressure on healthcare systems, there will be a lack of financial investment in new modified drugs which could be produced and manufactured in eco-friendly way. In particular, lack of investment in funding AMR combating projects, which could lead to significant damage to humankind and the environment at the same time due to not taking appropriate measures during manufacturing and managing manufacturing wastewaters in an eco-friendly way. The majority of the respondents from generic pharm reported limited to no investment on green process development, as the companies' focus is on remaining competitive in the market by lowering production costs using low cost technologies. Though there was an indication of this barrier in previous studies by Velva and Jr (2017) and Clark et al (2010), there was no empirical evidence for it.

The findings are somewhat in line with the study of Velva and Jr (2017), Slater et al (2010), and Parez-Vega et al., (2012). However, all these studies lack a account of how cost has become a key barrier for the pharma sector, due to the lack of empirical evidence. Additionally, the cost of production as a barrier was highlighted merely based on assumptions

without empirical evidence and therefore, it was not possible to establish this as key indicator for measuring the concept of a green barrier for the pharma sector. This investigation has been able to fill these these knowledge gaps.

Cultural issues

It is important to highlight here that though the study by Lazuras et al (2011) urged the need for employee involvement for the creation of a green culture in general, the reason why there is a need to build such a culture was actually not known empirically. None of the previous studies either in pharma literature or in generic green supply chain literature have identified this barrier. Even when Slater et al (2010) expressed his concern for manufacturers' mentality to invest time and money on extra validation process for green technology, there was no empirical evidence of such concern. This study's findings clearly indicated that the lack of employee green mind set and their sceptical view towards green adoption might have a negative impact on overall green performance. This is how it has contributed as new knowledge in the existing body of literature. Furthermore, none of the previous literature in pharma has highlighted this barrier.

Some of the leading innovative pharma have faced difficulties in a few geographical areas for promoting greener waste management and/or complying with group-wide waste management strategy. Those geographical areas have a negative perception on the waste incineration process and the public perception is that there could be negative environmental impact from suboptimal combustion of wastes (e.g., dioxin formation) or from the potential toxic effects of the resulting incinerator ash. Though it was not clearly known in the report why there is such a negative perception on this, the finding is somewhat in line with Kallaos et al (2007), where the author raised the issue of metal ash from the incineration plant finally going through landfill disposal, which has negative impact on the environment. Additionally, the incineration process being carried out at the correct temperature is the key to dealing with complete and/or incomplete burning to avoid negative environmental impact as highlighted in Kallaos et al (2007).

Lack of standardisation in equipment and processes

The study clearly indicated that process and product variations have become one of the key problems for pharma for adopting a standardized green technology. While it is easy to streamline and standardize the recycling process of a car, it is almost impossible to do so for

solvent recycling within a drug manufacturing site. Unique drug processes will require unique equipment settings for solvent recycling. Retrofitting versus new facility design for a new process or modified process is one of the crucial strategic decisions for companies either to add on a recycling loop into the existing system or install a new process with a recycling facility. So, the trade-off between selection of retrofitting and new facility design due not to have the opportunity to standardize all recycling process across different drug processes is a critical issue for companies. It is important to highlight here that though this finding is somewhat in line with some green supply chain related studies such as Zhu and Geng (2013), and Luthra et al (2016), where they have highlighted resources and technologies as a barrier, none of the previous literature in the pharma sector has highlighted how complicated equipment and related engineering complexities can be a barrier to adopting green practice in the pharma sector. Most importantly, none of these studies have explained the scope of possible green practice adoption in the environment of high varieties of processes with higher varieties of equipment and engineering requirements with limited scope for standardized green technologies adoption.

Lack of standardized waste kaizen

While process wise waste measurement is the key measure for controlling waste, the unique features of each drug process have made it difficult to put in place a standardized measure and control the overall process waste across manufacturing sites. It is important to note here that to the best of the researcher's knowledge none of the previous literature in the pharma sector has highlighted this barrier. Though this finding could be somewhat in line with the concept of the technological barrier outlined in the previous green supply chain literature of Zhu and Geng (2013), Li et al (2015), Govindan et al (2014b), they had a very myopic focus on understanding in-depth operational capability and / or incapability for undertaking a particular green practice within an environment where varieties and stringent product quality are the key.

Time to market

Time has been a crucial factor in pharma – both in the case of innovative and generic development and production. The time to market for a car producer and the time to market for a drug producer are hugely different in marketing philosophy. This is because for drug producers, it is vitally important that a drug is ready on time with streamlined safety, efficacy, and quality to save a life, while cost effectiveness and competition are already built in into

this. The study clearly indicates that the nature of pharma drug development with limited patent timelines but with time consuming regulatory approval for certifying and validating drug safety, efficacy and quality has been a significant challenge for the industry to incorporate green culture into the process.

Due to having a clear and precise tendency of quickly launching a drug in the market to enjoy exclusive sales rights for the longer term, companies pay close attention to quick development of the drug process. However, while it takes time to understand key parameters (e.g., safety of products while recycling solvent from the process) of a drug process, this nature of time constrained operational activities impedes the companies from investing extra time to develop green process. It is important to highlight here that though there was an initial assumption about this barrier (Taylor, 2016) there was no clear empirical evidence of how time to market could affect companies' decisions to adopt green. None of the previous studies in pharma sector claim this type of green barrier. The significance of this finding is crucially important for the regulatory bodies to reconsider the time fact for promoting green. For instance, the regulator could increase patent life for another five years to give them exclusive sales rights if the company demonstrates significant improvement in their process environmental footprint, like the way the Lyrica process was redesigned to curb significant amount of wastes.

Lack of data

PBT data is the key to developing a green drug data base for the prescribers as well as for purchasers to promote green drug production. Most importantly PBT data is significantly important for the manufacturers to control hazardous API discharge. Also, it is important for wastewater treatment companies to control and ensure the quality of surface water. Unfortunately, the study clearly indicates that the industry is still struggling to compile PBT data due to the lack of undertaking of eco-toxicological studies of the drugs which are already off-patent and have been in the market for a long time. None of the previous studies have empirically identified this barrier, though Clark et al (2010) highlighted the importance of PBT data for managing PIE. Additionally, there was no empirical evidence to show whether and how companies are being impeded from managing PIE issues due to the lack of relevant environmental toxicological data. Therefore, this barrier has enriched our understanding and contributed to the existing body of knowledge. So, this implicates that there should be an industry alliance, probably in the form of public-private initiatives, to conduct continuous

eco-toxicological studies of those old off-patent drugs. However, it is also important to highlight here that the eco-toxicological effects vary geographically. So, it requires a worldwide alliance to compile PBT data, which will ensure and could certify a drug as green with a degree of confidence.

Lack of environmental training and education

The results indicate that the industry significantly lacks green chemistry related training and education, especially in the case of generic pharma. The study also reveals that many important levels of employees such as medicinal chemists, process chemists, and process engineers, who are crucial decision makers on whether or how to adopt green chemistry technology in the drug process, are still unaware of green chemistry technology. It was also strange that there is low level of awareness of AMR across the companies. Only the environmental managers are aware of it rather than an industry wide awareness of it and the related precautionary activities such as observing, assessing, and measuring API discharge from the manufacturing site. Though there was an assumption in the studies of Clark et al (2010) and Kummerer et al (2009) that the relevant employees would require further environmental training for dealing with PIE, there was no empirical evidence of whether this could be faced as a barrier by pharma companies to apply green chemistry. The finding is also in line with the study of Watson (2012) and Matus et al. (2012). The findings on the low level of environmental education and training on AMR is also similar to the findings in the EU commission report (AMR Action Plan, 2017) which highlighted that the pharma industry in liaison with health service providers must be trained and educated on AMR impact, as there is still a low level of awareness.

8.3.2 Analysis and discussion on Green barriers felt by downstream pharma stakeholders

Operational barriers:

Drug waste management for high concerned patient groups, such as multiple complex morbidity, dementia, and patients in end of life care, is critically important to improving health care efficiency through drug optimization. The results indicate that due to the complex nature of polypharmacy, prescribing, dispensing and usages of drugs, they should be streamlined through a common way of communication across the GPs, patients, and pharmacists / nurses / carers. Similarly, to streamline end of patient life care it also requires a

streamlined and one stop shop type of communication exchange process among prescribers, users, and dispensers. As a significant proportion of drugs (e.g., 50%) are wasted due to drug nonadherence from these concerned groups of patients, the significance of improving the process of managing these patient groups are crucial in the context. The findings about this barrier also support the study of Daughton and Ruhoy (2010). For instance, they also highlighted the inefficient communications among the carers or doctors as one of the key issues of uncontrolled drug wastes. The finding of this barrier is also supported by Castensson and Ekedahl (2010), as they were also concerned about the inefficient and ineffective way communication is conducted among the GPs, carers, and dispensers. The finding is also in line with a previous study by El-Saifi et al (2017) where the author also mentioned the key challenges of drug non adherence originating from old aged with dementia group of patients (between 37% to 80%) who are seen to discontinue their medication before completing the cycle.

The study finding has also indicated that downstream pharma consumers like the NHS have not yet been efficient enough to assess the MUR / NMS outcomes to effectively measure its performance in terms of drug waste reduction. For instance, it is still not known how much drug waste has reduced or to what extent the drug usage is optimized from each MUR observation. So, the measurement for MUR/NMS efficiency is the key to reducing drug waste. Though the previous study by Latif et al. (2011) explains the process of conducting MUR, it did not pay any attention to how the lack of MUR/ NMS performance assessment could affect the downstream stakeholder's target, such as the NHS's key aim to reduce drug wastes. The same study also did not mention how robustness of MUR reporting by pharmacists is one of the key factors to improve efficiency of drug optimization. Though Latif et al (2011) highlighted the operational facts of MUR, they did not mention how pharmacists face difficulties to recruit patients for both MUR and NMS. Whilst MUR and NMS are two key patient intervening processes which have direct impact on potential drug optimization, the related barriers identified will have significant importance in the context.

Regulatory barriers:

The study clearly indicates that there is still a significant lack of clear direction on how to consider green related thinking when prescribing protocol. There is huge opportunity to guide prescribers to incorporate and highlight those drugs that have been continuously and widely identified in the water surface such as painkillers, birth control pills etc. Thus, prescribers

could be cautious prior to prescribing these categories of drugs. The eMC can also be populated with this key info, including excretion rate profiles, so prescribers can also consider this whenever necessary and possible to do so. It further indicates that the downstream prescribing guidance could incorporate these environmental criteria (e.g., excretion profile of an API, high environmentally concerned API) the way it guides the management and control of antibiotics driven by the issue of AMR. However, there is still a lack of relevant regulatory guidance on what and how to do it. It also indicates that this typical prescribing protocol would significantly reduce unwanted environmental loading of drugs. To the best of the researcher's knowledge this is the first study that identifies this regulatory shortcoming as a green barrier. Though Daughton (2014) had theoretically and technically analysed the possibility of considering excretion profiles of an API during prescribing, it did not take into consideration the views from GPs / prescribers on how they feel about it while prescribing – as quality and the safety of the patient is the key. The trade-off between API-excretion based prescribing and the safety of the patient is a critical area to explore in detail prior to considering the prescribing protocol. However, this study also indicates that if there is clear guidance on this typical prescribing protocol, including staff training, there is an opportunity to reduce unexpected environmental loading of API.

In addition to this myopic regulatory focus on prescribing, the study also indicates that drug waste management related regulatory advice across the downstream stakeholders is inconsistent. This inconsistency in regulatory advice has created a confusion of responsibility of the management of drug wastes. The study indicates a dubious situation for the public as well for some downstream local councils (or their appointed waste vendors) while managing drug containing household wastes. The question is that if a drug (apart from cytotoxic / cytostatic or cancerous drugs) is categorized as a non-hazardous substance which can be disposed of with normal household wastes, the influence of drug take-back legislation is suppressed in the context. To the best of the researcher's knowledge this is the first study that argues this typical green barrier in pharma. Though the finding is somewhat in line with Mudgal et al (2013), where the authors looked into the issue of PIE and possible solutions for it, highlighting ERA, REACH, IED, drug take back etc, it did not focus on this particular waste management issue. Evidently, this is the first study in the UK context for an overall assessment of green practices in pharma. This is how the study finding has contributed to the existing body of knowledge to enrich the field of green pharmaceutical supply chain.

8.4 Analysis and discussion on Green Performance

The related findings are important for all stakeholders involved. As there is clear evidence of environmental and economic benefits, though with varying degree across the industry players, most of the laggards and followers (like generic pharma) could significantly benefit from following and adopting those green practices to improve their environmental performance. Similarly, some performance measures which have emerged as key for the sector (e.g., amount of drug saving from patient intervention in the downstream) but not widely implemented yet are of great importance for policy makers to improve overall environmental performance. As there was no clear indication before on what key measures are being taken across the industry, the managers could enrich their understanding of this and could select the best fit for their operations. The subsequent sections present related insights for both upstream and downstream players.

8.4.1 Analysis and discussion on Green Performance for upstream pharma stakeholder

GHG emission and energy related performance measures

The study has clearly indicated that the pharma industry is highly committed to reducing its direct and indirect carbon emission. Though there is a wide range of measures used based on company operations, scope 1, scope 2 and ozone depletion, related emission measures have been considered across the industry. While the entire industry has significantly progressed to reduce operational and energy related carbon emission, the innovative sector itself has been a pioneer for leading green innovation for carbon reduction. Similarly, but to a comparatively slower scale, both generic and bio pharma have also been able to tackle and reduce operational carbon emission by adopting related green practices.

The study finding also indicates that innovative companies have saved a significant amount of costs and carbon emissions from adopting two strategies predominantly: one is to increase waste reduction capacity across the sites, and two is investing on energy efficiency projects. In particular, local production of energy from CHP has been highly successful across the industry and the related carbon reduction achieved. It is also clear that generic and bio pharma could also speed up in investing more in CHP technology and other related energy kaizen projects to save both costs and emissions.

One of the obvious shortcomings is that process-based energy requirements measures are still not widely available. As each process requires different sets of materials and equipment and

related engineering, it is difficult to provide a unique measure. So, it requires investment and time. However, process centric energy assessment would be the key to claiming an API as green in terms of energy footprint.

Energy kaizen projects have been significantly successful in terms of saving energy and related costs across the industry. It is also true that innovative companies have significantly reduced VOC emission by promoting green chemistry-based drug production (e.g., reduce usage of higher impact chemicals such as less use of organic chemicals). However, the generic and bio pharma sector are still far off adopting such process change to reduce VOC emission. As organic chemicals are the key building block for chemical-based API production, the impact on VOC from generic production is huge. So, alternative greener chemicals must be adopted.

Refrigeration and use of CFC based products are another key challenge for pharma to comply with and reduce F-gas related emission. In particular, inhaler drug items are the key focus. Interestingly, innovative companies have already been taking the lead in dealing with this by incorporating less impactful chemicals to lower the CFC emission. Though companies are using ammonia chillers for refrigeration to tackle CFC emission from refrigeration systems, the trade-off between energy requirements to run CFC-free refrigeration and alternative chemicals still needs to be addressed in detail. However, whilst the employee-based or sales-based carbon emission are effective indicators, they lack inclusiveness in measuring performance as in line with several previous studies: Beamon (1998); Beamon (1999); and Hervani et al. (2005), for instance, not considering scope 2 emissions. Therefore, it is important to consider all other dimensions (e.g., VOC, ODS, scope 2 etc) of emissions.

Though the findings are somewhat in line with the previous green supply chain literature such as Zhu et al. (2013); Zhu and Sarkis (2007); Zhu and Sarkis (2004); Perotti et al. (2012); Eltayeb et al. (2011); ; Green et al. (2012); Laosirihongthong et al. (2013); and Li (2014), the authors have predominantly focused on overall air emission rather than the breakdown of each GHG emissions dimension. Additionally, to the best of the researcher's knowledge, none of the previous studies in the pharma sector have focused on identifying and ranking the key sub level GHG measures across different industry players in the chosen research context.

Materials related performance

As solvents are the costliest raw materials used in pharma process, the industry has measured the overall solvent used across the sites. However, while it is important to measure solvent input for both cost efficiency and environmental footprint (e.g., how much hazardous solvent is used etc), the industry has recently discovered process centric measures where all input and output materials are measured. The use of these measures has significantly reduced the usage of raw solvents, especially in the case of innovative pharma process. Interestingly, while generic and bio pharma could significantly benefit from applying this process-based measure or PMI, it has not been widely used in their operations. One of the obvious reasons is that being cost-focused businesses, generic companies have limited scope for investing in PMI development.

Though the ROI from PMI application is receiving attention from the other stakeholders in the industry, the generic sector is also expected to adopt it soon. For bio pharma, PMI based process development is more complicated due to the complicacy in equipment and engineering expertise. Being a water exhaustive process, a bio-based process could be one of the most benefitted sectors in the industry from considering PMI measures. Hence, companies have already started developing such PMI for the bio-based process. However, water efficiency projects are also significantly reducing freshwater usages and related energy costs. The findings are also in line with the previous green supply chain literature such as Eltayeb et al. (2011), Chiou et al. (2011), Laosirihongthong et al. (2013), where the authors have predominantly focused on measuring the amount of resource consumption - less consumption of gas, water, electricity, petrol, and reduced material consumption. However, the concept of PMI and usage of recovered materials instead of using virgin materials in the process have added a new dimension of measuring the concept of 'Material reduction' specifically in the context of pharma, which has not been published in any pharma supply chain related paper. In particular, none of the previous studies highlighted the importance of process-based measures. The ranking of each measure in the sector has also provided a unique feature in the measurements to understand the importance of each measure taken.

Toxicity and waste efficiency related performance

This performance measure has been paid significant attention by the industry for combatting PIE and AMR related issues. Amounts of hazardous wastes streams from production site are the key measure to determine the overall toxicity levels of the effluent. It is remarkable that though there is an inventory for input raw materials and solvents for a process, the

identification and measure of individual raw materials and solvents from wastewater treatment is significantly complex, time consuming, costly and sometimes impossible process. Hence, the assessment of wastewater is considered as thoroughly as possible to protect the natural environment. While it is impossible to completely eliminate hazardous waste from the pharm process, most of the innovative companies' operations have been sought to continuously reduce their hazardous wastes by converting the waste into recycling, reuse and /or waste to energy. The industry has significantly undergone a massive transformation from non-conversion to conversion of wastes leading to zero landfill.

In particular, innovative companies are taking the lead towards the zero landfill agenda. Lower amounts of hazardous wastes produced from a process indicate that the process has increased its application of MET practice. This could only happen when companies have proactively taken the initiatives to adopt green practices. For instance, in order to eliminate the presence of halogenated elements (e.g., chlorine, fluorine etc) in the effluent, it is mandatory to reduce usages of those in the production process and more proactively design the process without those elements. Innovative companies have also taken the lead for such green adoption to reduce hazardous wastes effluents. However, the complexity remains in the early drug design and development phase. This is because evidently halogenated elements are useful for safety and efficacy of drugs to the human body. So, this may happen only case by case. This deign specification for reducing hazardous waste is also in line with the assumption of Leder et al (2015) and Kummerer et al (2009) about the difficulty of modifying the early phase of drugs to replace halogenated substances with greener alternatives.

Therefore, a drug process being very unique in nature, the companies would need to produce a database which should record two aspects from the beginning of drug R&D: one is which API or intermediate products could be produced halogen free (e.g., chlorine, fluorine free etc) without compromising the safety and efficacy of drugs; and two is which drugs are not possible considering the safety and efficacy of drugs to the human body. This categorization will inform future researchers about what to avoid in their next drug discovery process, which ultimately will lead to lower hazardous wastes in the effluent. It is also remarkable that due to the issues with toxic bottom ash from drug incinerators, some companies have also sought to divert the hazardous waste to more recycling, reuse and the waste to energy process. This kind of waste diversion rate has been increasing for three specific reasons: one is to comply with waste legislation, two is cost savings from waste to energy or recycling, and three is

responsible business sense. However, both cost and operational effectiveness for each option in the waste hierarchy for different pharma waste streams are still unknown.

Additionally, driven by the facts of ERA, PIE and AMR, companies' manufacturing sites are taking special arrangements for measuring and controlling API discharge into surface water. In particular, innovative companies are proactively using up-to-date research data (PBT data from eco-toxicological studies) to control their API discharge in liaison with local water regulatory bodies. In addition to this, companies are also benefitted from measuring traditional wastewater quality measures such as BOD, COD and TSS. However, it is important to highlight here that the issue of PIE has extended the traditional measure of TSS and actively include API into TSS. These measures are significantly important to ensure water quality for aquatic life.

Though the findings are also in line with previous green supply chain literature, such as Chiou et al. (2011); Zhu et al. (2013); Zhu and Sarkis (2007); Zhu and Sarkis (2004); Perotti et al. (2012); Green et al. (2012); and Li (2014), where the authors have predominantly focused on measuring the amount of solid waste generation, and measuring the amount of hazardous waste reduction, this study has extended the measuring concept of 'Waste reduction' by looking through the lens of the 'waste hierarchy'. Whilst the previous literature has provided an incomplete assessment, which lacks inclusiveness of the measure, this investigation has filled this gap. Additionally, the sub measures identified here underpinned by the 'waste hierarchy' model of waste management are crucial for all processing related sectors. So, this measure could also be replicated into the related sectors. However, none of the studies in the pharma supply chain area have outlined these sub measures to enrich the concept of waste reduction in the pharma context, outlining the ranking of each sub measure. The related performance captured has also provided a good grounding for the industry to be motivated to adopt related green practices for reducing, as well as managing, wastes.

Though the two sub measures are in line with previous green supply chain studies in the chemical and related sector such as Zhu et al. (2013); Zhu and Sarkis (2007); Zhu and Sarkis (2004); Perotti et al. (2012); Eltayeb et al. (2011); Green et al. (2012); Laosirihongthong et al. (2013); Li 2014; and Zailani et al. (2012), these studies provided the related measures like 'Consumption of Hazardous/harmful /toxic materials' and 'emission of COD' (Wagner et al., 2005). However, they lack inclusiveness, universality and consistency in the case of the pharma sector, because, not only COD, but also the other key micro level measures, such as

BOD, TSS, nitrogen, phosphorus and API discharge, are important for the pharma sector. None of the previous literature in the pharma sector has provided such a set of inclusive measures which are crucially important for the sector.

Cost/economic performance of green practices

While cost savings from green supply chain practices adoption in the automotive and other sectors is well known, cost savings from pharma operations such as cost savings from solvent recycling is comparatively new in the body of GSCM knowledge. It is remarkable that cost savings from energy efficiency, cost savings from water efficiency and saving from materials efficiency are becoming well established phenomena across the industry and hence there is an ample opportunity to learn from these cases and to apply them to other process-related industries, such as the food production or solvent production sector.

However, in many cases the cost savings are interrelated with multiple practice adoption. For instance, cost savings from energy efficiency are not only directly from using energy efficient appliances and equipment in the process, but also via the recycling process or via the wastes reduction process. As materials and energy are highly interrelated, cost savings assumptions are not solely relying on one aspect. It is also notable that RCM or resource conservation measures have been used very successfully in terms of saving costs via energy and raw materials savings.

On the other hand, the scopes of cost savings opportunity from solvent recycling or related process modifications (e.g., replacing raw chemicals with greener ones) are highly limited for generic pharma due to cost, time and regulatory complexity to validate the modified process change. It is important to highlight here that though most of the cost measures are in line with other studies in the green supply chain literature, such as Zhu et al. (2013); Zhu and Sarkis (2004); Perotti et al. (2012); Green et al. (2012); Laosirihongthong et al. (2013); and Zailani et al. (2012), none of the studies in the pharma have identified these measures for measuring the economic/cost performance from applying green practices. Understanding some of these cost measures in the context of the pharma sector is crucially important for assessing a particular green investment. This is because, for instance, it was never known what factors are involved in measuring ‘cost of green production’ and ‘cost of green technology’ in the case of green pharma operations. For instance, it was not previously known how regulatory issues could be a prime cost and time factor for incorporating green credentials into the existing drug process to reduce the overall environmental footprint.

8.4.2 Analysis and discussion on Green Performance for downstream pharma stakeholder

Environmental related

The study indicates that drug adherence has significantly improved among those patients who had been consulted for MUR. The degree of drug adherence improvement levels as a measure is significant to the context because drug non-adherence is one of the key reasons for unwanted environmental loadings of drugs. Most importantly, MUR recruits only those groups of patients who are hugely responsible for drug wastes or ineffective usages of drugs. Therefore, MUR and related patient interventions can be a guiding principle across the globe to deal with PIE. However, it is important at the same time to assess the trade-off between MUR costs and healthcare benefits including PIE benefits. Interestingly, though there is huge scope for measuring MUR success by means of number of drugs (even by drug category) and calculate related costs, the industry leader has not yet felt this benefit of measuring it. The key focus remains lowering hospital admissions and/or lowering GP appointments rather than extending the understanding of MUR intervention and related success in PIE. It is also remarkable that the upstream industry leaders who are actively working with both internal and external stakeholders to combat PIE have not yet been seen to cooperate with downstream customers (NHS) to grab this opportunity. This significance of understanding is also in line with the assumption of Kummerer et al (2009) and Clark et al (2010) who advocated for green collaboration across the chain, which is more likely to provide a 360 degree view to tackle the issue of PIE.

The study finding also indicates that there is one obvious obstacle for generating the actual drug adherence level from MUR intervention. As there is no follow up for MUR, it may be sometimes difficult to manipulate the actual adherence level. So, initial anticipation can be more effective if there is a follow up phone call or review as part of MUR to observe the effectiveness of the program. Also, MUR comprises only a few classes of diseases – the non-adherence will largely remain a problem, as other classes of patients are not being regularly reviewed.

It is important to highlight here that though the previous literature, such as Latif et al. (2011), has partially outlined the operational aspects of MUR, none of the studies in pharma sector have looked into it from an environmental supply chain perspective and not identified these

three kinds of prospective measures for reducing drug waste leading to controlled loading of drug substances via the use-and-disposal phase.

The measures identified for reducing drug wastes could not only save healthcare costs but also environmental loading of drugs to deal with the unprecedented issues of PIE and AMR. These measures could have been adapted to other developed and developing countries as well to deal with the upcoming global threat of PIE and AMR.

In the case of patient return management, the industry could benefit if they measure return type (e.g., prescription data, or OTC, or category of drugs), which eventually can be compared with regional drug sales data. Though the majority of drug wastes amount will be missing from this calculation, as evidence suggest that still the majority of people dispose of their medicine via household wastes, still the amount will be a helpful measure for the industry to save costs. This kind of measure will help the industry to roadmap new strategy to deal with the drug wastes issues. For instance, if we get the difference between total sales data within a particular region of the country (e.g., in England) and the total amount of returned drugs for the last one or two years, then we would be able to assess the overall effectiveness of all efforts (e.g., MUR, NMS, or other interventions and drug waste campaign) being taken to deal with drug wastes. Though this reflection somewhat links with the assumption of Vollmer et al (2010), they did not consider the counting of return drugs. Reuse of drugs in hospitals is also another rudimentary option of drug waste reduction. However, it requires a unique process across all CCGs to record the types and categories of drugs savings from reuse. Though the fragmented approach to recording drug reuse in some local CCGs is definitely influential for other CCGs, a holistic and unified approach of how drugs can be reused and how they can be recorded to measure costs and amounts saved across all CCGs is required.

It is important to highlight here that though there are some studies that outline drug waste reduction practices (Gotz and Deffener, 2010; Kummerer. 2009; Mudgal et al., 2013), none of them have focused on identifying relevant environmental measures. Though Clark et al (2010) has highlighted a need for stakeholder wide assessment for reducing drug wastes, none of the studies in pharma sector have attempted to do it. However, this investigation has provided solid practical evidence of how downstream pharma stakeholders are currently dealing with drug waste reduction, though the overall extent of applying the measures across downstream stakeholers is still low, and it is expected to be enhanced by undertaking more

stringent measures like MUR, NMS. Low adoption levels of the related measures (especially in the case of wastewater and waste management companies) is due to the fact that they have not yet been motivated by any driver substantially to consider such measures for reducing the loading of drug substances in the environment.

Cost / economic related

Significant cost savings from patient intervention and drug recycling have been sought as a rudimentary approach for reducing healthcare and drug supply chain costs. However, interestingly, the cost savings captured have been sought as a fragmented effort via small lean projects rather than a regular ongoing practice. Reuse of drugs through re-dispensing within hospital wards and the related cost savings has been really sought as promising. Similarly, reuse of patients' own medicines during hospital admission has also reduced significant amount of savings. It is remarkable that none of the previous studies in pharma supply chain have discussed and identified related cost measures from applying related green use-and-disposal practices such as MURs/NMS. Additionally, though the viability and operational aspects of conducting MURs in the pharmacy were highlighted in the literature (Latif et al., 2011), they have never looked into this from environmental cost benefit perspective, such as cost measures from applying MURs. The findings from both interviews and reports on the limitations of measuring the key performance (e.g., cost savings from drug waste reduction) from conducting MURs and NMS will have profound impact on the key stakeholders such as NHS, PSNC to rethink in order to create these kinds of services policies.

8.5 A refined conceptual model

After synthesizing the key findings of the study in line with previous literature, it is obvious that the initial conceptual model has significantly been advanced in different dimensions under green practice, green drivers, green barriers, and green performance. The figure 8.1 below attempts to highlight a refined conceptual model of the study.

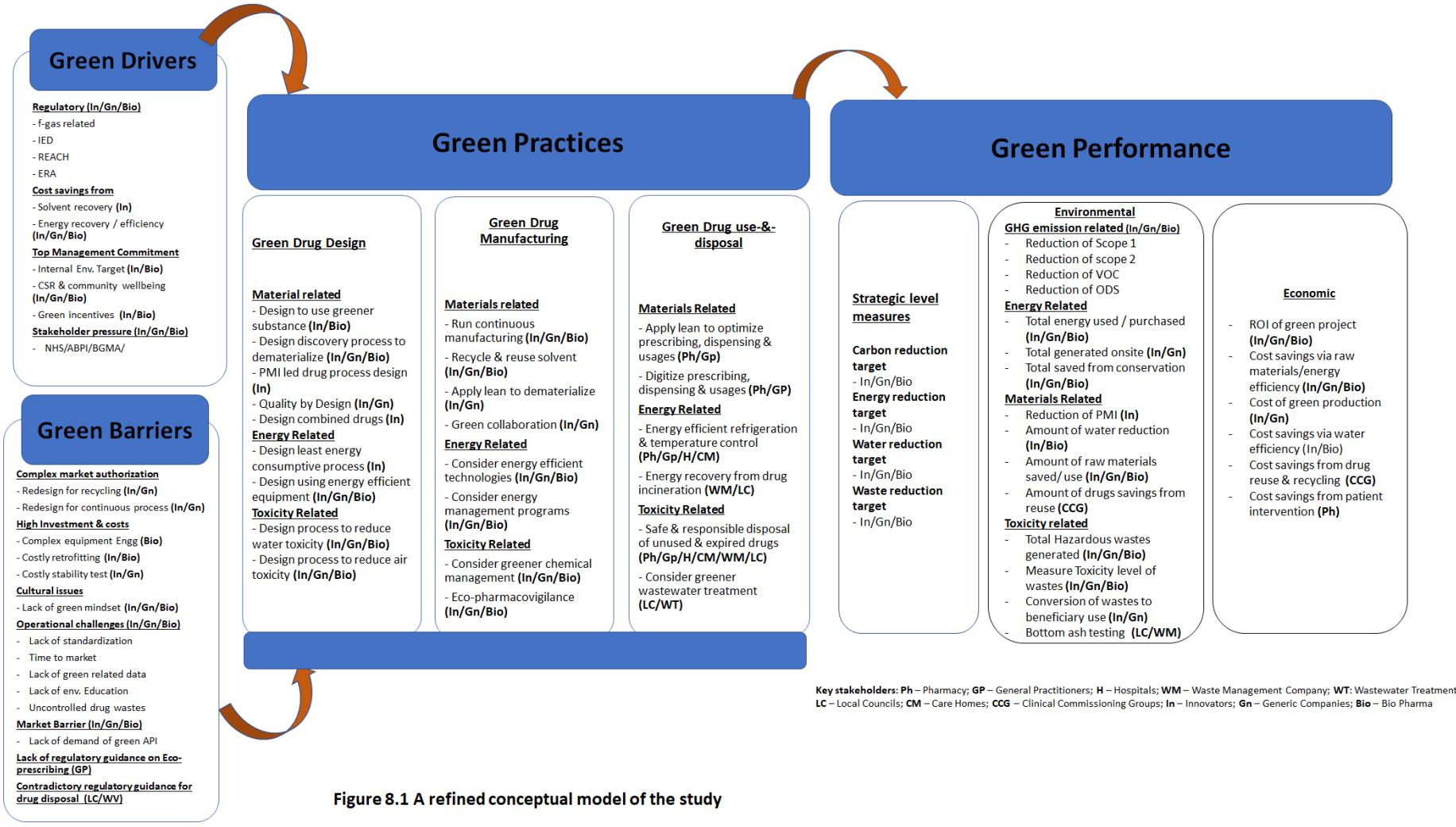


Figure 8.1 A refined conceptual model of the study

8.6 Synthesise the empirical contribution of the study

The study findings will undoubtedly influence the practitioners to greening pharma operations in individual supply chain stakeholder level. This is because empirically-led some unique green practices, drivers, barriers, and performance measures have significantly advanced the initial vague understanding on GSCM in pharma sector. With regards to green practices, some unique green practices and their intensity of adoption across key supply chain stakeholders have enriched the scope of green operations in both upstream and downstream supply chain. For instance, the innovators and bio-based pharma's tendency of *designing drug process to run greener (biocatalytic) reaction* would significantly reduce materials waste and water toxicity during bulk manufacturing phase across the globe. Such green design also aims to increase the effectiveness and efficacy of drugs compared to traditional chemicals-based drug process. Such unique observation aims to promote more green pharma products in future, especially generic version of drugs. Because the regulatory bodies could be convinced through providing related environmental and cost benefits. Such unique observation has also enriched Challener's (2016) initial concepts of biocatalysis and its potential uses in pharma operations. *Design drug discovery process through applying artificial intelligence* (e.g., focused library with 3D view, structure-based drug design, DNA-encoded library etc) reduces the usages of chemicals-based testing materials. Exhaustive chemicals screening has been significantly reduced in the innovative sector through using in-silico based testing. Such unique green design approach could not only influence the innovators globally but also other stakeholders such as generic R&D activities. *Whether and how PMI could be considered during drug process design* phase was never known. Such unique design criteria could significantly influence the pharma companies across all stakeholders to redesign the existing drugs in the market for improved cost and environmental benefits. This is because the existing process data (e.g., input/output materials, safety, quality parameters etc) for generic drugs are in abundance for assessment. So, PMI based drug process evaluation could significantly reduce environmental footprint from generic production across the globe. This unique observation of PMI led drug design has significantly advanced the initial understanding of how manufacturing wastes can be controlled for each drug process (Roschangar et al., 2017; Henderson et al., 2010; Jimenez-Gonzalez, 2011). While it is clear in the study that *quality by design principle could significantly reduce environmental footprint* in the generic sector, the companies need to find out the trade off between environmental gain and related resources required for longer term.

As such unique design principle considers possible quality variations within early process design, wastes related to quality inconsistencies will be improved significantly. Generic drugs will predominantly gain most out of it as they already have historic process data that can be exploited in the redesigning phase of drugs. *Design and develop manufacturing process through validating energy efficient equipment system* (e.g., single use technology) was identified as one of the potential green practices for the sector, especially for bio pharma or innovative pharma with biobased production for reducing process energy consumption. The study confirms that such design has significantly reduced the requirements of cleaning chemicals and related raw materials and energy during manufacturing. As biobased drug production including biosimilar is in surge, such process design will have significant impact in biobased drug manufacturing. *Consider some unique energy management programs* such as zero accidental promotion, energy kaizen, and energy audit has significantly reduced the overall energy requirements from the process during manufacturing across the sector. Such unique observation has significantly advanced Clark et al's (2010) initial concept of developing energy efficient manufacturing. Additionally, Watson (2012) did not cover how pharma producers can deploy process-based kaizen and lean activities to reduce energy consumption. Some key process-based energy kaizen such as reduce wastewater, product specific energy measure, routine leak detection, process optimization tool (e.g., BRITEST), efficient process calibration, etc could be generalized across the sector with few exceptions. For instance, the study also indicates that bio pharma processes have sought to be more sensitive and complex to optimize their process through adopting those energy programs. To reduce drug wastes from the downstream supply chain, pharmacy and GPs play a significant role through *the digitization of prescribing and dispensing operations*. Consistent communication among GPs, / prescribers, pharmacists and patients through EPS – eRD and EPS – ET system has significantly reduced the accumulation of unwanted drugs in the customer zone. Such unique observation will have immediate impact on PIE. Such unique concept can also be applied other parts of the world regardless of different healthcare mechanism in individual countries as the interactions among patients, doctors and pharmacy are in common. Such green practice could potentially reduce the environmental loading of unwanted drugs during usages phase to mitigate the global threat of PIE and related AMR effect. *Recover energy from drug incineration* process was identified as another potential energy reduction related disposal practices in the far downstream waste vendors. Such unique drug disposal related practice is significantly important for the context and all over the world as incineration is becoming a common practice. As cytotoxic and related cancerous drugs

production will continue to increase globally, high temperature (more than 1100 degree) incineration with energy recovery will be a greener alternative to save energy for pharma operations. *Reuse of drugs* that have not left the hospital premises, and reuse of patient own medication (POD) when hospitalised have shown significant cost savings as well as environmental savings. Such reuses involved safety, quality, and potency check of the drugs prior to administering them. Such unique observation has changed previous perception of 'zero salvage value of drug recycling' (e.g., Xie and Breen, 2012). This unique observation has also indicated us to think possible ways of reusing pharmacy take-back through a dedicated quality assurance pharmacy to check the safety, efficacy, and potency of returned drugs.

With regards to green drivers, some unique drivers and their intensity across key supply chain stakeholders have advanced our understanding on the scopes of GSCM in pharma. For instance, *f-gas related regulation* has significantly forced the innovators to redesign the inhalers products to replace CFC with HFA including new formulation technique such as pressurised meter dosed inhaler. As inhalers are one of the biggest sources of greenhouse gas emission, this regulation has tremendous influence on greening pharma products through redesigning efforts. Such unique driver will not only drive the companies innovate new drug design technique but also improve overall greenhouse gas emission rates for each product produced. While we have seen pharma operations are generally exempted from *REACH*, the study clearly identified that 'intermediate drug substances' produced during multistage production process is the key concern for the manufacturers. This is because intermediate chemicals substance must be registered under *REACH,* which has influenced the producers (especially innovators) to innovate new process design (e.g., biocatalysis based drug process design) to reduce intermediate by-products. However, generic pharma is under serious threat from REACH as they have limited scopes of such green innovation. Hence, the production cost is like to increase unless there is clear trade-off between process changes related costs and related regulatory fines. Such unique observation has provided an early indication to the generic leader to address this issue. This unique observation on REACH has significantly advanced Clark et al (2010) and Kummerer et al's (2010) initial concerns of the REACH over pharma operations. The study has also confirmed that *ERA regulation* has significantly forced the innovative pharma to track, trace and compile PBT data for each class of drug process regardless of new and/or old drug process to assess potential environmental impact of drug substances. However, such unique observation has clearly indicated the regulators (e.g.,

EMA, FDA) to apply same ERA application for generic pharma prior to approving generic batch production. But government incentives are essential to do such regulatory change to allow them compete and keep the cost lower and affordable to all. This would significantly reduce aquatic pollution and PIE impact. *Drug take back legislation* has forced equally all downstream healthcare players (e.g., pharmacy, GPs, Hospitals, care homes etc) to build robust SOPs (Standard Operating Procedures) to collect and dispose unused / unwanted drugs through approved waste vendors. Such unique observation is significantly important for pharma to understand the mitigation efforts of PIE to date. As the concept of green drug is still in debate, such reactive practice would be predominant to reduce unnecessary environmental loading of drugs. Vollmer et al (2010) and Clark et al (2010) were unable to disclose such importance of drug take back legislation. Cost savings was seen another profound green driver for the industry. The industry has achieved significant cost savings from energy and water efficiency projects. While innovators have *saved significant costs* from solvent recovery projects, biopharma from water recovery projects. It was clear in the study that though generic pharma has already felt such cost savings force the process change related regulatory bureaucracy is still the key concern for them. Such unique observation would encourage further innovation and convince the regulatory bodies to find a trade-off for them. Varieties forms of *monetary incentives* forced the pharmacies to optimize the drug usages. Driven by the incentives significant drug wastes reduction was achieved through different types of medical interventions (e.g., MUR, NMS, regular / planned / unplanned patient interventions through projects). It clarifies and advances the study of Latif et al (2013) and McDonald et al (2010). A clear trade-off between medical intervention project and related benefits in terms of drug wastes and related costs was evidenced, which eventually contribute to combating PIE and reduce health care costs. Under *top management commitment, community wellbeing and corporate responsibility* was found to be a greater driver for most of the innovators and some generic pharma to adopt green practices, especially ERA related environmental assessment. This has led them to innovate more greener chemical synthesis routes. Such unique finding is not only valuable for pharma but also enrich existing GSCM concept through observing how community wellbeing and corporate responsibility force the companies for business innovations and achieve competitive advantages.

The study has identified some unique barriers that have significantly advanced our understanding how and what capabilities the pharma industry will require to develop to

overcome environmental degradation. For instance, while generic pharma is a promising sector to cultivate green through redesigning existing manufacturing process, related *marketing authorization process* has hampered them to do so. As generic manufacturers have ample process data (e.g., temperature, uniformity, melting point, safety, efficacy etc), redesigning greener alternative would be much easier for them. However, the redesigned process may require additional validity test (both internally and externally) in terms of safety, quality, and efficacy of drugs prior to marketing authorization, which incur extra costs. It also may require longer time (more than two and half years) to get approved. So, lead time to market is uncertain, which may eventually lead to loosing market share. Such unique observation has indicated the sector to address it with an utmost priority to exploit the green innovation and gain competitive advantages. Due to the *unique nature of each drug process and related equipment differences*, it is sometimes impossible to apply standardized green technology. For instance, drug recycling for each drug process is different and thus it requires specific equipment engineering capacity and capability for each process either in a new facility or through complex retrofitting. Such unique observation has clearly indicated that companies will need to invest more on innovations so that retrofitting remains less complex and less costly for adopting such changes for green adoption. As *time to market* is crucial for pharma compared to any other product to adjust on time supply with optimum safety, quality and efficacy of the drug products, companies were seen to be reluctant to allocate time to innovate green technology unless there is a confirmed financial gain. For innovators they have very tight and limited time for recovering expensive R&D costs. For generic they are also under serious pressure from competitors to gain early market share. Such unique observation of time to market has indicated the sector to consider more optimization projects to reduce lead time while also exploiting green innovations. The study identified some *high concerned patients' groups (e.g., patient with end-of-life care, dementia, polypharmacy) who are the prime concerns of drug wastes.* The scopes of drug prescribing and dispensing optimization is significantly low for these groups of customers. Such unique barrier has indicated us to focus on restructuring the downstream healthcare operations system to innovate optimization such as just-in-time approach of drug administering under closed supervision of healthcare professionals. *Lack of green related* data has indicated the companies to invest more on R&D, especially in the PIE and ERA field to enrich the PBT data for each drug class. While the GPs appreciate and understand the PIE, prescribing practice and related decision space does not really supportive. This unique observation has indicated us to redesign the existing regulatory guidance to allow the GPs for making a

complex and multifactorial decision making prior to choosing a drug based on its environmental assessment. For instance, choose drug with lower excretion rate whenever practically possible. Such unique barrier has also indicated us to build more PIE training and development capabilities for GPs. While reactive approaches (e.g., safe disposal of drugs) is still the key to mitigate PIE and related AMR impact, *dubious regulatory approach* has hampered safe disposal of drugs. It was revealed in the study that the legal waste categorization and 'drug take-back' legislation is contradictory and dubious in nature, which creates confusion among the public. Such unique observation of the barrier has clarified that though all downstream pharma stakeholders attempt to encourage drug take back through appropriate SOPs, majority of unwanted / expired drugs goes through household garbage. Hence, it is vital for the regulator to disseminate the clear message to the patients and inhabitants about the safe disposal of drugs.

With regards to performance measures and related performance impact captured, some unique performance measures have significantly advanced the scope of GSCM in pharma. For instance, '*amount of energy saved from conservations and efficiency improvements'* was found as one of the successful measures among most of the innovators and some generic and bio pharma. This measure has saved significant amount of materials, water and energy from the process. The measure will undoubtedly encourage bio pharma processes as it consumes significant amount of water. Similarly, generic pharma as laggards will also be motivated to consider more relevant optimization projects. While pharma process wastes have traditionally been a huge concern in the process industry, '*amount of hazardous wastes converted to beneficial use'* as a measure has been identified as a rudimentary change in the industry. Though the innovative companies have become leaders for innovating such green technologies (e.g., waste to energy projects), generic and bio pharma are also becoming motivated to invest on such technologies for long term profitability and sustainability. Such unique observation has indicated the industry to set their internal goal as 'zero waste to landfill' in the coming days through promoting more recycling, reusing and recovery practices for each drug process. Some unique economic measures and related performance captured have also become prime examples for entire industry to go green. For instance, *ROI of green projects, cost savings from materials / energy efficiency, cost savings from medical intervention, and cost savings from drug recycling*. Significant ROI from solvent recovery projects within innovative sector has been one of the key attractions for the laggards and followers in the industry to go green. Such unique observation has also explained why the

generic pharma sector is becoming more aggressive to deal with regulatory bodies to relax the marketing approval process of redesigned manufacturing process. This is because those generic pharma with such unique manufacturing process (e.g., built in solvent recovery) will certainly reap significant amount of profits through cost reduction, as it would significantly reduce purchasing of expensive solvents. While the downstream pharmacy / GPs or local clinical commissioning groups (CCG) has recently started understanding the importance of measuring cost savings from each medical intervention project, the study has provided tremendous opportunity for them to take this measure on board. When MUR has already been proved to be a successful medical intervention through reducing unnecessary wastes of drugs and related costs, other related (e.g., formal / informal) medical interventions could be imposed by the local CCG for such dual (e.g., economic, and environmental) savings. Similarly, the unique observation of 'cost savings from drug recycling (e.g., POD)' among some of the local CCG indicates another promising approach of reducing costs for NHS. If they are considered across all CCG there will be huge influx of cost savings for NHS as a whole. Certainly, it would extend the existing STP (Sustainable Development Plan) portfolio of NHS as the study has clearly shown the evidence of both environmental and economic sustainability through medical interventions and drug recycling scopes.

8.7 Chapter Summary

This chapter is served as a follow-up discussion on the key findings presented in the previous chapter. It has discussed key insights from the findings on each green practice, driver, barrier, and performance measure. It has also discussed how the findings on each aspect of green have addressed all the relevant research gaps identified in the literature review. It has also discussed how related green aspects have been enriched by this investigation. It has also clarified previous misconceptions and concerns wherever related. It has also discussed the related theoretical and practical implications of the key findings. Under green practice, the key indication was that though innovative pharma have become key green leaders in terms of applying green chemistry (or MET) related practices, there is significant scope for improvement for generic and bio pharma through learning from innovators. For instance, quality by design is identified as one of the key practices which will have a significant positive environmental impact on generic production. Similarly, continuous manufacturing, solvent recycling, promoting solvent selection, waste diversion, and eco pharmacovigilance were identified as a few of the key green approaches which could significantly green the pharma industry. However, both practitioners and policy makers must play a role here for

successful execution of green in pharma. More importantly, the generic production could significantly turn green if they are motivated to redesign their existing process for better environmental footprint through exploiting green chemistry principles, as we are predominantly concerned now for those off-patent drugs and their continued production and use. For instance, generic pharma could be incentivised (e.g., exclusive sales right) and they could be ensured for first track speedy marketing approval for those redesigned processes. The importance of adopting single-use technology is another rudimentary approach for bio pharma to reduce chemicals in the bio-based process. Effective prescribing, dispensing and usage of drugs are the key to dealing with unexpected environmental loading of drugs and reducing AMR impact. The existing prescribing policy must be reviewed to reduce unnecessary drug usages and/or unnecessary drug excretion and promote using environmental classification of drugs during prescribing.

Chapter Nine: Implication and Conclusion

This chapter reviews the background and scopes of the research. It also reviews the key findings in light of each research question and highlights its contribution to theory and practice. It also highlights the key roles played by all upstream and downstream stakeholders for greening pharma operations and the supply chain. Finally, it provides the key limitations of the study along with future research agendas.

9.1 Research background and scopes

This thesis has explored the scopes of green supply chain management in the pharmaceutical sector. The materials, energy, and toxicity related environmental impact of drug products, and more specifically the issues of PIE and related AMR, were the key motivation to explore the concepts of GSCM in pharma. The study has explored four key GSCM concepts: green practices, green drivers, green barriers, and green performance measures in the pharma context. Under green practices, it has focused on drug design and development related green practices, drug manufacturing related green practices and drug use-and-disposal related green practices. Each of these key green practices are explored under materials related, energy related and toxicity related green practices across three key stakeholders (innovators, generic and bio pharma) in the upstream supply chain and seven key stakeholders (pharmacies, GPs, hospitals (CCGs), care homes, local councils, waste vendors and wastewater treatment) in the downstream supply chain. The study has also explored key performance outcomes of the green practices adopted in the context. The performance outcomes were explored under four key areas: carbon emission related, materials related, energy related and toxicity related. The study applied a qualitative methodology using both interviews and environmental reports to explore the phenomenon of GSCM in pharma.

9.2 Research Contributions

While several contributions were discussed under several topics and sub-topics in the findings and discussion chapters and again in the previous section, this section presents some of the key contributions that the study has made to theory, practitioners and policymakers.

9.2.1 Contribution to theory

The study is evidently the first attempt to understand the scope of GSCM and its importance to greening the pharma sector. The study has provided a conceptual model of green practices for pharma (see appendix F) under three key environmental impact areas: materials, energy, and toxicity. An in-depth understanding of green drug design and development, green drug manufacturing and green drug use-and-disposal and related sub level green practices were developed. There was no previous study that focused on such an in-depth exploration of green related practices in the pharma context, though there were some initial fragmented green ideas with significant limitations (Watson, 2012; Xie and Breen, 2012; Clark et al., 2010; Kummerer et al., 2009). In addition, such detailed materials, energy and toxicity related sub green practices were not discussed in a single sector previously in the generic GSCM literature to understand each of the core green supply chain practices (e.g., green design, green manufacturing, green use-and-disposal). So, it shows the novelty of the work done. Remarkably, some of the green practices were never discussed in the pharma literature such as design and develop process for flexibility in quality (or, consider quality by design), design process to install energy efficient equipment (e.g., single use technology) system, energy management programs (e.g., ZAP), consider digital technology for optimized drug prescribing, dispensing and usages and energy recovery from drug incineration. So, they add to the existing body of GSCM literature and especially enrich the green related pharma literature as opposed to the existing works done such as study of Boltic et al. (2013), Clark et al., (2010), Sheldon (2010), and Plumb (2005).

In terms of green drivers, this is the first study to identify ten unique green drivers for pharma and understands each of them in-depth and their importance and relevancy across individual stakeholders. A few of the drivers, such as f-gas related regulation (and how it drives the companies to develop new CFC free inhalers) and medical intervention projects (e.g., MUR) to drive drug waste reduction, were never discussed in the previous literature. The impact and extent of drug take back legislation for safe disposal of drugs were never known before, though there was only theoretical indication of it in the study of Vollmer et al. (2010). There was no study that focused on identifying and understanding drivers of green drug use-and-disposal among the downstream pharma stakeholders. So, they add novelty to the work done.

In terms of green barriers, this is the first study to explore stakeholder wise green barriers and their relevancy and importance in the research context. As opposed to Kumar's (2019) work, this study provided a holistic view on barriers considering each key stakeholder involved in the supply chain. For instance, it was never known before that generic and innovative pharma

felt high level barriers to redesigning off-patent drugs for better environmental footprints. However, some barriers, such as cultural issues (e.g., sceptical mindset of managers towards green), lack of standardisation in equipment and processes, lack of standardized waste kaizen, uncontrolled drug wastes from high concerned patient groups, lack of performance measures of patient interventions scheme, lack of regulatory guidance on environmental consideration in prescribing, and contradictory regulatory guidance for disposing unused/expired drugs, were never discussed in the pharma literature before. So, they add to the existing body of knowledge.

In terms of performance measures, this is the first study to develop a performance measures model which clarifies the relevance and importance of each performance measure for individual stakeholders. More importantly, some of the performance measures, such as elemental level GHG emission (e.g., scope 1, scope 2, ODS, VOCs etc), amount of energy generated onsite, amount of hazardous wastes converted to beneficial use (e.g., waste to energy), amount of hazardous waste recycled/reuse/incinerate/landfill, ROI of green projects and cost of green production (e.g., cost of process changes and cost of single use technology), were never discussed in the previous pharma literature. So, they add to the existing pharma literature. Remarkably, none of the previous GSCM literature in general was focused on measuring elemental level GHG emission and their impact assessment, which was also a valid research gap outlined by Zhu et al., (2006), where the authors repeatedly urged the exploration of elemental level GHG emissions performance. So, it adds to the generic GSCM literature as well.

In addition, this is the first study which has compiled and provided a comprehensive green supply chain management literature review in the pharma sector. The systematic and synthesized literature review demonstrates the status of green design practice, green manufacturing practice, green purchasing practice, green distribution practice, and green use-and-disposal practices in a stringent regulated pharma environment. Similarly, the status of related green drivers, barriers and performance knowledge in pharma has enriched the existing green supply chain management literature such as study of Clark et al., (2010), McDonald et al., (2010), Ruhoy and Daughton (2008). This synthesised literature review has provided a new grounding of knowledge in the green supply chain management domain from where much future research in the pharma sector could be built upon. Additionally, this study has also contributed to understanding the key concepts of the pharma supply chain in general, as there is no study in the operations and supply chain management domain that has

comprehensively discussed the key characteristics of the pharma supply chain. For instance, it is the first attempt to clarify our understanding on downstream pharma supply chain and the interrelationships among the stakeholders involved in general, and in GSCM field.

Finally, another significant contribution of this study is that this is the first GSCM related study in the pharma sector which has been theoretically grounded. None of the previous research explores and explains key GCSM themes and sub themes underpinned by related management theory. This study has viewed green practices, drivers, barriers, and performance through key management theories such as EMT, DOI, and resource-based view (RBV), information theory, and institutional theory. Theory grounded green practices and other green concepts are widely accepted for their validity, richness and the insightful inferences made from them. However, the study has identified three core theories that have been further explored and enrich our existing understanding. The key theoretical contribution is further explained below.

Contribution to EMT theory

The study has contributed to EMT theory through advancing the current understanding of the key concepts of the theory. To the best of the researcher's knowledge, this is the first study to review EMT through pharmaceutical greening knowledge. This unique observation has helped the researcher to refine EMT led green understanding in pharma to enrich both the generic green field and especially the pharma sector. This EMT led understanding is significantly important for pharma to emphasize and influence the valid green related managerial decision making process. The most important and synthesized understanding of EMT theory is that the tension between economic growth and environmental protection lies at the heart of political modernization, technological breakthrough and social transformation (Terryn, 2010; Ewing, 2017). So, the net environmental protection within a particular context is dependent on the three key concepts: political modernization, technological breakthrough and social transformation. However, this particular study has predominantly supported and advanced the understanding within two dimensions of EMT: politics of pollution / political modernization and technological advancement. They are briefly discussed below.

- ***Politics of pollution / Political modernization***

The political modernization aspect of EMT ensures that there are adequate environmental policies and regulations in place to deal with unprecedented environmental degradation from

industrial and economic activities (Mol, 2010). Environmental reform policies and regulations are shifting from the traditional central role of the nation-state to a new, flexible, and more decentralised governance arrangement (Terryn, 2010). It is also evident that environmental governance is not limited to traditional exercise of the political state. Rather, the environmental governance is being formed with non-political institutions such as privatization, public-private partnership and NGOs for improving environmental footprint (Terryn, 2010). Hence, the form of environmental program, policy and regulations are being changed in a continuous fashion to meet the ongoing environmental demand. The cooperation and interactions between state regulators and regulated companies are the key to successful environmental policy reforms.

This study finds that given the significant environmental pressure in the research context, several state regulations such as F-gas related regulations, Industrial Emission Directive (IED), REACH regulations, waste regulations etc, emerged to tackle the emission and wastes. Each of these regulations was reformed in terms of emission limits and penalty through close cooperation between regulatory state and regulated sector / companies. The study also indicates that close cooperation with regulatory bodies ensures long-term sustainability in economic and environmental improvement. This also motivates the pharma companies to define their own environmental policies. The study findings can further enrich the role of multi stakeholders (e.g., government, NGOs, leading companies) in developing fruitful policy and regulation to deal with the unprecedented environmental crisis. For instance, the FDA and EMA develop ERA policy to deal with the global issue of PIE and related AMR. The findings clearly indicate that public-private initiatives such as IMI (Innovative Medicine Initiatives) and other non-governmental agencies such as PSNC are collectively working together with leading pharma companies to exchange information to better understand the current and future implications of environmental contamination of drugs and alternative solutions. ERA prior to drug authorization is one such policy effort. Such unique understanding also extends Mol's (2010) initial assumption on policy reformation. Close cooperation for greening pharma operations through effective policy reform could significantly encourage the other industry. For instance, the study findings also indicate a greater extent of voluntary environmental policy reform by the companies, which is the result of close cooperation among the stakeholders including the state government. This understanding also partially fulfils Sarkis' (2011) concern about EMT - the lack of evidence of effective mechanisms to encourage green cooperation along the supply chains.

In addition and most importantly, the unusual behaviour of regulatory and policy reform in the pharma sector adds new understanding of EMT. Though EMT was viewed from the traditional automotive sector to tourism via oil and textiles (Er et al., 2012; Terryn, 2010), it was never explored in the pharma context. Though EMT traditionally moves from curative and reactive policy to more preventative in nature, stringent environmental policy is not always straightforward in pharma operations due to the discovery nature of its operations. Also, safety and efficacy of the final product is key and cannot be compromised at any time across the life cycle. Hence, the nature of policy reform is sometimes complex, bureaucratic and time consuming, as it involves continuous multistage quality testing and related internal / external validation. For instance, the sector is struggling to influence the regulatory body to reform (or, relaxing) the policy of greening existing drug processes for better environmental and economic outcomes though there is huge scope for reforming policy from an industry perspective. Even though there is huge political and social pressure concerning PIE and AMR, the policy adoption (e.g., allowing all manufacturers to redesign their existing drug process) is still not so straightforward, which will require ongoing and incremental adaptation of socio-economic environment. These empirical observations extend and contribute to the initial EMT debate on radical versus incremental environmental reform by York et al (2010).

- ***Technological advancement / technological breakthrough***

Technological breakthrough is another key aspect of EMT. This is also historically known as 'Super industrialization' process (Terryn, 2010). This aspect of EMT ensures a cleaner production process driven by regulations. To support and advance the EMT theory, the study findings indicate that the technological advancement not only ensures greener production but also achieves longer-term financial benefits through environmental reform. For instance, driven by the necessity of reducing their environmental footprint, pharma companies have introduced industry 4.0 across the supply chain from initial drug discovery to final distribution through cleaner production. Though EMT led institutional pressure and related technological advancement are predominant in the existing literature (Zhu, et al., 2012; Er, et al., 2012; Murphy and Gouldson, 2000), little was known on how voluntary policy reform and business benefits drive companies towards technological breakthrough. The study has advanced this understanding. For instance, many leading pharma companies are investing in nano technology based drug formulation, in-silico based drug testing, high throughput screening via focused library driven by voluntary internal environmental policy and targets alongside long-term financial projection through reducing development timelines. The

findings also indicate that companies can increase their competitive advantages through technological advancement. For instance, pharma companies are continuously investing in science and technology to become unique producers of drugs to create competitive advantage. Discovery and application of green chemistry (or MET) is one such technological breakthrough for the pharma sector.s This technological advancement has helped the sector to create unique drug processes to reduce waste and toxicity as well as gain financial benefits through environmental savings. For instance, the bio based drug process has significantly improved materials, energy and toxicity profiles and related costs savings. Hence, companies are actually exploiting technologies as new business opportunity rather than costs (Zhu et al., 2012). The study findings also indicate that the majority of the technological innovations occur in the upstream drug design and development phase (e.g., nano technology based drug formulation, MET led process design etc) rather than in the downstream supply chain. This understanding also supports and extends Huber's (2008) EMT led observation which studied German companies and identified that most of the innovation is held in the upstream. This is how the understanding of the role of science and technology in environmental reform underpinned by EMT is enriched.

Contribution to DOI theory

The study has contributed to DOI theory through extending the understanding of how green innovation is adopted and diffused in such discovery oriented and highly regulated environments like pharma over time. To the best of the researcher's knowledge, this is the first study to review DOI theory through pharmaceutical green supply chain knowledge. This unique observation has helped the researcher to refine the green adoption process in pharma to enrich both the generic green supply chain field and especially in the pharma sector. This DOI led understanding for managers and practitioners is significantly important to learn from the early green adopters and understand the process of related green practices adoptions to further encourage, emphasize, and influence the sector to go green. This DOI led green pharma reflection will undoubtedly enrich our existing understanding of why managers should implement green practices on time and align them with business strategy.

Application of the innovation diffusion mechanism (Rogers, 2003) in pharma is also understood. The research findings of this study clearly indicate that green chemistry or MET related practices are the key green innovation for the pharma sector. It is also clear that MET related green innovation was initially communicated among the process engineers within

companies for looking at the alternatives to toxic chemicals use in the process. However, as time passed, the key concepts of MET started communicating further among the far upstream medicinal chemists and scientists through a formal knowledge dissemination hub called the ACS GCI pharmaceuticals round table where all interested companies join together to foster green chemistry innovation in response to environmental degradation. The ACS GCI pharmaceutical roundtable plays a key role in diffusing the materials, energy and toxicity related green innovation continuously. In particular, this green social system has motivated the scientists and chemists to think of designing green drug processes with lower materials, energy and toxicity impact. The application of green chemistry was successfully diffused among the leading innovative pharma companies through successful coordination across the supply chain stakeholders. For instance, when the far downstream waste management vendors were facing difficulty processing toxic manufacturing wastes, it was communicated to the far upstream process chemist via process engineers to develop greener alternatives (e.g., solvent with lower environmental impact) for reducing toxicity during waste processing. As time passed, this coordination matured among the leading innovators to fully diffuse the MET practices. Such unique diffusion mechanism of green extends core theory of DOI (Rogers, 2003; Sarkis et al., 2011).

DOI theory also suggests that the rate of adoption of each innovation is dependent on relative advantage, compatibility, complexity, trialability and observability (Rogers, 1995). It also ranks the adopters as early adopter, follower and laggards. Although GSCM is attributed as environmental innovation having all the characteristics of innovation (Zhu, et al., 2012), it is a difficult, complex and time consuming exercise to diffuse this innovation into the multidimensional supply chain channels. The variation of green chemistry adoption rates across the pharma industry can be explained using this DOI concept. For instance, whilst the majority of the innovative pharma identify the relative advantages of adopting MET related practices to deal with environmental degradation, many generic pharma were seen as reluctant to adopt some of the MET related practices (e.g., solvent recycling, continuous manufacturing, quality by design) due to the incompatibility with the existing environmental framework. For instance, as indicated in the study, some of the generic companies follow lean activities for financial gain rather than aligning them to existing environmental practice. The result also indicates that some of the generic companies expressed their fear of losing their manufacturing license if they adopted a new MET led green manufacturing practice within the existing manufacturing process. So, for them, there was an incompatibility issue

for adopting green. Being mostly cost focused, the majority of the generic pharma were seen to face complex (e.g., multi stage time consuming and costly process validation) regulatory validation and approval for green process design of existing drugs in comparison with the other pharma companies. This complexity has significantly reduced their opportunity to adopt green chemistry related practices. The innovators have a huge opportunity, in terms of financial investment to trial and test the related green innovation, to understand and project ROI value for each green chemistry related practice compared with generic pharma companies. Hence, the perceived benefits from green related practices in terms of observability are higher in innovators than generic. Also, the innovators in general became early adopters of MET adoption across the sector while generic pharma in general were seen as followers. For instance, generic pharma became motivated to adopt solvent recycling while observing the related environmental and financial benefits exercised by the innovators. Hence, generic pharma became followers in terms of applying solvent recycling. This is how the overall green adoption rate and related success by innovators is higher than with generic pharma.

Contribution to RBV theory

The study has contributed to RBV theory through advancing the understanding of how green innovation enables the pharma companies to increase competitive advantages. To the best of the researcher's knowledge, this is the first study to review RBV theory through pharmaceutical green supply chain knowledge. This unique observation has helped the researcher to refine the importance of green adoption in pharma to enrich both the generic green supply chain field and especially in the pharma sector. This RBV led green pharma knowledge for managers and practitioners is significantly important for learning why pharma companies need to focus on developing organizational resources and capability of utilizing those resources effectively and efficiently for continuous green innovation. This RBV led green pharma reflection will undoubtedly enrich the existing understanding on the importance of green supply chain in pharma context (Sarkis et al, 2011; Barney, 1991).

The study findings clearly indicate that pharma companies, especially the leading innovators, have successfully developed some unique resources, such as top management commitment, significant financial investment on drug R&D, internal and external training on green chemistry, in-house green solvent database management, green recognition programs, green related knowledge transfer, environmental investment and supplier development for greening.

These resources have been explored and utilized in such a manner that the pharma companies (especially the leading innovators) were seen to develop drug processes to manipulate the relevant diseases. A new drug discovery and related green process development is a combined effort of all those resources. Those companies develop dynamic capability through exercising an internal and external green related knowledge exchange process (Carter and Carter, 1998; Sarkis et al., 2011). For instance, the leading innovative pharma companies exchange green related internal knowledge from far downstream waste vendors to far upstream drug discovery units through purchasing, manufacturing and use and disposal. Green chemistry related internal training among the scientist, chemists and chemical engineers has eventually enabled the companies to innovate green chemistry based process design, which is unique, rare, and inimitable. This unique design also follows non-substitution (Govindan et al., 2014). Thus, the newly designed green drug process creates competitive advantages. For instance, the study shows that such rare drug design (e.g., biocatalyst based drug process) has actually helped the organizations to bring production cost down through environmental savings and increase monopoly sales revenue. The sector has also developed many active external R&D collaborations for external knowledge sharing, which has continuously helped the companies (especially innovative pharma) to enrich PBT data to deal with PIE and the related environmental impact.

Similarly, the unique approach to solvent recycling and continuous manufacturing through internal (e.g., in-house green chemistry team) and external organizational (e.g., participating ACS GCI pharmaceutical roundtable / external research collaboration etc) learning has enabled the companies to increase competitive advantages in terms of green image, lowered solvent costs and reduced environmental footprint. Therefore, those internal resources must be developed and utilized in an effective and efficient manner (Zhu and Geng, 2013). It is also important to note here that in light of the RBV, the pharma companies could also equip themselves with the appropriate resources to reduce the related green barriers. For instance, pharma companies across the sector could potentially increase their competitive advantages through developing a new MET led training program for those employees who are involved in discovery and drug design and the drug manufacturing process, it will help the sector in improving employees' green mindset. Similarly, the drug R&D and manufacturing process could be further streamlined through automation such as innovating further how nano technology based formulation is possible for all classes of existing drugs.

9.2.2 Contributions to practitioners

The findings are significantly important for the pharma sector, as previously policy makers and pharma stakeholders had limited understanding of how and what green practices to consider during the drug design, manufacturing, and use-and-disposal phase (Clark et al., 2010; Vollmer et al., 2010; Mcdonald et al., 2010). The findings provide the practitioners with a green practice model (see appendix F) which could be adopted by each stakeholder in greening the pharma supply chain. This green practice model could significantly be useful for the followers and laggards in the sector, such as generic pharma, to learn from the green leaders, such as innovative pharma.

Similarly, the green drivers related findings are also significant for the pharma sector, as the practitioners across all stakeholders did not have a clear understanding of the key factors that could drive them to adopt green. The findings will undoubtedly help those practitioners to review their existing operational strategy to adopt green. For instance, generic pharma practitioners could implement MET based training for all relevant employees to promote not only environmental footprint but also increase competitive advantages through cost savings like in the innovative pharma sector. Similarly, both bio pharma and generic pharma practitioners could consider incentives awards for green innovations in their existing strategy. The findings on stakeholder pressure will undoubtedly alert the practitioners to think of exploring PIE related projects as opposed to limited version of previous understanding (Watson, 2012; Clark et al., 2010).

The findings on green barriers are also important for the pharma sector, as the practitioners across all stakeholders did not have clear understanding of the factors that impede them to adopt green. The findings will undoubtedly help those practitioners to review their existing operational strategy to accommodate and increase related resources to reduce/eliminate the barriers. For instance, the findings will influence practitioners (especially from generic pharma) to rethink their operations strategy for the longer-term through reviewing the trade-off between 'costs of existing process changes (e.g., replacing with greener solvent /change mode of manufacturing, /install recycling etc)' and 'potential long-term cost savings from solvent cost/energy cost/disposal costs etc)', which were even unknown in the recent study of Kumar (2019). The findings will also help the other external NGOs (e.g., British Generic Manufacturers Association - BGMA or Association of British Pharmaceutical Industry – ABPI) to influence the policymakers to review existing policy on approving redesigned greener drug processes. The practitioners from generic pharma could also benefit from providing further education and training on green chemistry or MET practices among the

operations managers to increase their levels of awareness to mitigate their sceptical notions towards green practice, such as distortion of drug quality due to adopting green. The findings on the lack of standardized equipment systems will also help practitioners to invest more in new technologies to overcome the challenges to adopting recovery projects in line with the theory of the resource-based view. The practitioners in the downstream will also be able to develop new streamlined drug management systems (e.g., more supervised consumption) for those of high concerned patient groups to reduce unnecessary drug wastes, which were unknown in the previous study such as Vollmer et al., (2010), Castensson and Ekedahl, (2010). Also, the pharmacy and related service negotiation agency, like PSNC, will be able to focus on investing to measure performance (e.g., number of drugs saved in terms of cost) of all related medical intervention projects like MUR/NMS etc. This is how the related findings significantly contribute to practice.

The performance measures related finding has significant implication for practitioners. For the relevant stakeholders who are still confused and/or struggling to validate the key performance indicators, this key finding will help them to embrace these measures, specially the late majority and laggards in the field. Also, the early adopters could be benefitted and be able to increase competitive advantages by applying these performance measures. The key findings on environmental and cost/economic performance could significantly increase confidence levels in the followers and laggards in the industry to adopt green practices, which never known in the previous study such as the study of Dunn (2013) and Boltic et al. (2013). In particular, practitioners from generic pharma could significantly improve their environmental and economic performance by adopting these measures which have already shown many win-win business cases, such as significant cost savings from solvent recycling and continuous manufacturing in the longer term. So, the relevant findings on measures and related performance impact are crucial for generic pharma practitioners. The findings will also help the practitioners to understand the significance of adopting each of these measures. For instance, companies will be able to control and reduce their disposal costs significantly by adopting a simple measure called ‘Amount of Hazardous waste generated’. Similarly, in the downstream the stakeholder local CCGs could be further influenced by the findings to adopt more drug reuse and recycling projects like POD/green bag schemes as well as more patient intervention schemes like MUR/NMS across the country or where economically viable.

Given the significance of the individual stakeholder efforts to greening pharma supply chain, each stakeholder must get a better understanding on each green practices available and related drivers, barriers, and performances. Hence, it is expected to develop an interactive online tool that will enable respective participants to get a better understanding of the best practices, drivers, and barriers.

9.2.3 Contribution for policymakers

The study offers related policymakers a grounding in understanding the scopes of greenness in the pharma sector. The study findings on green practices, drivers, barriers, and related performance have clearly indicated the scopes of policy improvement. So, the related findings are significant for policy makers to review their existing policy to further motivate the industry, especially those who are still far behind, generic and bio pharma, to go green. For instance, it must be a worrying fact for policymakers why generic pharma have the lowest adoption even though they are responsible for producing the lion's share of off-patent low cost drugs and they pose significant environmental damage from excessive use of natural resources and unexpected loading of drugs concentration from production facilities. As indicated in the findings, the key challenge for them to go green is the complex marketing authorization process for modified drugs. The challenge was also highly felt by the innovators as well. So, the policy makers (e.g., FDA/EMA/ MHRA) can intervene and review their actions / enactment to foster green for generic pharma. Such understanding also extends the initial work done by Dunn (2013) focused on bureaucratic view on accepting green process.

For instance, there is significant opportunity for the industry to reduce MET related environmental footprint and related cost savings from redesigning the existing (off-patent) drug process. So, the findings will influence policymakers to intervene into the process of approving redesigned (off-patent) drug processes through two way talk between industry leaders and policymakers. For instance, if the policymakers introduce a first track approval process for greener drugs (redesigned off-spatent), the related green practice adoption would be increased significantly. Similarly, the findings on time pressure to market will also influence policymakers to allow more time (e.g., increase patent for five more years) to motivate the innovators to focus on green process development in the early stage of drug development rather than allow the companies to redesign off-patent drugs. It further extends the related assumptions by Leder et al (2015) and Kummerer (2009). Findings on significant

win-win cases of solvent recovery, continuous manufacturing and other MET related green practices will influence the decision on reviewing policy when it comes to approving the greener drug process (redesigning off-patent drugs).

Therefore, policymakers (FDA/EMA/MHRA) could intervene in how to streamline the validation process of a process change (e.g., change equipment, raw materials, mode of manufacturing, retrofit recycling etc) so the companies could invent more green technology, like MET practice. As per the findings, a process is well understood (in terms of optimization) as time passes and through matured levels of production, so, arguably, process change is urgent for a better environmental footprint. So, the policy makers must play a role here. The industry will significantly improved their greenness, as the related streamlined marketing authorization process will significantly foster the companies from all stakeholders to adopt quality by design principle to adjust all quality variations due to varieties of process changes such as retrofit recycling, changing mode of manufacturing from batch to continuous, changing with greener materials and developing combined drugs. Such understanding also enriched significantly the study of Plumb (2005) focused on the scope of batch and continuous manufacturing.

Remarkably, none of the existing regulatory guidance, such as cGMP, GDP and GLP focused on greener process design and development, green manufacturing, and green distribution (Brhlikova et al., 2007; Clark et al., 2010; MHRA, 2015; Bellm, 2015). Rather they only focused on PIE monitoring issues and avoided the wider impact of drugs on natural resources. As the industry adheres to cGMP, GDP and GLP, the study findings will influence the policy maker to rethink whether the existing guidance can be revised to add a separate section for the practitioners to follow some generic guidance for green drug design and development under GLP, green drug manufacturing under cGMP and green drug use-and-disposal under GDP. This rudimentary approach will significantly improve the greenness of the sector. The cGMP could also ensure that all employees or operators involved in drug R&D and manufacturing must be trained on MET to avoid the sceptical behaviour of green adoption in their roles, and can come with innovative green ideas.

As emerged in the study, the PIE related AMR impact is becoming a new threat for humankind. So, the API discharge and its continuous assessment (e.g., eco pharmacovigilance programs) must be regulated. The findings should clearly motivate policymakers to review their existing policy to promote ERA further across the industry. For

instance, the policymakers (e.g., FDA/EMA/MHRA) could review existing drug approval process or review existing cGMP to provide further stringent regulatory thresholds to manage PIE (e.g., set stringent API discharge limits) as only innovative big companies are now currently taking voluntary measures to assess their API discharge into the water. This is urgently required because we will need to enrich the PBT data for all existing drugs products to control the AMR issue as soon as possible before any other pandemic happens. The findings also influence policymakers to understand the trade-off between 'enriching PBT data for existing APIs in the market to control PIE' and 'MET led redesign process for existing APIs in the market'. Such understanding has also significantly improved initial view of PIE and related AMR management by Bound and Voulvoulis, (2005) and Sumpter, (2010).

As emerged in the study, patient excretion is one of the biggest sources of PIE. So, the findings on the lack of regulatory guidance on environmental consideration in prescribing experienced by GPs will also influence the relevant policymakers (e.g., GMC –General Medical Council) to rethink whether the prescribing policy can be reviewed, and if the GPs can be trained and educated about PIE, and if they can incorporate some classes of drugs (which are under serious concern) into the EMC guidance. The policymakers will also be able to review the existing policy to establish whether some environmental guidance (e.g., considering excretion rate into consideration wherever practical) can be incorporated into EMC for the GPs to consider, which were never concluded by the work done by Doughton and Ruhoy (2013) and Bound and Voulvoulis (2005).

As drug non adherence was identified as another significant source of PIE, the findings on hypothetical performance measures (e.g., anticipating improved drug adherence level) for different medical intervention schemes (e.g.., MUR/NMS etc) will also influence the relevant policymakers or service providers such as PSNC. They will have crucial implications for the relevant top management or service provider (e.g., PSNC) for their ignorance of this matter. As for example, whilst the introduction of MURs and NMS involves significant operational and cost/economic investment by the government, the hypothetic nature of performance measures and lack of actual measures through follow up systems is clearly missing, which could have a serious implication on the return on investment of such projects if applied in other contexts (except not for profit organizations). This is how the key findings also contribute to policy, which were never affirmed from the previous study such as study of Latif et al. (2013) and McDonald et al. (2012).

Also, the findings on contradictory regulatory guidance for disposing unused/expired drugs will influence policymakers to review and clarify the guidance to convey and motivate the public for safe disposal of drugs. For instance, the policy maker could categorize all drug wastes (regardless of industry or household waste stream) as 'potentially hazardous' (considering the ongoing scientific evidence of PIE) so the general public and local councils will be more concerned about safe disposal of drugs. This is how the related findings in the study significantly contribute to policy. Additionally, the findings on monetary incentive drivers for downstream players will influence the related policy makers (e.g., local CCG / NHS) to review the trade-off between 'cost of MUR related incentive programs to reduce drug waste' and 'cost of current level of drug waste generated and related environmental damage'.

In a nutshell, the study has clearly indicated all possible aspects where the relevant policymakers could play a role in the greening of the pharma sector. Table 9.1 has conceptualized the scopes of key potential policy improvements linked to the study findings.

Table 9.1 Conceptualization of the scopes of potential policy improvement linked to the study findings.

Relevant policy makers / key service providers	Scopes of potential policy improvements
FDA / EMA / MHRA	• Streamlined validation / marketing approval of process changes • Incentivise the innovators (e.g., increase patent) for green process development • cGMP – include a generic green road map during production in line with APIs monitoring (e.g., written policies and protocols submitted by the companies to follow solvent selection guide etc) • GLP – include a generic green road map during R&D (e.g., use more in-silico tests) • GDP – include a generic green road map during use and disposal (e.g., written policies and protocols submitted by the approved distributor to demonstrate how the drug will be used and disposed) • In liaison with the leading innovators, they can develop a web-based interactive tool to identify the best green practices /or, most important green driver / or, most important green barriers for individual stakeholder. This tool could be used by the operations managers to understand each practice / driver / barrier in detail prior to investing on

Relevant policy makers / key service providers	Scopes of potential policy improvements
	a green project. Similar tool could be developed for downstream stakeholders.
GMC (General Medical Council) or Department of Health	• Organize meetings, conferences, and invite medical experts to review how environmental considerations could be incorporated in prescribing • Coordinate with local environmental agency and water industry research (UKWIR) to obtain up to date research data on PIE, and alert all prescribers about those APIs of high concern and see alternative prescribing (whenever practically possible) • Review the EMC guidance to consider lower exertion rate related drugs whenever practically possible as EMC could organize similar drugs with different excretion rate • Review PBT data for similar class of drugs so the lower impact one (or, best alternative one) could be selected by the GPs whenever practically possible • Review the existing medical school syllabus and include the key findings of the study (e.g., issue of PIE and its consequences, eco-friendly alternative treatment and drugs prescription, prescribing opportunity with lower excretion profile of a drug and related drivers and barriers, scopes of encouraging patients for effective use of drugs and safe disposal, increase the awareness of drug take back view etc) to increase awareness among next generation doctors
GPhC (General Pharmaceuticals Councils)	• Review the existing pharmacy school syllabus and include the key findings of the study (e.g., issue of PIE and its consequences, optimized drug dispensing process with effective medicine usage review, how to encourage local community patient to reuse of drugs – POD, understand the scopes of unwanted drug wastes, ensure safe disposal of household unwanted drugs, increase the awareness of drug take back view etc) within community pharmacy practice module to increase awareness among next generation pharmacists. • However, essentially driven by wider sustainability, both GMC and GPhC could persuade the UK department of education to include some key findings of the study (e.g., importance of safe and effective use of drugs, how to dispose unwanted/surplus drugs safely, etc.) within school curriculum to increase awareness among the next generations.
UKWIR (UK Water industry Research)	• Co-ordinate with pharma companies to feedback to them on APIs concentration level into their incoming sewage effluent on regular basis • Combined investment on PIE projects

Relevant policy makers / key service providers	Scopes of potential policy improvements
DEFRA /EA (Environmental agency)	• Create pressure through mandatory regulatory limit of API discharge for the pharma companies to adhere to the limits • Specific guidance to the local councils on how to deal with household drug wastes (e.g., promote special collection of household drug wastes); as household garbage still remains the main source of drug disposal by people, so, pharmacy take back still not enough. Alternatively, appropriate household fine can be imposed (like not adhere to car parking) to promote drug take back scheme. • As drugs waste (except all cancerous drugs) is not considered as hazardous in the current waste guidance, people have the perception that they could dispose of them via household garbage and are reluctant to take them back to the pharmacy. Guidance must be reviewed for the sake of wider wellbeing.

9.3 Review of research findings

This thesis has proposed to answer four key research questions. This section will review and highlight the answers to each research question in light of findings and its contribution to theory and practice.

Research question one

What green practices are implemented by individual pharma sector stakeholders and what is the extent of their implementation?

Green drug design and development Practices

In the case of the green drug design and development phase, the study identified ten different sub level green practices under three key categories: materials, energy, and toxicity. The key materials related design practices identified across the key stakeholders (innovators, generic and bio pharma) are: design and develop manufacturing process to use greener substances, design and develop drug discovery process to reduce chemical based testing, design process to consume fewer raw materials by applying process metric (e.g.., PMI), design and develop drug manufacturing process for flexibility in quality (Quality by Design), design packaging for material efficiency and design combined drug (e.g., use multiple active substances) for

material efficiency. The key energy related design practices identified across the stakeholders are: design and develop manufacturing process for least energy consumption by evaluating alternative process, and design and develop manufacturing process by installing and validating energy efficient equipment system (e.g., reaction vessel). The key toxicity related design practices identified across the stakeholders are: design and develop bio-based drug process to reduce water toxicity and design and develop drug process to reduce air toxicity.

However, the extent of implementation of the relevant green design practices among the stakeholders varied significantly. Overall, innovators were high-level adopters for most of the practices followed by bio pharma and generic. The result of innovators' high level green adoption is also consistent with Watson's (2012) study. Generic were the lowest adopter. Some practices were only considered by innovators and not considered at all by both generic and bio pharma, such as design process to consume less raw materials by applying process metric (e.g.., PMI) and design combined drugs. Both generic and bio pharma were seen to pay equally low attention to adopt air toxicity reduction related design practice.

Green drug Manufacturing

In the case of green drug manufacturing, the study identified nine sub level green practices under materials, energy and toxicity related. The key materials related green practices identified across the industry are: run continuous mode of manufacturing, recycle and reuse solvents, consider lean operations for materials reduction, and consider green collaboration for materials efficiencies. The key energy related green practices identified across the industry are: consider energy efficient technologies and consider energy management program. The key toxicity related green practices identified are: consider greener chemical (e.g., solvent/reagents etc) management, monitor and control environmental toxicity of drug substances (eco-pharmacovigilance), and consider responsible waste management for toxicity reduction. The findings also support the studies of Slater et al (2010) and Clark et al (2010).

However, the extent of implementation of relevant green practices among the stakeholders varied significantly. Overall, innovators were high-level adopters of most of the practices compared with other stakeholders. On average, both generic and bio pharma were found to have similar (low) levels of adoption. Higher adoption of green was also highlighted in the study of Watson (2012). Some practices, such as adopting lean operations for materials reduction, were found to be almost equally attractive to all stakeholders. Some practices, such as green collaboration for materials efficiency, were not considered by bio pharma at all.

Green drug use-and-disposal

In the case of green drug use-and-disposal, the study identified six key sub level green practices under materials (drug waste) reduction, energy reduction and toxicity reduction across seven key stakeholders: pharmacies, GPs, hospitals (CCG), care homes, local councils/waste vendors, and waste water companies. The key materials or drug waste reduction related practices identified are: consider lean operations for optimized prescribing, dispensing and usages, and consider digital technologies for optimized prescribing, dispensing and usages. The key energy related practices identified are: energy efficient refrigeration system and temperature control, and energy recovery from the drug incineration process. The key toxicity related practices identified are: safe and responsible disposal management of unused and expired drugs, and consider greener wastewater treatment options.

However, the extent of the implementation of relevant green practices among the relevant stakeholders did not vary significantly. Pharmacies and GPs were seen to have almost the same (high) levels of adopters for drug waste reduction related practices. Both care homes and hospitals were also seen to have similar (medium) levels of adoption for drug waste reduction. Overall, pharmacies and GPs were seen to be high level adopters of drug waste reduction and safe disposal related practices followed by hospitals and care homes.

No study to date has provided a detailed understanding of green drug design and development and related sub level green practices under materials, energy and toxicity. In particular, practices such as design and develop drug manufacturing process for flexibility in quality (or, quality by design), design and develop drug process to reduce chemical based testing, design combined drugs, design and develop the manufacturing process by validating energy efficient equipment system and design and develop the bio based process, including their relevance / non relevance and extent of implementation for each stakeholder have not been explored previously in the pharma sector, and the related findings have significantly added to the novelty of this study.

In addition, the concept of quality by design had not been discussed before in the generic GSCM literature. The concept of ‘quality by design’, a strategic design space where possible process variation parameters are considered in the early chemical process design so that they could be controlled / prevented in the actual bulk manufacturing process, was not known in the existing GSCM studies. This green design concept could be applied in the similar

chemicals process industries where lots of wastes are induced due to variations in batch quality. This could be very useful especially for those industries where product development and manufacturing sectors are under stringent regulations, e.g. food textiles etc. Therefore, the related sub level green indicators can be used to measure the greenness of a new or existing drug process in the pharma sector, which we did not have it. This new measuring model is a unique contribution to the pharma sector.

A detailed understanding of green drug manufacturing and related sub level green practices under materials, energy and toxicity, particularly practices such as continuous mode of manufacturing, solvent recycling, and eco-pharmacovigilance, including their relevance / non relevance and extent of implementation for each stakeholder, has not been explored previously in the pharma sector, and thus the related findings have significantly added to the novelty of this study. Whilst the concept of recovery practices in the discrete industries is well covered in the green supply chain literature, consideration of solvent recovery options in the process and related industries has not been well covered in the general green supply chain management studies. So, this green manufacturing concept has enriched green related literature in pharma as well as in other generic GSCM literature. Also, the concept of eco-pharmacovigilance has further enriched the 'product stewardship' concept or the key concept of 'green product management' under green manufacturing, which was less discussed in the previous supply chain / green supply chain literature, and the concept was very novel in pharma. Only a little indication of this practice was seen in the study of Clark et al (2010). As per eco-pharmacovigilance, the continuous monitoring of the environmental impact of a particular product (particularly chemicals) when the product remains in consumer usage phase would significantly reduce detrimental harm to both humankind and the environment. The concept of eco-pharmacovigilance can be adopted to any other process-based industry like leather / leather goods processing, textiles, foods, plastic / metal processing, organic chemicals etc for a better environmental footprint. Therefore, the related sub level green indicators can be used to measure the greenness of a drug process in the pharma sector, which was not previously the case. Additionally, the related indicators under materials, energy and toxicity could also be applied to other process industries to measure the greenness of a process. This new measuring model is a unique contribution to the pharma sector.

Detailed understanding of green drug use-and-disposal and related sub level green practices under materials (drug wastes), energy and toxicity, particularly practices such as patient interventions (MUR/NMS), lean prescribing, dispensing and usages, and drug reuse,

including their relevance / non relevance and extent of implementation for each stakeholder has not been explored previously in the pharma sector, and thus the related findings have significantly added to the novelty of this study. However, in the previous literature, only a narrowed focus on MUR was observed in McDonald et al.'s (2010) study.

In addition, to the best of the researcher's knowledge, no previous study in the generic GSCM literature has viewed each green supply chain management practice from three core environmental impacts – materials, energy, and toxicity. This is the first empirical study which has applied the GSCM approaches to combating these two pressing issues - PIE /AMR - in the pharma sector. Though the concepts of medical interventions (e.g., medicine usage review, new medicines service etc) and product (drug) disposal awareness are covered in the general pharma literature (Latif et al., 2011; McDonald et al., 2010), the concepts were never discussed through the lens of the green supply chain approach to enrich the concept of green use-and-disposal.

The findings are significantly important for the pharma sector, as previously policy makers and pharma stakeholders had limited understanding of how and what green practices to consider during drug design and development, drug manufacturing and the drug use-and-disposal phase. The findings provide practitioners in the UK or any other context with a set of detailed green practices which could be adopted by each stakeholder in greening the pharma supply chain. The findings could significantly be useful for the followers and laggards in the sector, such as generic pharma, to learn from the green leaders, such as innovative pharma. The findings are also significant for policy makers to review their existing policy to further motivate the industry, especially those who are still far behind, such as generic and bio pharma, to go green. For instance, it must be a worrying fact for policymakers that generic pharma have the lowest adoption, as the lion share of drugs are being produced by them and they pose significant environmental damage from excessive use of natural resources and unexpected loading of drugs concentration from production facilities. So, the policymakers can intervene and they can review their actions / enactment to foster green.

From a theoretical perspective, the study has developed a detailed green practice model for the pharma sector (see appendix F). The model covers all materials, energy and toxicity related green practices for a complete environmental impact solution for pharma. This new model for pharma green practice is a significant research contribution. This is because each indicator in the model is built upon the related insights from interviews and reports, which is

the core of the theory building approach (Venkatraman, 1989). The study also advances the theoretical stance of GSCM, as it enriches the existing GSCM literature. It is also important to highlight that the key background theory, such as ecological modernization theory, diffusion of innovation, resource-based view and resource dependency theory, are the basis of this new green practice model. Each of these theories can explain how each stakeholder has adopted those green practices in the context.

In a nutshell, this research question was sufficiently answered and explored the relevant evidence in detail to conceptualize the new green practice model for pharma. Such comprehensive investigation on green practices in the pharma sector has not been undertaken before and there was no such green practice model referenced previously and hence, it contributes significantly.

Research Question 2

What are the drivers faced by individual pharma sector stakeholders for adopting green practices and what is their perceived importance?

The important green drivers for upstream pharma supply chain stakeholders (innovators, generic and bio pharma) identified in this study are: government regulations, such as f-gas related regulation, industrial emission directive (IED), REACH regulation, ERA of drug for marketing authorization; business benefits related, such as cost savings opportunity; top management commitment related, such as internal environmental targets; community wellbeing and corporate responsibility; incentives and awards for green innovations; and stakeholder pressures. The extent of pressure exerted from each driver by individual stakeholders varies significantly. In general, innovative pharma faced considerable pressure from all types of drivers compared to others. Generic and bio pharma in general experienced between low to medium level pressure. One of the key reasons for this difference was the operational requirements for the process/plant. Innovators have felt significant corporate responsibility pressure to adopt many green practices, whereas both generic and bio pharma felt low levels of pressure.

The important green drivers for downstream pharma stakeholders (e.g., pharmacies, GPs, hospitals, and care homes) identified in the study are: drug take-back legislation, financial incentives for medical intervention, and high healthcare costs (high cost of drugs). Pharmacies, hospitals, and care homes were seen to feel high levels of pressures from drug

take back legislation. The relevance / importance of financial incentives was predominantly felt by the pharmacies. GPs and hospitals felt a high level of cost pressure. However, one of the key reasons for this variation was the level of responsibility and accountability of each stakeholder in the supply chain. For instance, pharmacies do not exert such high cost pressure, as they are reimbursed by the NHS.

A detailed understanding of each driver (both upstream and downstream) identified in the study including their relevance / non relevance and extent of pressure exerted on each stakeholder has not been explored previously in the pharma sector, and thus the related findings have added significantly to the novelty of this study. For instance, none of the previous studies has identified and explored how and to what extent ERA can drive companies to adopt eco-pharmacovigilance practices. Similarly, REACH regulation mostly influenced the innovative pharma rather than generic pharma. This is because generic pharma is mostly involved in formulation rather than API production and there is less scope of producing byproducts, which was not known in previous studies. Though there was a little indication in the study of Clark et al (2010) about REACH, it was not focused on different pharma stakeholders. It was also never empirically known that achieving cost efficiencies and internal environmental commitment are topmost key drivers for innovative pharma companies to adopt green practices. This is the first study which has provided a comprehensive picture of what, how and why the key regulations, such as REACH, ERA, IED, and waste hierarchy, have driven the pharma stakeholders (especially the innovative companies) to adopt green practices. In the downstream, it was never previously known whether and how drug take back could drive pharmacies, GPs, hospitals, and care homes together to undertake related green practices to ensure the safe disposal of drugs. Though there was a little indication of the drug take-back legislation in the literature of Vollmer et al (2010), it was unknown how the legislation drives the downstream pharma stakeholders to adopt green practices / related streamlined activities. Similarly, how monetary incentives help downstream stakeholders to reduce drug waste had not been discussed in detail previously, though the related operational perspective was slightly indicated in the study of Latif et al. (2010). Also, no previous study has focused on identifying the green drivers for downstream pharma stakeholders for adopting green use-and-disposal related practices.

The findings are significant for the pharma sector, as the practitioners across all stakeholders did not have clear understanding of the factors that could drive them to adopt green. The findings will undoubtedly help those practitioners to review their existing operational strategy

to adopt green. For instance, generic pharma practitioners could implement MET based training for all relevant employees to promote not only environmental footprint but also increase competitive advantages through cost savings like those achieved in the innovative pharma sector. Similarly, both bio pharma and generic pharma practitioners could consider integrating incentives awards for green innovations into their existing strategy. The findings on stakeholder pressure will undoubtedly alert practitioners to think of exploring PIE related projects. This is how the study significantly contributes to practice.

The findings are also significant for related policy makers. For instance, the policy makers (e.g., FDA, EMA) could review the existing drug approval process or review existing cGMP to provide further stringent regulatory thresholds to manage PIE (e.g., set stringent API discharge limits), as only innovative big companies are now currently taking voluntary measures to assess their API discharge into the water. When PIE related AMR is becoming a new threat for humankind, the API discharge, and its continuous assessment (e.g., eco pharmacovigilance programs) must be regulated. So, the findings should clearly motivate policymakers to review their existing policy to promote ERA further across the industry. This is because the PBT data will need to be enriched for all existing drugs products to control the AMR issue as soon as possible before any other pandemic happens. The findings also influence policymakers to better understand the trade-off between 'enriching PBT data for existing APIs in the market to control PIE' and 'MET led redesign process for existing APIs in the market'. Additionally, the findings on monetary incentive drivers for downstream players will influence the related policymakers (e.g., local CCG / NHS) to review the trade-off between 'cost of MUR related incentive programs to reduce drug waste' and 'cost of current level of drug waste generated and related environmental damage'. This is how the study findings significantly contribute to practitioners and policymakers.

With regards to theoretical contribution, the adoption process of related green practices driven by the external regulatory factors identified in the study underpins, explains, and supports institutional isomorphism such as coercive, normative and mimetic (DiMaggio and Powell, 1983). Also, cost savings and internal environmental management drivers can be explained through the lens of the resource based view (Gonzalez-Torre et al., 2010; Zhu and Geng, 2013), as pharma companies, especially innovators, have increased their internal capability of green chemistry learning through training and education to adopt green practices. To the best of the researcher's knowledge this is the first study to explain the

application of several management theories to understand the green drivers in the pharma context and claim the novelty of the research work done.

In a nutshell, the second research question was comprehensively answered. To the best of the researcher's knowledge, there was no previous research in the pharma sector which conducted such comprehensive investigation to understand the relevant green drivers across the pharma sector and significantly adds to the research contribution made by the study.

Research Question 3

What are the barriers faced by individual pharma sector stakeholders for adopting green practices and what is their perceived importance?

The important green barrier for upstream pharma supply chain stakeholders (innovators, generic and bio pharma) identified in this study are: complex marketing authorization process for greener drugs (redesigned off-patent), high investment and cost, cultural issues, lack of standardisation in equipment and processes, time to market, lack of green related data, lack of environmental education and training, and lack of demand for green APIs. The extent of barriers felt by individual stakeholders varies significantly. In general, generic pharma faced the highest pressure from all types of barriers followed by bio pharma and innovative pharma. However, some of the barriers were felt almost equally by all stakeholders. For instance, complexity in marketing authorization of a redesigned drug was highly felt both by innovative and generic pharma. For generic pharma, cost was one of the topmost barriers to adopting or redesigning existing process. For both generic and innovative pharma, lack of standardized equipment systems and time pressure to market were severe challenges to adopting green practices, such as solvent recycling and continuous manufacturing. Lack of environmental training and education was one of the big challenges felt by both generic and bio pharma.

The important green barriers for downstream pharma stakeholders (e.g., pharmacy, GP, hospitals, and care homes) identified in the study are: uncontrolled drug wastes from high concerned patient groups, lack of performance measures of medical intervention schemes (e.g., NMS/MUR), barriers to getting patients' consent for conducting medical intervention (e.g., MUR/NMS), time constraints, lack of regulatory guidance on environmental consideration in prescribing, and contradictory regulatory guidance for disposing of unused/expired drugs. In general, pharmacies, GPs, and care homes faced the significant

challenge of managing drug wastes from high concerned patient groups, where pharmacies and GPs have faced significant challenges from a lack of performance measures of patient interventions schemes (e.g., NMS/MUR) and time constraints. For GPs, they mostly felt the lack of regulatory guidance on environmental consideration in prescribing to deal with PIE. For local councils and/or waste vendors, they felt moderate challenged by contradictory regulatory guidance for disposing unused/expired drugs.

Detailed understanding of each barrier (both upstream and downstream) identified in the study, including their relevance / non relevance and extent of challenges faced by each stakeholder, has not been explored previously in the pharma sector, and thus the related findings have significantly added to the novelty of this study. For instance, though previous studies highlight about costly and time consuming marketing approval process of redesigned off-patent drugs (Slater et al., 2010; Clark et al., 2010), none of the previous studies identified the extent of this challenge, and how individual stakeholders faced this challenge and the related consequences. None of the studies before identified it as one of the top green barriers in pharma that impedes green adoption. It was also not known before that the generic pharma sector felt a severe lack of green mindset among operations managers to adopt green. Lack of standardized equipment systems was also not identified as a top barrier for both innovators and generic pharma. Lack of regulatory guidance for prescribers to consider environmental aspects was never identified as a barrier in downstream pharma. Contradictory regulatory guidance for disposing unused/expired drugs was never identified before as a barrier for adopting green drug use-and-disposal related practice.

The findings are significant for the pharma sector, as the practitioners across all stakeholders did not have a clear understanding on the factors that impede them to adopt green. The findings will undoubtedly help those practitioners to review their existing operational strategy to accommodate and increase related resources to reduce/eliminate the barriers. For instance, the findings will influence the practitioners (especially from generic pharma) to rethink their operations strategy for the longer term through reviewing the trade-off between 'costs of existing process changes (e.g., replacing with greener solvent /change mode of manufacturing, /install recycling etc)' and 'potential long term cost savings from solvent cost/energy cost/disposal costs etc)'. The findings will also help the other external NGOs (e.g., the British Generic Manufacturers Association - BGMA and the Association of British Pharmaceutical Industry – ABPI) to influence the policymakers to review existing policy on approving redesigned greener drug processes. The practitioners from generic pharma could

also benefit from providing further education and training on green chemistry or MET practices among the operations managers to increase their level of awareness to mitigate against sceptical notions towards green practice, such as distortion of drug quality due to adopting green. The findings on lack of standardized equipment systems will also help the practitioners to invest more in new technologies to overcome the challenges to adopt recovery projects in line with the theory of the resource-based view. The practitioners in downstream will also be able to develop new streamlined drug management systems (e.g., more supervised consumption) for those of high concerned patient groups to reduce unnecessary drug wastes. Also, the pharmacies and related service negotiation agencies like PSNC will be able to focus on investing in measuring performance (e.g.., number of drugs saved in terms of cost) of all related medical intervention projects like MUR/NMS etc. This is how the related findings significantly contribute to practice.

The findings significantly contribute to relevant policymaking. For instance, there is considerable opportunity for the industry to reduce the MET related environmental footprint and related cost savings from redesigning existing (off-patent) drug processes. In line with the theory of diffusion of innovation (Murphy & Gouldson, 2000), as time goes, companies learn more about green chemistry innovation and increase their opportunities to widen their capability to adopt green. However, the findings will influence the policymakers to intervene into the process of approving redesigned (off-patent) drug processes through a two way talk between industry leaders and policymakers. For instance, if the policy makers introduce a first track approval process for greener drugs (redesigned off-patent), the related green practice adoption will be increased significantly. Similarly, the findings on time pressure to market will also influence the policymakers to allow more time (e.g., increase patent for five more years) to focus on green process development in the early stages of drug development rather than allowing the companies to redesign off-patent drugs. The findings on the lack of regulatory guidance on environmental consideration in prescribing felt by GPs will also influence the relevant policymakers to rethink whether the prescribing policy can be reviewed and the GPs can be trained and educated about PIE and incorporate some classes of drugs (under serious concerns) into the EMC. The policymakers will also be able to review the existing policy to establish whether some environmental guidance (e.g., considering excretion rates wherever practical) can be incorporated into EMC for the GPs to consider. Also, the findings on contradictory regulatory guidance for disposing unused/expired drugs will influence the policymakers to review and clarify the guidance to convey and motivate the

public for the safe disposal of drugs. For instance, the policymakers could categorize all drug wastes (regardless of industry or household waste stream) as 'potentially hazardous' (considering the ongoing scientific evidence of PIE) so the general public and local councils will be more concerned about safe disposal of drugs. This is how the related findings in the study significantly contribute to policy.

With regards to the theoretical contribution, the adoption process of related green practices through eliminating those barriers identified in the study underpins, explains, and supports the EMT (Ecological Modernization Theory), Information theory, the resource-based view and diffusion of innovation. For instance, the relevant barriers such as time pressure, complexity in greener drug process approval etc, will initiate new policy to promote green which is underpinned by the theory of EMT (Murphy & Gouldson, 2000; Sarkis et al., 2011). To the best of the researcher's knowledge this is the first study to explain the application of several management theories to understanding the green barriers in the pharma context and claim the novelty of the research work done.

In a nutshell, the third research question was comprehensively answered. To the best of the researcher's knowledge, there was no previous research in the pharma sector that conducted such comprehensive investigation to understand the relevant green barriers across the pharma sector and significantly adds to the research contribution made by the study.

Research Question 4

What green performance measures (in terms of environmental and economic) are used, and related (environmental and economic) benefits captured by individual pharma sector stakeholders and what is their perceived importance?

The important green performance measures for upstream pharma supply chain stakeholders (innovators, generic and bio pharma) identified in this study to capture environmental performance are: reduction of scope 1 emission, reduction of scope 2 emission, reduction of VOC, reduction of ODS, total energy use, amount of energy purchased and total use of energy generated onsite, amount of energy saved from conservation and efficiency improvements, reduce PMI (Process Mass Intensity), amount of water reduction, amount of raw materials (e.g. API, excipient / solvent, etc) use/saving/reduction, amount of wastes (non-hazardous) generated, amount of (non-hazardous) wastes recycled/reused/incinerated/landfill, amount of hazardous waste generated, measure toxicity

level of wastes, amount of hazardous wastes converted to beneficial use (e.g., waste to energy), and amount of hazardous waste recycled/reused/incinerated/landfill. However, the actual performance induced for individual stakeholders varied significantly. Overall, innovative pharma was seen to capture high levels of environmental benefits compared to other stakeholders. Generic and bio pharma were seen to capture almost the same level (between low to medium in average) of environmental benefits. Remarkably, two of the environmental benefits - '*amount of energy saved from conservation and efficiency improvements*' and *'amount of water reduction'* - were equally captured (high level) by each stakeholder. Both generic and bio pharma were seen to achieve equal levels of environmental benefits in the case of many measures such as amount of wastes (non-hazardous) generated, measure of toxicity level of wastes and amount of hazardous wastes converted to beneficial use (e.g., waste to energy). It is also remarkable that bio pharma in a few cases showed high levels of environmental benefits in line with innovators, such as total energy use, amount of energy purchased, and total use of energy generated onsite. For economic measures, the key performance indicators identified across the industry were: *ROI of Green Project; Cost savings* (e.g., via raw material efficiencies; energy efficiency etc) *and Cost of green production* (e.g., cost of process changes, cost of single use technology etc). Overall, both innovators and bio pharma reported high levels of economic performance from green adoption while generic pharma were seen to underperform at the lowest level.

The important environmental performance measures for downstream pharma identified are: level of improvement in drug adherence, amount of (unused/expired) drugs returned to pharmacy by patients (anticipated measure, amount of drug saving from reuse, rate of waste diversion from landfill, bottom ash testing (from drug incinerators), and amount of carbon emission from drug incineration. While pharmacies reported high levels of improvement in drug adherence among patients after implementing medical interventions projects like MUR/NMS, hospitals reported high level of drug savings from drug reuse practice. There was low level of waste diversion rate among the local councils but a higher level improvement for those waste vendors who incinerate drug wastes. Bottom ash testing was reported as high by waste vendors with drug incinerators. The key economic performance measures identified in the downstream are: cost savings from drug reuse and recycling and cost savings from patient intervention. While some CCGs reported high levels of cost savings from drug reuse, few pharmacies reported medium levels of cost savings from patient interventions.

However, some of the barriers were felt almost equally by all stakeholders. For instance, complexity in marketing authorization of a redesigned drug was highly felt both by innovative and generic pharma. For generic pharma, cost was one of the topmost barriers to adopting or redesigning existing processes. For both generic and innovative pharma, lack of standardized equipment systems and time pressure to market were severe challenges to adopting green practices such as solvent recycling, continuous manufacturing etc. Lack of environmental training and education was one of the key challenges felt by both generic and bio pharma.

A detailed understanding of each performance measure (both upstream and downstream) identified in the study including their relevance / non relevance and extent of performance impact by each stakeholder has not been explored previously in the pharma sector, and thus the related findings have significantly added to the novelty of this study. In particular, the performance measures and related impact assessment for downstream pharma stakeholders was never discussed previously.

The related finding has significant implications for practitioners. This is the first study which has provided a comprehensive stakeholder wide green performance measure model with clear indicators for the pharma industry. For the relevant stakeholders who are still confused and/or struggling to validate the key performance indicators, this key finding will help them to embrace these measures, especially the late majority and laggards in the field. Also, the early adopters could benefit from and be able to increase competitive advantages by applying these performance measures. The key findings on environmental and cost/economic performance could significantly increase confidence levels in the followers and laggards in the industry to adopt green practices. In particular, practitioners from generic pharma could significantly improve their environmental and economic performance by adopting these measures which have already shown many win-win business cases, such as significant cost savings from solvent recycling and continuous manufacturing in the longer term. So, the relevant findings on these measures and the related performance impact are crucial for generic pharma practitioners. The findings will also help practitioners to understand the significance of adopting each of these measures. For instance, companies will be able to control and reduce their disposal costs significantly by adopting a simple measure called ‘Amount of Hazardous waste generated’. Similarly, in the downstream the stakeholder local CCGs could be further influenced by the findings to adopt more drug reuse and recycling projects like the

POD/green bag schemes as well as more patient intervention schemes like MUR/NMS across the country or where economically viable.

The findings also contribute to relevant policy making. For instance, findings on significant win-win cases of solvent recovery, continuous manufacturing and other MET related green practices will influence the decision on policy review when it comes to approving the greener drug process (redesign off patent drugs). The findings on hypothetical kinds of performance measures (e.g., anticipating improved drug adherence levels) for different medical intervention schemes (e.g., MUR/NMS) will also influence the relevant policymakers. It will have crucial implications for the relevant top management for their ignorance in this matter. As for example, whilst the introduction of MURs and NMS has meant significant operational and cost/economic investment by the government, the hypothetical nature of performance measurement and lack of actual measurement through follow up systems is clearly missing, which would have serious implications on return on investment of such projects if applied in other contexts (except not for profit organizations). This is how the key findings also contribute to policy.

Regarding theoretical contribution, the mechanism of performance improvement through applying relevant green measures can be underpinned and explained through EMT and the resource-based view. To the best of the researcher's knowledge this is the first study to explain the application of several management theories to understand the green performance measures and related performance impact in the pharma context, and claim the novelty of the research work done.

In a nutshell, the fourth research question was comprehensively answered. To the best of the researcher's knowledge, there was no previous research in the pharma sector that conducted such a comprehensive investigation to understand the relevant green performance measures and related performance impact across the pharma sector and this significantly adds to the research contribution to the study. Additionally, this is the first study to explore stakeholder wise green attempts in pharma sector. Table 9.1 below summarizes the key roles played by each stakeholder to greening the pharma supply chain. There was no such empirical study found previously to conceptualize the role of each key stakeholder to greening the pharma sector. Table 9.2 can be used as a green road map for practitioners as well as by policymakers to motivate the sector to go green.

Table 9.2 Summary of the key roles played by each stakeholder to greening pharma supply chain (Source: insights from study findings)

Stakeholders	**Key role played to greening pharma supply chain**
Innovators	• Design and develop drug process with less environmental impact in terms of materials, energy, and toxicity, which have significant positive environmental impact during manufacturing and disposal. Such design aspect is significant to deal with PIE/AMR. Significant environmental savings when the drug is gone off-patent. • Design drug discovery process to use more in-silico tests than chemicals raw materials exhaustive testing in labs. Similar digitization process can be followed by other bio pharma involved in discovery process • Promote redesign of existing drugs (off-patent) process for better environmental footprint. It could be followed by generic manufacturers. The more redesigning of existing drugs (for better environmental footprint in terms of materials, energy, and toxicity), the more possibility of reducing PIE impact. • Conduct ERA of each new drug as well as off-patent drugs to enrich toxicity (PBT) related understanding, which significantly helps manufacturers to control API discharge limits from all manufacturing plants across all stakeholders. • Design and develop drugs with quality by design principle which has significant positive environmental impact during mass production (either under patent or off-patent), as quality variation related batch wastes are significant in the industry • Use onsite generated energy such as wind turbine and CHP • Active participation on chemical footprint programs and green chemistry innovation programs through ACS GCI pharmaceutical round table, which has significant impact on disseminating green chemistry related knowledge across the industry • Convert waste to beneficial use (e.g., waste to energy)
Generic Pharma	• Planning to redesign drug (off patent) process for better environmental footprint • Planning to standardize the manufacturing equipment system to reduce process wastes through adopting more solvent recycling processes. Significant cost savings are expected from solvent recycling. • Run continuous mode of manufacturing at a moderate level but planning to adopt more • Consider lean projects including energy efficiency projects for both operations and environmental benefits • Persuade policy makers for relaxing marketing approval process of greener drugs

Stakeholders	Key role played to greening pharma supply chain
	(re-design off-patent) and provide incentives to promote more greener process • Persuade manufacturing managers to change their sceptical view on green chemistry (e.g., fear of quality failure / fear of green validation etc) • Persuade top management to provide further education and training on green chemistry application
Bio Pharma	• Design and develop bio-based drug process with lower chemical impact • Planned to invest more on continuous fermentation and extraction process for better environmental footprint • Adopt solvent (inorganic) recycling and consider water reduction related lean projects to reduce water use • Adopt innovative manufacturing such as sing use technology to reduce chemicals usages
Pharmacy	• Ensure optimized dispensing through using appropriate medical intervention (e.g., MUR/NMS) which has significantly reduced drug non-adherence • Monitor and report prescribers' prescribing habit to ensure effective use of drugs • Prevent and control unnecessary re-dispensing; use of e-prescription checker (EPS-PT) to ensure effective re-dispensing of repeat prescription • Encourage patients to return their unused/expired drugs to pharmacy for safe disposal • Alert policymakers to review and adopt rigorous performance measures to measure the outcomes of all types medical intervention projects (e.g., MUR)
GPs	• Consider rationale prescribing practice (focus underlying reasons than treating symptoms only) • Follow anti-microbial prescribing guidelines to deal with AMR • Prescribe alternative therapy (e.g., lifestyle related diet, exercise etc) where applicable • Significant reduction in unnecessary repeat prescriptions due to adopting digital prescribing process (EPS/eRD) • Persuade policy makers to review prescribing guidance to consider environmental classification of drugs; and persuade for environmental training (e.g., awareness on PIE and drugs usage) for healthcare employees
Hospitals (CCGs)	• Promote drug reuse and recycling through using patient own medicine during hospital stay and recycle the left-over drugs from ward back to hospital pharmacy; significant drugs were saved which would have been wasted
Care Homes	• Co-ordinate with GPs, pharmacies, hospitals, and independent quality inspector (CQC) to adhere to best practice (e.g., follow MAR chart, in-bound medical

Stakeholders	Key role played to greening pharma supply chain
	intervention etc) for effective and efficient usage of drugs
Local councils	• Persuade policy makers to promote more landfill diversion of household wastes as majority of household in the context still use household garbage as the main source of unwanted drug disposal • Persuade policy making to clarify the confusion between 'drug take back legislation' and the definition of 'hazardous drug wastes and disposal' under general waste management guidance. • Provide special and separate collection of household drugs upon request
Waste vendors	• Ensure correct segregation of wastes at source; all drug waste is incinerated at high temperature; incinerated bottom ash are recycled
Wastewater	• Monitor concentration of APIs with high concerns (e.g., EEA, diclofenac etc) • Co-operate with UK water industry research to continuously share APIs concentration and related PIE impact data and knowledge for effective treatment of wastewater • Adopt advanced wastewater system (e.g., advanced oxidation, activated sludge etc) to remove APIs concentrations from the incoming sewage water prior to release into the environment.

9.4 Limitations and suggestions for future research

Though the research was carried out in line with all relevant research protocols in the chosen context, the thesis still has some limitations that are summarized below:

- The pharma sector considered in the study includes the key stakeholders (innovators, generic and bio pharma) but excludes two other stakeholders, namely raw materials suppliers / organic solvent producers and bio-similar drug producers. Future research could include them.
- Though the study considered all possible variations in the sample such as API production, formulations, drug design and discovery, re-design of existing drugs process, bio based production, chemical based production, liquid formulation and solid formulation, future research could focused purely on understanding 'the scope of greenness of tablet design and manufacturing' or 'the scope of greenness of liquid product manufacturing' to gain a deeper understanding of the process variations and their relevance to green operations.

- As the study focused on the UK context, it is urgent to conduct similar study in other contexts, as the drivers and barriers of green adoption may vary across the globe due to different regulatory and socioeconomic factors, consequently the green adoption levels and performance may vary. So, the country specific MET practice and related drivers and barriers or some other aspects which have not covered in this study could be different. In particular, the practices, drivers and barriers for downstream pharma would be significantly different from the UK context due to the differences in healthcare service and related operations. For instance, if the healthcare service and related operations are completely privatized in the context, the related findings in the downstream (especially, in case of pharmacy, GPs, hospitals, and care homes) will be significantly different.
- Though the extent of each practice, driver, barrier and performance impact were predominantly measured using qualitative judgement and report rating, future research could validate the existing models of green practice, green drivers, green barrier and green performance using a survey method. Future research could also validate the impact of green practices on performance.
- Future research could also further explore the impact of the quality by design aspect on environmental performance in terms of materials, energy and toxicity across innovators, generic and bio pharma. This will have a significant impact on practice and policymaking.
- As counterfeit drugs are becoming growing concern for significant economic and environmental loss across the globe, there is a future need for analysing the green practices (e.g., especially 'reverse logistics for end-of-life treatment') in counterfeit drug supply chain.

Despite these limitations, this study attracts academic researchers, policymakers, and practitioners due to the unprecedented levels of environmental degradation from pharma operations. Whilst sustainability led GSCM, an innovative management system, aims to broaden its knowledge across diversified industries, with diversified products and processes, the study has ultimately served its purpose in the wider context of environmental sustainability.

References

Accorsi, R., Cascini, A., Cholette, S., Manzini, R. and Mora, C. (2014) 'Economic and environmental assessment of reusable plastic containers: A food catering supply chain case study', *International Journal of Production Economics,* 152, pp. 88-101.

Asamoah, D., Abor, P. and Opare, M. (2011) 'An examination of pharmaceutical supply chain for artemisinin-based combination therapies in Ghana', *Management Research Review*, 34 (7) pp. 790 – 809.

Abahussain, E., Ball, D. and Matowe, W. (2006) 'Practice and opinion towards Disposal of Unused Medication in Kuwait', *Medical Principles and Practice*, 15, pp. 352–357.

Abahussain, E., Waheedi, M. and Koshy, S. (2012) 'Practice, awareness, and opinion of pharmacists towards disposal of unwanted medications in Kuwait', *Saudi Pharmaceutical Journal*, 20, pp. 195 – 201.

Amemba, C.S., Nyaboke, P.G., Osoro, A. and Mburu, N. (2013) 'Elements of Green Supply Chain Management', *European Journal of Business and Management*, 5(12), pp. 51 - 61

Ashby, A., Leat, M. and Hudson-Smith, M. (2012) 'Making connections: a review of supply chain management and sustainability literature', *Supply Chain Management: An International Journal,* 17(5), pp. 497 – 516.

Ayres, R.U. and Kneese, A.V. (1969) 'Production, consumption, and externalities', *The American Economic Review,* 59 (3), pp. 282–297.

Ahi, P. and Searcy, C. (2015) 'An analysis of metrics used to measure performance in green and sustainable supply chains', *Journal of Cleaner Production*, 86, pp. 360-377.

Ahi, P. and Searcy, C. (2013) 'A comparative literature analysis of definitions for green and sustainable supply chain management' *Journal of Cleaner Production*, 52, pp. 329-341.

Abdel-Baset, M., Chang, V. and Gamal, A. (2019) 'Evaluation of the green supply chain management practices: A novel neutrosophic approach, Computers Industry', *Computers in Industry*, 108, pp. 210 – 2020. Available at: http://fs.unm.edu/neut/EvaluationOfTheGreenSupply.pdf (Accessed: 11th Nov 2020)

Albino, V., Dangelico, R.M. and Pontrandolfo, P. (2012) 'Do inter-organizational collaborations enhance a firm's environmental performance? A study of the largest U.S. companies', *Journal of Cleaner Production*, 37, pp. 304–315.

Arnum, P.V. (2009) 'Building sustainability into the supply chain and pharmaceutical operations', *Pharmaceutical Technology Sourcing and Management*, 5 (10). Available at: http://www.pharmtech.com/building-sustainability-supply-chain-and-pharmaceutical-operations (Accessed: 28th Dec 2020).

Azevedo, S.G., Carvalho, H., Duarte, S. and Cruz-Machado, V. (2012) 'Influence of Green and Lean Upstream Supply Chain Management Practices on Business Sustainability', *IEEE Transactions on Engineering Management,* 59(4), pp.753–765.

Azevedo, S.G., Carvalho, H. and Cruz Machado, V. (2011) 'The influence of green practices on supply chain performance: A case study approach', *Transportation Research Part E: Logistics and Transportation Review*, 47(6), pp. 850–871.

Anastas, P. and Kirchhoff, M.M. (2002) 'Origins, current status, and future challenges of green chemistry', *Accounts of Chemicals Research*, 35 (09), pp. 686-694

Agalloco, J. and Desantis, P. (2005) 'Validation', in: Nusim, S.H. (ed.) *Active Pharmaceutical Ingredients.* Florida: Taylor & Francis Group, pp. 203-231.

Asif, M., Searcy, C., Santos, P.D. and Kensah, D. (2013). 'A Review of Dutch Corporate Sustainable Development Reports', *Corporate Social Responsibility and Environmental Management*, 20, pp. 321–339

Apple (2019) *Environmental Responsibility*. Available at: https://www.apple.com/environment/pdf/Apple_Environmental_Responsibility_Report_2019.pdf (Accessed: 23rd Nov 2020)

Addidas (2017) *Addidas sustainability progress report*. Available at: https://www.adidas-group.com/media/filer_public/08/7b/087bf055-d8d1-43e3-8adc-7672f2760d9b/2016_adidas_sustainability_progress_report.pdf (Accessed: 12th Dec 2020]

Andersen, M.K. and Massa, I. (2000). 'Ecological Modernization – Origins, Dilemmas and Future Directions', *Journal of Environmental Policy & Planning*, Vol. 02, pp 337-345.

AMR Action Plan (2017) *EU Action on Antimicrobial Resistance*, Available at: https://ec.europa.eu/health/antimicrobial-resistance/eu-action-on-antimicrobial-resistance_en (Accessed: 21st Dec 2020)

AstraZeneca (2017) *Pharmaceuticals In The Environment.* Available at: https://www.astrazeneca.com/content/dam/az/PDF/2018/A2E303_Pharmaceutical%20in%20the%20environment_A4_Final_V4.pdf (Accessed: 10th Oct 2018)

AstraZeneca (2015) *Responding to a changing world: Our sustainability journey*. Available at: https://www.astrazeneca.de/content/dam/az-de/pdfs/Sustainability_update_2015.pdf (Accessed: 28th Dec 2020).

AstraZeneca (2018) *Leading with Health.* Available at: https://www.astrazeneca.com/content/dam/az/Sustainability/2019/Sustainability_Report_2018.pdf (Accessed: 28th Dec 2020)

Beamon, B.M. (1999) 'Designing the green supply chain', *Logistics Information Management*, 12 (4), pp. 332–342.

Beamon, B.M. (1998) 'Supply chain design and analysis: Models and methods', *International Journal of Production economics*, 55, pp. 281-294.

Bound, J. and Voulvoulis, N. (2005) 'Household Disposal of Pharmaceuticals as a Pathway for Aquatic Contamination in the United Kingdom', *Environmental Health Perspective*, 113 (12), pp. 1705 – 1711.

Bound, J., Kitsou, K. and Vouvoulis, N. (2006) 'Household disposal of pharmaceuticals and perception of risk to the environment', *Environmental Toxicology and Pharmacology,* 21, pp. 301–307

Balasubramanian, S. and Shulka, V. (2017) 'Green Supply Chain Management: The Case of the construction sector in the United Arab Emirates (UAE)', *Production Planning and Control,* Available at: https://eprints.mdx.ac.uk/21870/1/PPC%20Accepted%20Version.pdf (Accessed 12th Oct 2018)

Boltic, Z., Ruzic, N., Jovanovic, M., Savic, M., Jovanovic, J. and Petrovic, S. (2013) 'Cleaner production aspects of tablet coating process in pharmaceuticalindustry: problem of VOCs emission', *Journal of Cleaner Production*, 44, pp. 123-132

Bag, S., Telukdarie, A., Pretorius, J. and Gupta, S. (2018) 'Industry 4.0 and supply chain sustainability: framework and future research directions', *Benchmarking: An International Journal*, 3, dOI 10.1108/BIJ-03-2018-0056

Bullock, A. and Walsh, M. (2013) 'The Green Supply Chain', *Logos*, 24(2), pp.16–23.

Brandenburg, M., Govindan, K., Sarkis, J. and Seuring, S. (2014) 'Quantitative models for sustainable supply chain management: Developments and directions', *European Journal Of Operational Research,* 233, pp. 299-312

Banshal, P. and Roth, K. (2000) 'Why Companies Go Green: A Model Of Ecological Responses', *Academy of Management Journal*, 43 (4), pp. 717-736

Blome, C., Hollos, D. and Paulraj, A. (2014) 'Green procurement and green supplier development: antecedents and effects on supplier performance', *International Journal of Production Research*, 52(1), pp. 32-49

Berry, M.A. and Rondinelli, D.A. (1998) 'Proactive Environmental Management: A New Industrial Revolution', *The Academy of Management Executive*, 12 (2), pp. 38 -50

Balon, V., Sharma, A. and Barua, M. (2016) 'Assessment of Barriers in Green Supply Chain Management Using ISM: A Case Study of the Automobile Industry in India', *Global Business Review,* 17(1), pp. 1–20

Ball, A. and Craig, R. (2010) 'Using neo-institutionalism to advance social and environmental accounting', *Critical Perspectives on Accounting*, 21, pp. 283-293.

Barney, J.B. (1991) 'Firm resources and sustained competitive advantage', *Journal of Management*, 17 (1), pp. 99–120

BGMA (2020) *About Generics: Industry Overview*. Available at: https://www.britishgenerics.co.uk/about-generics.html (Accessed: 10th Dec 2020)

Boulaksil, Y. and Fransoo, J.C. (2010) 'Implications of outsourcing on operations planning: findings from the pharmaceutical industry', *International Journal of Operations & Production Management*, Vol. 30 (10), pp. 1059 – 1079

Buvailo, A. (2020) *The Evolving Pharma R&D Outsourcing Industry: A Bird's-eye View*. Available at: https://www.biopharmatrend.com/post/146-the-evolving-pharma-rd-outsourcing-industry-a-birds-eye-view/ (Accessed: 21st Dec 2020)

Brhlikova, P., Harper, I. and Pollock, A. (2007) 'Good Manufacturing Practice in the Pharmaceutical Industry', Working Paper 3, University of Edinburgh.

Bellm, D. (2015) *Operational Excellence in the Pharmaceutical Industry- An architecture for Emerging Market.* PhD Thesis. University of St. Gallen.

Bountra, C., Lee, W. and Lezaun, J. (2017) 'A New Pharmaceutical Commons: Transforming Drug Discovery', *Oxford Martin Policy Paper,* University of Oxford.

Biotage (2018) *Reducing Environmental Impact of Chemical Purification in Drug Discovery*. Available at: https://selekt.biotage.com/blog/reducing-environmental-impact-of-chemical-purification-in-drug-discovery (Accessed: 21st Dec 2020).

Bajpai, P. (2018) *The Changing API Industry*. Available at: https://www.biospectrumasia.com/opinion/33/12303/the-changing-api-industry.html (Accessed: 12th Aug 2020).

Braal, H.D. (2009) 'Sustainability in green pharmaceutical production. *Green Pharma', Pharmaceutical Technology Europe,* 21(1), Available at: https://www.pharmtech.com/view/sustainability-green-pharmaceutical-production (Accessed: 21st Dec 2020)

Braund, R., Peake, B. and Shieffelbien, L. (2009) 'Disposal Practices for unused medications in New Zealand', *Environment International,* 35, pp. 952–955.

Blair, B.D., Crago, J.P., Hedman, C.J. and Klaper, K..D. (2013) 'Pharmaceuticals and personal care products found in the Great Lakes above concentrations of environmental concern', *Chemosphere,* 93, pp. 2116-2123

Breen, L., Xie, Y. and Thiaray, K. (2010) 'New solution for old problem: how to reduce the volume of waste medicines', *The Pharmaceutical Journal*, 284, pp. 425-428

Braybrook, S., John, D. N., and Leong, K. (1999) 'A survey of why medicines are returned to pharmacies', *The Pharmaceutical Journal, 263*, pp. 7063

Butt, T., Lockley, E. and Oduyemi, K. (2008) 'Risk assessment of landfill disposal sites – State of the art', *Waste Management,* 28, pp. 952–964.

Burrell, G. and Morgan, G. (1979) *Sociological Paradigms and Organisational Analysis*, England: Ashgate Publishing.

Bryman, A. (2016) *Social research methods.* 5th edn. New York: Oxford university press.

Bryman, A. and Bell, E. (2015) *Business research methods*. 4th edn, Oxford: Oxford university press.

Babbie, E. (1995) *The Practice of Social Research*. 7th edn. Harrisonburg: Wadsworth Publishing.

Byrene,R. (2012) *Medicine Waste Stakeholder conference,* Nine CCG group.

Barney, J.B. (1991) 'Firm resources and sustained competitive advantage', *Journal of Management,* 17 (1), pp. 99–120

Clark, J.H., Breeden, S.W. and Summerton. L. (2010) 'Pharmaceuticals in society', in Kummerer, K., and Hempel, M. (ed.) *Green and Sustainable Pharmacy.* Berlin: Springer, pp. 30-45

Chen, B. (2016) 'Energy, ecology and environment: a nexus perspective', *Energ. Ecol. Environ*, 1(1), pp. 1–2

Chan, A.P.C, Darko, A. and Olanipekun, A.O. (2018) 'Critical barriers to green building technologies adoption in developing countries: The case of Ghana', *Journal of Cleaner Production,* 172, pp. 1067 -1079.

Choudhury, A.K.R. (2017) 'Green Chemistry and Textile Industry', *Journal of Textile Engineering & Fashion Technology,* 2(3), pp. 1–12.

Cubasch, U., D. Wuebbles, D. Chen, M.C. Facchini, D. Frame, N. Mahowald, and J.-G. Winther (2013) Introduction. In: Climate Change 2013: The Physical Science Basis. Contribution of Working Group I to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change [Stocker, T.F., D. Qin, G.-K. Plattner, M. Tignor, S.K. Allen, J. Boschung, A. Nauels, Y. Xia, V. Bex and P.M. Midgley (eds.)]. Cambridge University Press, Cambridge, United Kingdom and New York, NY, USA.

Available at: http://www.ipcc.ch/pdf/assessment-report/ar5/wg1/WG1AR5_Chapter01_FINAL.pdf (Accessed: 29th Nov 2016)

Corbett, JJ, Winebrake, JJ, Green, EH, Kasibhatia, P, Eyring, V and Lauer, A. (2007) 'Mortality from ship emissions: a global assessment', *Environmental Science and Technology*, 41 (24), pp. 8512

Catalano, V. (2005) 'Materials Management', in: Nusim, S.H. (ed.) *Active Pharmaceutical Ingredients.* Florida: Taylor & Francis, pp. 305-318.

Carter, C.R. and Rogers, D.S. (2008) 'A framework of sustainable supply chain management: moving toward new theory', *International Journal of Physical Distribution & Logistics Management*, 38 (5), pp. 360-387

Carter, C.R. Kale, R. and Grimm, C.M. (2000) 'Environmental Purchasing and Firm Performance: an empirical investigation', *Transportation Research Part E*, 36, pp. 219-228

Çankaya, S.Y. and Sezen, B. (2019) 'Effects of green supply chain management practices on sustainability performance', *Journal of Manufacturing Technology Management,* 30 (1), pp. 98-121

Christopher, M. (2000) 'T'he agile supply chain – competing in volatile markets', *Industrial Marketing Management*, 29 (1), pp. 37-44

Chin, T.A., Tat, H.H. and Sulaiman, Z. (2015) 'Green Supply Chain Management, Environmental Collaboration and Sustainability Performance', *12th Global Conference on Sustainable Manufacturing, Procedia CIRP,* 26, pp. 695-699.

Cullinane, S., and Edwards, J. (2010) 'Benefits and costs of switching to alternative fuels', in McKinnon, A., Cullinane, S., Browne, M. and Whiteing, A. (ed.) *Green Logistics – Improving the environmental sustainability of logistics.* UK: Kogan Page Limited, pp. 305-318.

Christmann, P. and Taylor, G. (2001) 'Globalization and the Environment: Determinants of Firm Self-Regulation in China', *Journal of International Business studies*, 32, pp. 349-458.

Carter, C.R. and Carter, J.R. (1998) 'Inter organizational determinants of environmental purchasing: initial evidence from the consumer products industries', *Decision Science,* 29 (3), pp. 659–684

Chircu, A., Sultanow, E. and Saraswat, S.P. (2014) 'Healthcare RFID In Germany: An Integrated Pharmaceutical Supply Chain Perspective', *The Journal of Applied Business Research, 30 (3), pp. 737-752*

Castiaux, E. (2010) 'An Introduction to Cold Chain Management', *Journal of GXP Compliance,* 14, (4), pp. 19-22.

Comley, J. (2006) 'Tools and Technologies that Facilitate Automated Screening', in Mannhold, R., Kubinyi, H. and Folkers, G. (ed.) *High Throughput Screening in Drug Discovery.* Weinheim: WILEY-VCH. pp. 35-40.

Christina, G., Sheng-chien, C., Ernst, W. and Eric, M. (2006) 'Improving Energy Efficiency in Pharmaceutical Manufacturing Operations -- Part I: Motors, Drives and Compressed Air Systems', *Pharmaceutical Manufacturing Magazine*, Available at: https://www.osti.gov/biblio/923192 (Accessed: 11th Aug 2020)**.**

Challener, C. (2016) 'Going Green With Biocatalysis', *Pharmaceutical Technology Journal, 40 (8), pp. 24-25*

Chaudhari, S.P. and Patil, P.S. (2012) 'Pharmaceutical Excipients: A review', *International Journal of advances in pharmacy, biology, and chemistry,* 1(1).

Castensson, S. and Ekedahl, A. (2010) 'Pharmaceutical Wastes: The Patient Role', in Kummerer, K. and Hempel, M. (ed.) *Green and Sustainable Pharmacy.* Berlin: Springer. pp. 190-206.

Chaturvedi, U., Sharma, M., Dangayach, G.S. and Sarkar, P. (2017) 'Evolution and adoption of sustainable practices in the pharmaceutical industry: An overview with an Indian perspective', *Journal of cleaner production*, 168, pp. 1358-1369

Chris I.E. and Bell-Hanyes. (2010) 'A model for quantifying strategic supplier selection: evidence from a generic pharmaceutical firm supply chain', *International Journal of Business, Marketing, and Decision Sciences*, 3 (2), pp. 25-30

Catizone, D. (n.d.) Best Practice in Cold Chain Logistics Planning, QuickStat, Avilable at: http://quickstat.quick.aero/ (Accessed: 7th July 2017)

Cullinane, S. and Edwards, J. (2010) 'Benefits and costs of switching to alternative fuels', in McKinnon, A., Cullinane, S., Browne, M. and Whiteing, A. (ed.) *Green Logistics – Improving the environmental sustainability of logistics,* UK: Kogan Page.

Creswell, J. W. (2013) *Research design: Qualitative, quantitative, and mixed methods approaches*. Canada: Sage publications.

Chiou, T.Y., Chan, H.K., Lettice, F. and Chung, S.H. (2011) 'The influence of greening the suppliers and green innovation on environmental performance and competitive advantage in Taiwan', *Transportation Research Part E: Logistics and Transportation Review*, 47(6), pp. 822–836.

Dewberry, E. (1996) Eco-design. PhD thesis. The Open University.

Darnall, N. and Kim, Y. (2012) 'Which Types of Environmental Management Systems Are Related to Greater Environmental Improvements?', *Public Administration Review*, 72 (3), pp. 351–365.

Drohomeretski, E., Costa, S.G.D. and Lina, E.P.D. (2014) 'Green supply chain managementDrivers, barriers and practices within theBrazilian automotive industry', *Journal of Manufacturing Technology Management,* 25 (8), pp. 1105-1134

Dunn, P. J. (2012) 'The Importance of Green Chemistry in Process Research and Development', *Chem. Soc. Rev,* 41, pp. 1452–1461

Dunn, P. J. (2013) 'Pharmaceutical Green Chemistry process changes – how long does it take to obtain regulatory approval?', *Green Chem*, 15, pp. 3099–3104

Ding, B. (2018) 'Pharma Industry 4.0: Literature review and research opportunities in sustainable pharmaceutical supply chains', *Process Safety and Environmental Protection*, 118, pp. 115-130

DEFRA (2018) *Our Wastes, Our Resources: A Strategy for England*. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/765914/resources-waste-strategy-dec-2018.pdf (Accessed: 23rd Dec 2020)

Defra (2017) *Digest of Waste and Resource Statics – 2017 edition*. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/607416/Digest_of_Waste_and_Resource_Statistics__2017_rev.pdf (Accessed: 13th Aug 2017)

Dubey, R., Gunasekaran, A., Papadopoulos, T. and Childe, S. (2015) 'Green supply chain management enablers: Mixed methods research', *Sustainable Production and Consumption*, 4, pp. 72-88

Dubey, Rameshwar, Gunasekaran, Angappa and Papadopoulos, Thanos (2017) 'Green supply chain management: theoretical framework and future research directions', *Benchmarking: An International Journal*, 24 (1), pp. 184-218.

Donnelly, K., Beckett-Furnell, Z. and Traeger, S. (2006) 'Eco-design implemented through a product-based environmental management system', *Journal of Cleaner Production*, 4, pp. 1357-1367

Deutz, P., McGuire, M. and Neighbour, G. (2013) 'Eco-design practice in the context of a structured design process: an interdisciplinary empirical study of UK manufacturers' *Journal of Cleaner Production*, 39, pp. 117–128.

Dekker, R., Bloemhof, J. and Mallidis, I. (2011) 'Operations Research for Green Logistics – An overview of aspects, Issues, Contributions and Challenges', 219 (3), pp. 671- 679

Delmas, M. and Montiel, I. (2009) 'Greening the Supply Chain: When Is Customer Pressure Effective*?',* *Journal of Economics & Management Strategy,* 18 (1), pp. 171–201

Dell (2020) *Corporate Social Responsibility Report*. Available at: https://corporate.delltechnologies.com/content/dam/delltechnologies/assets/corporate/pdf/progress-made-real-reports/dell-fy19-csr-report.pdf (Accessed: 12th Dec 2020).

DiMaggio, P.J. and Powell, W.W. (1983) 'The iron cage revisited institutional isomorphism and collective rationality in organizational fields*', American Sociological Review,* 48 (2), pp. 147–160.

Deloitte (2014) *Life Science Outlook – 2015: United Kingdom.* Available at: https://www2.deloitte.com/content/dam/Deloitte/global/Documents/Life-Sciences-Health-Care/gx-lshc-2015-life-sciences-report-united-kingdom.pdf (Accessed: on 23rd Nov 2020)

D'Aquila, D. Snyder, M., Kahle, K. and Tomko, K. (2017) 'Benchmarking Biopharma's Carbon Footprint', *Pharma Manufacturing,* Available at: https://www.pharmamanufacturing.com/articles/2017/benchmarking-biopharmas-carbon-footprint/ (Accessed: 21st Dec 2019)

Dondero, E. and Palmer, M. (2012) 'Optimizing the Energy Efficiency of Research and Manufacturing Processes', *Pharma Manufacturing,* Available at: https://www.pharmamanufacturing.com/articles/2012/079/ (Accessed: 20th Dec 2020)

Dunn, P. (2012) 'The Importance of Green Chemistry in Process Research and Development', *Chemical Society Review*, 41, pp. 1452–1461

Daughton, C. and Ruhoy, I.S. (2013) 'Lower-dose prescribing: Minimizing "side effects" of pharmaceuticals on society and the environment', *Science of the Total Environment,* 443, pp. 324-337

Daughton, C.G. (2014) 'Eco-directed sustainable prescribing: feasibility for reducing water contamination by drugs', *Science of the total environment*, 493, pp. 392–404

Denscombe, M., (2008) 'Communities of Practice: A Research Paradigm for the mixed methods approach'. *Journal of Mixed Methods Research,* 2(3), pp. 270–283.

Drohomeretski, E., Gouvea da Costa, S., and Pinheiro de Lima, E. (2014).'Green supply chain management: drivers, barriers and practices within the Brazilian automotive industry', *Journal of Manufacturing Technology Management*, 25(8), pp. 1105-1134

Dusek, G.A., Yurova, Y.V. and Ruppel, C. (2015) 'Using Social Media and Targeted Snowball Sampling to Survey a Hard-to-reach Population: A Case Study', *International Journal of Doctoral studies*, 10, pp. 279-299.

Daughton CG. (2003) 'Cradle-to-cradle stewardship of drugs for minimizing their environmental disposition while promoting human health. I. Rationale for and avenues toward a green pharmacy', *Environ Health Perspective,* 111, pp. 757–774

EEA (2016) *Environmental Indicator Report - In support to the monitoring of the 7th Environment Action Programme, European Environmental Agency*, Luxembourg: Publications Office of the European Union

EPA (2020) *Greenhouse Gas Emission: Global Greenhouse Gas Data, United States Environmental Protection Agency*. Available from: https://www.epa.gov/ghgemissions/global-greenhouse-gas-emissionsdata#:~:text=Since%201970%2C%20CO2%20emissions,been%20the%20second%2Dlargest%20contributors (Accessed: 12th Oct 2020)

EFPIA (European Federation Of Pharmaceutical Industries and Association) (2018) *The Pharmaceutical Industry in Figures.* Accessed at: https://www.efpia.eu/media/361960/efpia-pharmafigures2018_v07-hq.pdf (Accessed:11th July 2019]

EEA (2012) *Environmental Challenges in a Global Context, European Environmental Agency*. Accessed at: https://www.eea.europa.eu/soer/synthesis/synthesis/chapter7.xhtml, [Accessed: 12th July 2019).

Erkman, S. (1997) 'Industrial ecology: an historical view', *Journal of Cleaner Production,* 5 (1–2), pp. 1–10.

EPA (2018) *Ocean Acidification*. Available at: https://www.eea.europa.eu/data-and-maps/indicators/ocean-acidification-2/assessment (Accessed: 23rd Dec 2019]

Environmental Protection UK (2019) *Air Pollution Sources.* Available at: https://www.environmental-protection.org.uk/policy-areas/air-quality/about-air-pollution/air-pollution-sources/ [Accessed: 23rd Jun 2019]

Eltayeb, T.K., Zailani, S. and Ramayah, T. (2011) 'Green supply chain initiatives among certified companies in Malaysia and environmental sustainability: Investigating the outcomes', *Resources, Conservation and Recycling*, 55(5), pp. 495–506.

Ellram, L., Tate, W. and Carter, C. (2008) 'Applying 3DCE to environmentally responsible manufacturing practices', *Journal of cleaner production*, 16, pp. 1620-1631

Esenduran, G., Kemahlıo glu-Ziya, E. and Swaminathan, J.M. (2012) 'Product Take-Back Legislation and Its Impact on Recycling and Remanufacturing Industries', in Boone, T., Jayaraman, V. and Ganeshan, R . (ed.) *Sustainable Supply Chian.* USA: Springer, pp. 129-132

Er, A.C., Mol, A.P.J. and Koppen, C.S.A. (2012) 'Ecological modernization in selected Malaysian industrial sectors: political modernization and sector variations', *Journal of cleaner production,* 24, pp. 65-75

Evaluate Pharma (2019) *World Preview 2019, Outlook to 2024*. Available at: https://info.evaluate.com/rs/607-YGS-364/images/EvaluatePharma_World_Preview_2019.pdf [Accessed: 20th Dec 2020]

EFPIA (European Federation Of Pharmaceutical Industries and Association) (2018) *The Pharmaceutical Industry in Figures*. Available at: https://www.efpia.eu/media/361960/efpia-pharmafigures2018_v07-hq.pdf (Accessed: 11th July 2019).

Evans, D. (2009) 'Case Study: creating a blueprint for pharmaceutical distribution', *Pharmaceutical Technology Europe,* May 2009.

Eglese, R. and Black, D. (2010) 'Optimizing the routing of vehicle', in McKinnon, A., Cullinane, S., Browne, M. and Whiteing, A. (ed.) *Green Logistics – Improving the environmental sustainability of logistics,* UK: Kogan Page Limited.

Easterby-Smith MPV, Thorpe R and Lowe A. (2001) *Management Research: An Introduction*, London: Sage.

Eisenhardt, K.M. (1989) 'Building theories from case study research', *Academy of Management Review*, 14(4), pp. 532-550.

El-Saifi, N., Moyle, W., Jones, C. and Tuffaha, H. (2017) Medication Adherence in Older Patients With Dementia: A Systematic Literature Review, Available at: https://pubmed.ncbi.nlm.nih.gov/28539102/) Accessed: 23rd Jun 2020.

Ewing, J.A. (2017) 'Hollow Ecology: Ecological Modernization Theory and the Death of Nature', *Journal of World-system Research*, 23(1), pp. 126 – 155

Er, A.C., Mol, A.P.J. and Koppen, C.S.A.V. (2012). 'Ecological modernization in selected Malaysian industrial sectors: political modernization and sector variations', *Journal of cleaner production*, 24, pp. 66 – 75

Fortes, J. (2009) 'Green Supply Chain Management: A Literature Review Supply Chain Management: Back to the Basics, *Otago Management Graduate Review*, 7, pp. 51–62.

FDA (2019) *New Drug Therapy Approvals 2019, Food And Drug Administration, USA,* Available at: https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/new-drug-therapy-approvals-2019#:~:text=In%202019%2C%20CDER%20approved%2048,Biologics%20License%20Applications%20(BLAs). (Accessed: 8th Aug 2020)

Flowers, P. (2009) 'Research Philosophies – Importance and Relevance', *Research Philosophies – Importance and Relevance*, 1(3), pp. 1–5.

Feilzer, M. Y. (2009) 'Doing Mixed Methods Research Pragmatically: Implications for the Rediscovery of Pragmatism as a Research Paradigm', *Journal of mixed method research,* 4(1), pp. 6-16.

Fusch, P.I. and Ness, L.R. (2015) 'Are we there yet? Data saturation in qualitative research', *The Qualitative Report*, 20(9), pp. 1408.

Frost, A. (2011) *Going green: prospects for SMEs to attain ISO 14001 and the challenges they face in the process,* PhD Thesis: Aston University.

Gotz, K. and Deffner, J. (2010) 'Options for a More Environmentally Friendly Handling of Pharmaceuticals'. in: Kummerer, K. and Hempel, M. (ed.) *Green and Sustainable Pharmacy.* Berlin: Springer. pp.161-175.

Glassmeyer ST, Hinchey EK, Boehme SE, Daughton CG, Ruhoy IS, Conerly O, Daniels RL, Lauer L, McCarthy M, Nettesheim TG, Sykes K and Thompson VG. (2009) 'Disposal practices for unwanted residential medications in the United States'. *Environ Int*, 35, pp. 566−572

Govindan, K., Kannan, D. and Shankar, M. (2015) 'Evaluation of green manufacturing practices using a hybrid MCDM model combining DNAP with PROMETHEE', *International Journal of Production Research*, 53 (21), pp. 6344-6371.

Govindan., K., Sarkis, J., Jabbour, C., Zhu, Q. and Geng, Y. (2014a) 'Eco-Efficiency based green supply chain management: Current status and opportunities', *European Journal Of Operations Research,* 233, pp. 293-318

Govindan, K., Kaliyan, M., Kannan, D. and Haq, A.N. (2014b) 'Barriers analysis for green supply chain management implementationin Indian industries using analytic hierarchy process', *International Journal Of Production Economics*, 147, pp. 555-568

Gupta, S. and Palsule-Desai, O.D., (2011) 'Sustainable supply chain management: Review and research opportunities', *Management Review*, 23(4), pp. 234–245. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0970389611001017 (Accessed: 31st July 2017)

Green, K.W., Zelbst, P.J., Meacham, J. and Bhadauria,V.S. (2012) 'Green supply chain management practices: impact on performance', *Supply Chain Management: An International Journal,* 17 (3), pp. 290–305

Gopalakrishnan, K., Yusuf, Y. Y., Musa, A., Abubakar, T., and Ambursa, H.M. (2012)' Sustainable supply chain management: A case study of British Aerospace (BAe) Systems', *International Journal of Production Economics, 140(1), pp. 193–203.*

Gupta, M.C. (1994) 'Environmental management and its impact on the operations function', *International Journal of Operations & Production Management,* 15 (8), pp. 34-51

Gaussin, M., Hu, G., Abolghasem, S., Basu, S., Shankar, M. and Bidanda, B. (2013) 'Assessing environmental footprint of manufactured products: A survey of current literature', *International Journal of Production Economics,* 145, pp. 515- 523.

Garnett, T. (2007) 'Food refrigeration: what is the contribution to greenhouse gas emissions and how might emissions be reduced?' *A working paper produced as part of the Food Climate Research Network,* Available at: *https://tabledebates.org/sites/default/files/2020-10/FCRN%20refrigeration%20paper%20final.pdf* (Accessed: 23rd Dec 2020).

Graci, S. and Dodds, R. (2008) 'Why Go Green? The Business Case for Environmental Commitment in the Canadian Hotel Industry', *Anatolia: An International Journal of Tourism and Hospitality Research*, 19 (2), pp. 250-270.

Gonzalez-Torre, P., Alvarez, M., Sarkis, J. and Adenso-Dıaz, B. (2010) 'Barriers to the Implementation of Environmentally Oriented Reverse Logistics: Evidence from the Automotive Industry Sector', *British Journal of Management*, 21, pp 889–904

Gunasekaran, A., Patel, C. and McGaughey, R.E. (2004) 'A framework for supply chain performance measurement', *International Journal Of Production Economics*, 87, pp. 333-347

Gad, S.C. (2008) Pharmaceutical Manufacturing Handbook – Production and process, New Jersey: John Wiley & Sons, Inc.

Glassmeyer ST, Hinchey EK, Boehme SE, Daughton CG, Ruhoy IS, Conerly O, Daniels RL, Lauer L, McCarthy M, Nettesheim TG, Sykes K, and Thompson VG. (2009) 'Disposal practices for unwanted residential medications in the United States', *Environ Int,* 35, 566−572

Geijo, F. (2000) 'Quality management in analytical R&D in the pharmaceutical industry: Building quality from GLP', *Accreditation and Quality Assurance,* **5,** pp. 16–20

HCWH Europe (2016) *Reducing Antimicrobial Resistance – how healthcare professional can help*. Available at: https://noharm-europe.org/sites/default/files/documents-files/4560/HCWHEurope_AMR_Factsheet_Dec2016.pdf (Accessed: 12th Dec 2020)

Hajmohammad, S., Vachon, S., Klassen, R.D. and Gavronski, I. (2013) 'Lean management and supply management: their role in green practices and performance', *Journal of Cleaner Production*, 39, pp. 312–320

Hsu, C.W. and Hu, A. H. (2008) 'Green supply chain management in the electronic industry', *International Journal of Environmental Science & Technology*, 5(2), pp. 205–216.

Handfield, R.B., Walton, S.V., Seegers, L.K. and Melnyk, S.A. (1997) 'Green' value chain practices in the furniture industry', *Journal of Operations Management 15* (4), pp. 293 - 315

Hsu, C.C., Tan, K.C. and Zailani, S.H.M. (2016) 'Strategic orientations, sustainable supply chain initiatives, and reverse logistics empirical evidence from an emerging market', *International Journal of Operations & Production Management*, 36 (1), pp. 86-110

Ho, L., Dickinson, N. and Chan, G. (2010) 'Green procurement in the Asian public sector and the Hong Kong private sector', *Natural Resources Forum*, 34 (1), pp. 24-38

Hardisty, J. (2011) 'Plastic Explosion', *Pharmaceutical Manufacturing and Packing Sourcer (PMPS)*, Available at: http://www.samedanltd.com/magazine/15/issue/152/article/2927 (Accessed: 7th July 2017)

Hervani, A. A., Helms, M.M. and Sarkis, J. (2005) 'Performance measurement for green supply chain management', *Benchmarking: An International Journal*, 12(4), pp. 330–353.

Hughes, J.P., Rees, S., Kalindjian, SB. and Philpott, KL. (2011) 'Principles of early drug discovery', *British Journal of Pharmacy*, 162(6), pp. 1239–1249, Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3058157/ (Accessed: 12th Aug 2020)

HDMA Report (2009) *Understanding the Drivers of Expired Pharmaceutical Returns*. Available at: http://www.nacds.org/pdfs/membership/understanding_drivers.pdf (Accessed: 20th Jul 2017)

Holzer, A. (2010) 'Do Pharmaceuticals in the Environment Present an Investment Risk?', in Kummerer, K. and Hempel, M. (ed.) *Green and Sustainable Pharmacy.* Berlin: Springer. pp. 287-292

Henderson, R.K., Constable, D.J.C. and Jimenez-Gonzalez. (2010) 'Green Chemistry Metrics', in Dunn, P.J., Wells, A.S. and Williams, M.T (ed.) *Green Chemistry in the Pharmaceutical Industry.* Germany: Wiley-VCH Verlag GmbH & Co.

Holden, M.T. and Lynch, P. (2004) 'Choosing the Appropriate Methodology: Understanding Research Philosophy', *The Marketing Review*, 4, pp. 397–409

Hofer, C., Cantor, D.E. and Dai, J. (2012) 'The competitive determinants of a firm's environmental management activities: Evidence from US manufacturing industries', *Journal of Operations Management*, 30(1-2), pp. 69–84

Huber, J. (2008) 'Technological environmental innovations (TEIs) in a chain-analytical and life-cycle-analytical perspective', *Journal of Cleaner Production*, 16 (18), pp. 1980–1986

IBIS (2018 a) *Pharmaceutical Wholesaling in The UK*, IBISWorld Industry Report G46.460

IBIS (2018 b) *Pharmaceuticals Preparations Manufacturing in the UK*, IBISWorld Industry Report C21.200

IPCC (2013 a) Summary for Policymakers. In: Climate Change 2013: The Physical Science Basis. Contribution of Working Group I to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change [Stocker, T.F., D. Qin, G.-K. Plattner, M. Tignor, S.K. Allen, J. Boschung, A. Nauels, Y. Xia, V. Bex and P.M. Midgley (eds.)]. Cambridge University Press, Cambridge, United Kingdom and New York, NY, USA. Available at: http://www.ipcc.ch/pdf/assessment-report/ar5/wg1/WG1AR5_SPM_FINAL.pdf (Accessed: 29th Nov 2014]

IPCC (2018) In V. Masson-Delmotte, P. Zhai, H.-O. Pörtner, D. Roberts, J. Skea, P. R. Shukla, et al. (Eds.), Global warming of 1.5C.An IPCC special report on the impacts of global warming of 1.5 C above pre-industrial levels and related global greenhouse gas emission pathways, in the context of strengthening the global response to the threat of climate change, sustainable development, and efforts to eradicate poverty. Geneva, Switzerland: World Meteorological Organization. In Press.

IPCC (2019) Summary for Policymakers. In: Climate Change and Land: an IPCC special report on climate change, desertification, land degradation, sustainable land management, food security, and greenhouse gas fluxes in terrestrial ecosystems [P.R. Shukla, J. Skea, E. Calvo Buendia, V. Masson-Delmotte, H.-O. Pörtner, D. C. Roberts, P. Zhai, R. Slade, S. Connors, R. van Diemen, M. Ferrat, E. Haughey, S. Luz, S. Neogi, M. Pathak, J. Petzold, J. Portugal Pereira, P. Vyas, E. Huntley, K. Kissick, M. Belkacemi, J. Malley, (eds.)]. In press. Available at: https://www.ipcc.ch/site/assets/uploads/sites/4/2020/02/SPM_Updated-Jan20.pdf (Accessed: 12th Oct 2020].

IPCC (2013 b) Climate Change 2013: The Physical Science Basis. Contribution of Working Group I to the Fifth Assessment Report of the Intergovern- mental Panel on Climate Change [Stocker, T.F., D. Qin, G.-K. Plattner, M. Tignor, S.K. Allen, J. Boschung, A. Nauels, Y. Xia, V. Bex and P.M. Midgley (eds.)]. Cambridge University Press, Cambridge, United Kingdom and New York, NY, USA, 1535 pp

ISWA (2018) *Global Waste Management Outlook – Summary for Decision Maker, International Solid Waste Association (ISWA) General Secretariat,* Available at: https://www.iswa.org/fileadmin/galleries/Publications/ISWA_Reports/GWMO_summary_web.pdf [Accessed: 12th Dec 2020]

Jimenez-Gonzalez, C. (2000) *Life cycle assessment in Pharmaceutical Application*, PhD Thesis. North Carolina State University

Johnson & Johnson (2017) *Position on Antimicrobial Resistance*, Available at: https://www.jnj.com/about-jnj/policies-and-positions/our-position-on-antimicrobial-resistance [Accessed: 10th Aug 2019]

Jelinski, L.W., Graedel, T.E., Laudise, W.D., McCall, D.W. and Patel, K.N., (1992) 'Industrial ecology: concepts and approaches', *Proceedings of the National Academy of Sciences*, 89 (February), pp. 793–797

Jaberidoost, M., Olfat, L., Hosseini, A., Kebriaeezadeh, A., Abdollahi, M., Alaeddini, M. and Dinarvand, R. (2015) 'Pharmaceutical supply chain risk assessment in Iran using analytic hierarchy process (AHP) and simple additive weighting (SAW) methods', *Journal of Pharmaceutical policy and practice*, 8 (9).

Jaseem, M., Kumar, P. and John, R. (2017) 'An overview of waste management in pharma industry', *The Pharma Innovation Journal,* 6(3), p. 158-161.

Jesson, J., Pocock, R. and Wilson, K. (2005) 'Reducing medicines waste in the community', *Primary Health Care Research and Development*, 6, pp. 117–124

Jimenez-Gonzalez, C., Ponder, C.S., Broxterman, Q.B. and Manley, J.B. (2011) 'Using the Right Green Yardstick: Why Process Mass Intensity Is Used inthe Pharmaceutical Industry To Drive More Sustainable Processes', *Organic Process Research & Development*, 15, pp. 912-917

Jabbour, A.B., Jabbour, C., Govindan, K., Kannan, D. and Arantes, A.F. (2014) 'Mixed methodology to analyze the relationship between maturity of environmental management and the adoption of green supply chain management in Brazil', *Resources, Conservation and Recycling,* 92, pp. 255-267

Kummerer, K. (2009) 'The Presence of Pharmaceuticals in the Environment due to human use – present knowledge and future challenge', *Journal of Environmental Management, 90, pp. 2354-2366.*

Kummerer, K. (2010) 'Rational Design of molecules by life cycle engineering', in Kummerer, K. and Hempel, M. (ed.) *Green and Sustainable Pharmacy.* Berlin: Springer. pp. 135-145

Kummerer, K. (2001) 'Introduction: Pharmaceuticals in the environment', in Kummerer, K. (Ed.) *Pharmaceuticals in the environment*. Germany: Springer. pp. 4-7

Kumar, A., Zavadskas, E.K., Mangla, S.K., Agrawal, V., Sharma, K. and Gupta, D. (2019) 'When risks need attention: adoption of green supply chain initiatives in the pharmaceutical industry', *International Journal of Production Research,* 57 (11), pp. 3554–3576

Kyoto Protocol (1998) *Protocol to the United Nations framework convention on climate change.* Avaiable at: http://unfccc.int/resource/docs/convkp/kpeng.pdf (Accessed: 21st Oct 2014)

Kainuma, Y. and Tawara, N. (2006) 'A multiple attribute utility theory approach to lean and green supply chain management', *International Journal of Production Economics*, 101(1), pp. 99–108. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0925527305001362 [Accessed: 12th Nov 2016].

Kumar, S., Teichman, S. and Timpernagel, T. (2012) 'A green supply chain is a requirement for profitability', *International Journal of Production Research*, 50(5), pp. 1278–1296.

Kitcher, P.S. (2013). '*Philosophy of Science. Encyclopaedia Britannica Online',* Available at: http://www.britannica.com/EBchecked/topic/528804/philosophy-of-science (Accessed: 17th March 2016).

Koberg, E. and Longoni, A. (2019) 'A systematic review of sustainable supply chain management in global supply chains', *Journal of Cleaner Production*, Available at: http://www.samiagamoura.com/_media/group2-papersystematicreview.pdf (Accessed: 20th Nov 2020)

Kazancoglu, Y., Kazancoglu, I., Sagnak, M. (2018) 'Fuzzy dematel-based green supply chain management performance: application in cement industry', *Industrial Management & Data Systems*, Available from: https://fardapaper.ir/mohavaha/uploads/2018/04/Fardapaper-Fuzzy-DEMATEL-based-green-supply-chain-management-performance-Application-in-cement-industry.pdf (Accessed: 11th Aug 2020)

Kallaos J, Wheeler K, Wong C. and Zahller M. (2007) *Pharmaceuticals in wastewater streams: Disposal practices and policy options in Santa Barbara.* Masters Project: Donald Bren School of Environmental Science and Management.

Katzung, B., Masters, S. and Trevor, A. (2012) *Basic and Clinical Pharmacology*, 12th edn. USA: The McGraw-Hill.

Kuspis DA. And Krenzelok EP (1996) 'What happens to expired medications? A survey of community medication disposal', *Veterinary and Human Toxicology*, 38(1), pp. 48−49

Kotchen, M., Kallaos, J., Wheeler, K., Wong, C. and Zahller, M. (2009) 'Pharmaceuticals in wastewater: Behaviour, preferences, and willingness to pay for a disposal program', *Journal of Environmental Management,* 90, pp. 1476- 1482

Kam, B., Christopherson, G., Smyrnios, K. and Walker, R. (2006) 'Strategic Business Operations, Freight Transport and Eco-efficiency: A Conceptual Model', in Sarkis, J. (ed.) *Greening the Supply Chain.* London: Springer.

KNAPPE (2008) *Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters*, Available at: http://environmentalhealthcollaborative.org/images/KNAPPE_REPORT_FINAL.pdf (Accessed: 12th Aug 2017)

Krippendorff, K. (1980) *Content Analysis: An Introduction to Its Methodology*. Canada: Sage Newbury Park.

Krippendorff, K. (2004) *Content Analysis: an Introduction to its Methodology*. 2nd edn. Canada: Sage Publications.

Li, C., Liu, F., Tan, X. and Du, Y. (2010) 'A methodology for selecting a green technology portfolio based on synergy', *International Journal of Production Research*, 48 (24)

Li, J., Pan, S.Y., Kim, H., Linn, J.H. and Chiang, P.C. (2015) 'Building green supply chains in eco-industrial parks towards a green economy: Barriers and Strategies', *Journal Of Environmental Management, 162, pp. 158 – 170,*

Li, Y. (2014) 'Environmental innovation practices and performance: moderating effect of resource commitment'*, Journal of cleaner production, 66, pp. 450-458*

Leder, C., Rastogi, T. and Kummerer, K. (2015) 'Putting benign by design into practice-novel concepts for green and sustainable pharmacy: Designing green drug derivatives by non-targeted synthesis and screening for biodegradability', *Sustainable Chemistry and Pharmacy*, 2, pp. 31-36

Linton, J., Klassen, R. and Jayaraman, V. (2007) 'Sustainable supply chains: An introduction', *Journal of Operations Management*, 25(6), pp. 1075–1082. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0272696307000149 (Accessed: 9th Jul 2017).

Laurent A. and Owsianiak M. (2017) 'Potentials and limitations of footprints for gauging environmental sustainability', *Current Opinion in Environmental Sustainability* 25, pp. 20–27.

Lintukangas, K., Hallikas, J. and Kahlkonen. (2013) 'The Role of Green Supply Management in the Development of Sustainable Supply Chain', *Corporate Social Responsibility Environmental Management*, 22, pp. 321–333

Lee, S.M., Tae Kim, S. and Choi, D. (2012) 'Green supply chain management and organizational performance,' *Industrial Management & Data Systems*, 112 (8), pp. 1148–1180

Luthra, S., Mangla, S.K., Xu, L. and Diabat, A. (2015) 'Using AHP to evaluate barriers in adopting sustainable consumptionand production initiatives in a supply chain', *International Journal of Production Economics,* 181, pp. 342-349.

Lee, M., Tansel, B. (2012) 'Life cycle based analysis of demands and emissions for residential water-using appliance', *Journal of Environmental Management*, 101, pp. 25-81.

Laosirihongthong, T., Adebanjo, D. & Choon Tan, K. (2013) 'Green supply chain management practices and performance' *Industrial Management & Data Systems*, 113 (8), pp. 1088–1109

Liu, Y., Zhu, Q. and Seuring, S. (2017) 'Linking capabilities to green operations strategies: the moderating role of corporate environmental proactivity', *International Journal of Production Economics*, 187, pp. 182-195

Larney, M., Aardt, A.M . (2004) 'Recycling of Textiles: The South African Scene', *Journal of Family Ecology and Consumer Sciences*, 32, pp. 60-69

Li, X., Hamblin, D. (2016) 'Factors impacting on cleaner production: case studies of Chinese pharmaceutical manufacturers in Tianjin China', *Journal of Cleaner Production,* 131, pp. 121-132.

Lazuras, L., Ketikidis, P.H. and Bofinger, A.B. (2011) Promoting Green Supply Chain Management: The role of the human factor, *15th Panhellenic Logistics Conference and 1st Southeast European Congress on Supply Chain Management.*

Larsson DGJ. (2014) 'Pollution from drug manufacturing: review and perspectives', *Philosophical Transactions of the Royal Society, Available at: https://royalsocietypublishing.org/doi/pdf/10.1098/rstb.2013.0571* (Accessed: 21st Dec 2020).

Lennane, A. (2014) 'Pharma shippers consider sea freight - but insist it's not all about price', Available at: https://theloadstar.co.uk/astrazenica-supply-chain/ (Accessed: 6th July 2017)

Leal Jr, I. and D'Agosto, M. (2011) 'Modal Choice Evaluation of Transport Alternatives for Exporting Bio-ethanol from Brazil', *Transport Research Part D.* 16, pp. 201- 207.

Latif, A., Pollock, K. and Boardman, H. (2011) 'The contribution of the Medicines Use Review (MUR) consultation to counseling practice in community pharmacies', *Patient Education and Counselling,* 83, pp. 336–344

Latif, A., Boardman, H.F. and Pollock, K. (2013) 'Understanding the patient perspective of the English community pharmacy Medicines Use Review (MUR)', *Administrative Pharmacy*, 9, pp. 949-957

Mudgal, S., Toni, A.D., Lockwood, S., Sales, K. and Backhaus, T. (2013) 'Study on the environmental risks of medicinal products, Final Report prepared for Executive Agency for Health and Consumers', *BIO Intelligence Service*.

Min, H., and Galle, W.P. (1997) 'Green purchasing strategies: Trends and implications', *Journal of Supply Chain Management,* 33(3), pp. 10–17.

Massoud, M.A., Makarem, N. and Ramadan, W. (2015) 'Environmental Management Practices in the Lebanese pharmaceutical industries: implementation strategies and challenges,' *Environ Monitoring and*

Assessment, Available at: https://link.springer.com/article/10.1007/s10661-015-4290-3 (Accessed: 12th Dec 2020)

Mebratu, D. (1998) 'Sustainability and Sustainable Development: Historical and Conceptual Review', *Environmental Impact Assessment Review,* 98, pp. 493–520. Available at: http://www.is.cnpm.embrapa.br/bibliografia/1998_Sustainability_and_sustainable_development_Historical_and_conceptual_review.pdf (Accessed: 9th Jul 2017)

Mol, A.P.J. (2010) 'Ecological modernization as a social theory of environmental reform', in Redclift, M. R, Woodgate, G. (ed.) *The International Handbook of Environmental Sociology,* UK: Edward Elgar Publishing Limited. pp. 63-77

Morelli, J. (2011) 'Environmental Sustainability – a definition for environmental professional', *Journal of Environmental Sustainability,* 1(1), pp. 19-22

Mishra, N., Kumar, V. and Chan, F.T.S. (2012) 'A multi-agent architecture for reverse logistics in a green supply chain', *International Journal of Production Research*, 50(9), pp. 2396–2406.

Mutingi, M. (2013) 'Developing green supply chain management strategies: A taxonomic approach', *Journal of Industrial Engineering and Management*, 6(2), pp. 525–546.

Muduli, K., Govindan, K., Barve, A. and Geng, Y. (2013) 'Barriers to green supply chain management in Indian miningindustries: a graph theoretic approach', *Journal Of Cleaner Production*, 47, pp. 335-344.

Maditati, d., Munim, Z. and Schramm (2018) 'A review of green supply chain management: From bibliometric analysis to a conceptual framework and future research directions', *Resources, conservation and Recycling*, 139, pp. 150 – 162

McKinnon, A. and Edwards, J. (2010) 'Opportunities for improving vehicle utilization', in McKinnon, A., Cullinane, S., Browne, M. and Whiteing, A. (ed.) *Green Logistics – Improving the environmental sustainability of logistics,* UK: Kogan Page Limited.

McKinnon, A., Allen, J. and Woodburn, A. (2010) 'Development of greener vehicles, aircraft, and ships', in McKinnon, A., Cullinane, S., Browne, M. and Whiteing, A. (ed.) *Green Logistics – Improving the environmental sustainability of logistics,* UK: Kogan Page Limited

McKinnon, A. (2010 a) 'Environmental Sustainability- A new priority of logistics manager', in McKinnon, A., Cullinane, S., Browne, M. and Whiteing, A. (ed.) *Green Logistics – Improving the environmental sustainability of logistics,* UK: Kogan Page Limited.

McKinnon, A. (2010 b) 'Increasing fuel efficiency in the road freight sector', in: McKinnon, A., Cullinane, S., Browne, M. and Whiteing, A. (ed.) *Green Logistics – Improving the environmental sustainability of logistics,* UK: Kogan Page Limited.

Marchant (2010) 'Reducing the environmental impact of warehousing', in McKinnon, A., Cullinane, S., Browne, M. and Whiteing, A. (ed.) *Green Logistics – Improving the environmental sustainability of logistics,* UK: Kogan Page Limited.

McDougall, F.R., White, P.R., Franke, M. and Hindle, P. (2001) 'Integrated Solid Waste Management: A Life Cycle Inventory', Blackwell Science.

Murphy, J. and Gouldson, A. (2000) 'Environmental policy and industrial innovation: integrating environment and economy through ecological modernisation', *Geoforum*, 31(1), pp. 33–44.

Matus, K.J.M., Anastas, P.T., Clark, W.C. and Zimmerman, J.B. (2012) 'Barriers to the Implementation of Green Chemistry in the United States', *Environmental Science & Technology*, The American Chemical Society. Washington.

Milne, Sarah. and Mahanty, S. (2019) 'Value and bureaucratic violence in the green economy', *Geoforum*, 98, pp. 133-143

Mathiyazhagan, K., Govindan, K., NoorulHaq, A. and Geng, Y. (2013) 'An ISM approach for the barrier analysis in implementing green supply chain management', *Journal of cleaner production*, 47, pp. 283-297.

McBeath, B. (2012) 'Carton-level Temperature tracking For Cold Chain Pharmaceuticals – Why Now?', *Chain Link Research*, Available at: http://www.clresearch.com/research/detail.cfm?guid=5DA376BB-3048-79ED-994B-1416CFF76450 (Accessed: 20th June 2017).

MHRA (2015) *Rules and Guidance for Pharmaceutical Manufacturers and Distributors*, London: Pharmaceutical Press

Mongiardo, S. and Bobrow, E. (2005) 'Design and Construction of facilities', in Nusim, S.H. (ed.) *Active Pharmaceutical Ingredients.* Florida: Taylor & Francis Group. pp. 127-166.

Moscrop, P. (2018) 'The Rise of Hazard Chemistry in Drug Development', *Pharma Manufacturing*, Available at: https://www.pharmamanufacturing.com/articles/2018/the-rise-of-hazard-chemistry-in-drug-development/ (Accessed: 12th Dec 2020)

McCullah, M.C., Schim, S. and Ortner, P. (2012) 'Drug disposal among hospice home care nurses: A pilot study of current practice and attitudes', *Journal of Pain and Symptom Management,* 43 (2), pp. 287-292.

Mollan, Jr., and Lodaya, M. (2004) 'Continuous processing in pharmaceutical manufacturing', *Pharmaceutical Manufacturing Magazine*, pp. 1-9.

McDonald, R., Cheraghi-Sohi, S., Sanders, C. and Ashcroft, D. (2010) Professional status in a changing world: The case of medicines use reviews in English community pharmacy, *Social Science & Medicine,* 71 (3), pp. 451 – 458.

Mackridge, A.J. and Marriott, J. (2007) 'Returned Medicines: waste or a wasted opportunity?', *Journal of Public Health,* 20 (3), pp. 258-262

Morgan, D.L. (2007) 'Paradigms Lost and Pragmatism Regained: Methodological Implications of Combining Qualitative and Quantitative Methods', *Journal of Mixed Methods Research*, 1(1), pp. 48–76.

Massoud, M.A., Makarem, N. and Ramadan, W. (2015) 'Environmental Management Practices in the Lebanese pharmaceutical industries: implementation strategies and challenges', *Environmental Monitoring and Assessment,* Available at: https://link.springer.com/article/10.1007/s10661-015-4290-3 (Accessed: 23rd Dec 2020)

Montabon, F., Sroufe, R., and Narasimhan, R. (2007) 'An examination of corporate reporting, environmental management practices and firm performance', *Journal of Operations Management, 25(5),pp. 998–1014*

Morali, O. and Searcy, C. (2012) 'A Review of Sustainable Supply Chain Management Practices in Canada', *Journal of Business Ethics*, 117(3), pp. 635–658.

Mol (2010) 'Ecological Modernization as a Social Theory of Environmental Reform', in Michael R. Redclift and Graham Woodgate. Cheltenham, (ed.) *The International Handbook of Environmental Sociology,* UK: Edward Elgar Publishing, pp. 63 – 76.

Nag, O.S. (2020) *The World's Most Polluting Industries, Environmental Report by Worldatlas*, Available at: The World's Most Polluting Industries - WorldAtlas (Accessed: 10th Dec 2020)

NHS Waste Management Campaign (2017) *Medicine Waste UK*. Available at: www.medicinewaste.com (Accessed: 10th Dec 2018)

Nusim, S.H. (2005) 'Plant Operations', in Nusim, S.H. (ed.) *Active Pharmaceutical Ingredients.* Florida: Taylor & Francis Group. pp. 285-300

Nunes, B. T. S. (2011) *Greening Operations: An Investigation of Environmental Decision Making.* Ph.D. Thesis. Aston University UK.

Ninlawan, C., Seksan, P., Tossapol, K. and Pilada, W. (2010). The Implementation of Green Supply Chain Management Practices in Electronics Industry, *Proceedings of the International multi conference of Engineering and computer scientists*, 1 (3), March 17 – 19, Hong Kong.

Novartis (2017) *Corporate Responsibility Report*, Available at: https://www.novartis.com/sites/www.novartis.com/files/novartis-cr-performance-report-2017.pdf (Accessed: 23rd Dec 2020)

Nokia (2019) *Nokia steps up commitments to limit global warming to 1.5° C,* Available at: https://www.nokia.com/about-us/news/releases/2019/09/23/nokia-steps-up-commitments-to-limit-global-warming-to-15degc/ (Accessed: 12th Dec 2020)

Narhi, M. and Nordstrom, K. (2008) 'National GMP regulations and Codes and International GMP guides and Guidelines: Correspondence and Differences', in Gad, S.C. (ed.) *Pharmaceutical Manufacturing Hand Book: Regulations and Quality.* New Jersey: John Wiley & Sons, Inc. pp. 314-320.

Noakes, T.J. (1995) 'CFCs, their replacements, and the ozone layer', *Journal of aerosol medicines,* 8(1)

Nawrat, A. (2018) *Pharma and the environment: Why pollution remains a worrying trend,* Available at: https://www.verdict.co.uk/pharma-and-the-environment/ (Accessed: 21st Dec 2020)

Narayana, S.A., Pati, R.R. and Vrat, P. (2014) 'Managerial research on the pharmaceutical supply chain–A criticalreview and some insights for future directions', *Journal of Purchasing & Supply Management, 20, pp. 18-40*

Neuman, W.L. (2014) *Social Research Methods: Qualitative and Quantitative approaches*, 7th edt. England: Pearson

Neuendorf, K.A. (2002) *The Content Analysis Guidebook.* Canada: Sage Publications, Thousand Oaks, CA.

OECD (2012) *OECD Environmental Outlook to 2050,* OECD Publishing. Available at: https://www.oecd.org/g20/topics/energy-environment-green-growth/oecdenvironmentaloutlookto2050theconsequencesofinaction.htm (Accessed: 21st Dec 2020).

O'Rourke, D., Connelly, L. and Koshland, C. (1996) 'Industrial ecology: a critical review', *International Journal of Environment and Pollution*, 6 (2/3), pp. 89-112

Otto, R., Ostino, A.S. and Schrader, U. (2014) *Rapid growth in Biopharma: Challenges and Opportunities, McKinsey & Company Report*. Available at: https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/rapid-growth-in-biopharma (Accessed:12th Dec 2020).

Ombaka, E. (2009) 'Current status of medicines procurement', *Global Conference Proceedings: Medicines Procurement, Am J Health-Syst Pharm* , 66 (3), pp. 521 - 528

Perez-Vega, S., Rivas, E., Ochoa, I. and Sharratt, P.N. (2013) 'A system view of solvent selection in the pharmaceutical industry: towards a sustainable choice', *Environ Development and Sustainability, 15 (1- 21)*, Available at: https://link.springer.com/article/10.1007/s10668-012-9365-5 (Accessed: 21st Dec 2020)

Perotti, S., Zorzini, M., Cagno, E. and Micheli, G.J.L. (2012) 'Green supply chain practices and company performance: the case of 3PLs in Italy', *International Journal of Physical Distribution & Logistics Management*, 42(7), pp. 640–672.

PMEL Carbon Program (2018) *What is Ocean Acidification? – The Chemistry,* Available at: https://www.pmel.noaa.gov/co2/story/What+is+Ocean+Acidification%3F (Accessed: 12th April 2019]

Parameswaran, S. (2013) 'Toxic waste 'major global threat', BBC NEWS, accessed via: https://www.bbc.co.uk/news/science-environment-24994209 (Accessed: 7th Jul 2020)

Paksoy, T., and Weber, G. (2011) 'A Multi Objective Model for Optimization of a Green Supply Chain Network', *Global Journal of Technology & Optimization,* 2, pp. 84- 94

Plambeck, E. L. (2012) 'Reducing greenhouse gas emissions through operations and supply chain management', *Energy Economics*, *34*, pp. 64 -74.

Porter, M.E. and Van der linde, C. (1995) 'Toward a New Conception of the Environment-Competitiveness Relationship', *Journal of Economic Perspectives*, 9(4), pp. 97–118.

Pfizer (2020) *Lyrica Improves Environmental Performance*. Available at: https://pfe-pfizercom-d8-prod.s3.amazonaws.com/responsibility/protecting_environment/Lyrica_Goes_Green.pdf (Accessed: 21st Dec 2020)

PSNC (2017) *About Community Pharmacy*, Available at: https://psnc.org.uk/psncs-work/about-community-pharmacy/ (Accessed: 7th July 2017)

Poleto, M., Rusu, V., Grisci, B., Dorn, M., Lins, R. and Verli, H. (2018) 'Aromatic Rings Commonly Used in Medicinal Chemistry: Force Fields Comparison and Interactions With Water Toward the Design of New Chemical Entities', Available at: https://www.frontiersin.org/articles/10.3389/fphar.2018.00395/full (Accessed: 1st Nov 2020)

PhRMA (2015) *Biopharmaceutical Research & Development: The Process Behind New Medicines*, Available from: http://phrma-docs.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf (Accessed: 1st Aug 2020)

Pharma Intelligence (2019) *Pharma R&D Annual Review 2019*, Available at: https://pharmaintelligence.informa.com/~/media/informa-shop-window/pharma/2019/files/whitepapers/pharma-rd-review-2019-whitepaper.pdf [Accessed: 1st Nov 2020)

Plumb, K. (2005) 'Continuous processing in the pharmaceutica industry Changing the Mind Set, Institution of Chemical Engineers Trans IChemE, Part A', *Chemical Engineering Research and Design*, 83 (6), pp. 730–738

Pratyusha, K., Gaikward, N., Phatak, A. and Chaudhari, P. (2012) 'Review on: waste material management in pharmaceutical industry', *International Journal of Pharmaceutical Science Review and Research*, 16(2), pp. 121-129.

PR Newswire (2015) *Pharmaceutical Packaging Market Worth $80 Billion by 2020,* Available at: https://www.prnewswire.com/news-releases/pharmaceutical-packaging-market-worth-80-billion-by-2020-512909341.html [accessed: 12th Aug 2020]

Pharma Manufacturing (2015) *Controlling emissions the BAT way*, available at: https://www.pharmamanufacturing.com/articles/2015/controlling-emissions-bat-way/ (Accessed: 1st Nov 2020)

PSNC (2019) *LLR LPC Medicines Wastage Stop Think Reorder Campaign*, Available at: https://psnc.org.uk/leicestershire-and-rutland-lpc/our-news/llrlpc-medicines-wastage-stop-think-reorder-campaign/ (Accessed: 12th Dec 2020)

Persson, M., Sabelstrom, E. and Gunnarsson, B. (2009) 'Handling of unused prescription drugs- knowledge, behaviour, and attitude among Swedish people', *Environmental International,* 35, pp. 771–774

Polterauer, P. (2012) 'Is Pharma Recognizing value of procurement?', *PharmaExce*, Available at: https://www.pharmexec.com/view/pharma-recognizing-value-procurement [Accessed: 12th Dec 2020)

Peterson, J.M. and Anderson, J.M. (2002) "Trial" Prescriptions to Reduce Drug Wastage: Results From Canadian Programs and a Community Demonstration Project', *The American Journal of Managed Care*, 8 (2), pp. 151-158

Pomerantz, J. (2004) 'Recycling Expensive Medication: Why not?', *MedGenMed,* 6(2), Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1395800/ (Accessed: 8th Aug 2017)

Priporas, CV., Stylos, N. and Fotiadis, A.K. 2017. 'Generation Z consumers' expectations of interactions in smart retailing: A future agenda', *Computers in Human Behaviour*, 77, pp. 374-381.

PMLiVE (2013) *AstraZeneca supports NHS medication passport app*, Available at: http://www.pmlive.com/blogs/digital_intelligence/archive/2013/april/astrazeneca_supports_nhs_medication_passport_app_473164 (Accessed on 12th Dec 2020)

Quariguasi Frota Neto, J., Walther, G., Bloemhof, J., van Nunen, J. A. E. and Spengler, T. (2010) 'From closed-loop to sustainable supply chains: the WEEE case', *International Journal of Production Research*, *48* (15), pp. 4463–4481.

Qu, Y., Zhu, Q., Sarkis, J., Geng, Y. and Zhong, Y. (2013) 'A review of developing an e-wastes collection system in Dalian, China,' *Journal of Cleaner Production*, 52, pp. 175-184

Rusinko, C. (2007) 'Green Manufacturing: An Evaluation of Environmentally Sustainable Manufacturing Practices and their Impact on competitive outcomes', *IEE Transactions On Engineering Management,* 54 (3)

Roschangar, F., Colberg, J., Dunn, P., Gallou, F., Hayler, J.D., Koenig, S.G., Kopach, K., Leahy, D., Mergelsberg, I., Roger, J.T., Sheldon, R. and Senanayake, C.H. (2017) 'A Deeper Shade of Green: Inspiring Sustainable Drug Manufacturing', *Green Chem*, *The Royal Society of Chemistry*.

Roschangar (2018) *How a green manufacturing metric can inspire process innovation, Interview with Dr. Frank Roschangar, Director of Process Research & Global External Chemistry Management at Boehringer Ingelheim.* Avilable at: https://www.boehringer-ingelheim.com/corporate-profile/sustainability/green-chemistry/interview-roschangar (Accessed: 8th Aug 2019)

Roberson, C. (2016) 'The Greening of the Cold Chain', *Pharma Logistics IQ*, Available at: https://www.pharmalogisticsiq.com/logistics/columns/the-greening-of-the-cold-chain (Accessed on 12th Feb 2020).

Rogers, P. (2007) *Rogers Review: National enforcement priorities for local authority regulatory services*, UK: Cabinet Office.

Rehman, M., Seth, D. and Srivastava, R. (2016) 'Impact of green manufacturing practices on organizational performance in Indian context: An Empirical study', *Journal of Cleaner Production,* 137, pp. 427-448.

Rao, P. and Holt, D. (2005) 'Do Green Supply Chains lead to competitiveness and economic performance?', *International Journal of Operations and production Management*, 25 (9), pp. 898-916

Rogers, E.M. (1995) 'Diffusion of Innovation, [Online], 3rd edn. Free Press, New York. Available at: http://teddykw2.files.wordpress.com/2012/07/everett-m-rogers-diffusion-of-innovations.pdf (Accessed: 6th Jan 2017)

Rausch, K.D. and Powell, G.M. (1997) 'Dairy Processing Methods to Reduce Water Use and Liquid Waste Load', *Cooperative Extension Service*, Kansas State University, Manhattan

Rees, H. (2011) *Supply Chain Management in the Drug Industry: Delivering Patient Value For Pharmaceuticals and Biologics*, New Jersey: John Wiley & Sons, Inc.

Rosas, C.B. (2005) 'Process design', in Nusim, S.H. (ed.) *Active Pharmaceutical Ingredients,* Florida: Taylor & Francis Group. pp. 9-15

Roig, B. and Touraud, E. (2010) 'Regulations and the pharma incentives', in Kummerer, K., Hempel, M. (ed.) *Green and Sustainable Pharmacy,* Berlin: Springer. pp. 279-285

Rogers, L. and Jensen, K.F. (2019) 'Continuous manufacturing – the green chemistry promises?', *Green Chem*, 21, pp. 3481-3498

Rogers, E.M (2003) 'Diffusion of Innovation', fifth ed. New York: Free Press

ResearchNester (2020) 'Pharmaceutical Solvent Market: Global Demand Analysis & Opportunity Outlook 2024', Available at: https://www.researchnester.com/reports/pharmaceutical-solvent-market-global-demand-analysis-opportunity-outlook-2024/418 (Accessed: 12th Aug 2020)

RSC (2018) 'Elements in danger', *Royal Society of Chemistry*, Available at: https://www.rsc.org/new-perspectives/sustainability/elements-in-danger/ (Accessed: 21st Dec 2020)

Ruhoy, I.S., and Daughton, C.G. (2008). 'Beyond the medicine cabinet: An analysis of where and why medications accumulate', *Environment International*, 34, pp. 1157-1169

RSC (2019) 'Green Chemistry – Cutting edge research for a greener sustainable future', *Royal Society of Chemistry*, Available at: https://www.rsc.org/journals-books-databases/about-journals/green-chemistry/ (Accessed: 21st Dec 2020)

Raju, G., Sarkar, P., Singla, E., Sing, H. and Sharma, R.K. (2016) 'Comparison of environmental sustainability of pharmaceutical packaging, *Perspectives in science*, 8, pp. 683-685

Savage, C.J., Roberts, K.J., and Wang, X.Z. (2006) 'A holistic analysis of pharmaceutical manufacturing and distribution: are conventional supply chain techniques appropriate?', *Pharmaceutical Engineering*, pp. 10-18.

Sumpter, J.P. (2010) 'Pharmaceuticals in the environment: Moving from a problem to a solution', in Kummerer, K., Hempel, M. (ed.) *Green and Sustainable Pharmacy.* Berlin: Springer. pp. 10-16

Slater, C.S., Savelski, M.J., Carole, W.A. and Constable, D.J.C. (2010) 'Solvent use and waste issues', in Hickey, A.J. and Ganderton, D. (ed.) *Pharmaceutical Process Engineering*. New York: Informa healthcare.

Srivastava, S.K. (2007) 'Green supply-chain management: A state-of-the-art literature review', *International Journal of Management Reviews*, 9(1), pp.53–80

Sangwan, K.S. and Choudhary, K. (2017) Benchmarking Manufacturing Industries based on Green Practices, *Benchmarking: An International Journal,* 25 (6), pp. 1746-1761

Singh, R.K., Kumar, R. and Kumar., P. (2016) 'Strategic Issues in pharmaceutical supply chains: a review', *International Journal of Pharmaceutical and healthcare marketing*, 10 (3), pp. 234-257

Sarkis, J. (2001) 'Manufacturing's role in corporate environmental sustainability - Concerns for the new millennium, *International Journal of Operations & Production Management*, 21 (5/6), pp. 666 – 686

Seuring, S. and Muller, M. (2008) 'From a literature review to a conceptual framework for sustainable supply chain management', *Journal of Cleaner Production*, 16, pp. 1699–1710

Seuring, S., Sarkis, J. and Muller, M., Rao, P. (2008) 'Sustainability and supply chain management – An introduction to the special issue', *Journal of Cleaner Production*, 16 (15), pp. 1545–1551. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0959652608000334 (Accessed: 27th Oct 2017)

Suryanto, T., Haseeb, M. and Hartani, N. (2018) 'The Correlates of Developing Green Supply Chain Management Practices: Firms Level Analysis in Malaysia', *International Journal of Supply Chain Management*, 7 (5).

Sarkis, J. (2003) 'A strategic decision framework for green supply chain management,' *Journal of Cleaner Production*, 11(4), pp.397–409. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0959652602000628 (Accessed: 22nd Feb 2017)

Srivastava, S.K. (2008) 'Network Design For Reverse Logistics', *OMEGA, The International Journal Of Management Science,* 36, pp. 535-548

Stern, M.O., Ayres, R.U. and Saxton, J.C. (1973) 'Tax strategies for industrial pollution abatement', *Transactions on Systems Man and Cybernetics,* 3(6), pp. 588–603.

Scur, G., Barbosa, M. (2017) 'Green supply chain management practices: Multiple case studies in the Brazilian home appliance industry', *Journal of cleaner production,* 141, pp. 1293- 1302

Seuring, S. (2004) 'Industrial ecology, life cycles, supply chains: differences and interrelations', *Business Strategy and the Environment,* 13, pp. 306–319.

Soete, W.D., Jiménez-González, C., Dahlin, P. and Dewull, J. (2017) 'Challenges and recommendations for environmental sustainability assessments of pharmaceutical products in the healthcare sector', *Green Chem,* 19, pp. 3493.

Sroufe, R. (2003) 'Effects of environmental management systems on environmental management practices and operations', *Production and operations management,* 12 (3), pp. 416-432

Shen, B. (2014) 'Sustainable Fashion Supply Chain: Lessons from H&M'*, Sustainability,* 6, pp. 6236-6249

Salam, M.A. (2011) 'Creating Sustainable Supply Chain Through Green Procurement', *International Journal Of Business Insights and Transformation,* 3 (3), pp. 84-89

Shi, V.G., Koh, S.G.L., Baldwin, J. and Gucchiella, F. (2012) 'Natural resource based green supply chain management', *Supply Chain Management: An International Journal*, 17(1), pp. 54–67

Sarkis, J., Zhu, Q. and Lai, K. (2011) 'An organizational theoretic review of green supply chain management literature', *International Journal of Production Economics*, 130 (1), pp. 1–15.

Setiawati, C. I. and Sitorus, P. MT. (2016) 'Green Manifestation of Eco-Driver for Excellent Performance', *Journal of social science and Humanities*, 24 (5), pp. 245-256

Suchman, M.C. (1995) 'Managing legitimacy: strategic and institutional approaches', *The Academy of Management Review*, 20 (3), pp. 571-610

Settanni, E., Harrington, T.S. and Srai, J.S. (2017) 'Pharmaceutical supply chain models: A synthesis from a systems view of operations research', *Operations Research Perspective*, 4, pp. 74-95

Shah, N. (2004) 'Pharmaceutical supply chains: key issues and strategies for optimisation', *Computers and Chemical Engineering*, 28, pp. 929-941

Smiciklas and Sljivic-Ivanovic. (2016) *Radioactive contamination of the soil: Assessment of pollutants Mobility with Implication to Remediation Strategies,* Available at: https://www.intechopen.com/books/soil-contamination-current-consequences-and-further-solutions/radioactive-contamination-of-the-soil-assessments-of-pollutants-mobility-with-implication-to-remedia (accessed: 11th Aug 2020)

Solon, E.G. (2012) **Use of Radioactive Compounds and Autoradiography to Determine Drug Tissue Distribution Available at:** https://pubs.acs.org/doi/abs/10.1021/tx200509f# (Accessed: 11th Aug 2020)

Srai, J., Harrington, T., Alinaghian, L. and Phillps, M. (2015) 'Evaluating the potential for the continuous processing of pharmaceutical products - a supply network perspective', *Journal of Chemical Engineering and Processing*, Available from: https://www.repository.cam.ac.uk/bitstream/handle/1810/249104/Srai%20et%20al%202015%20Journal%20of%20Chemical%20Engineering%20and%20Processing.pdf?sequence=1&isAllowed=y (Accessed on 12th Aug 2020)

Schneider, R.K. (2008) 'Clean-Facility Design, Construction, and Maintenance Issues', in Gad, S.C. (ed.) *Pharmaceutical Manufacturing Hand Book: Production and Process.* New Jersey: John Wiley & Sons, Inc. pp. 201-230

Start (2008) *Management Strategies for Pharmaceutical residues in Drinking Water*, Available at: http://www.start-project.de/downloads/start_Practical_Guide.pdf (Accessed: 12th Aug 2017)

Sheldon, R. (2010) 'Introduction to Green Chemistry, Organic Synthesis and Pharmaceuticals', in Peter J. Dunn, Andrew S. Wells and Michael T. Williams. (Ed.) *Green Chemistry in the Pharmaceutical Industry.* Germany: Wiley-VCH Verlag GmbH & Co.

Sundgren, M. (2004) 'Managing Organizational Creativity in pharmaceutical R&D', PhD thesis.

Schneider, J.L., Wilson, A. and Rosenbeck, J.M. (2010) 'Pharmaceutical companies and sustainability: an analysis of corporate reporting,' *Benchmarking: An International Journal,* 17 (3), pp. 421-434

Siew, A. (2015) 'Exploring the potential of Continuous coating', *Pharmaceutical Technology, 39 (11), pp. 44-4.* Avilable at: http://www.pharmtech.com/exploring-potential-continuous-coating?pageID=2 (Accessed: 24th May 2017).

Schiff, G.D., Galanter, W.L., Duhig, J., Loddce, M.A., Koronhowski, M.J. and Lambert, B.L. (2011) Principles of Conservative Prescribing, *Arc Intern Med*, 171 (16), pp. 1433-1440

Schafer, T. (2017) 'Rethinking Solvent Recycling', *Pharmaceutical Manufacturing*, (19th Nov) Available from: https://www.pharmamanufacturing.com/articles/2017/rethinking-solvent-recycling/ (Accessed: 23rd Dec 2020)

Shand, J. (2003) *Fundamentals of Philosophy.* London: Routledge Publication.

Solem, O. (2003) 'Epistemology and logistics: A critical overview', *Systemic Practice and Action Research*, 16, pp. 437–454.

Saunders, M. L., Thornhill, A. and Lewis, P. (2016) *Research methods for business students*, 7th edn.. Italy: Pearson

Saunders, M.N.K., Thornhill, A. and Lewis, P. (2009). *Research Methods for Business Students.* 3rd Edition edn. UK: Pearson Education Limited

Spens, K.M. and Kova ´cs, G. (2006), 'A content analysis of research approaches in logistics research', *International Journal of Physical Distribution & Logistic Management,* 36 (5), pp. 374-390

Tian, Y., Govindan, K. and Zhu, Q. (2014) 'A system dynamics model based on evolutionary game theory for green supply chain management diffusion among Chinese manufacturers', *Journal of Cleaner Production*, 80, pp. 96–105.

Tseng, M., Islam, M., Karia, N., Fauzi, F. and Afrin, S. (2019) 'A literature review on green supply chain management: Trends and future challenges', *Resources, Conservations & Recycling*, 141, pp. 145–162

The Telegraph (2018) 'Pharmaceutical Pollution Linked To Rise In Superbug', The Telegraph News, 11th Sep. Available at: https://www.telegraph.co.uk/global-health/science-and-disease/pharmaceutical-pollution-linked-rise-superbugs/ (Accessed: 12th Oct 2020)

Taylor, D. (2016) 'The Pharmaceutical Industry and the Future of Drug Development', in Verma, K. (2013) *Base of a Research: Good Clinical Practice in Clinical Trials. J Clin Trials*

Tseng, M.-L., Chiu, S.F., Tan, R.R. and Siriban-Manalang, A.B. (2013) 'Sustainable consumption and production for Asia: sustainability through green design and practice', *Journal of Cleaner Production*, 40, pp. 1–5.

Tuni, A., Rentizelas, A. and Duffy, A. (2018) 'Environmental performance measurement for green supply chains: a systematic analysis and review of quantitative methods', *International Journal of Physical Distribution & Logistics Management*, doi: 10.1108/IJPDLM-02-2017-0062

Toke, L.K., Gupta, R.C. & Dandekar, M., (2010) 'Green Supply Chain Management: Critical Research and Practices', *International Conference on Industrial Engineering and Operations Management,* Dhaka, Bangladesh, January 9 – 10.

Tata Strategic Management Group (2014) *Green Logistics: Redesigning logistics for a better tomorrow,* Available at: http://www.tsmg.com/download/reports/Green_Logistics.pdf (Accessed: 16th July 2017).

Touboulic, A. and Walker, H. (2015) 'Theories in sustainable supply chain management: a structured literature review' *International Journal of Physical Distribution & Logistics Management*, 45(1/2), pp. 16-42.

Taylor, D. (2010) 'Ecopharmacostewardship – A Pharmaceutical Industry Perspective', in Kummerer, K., Hempel, M. (ed.) *Green and Sustainable Pharmacy.* Berlin: Springer. pp. 130-132

Takebe, T., Imai, R. and Ono, S. (2018) 'The Current Status of Drug Discovery and Development as Originated in United States Academia: The Influence of Industrial and Academic Collaboration on Drug Discovery and Development', *Clinical and Translational Science*, 11, pp. 597-606

Triggle, DJ. (2010) 'Pharmaceuticals in society', in Kummerer, K., Hempel, M. (ed.) *Green and Sustainable Pharmacy.* Berlin: Springer.

Tait, K.D. (2017) *Pharmaceutical Industry. Encyclopedia of Occupational Health and safety*, Fourth edn. Available at: http://www.ilocis.org/documents/chpt79e.htm (Accessed: 23rd May 2017)

Teni, F., Surur, A., Belay, A., Wondimsigegn, D., Gelayee, D., Shewamene, Z., Legesse, B. and Birru, M. (2017) 'A Household survey of medicine storage practices in Gondar Town, northwestern Ethiopia', *BMC Public Health*, DOI 10.1186/s12889-017-4152-8

Trautwein, C., Berset, J-D., Wolschke, H. and Kummerer, K. (2014) 'Occurrence of the antidiabetic drug Metformin and its ultimate transformation product Guanylurea in several compartments of the aquatic cycle', *Environmental International, 70, pp. 203-2012*

Tucker, J.L. (2006) 'Green chemistry- a pharmaceutical perspective', *Org Process Res Dev*, 10, pp. 315

Teunter, R., Inderfirth, K.,Minner, S. and Kleber, R. (2003) 'Reverse Logistics in a Pharmaceutical company: a case study', *Econometric Institute Research Report*, Available at: https://repub.eur.nl/pub/909/ (Accessed: 21st Nov 2020).

Thach, A.V., Brown, C.M. and Pope, N. (2013) 'Consumer perceptions about a community pharmacy-based medication take back program', *Journal of Environmental Management,* 127, pp. 23-27

Tellis, W.M. (1997) 'Application of a case study methodology', *The Qualitative Report*, 3 (3), pp. 1-19

Theodorakopoulos, N., Ram, M., and Kakabadse, N. (2015) 'Procedural justice in procurement management and inclusive interorganizational relations: An institutional perspective', *British Journal of Management*, 26(2), pp. 237-25.

Tsanis, K. (2013) 'Examination of political behaviour by middle managers in International Partnerships: A strategy process approach', *PhD thesis*: The University of Edinburg.

Tracy, S. J. (2010) 'Qualitative quality: Eight ''big-tent'' criteria for excellent qualitative research', *Qualitative Inquiry*, 16, pp. 837-851

Tangpong, C.(2011) 'Content analytic approach to measuring constructs in operations and supply chain management', *Journal of Operations Management*, 29(6), pp. 627–638

Turker, D. and Altuntas, C. (2014) 'Sustainable supply chain management in the fast fashion industry: An analysis of corporate reports', *European Management Journal*, 32(5), pp. 837–849

Terryn, I.C. (2010) 'The use of ecological modernization theory for the greening of the tourism industry', *Journal of Tourism Challenges and Trends*, 3(1), pp. 65-82

UN Environment (2019) *Tackling Global Water Pollution,* Accessed at: https://www.unenvironment.org/explore-topics/water/what-we-do/tackling-global-water-pollution, (Accessed: 12th July 2019)

UNEP (2019) *Global Resources Outlook – Natural Resources for The Future We Want, United Nations Environment Programme,* Available at: Assessing Global Resource Use: A systems approach to resource efficiency and pollution reduction (resourcepanel.org) (Accessed: 10th Oct 2020)

UK Department of Social and Healthcare (2019) *Antimicrobial resistance: UK launches 5-year action plan and 20-year vision.* Available at: https://www.gov.uk/government/news/antimicrobial-resistance-uk-launches-5-year-action-plan-and-20-year-vision, (Accessed: 12th July 2019)

UN Environment (2019) *Tackling Global Water Pollution*. Available at: https://www.unenvironment.org/explore-topics/water/what-we-do/tackling-global-water-pollution, (Accessed: 12th July 2019)

UN Water (2017) *UN World Water Development Report, Wastewater: The Untapped Resource*, Available at: http://www.unesco.org/new/en/natural-sciences/environment/water/wwap/wwdr/2017-wastewater-the-untapped-resource/ (Accessed: 23rd Dec 2018)

UNDESA (2014) *International Decade for Action 'Water For Life' 2005 – 2015, UN Water*. Available at: https://www.un.org/waterforlifedecade/quality.shtml [Accessed on 12/12/2020]

Uthayakumar, R. and Priyan, S. (2013) 'Pharmaceutical supply chain and inventory management strategies: Optimization for a pharmaceutical company and a hospital', *Operations Research for Healthcare*, 2 (3), pp. 52-64

Ubeda, S., Arcelus, F.J. and Faulin, J. (2010) 'Green Logistics at Eroski: A Case Study', *International Journal of Production Economics,* 131, pp. 44-51.

U.S. General Accounting Office (1996) *Content Analysis: a Metho-dology for Structuring and Analyzing Written Material*. GAO/PEMD, Washington, DC.

Vollmer, G. (2010) 'Disposal of Pharmaceutical Waste in Households- A European Survey', in Kummerer, K., Hempel, M. (ed.) *Green and Sustainable Pharmacy.* Berlin: Springer, pp. 176-180.

Veleva, V., Hart, M., Greiner, T. and Crumbley, C. (2003) 'Indicators for measuring environmental sustainability: A case study of the pharmaceutical industry', *Benchmarking International Journal*, 10, pp. 107–119.

Vanalle, R.M., Ganga, G.M.D., Godinho Filho, M. and Lucato, W.C. (2017) 'Green supply chain management: an investigation of pressures, practices, and performance within the Brazilian automotive supply chain', *Journal of Cleaner Production,* 151, pp. 250-259.

Verma, D., Dixit, R.V. and Singh, K. (2018) 'Green Supply Chain Management: A Necessity for Sustainable Development', *Journal of Supply Chain Management*, 15(1), pp. 40 - 58

Vachon, S. and Klassen, R.D. (2008) 'Environmental management and manufacturing performance: The role of collaboration in the supply chain', *International Journal of Production Economics*, 111(2), pp. 299–315.

Veleva, V. and Jr, B.W.C. (2017) 'Benchmarking green chemistry adoption by "big pharma" and generics manufacturers', *Benchmarking: An International Journal,* 24 (5), pp. 1414 - 1436

Vachon, S. (2007) 'Green supply chain practices and the selection of environmental technologies', *International Journal of Production Research*, 45(18-19), pp. 4357–4379. Available at: http://www.tandfonline.com/doi/abs/10.1080/00207540701440303 (Accessed: 26th Feb 2016).

Vachon, S. and Klassen, R.D. (2006) 'Extending green practices across the supply chain: The impact of upstream and downstream integration', *International Journal of Operations & Production Management*, 26(7), pp. 795–821.

Vinci, (2018) *Climate Change and CDP report*, Available at: https://www.vinci.com/publi/vinci/2018_CDP_Climate_Change_Response_VINCI.pdf (Accessed: 1/11/2020).

Vaisala, (2012) *'GMP Warehouse Mapping: Step by step guidelines for validating life science storage facility-White Paper*, Available at: http://www.vaisala.com/Vaisala%20Documents/White%20Papers/CEN-LSC-AMER-GMP-Warehouse-Mapping-White-Paper-B211170EN-A.pdf (Accessed: 7th July 2017)

Vellinga, A., Cormican, S., Driscoll, J., Furey, M., O'Sullivan, M. and Cormican, M. (2014) 'Public practice regarding disposal of unused medicines in Ireland', *Science of The Total Environment,* 478, pp. 98-102.

Venkatraman, N. (1989) 'The concept of fit in strategy research: Toward verbal and statistical correspondence', *Academy of management review,* 14(3), pp. 423-444.

Weraikat, D., ZanJani, M.K. and Lehoux, N. (2016) 'Coordinating a green reverse supply chain in pharmaceutical sector by negotiation', *Computers and Industrial Engineering*, 93, pp. 67 – 77

Woodburn, A. and Whiteing, A. (2010) 'Transferring freight to 'greener' transport mode', in McKinnon, A., Cullinane, S., Browne, M., Whiteing, A. (ed.) *Green Logistics – Improving the environmental sustainability of logistics,* UK: Kogan Page Limited.

WCS (1980) 'World Conservation Strategy, International Union For Conservation Of Nature and Natural Resources, IUCN-UNEP-WWF.

WPA (2017) *World Population Ageing*, https://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2017_Highlights.pdf , (Accessed: 12th July 2019)

WECD (1987) World Commission on Environment and Development - Our Common Future, United Nation.

WHO (2010) 'Global Health Risk: Mortality and burden of disease attributable to selected major risks', Available at: https://www.who.int/healthinfo/global_burden_disease/GlobalHealthRisks_report_full.pdf (Accessed: 11th July 2019)

WHO (2018) *Climate Change and Health, World Health Organization Report*, Available at: https://www.who.int/news-room/fact-sheets/detail/climate-change-and-health (Accessed: 12th Oct 2020).

WHO (2019) *Drinking Water, World Health Organization Report*, Available at: https://www.who.int/news-room/fact-sheets/detail/drinking-water (Accessed: 12th Oct 2020)

WHO (2016) The Public Health Impact Of Chemicals: Knowns and Unknowns - International Program On Chemical Safety, World Health Organization Report, Geneva, Switzerland.

WHO (2003) *Adherence to long term therapies: Evidence for action*. Available at: https://www.who.int/chp/knowledge/publications/adherence_full_report.pdf?ua=1 (Accessed: 12th Nov 2018).

WHO (2011) *Annex 9: Model guidance for the storage and transport of time- and temperature–sensitive pharmaceutical products, WHO Technical Report Series, No. 961*, Available at: https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/distribution/trs961-annex9-modelguidanceforstoragetransport.pdf?sfvrsn=b80e925f_2 (Accessed: 23rd Oct 2018).

WBG (1998) 'Pharmaceutical Manufacturing', *Pollution Prevention and Abatement Handbook.*

WHO (2000) T*he Use of Essential drugs, WHO Technical Report Series No. 895,* Available at: *https://apps.who.int/iris/handle/10665/42373* (Accessed: 12th Dec 2017)

WHO (2002) *Practical Guidelines on Pharmaceutical Procurement for Countries with Small Procurement Agencies, World Health Organization,* Available at: https://apps.who.int/iris/handle/10665/206932 (Accessed: 2nd Dec 2018).

Wu, J., Dunn, S. and Forman, H. (2012) 'A Study on Green Supply Chain Management Practices among Large Global Corporations', *Journal of Supply Chain and Operation Management*, 10 (1), pp.182–194.

World Energy Council (2016) *World Energy Resources.* Available at: https://www.worldenergy.org/assets/images/imported/2016/10/World-Energy-Resources-Full-report-2016.10.03.pdf (Accessed: 20th Dec 2019).

World Bank (2018) *What A Waste 2.0 – A Global Snapshot of Solid Waste Management to 2050, World Bank Group,* Available at: http://documents1.worldbank.org/curated/en/697271544470229584/pdf/132827-PUB-9781464813290.pdf (Accessed: 21st Dec 2020)

Wu, J., Dunn, S. and Forman, H. (2012) 'A Study on Green Supply Chain Management Practices among Large Global Corporations', *Journal of Supply Chain and Operations Management*, 10 (1), pp. 182-194

Wong, C.W.Y., Lai, K., Shang, K., Lu, C. and Leung, T.K.P. (2012) 'Green operations and the moderating role of environmental management capability of suppliers on manufacturing firm performance', *International Journal of Production Economics*, 140, pp. 283-294

Walker, H., Sisto, L.D. and McBain, D. (2008) **'**Drivers and barriers to environmental supply chain management practices: Lessons from the public and private sectors', Journal of Purchasing and supply management, 14 (1), pp. 69-8

Whitehouse (2018) *P&G: why have zero waste to landfill goals, and how do we do it?* Available at: https://www.cosmeticsdesign-europe.com/Article/2018/11/09/P-G-why-have-zero-waste-to-landfill-goals-and-how-do-you-do-it (Accessed: 12th Nov 2020)

WHO (2007) '*Quality Assurance of Pharmaceuticals. A Compendium of Guidelines and Related Materials. Volume 2, Good manufacturing practices and inspection'*, Available at: http://www.who.int/medicines/areas/quality_safety/quality_assurance/QualityAssurancePharmVol2.pdf (Accessed: 15th May 2017).

Watson, W. J. W. (2012) 'How do the fine chemical, pharmaceutical and related industries approach green chemistry and sustainability?', *Green Chem*. 14, pp. 251−259.

Weele, A. and Tubergen, K. (2017) 'Responsible Purchasing: Moving from Compliance to Value Creation in Supplier Relationships', in Bouchery, Y., Corbett, C.J., Fransoo, J.C., Tan, T. (ed.) *Sustainable Supply Chain: A research based text-book on Operations and Strategy.* Switzerland: Springer. pp. 268-277.

Woodburn, A. and Whiteing, A. (2010) 'Transferring freight to 'greener' transport mode', in McKinnon, A., Cullinane, S., Browne, M., Whiteing, A. (ed.) *Green Logistics – Improving the environmental sustainability of logistics,* UK: Kogan Page Limited.

Weber, R.P. (1990) *Basic Content Analysis*. Canada: Sage publications

Wolfe, R.A., Gephart, R.P. and Johnson, T.E. (1993) *Computer-facilitated qualitative data analysis: potential contributions to management research, Journal of Management* 19 (3), pp. 637–660

Wagner, M. (2005) 'How to reconcile environmental and economic performance to improve corporate sustainability: corporate environmental strategies in the European paper industry', *Journal of Environmental Management*, 76, pp. 105-118

Xie, Y. and Breen, L. (2012) 'Greening community pharmaceutical supply chain in UK: a cross boundary approach', *Supply Chain Management: An International Journal*, 17(1), pp. 40-53.

Xu, A., Hu, X., Gao, S. (2012) 'Review of Green Supply Chain Management, *Eleventh Wuhan International Conference on e-Business*, 26th May.

Yalabik, B., Chhajed, D. and Petruzzi, N.C. (2014) 'Product and sales contract design in remanufacturing', *International Journal of Production Economics*, 154, pp. 299–312. Available at: http://linkinghub.elsevier.com/retrieve/pii/S092552731300412X (Accessed: 22nd Nov 2017)

Younis, H. and Sundarakani, B., Vel, P. (2016) 'The impact of implementing green supply chain management practices on corporate performance', *Competitiveness Review*, 26 (3), pp. 216 – 245.

York, R., Rosa, E.A., Dietz, T. (2010) 'Ecological modernization theory: theoretical and empirical challenges', in Redclift, M. R, Woodgate, G. (ed.) *The International Handbook of Environmental Sociology,* UK: Edward Elgar Publishing Limited. pp. 77-87

Yin, R.K. (2009) *Case study Research Design and Methods*, United Kingdom: Sage Publications.

Zhu, Q., Sarkis, J. and Lai, K. (2012) 'Green supply chain management innovation diffusion and its relationship to organizational improvement: An ecological modernization perspective', *Journal of Engineering and Technology Management*, 29(1), pp. 168–185. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0923474811000506 (Accessed: 15th Jul 2017].

Zhang, B., Wang, Z., Yin, J. and Su. L. (2012) 'CO2 emission reduction within Chinese iron & steel industry: practices, determinants and performance', *Journal of Cleaner Production*, 33, pp.167–178. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0959652612001990 (Accessed: 8th Jan 2017).

Zhang, J. (2011) 'New Global Pharmaceutical Outsourcing Trends' *Pharmaceutical Online*, (29th December). Available at: https://www.pharmaceuticalonline.com/doc/new-global-pharmaceutical-outsourcing-trends-0001 (Accessed: 13th June 2017)

Zhu, Q., Geng, Y. and Lai, K.H. (2010) 'Circular economy practices among Chinese manufacturers varying in environmental-oriented supply chain cooperation and the performance implications', *Journal of environmental Management*, 91, pp. 1324 – 1331

Zhu, Q., Sarkis, J. and Lai, K. (2013) 'Institutional-based antecedents and performance outcomes of internal and external green supply chain management practices', *Journal of Purchasing and Supply Management*, 19 (2), pp.106–117.

Zhu, Q. and Sarkis, J. (2004) 'Relationships between operational practices and performance among early adopters of green supply chain management practices in Chinese manufacturing enterprises', *Journal of Operations Management*, 22 (3), pp. 265–289

Zhu, Q., Sarkis, J. and Lai, K. (2007 a) 'Green supply chain management: pressures, practices, and performance within the Chinese automobile industry,' *Journal of Cleaner Production*, 15 (11-12), pp. 1041–1052

Zhu, Q., Sarkis, J. and Lai, K. (2008) 'Green supply chain management implications for closing the loop', *Transportation Research Part E: Logistics and Transportation Review*, 44 (1), pp. 1–18.

Zhu, Q. and Geng, Y (2013) 'Drivers and barriers of extended supply chain practices for energy saving and emission reduction among Chinese manufacturers', *Journal of Cleaner Production*, 40, pp. 6–12.

Zhu, Q., and Sarkis, J. (2006) 'An inter-sectoral comparison of green supply chain management in China: Drivers and practices,' *Journal of Cleaner Production*, *14* (5), pp. 472–486.

Zhu, Q., and Sarkis, J. (2007) 'The moderating effects of institutional pressures on emergent green supply chain practices and performance', *International Journal of Production Research*, *45, pp.* 18-19

Zailani, S., Jeyaraman, K., Vengadasan, G. and Premkumar, R. (2012) 'Sustainable supply chain management (SSCM) in Malaysia: A survey', *International Journal of Production Economics*, 140 (1), pp. 330–340.

Zhang, Y., Li, Z., Qi, T., Zheng, S., Li, H. and Xu, H. (2004) 'Green Manufacturing Process of Chromium Compounds', *Environmental Progress,* 24 (1), pp. 44-50

Zailani, S., Jeyaraman, K., Vengadasan, G., Premkumar, R. (2012) 'Sustainable supply chain management (SSCM) in Malaysia: A survey', *International Journal of Production Economics*, 140 (1), pp. 330–340

Zsidisin, G. A. and Siferd, S.P. (2001) Environmental purchasing: A framework for theory development, *European Journal of Purchasing and Supply Management*, 7 (1), pp. 61–73.

Zhu, Q., Liu, Q. (2010) 'Eco design Planning in a Chinese Telecommunication network company – Benchmarking its parent company', *Benchmarking: An International Journal,* 17 (3), pp. 363-377

Zhu, Q., Sarkis, J. and Lai, K. (2011) 'An institutional theoretic investigation on the links between internationalization of Chinese manufacturers and their environmental supply chain management' *Resources, Conservation and Recycling*, 55(6), pp. 623–630

Zhu, Q., Sarkis, J., Cordeiro, J.J. and Lai, K.H. (2008 a) 'Firm-level correlates of emergent green supply chain management practices in the Chinese context', *Omega: the International Journal of Management Science*, 36 (4), pp. 577–591.

Zhu, Q. and Sarkis, J. (2004) 'Relationships between operational practices and performance among early adopters of green supply chain management practices in Chinese manufacturing enterprises' *Journal of Operations Management*, 22 (3), pp. 265–289.

Appendix 1

Interview Protocol

Script prior to interview:

I would like to thank you for willing to participate in the interview aspect of my study. As I have mentioned to you before, my study seeks to understand the existing green/environmental practices, and related drivers (motivations) and barriers prior to implementing these green practices in the pharmaceutical sector. The study also seeks to understand the relevant performance induced from implementing the green practices.

This interview will last approximately one hour. I will be asking you about the green/environmental practices, related motivators (drivers), barriers, and performance measures currently being used at your department/company. I will be also asking you to demonstrate the interrelationships between these green practices, drivers, barriers, and organizational performance (in terms of environmental, economic, and operational).

I have your consent form indicating that I have your permission (or not) to audio record our conversation. Please confirm if you are still okay and allow me to record our conversation:

___Yes ___No

If yes: Thank you! Please let me know if at any point you want me to turn off the recorder or keep something you said off the record.

If no: Thank you for letting me know. I will only take notes of our conversation.

Before we begin the interview, do you have any questions? [Discuss questions]

If any questions (or other questions) arise at any point in this study, you can feel free to ask them at any time. I would be more than happy to answer your questions. Also, the name of the interviewee and your organization will be anonymous throughout the research report.

Interview Questions:

1. Could you please tell me about the environmental activities/ green practices implemented in your department/company?
2. Realizing the issue of pharmaceuticals in the environment (PIE), what initiatives/services/practices have you undertaken? If no, why?
3. What motivates you / your company to implement these environmental activities /services/ green practices?
4. Can you explain how and to what extent these motivations influence you / your company to implement these environmental activities/practices?
5. What are the perceived benefits of implementing these activities/services/environmental practices? If not, why?
6. Can you explain the challenges you have faced prior to implementing each of the activity/service/environmental practices you have highlighted?
7. Can you explain how and to what extent these challenges impede you to implement the activities/services/green practices you have highlighted?
8. Can you explain how these services/activities/practices impact on your organizational performance (in terms of environmental/economic/operational)?
9. Do you measure performance of these green activities/services/practices that you have implemented? If yes, how, and what are those measures? If no, why?
10. Can you explain what are the actual performances (in terms of environmental/economic/operational) achieved after implementing each activity/service/green practice separately, and how?
11. Realizing the unprecedented level of government pressure for reducing GHG emission, can you please explain how do you manage different types of GHG emission (e.g., scope 1, scope 2 and scope 3) at your department/company?

Appendix 2

MIDDLESEX UNIVERSITY

PARTICIPANT INFORMATION SHEET (PIS)

Participant ID Code: 03201802

1. Study title

Green Supply Chain Management in the Pharmaceutical Sector: An Investigation in the UK context

2. Invitation paragraph

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part.

Thank you for reading this.

3. What is the purpose of the study?

The presence of human pharmaceuticals in the water cycle, particularly drinking water, is now well established. Humans are unintentionally exposed to very low concentrations of medicinal products via daily intakes of drinking water, leaf crops, root crops, fishes, dairy products, and meats. The entry of drug residues into the environment can be via patient's excretion (80%), inappropriate disposal (e.g., via sink/toilet/garbage) of unused drugs (10%)

and via manufacturing discharge (2%). The concentration of drugs in the environment may destroy natural ecosystem and negatively impact on aquatic environment. Though an immediate negative consequence on human health is still subjected to ongoing research, scientific predictions are available such as threats for unborn baby/foetus, renal failure and affected human cells due to consumption of contaminated water. Therefore, the pharmaceutical sector stands on a precautionary phase to deal with it. Greenhouse Gas emissions across the supply chain, solvent wastes, packaging wastes, and other related emissions are also serious matter of environmental concerns.

To deal with this unprecedented environmental degradation, pharmaceutical sector must establish green / environmental practices across the supply chain. This project aims to understand the status of greening efforts in the UK pharmaceutical sector. It aims to identify green practices employed by each key player (e.g., R&D, API producers, formulators, distributors, retail pharmacies, GPs etc) in the supply chain. It also aims to understand the motivations and challenges for implementing the green practices. It also aims to understand the performance outcomes due to implementing the green practices.

4. Why have I been chosen?

It is important that we assess as many participants as possible, and you have indicated that you are interested in taking part in this study. Being an important and key player in the pharmaceutical supply chain, your operational decisions, and daily activities in relation to each aspect of operations are crucial for greening pharmaceutical sector. So, your valuable insight and practical experiences could significantly contribute towards the execution of this project aims. You are one of the valuable participants out of thirty for this research project.

5. Do I have to take part?

It is up to you to decide whether to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign on a consent form***. If you decide to take part, you are still free to withdraw at any time and without giving a reason***. If you do decide to withdraw from the study then please inform the researcher as soon as possible, and they will facilitate your withdrawal. If, for any reason, you wish to withdraw your data please contact the researcher within a month of your participation. After this data it may not be possible to withdraw your individual data as the results may have already been published. However, ***as all data are anonymised, your individual data will not be identifiable in any way***.

6. What will I have to do?

- You will be participated in an interview upon agreed with your best available time and method (by Skype/telephone/face-to-face/via email). This project is expected to finish by December 2019. If it requires any further information after interview, you may be expected for a follow up contact (via email) between this time frame.
- It is expected that you will be contacted once for interview, but it can be more than once (as follow up request via email) if it requires any further clarification.
- The interview session will take approximately an hour. You will be sent off an interview protocol containing the types of expected interview questions in advance prior to participating in the interview session. The interview will be audio recorded.
- The participant will be agreed on a date, time, and venue (only in case of face to face interview) for participating in the interview session.

Please note that to ensure quality assurance and equity this project may be selected for audit by a designated member of the committee. This means that the designated member can request to see signed consent forms. However, if this is the case your signed consent form will only be accessed by the designated auditor or member of the audit team.

7. Will I have to provide any bodily samples (i.e. blood/saliva/urine)?

NO

8. What are the possible disadvantages and risks of taking part?

No known risk in participating in this project.

Appropriate risk assessments for all procedures have been conducted and will be followed throughout the duration of the study.

9. What are the possible benefits of taking part?

We hope that participating in the study will help you. However, this cannot be guaranteed. The information we get from this study may help us to establish a set of effective and efficient green / environmental practices which could be implemented in your company not only for contributing to the wider community (via reducing pharmaceutical concentration into the environment) and deal with regulations but also it aims to improve operational, economic and environmental performance of your company. The research results may also help you to recognize the relevant challenges (or barriers- e.g., regulations, skilled manpower etc) for implementing green practice. Proactive actions could be taken accordingly to green your company / supply chain. It may also help you to identify and understand the important motivations (e.g., regulatory pressure for reducing drug wastes and safe drug disposal,

demand for reducing environmental burdens from your suppliers/customers, demand for greener drugs such as bio-drug production etc) for implementing green practices which may not only help you to become green but also direct you for new business opportunities.

9. Will my taking part in this study be kept confidential?

The research team has put several procedures in place to protect the confidentiality of participants. You will be allocated a participant code that will always be used to identify any data you provide. Your name or other personal details will not be associated with your data, for example, the consent form that you sign will be kept separate from your data. All paper records will be stored in a locked filing cabinet, accessible only to the research team, and all electronic data will be stored on a password protected computer. All information you provide will be treated in accordance with the UK Data Protection Act.

10. What will happen to the results of the research study?

The results of the research study will be used as part of a Postgraduate dissertation. The results may also be presented at conferences or in journal articles. However, the data will only be used by members of the research team and at no point will your personal information or data be revealed.

11. Who has reviewed the study?

The study has received full ethical clearance from the Research ethics committee who reviewed the study. The committee is the Business School Research Ethics Committee.

12. Contact for further information

If you require further information, have any questions, or would like to withdraw your data then please contact:

Researcher:
Md Mostain Belal
PhD Candidate
University of Middlesex
Email: mb1965@live.mdx.ac.uk

Project Supervisor
Dr Vinaya Shukla
Senior Lecturer in Operations Management
Middlesex University Business School
The Burroughs,

Hendon London
NW4 4BT
Phone: 020 8411 4247
Email: v.shukla@mdx.ac.uk

Thank you for taking part in this study. You should keep this participant information sheet as it contains your participant code, important information and the research teams contact details.

Appendix 3 (a)

Drug Design and Development

A pharmaceutical supply chain starts with innovations and discovery activities which are known as drug research and development or R&D (Taylor, 2016). Drug R&D activities are crucially important for pharma industry and it has been identified very special compared to other discrete industry product R&D due to the involvement of challenging discovery process, risky high investment (between 500 million to a billion) and long developmental phase (between 10 to 15 years) (Taylor, 2016; Reese, 2011). The entire discovery process from a particular disease to a final drug can be divided into two major tasks – 'Drug Design' (Pre-clinical activity) and 'Drug Development' (clinical trial). Figure 2.5 shows the overall steps in drug design and development process.

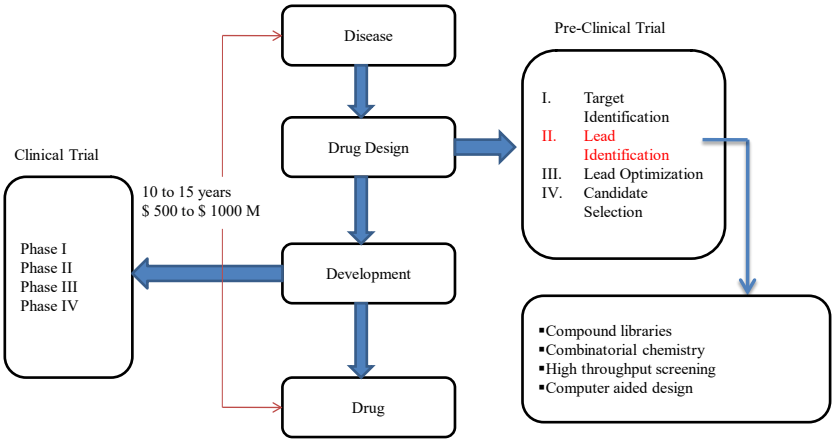


Figure: 2.5 Overview of drug design and development process (Source: Adapted from Taylor, 2016; Clark, 2010)

Drug design starts with research into a particular illness or disease of interest. Due to a complex, time consuming (10 to 15 years) and very expensive ($500 – 1000M) process, decision and research interest on a particular disease depends on multiple factors. For instance, to consider the extent of current medical needs, available of current therapy, novel approach to the management of the disease, commercial opportunity etc (Taylor,2016). The research process can be undertaken within the research laboratories of the pharmaceutical companies or in academia, government research organizations, or small research-based biotech companies, or any combination of these. Once the disease of interest is strategically evaluated and fixed, researchers start working on identifying a specific receptor or target- which is generally termed as 'Target Identification'. Experiments start on identifying a suitable drug molecule after the target is identified- which step normally termed as lead identification and lead optimization (Taylor, 2016; Wells and Arkins, 2010). The steps involved in drug design are described briefly below:

Target Identification: Biological targets are most often proteins or enzymes[3] that are believed to be involved in a disease. The process of identifying the causes of a particular disease is challenging and can be a very long process; because the human genetic space is huge (~20,000 human genes that code for protein) and lots to search to find out which gene is

[3] An enzyme is a class of large proteins, which can catalyze a broad spectrum of biochemical reactions; it is formed in living cells.

causing the disease (Wells and Arkins, 2010). The target can be a wide variety of things: particular cell type, enzyme, gene, pathway or processes; and it is estimated that more than 500 targets are currently under investigation in the research pharmaceutical companies (Taylor, 2016). Different target sites show different types of mechanism of actions. Clear understanding of a specific target within the body (e.g., 3D structure of a target protein and its mechanism of action) is prerequisite to move forward identifying a particular drug molecule that may interact with the targeted site for a better therapeutic effect.

Lead Identification: Once the target or a specific receptor has been identified, the next step is to hunt for an appropriate substance that might have optimal characteristics to manipulate the target site. The process of identifying the substance is termed as Lead Identification or lead compound identification. Though the more scope of screening of compounds the more chances of getting a lead compound, it is impossible to screen all the possible compounds in the universe. Because the chemical space[4] is vast within this universe and it is estimated that one can build ~10^{62} possible drug molecular structures with molecular weight less than 500 (Triggle, 2010). So, the difficulty is how efficiently a drug molecule can be selected from the vast array of chemicals. However, to date many efforts exist to optimize this stage to identify lead compound, for instance: usage of compound libraries.

Like a collection of books, compound library is a collection of compounds. The collection can be of real stored chemicals and/or virtual chemicals compound. The library stores wide variety of compounds and relevant technical data such as chemical structure, purity, quantity, and physicochemical characteristics of the compounds which can be used for initial screening against a known biological target. Companies are continuously storing compounds' data and thus enriching their library for a successful lead identification through screening. For instance, Aurora Fine Chemicals has a compound library containing more than 18 million substances and a compound library for a pharmaceutical company will now typically contain samples of 1-2 million different substances (Taylor, 2016).

However, screening process in the lead identification stage could also be optimized by using a technology called high Throughput Screening or HTS. It is an automatic technique in which thousands to millions of compounds can be tested (either against a known target or non-validated target) for identifying lead compound in a short period of time. Though there are some other methods (e.g., structure-based design) available for compound screening, HTS is

popular and widely used method. Identifying a final drug molecule from a huge chemical space is an exhaustive exercise and it involves a series of compound testing (figure: 2.4). HTS experiment involves three basic steps: sample preparation, sample handling and data readouts. Library collections, either in-house built or commercially purchased, are usually stored on 96 or 384-well microtiter plate. However, the number of wells is multiples of 96. Whenever required, samples from stock plates are copied onto assay[5] plates for HTS experiment. Dedicated liquid handling robots are used to add reagent to the multiples wells for screening the compounds. Though there are different readouts available for different HTS, many HTS are interpreted through optical measurement- colour changes in cells and in liquid reaction-which is known as fluorescence signals.

In HTS technique, automated equipment can be used to apply simple biochemical assays to very large number of chemicals in a short period of time: throughput can range from 50 000 to 100 000 samples a day (Taylor, 2016). Recently developed ultra-high throughput screening (UHTS) technique allow assay rates of 1 000000 a day. There are two different screening paradigms used in the pharmaceutical companies – 'random screening' and 'focused library screening' (Smith and Griebenow, 2006). In random screening, the entire library compound is tested in an assay. The libraries can be built from historical collections, natural products, combinatorial synthesis and third-party collaboration. When applying a random screening, pharmacophore[6] knowledge of the target is not essential. The assay is used here as filter to identify the promising hits that justify further analysis for lead finding. This unbiased and diverse large library screening increases the probability of finding a new biologically active compound. After initial screening and in a subsequent review process, a more complex assay will be used to refine the initial group, which might contain several hundred compounds. It normally goes down to a more manageable number which is normally less than 10. In contrast, focused library screening uses a small set (normally subset of the entire library) of compound assays and the results are statistically analysed. Based on the statistical models, additional screening is performed to produce improved versions.

This stage could also optimize by using computer software which is called computer aided drug design. In this process of drug design, a three-dimensional representation of a target protein can be visualized, and it is possible to infer how a small drug molecule might interact

[5] Assay is test systems on which to evaluate the effects of chemical compounds on cellular, molecular or biochemical processes of interest.
[6] Pharmacophore- "a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecule's biological activity" (Gund, 1977)

with a specific area of target. The objective of this design is to build computer models of the target, which involves thousands of different variables. Simulation of different models shows how different chemical structures interact with the target, leading to new knowledge that will guide medicinal chemists to synthesize the best chemical structures (Sundgren, 2004).

After successful lead identification, companies intend to patent the molecule, though a further 10 years of development work needed before a drug could be submitted for marketing authorization.

Lead Optimization: Lead optimization endeavours to reduce the number of potential leads from 10 – 15 down to 3 – 4 substances (Taylor, 2016). The chemical structure of the lead compound is improved through modification of the molecule in such a way that it can avoid unwanted side effects, while maintaining pharmacological properties (Sundgren, 2004). In this stage, it is also examined which parts of the molecule are important to biological activity and which are not, and optimize the lead further accordingly (Clark et al., 2010). It will usually take 2- 3 years of detailed pre-clinical experimentation using in silico, in vitro and in vivo techniques[7]. Design of process chemistry will also be initiated to manufacture trial batches of the substances (the active ingredients) for use in the subsequent clinical trial and eventually for full-scale manufacture (Taylor, 2016).

Candidate drug selection: In parallel with lead optimization, 'druggability[8]' of the lead substances is explored. Druggability ensures that the selected active ingredient can be converted into a form that could be taken by a patient such that the substance can interact with the target. This will further inform and confirm the relevant pharmacodynamics and pharmacokinetics information. Followed by these activities, a candidate drug, and potentially a second-best alternative candidate, will have emerged. The alternative candidate is normally replaced with the lead candidate if there are any unexpected problems arise during the clinical trials.

Clinical Trial: Based on confirmation from the scientific team, further business analysis is undertaken to take final commercial decision on the candidate drug forward into clinical trial. The clinical trials involve four distinct phases. Clinical trials intend to justify whether the drug works as anticipated in the pre-clinical stages. A candidate drug takes from six to ten

[7] In silico is the observation of biological actions using computer simulation; in vivo is the observation of biological actions on living organism; in vtro is the observation of biological actions in test-tube experiments
[8] Druggability is the ability of a drug molecule to interact with a target

years to complete the first three phases (Taylor, 2016). Good Clinical Practice (Verma, 2013) is followed prior to clinical trial. Different milestones in different phases are presented in the figure 2.6.

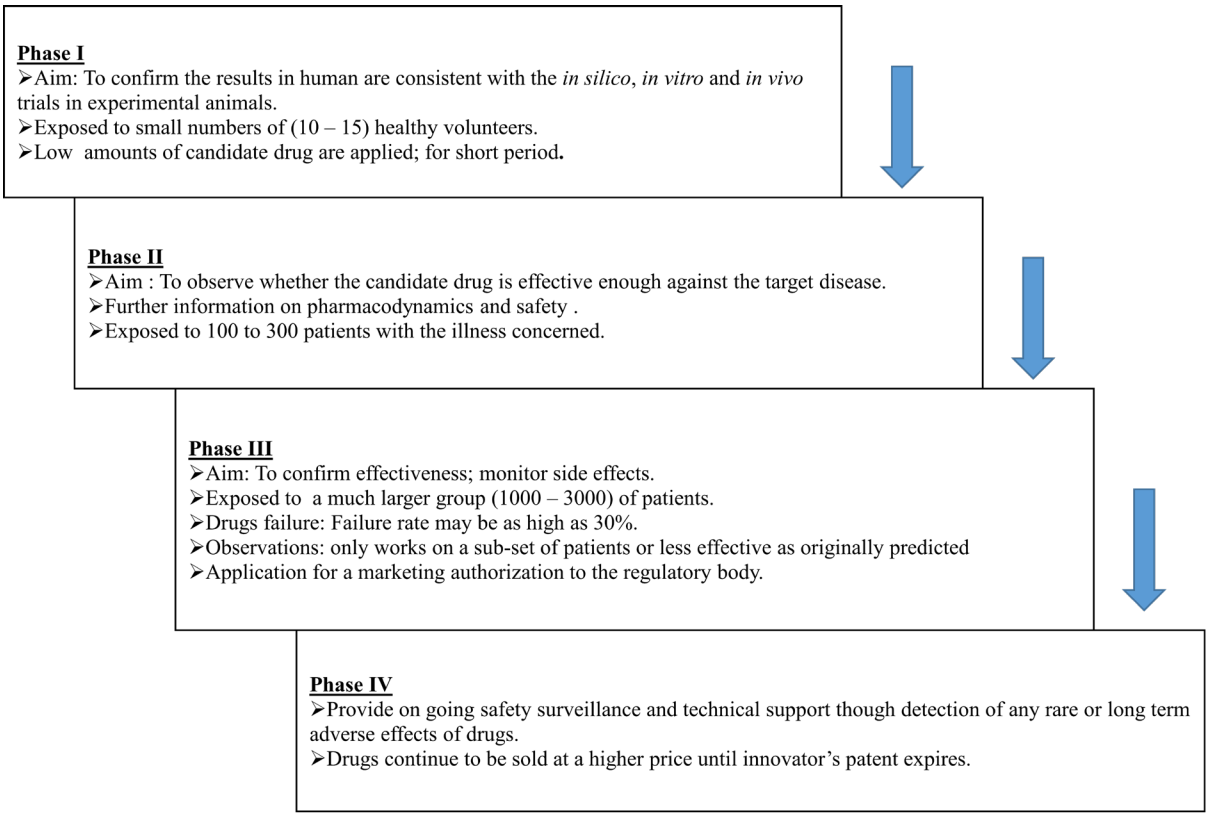


Figure 2.6. Overview of drug development process (clinical Trial); adapted from Taylor (2016)

Based on the overview of drug design and development process, it is assumed that the drug discovery process has been fundamentally deviated from the natural occurrence to more systematic with the advent high throughput screening technology, 3D manipulation of protein, molecular biology, etc. However, although the paradigm shift from natural products (bio based) to more synthetic pharmaceuticals (chemical based) could bring commercial success, it could be a major concern of environmental protection at the same time due to consuming huge amount of resources.

Apart from the new drug development, the research and development also focus on improving the existing drugs in the market. When the patent for the new drug expires (normally after 15-20 years from the patent date by the innovator), it becomes generic drugs. Generic drugs are those drugs that are produced by using the same formula provided by the originator (or, called branded manufacturer). This generic form can be also modified (using

exhaustive chemicals reactions and testing) over time either for lowering the manufacturing costs via modifying the manufacturing process or incorporating new substances to further develop.

Appendix 3 (b)

Drug Manufacturing Process

Drug manufacturing is a two-stage process which involves Active Pharmaceutical Ingredients (API) production and formulation. A drug contains two key ingredients: API and excipient. The API is a chemical or biochemical ingredient which has a therapeutic effect, whilst the excipients have no therapeutic effect but are necessary to ensure the final dosage form acts as intended (Plumb, 2005). There is a range of excipients available for usages, such as water, lactose, starch, sugar, colouring etc. Drug manufacturing is crucially sensitive as it involves huge raw materials and energy investments (Rees, 2011), so there is huge potential for environmental damage as well. API production stage involves a series of unit chemical operations (e.g., reaction, separation, purification, drying etc) to synthesize the active ingredient. Most of the operational units use considerable amount of varieties chemicals such as solvents, reagents, water etc. At this stage, a commercial process is developed based on the lab scale process provided by the R&D. The process design determines the manufacturing mode (batch or continuous), solvent recovery or recycling facility, material and energy balances, equipment types, capacity, plant layout, process safety etc and other related operational parameters for successful manufacturing (Rosas, 2005). In the formulation stage, APIs are mixed with excipients to produce a final dosage form such as Tablets, capsules, liquids, ointment etc. through some chemicals and mechanical process. Detailed drug manufacturing process is described below:

These two stages drug manufacturing is predominantly carried out in different plants and can involve multiples manufacturers. The manufactured API is shipped to a formulation plant for preparing the final dosage form or pharmaceutical products. However, some large research-based companies (e.g., AstraZeneca, Pfizer) may have their own manufacturing facilities for API production. Figure 2.7 shows a schematic view of Pharmaceutical products manufacturing process.

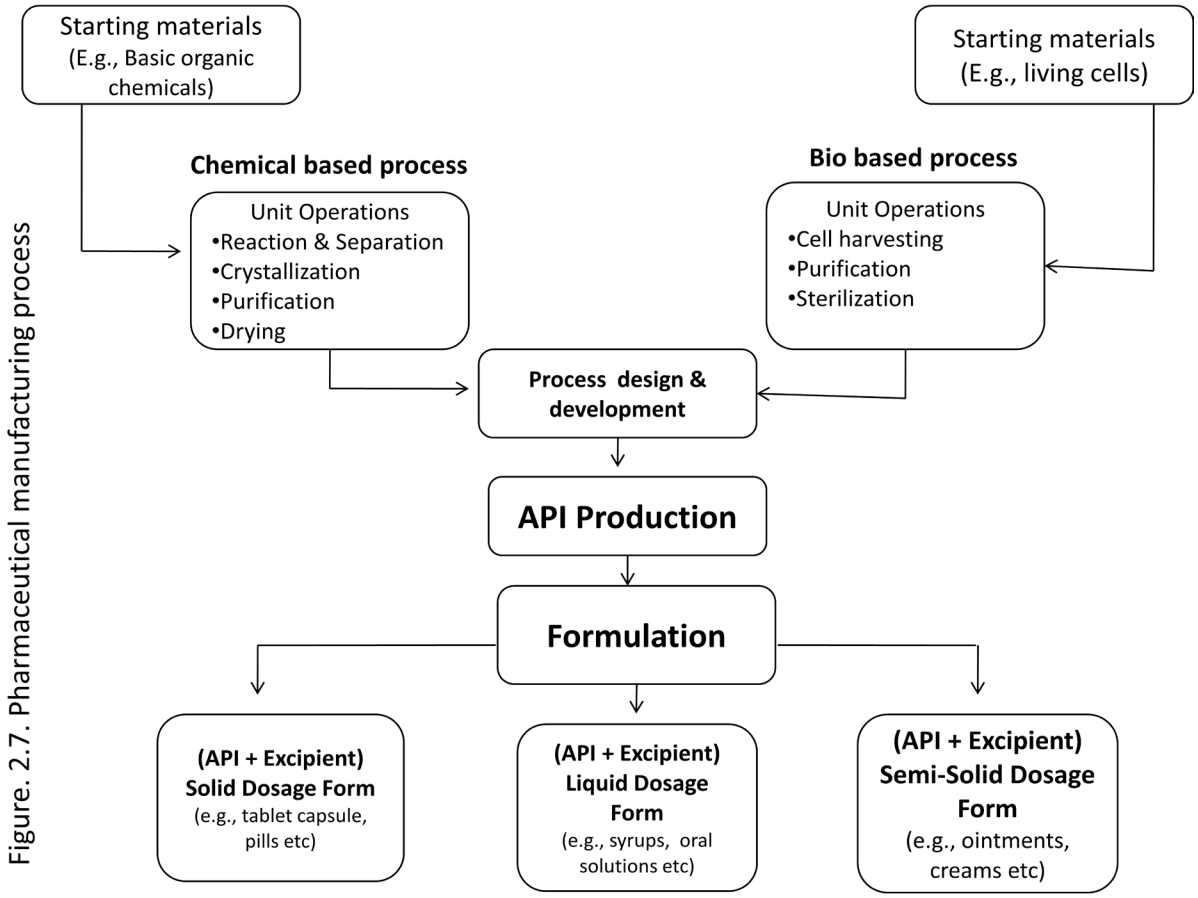


Figure. 2.7. Pharmaceutical manufacturing process

The API of drug can be either chemical based or biobased. It is assumed that the perceived environmental impact of bio-based drugs (Clark et al., 2010; Daughton and Ruhoy, 2010; Kummerer, 2009) is comparatively lower than chemical based one. The API production process involves a series of chemical synthesis having series of unit operations: reaction & separation, crystallization, purification and drying. For the commercial manufacturing purpose, the chemical engineers just scale up the process which was initially designed by the scientists and/or medicinal chemists in the lab. Consistent Quality, safety, efficacy, and stability are of paramount importance for each manufactured batch. In the reaction and separation stage, chemical reaction is occurred in a reaction vessel using varieties of chemical substances (e.g., solvents, reagents, reactants, waters, etc) or other necessary chemicals substances. It also involves continuous reaction by heating and/or cooling and separating materials from the reaction vessel as per the process requirements (Slater et al., 2010).

Crystallization is a process by which the solvents used in the reaction and separation stage are almost completely removed from the product by means of a solid substance. In this process solid is separated from solution. In pharmaceutical industry, crystallization is usually performed on a small scale from solutions. Crystallinity of a solid substance determines its

physicochemical properties and stability of a drug (Hickey and Ganderton, 2010). The main importance of crystallization is in the purification of the final product. A crystalline powder is easily handled, is sTable. Product purity and consistency are of paramount importance in the API production. Hence, it puts a great deal of pressure on the mastery of purification methods, mostly on those based on crystallization from solution (Rosas, 2005). To ensure appropriate purity and the desired crystalline form, a recrystallization step is performed in the final isolation of the product to ensure the bioavailability of the dug molecule or API. Though it incurs further cost, there are significant advantages. There are also some intermediate chemicals substances that are produced in each stage. In the drying process, water or other liquid is removed from the solution or different type of mixtures (Hickey and Ganderton, 2010). Drying improves handling characteristics and stabilizes moisture sensitive materials, such as aspirin and ascorbic acid. Sometimes milling, another unit operation for reducing the particle size of the final solid particulate, is done after drying.

In a nutshell, in a typical API manufacturing plant, a commercial chemical process is designed containing all or some of the above unit operations as per the product requirements. At the same time, it involves multiple decisions making on materials, energy, equipment choice, equipment size and material capacity, specific design problems, process safety, process technology, environmental safety, site location, plant layout, process to be designed in the existing plant or in new plant, process control to handle (highly exothermic) reaction which produce huge amount of heats, scale up, solvents selection, solvent recycling or reusing, adjust material throughput, manufacturing mode – batch or continuous, arrangement, etc.

In pharma process the ‘arrangement of equipment’ and ‘flexibility’ in the manufacturing process are important determinants for energy and material use. The arrangement of equipment can be seen in two extremes: ‘dedicated-specialised purpose’ which allows least flexibility and ‘non-dedicated general purpose’ which allows highest flexibility in arranging the process industry equipment (Abdullah, 2003). A dedicated process may be easier to manage with unchanging processing parameters, but it may not be the most cost effective or strategic (Mongiardo and Bobrow, 2005). A dedicated process is viable and ideal for a one-product organization or high-volume product. Non-dedicated or campaign style facility will allow the manufacturers to better utilize assets, integrating different product manufacturing using similar equipment configuration (Nusim, 2005).

In the formulation process, one or more APIs are mixed with a number of excipients followed by a number of physical manipulations (e.g., drying, size reduction, size enlargement, filtration and sterilization) to form a final pharmaceutical product or a final dosage form (Plumb, 2005). Figure 2.8 shows the formulation process in the pharmaceutical industry.

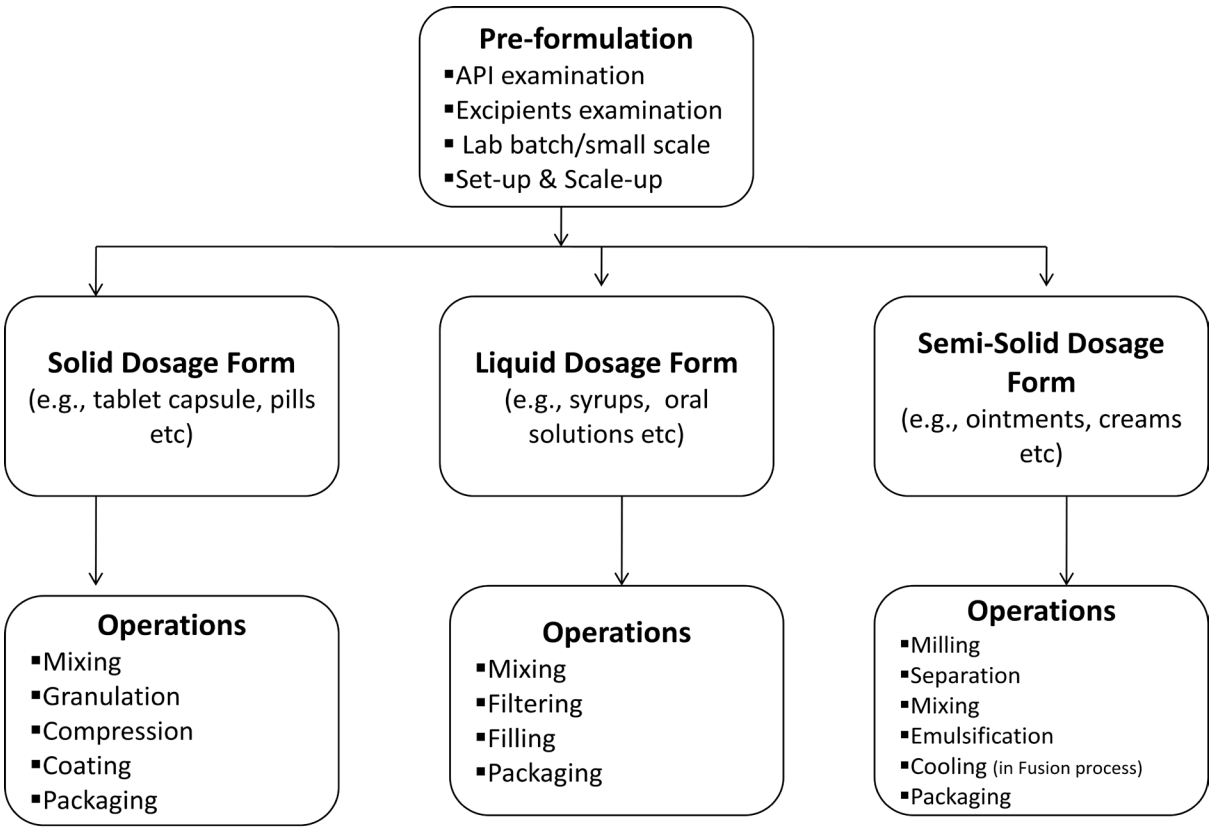


Figure 2.8 Formulation process in the pharmaceutical industry

Quality and stability testing of the API is important prior to start formulating dosage form as, they tend to react with drug components, other excipients, and also the packaging system (Chaudhari and Patil, 2012). Though there are different dosage or drug administration form (e.g., solid, liquid etc) exist, solid dosage like Tablet are predominant, i.e., 80% of the dosage form is Tablet (Conway, 2008; Sarantopoulos et al, 1995). A formulation manufacturing process also involves several chemical and mechanical unit operations depending on the dosage form produced. Figure 3.7 shows an overview of solid dosage manufacturing process.

Both APIs and excipients are weighed separately according to the formulation guidelines for perfect proportioning and get ready for blending. Almost any dosage form starts with mixing and blending the active agents with the inert excipients. This is one of the most basic of pharmaceutical unit operations, but it can be one of the most challenging to control as well.

This is because solid formulations contain multiple excipients (e.g., fillers, Tableting agents, disintegrants) to product quality, safety, and efficacy. Excipients from different vendors may behave differently due to their particle size and shape and other factors, and their tendency to form aggregates (Kemeny and Stuessy, 2012).

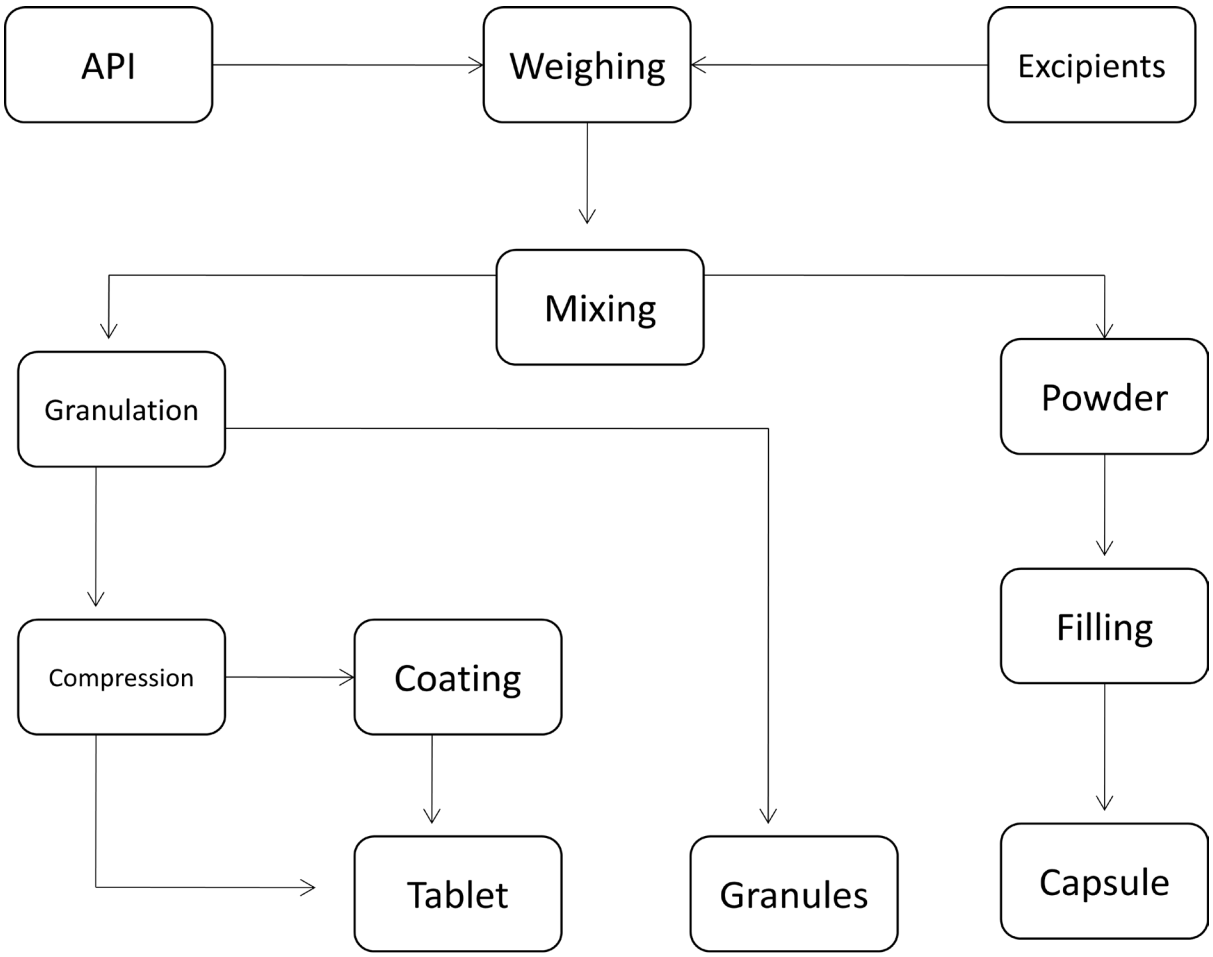


Figure 3.7. Solid Dosage Manufacturing process

For Tablet and pill, the blended materials go through the granulation process (in granulator) and sieving process which turns the materials into a mass of homogenous granules (Sarantopoulos et al, 1995). In granulation process, powder particles adhere to one another to increase the particle size and form agglomerates Granulation is important to increase the uniformity of the drug substances in a solid dosage and appearance of the drug. Wet and dry

granulations are the most widely used technique for the granulation of API and solid dosage formulation. More than 70% of Tablets are designed and developed using wet granulation technique. In wet granulation, the active ingredients and excipients are wetted with aqueous or solvent solutions to produce granules with enlarged particle sizes. The granules are then dried, mixed with lubricants (e.g., magnesium stearate), disintegrants or binders, then undergoes compression process into Tablets (Tait, 2017). Compression is a typical mechanical action by which granulated powder is compressed into Tablet. Depending on the Tablet types, Tablet may skip or go through the step of coating, colouring, and printing for identification purposes. Tablets may be coated for several reasons such as - to improve the appearance, for taste-and-odour-masking purposes, to protect the API from moisture, oxygen, or the gastric environment of the stomach (e.g., using acid-resistant coating), to control drug release etc (Siew, 2015).

Appendix 3 (c)

Drug distribution

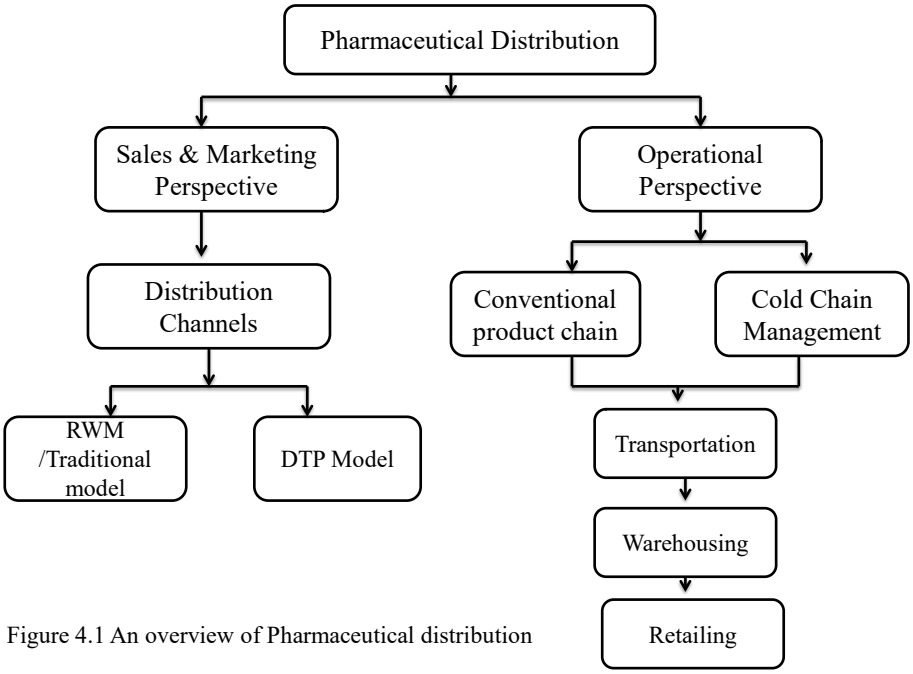


Figure 4.1 An overview of Pharmaceutical distribution

Sales and Marketing Perspective

In pharmaceutical distribution, the sales and marketing perspective is predominantly embedded with cost, time, and transparency. Cost reduction is continuously becoming an ongoing agenda due to have limited national budget on health service (Office of Fair Trading, 2007). While searching different marketing channels of pharmaceutical products in the existing literature, two distinct channels have been identified, such as RWM (Reduced Wholesaler Model) and DTP (Direct to Pharmacy) model (Kanavos et al., 2011; Chakrabarti et al., 2012; Gorecki, et al., 2012).

RWM Model - In RWM model of pharmaceutical distribution, pharmaceutical manufacturers use one or more (ideally up to 3) wholesalers in the traditional manner to distribute products (Kanavos, et al. 2011). In this traditional model, manufacturers sell to all wholesalers at a discount of 12.5 per cent to the manufacturer's list price, and the wholesalers would take title of goods. Thus, a transactional buyer/seller relationship between

manufacturers and wholesalers has emerged (Chakrabarti et al. 2012). As the wholesalers purchase the stock, they can offer a discount to the retail pharmacy. The discount will depend on volume purchased by the retail pharmacies but the average discount to the list prices is around 10.5 per cent (Office of Fair Trading, 2011). Though the origin of this arbitrary discounting practice is unknown, it has become a widespread convention that is vigorously defended by wholesalers. In this model, the wholesalers compete to become a principle wholesaler to a pharmacy. The retail pharmacies can select the principle wholesaler and secondary wholesaler based on amount of discount offer, delivery time, service levels etc.

The pharmaceutical wholesalers can be categorised into different types. There are two different types of wholesalers based on the range of products offered – full line wholesalers and short-line wholesalers. Full-line wholesalers are capable for supplying the entire range of prescription medicines (around 12000 lines). Hence, they are accounted for vast majority of sales to retail pharmacies. Short-lines wholesalers supply a limited range (around 2000 lines) of prescription medicines, particularly generics, parallel imports, and popular branded medicines. The full-line /short-line wholesalers can be further categorised as national and regional level.

Short-line wholesalers can be distinguished from full-line wholesalers by virtue of lower delivery frequency, smaller product range and lower prices which are made possible by lower costs (Office of Fair Trading, 2011). Retail pharmacies tend to have one principle full-line wholesalers for the primary source of drugs, and another full-line wholesaler as secondary source if any item is stocked out in the principle wholesalers. Some retail pharmacies may deal with only one full-line wholesalers along with one or more short-line regional wholesalers to meet their demand. In the UK, there are eleven full-line pharmaceutical wholesalers, and out of them only the largest three – UniChem, AAH and Phoenix – operate at national levels. The rest of the wholesalers are much smaller and operate on a regional basis.

DTP Model – In DTP model of pharmaceutical distribution, manufacturers sell direct to pharmacies and appoint one or more LSPs (Logistics Service Providers) who are paid a negotiable fee to deliver the medicines on their behalf. Under this scheme, instead of competing to supply pharmacies, wholesalers compete primarily to become a manufacturer's appointed LSP (Office of Fair Trading, 2011). Under this arrangement, the wholesaler never owns the stock and, consequently, is not able to offer any discount on it. Though majority of

pharmacy sales continue to originate from (full line) wholesalers, the proportion of pharmacy sales in the UK originating directly from the manufacturers has been significant over the past three years (Kanavos, et al. 2011). Figure 4.2 shows the possible channels that connect manufacturers with final consumers. Figure 4.4 has conceptualised both distribution models.

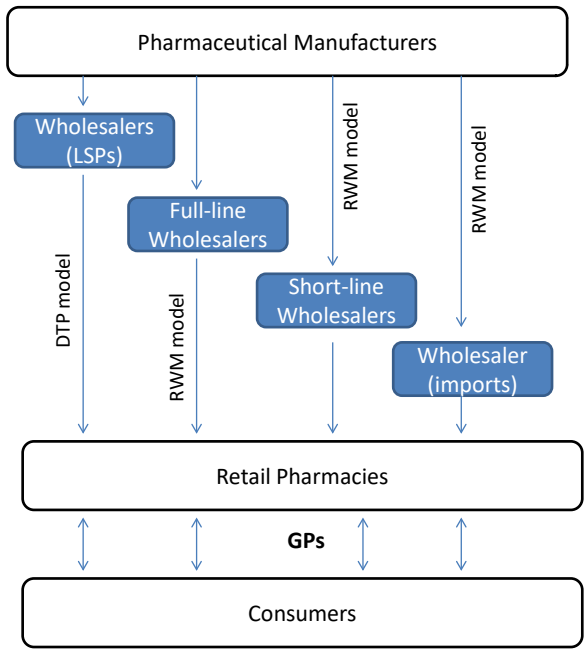


Figure 4.2 Pharmaceutical distribution channels

Pharmaceutical companies are continuously adopting DTP model due to the many benefits over the traditional wholesaler model, such as:

- ✓ DTP provides greater visibility in the supply chain.
- ✓ Control of brand image.
- ✓ Reducing counterfeit medicine.
- ✓ Efficiencies foe manufacturers.
- ✓ Closer relationship with suppliers.
- ✓ Under this scheme, Pfizer has appointed UniChem as its exclusive distributor (or LSP) and the company believes that it will be more responsive to stock-shortage or product recall situation; and will be able to predict end-user demand accurately and to match the production and distribution processes with end user demand (Office Of Fair Trading, 2011). Figure 4.3 below shows Pfizer's DTP model in the UK.

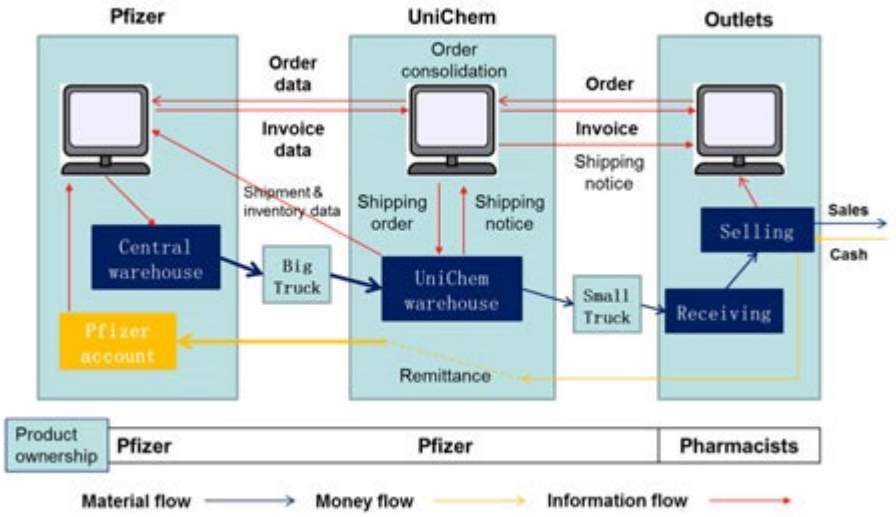


Exhibit 2: Pfizer's Direct-to-Pharmacy model in the U.K.

Figure: 4.3 Pfizer's DTP model. Adapted from Lacocca and Zhao (2015).

Figure 4.4 RWM / Traditional wholesale model and DTP model. Adapted from (Office of Fair Trading, 2011).

RWM / Traditional model

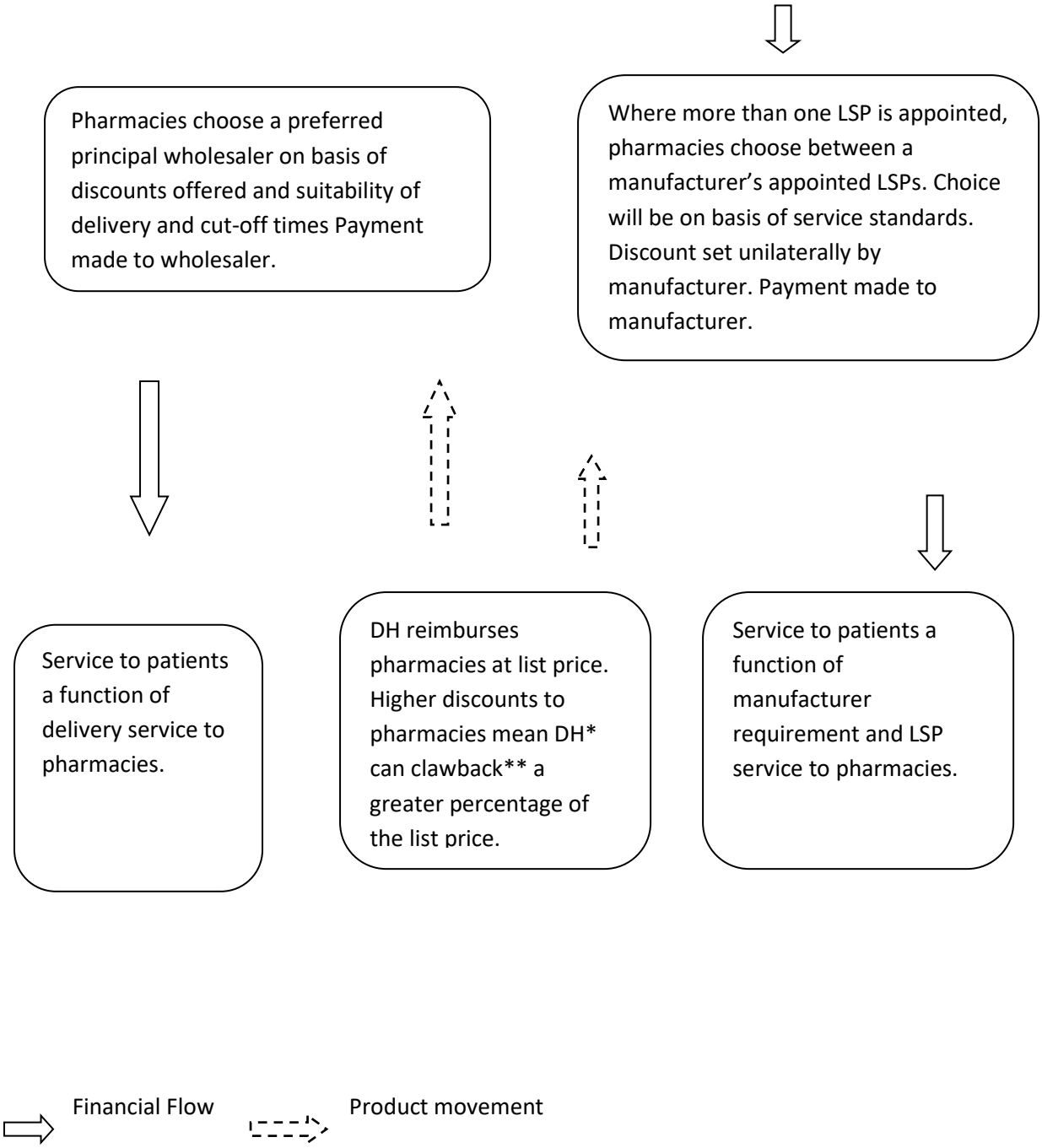
Manufacturers sell to all wholesalers at a discount of 12.5 per cent to the list price.

Wholesalers purchase branded medicines at a discount of 12.5 per cent. Wholesalers compete to become principal wholesaler to pharmacies. Competition is on the basis of discount and service standard.

DTP Model

Manufacturers specify the service level required from LSPs. Appointed LSPs are paid agreed sums for delivery. Manufacturers set the discount level offered to pharmacies.

Wholesalers compete to be appointed as a manufacturer's LSP. LSPs are paid delivery fees by the manufacturer. Service standard set by manufacturer. Where there is more than one LSP, they compete on service quality for pharmacies' business.



DH*- UK Department of Health

Clawback**- Clawback means that the NHS effectively pays less than list price for branded medicines; According to the PSNC (*Pharmaceutical Services Negotiating Committee)*, nationally the deduction is about 10 per cent of value at list prices

Operational perspective

Whilst sales and marketing aspects predominantly focus on cost, operational aspects of pharmaceutical distribution mainly focus on quality, efficacy, delivery time and environment. In pharmaceutical distribution, there are three core operational areas – transportation, warehousing, and retailing, which may have direct impact on product quality, efficacy, delivery, and environment. However, taking decision on each of the core operational areas could be significantly influenced based on whether they dealing with conventional product chain (where products are not sensitive to temperature and moisture) or cold chain management (where products are highly sensitive to temperature and moisture). In the conventional product chain, storage and transportation do not require any stringent arrangement such as cold packaging, temperature, and moisture monitoring devices etc, whereas the cold chain product requires them. The main characteristics and an overview of cold chain management have been presented in Table 4.1. However, product integrity is the top priority in both cases and, therefore it is mandatory to follow Good Distribution Practice (GDP), Good Storage Practice (GSP) guidelines throughout transportation and storage.

Table 4.1 An overview of Pharmaceutical Cold Chain Management

Definition	"Cold chain can be defined as the supply and distribution chain for products that must be kept within a specific temperature range" (Castiaux, 2010; pp19). The cold chain refers to the logistic system which is managed by the temperature sensitively from the point of origin to the point of consumption (Putri et al. 2012).
Sensitivity	A temperature sensitive drug may lose its integrity, stability, or potency if exposed to inappropriate temperatures within the supply chain.
Storage temperature	During storage and transport the drug temperature must be held between refrigeration temperatures of 2 to 8 degree centigrade. However, it varies from product to product.
Special transport and storage Packaging	The shipping requires temperature-controlled packaging such as insulated containers with the appropriate proven quantity of refrigerants (e.g., dry ice). The transport packaging solution for cold chain management is an ongoing

	innovation.
Monitoring	The temperature must be monitored thoroughly from warehouse storage facility to final retail storage via transportation storage including transits. Monitoring temperature in different stages of storage conditions during distribution is critical and challenging.
Common cold chain challenges	✓ Unproven Packaging System: If the packaging system has not been tested to perform under specific conditions – the shipper is open to a great deal of risks. ✓ Monitoring Temperature: Selection of a temperature monitoring device could be assessed against available device monitoring technology. ✓ Establishing Contingencies: Proactive planning in case of unplanned delay or rerouting.
Regulations	All storage and handling practices must follow GMP, GDP and GSP. WHO (2011) has provided a technical guideline for the storage and transport of time- and temperature – sensitive pharmaceutical products?
Cold Supply chain trend	Most shipments of biological drugs are transported via cold chain. It is estimated that the average growth of temperature sensitive products will be 15% per year and this growth exceeds that of the rest of the pharmaceutical industry (Castiaux, 2010). It has also been reported that biologics market share has been doubled in the past ten years and, it was projected that by 2016, eight of the top ten best-selling global drug products (and 83% of the top 10's revenue) will be biologics, requiring a 2 to 8 degree centigrade / do-not-freeze storage and handling regime (McBeath, 2012). Controlled room temperature (between 15 to 30 degree Celsius) products are also increasing.

Transportation

To serve a customer, pharmaceutical products are required to transport from one location to another location. Products can be travelled either long distance or short depending on the position of distribution centre from the customer. Hence, the distribution models of a pharmaceutical company will have a profound impact on its transportation system. A transport system can be established based various factors. For instance, Kam et al. (2006) have suggested that a transport system is composed of two sub-systems: Physical components

and a social system. The physical components include the vehicle (e.g., car, train, vessel, aircraft), the energy source (e.g., petrol, liquefied petroleum gas, diesel oil, electricity) and infrastructure (e.g., road, railway, airport, harbour). The social system includes the vehicle operators and organizations. Figure 4.5 shows the components of a transport system.

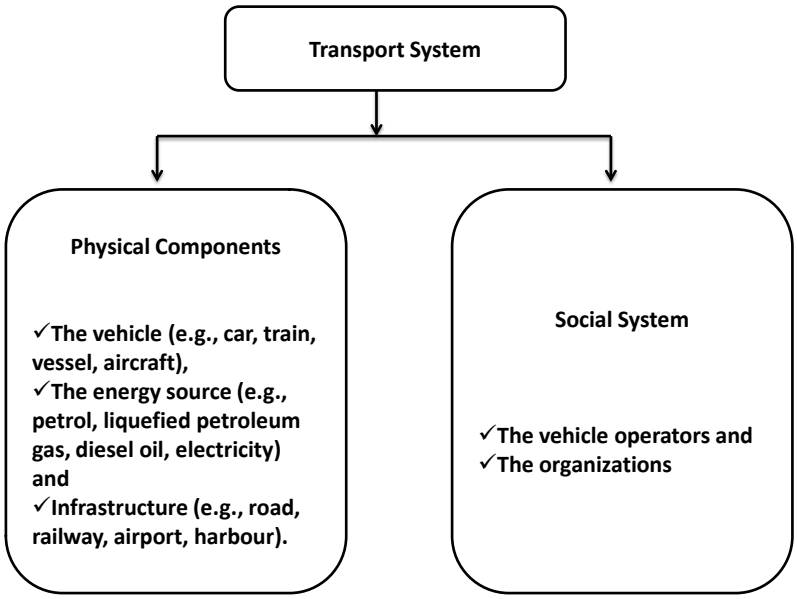


Figure 4.5 Components of a Transport system. Adapted from Kam et al. (2006)

The authors have further suggested that conceptually, the choice of delivery vehicles, the scheduling of deliveries, and decisions concerning frequency and mode of product delivery, and type of fuel to use represent company responses to the joint actions of three main sets of factors. The first factor relates to external influences, covering economic, political, social, and physical issues. These external influences set the stage and the context within which business entities operate. The second set of factors relate to company demographics, such as size and nature of business and internal policy environments The internal environmental elements include company's mission, long-term goals, competitive positions, and resource constraints along with other characteristics commonly examined under a SWOT (strengths-weaknesses-opportunity-threats) analysis. The final set of factor involves the state of available technology, enabling firm to select cost-efficient solutions from a technically feasible set.

While searching for pharmaceutical transportation system in the existing literature, the conceptual understanding is completely blurred and disjointed. Hence, an attempt has been made here to conceptualise the entire transportation system in the pharmaceutical distribution

process based on the researcher's own understanding and some disjointed efforts in the related industries. This effort has been presented in the figure 4.6.

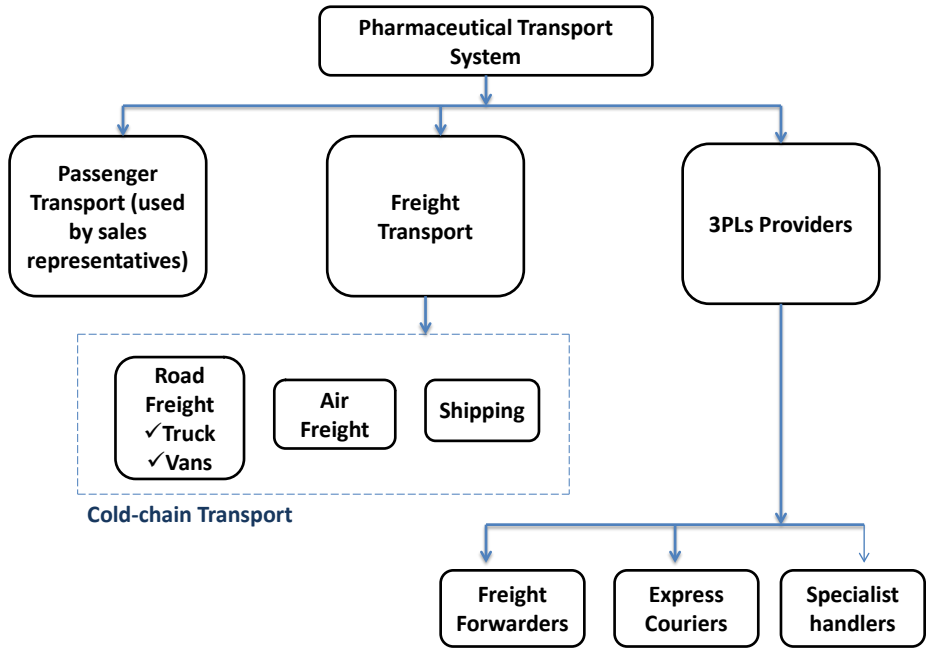


Figure 4.6 Pharmaceutical Transport System

Passenger Transport

It is vitally important that research companies need to ensure that any new medicines are brought rapidly to the attention of as many doctors as possible. This exercise is also done prior to promoting branded generic products as well. It has traditionally been done by using sales representatives who call personally on doctors to provide them with information. Major pharmaceutical companies have many sales forces whose only efficient means of transport is the motor car (Taylor, 2010). It was reported that AstraZeneca's 90% of business travels (by car) was associated with sales and marketing (AstraZeneca, 2008).

Freight Transport

Pharmaceutical companies have been sought to transport their products by using traditional freight transports such as the road freight (e.g., truck, vans etc), the air freight and more recently the shipping. The characteristic of each freight transport is presented below:

Road Freight (Truck): In pharmaceutical industry, they are used to travel long distance and across the border, and for carrying bulk products. The general features of truck below have been adapted from McKinnon et al. (2010).

- It carrying capacity depends on gross weight and dimensions of vehicles. The weight and dimension of these longer and heavier vehicles (LHVs) can be limited in some countries. But, in the UK there is no legal limit on vehicle height and clearances at most bridge and tunnels can accommodate trailers up to five meters high.
- The LHVs (body) can be made of either steel or aluminium.
- They are conventionally run by diesel fuel. However, engine and exhaust system of these LHVs are considering to be redesigned to achieve energy efficiency or reducing fuel consumption.

Road Freight (Vans): In pharmaceutical industry, they are used most frequently in the regional area to travel short distance, and for carrying a small number of products. Most of the features below have been adapted from McKinnon et al. (2010).

- They can be a wide range of styles, weights, and sizes. They can be categorized by gross weight as small (car-derived/ micro), medium and heavy vans. Table 4.2 shows these three categories.

Table 4.2 Summary of the typical size, weight, and fuel efficiency attributes of vans. Adapted from McKimmon et al. (2010).

Attributes	Small Vans	Medium Vans	Heavy Vans
Typical gross weight (tonnes)	Up to 1.8	1.8 to 2.6	2.6 to 3.5
Typical payload (tonnes)	0.4 to 0.8	0.8 to 1.2	1.2 to 2.0
Typical load space (m3)	1 - 3	4 – 8	7 - 17
Typical fuel Consumption (Litres per 100 km)	7.1 – 5.1	9.4 – 7.1	14.1 – 8.1
Example models	Vauxhall Corsa Citroen Berlingo Renault Kangoo	Ford Transit VW Transporter Renault Trafic	Ford Transit Mercedes Sprinter Iveco Daily

- Vans have a far wider range of uses than truck. It was reported that in the period of 2002-03 in Britain commuting accounted for 39 per cent of all van journeys, servicing for 23 per cent, goods collection and delivery for 22 per cent, and personal journeys for 16 per cent.
- A sizeable number of vans make use of auxiliary equipment including refrigeration, air conditioning, heating, pumps, fans, and power steering. The power source of these equipment is the vehicle engine.
- Van operators have extremely varying requirements in terms of load space, payload (carrying capacity in weight), vehicle length, and vehicle body requirements. For instance, vans used for carrying pharmaceutical products may require additional space due to special cold packaging and to set up temperature monitoring equipment.
- It has been reported that van traffic in the UK has been increased by 3.4%
- As business seeking to reduce stock level and to follow JIT, vans provide greater flexibility. It has also been reported that majority of vans are used for service industries and only around one-third for freight.
- Van manufacturers try to use lighter materials (for the chassis, body, and internal racking system) where possible to reduce tare (or empty) weight of the vehicle and hence maximize payload.
- Vans have been sought to deviate from petrol to diesel engine due to have greater fuel efficiency. It was estimated that diesel vehicles have a fuel economy advantage of approximately 20 to 40 per cent over petrol vehicles (EIA, 2009).
- Although a wide range of alternative fuelled vans is available such as LPG (Liquefied Petroleum Gas), CNG (Compressed Natural Gas), biofuels, and electric and hybrid vehicles, diesel users are predominant.

Air Freight: Pharmaceutical companies are highly dependent on-air freight due to the outsourcing nature of business across the globe, and to lessen the time to market. Pharmaceutical products have been identified as one of the top ten exports-imports categories between UK and EU (FTA, 2017). The frequencies in the outside EU are also significant. It has been reported that the growth of air-cargo services in general is predicted to accelerate over the next 20 years (McKinnon et al. 2010). Some of the features as below:

- Load consolidation in aviation reduces energy consumptions. Fuel efficiency can be increased by reducing weight of the airframe. The engine is mainly powered by kerosene fuel, though biofuel/kerosene blend is recently used for trial flights (Airbus, 2008).
- Although goods are travelling in the same passenger aircrafts, the passenger aircrafts are being converted into cargo operations to increase the carrying capacity.
- The belly-hold capacity of new passenger aircraft is also expanding to increase the cargo induced revenue. It was anticipated that the average payload weight will increase by a fifth, from 52.9 to 64.1 tonnes between 2006 and 2026 (Airbus, 2008).
- For the emergence of JIT philosophy and time-sensitive products, the cargo operations often must sacrifice load efficiency for service quality (McKinnon et al., 2010).

Shipping: Pharmaceutical companies have recently been strategically leaning towards shipping over air cargo. The industry has experienced many benefits over air cargo. However, it has been reported that 80% of the excursions (i.e., when shipments are not treated correctly) occurred in air freight, 1% on ocean and 18% by road (Lennane, 2014). The author has also reported that air freight is 78% more expensive per kilo than sea. This mode of shipping is also traditionally known as most environmentally friendly (Bode et al., 2002). Global leader in the pharmaceutical industry, AstraZeneca is expected to use more shipping service (Taylor, 2010). Some of the general features of this mode of transport have been highlighted from McKinnon et al. (2010):

- This mode of transport consumes low amount of energy per unit of freight movement. For instance, a 3700 TEU (Twenty-foot Equivalent Unit) container ship uses only 0.02 kilo watts to move one ton one kilometres as opposed to 0.06kWs for diesel powered rail freight, 0.18 kW for a heavy truck and 2 kW for air freight moved in a Boeing 747-400
- They are powered by petrol and diesel. Increased ship (carrying) capacity reduces fuel consumption per TEUs. It is further suggested that larger ships tend to be more sTable they require less ballast water and hence consume less fuel transporting this additional weight (McKinnon et al. 2010).

Cold-chain Transportation

It has been reported that temperature excursions account for $2.5 – 12.5 billion of pharmaceutical product loss each year, according to the International Air Transport Association (IATA), the Montreal based trade group that represents airlines (Shanley, 2016). In order to maintain the cold chain for time - and temperature - sensitive pharmaceutical products (TTSPPs) such as vaccines, insulin or other biologics, special cold packaging (according to the manufacturer's requirements and relevant GMP and GDP regulations) must be ensured prior to storing inside the transport. The required temperature must be maintained throughout the entire journey regardless of the type of transport used. The type of transport used (e.g., trucks or vans) may also have a required amount of cold and/or freezing storage capacity (or compatible with the products) and a continuous temperature monitoring equipment installed. Though it is not always mandatory or expected for the vehicles to have cold or freezing capacity, the mode of transport has to be compatible for storing cold packaged pharmaceutical products during transportation from point A to B and the carrier is made responsible for maintaining load temperatures within the transport temperature profile defined for each product (WHO, 2011).

To better understand and conceptualize the entire cold-chain transportation process, the discussion will follow a flow chart presented in the figure 4.7 below.

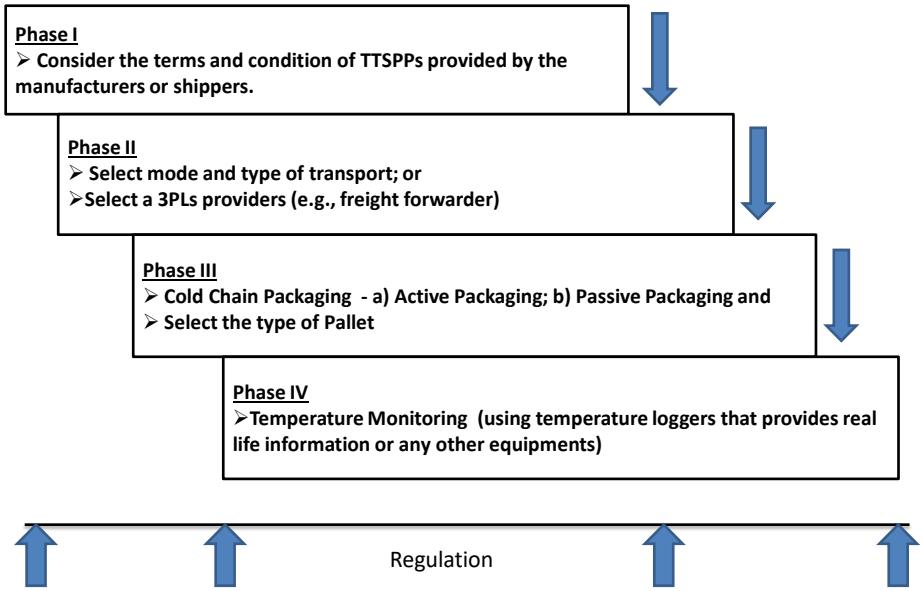


Figure 4.7 Sequence of operations in the Cold-chain transportation system

Phase I: In this phase the type of TTSPPs is assessed based on the temperature or other products handling requirements set by the manufacturers or shippers. Though some pharmaceutical products and specifically biological drugs are traditionally temperature sensitive, literatures show that temperature requirements vary from product to product. Additionally, some other factors such as light, humidity etc may be incorporated into it. Therefore, it is important to have prior knowledge about the requirements of the TTPPs. Table 4.3 below has attempted to presents some of the TTSPPs and their temperature and other handling requirements.

Table 4.3 Storage condition of some cold-chain products.

TTSPPs	Required temperature range	Other storage conditions	References
Biopharmaceuticals	Lower temperature	-	Shanley , 2016
Small molecule-based pharmaceuticals	Controlled temperature (15°F to 25°C)	-	Shanley, 2016
A dramatic increase in demand for storing product at ultra-low	Ultra-Low temperature: -40°C down to -196°C	-	Shanley, 2016

temperatures			
Cell – and gene – based therapies	at temperatures -238°F and below	-	Shanley, 2016
Biologic materials (e.g., blood, tissue, reproductive materials)	cryogenic temperatures (-150 °C)	-	Markarian, 2015
Clinical supplies	2-8 °C	-	Markarian, 2015
APIs	Deep frozen	-	Schmitz, 2016
Emulsion	Cool	protected from light, high temperature or freezing	Shafaat et al. 2013
Suspension	Cool (below 25°C)	Protect from heat and sunlight	Shafaat et al. 2013
Ointment	Cool	Protect from sunlight; kept in closed container to prevent the loss of volatile constituents	Shafaat et al. 2013
Syrup	Cool (below 25°C)	Protect from light and sun light; kept in dark place	Shafaat et al. 2013
Injection	Cool (below 25°C)	-	Shafaat et al. 2013
Insulin	Between 2 to 8 °C	Protect from moisture and light	Shafaat et al. 2013
Refrigerated Vaccines	Between 2 to 8 °C	-	Shafaat et al. 2013

Frozen vaccine	optimum temperature is (–15°C)	-	Shafaat et al. 2013

Phase II: The decision on choosing the mode and type of transport for shipping is multifaceted. Product integrity, supply chain visibility, cost, on time delivery, temperature monitoring equipment, refrigerating/freezing capacity of the vehicle, loading capacity of the vehicles, transport routes (modes and nodes), potential risks and mitigation strategies are few of them. However, Markarian (2015) has suggested that cost, temperature, and timing are all important in selecting the appropriate mode of transportation for a temperature sensitive shipment. It is suggested that prior to selecting the 3PLs provides it is vitally important to select the most experienced transportation provides who are up to date with the latest technology for monitoring temperature and capable of understanding the regulatory (GMP, GDP, GSP) requirements for handling cold chain pharmaceutical products (Catizone, nd).

Phase III- Cold Chain Packaging: Packaging is the key in cold-chain transportation. Inappropriate packaging or wrong materials used in packaging could damage the product integrity and efficacy. Decision on choosing a type of packaging (either active or passive) prior to transporting any TTSPP depends on the mode and type of transport chosen considering the relevant strategic options in phase II. For instance, stock packed for transport within a refrigerated van may not have thermal insulation whereas stock transported in non-refrigerated transport may be packed in an insulated box with ice packs (MHRA, 2015).

Before discussing different types of packaging options, it would be better to show different layers of pharmaceuticals packaging for the transportation purposes while the products leaving manufacturing warehouses or distributors warehouses. Figure 4.8 shows different layers of pharmaceutical packaging.

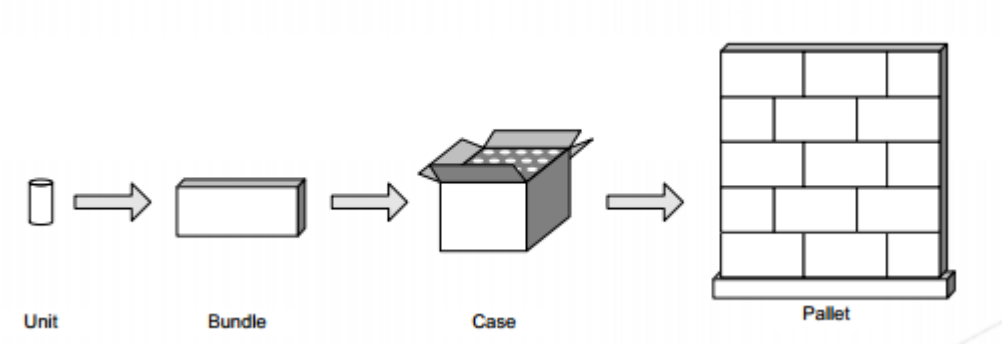


Figure 4.8 Layers of pharmaceutical packaging. Source: Holliday (2013).

The main features described in a whitepaper (Catizone, n.d.) of different cold-chain packaging systems are highlighted below:

a) Passive Packaging Container

- ✓ Passive packaging or passive shipping configurations are manufactured systems that are typically insulated with polystyrene, polyurethane[9] or vacuum insulated panels[10].

Figure 4.9 Passive packaging for cold chain transportation. Source: Google Image.

- ✓ It has been suggested that new form of PCMs (phase change materials) such as paraffin or salt-based solutions are also available. These PCMs allow for more precise temperature control to maintain product stability over long distances or through extreme climates (Shanley, 2016b).
- ✓ Many have been pre-qualified to hold a particular temperature for a certain amount of payload capacity for a specified period such as 24, 72, or 96 hours.
- ✓ With this configuration, the shipper creates the environment based on the manufacturer's exact specifications using gel packs or other types of phase change materials[11] to maintain the desired temperature.

[9] Polystyrene and polyurethane are polymeric (or plastic) materials that have good insulting property.
[10] A **vacuum insulated panel** (VIP) is a form of thermal insulation consisting of a gas-tight enclosure surrounding a rigid core, from which the air has been evacuated (Wikipedia).
[11] Phase change materials (PCMs) are those materials that can store heat within a narrow temperature range. Ice is an excellent PCM for maintain temperature at 0°C. However, PCMs have been developed for use across a broad range of temperatures, from -40°C to more than 150°C. (Source: http://www.puretemp.com/stories/understanding-pcms).

- ✓ Passive configuration can vary in costs, from very basic inexpensive polystyrene coolers to more complex configurations using phase change materials and vacuum insulated panels costing hundreds of dollars.
- ✓ Certain configurations have reverse logistics capabilities for reuse.
- ✓ They can be shipped anywhere for year-round use.

b) Active Packaging Container

- ✓ Active packaging system or active shipping configuration has built in cooling and/or heating system or may work using dry ice as a coolant and system to push cool air into the payload area to maintain a specific set temperature.
- ✓ They are termed as advanced temperature controls that are often powered by electricity and/or battery.

Figure 4.10 Active packaging container for cold chain transportation. Source: Google image.

- ✓ They are ideal for large shipments as they are generally designed to hold one or more pallets, though smaller units are also available.
- ✓ In case of temperature falls outside the range, batteries are replenished, or the system may have an added feature that enables it to be plugged in during a delay to maintain operation.

- ✓ No warehousing required since unit is typically leased, not owned.
- ✓ Highly secure and low risk of theft.
- ✓ Environmentally friendly and no need to dispose packaging.
- ✓ Cost effective when payload is maximised.

Pallet Type: As seen earlier pallet is of one of the final layers of packaging, where cases are piled together to form a pallet. To avoid confusion, here pallet is discussed as 'a packaging material' rather than 'a layer of packaging'. In pharmaceutical transportation and distribution, pallet (a plastic or wooden material on which all cases are stand and piled to form a layer of packaging) plays an important role for smooth and safety handling without compromising product efficacy. The pallet is used to enable the rapid, inexpensive movement of goods by making them easily accessible to mechanical handling (Connors, 2017). Three different types of pallets (wooden, plastic and metal) are used (figure 3.11).

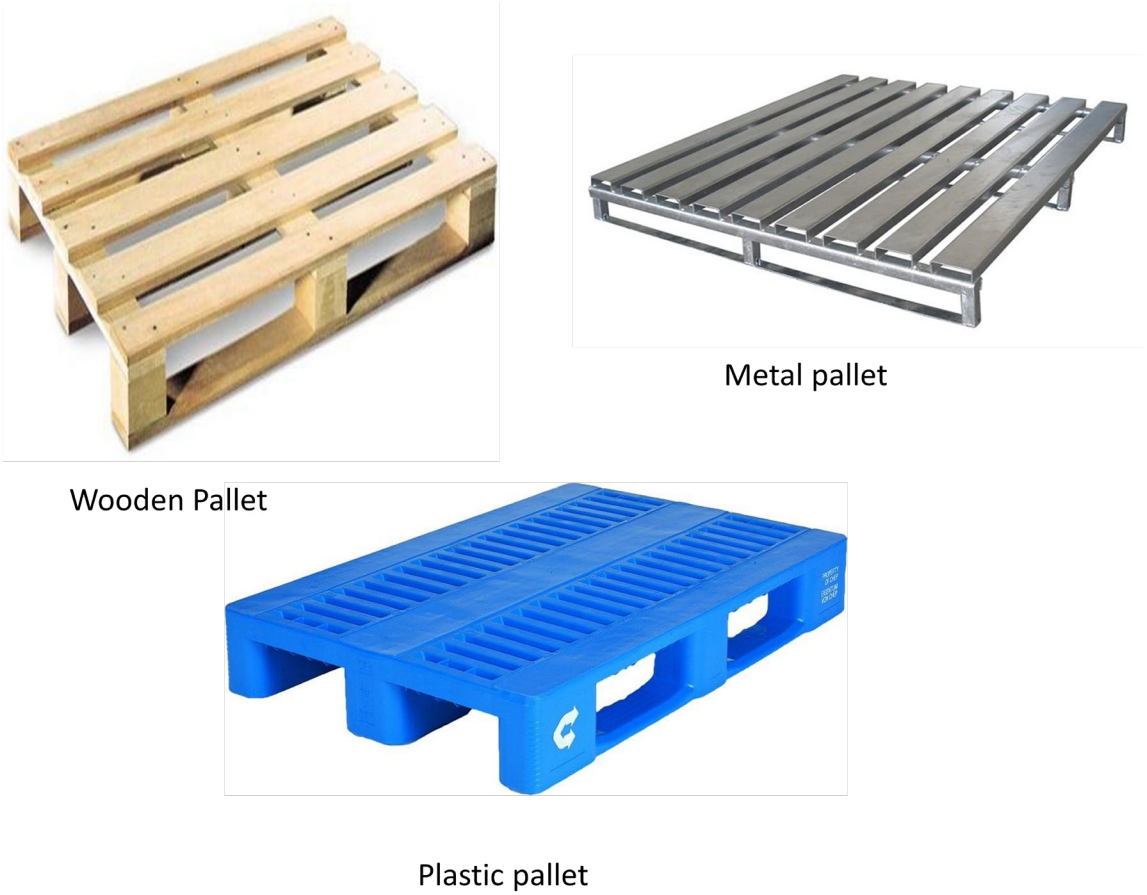


Figure 3.11 Types of pallet used in pharmaceutical transpiration and distribution

The invention of pallet is relatively recent and was introduced with a philosophy that palletised load could handle more goods with fewer people, freeing up men for military service (Hardisty, 2011). The characteristics of different types of pallets are significantly

important for product quality and efficacy. It is estimated that wooden pallets are dominant in the pharmaceutical market. However, it is mandatory to understand the features of these different types of pallets prior to selecting as a packaging material. Some of the features are highlighted below based on Connors, (2017) and Hardisty, (2011):

Wooden Pallets

- They pose the most challenges to sanitation.

- Possibility to be damaged by handling equipment.

- The absorptive nature of wooden pallet allows for bacteria growth. That is, water absorbed into a wooden pallet can become a breeding ground for bacteria and microorganism.

Plastic Pallet

- They are primarily made of Polyethylene.

- Plastic pallets can be readily washed and disinfected, making them ideal for the support of a clean, contaminant-free manufacturing environment.

- It provides low friction between the pallet and the product it is carrying.

- More costly than wooden one but it provides long time cost savings (because it lasts 10 – 15 times longer than wooden one).

- Burns hotter than wood in the event of fire.

Metal Pallet

- They are normally constructed from metals such as aluminium and stainless steel.

- Easy to sanitize, and resist contamination build up.

- Costly but it provides long term cost savings (because it lasts 10 – 15 times longer than wooden one).

Phase IV- Temperature Monitoring: This is the final operational strategy in cold-chain transportation management. Continuous temperature monitoring of the TTSPPs from the source to destination is the most crucial operational part of cold-chain transportation management. It has been suggested that regardless of the packaging system chosen companies should always employ some sort of temperature monitoring device (Catizone, n.d.). Now the concern here is that what types of temperature monitoring equipment are

available and what are the points of monitoring in the cold-chain transportation process. The Table 4.4 below presents available temperature monitoring devices and their features.

Table 4.4 Temperature monitoring devices in cold-chain transportation.

Type of Device	Features	Reference
USB-enabled	Data is gathered by a drive that is connected to a USB port in the temperature monitoring device. Upon delivery it is removed from the device and connected to a computer's USB port	Catizone, n.d.
GPS-enabled sensor	Designed for real-time track and trace capability. through custom-designed software that monitors, records, and reports on location, temperature, motion, shock, exposure to light (i.e., when the box opens), atmospheric pressure, and remaining battery life	Shanley, 2016b
New types of RFID, such as ISO 18000-6C Class 3 battery assisted passive	The device can be put into the inner carton before it is sealed at the factory, so that the temperature is monitored all the way from source to final destination without having to open or unpack the carton. The RFID reader can automatically read which drugs were delivered and their temperature history, and then transmit that information via a cloud-based service to the manufacturer and other interested and authorized parties	McBeath, 2012

However, it has been suggested that getting forensic and historical data at the end of the supply chain only document waste, rather than preventing it (McBeath, 2012). Hence, the author has urged to monitor temperature on carton-level. Figure 4.12 has demonstrated different level of temperature monitoring. It has been suggested that monitoring should be done as close to the products itself as is practical and affordable. In practice, monitoring is done at one the levels below:

- Vehicle/container interior
- Pallet exterior or interior
- Case or carton exterior

Figure 4.12 Potential Temperature Measurement Points in Typical Pharmaceutical 'Packing Hierarchy'. Adapted from McBeath, (2012.)

3PLs Provider

Recent research has shown that temperature-controlled transportation is identified as one of the top three pharmaceutical supply chain issues which require attention (LogiPharma Research, 2015). The research has also outlined that pharmaceutical companies are predominantly dependent on third party logistics providers and this trend will continue soon. Pharmaceutical companies normally use freight forwarders, express couriers, and specialist handlers for transporting their products. Some of their features have been highlighted from Rees, (2011).

Freight Forwarders

- They typically deal with larger shipments using a range of transport modes.
- They tend to offer value-added services that lighten the load for those engaged in administration. This could involve raising customs documentation, clearing goods through customs, settling duty and tax deferments and payments, and arranging additional forwarding.
- Freight forwarders offer a cost-effective solution for large consignments that require less specialist handling.

Express Courier

- They have been well known on moving smaller quantities of goods quickly
- They run their operation based on hub and spoke system, whereby there is a present network through which all shipments must travel
- Hubs are set up at strategic locations around the world.

Specialist Handlers

- They are called specialist shippers such as World Courier, Marken, Yourway Transport, and Life-Con, which has emerged in recent years around the needs of companies engaged in clinical trial supplies
- They are specialised in handling TTSPPs. For instance, they can get into the airport facilities to re-ice shipments that need top-up of dry ice due to an unexpected delay.

Relevant Regulation

While searching for good distribution practice (GDP) related regulation specifically cold-chain transportation relevant, many different guidelines have been identified for using across the globe. This is, however, particularly important to understand both export and import countries' laws and customs for moving pharmaceutical goods across the borders. Owing to the main focus of this study it outlines the 'UK Guidance On Wholesale Distributions' (as part of cGMP) which covers two relevant areas – a) Control and Monitoring of Storage Area, and b) Transportation of Cold Chain Goods. Two additional guidelines by WHO are also widely recognised. Table 4.5 below summarizes them.

Table 4.5 Cold-chain transportation related regulations

Guidelines	Cold-chain transportation relevance
Current Good Manufacturing Practices (cGMP): 'UK	a) Control and Monitoring of Storage Area, and

Guidance on Wholesale Distributions'	b) Transportation of Cold Chain Goods
WHO Technical Report Series, No. 908, 2003	Guide to good storage practices for pharmaceuticals
WHO Technical Report Series, No.961, 2011	Model guidance for the storage and transport of time – and temperature – sensitive pharmaceutical products.

4.2.2.2 Warehousing

A pharmaceutical warehouse is a commercial building for storage of pharmaceutical products under specific conditions (e.g., temperature, humidity) specified by the manufacturers. Warehouses can be used by the manufacturers, wholesalers, exporters, importers, logistics service providers (LSPs). They can be small to large based on the demand and location such as national or regional level distribution. The entire pharmaceutical warehousing operations are composed of four distinct functional areas – receiving, storage, picking and packaging, and dispatch. The storage process includes different types of racking and shelving. The storage area is temperature and humidity controlled. Figure 4.13 shows different functional areas of a Pharmaceutical warehouse.

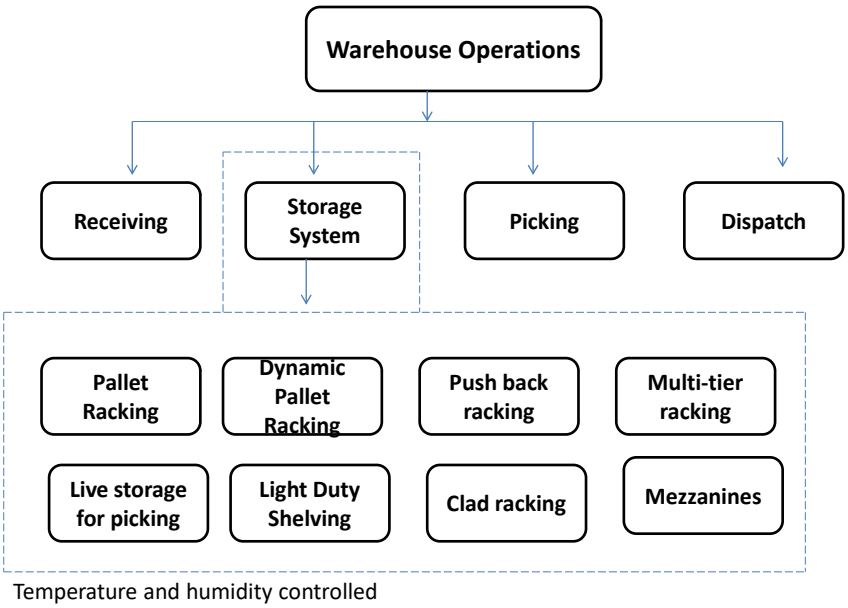


Figure 4.13 Pharmaceutical warehouse operations

Receiving Doc:

Pharmaceutical cartons delivered on pallets are arrived in the warehouses and unloaded in the receiving doc after a quality check. Each pallet is then scanned to keep and update the stock keeping unit (SKU) information in the Warehouse Management System (WMS), and then move them to the designated storage area (according to the product categories) using automated roller conveyor system. In case of small warehousing where the automated conveyer is not installed, the products pallets can be carried on using internal transport.

Storage System

Depending on the size, access to available technology, investment, geographic location, type of whole sell (e.g., full-line wholesaler/short-line wholesaler), and types of SKU (e.g., fast moving drugs), different types of storage systems (or racking/shelving system) have been sought to install in the pharmaceutical warehouses, such as pallet racking, live storage for picking, light-duty shelve, push-back racking, dynamic pallet racking, drive in pallet racking, mezzanines etc. Each of them has specific features for achieving storage and handling efficiency. Some of their features are highlighted below: (most of the features are demonstrated from the ATOX website – www.atoxgrupo.com)

Pallet Racking

- Racking is designed for the storage of palletised products with a wide selection of products.
- The layout of this type of warehouse is conditioned by the characteristics of the trolley or lifting resources and the height of the warehouse.
- Direct access to products. Perfect for working with a wide selection of goods.
- Easy stock control.
- Adapts to any space, size, or product weight to be stored.

Dynamic Pallet Racking

- In this type of storage system, racks for the storage of palletised products which incorporate a roller path with a slight slope for moving the pallets.
- This movement occurs by the action of gravity.
- Optimal for perishable products. FIFO: first in, first out.

- Improved handling times.
- Better use of space. No aisles needed between pallets.
- No risk of damage to the structure.

Push back racking:

- System designed to build storage for palletised products which requires a fair degree of rotation.
- Pallets are sitting on wagons which can be moved by pushing.
- Better use of space.
- No aisles needed between pallets.
- Improved handling times.
- No risk of damage to the structure.

Multi-tier Racking

- Manual storage system that provides optimum use of height and warehouse space.
- Aisles with different levels in height accessed by stairs.
- Direct and safe access to each load level.
- High aisles and stairs to make the most of your space.

Live storage for Picking

- This type of storage is used when there is a need for high density storage of the same items.
- Palletised or containerised goods are stored on a gravity fed roller storage system that sits in a framework of pallet racking or shelving. The system offers the options of either loading and unloading from one side (LIFO - last in, first out) or loading from one side and retrieval from the other side (FIFO - first in first out).
- Dynamic pallet racking and Push back pallet racking are under this storage system.

- Carton live storage is also under this system where the system works on the same principle as pallet live or push back racking with goods stored in cartons or totes.

Light Duty Shelving Units

- This type of storage is used for very low turnover products. This type of system facilitates the classification of products and the picking of orders. In this system, the operators of each sector crisscross the aisles assigned to them to pick the items from the shelves and place them into the order picking container or tote (Mecalux Case Study-1, n.d).

Clad racking

- In this system the structure of the building is formed by the racks themselves and the outer cladding is coupled to them. For the structural design of a clad-rack warehouse, the weight of the racking is considered (Mecalux Case Study-2, n.d).
- Large storage capacity at high altitude.
- Execution time and cost maximisation without any need for prior building construction.
- Control and security of the stored products.

Mezzanines

- These can double or triple premises floor space by making the most of the height of the warehouse.

- Multi-tier shelving with an integrated mezzanine floor is ideal when a large picking area is required, with limited floor space (Dexion Report, n.d).

- They provide translucent spaces by using the shelving as a support.

- Doubling or tripling of premises floor space.
- Possibility of mounting a closed office on the mezzanine.
- Easy assembly.
- Design fits all needs.

Temperature and Humidity Mapping

It is a regulatory requirement to mapping temperature and humidity of warehouses for environmentally sensitive life science products. Consequently, pharmaceutical warehousing facilities are confronted to shifting their philosophy from quality-by-test to quality-by-design (Vaisala, 2012).

It is apparent that temperature and humidity may vary within different storage space with different racking system installed in different locations of warehouse. This temperature variation leads to product damage and wastes and significant financial loss. This variation in temperature can be based one:

- Layout of racks, shelves, and pallets which obstruct airflow.
- Temperature gradients between the cooler floor and warmer air near the ceiling.
- Location of HAVC control system.
- The capacity of diffusers or fans to adequately circulate air.

Therefore, it is vital that the risky area in the warehouse where temperature deviations occur will need to be identified and determine the sensor location and distribute them accordingly in a mapping process. It is suggested that a walk-in chamber or small warehouse is often mapped in three dimensions with 15 sensors where distance between sensors is no greater than 6 meters (Vaisala, 2012). In case of a large warehouse, sensors can be set as far as 60 meters apart with additional sensors in vulnerable areas affected by drafts from loading docks, heat or cold from external walls, solar heating from windows, heat generated from artificial lights, air circulation from traffic or the HVAC system, temperature extremes in poorly insulated areas, localized effects of space heaters and air conditioners, and drafts from typical warehouse activity (Vaisala, 2012). Humidity sensors could be distributed as few as one for every six temperature sensors. Vaisala (2012) recommends nine points process for successful mapping of a warehouse or other regulated storage space:

I. Create a validation plan
II. Identify areas at risk
III. Develop protocol information
IV. Determine sensor distribution
V. Select suitable technology
VI. Set up mapping equipment
VII. Conduct test and review data

VIII. Make modifications

IX. Document and schedule mapping tests

Picking and Dispatch

Picking system can be involved both fully automation or manual or the combination of them depending on the racking system installed in a typical warehouse. Picking is controlled by the Warehouse Management System (WMS). Operators are assigned to a specific picking zone or aisle. When an order is received it can be processed by automatic picking and packing. It is also possible that upon receiving an order the LED sensors are flashed out as an indicator for the operator to pick that product case from the rack and put them on automatic conveyer belt for moving to dispatch area. It is important to note that products are also stored in tote (rather than on palletised case) which can travel along the conveyer whenever needed to pick. While picking from light duty shelving, a RF enabled scanning device is used to scan and pick the required product from a storage tote and put them into a shipping tote. Batch picking is recommended in the pharmaceutical warehouse (Daxion Report, n.d.). The shipping tote is then passed on to the despatch area using conveyer. The lead sealing machine is used to seal the tote. Manual case and carton packaging are also available as well. A typical warehouse stores and handles thousands of totes and other packaging materials.

Retailing

Retail pharmacies either chain or independent, hospital pharmacy and clinics purchase drugs from wholesalers and sometimes from the manufacturers directly. These retailers play an important role especially for generating demand both for generic and over the counter products through interacting with physicians or patients. The technical knowledge flow is maintained between pharmacists and physicians on daily basis, which may also have a great impact on generating demand for products. Repeat prescriptions from these retailers can be another major source of demand (deterministic). Retailers also work closely with both wholesale distributors and manufacturers for smooth inventories and product recalls when necessary.

Community pharmacists, previously known as chemists, are part of NHS family. It is estimated that everyday about 1.6 million people visits a pharmacy in England (PSNC, 2017). They provide varieties of services across the nation. The entire operations of a community

pharmacy or any retail pharmacy may have several functional areas as depicted in figure 4.14. Some of the operational perspectives outlined here are based on a personal communication with a Pharmacy Technician in London, UK.

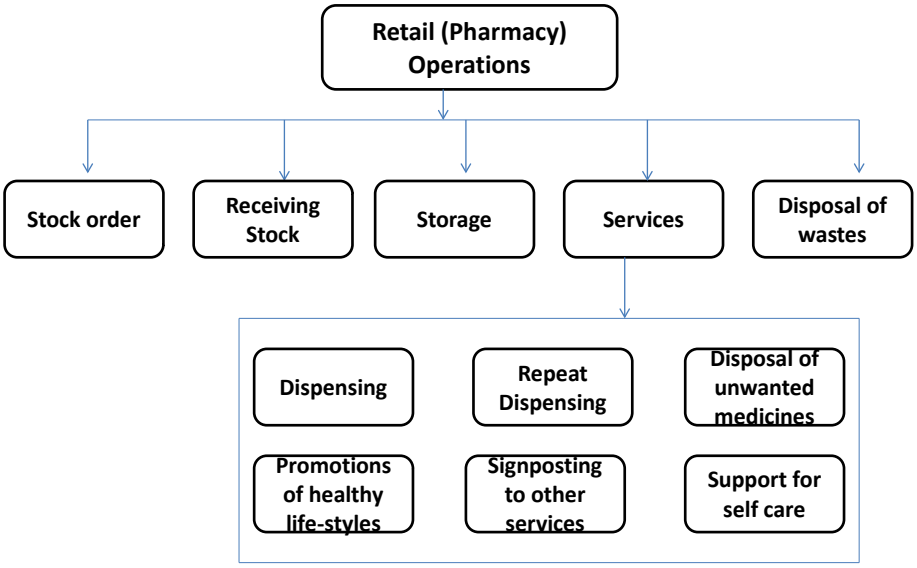


Figure 4.13 Functional areas in a retail (pharmacy) operations

Stock Order:

- Both manual and computer-based inventory controlled. A retail pharmacy normally uses integrated system software provided by an IT solutions provider. This system software connects a retailer with a pull of suppliers to manage the stock efficiently.
- It is a normal practice for a small retail pharmacy that when a prescription is being processed (prior to dispensing a particular medicine) using the system software the system automatically asks if the operator wants to order the dispensed item and can save it to process them at the end of business day.
- Retail pharmacies always try to keep the fast-moving drugs in stock, such as, Amlodipine, Lansoprazole, Omeprazole, Atenolol, Paracetamol etc. In general, they order slow moving drugs only when they receive a prescription for it. Short expiring date medicines are used first to maintain the stock rotation.

Receiving Stock:

- Quality of the case/carton/items is visually checked if there is any damage while receiving incoming stock. Expiry date, price, correct label, and quantity are also checked. Unexpected items are retuned.

Storage

- In retail pharmacy, majority of shelving or racking systems are manual, though some of them are installing automatic storage racking. In both cases, the incoming boxes or cartons are disassembled to shelving. The temperature-controlled drugs are kept in refrigerator under specific conditions.

Services

PSNC (Pharmaceutical Services Negotiating Committee) has outlined the major pharmacy services as below under the NHS Community Pharmacy contract.

Dispensing and repeat dispensing service: Depending on the type of prescriptions prescribed by the GP, dentists or nurses, the pharmacists are responsible to provide the patients with correct labelling. They also process repeat prescriptions which are normally processed and dispensed in a specific interval as instructed by the GPs. Some of them may be processed and packed into a special box (which is termed as 'Dosette box') for disabled people or those with special requirements.

Disposal of Unwanted Medicine: The local community pharmacy takes any unused medicines from the patients for safe disposal.

Promotion of Healthy Lifestyles: This service provides advice on keeping healthy; this could be advice on healthy eating, stopping smoking and exercise.

Signposting to other services: Local community pharmacy provides patients with contact details for additional help if needed from other healthcare professionals, social services, or voluntary organisations.

Support for self-care: Pharmacy also provides people with advice on treating minor illnesses, e.g. coughs and colds or long-term conditions such as arthritis or diabetes. They also support people to buy medicines which are available over the counter from the pharmacy without a prescription.

MURs (Medicine Use Reviews): An MUR is a consultation between the pharmacist and a patient to discuss how the patients use their medicines and to find out more about them. This service is useful to reduce the medicines wastes.

New Medicine Service (NMS): It has been reported that people who have received first prescription for asthma, lung conditions, type 2 diabetes, high blood pressure, and controlling blood clots, between 30% to 50% of prescribed medicines are not taken by those patients as recommended (PSNC, 2017). NMS can help to control over this wastage through finding out more about the new medicines they are taking, associated problems they are having, their concern about new dosages etc.

Disposal of Wastes

Like dispensing and stoking pharmacies follow SOPs (Standard Operating Procedures) for disposal of unused medicines from the customers or in-house expired medicines. Unused, expired medicines and related packaging materials are reserved into specific recycling bins. Either local councils or 3PLs collect them for safe disposals (e.g., recycling or incineration according to the class of drugs). In case of CD (Controlled Drug)[12], they must be disposed under the supervision of either pharmacist or other responsible person.

[12] CD (Controlled Drug) - Some prescription medicines are controlled under the Misuse of Drugs legislation (and subsequent amendments). These medicines are called controlled medicines or controlled drugs. Examples include: morphine, pethidine, methadone. (NHS, 2015).

Appendix 4

Key Pharma Regulation

Good Laboratory practice (GLP)

GLP guidance ensures that the designated inspector should inspect the facilities that carry out non-clinical studies (e.g., drug discovery: target identifications, lead identifications, lead optimizations etc) for submission to domestic and international regulatory authorities to assess the safety of new chemicals to humans, animals and environment (MHRA, 2015). This inspection is based on and in line with relevant EC directives. The program is only open to the UK facilities and run by the UK GLP Monitoring Authority (UK GLPMA). However, an extended guidance must be followed if any part of the drug developmental works is outsourced. The monitoring inspection involves key three areas: a review of GLP quality system, an inspection of facilities, and an audit of competed and on-going studies (MHRA UK Gov, 2014).

The focus of quality assurance is that the test facility management should establish a mechanism to confirm that their quality assurance programmes comply with the requirements of GLP, and the quality function should comply with established policies and procedures. Test facility management must also ensure that a well-defined SOP (Standard Operating Procedure) is produced and followed as per the GLP requirements.

Among other tests, GLP also sets to conduct environmental fate and environmental toxicity test. The facilities that conduct discovery / laboratory based chemical testing should provide with a test to demonstrate the impact of the testing chemicals (test item) through the status of biodegradation (most commonly) in soil, sediment and sewage sludge – i.e., soil metabolism studies, plant metabolism studies and fish bioaccumulation studies (MHRA GLP Guidance, 2015). The guidance also requires the laboratory facility to conduct (either laboratory based or non-field studies) environmental toxicity studies for the testing chemicals. It should provide with the studies that determine the toxic effects of the test item on aquatic (fish, daphnia, algae etc) and terrestrial organism (earthworm, bees, beneficial arthropods etc).

Good Clinical Practice (GCP)

GCP ensures that the designated person should inspect clinical trials for compliance with good clinical practice which provides assurance on the rights, safety, and well-being of trial subjects. It also assures that the results of the clinical trials are credible and accurate (MHRA, 2014). The GCP is a well-designed and internally recognized ethical and scientific quality requirements that must be followed when designing, conducting, recording, and reporting clinical trials that involve people. Ideally, the inspection is done based on risk-based compliance program. They can be either system based or trial specific. In the case of the system-based inspection, the inspector examines the entire system applied by an organization to conduct clinical trial research. The inspector will select several trials to assess how the organization's trial process are applied and whether or to what extent they are in line with the GCP guidance. In the case of trial specific GCP inspection, the inspector assesses clinical trials that have been completed and reported. As each organization is given a risk assessment score, and inspections are prioritised for the organizations with the highest risk assessment score.

Good Manufacturing Practice

As per EMA (The European Medicine Agency) the requirements for GMP are three folds:

- Medicines are of consistent high quality
- Medicines are appropriate for their intended use and
- The medicines meet the requirements of the marketing authorization or clinical trial authorization.

The GMP guidance in the UK follow the guidelines by EMA. The guidance has divided into three core areas: Part -1 – Basic requirements for medicinal products (see Table 1 below), Part – 2 – Basic requirements for active substances used as starting materials and Part – 3 – GMP related documents. The guidance has also special focused on different types of specialised formulations (e.g., manufacture of sterile medicinal products, manufacture of radiopharmaceuticals, manufacture of herbal medicinal products, manufacture of liquid, creams, and ointments etc).

Table 1: Basic requirements for medicinal products (Adapted from MHRA, 2014)

Key Focus of the GMP	Key Basic requirements
Pharmaceutical Quality System	- GMP applies to lifecycle stages from the manufacture of investigational medicinal products, technology transfer, commercial manufacturing through to product discontinuation. - Facilitate innovation and continuous improvements - Requires site-specific risk management - Product and process knowledge is managed - Drugs are designed and developed in such a way that takes account of the requirements of good manufacturing practice - Manufacture, supply and use of the correct starting and packaging materials - Effective monitoring and control system for process performance and product quality - Product and process monitoring is done on batch wise - Necessary controls on intermediate products - Planned changes in process and their regulatory approval - Root cause analysis in the case of quality deviation, suspected products defects, and related problem - The pharmaceutical quality management system should be defined and documented. - Instruction and procedures (e.g., in the form of SOPs) must be clear
Personnel	- Must have an organizational chart showing the interrelationships between roles (e.g., how head of production interacts with quality control) - Senior management is responsible to ensure an effective quality management system is in place to achieve quality objective by employing the right people in right place with right knowledge and experience
Premise & Equipment's	- Allow appropriate premises of production so there is minimal to none risk of contamination of products - Premises are maintained, cleaned, and disinfected as per the detailed written procedure - Working and in-process storage are kept avoiding confusion and contamination - Specific provision is taken when dust is generated (e.g., during sampling, weighing, mixing, and processing operations, packaging of dry products) to avoid cross-contamination - Highly active materials and products should be stored in safe and secure area - Equipment should be installed in such a way as to prevent any risk of error or of contamination. - Repair and maintenance works should not present any hazards

Key Focus of the GMP	Key Basic requirements
Documentations	- Two types of documentation to manage and record GMP compliance: instructions (directions, requirements) and records/reports. - Batch documentation must be kept for at least five years after completion - For each product batch to be manufactured, a detailed approved written manufacturing formula and processing instruction should be in place. - Detailed stage wise processing instruction (e.g., checks on materials, pre-treatments, sequence for adding materials, critical process parameters such as time & temperature etc) - BPR (Batch Processing Records): it should be kept for each batch produced. Similarly, a batch packaging record is also produced. - The procedure for sampling for quality purpose must be in written format. - The process of testing any materials (in any stages of manufacturing) must be in written format
Production	- All incoming materials must be checked as per the order / specifications. - All materials and products must be stored in appropriate conditions established by the manufacturers - Address the scope of cross contamination and proactive measures to reduce it. Unexpected cross contamination may occur from uncontrolled release of dust, gases, vapours, sprays or organisms from materials and product in process, from residues on equipment, and from operators' clothing. - Any significant change in production process or formula (e.g., change in raw materials, or change in equipment which may affect product quality) will require revalidation of the changed process. - Only those materials which have been released by the quality control department should be used - The reprocessing of rejected materials and products will only be accepted if the quality of the final product is not affected, if the specifications are met, and if it is done in accordance with a defined and authorized procedure after evaluating of the risks involved.
Quality controls	- Sampling, specifications, and testing: Adequate facilities, trained personnel, approved procedure are in place for sampling and testing starting materials, packaging materials, intermediates, bulk, and finished products. - Test methods must be validated - Batches of products are only released for sale when the Qualified Person certifies to do so - Review of supply chain traceability of active substances and packaging materials

Key Focus of the GMP	Key Basic requirements
	- A review of all batches that failed to meet established specifications and their investigations - A review of the stability monitoring program and any adverse trends - Quality risk management procedure in place
Outsourced activities	- There must be a written contract between the contract giver and the contract acceptor which clearly establishes the key responsibilities (e.g., clear demonstration of quality management system for each batch produced) for each party - The contract giver is responsible to ensure process are in place to assure the control of outsourced activities. - The contract acceptor should not subcontract to a third party any part of the works assigned and entrusted to him. - The contract should allow the contract giver to audit outsourced activities

Good Distribution Practice (GDP)

The key aim of GDP is to ensure that a pharma wholesale distributor maintains the minimum standards to ensure that the quality and integrity of medicines is maintained throughout the supply chain (EMA, 2019).

As per EMA guidelines (2019) the compliance with GDP ensures that the medicines in the supply chain are authorised in accordance with European Union (EU) legislation. It also ensures that the medicines are stored in the right conditions (e.g., time and temperature) at all time throughout the supply chain. It also ensures unexpected cross contamination from other materials or products or other microorganisms. The GDP also ensures that there is a well-defined procedure (e.g., a tracing system in place) to deal with product recall process.

The GDP guideline also applies to the sourcing, storage and transportation of active pharmaceutical ingredients and other ingredients used in the production of the medicines (EMA, 2019). The key highlights from the GDP guidelines (2013) as below:

- The wholesale distributors must maintain a quality system outlining responsibilities, processes, and risk management principles in relation to their activities. The quality system should entail the organizational structure, procedures, process, and resources. The quality system should also extend to incorporate the control and review of outsourced activities related to the procurement, holding, supply or export of medicinal products.

- The premises should be such that the storage conditions are maintained thoroughly. The area should have adequate lighting to enable all operations to be carried out accurately and safely.
- Receiving and despatch bays should protect products from adverse or any unexpected weather condition.
- Appropriate and approved cleaning agents and equipment should be used to avoid cross contamination.
- Key environmental factors (e.g., temperature, light, humidity, and cleanliness) must be considered in the storage area.
- The temperature monitoring equipment (e.g., temperature logger) should be placed in such a way so there even distribution and control of temperature.
- To avoid temperature excursion related wastes and / or contamination, an appropriate alarm system should be in place to provide alarms when there are excursions from pre-defined storage condition.
- The equipment repairs, maintenance and calibration operations should be carried out in such a way that the integrity of the medicinal products is not compromised.
- Medicines should be storage and handled in such a way as to prevent spillage, breakage, contamination, and mix-ups.
-

Good Pharmacovigilance Practice (GVP)

GVP ensures the ongoing safety of drugs while they are in the market. GVP is a well-defined system considered by the marketing authorization holder of a drug to fulfil its legal tasks and responsibilities in relation to the continuous monitoring and assessment of risks (e.g., adverse reaction, unexpected side effect etc) from the authorized drugs. Some key highlights from the practice are as below (EMA, 2019):

- A well-defined process for cooperation between marketing authorization holders, competent authorities, public health organization, patients, healthcare professionals, learned societies and related other bodies as per the legal provision.
- A well-structured process must be in place for related resources and tasks allocations, which will ultimately support the proactive, risk-proportionate, continuous, and integrated conduct of pharmacovigilance.
- It is vital that the marketing authorization holder monitor the safety profile of the drugs continuously and evaluate the benefit-risk of the authorized drugs

- Schedule, prepare, submit, and assess the periodic safety of the drug product in an ongoing fashion.
- Routine pharmacovigilance inspection: produce individual case safety reports, follow up and outcome recording.

Appendix 5

Pharma Green Practice Model

Key green practices	Materials related	Energy related	Toxicity related
Green drug design and development	✓ *Design and develop manufacturing process to use greener substances* ✓ *Design and develop drug discovery process to reduce chemical-based testing* ✓ *Design process to consume less raw materials by applying process metric (e.g.., PMI)* ✓ *Design and develop drug manufacturing process for flexibility in quality (Quality by Design* ✓ *Design packaging for material efficiency* ✓ *Design combined drug (e.g., use multiple active substances) for material efficiency*	✓ *Design and develop manufacturing process for least energy consumption by evaluating alternative process* ✓ *Design and develop manufacturing process by installing and validating energy efficient equipment system (e.g., reaction vessel)*	✓ *Design and develop bio-based drug process to reduce water toxicity* ✓ *Design and develop drug process to reduce air toxicity*

Key green practices	**Materials related**	**Energy related**	**Toxicity related**
Green drug manufacturing	✓ *Run continuous mode of manufacturing* ✓ *Recycle and reuse solvents* ✓ *Consider lean operations for materials reduction* ✓ *Consider green collaboration for materials efficiencies*	✓ *Consider energy efficient technologies* ✓ *Consider energy management program*	✓ *Consider greener chemical (e.g., solvent/reagents etc) management* ✓ *Monitor and control environmental toxicity of drug substances (eco-pharmacovigilence)* ✓ *Consider responsible waste management for toxicity reduction*
Green drug use-and-disposal	✓ Consider lean operations for optimized prescribing, dispensing and usages ✓ Consider digital technologies for optimized prescribing, dispensing and usages	✓ Energy efficient refrigeration system and temperature control ✓ Energy recovery from drug incineration process	✓ Safe and responsible disposal management of unused and expired drugs ✓ Consider greener wastewater treatment options

Appendix 6: Findings on Materials related green drug design

Design pharma packaging for material efficiency

As revealed in the study, pharma packaging plays a crucial role to protect the product integrity and stability during storage and distribution. It was also evident in the investigation that while the selection of packaging raw materials is highly sensitive (especially primary packaging system) to product quality, pharma companies have sought to employ four key green considerations (see Table 4.4 below) during the R&D phase to save materials and related resources.

Table 4.4 Key green consideration during packaging design (Source: Interviews and Reports)

- ✓ Design and /or re-design pack size
- ✓ Consider renewable packaging materials
- ✓ Consider recycled packaging materials
- ✓ Consider life-cycle impact of packaging

These green aspects demonstrate the scopes of considering green packaging materials, especially in secondary and tertiary packaging design. The study clearly reveals that these green aspects have great potential to reduce materials and related energy efficiency in the case of final API packaging and/or final formulation packaging. The majority of the innovative pharma respondents interviewed have mentioned that they have adopted these practices, whereas very few of the generic, and no bio pharma have adopted it. The study also reveals that pharma primary packaging involves using bottles, blister packs, vials etc; for secondary packaging it uses cartons, leaflets etc; and for tertiary packaging it uses shipping boxes, pallets and shrink wrap etc. Each of these four key green packaging related design practices is explored below:

Design and /or re-design pack size

The investigation of interviews and reports found that the majority of innovative pharma have redesigned the primary blister pack to reduce volume, weight, and thickness of the packaging. The interviewees and reports revealed that resizing blister packs can reduce significant amounts of plastic foil consumption, by simply increasing position of the maximum number of tablets on each foil blister strip. Some innovators have also highlighted in the report that

resizing of packaging is also done by developing more nano technology-based drugs, as it significantly reduces the drug shape and size. It was also reported however that the design also ensures that the drugs are not losing their functionality and stability. For instance, one of the leading innovative pharma (In-02) reported that it has resized its antibiotic packaging system which has increased the number of tablets from four to six without hampering the product's functionality and stability. The report has also outlined the importance of this design saying that – "***we reduce our foil consumption by 30% and overall pack size by 25%. This ultimately resulted in a reduction of 155 tonnes CO2- equivalents emissions since July 2012, as well as cost and efficiency savings for us".*** A similar design concept was also outlined by one of the respondents interviewed from an innovative pharma (B-site 1) for reducing aluminium foil consumption in the manufacturing phase.

Consider Renewable and recycled packaging materials

It was also evident in the study that some leading innovative pharma companies have undertaken many sustainable packaging initiatives to optimize packaging systems for material and related energy efficiency improvement. For instance, one of the leading innovative pharma (In-03) has reported that it conducts environmental sustainability assessments of packaging materials prior to manufacturing and especially in the product design and development phase. The company further highlighted three measures by which it has been able to reduce resource consumption. The measures are: *reduce packaging size and materials used; switching to materials from recycled or renewable sources; and using materials that can be easily recycled*.

It was also revealed in the study that some innovative (as well as some generic) pharma companies consider recycled materials in secondary and tertiary packaging. For instance, one of the leading innovative big pharma (In-01) reported how recycled packaging materials have been used to induce significant materials and related energy efficiency performance. It has reported that one of its products (e.g., Norvasc's) folding cartons were made from recycled cardboard. This packaging system uses a typical cardboard (commercially termed as GD2) which is made from recycled wood pulp rather than using mechanical pulp (commercially termed as GC2), which is the current standard packaging for the pharmaceutical industry. It further highlighted the key environmental benefits– "***The process for making GD2 cardboard uses one-third less energy, two-thirds less water, produces half the carbon dioxide emissions and costs slightly less than GC2".***

Similar design attempts have also been revealed by some generic pharma. For instance, one of the leading generic pharma (Gn-04)has reported using a sustainable packaging system. It further explains that it has replaced plastic drums with paper fibre drums in the case of one of its drug products (e.g., Omeprazole) manufacturing. This greener replacement results in significant energy reduction and related emission - approximately 490 tonnes of CO2 emission per annum as reported.

Consider life-cycle impact of packaging

Some of the innovative pharma companies investigated have also considered the life cycle impact of packaging in the early package design phase. The majority of them have considered water, energy, and emission impact. The key life cycle stages that are being considered are production, distribution and disposal phases. It was also found that a few companies are using in-house built life cycle inventory data while a few others rely on external data sources (e.g., third party companies who provide life cycle inventory data to their clients) to identify alternative greener packaging options. For instance, it was evidenced in the interviews (e.g., respondent from A; B-site 2) that companies have already started examining, storing, tracking, retrieving and managing life cycle data from some of the existing product portfolios prior to designing a new packaging option. Another respondent from a leading innovative pharma (D-site 2) has also highlighted that the considerations of LCA are high on the agenda prior to designing and selecting a new product packaging option. This was also evidenced in the reports.

However, the study also revealed that building a reliable and robust life cycle inventory database is the key challenge for life cycle impact assessment. What also emerged from the investigation is that being an intellectual R&D process, manufacturers are conservative to share related (material / energy / emission) information in most of the cases. Additionally, a number of innovators have also highlighted that there is a concern of the consistency of the external LCA database. Hence, the study reveals that pharma companies rely on multiple data sources (external journal or industrial publications, commercial databases etc) to build their own life cycle inventory data. For instance, one innovative pharma (In – 05) highlighted that it undertook several LCA studies since 2012 to compare the environmental impacts of various aluminium-based blister packaging options using their in-house built LCA tool.

Design combined drug (e.g., use multiples active substances) for material reduction

The study reveals that some companies reduce usage of raw materials by designing a drug with a combination of two or more existing APIs in the market. It was further evidenced that the innovative pharma sector, in particular, invested in designing this typical combined drug for some complex diseases such as HIV/AIDS, diabetes, and cardiovascular disease for providing effective therapeutic benefits as well as environmental sustainability benefits. For instance, one of the innovative companies (In-08) has reported that a medicine (called SYMTUZA) for HIV treatment was designed for a combination of four different APIs in a single tablet formulation. Each bottle of SYMTUZA is now replacing four bottles of individual medicines, each of which contains only one of the four active ingredients. The company has further outlined that this combined design has resulted in a 27% raw material reduction in drug product manufacturing, and a 72% primary packaging reduction, and a 60% reduction in water usage needed to clean the equipment in the drug product manufacturing process.

It was also found that the practice is still not common in generic and bio pharma companies. For generic pharma costs of development of such combined drugs is the key barrier, whereas manufacturing complexities are the key burden for biopharma. A number of interviewees agree that the key driver for developing such combined drugs for innovative pharma is to lower the R&D developmental timeline as well as reducing R&D costs. The respondents have also highlighted that it is also comparatively easier to obtain regulatory approval for such combined drug as the existing scientific data (e.g., safety and efficacy) on APIs are already established.

For instance, one of the respondents (C), a senior principle environmental scientist from a leading innovative pharma, explained that in general whilst a new drug R&D costs half a billion to one billion dollars, the combined drug development needs only between 10 to 15 million dollars. The respondent also highlighted that materials and related costs savings are also achieved via reducing patient drug non-adherence apart from the actual materials savings from combined drug manufacturing. However, the investigation also reported one of the key challenges to manufacturing such combined drugs as the physical and chemical incompatibility among the selected APIs mixed.

Appendix 7: Application of AI in drug design and development

Laboratory Information Management System (LIMS)

In addition to other AI and advanced technologies highlighted above, Integrated Electronic Laboratory program or Laboratory Information Management System (LIMS) and automation in lab quality testing have also emerged in this investigation, both in the interviews and the reports. The study (predominantly from reports analysis) reveals that the electronic laboratory program consists of automated data capture for lab measurements, electronic notebooks, and a streamlined resource management tool. Both reports and interview evidence suggest that some of the bio pharma and generic pharma have highlighted that this system not only helps R&D scientists and chemists to streamline process materials but also ensures lab safety, efficiency, effectiveness on waste reduction and compliance in line with GMP. For instance, one of the leading bio pharma (B-18) reported that designing into this tool has significantly reduced the usages of thousands of millions of paper documents for each process development. Another generic pharma (Gn-09) has also outlined and stressed the installation of LIMS for material efficiency in the R&D laboratory.

Automation of lab quality testing

The investigation (both interviews and reports) reveals that installing an automation system in lab quality testing has significantly saved analysis time and chemical usage in the R&D laboratory, especially in the innovative and bio pharma R&D process. The majority of the interviewees agreed that the quality testing (in terms of safety, efficacy of the promising drug substances) of key chemicals (e.g., API, excipients and intermediate chemical substance) in the R&D labs is a time consuming and materials exhaustive process. However, as per the reports, few of the innovative and bio pharma have realized that automated instrumentation design in the process accelerates the testing process with accuracy and reduces unnecessary samples wastes. For instance, a biopharma company (B-18) has outlined that the quality automation (designed into the process) that replaced the old manual quality testing has reduced the analysis time by 75 percent and 80 percent materials reduction. Additionally, it was further reported that while the traditional manual quality testing requires 1 to 2 litres of chemicals per sample, the new automation requires only 250 ml of chemicals for quality testing.

Appendix 8: Green solvent selection and related evidence

Now, the question is how companies select green solvents. The investigation further reveals that the chemists and developmental scientists have been using an ***in-house solvent selection guide*** to select greener solvent and avoid the solvents of environmental concern. The study further reveals that as the usage of solvents is amplified during the commercial manufacturing phase and the scope of changing solvents during the manufacturing phase is nearly impossible due to costly and time consuming regulatory (re)-validation of the process, designing drug processes using green solvent in the early R&D phase is the key to success. Given the key importance of considering green solvents in early drug R&D process development, the leading innovative pharma companies have sought to develop in-house solvent selection guides for the R&D scientists and chemists. For instance, one of the leading innovative pharma (In – 03) reported that they have developed a solvent database where each solvent is ranked as red (not recommended), yellow (recommended) and green (highly recommended) based on health, safety, environment, and process operationalizing data. Process scientists and chemists are guided to strictly follow this solvent selection guide, as revealed by some respondents participated from innovative pharma.

Depending on the type of application of each solvent (e.g., as coating spray or cleaning agent or drug synthesis etc), business needs, costs and the culture of organization, different companies (e.g., In – 01, In – 02, In – 03, In – 11) have produced different solvent selection guides. They also follow slightly different methods of solvent ranking and consider different selection criteria. For instance, while company In – 01 focuses on developing a database of a number of solvents based on lifecycle data, company In – 03 is not currently considering the lifecycle data of the solvent due to data unavailability but is considering other environmental data provided by the suppler, such as carbon footprint and solubility in water. As per the investigation, it was evident that most of the innovative and bio pharma companies, and some of the generic companies, follow the ACS GSCI pharmaceuticals roundtable's guidelines for the design process to use greener substances. This guideline has provided some key solvent selection criteria. The key solvent selection criteria that are being considered (more or less) by the industry are shown in Table 4.8.

Table 4.8 Solvent selection criteria (based on environmental assessment) across the industry (Source: Interview, reports).

- ✓ Carbon footprint (not lifecycle) of the solvent production
- ✓ Biodegradability of the solvent (e.g., whether they are soluble in water or miscible)
- ✓ VOCs profile while apply
- ✓ Ease of recyclability of the solvent
- ✓ Carcinogenic property
- ✓ Ozone depleting potential
- ✓ Renewable source of solvent

However, some interviews from innovative and some from bio pharma have further revealed that solvent selection is still a qualitative process and requires continuous consultation with stakeholders involved, such as chemists, medicinal scientists, process engineers, and downstream waste vendors, to select a green solvent. For instance, one of the respondents (c) from a leading innovative pharma outlined that the company has been using a 'solvent avoidance database' to reduce the use of hazardous materials in the manufacture of their drugs. The respondent further elaborated on the topic by saying: ***"... ... so we have a safety health and environment kind of trigger process; kind of look at green decision making in every point in drug development processes, in the manufacturing development, in the process development of drug... ..."*** Examples of some listed green solvents and the solvents with high concern found in the study are presented in Table 4.9 below.

Table 4.9 Examples of some green solvents commonly used across the industry and examples of Highly Hazardous solvents that were commonly avoided (Source: Interviews and reports).

Solvent selection	
Examples of Green solvents commonly used	**Examples of Highly Hazardous solvents commonly avoided**
Water Acetone Ethanol Ethyl acetate Isopropyl acetate Methanol	Diethyl ether Benzene Chloroform Carbon tetrachloride DCE

Though small in size, some generic companies had also developed solvent selection guides to help their R&D teams to select green solvents. The guide was used by the formulation scientists, process engineers and process scientist for selecting a priority solvent or reagent based on their toxicity indication on the database/solvent selection guide. For instance, it was reported by one of the generic pharma (Gn -04) that they used ethanol over methanol in the process as ethanol is less toxic than methanol. This solvent selection database was also used in quality testing for reducing environmental toxicity, as explained by the respondent. Some other respondents from generic pharma also highlighted that usage of toxic solvents in commercial manufacturing increase production costs significantly due to the treatment and disposal of these toxic by-products. So, designing a process to use greener solvents through using a appropriate solvent selection guide / database is a key environmental success factor.

However, some bio pharma companies found it difficult to follow solvent selection guidance to select greener solvents, as some hazardous chemicals are essentials for R&D work. For instance, a respondent from a biopharma (J – 1) mentioned that though they had some precautionary principles to avoid toxic chemicals in the process they did not have any formal solvent selection database. The respondent also outlined that though they tried their best to use chemicals which are less toxic, it was not always so easy because some chemicals are toxic and there is no alternative to using them.

Appendix 9: Findings on Toxicity (air) related design activity

Redesign R&D process equipment settings to curb VOCs

The investigation also reveals that the drug R&D process frequently produces VOCs due to usage of organic solvents, especially during HPLC operation. HPLC is a common process of separation and purification of an intermediate drug substance within a drug design and development process, as was discussed in the reports. It was also highlighted in the reports that VOCs negatively impact both human health and the environment. In particular, it indirectly increases GHG emission. Therefore, the companies (especially innovative and bio pharma) have designed their R&D process (specially the HPLC process) in such a way so there are no or less VOCs emissions. To deal with emitted VOCs from the process, both innovative and bio pharma companies have stressed the importance of equipping the HPLC and waste hood with special absorbing filters which can retain VOCs rather than releasing

them into the atmosphere. For instance, remarkably, one of the Bio pharma (B -08) reported on how to deal with ozone depleting GHG gas, such as VOCs (volatile organic compounds) emitting from the R&D process activities. It reported that a significant proportion of VOCs is emitted during a liquid chromatography (HPLC) process. So, to stop this emission they have redesigned the entire HPLC process and considered a typical absorbing filter to absorb VOCs from the process rather than to emit into the environment. They also replace all of the high potential ozone depleting substance such as fluorocarbons containing equipment with lower impact substances such as hydrofluorocarbons (HFC) and non-fluorocarbons (NON) from the HLPC process, which do not have an ozone layer depletion effect. Additionally, one of the respondents from a bio pharma (I) also outlined that the typical HPLC design (considering lower greenhouse potential impact substances) also reduces the run time. But it is more costly due to the regulatory approval process. Compared to bio pharma and innovative pharma, again, though generic pharma uses HPLC process frequently, they had not sought to consider this green design aspect.

Appendix 10: Findings on materials related green drug manufacturing practices

Consider lean operations for material reduction

Like other industries, whilst lean has been a well-known cost reduction philosophy in pharma, at the same time many pharma companies have considered lean activities for reducing environmental footprints (materials and related energy) and the related cost savings. This investigation has discovered seven of such lean operations across the pharma industry. Table 4.15 lists the key lean operations applied across the industry. The subsequent section presents the findings in detail on each of the lean practices.

Table: 4.15 Key lean practices across the industry for materials savings (Source: Interviews and reports)

Key lean operations

- ✓ *Reduce water consumption*
- ✓ *Reduce packaging materials*
- ✓ *Consider efficient & effective QC lab management to dematerialize*
- ✓ *Consider critical equipment parameters to dematerialise*

Reduce water consumption

Given the significant consumption of water in the pharma process, most respondents recognised the need to conserve water and were found to be taking significant steps in this direction, especially those in the innovative and bio-pharma sub-sectors. Though the entire industry in general has undertaken water reduction initiatives, the scopes and levels of adoption vary across the sectors. For example, as per the findings, the majority of innovative pharma is predominantly considering internal water efficiency targets, employees' mindset for water savings, increased production efficiency, waterless (or mechanical) cooling systems, site specific water conservation programs, and closed loop cooling system, while the majority of bio pharma has predominantly initiated the use of waterless cooling systems to save water. For instance, one of the respondents (B – site 1), an EHS manager from a leading innovative pharma company's formulation plant, highlighted three key activities to conserve water: setting targets, objectives and measures on a yearly basis to gain water efficiency across the plant, modification of employees behavioural strategies for consuming less water (e.g., training employees how to become efficient water user across the plant) and conducting continuous improvement projects to identify and implement key water reduction activities. The respondent has highlighted on this thread that – ***"... because there is plenty of water that we use as part of cleaning of vessels and we try to come up with such ideas and suggestions to improve ..."***

As revealed in the study, continuous cooling and heating are the basic requirements to run an API process. It was also evident that water is the key source for cooling some specific unit operations such as during the crystallization in the process. As per the majority of the reports and interviewees, the pharma industry (the majority of bio and innovative pharma but a very low number of generic pharma) has applied two techniques to optimize this cooling process for reducing water consumption. For instance, applying waterless cooling, which means using

a mechanical cooling process (without water supply via pipes), and another one is to apply a closed loop cooling system which means that water is collected from a cooling tower (after cooling process is complete) and it is recirculated (via advanced equipment engineering system) again for next process cooling, as revealed in the study. As revealed by the reports, in closed loop cooling systems, some bio pharma and innovative pharma companies across the industry have also sought to recover process wastewater and reuse it for cooling purposes via special equipment engineering.

As observed in the investigation, it is crucially important to outline here that though there is huge potential for those companies (where water sources are abundant) to reduce water consumption in the process and related energy reduction by implementing water cooling systems rather than mechanical cooling, the adoption of this practice across the industry is very low. One of the leading innovative pharma (In - 05) has advocated that – ***"... ... we encourage the use of water for cooling at these sites where water is abundant, no contamination is possible and water can be returned to the aquatic environment without treatment, because it saves significant quantities of energy and associated GHG emissions".***

In the case of bio pharma, as per the interviewees and reports, waterless cooling systems is a predominant lean practice to reduce water consumption from the bio process. However, a few bio pharma companies also highlight that though both of the lean techniques reduce usage of fresh water, the mechanical cooling process is still a bit controversial due to it using more energy than other techniques (closed loop cooling). For instance, one of the bio pharma companies (B – 05) outlined that the mechanical process of cooling water would increase energy usage and it would require finding another trade-off, such as if the plant uses the energy originated from in-site wastes processing. Still, this controversy over the process of waterless cooling system or mechanical cooling process has been considered across all industry segments to save water.

A wide variety of water reduction activities and management programs that have been identified in the environmental reports are presented in Table 4.16 below. It also shows the intensity (/frequencies) of each practice / lean activity for each industry segment.

Table 4.16 Key water reduction activities & practices considered (based on report data)	Considered by individual industry players		
	Innovative Pharma (11)	Generic Pharma (20)	Biopharma (25)
√-Reducing water consumption through produciton efficiency improvements	√(55%)		
√-Water audit: Audit the production site to identify the opportunity to cut water use	√(9%)	√(5%)	
√-updated equipment to use waterless cooling systems	√(27%)	√(5%)	√(12%)
√-Prompt repairs and maintenance of steam-distribution systems and traps	√(18%)		
√-Process-water purification system optimization	√(9%)		√(4%)
√-Closed-loop cooling systems	√(9%)		√(4%)
√-Reducing water demand and increasing water reuse	√(9%)		√(8%)
√-collaborative and educational initiatives that support water stewardship	√(9%)		√(4%)
√-Use water Meter: Facility-specific water metering	√(18%)	√(5%)	√(8%)
√-Apply Automatic wash in place (WIP) concept for cleaning the process equipment		√(5%)	
√-Apply 'Hi-pressure Jets'/spray guns in practice for cleaning of process areas		√(5%)	
√-Consider lean projects (e.g., water saving programs) for water conservation	√(27%)	√(10%)	√(8%)
√-Consider water disclosure tools (e.g., WBCSD, CDP water etc)	√(55%)	√(5%)	√(4%)

However, as per the findings from the reports, a few generic manufacturers (e.g., Gn – 04) have considered two interesting types of technologies for reducing cooling water in the process. One example is automatic wash in place (WIP) which is a built in cleaning system within the process to clean-up process equipment more efficiently and another one is applying a new spray technology that uses high mechanical pressure to clean-up equipment. In both cases, water requirements are reduced.

Reduce Packaging materials

It is evident from the investigation that gaining efficiency in pharma packaging has not only reduced significant pressures on natural resources but also shown positive environmental impact on other life cycle stages such as storage, distribution and use-and-disposal phase. This is because it will then require a smaller amount of packaging for storage, transport, and disposal. For instance, one of the leading generic companies has outlined that it has implemented paper reduction initiatives across the plant that has achieved 70% to 80% resource conservation and gained significant cost savings. Three key lean activities for reducing the usage of packaging materials during manufacturing are presented in Table 4. 17.

Table 4.17: Key lean operations for reducing packaging materials
✓ Reduce the volume of the packaging materials ✓ Consider paperless Batch Process Records (BPR) ✓ Consider e-version of medication guide

- ✓ Reduce the volume of the packaging materials

It is important to note here that the scopes of optimizing primary and secondary packaging in the manufacturing phase is very less a(s they have already been designed in the R&D phase, so any changes would require regulatory approval for revalidating the modified packaging system. However, pharma manufacturers (especially generic) have been sought to reduce the volume of tertiary and other types of packaging materials, which are not directly relevant to product packaging such as packaging for storing intermediate products etc, in manufacturing plants.

This practice was highly relevant to generic pharma due to high volume of production. The majority of the respondents interviewed from the generic sector and the related reports analysed mentioned adopting this practice. For instance, one of the leading generic pharma (Gn – 04) highlighted that they have reduced the gauge size (from 400 to 200) of one of its frequently used polyethylene (which is called LDPE – low density polyethylene) bags which is used to store intermediate or semi-finished goods during manufacturing operations. This initiative has resulted in a 40% weight reduction of the polybags being used. Its further reports that it has also worked to optimize pack size for a few of their API and excipients for easy handling and to reduce spillage and contamination. This was also supported by the interviews. For instance, one of the respondents (E – Site 1) from a generic pharma outlined that they have taken plant-wide lean measures to reduce tertiary and other manufacturing related packaging, for instance, recycling, reducing and reusing whenever possible without compromising product quality. However, the respondent has further highlighted that it is sometimes difficult for them (as contract manufacturers) to choose greener packaging

materials (both secondary and tertiary) as it comes from their networked (focal) companies and there is no scope of optimization.

- ✓ Consider paperless Batch Process Records (BPR)

The study revealed that manufacturers must keep records of the manufacturing process or steps involved, and quality parameters etc in detail for each batch produced. This is known as Batch Process Records or BPR in the industry. As per most of the reports and interviewees across the industry, keeping BPR records for each batch on a regular basis is crucial for all types of manufacturers for product auditing, validation and getting marketing approval from regulators. Some of the interviewees also highlighted that the BRP record must be kept for at least one year after the expiry of the batch. As per the reports and interview, it has traditionally been done on paper, which not only requires significant amount of packaging raw materials but also induces related waste. A number of the interviewees also highlight that paper-based documentation also increases overall production inefficiencies due to human error, time and the related costs involved.

Because of the importance of the issue, the industry (especially innovative and a very low number of bio pharma) has planned to replace the traditional paper-based batch processing with new electronic batch processing records (eBPR) where all batch related data will be automatically captured electronically. For instance, one of the respondents (B – site 1) from a leading innovative pharma highlighted the usage of electronic document transfer technology like tablets and/or mobile apps for managing batch release documents. The respondent confirmed undertaking a project focused on creating a paperless manufacturing environment. This is expected to reduce a huge amount of related resources, as explained by the respondent. It was also supported by the environmental report produced by one of the bio pharma (B – 14) which stated that they had also taken an initiative to introduce electronic data recording for documenting process quality data.

As per the interviews and reports, though the importance of adopting eBPR was also severely felt by the generic sector due to having huge amounts of batch production each year on average, the majority of them are still sceptical about costs, time and administrative burdens in relation to this transformation.

- ✓ Consider e-version of medication guide

Each medication pack comes with a paper-based guideline for users to understand the possible side effects of taking them, or instructions how to take each dosage etc. The related papers wastes in pharma packaging is significant, as each pack of drugs produced and dispatched contains these paper-based guidelines. Due to the larger volume of production, the related resources waste for generic pharma is significant. Hence, some generic pharma reports state, they have introduced electronic guidance instead of the traditional paper guidance attached to the pack. For instance, one of the generic companies reported that the company has introduced an e-version of medication guide rather than a paper version for some of its products such as Atorvastatin Tablets, Omeprazole capsules, and Olanzapine. It has resulted in saving approximately 250 tonnes of paper per annum, as the company reported. However, none of the innovative and bio pharma has mentioned this.

Consider efficient & effective QC lab management to dematerialize

It was evident in the study that QC lab in pharma operation is occupied and scheduled with a sequential queue of sampling for quality tests, which is a raw materials (e.g., solvents, reagents, reactants, APIs, excipients) exhaustive process. The study also reveals that generally the phases of QC are pre-production QC (e.g., quality test of API, Excipients, or other solvents etc), in process QC (e.g., quality test of intermediate products) and end of batch QC (e.g., quality test of final batch). Compared to other sectors, the amount of related resources wastes is significant for generic pharma due to having larger production volume. Hence, the majority of the interviewees and reports in generic pharma reveal that in each case of QC testing, laboratory management, such as *raw chemicals (e.g., solvents) management for QC*, *cleaning of equipment system*, *digitizing lab equipment system for automation* etc, play a key role for saving raw materials during QC process across the lab. Interestingly, in the case of sampling process optimization for QC, the innovative pharma has taken the lead in adopting it. However, the industry in general has sought to focus on two key areas below:

- ✓ Effective and efficient sampling process for QC

The study reveals how pharma manufacturers can be effective and efficient in sampling of raw, semi-finished and / or finished products for quality control purposes. Most of the innovative respondents have realized the importance of effective and efficient sampling processes, while generic pharma respondents could have benefitted most by adopting it. The respondents have stressed that as the sampling activities involve usage of huge amounts of chemicals for QC operations (e.g., cleaning the sampling booth, equipment etc), it is

mandatory to take the right decision on sampling. Most of the respondents highlight that strong supplier involvement (e.g., supplier audit) and commitment has helped them to reduce the requirements of sampling. For instance, one of the respondents (B – site 1) from a leading innovative pharma has confirmed that if the APIs coming from their own networked companies (reliable internal/external input suppliers), they will be relaxed about sampling for quality requirements due to maintaining the similar quality approaches among them. Most importantly, some other respondents (e.g., D – site 2) have highlighted that during formulation, a routine sampling (prior manufacturing and in-process) of APIs to check stability will reduce the chance of raw materials waste significantly in the commercial phase.

- ✓ Digitization of QC lab (e.g., QLMS)

The investigation also reveals that Quality Laboratory Management System (QLMS) is an integrated web based system which actually enables the manufacturing managers to manage lab resources (e.g., raw materials inventory, in process testing equipment, sampling ques for batches etc) efficiently and effectively. This practice was highly relevant to the generic sector due to the higher production volume and regular batch-wise QC requirements. The majority of the reports from generic companies highlight that the QC lab managers also can capture data directly from the equipment to reduce human intervention and errors. For instance, one of the generic companies (Gn – 13) has reported into this thread that they have employed most cutting-edge technologies, such as automation in QC lab, and this has resulted in a significant decrease in their energy and water consumption. Another generic pharma (Gn – 10) has highlighted that ***"…All plants have Independent full-fledged Quality Control Laboratories which consists of instrumentation, chemical, microbiological and packaging material testing sections…"***

However, some other companies (e.g., Gn – 14) have considered real time in-process stability testing of API, which has reduced unnecessary quality sampling and related materials usage in the process by capturing automatic in-process data. For instance, one of the leading generic pharma (Gn – 04) has explained: ***"…implementation of an auto sample preparator cum analyser instrument to minimize the errors during sampling, this also helps us to achieve consistent and precise results…"***

Consider critical equipment parameters to dematerialise

As per the findings from the investigation, this green aspect demonstrates how pharma manufacturers can optimize process through understanding and controlling the relevant key equipment parameters such as times/frequencies of equipment failure, time taken to fix / repair failed equipment etc. These equipment parameters are key to smooth running of process as highlighted in the study. It was also revealed in the reports that inefficient and ineffective measures to control and manage these parameters during manufacturing may incur significant amounts of materials waste due to batch failure or quality deviations. It also increases product lead time and related costs.

Due to having higher volume of production (especially in tablet formulations) a few generic pharma companies have mentioned adopting varieties of equipment efficiency and effectiveness parameters to reduce the number of equipment failures and related materials reduction. For instance, one of the leading generic pharma (Gn -04) companies has reported how effectively and efficiently it manages the critical equipment failures, which could significantly induce wastes and incur relevant costs of disposals. The company has highlighted some equipment parameters, such as failure mood effective analysis (FMEA), which aims to identify potential causes of critical equipment failure for those assemblies which run for 24/7. The company further reports that it also identifies relevant corrective and preventive actions and that the efficacy of the critical equipment assemblies is also measured using another two critical equipment parameters such as Mean Time To Repair (MTTR) and Mean Time Between Failure (MTBF). It further interprets that MTTR indicates the amount of time taken to repair the equipment, where MTBF indicates the frequency of equipment failure. Controlling these equipment parameters (e.g., setting a target for MTTR by operations manager etc) are crucial to streamlining the process. However, though these parameters are used in formulation, it is still not known whether they could be adopted in the API production environment as well.

Consider green collaboration for material efficiency

The findings from both the interviews and the reports reveal that collaboration between upstream medicinal chemists, scientists and downstream process engineers, formulations managers and waste vendors play a crucial role to optimize a drug process efficiently and effectively to reduce materials wastes and related energy. The investigation reveals that companies (predominantly innovative and a few generic pharma) have been sought to employ collaborative optimization process for materials and energy efficiency. As per the study, this

collaboration can be either intra or inter companies' efforts to collect feedback on environmental performance from downstream customers and liaise with upstream suppliers to modify and develop the process accordingly.

This practice is highly relevant to innovative pharma, as they are most likely to deal with re-design (or, improvement) and optimization of process. As per some of the respondents from innovative pharma, once the downstream manufacturing process is clearly understood, as time passes with mass production, the manufacturing or process engineers become able to provide the upstream scientists with ample data on different manufacturing parameters (e.g., flow rate, hardness of tablets, stability, hazardous byproducts and their complex treatment with energy footprint etc), which are the key determinants for successful process optimization to reduce unnecessary quality failure, wastes/by-products etc. For instance, one of leading innovative pharma (In - 05) companies has reported a similar cross-domain collaborative effort that has enabled them to optimize their manufacturing process significantly by reducing the need for solvents in the process. The report has further explained that this collaborative project has been achieved in less than two years and has enabled the site to gain a 77% reduction in hazardous wastes.

However, as per the findings from reports, realizing such importance of green collaboration projects, few generic pharma companies have developed a framework for effective communication between manufacturers, equipment providers and other key stakeholders to enrich understanding of the chemistry and critical parameters of a process for optimization. The forms of communications were 'regular self-audit' / internal audit and / or external audit. For instance, one of the generic companies (Gn – 17) has explained how it has optimized its production process for reducing unnecessary quality related wastes by combining both specialised industrial R&D teams and manufacturing teams together. The report also highlights that "… ***In this way we can optimise flow management throughout the manufacturing process and control the quality of our medicines"***

Appendix 11a: PAT led continuous manufacturing and related findings

The majority of the innovative pharma respondents (e.g., A, C, B - site 2, D – site 2, etc) had already adopted continuous manufacturing over batch (among a few of their product portfolios) for the last few years. For instance, one of the innovative pharma (In -08) reported

that it has changed its process of a product called 'Prezista' (for treating HIV/AIDS) – a 600 mg Tablet from batch to continuous - and got their regulatory approval in 2016. They have also reported significant amount of materials and energy savings from the new process in general, though the respondents were unable to provide exact statistics on environmental savings on continuous process.

It was also evident that most of the leading innovative pharma consider continuous mode of operations either a new and/or existing process regardless of bio-based / chemical-based processes. However, some of the respondents from innovative pharma (C, B – site 2) mentioned that they were going to consider continuous process particularly in new process development, rather than existing ones, for reducing time and cost-related regulatory burden. A few of them, such as one of the respondents, a *Sustainability and Utility Manager (B – site 2),* highlighted that some of their bio-based processes (e.g., fermentation and extraction) had become effectively continuous for saving raw materials (e.g., water) and improving product quality. Another respondent, the *Senior Principle Environmental Scientist (C),*outlined the extent and importance of applying this green practice for new drug processes as: ***".....the preferred production needs to be the continuous based production, and we only move to batch process if there are kind of safety or other logistical kind of concern that the continuous production may not achievable".***

Interestingly, though the potential savings (in terms of raw materials and related costs) from continuous bio process in some innovative pharma was also clearly evidenced, there is little evidence for adopting this green practice in the bio pharma sector. Most of the bio pharma respondents agree that the equipment settings (including scale up from lab process) for the continuous bio pharma process involve comparatively more complex engineering, and there is also lack of such equipment suppliers. On the other hand, as most of the generic pharma companies are involved in formulation, so continuous API production was less relevant for generic sector.

Appendix 11b: Scopes of solvent recycling and related findings

It was revealed in the interviews and reports that the industry (especially the innovative pharma segment) has been applying different types of chemical cum mechanical process (e.g., distillation) to extract useful chemical substances from wasted solvents (sometimes

termed as wastewater) and/or intermediate waste byproducts during the drug manufacturing process. As per the majority of respondents, after extracting the usable substances, if there is any amount of solid waste which cannot be recycled, it is sent off to the wastewater treatment plant. Those respondents and some other environmental reports have also confirmed that distillation is the key method of recycling used for better environmental footprint. Some of the respondents also confirmed that recycling was performed either via on-site based pre-installed recycling equipment design within the site of the manufacturing plant, or via off-site arrangement. Though on-site recycling is more environmentally friendly than off-site, the investigation revealed that recycling via toll processor (off-site) is predominant in the industry. As off-site recyclers handle multiples types of solvents from multiples customers, there is always a risk of producing lower graded recycled solvent due to product contamination, which would result in additional waste.

Evidence of benefits from recycling

The study also evidences a considerable amount of materials savings and related disposal cost savings which were achieved by solvent recycling during the manufacturing process. For instance, a leading innovative pharma API plant (B – site 2) highlighted that they have been using millions of litres of solvents every year to produce API. To eliminate the solvent wastes and to save related disposal costs the company has been able to recover 99% of the solvents used in the current process, as explained by the respondent. The respondent further explained the simple mechanism of how this works. For instance, they use steam produced from the boiler onsite to distil and separate the solvents based on the recovery specification. Similarly, another respondent from innovative pharma (D – site 1, R&D), a strategic business development manager, highlighted that they have been successful in conserving 99.5% of a solvent called acetone which was initially identified as environmentally toxic but they could not find any alternative to use. Similar findings were also evidenced in the reports. For instance, it was also highlighted in one of the leading innovative pharma reports (In – 05) that one of their sites now only needs to purchase 30% of the solvent, as the rest comes from recycled stream. It was also reported by one of the bio pharma (B - 24) that in 2017, the company has consumed 66.4% of ethanol during production process, which was recovered and reused.

The study also reveals that the industry spends a significant proportion of its manufacturing costs on purchasing different graded cleaning solvents for routine washes of process

equipment. Hence, in many instances, pharma companies have sought to use recovered solvents for cleaning purposes. As per the interviewees and reports, downgraded solvents, or lower quality recycled solvents (e.g., purified water) can be used in process equipment cleaning. For instance, one of the leading innovative pharma reports (In – 02) explains that it has redesigned a process in such a way that the waste solvents can be recycled and reused for cleaning the equipment in the R&D process. The report further explains that as the R&D process involves considerable amount of cleaning activities and it consumes huge amounts of chemicals (or solvents) for cleaning purposes, the new recycle and reuse approach will save millions of dollars by eliminating the need for expensive high-purity solvents for cleaning equipment.

Limitations / challenges of recycling

However, the study also reveals that solvent recycling involves a case by case assessment and not all solvents are recyclable. As per the interviews and reports, recyclability of a solvent is largely dependent on the types and nature of wasted solvent composition and equipment and engineering capacity and complexities for recycling, and the degree of purity of the solvent required. As per the respondents, in most cases there is no one fit engineering solution for all commercial manufacturing processes for recycling and that is why the amount of recycling and the quality of recycling vary from one manufacturing process to another, as different processes use different types of solvents. Therefore, it was inferred from the responses that a process of solvent recovery is only specific to that drug process and cannot be generalised for other processes. For instance, one of the respondents (A) from a leading innovative big pharma contributed to this topic saying: "…***the process is different for every drug because the solvents involved are different. The engineering, the equipment needed to separate these solvents is different, so it cannot be easily replicated across all of our sites…"***

So, as revealed by this study, the recycling viability of a particular process is largely dependent on the type of wasted solvents composition or the composition of byproducts involved in the process (see Table 4.11 above). For instance, according to some interviewees, the general assumption is that the lower the toxicity level, the higher the scopes of recycling. In another case, some of the pharma operations use toxic raw materials as inputs, so, they cannot be reused, recycled or recovered at the end of process, according to another respondent (G), a production manager from a generic pharma. The respondent also explained

that – ***"... you need to understand the limit of your recycling - otherwise that could cause injury to your people, if you try to regenerate it"***

Similarly, it was identified in the interviews that purified distilled water or water-based solvent is much easier to recycle back to the process than recycling solvent from other organic composition. For instance, a *Senior Principle Environmental Scientist* from a leading innovative pharma (C) highlighted that though there is lots of room for recycling, recovering and reusing of solvents, there are certain solvents that cannot be recycled due to levels of toxicity such as ionic solvent or ionic liquid, which actually worsen environmental footprint. The key solvents that are sought for recycling across the industry are presented in Table 4.14.

Table 4.14 Key chemical substances (Solvents) that have been sought for recycling across the industry (Source: Interviews and reports)

- ✓ Acetone
- ✓ Ethanol
- ✓ polyethylene glycol
- ✓ Metal catalysts (e.g., Palladium)
- ✓ Purified water
- ✓ Aluminium
- ✓ Tetrahydrofuran (THF)
- ✓ Acetonitrile

Appendix 12: Findings on CHP, CCHP and other related technologies / strategies (e.g., retrofitting)

As per the study findings, CHP or combined heat and power is also one of the key energy saving technologies adopted across the industry, especially by the innovative companies. As per the interviews and reports, CHP uses waste heat from the process and/or from the entire plant to boil water and produce steam to drive a turbine to produce onsite electricity as revealed from the reports. This process is also termed as cogeneration. The majority of the innovative reports highlighted adopting this practice and some of them also highlighted the related benefits. For instance, one of the leading pharma (In – 03) reported savings of 680 tonnes of energy related CO2 by cogeneration of CHP. It was also reported that co-

generation system or CHP technology can reduce overall plant energy costs by 50% and is especially ideal for the process that runs on continuous mode.

It was also evident in the interviews that though the source of energy may not necessarily be renewable, CHP technology is the effective and efficient source of process and/or plant energy. Though CHP is becoming common in innovative pharma, there is low level of adoption in generic pharma. As per a few respondents, the focus on CHP in the generic sector in general is still far off compared to others, as the generic companies are facing fierce competition in the market and there is less motivation to adopt green energy technology like CHP. The biopharma sector is still in the planning stage of adopting this due to heat recovery issues from the complex bio process. For instance, it was reported by one of the bio pharma (B - 06) that "we are introducing a co-generation system to reduce our use of purchased electricity, which is the main driver of CO2 emission increases"

As evident in the study, like CHP concept, a number of the innovative companies have also sought to adopt tri-generation or CCHP technology. As reported by them, CCHP technology supplies the manufacturing site simultaneously with electricity, heat, and cooling. A few of them have also demonstrated the key environmental benefits of adopting it. For instance, one of the leading innovative pharma (In – 05) has reported that the overall energy efficiency of their plant has been increased by 80% and has generated annual savings of one million dollars, and is expected to save 19000 tonnes of carbon dioxide equivalent (CO2e) per year.

Some of the innovative pharma, as revealed in the interviews, have also highlighted that retrofitting new processes within existing plants with updated equipment systems saves energy rather than investing in new plants for running new processes. For instance, one of the respondents (B – site 2) outlined that from an environmental perspective, they have continual capital investment on new processes for retrofitting, particularly when old equipment is approaching the end of its lifecycle. The respondents further highlighted that they conducted an environmental assessment, for example in assessing their chillers. Instead of using refrigerated gas with its global warming potential, they used automatic scheduling HVAC and a lighting system for avoiding unnecessary process cooling and/or heating, and made use of more environmentally friendly and energy efficient technology such as ammonia chillers; they also had global engineering standards requirements for their motors – so they replaced all the motors at end-of-life with the most energy efficient motors. This is how they made

retrofitting more energy efficient, rather than investing in a completely new plant for a new process unless there was an absolute requirement to do so.

As per the interviews, retrofitting was also evidenced among some of the generic pharma, but not in bio pharma. For instance, a respondent (E – site 2) from a generic pharma highlighted that they also tried to retrofit equipment and/or machineries for energy efficiency whenever it came to adopting a completely new and complex process, and avoided investing in a new plant. He has also discussed the massive energy saving from LED lighting installation across the plant. Furthermore, he mentioned the periodic maintenance of equipment and process machineries for achieving energy efficiency. However, the study found that, due to the low feasibility and high costs of revalidation of a process, retrofitting was almost non-existent in the bio pharma companies investigated.

Appendix 13: Findings on Energy kaizen and CI related initiatives

- Reduce wastewater

Another finding from the interviews is that a significant proportion of energy is used to treat wastewater, as it contains hazardous organic compounds. Therefore, some respondents from innovative companies realized the importance of considering the relevant lean program. For instance, a respondent (B – Site 2) from an innovative pharma stated that some lean programs for reducing energy, such as zero wastewater from process, reduce faulty calibration etc, are part of their every day operations for both their API production line and their formulation line. They have predominantly focused on reducing process wastewater which contain hazardous organic content and normally requires significant amounts of energy to be treated or dispose of.

- Product specific energy measures

As per the reports, some innovative companies also focus on product specific energy efficiency measures. For instance, one of the companies (In - 05) highlighted that they had assessed energy efficiency of one of their product portfolios (anti-infective API) and achieved up to a 30% energy efficiency improvement in the process over the last 10 years. The company further reports that energy intensity measurement helps plant managers in evaluating progress against targets and can set higher energy efficiency targets. However, this was not widely considered. The limitation of such energy measures was also highlighted in

the study, such as the lack of upstream energy data for input ingredients and lack of technology to measure process specific energy data.

- Routine Leak detection of process piping system

The investigation also reveals that a considerable amount of energy is lost from the pharma process due to gas leaks throughout the process piping system. So, there is huge scope for reducing process energy by routine detection of piping leaks. As per the reports, pharma companies (especially innovative and bio pharma but also a few generic ones) have adopted leak detection activities as part of the plant's continuous improvement plans. For instance, a generic company (Gn -06) reported that it had carried out a thorough examination for identifying the number of leaks across the production plant (entire piping system) using a technology called ultrasound measuring equipment. It has helped them to identify several leaks that induced energy loss across the production plant.

- Lean energy standard

However, as per the reports, some generic companies have predominantly adopted lean energy standards for their facilities. For instance, one of the generic pharma (Gn – 07) reported that it had been operating a lean energy program for the company's main manufacturing facilities since 2007. It further reports that it had defined four sets of lean energy standards: Prerequisite, Bronze, Silver and Gold. It also explained that each set of lean energy standards defines fourteen to thirty-five different energy efficiency related requirements (e.g., number of leak identified, efficiency of HAVAC, chillers, lighting improvements, motor upgrades, etc) that need to be achieved by a manufacturing plant to be endorsed for any specific standard.

- Process optimization program (e.g., Britest tool)

The study also reveals that a special process optimization program (called Britest tool) had also been adopted by the companies to reduce their process energy footprint. As per the findings from both interviews and reports, the key approach of 'Britest tool' is to understand batch variations within the pharma process through increasing knowledge of each process parameter including raw materials and process equipment. It also emerged that the 'Britest tool' is a lean effort managed by a third party consultant. It was revealed by a number of the innovative companies investigated (e.g., In – 03, 05 etc) that an experienced technical team normally produces a customized tool to deliver a tailored process insight to its client. It was

further reported that this tool was used to identify priorities for process improvement, build process understanding to identify key knowledge gaps between existing process and the expected mortification process. One of the reports (In – 03) also highlighted that the new tool had helped them to increase yields and reduce their plant energy footprint.

However, the scope of this lean program, or 'Britest Improvement tool', was further understood by some of the generic pharma investigated. According to their reports, this tool provides a Process Information Summary Map and a Process Definition Diagram which facilitates the identification of critical process parameters to understand the batch variations and related wastes. For instance, it was reported by one of the leading generic pharma (Gn – 06) that the Britest tool lean program had also helped selecting process equipment, using decision support system (e.g., ChemDecide software) to develop decision criteria and evaluate several equipment options using a range of decision making approaches. As per the findings, in a nutshell, this lean tool has helped the companies to understand process operations and related challenges. Figure 4.6 below shows how the Britest tool helps managers to reduce environmental footprint via process optimization as conceptualized from the findings. It was also revealed in the study that though the initial aims of the Britest tool were not environment focused, later the companies (especially innovative and generic) realized that it also has built in environmental benefits.

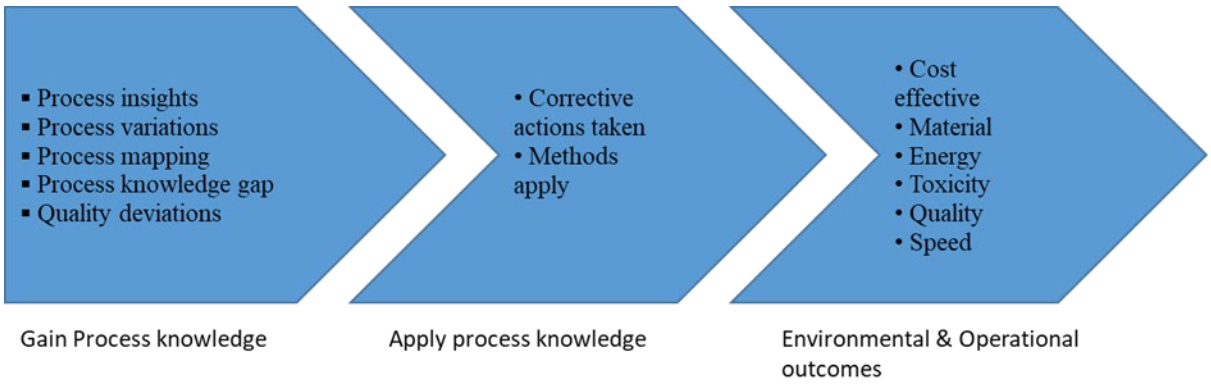


Figure: 4.6 Key benefits of Britest lean tools
(Source: conceptualize from the findings in the study)

- Efficient Process calibration

Process calibration from lab scale to mass production is another key area of improvement for savings materials and energy. In particular, the bio pharma sector in comparison with others has felt the importance of adopting this practice. This is because the equipment arrangement and related engineering is more complex in bio pharma than others, as revealed in the

investigation. Hence, the companies (predominantly bio pharma) have also considered related lean and CI projects to continuously review the manufacturing process and validation for effective and efficient process calibration from lab scale to commercial scale. For instance, one of the bio pharma (B - 21) reported that it had a dedicated operational excellence team in place for continuous improvement through tools like six sigma, Kaizen etc. It added that – "… across all of our sites, we use lean and six sigma methodologies to improve process efficiency and reduce defects, resulting in less waste generated"

- Other lean and kaizen projects

The application of lean, six sigma and Kaizen projects have also been highlighted while interviewing some of the leading innovative pharma respondents. For instance, some of the respondents from innovative pharma have highlight that similar to the Britest tool, they normally have contracts with third party contractors who oversee the process optimization applying kaizen and lean events to optimize energy, emission and wastes. For instance, one of the respondents from a leading innovative pharma (A) stressed that the key activity they are currently involved in is using a number of external consultants or specialists to provide services to improve plant efficiencies. The respondent further highlights this thread saying "… so we are running Kaizen event, which is some kind of lean process, where we assess the plants and we have a list of projects that could be implemented to save energy, reduce GHG footprint, and reduce water use...." A number of interviewees also confirmed that investors were very keen to invest in these kinds of lean and kaizen projects, as the payback period is justifiable and one of the respondents (B – site 2) reported that the payback period of such a kaizen project was two and half years.

The reports also revealed that most of the innovative pharma promoted different energy programs by offering process innovation awards. It was reported that employees are encouraged to come up with innovative ideas to reduce energy or materials consumption from the process through offering a process innovation awards. For instance, one of the leading innovative companies (In – 05) had introduced an environmental and sustainability awards program which was especially focused on energy efficiency. This awards program was to motivate process engineers, process chemists or scientists to come up with unique ideas to conserve process energy, as these awards are for those who develop energy saving, renewable energy projects or environmental projects, such as water footprint, sustainable packaging or waste and emission reduction.

Appendix 14: Findings on ERA / PIE related programs

ERA (or, PIE) programs

The investigation also reveals that several types of PIE programs are currently being invested in for ERA assessment. Three of them are key and lead the industry: iPIE, EPS (Ecopharmaco stewardship), GAIA Protocol programs. The key output of each project is to assess the ERA of APIs and increase understanding of the impact of APIs and their byproducts (metabolites) on aquatic life.

iPIE project

It was revealed in the interviews and reports that the consideration of PIE programs for ERA assessment is predominant among the leading innovative companies. The majority of innovative companies highlighted that they are working in line with the iPIE project. As per the study, the iPIE project is called the Intelligence-led Assessment of Pharmaceuticals in the Environment project and is supported by the Innovative Medicine Initiative, which is a public-private partnership coordinated by the European Commissions and industry group in collaboration with other academic and non-academic research organizations. Some innovative company reports also reveal that the iPIE project develops frameworks, computer models, and databases to support the companies for environmental testing of new and/or existing APIs. For instance, one of the leading innovative companies (In – 03) reported that they have participated in the iPIE project and they have been continuously providing eco-toxicity data to the iPIE project. It was also reported that iPIE was able to collect eco-toxicological and other related environmental data for almost 200 different pharmaceutical compounds. The information is shared among the participating companies and has proactively set minimum API discharge limits accordingly.

However, as per the study, only a small number of generic manufacturers are currently considering PIE programs due to the lack of related resources, and having low cost strategies in a fiercely competitive environment, and because they felt that the related responsibility predominantly lies on R&D based innovators. As an example, one of the generic company reports (Gn - 15) confirmed that it has conducted 550 environmental assessments of APIs as part of the PIE program. It was also revealed in the investigation that the bio pharma process

with low levels of chemicals application and usage of bio sourced raw materials is inherently considered and attributed as a low environmental toxicity producer, and hence, the iPIE project or other related ERA projects are of less interest.

EPS (eco-pharmaco stewardship) project

As per the investigation, EPS is a collaborative initiative incorporated by some key federations such as the European Federation of Pharmaceutical Industry (EFPIA), the medicines for Europe, and the Association of the European Self-Medication Industry (AESGP). It was also revealed from the interviews and reports that EPS is built upon life cycle concepts, as it considers the roles and responsibilities of all parties including public services, the pharmaceuticals industries, environmental experts, doctors, pharmacists and patients to deal with PIE. As per some innovative pharma reports, EPS follows three key principals: considering iPIE to identify potential environmental risks, the compilation of industry best practices enabling manufacturers to minimize environmental loading of APIs, and refining the existing ERA methods involved to become up-to-date and relevant. For instance, one of the companies (In – 04) outlined that participating in the EPS (by sharing toxicity data) has enabled them to plan a model for wastewater control limits for pharmaceutical residues at manufacturing facilities.

'GAIA Protocol'

A number of the innovative pharma reports revealed that GAIA, abbreviated as the 'Global Aquatic Ingredient Assessment' tool, is used to assess the potential end-of-life environmental impact of ingredients in new formulations. This tool evaluates biodegradability, persistence, bioaccumulation, and toxicity of formulations on a scale from 0 to 100 - the score of over 80 indicating a formulation is environmentally friendly with little or no environmental hazard, as reported by one of the innovative companies (In – 08).

Control API discharges from manufacturing site

It was also evident in the interviews and reports that as ERA data are becoming available through the significant PIE projects discussed above, pharma manufacturers (especially innovative ones) are strictly concerned about the discharge limit of each API in their product portfolio. As the interviews revealed, in general Environmental Quality Criteria (EQCs), a water quality standard set by the Environmental Agency, along with industry-accepted risk-assessment methods, is responsible for establishing procedures for managing and controlling

active pharmaceutical ingredients (APIs) in their wastewater. It was also identified in the interviews that the focal companies are also responsible for providing EQC requirements to their API suppliers.

As per the investigation, most of the leading innovative pharma and a few generic manufacturers felt the importance of monitoring the API discharge continuously throughout the production process. As revealed in the study, most of them have now set their internal target of APIs discharge amounts from each production site. This target has also been set for their suppliers to follow as well, if APIs are outsourced. For instance, one of the leading innovative pharma respondents (C) highlighted that they set their discharge limit far lower than the regulatory limit to be on the safe side. The respondent further contributed to this thread as – ***"we have a target we set out for compliance for all the sites to meet that discharge standard, and we meet that target for last few years (e.g., for five years)"***

As per the findings from interviews and reports, however, some generic manufacturing plants followed site specific API discharge management guidance. They developed a guideline to manage API discharge from the manufacturing operations. This guide is used by the employees in manufacturing plants to take effective, efficient, and immediate decisions if any accidental API discharge is produced in the site. For instance, one of the companies (Gn – 15) outlined that such API discharge guidelines also focus on equipment containment systems and cleaning processes. As per some respondents, this is highly relevant because API-contained equipment washes up liquid which may accidentally increase discharge concentration if not managed properly. Some other reports (e.g., Gn – 15) also highlighted that all aqueous manufacturing emissions are treated in the wastewater treatment plant, where the majority of the wastes are degradable and thus reduce the chance of environmental contamination of the APIs. Some other reports state that based on initial environmental assessment, the effluent is pre-treated using advanced technologies prior to final discharge into the environment.

Reduce antibiotic discharge - Responsible antibiotic manufacturing: The concept of site-specific API discharge management guidance has also been promoted to the responsible antibiotic manufacturing guidance by some of the innovative pharma as revealed in the study. A comprehensive review of the antibiotic manufacturing process along with additional control criteria on top of usual discharge limits was highlighted by some of the innovative companies investigated. For instance, one of the leading innovative pharma (In – 04) reported

that they are following a common Antibiotic Manufacturing Framework provided by AMR Industry Alliance, a non-profit organization raising its voice against AMR (Anti-Microbial Resistance) by providing guidance to the industry. It was also evident that this common antibiotic manufacturing framework has provided a methodology for responsible manufacturing, including the stringent management of discharge. The key management approaches of the Antibiotic Manufacturing Framework is also presented in Table 4.21.

Table 4.21 Key management approaches of Antibiotic Manufacturing Framework to deal with AMR (source: company reports)
Key aspects
Complying with local laws, environmental permits, company standards, and codes of conduct
Exercising appropriate duty of care for all discharges and waste streams containing antibiotics
Ensuring water and solid waste management programs are in place to prevent untreated discharge of manufacturing waste containing antibiotics
Completing appropriate training in line with industry best practices
Ensuring these environmental programs are evaluated periodically for efficacy

Realizing the importance of such clean antibiotic manufacturing, some of the innovative companies have undertaken proactive levels of internal targets to reduce API (antibiotic) discharge from their plants. For instance, it was reported by one of the leading innovative pharma (In – 05) that under the management approaches of Antibiotic Manufacturing Framework the company has set a 2020 target to limit the release of drug substance effluents from its manufacturing site to 10 times less than the predicted no effect concentration (PNEC) in receiving surface water to ensure negligible amounts of environmental discharge.

Appendix 15: Findings on 'Waste to beneficiary use', 'hierarchy of waste management' and 'Zero landfill'

Waste to beneficial use

As revealed in the interviews and reports, in the case of *waste to beneficiary use***,** the majority of the companies' key motivation is to convert wastes in such output so that companies can win operational costs out of the investments on different waste to beneficiary projects, such as 'waste to energy', or 'waste to raw materials' or 'waste to fertilizers' etc. Innovative pharma companies were found to adopt this extensively compared to any other sectors. Some examples of 'waste to beneficiary use' that have emerged from the study are presented in Table 4.23 below. For instance, one of the respondents (B – site 1) from a leading innovative pharma adds to this topic by stating that, ***"we try to achieve target of 80% of our waste is beneficial use – this means 80% of our wastes what we generate want to recover, recycle or to reuse".*** Another respondent (B – site 2) has stressed that they produce biomethane from solid organic wastes in their onsite treatment plant. This biomethane is later used to generate process energy. For instance, the respondent has outlined that ***"The Biomethane combusted the CHP engine – we reuse the heat and electricity back into our process from the waste materials"***

Table 4.23 Some examples of 'wastewater to beneficiary use' in pharma (Source: Interviews and reports)

- ✓ Wastewater converted to energy (gas/electricity)
- ✓ Wastewater converted to fertilizers
- ✓ Wastewater converted to raw materials (e.g., water, solvents etc)
- ✓ Wastewater converted into a benign, reusable plastic lumber
- ✓ Wastewater incineration with energy recovery
- ✓ Process wastewater (liquid production) is reprocessed for boiler
- ✓ Wastewater converting to ground irrigation water

The investigation also reveals that some innovative pharma companies have also made an external collaboration to identify an alternative solution for beneficial uses of process wastes. For instance, one of the companies (In – 08) highlighted that they have launched a 'waste-to-value' program at one of their manufacturing sites. The program is based on two external collaborations. As per the report, a dedicated external group is responsible for suggesting best

practice for recycling/reusing process wastes, whereas another dedicated external group oversees the end-to-end manufacturing process for efficiencies and effectiveness. For instance, another company (In – 11) employed a technology called reverse osmosis to treat process wastewater, where 40% of waste is recycled and used for toilet flushing and grounds irrigations.

However, as revealed in the reports, a few generic (e.g., Gn – 04) pharma and some bio pharma companies (e.g., B - 18) predominantly focus on recovering heat energy from process wastewater. The reports also reveal that as the majority of wastewater has calorific value (heat energy) with varying levels from high to low, a mechanical process called co-processing is used to recover heat energy to reuse it in the process.

Apply waste hierarchy

As revealed in the investigation, the majority of pharma companies adopted this waste management philosophy. As per the interviews, this follows six hierarchical stages: prevention, reuse, recycle, energy recovery, and landfill. In most cases the respondents from innovative pharma highlighted that they organise their process wastes as per the hierarchical order and landfill is considered as the last resort of waste treatment. For instance, one of the respondents (E – site 1) highlighted that they strictly follow the hierarchy at each of their manufacturing sites and if they cannot recycle process wastes, they recover energy from incineration of those wastewater streams. Another company report (B – 24) stressed the importance of reducing landfill operations and investing more on top waste hierarchy (prevention or reduction and solvent recycling) while realizing the fact that 76.6% of wastewater is produced from the amount of water input in their process. Being motivated by the hierarchy of waste management, one company (In – 05) reported that it does not dispose waste containing API into landfill anymore. Hence, as revealed in the study, more solvent recycling projects have been adopted by the company and the recycling rate of hazardous wastewater increased by 6% within one year. Similarly, for example, driven by this waste hierarchy another innovative company (In – 04) reused 233,000 tons of wastes (most of it as fertilizer) out of 294,000 tons of waste (both hazardous and non-hazardous stream) produced in a year.

As evident in the study, however, though both bio pharma and generic pharma are far behind in following the hierarchy of waste management compared to innovative companies, they have equally realized the importance of following waste hierarchy in terms of processing

process wastewater. Cost and regulatory burdens are the key for generic pharma, where bio pharma suffers from complex operational and safety issues such as lack of proper guidance and equipment systems for recycling without compromising the quality, safety and efficacy of final products. Still, it was revealed in the reports that the hierarchy of waste management motivated some generic and bio pharma companies to become more proactive in managing their wastes. For instance, one of the companies (Gn – 07) reported that they produce five year production forecasts to compare wastewater treatment capacity and capabilities with anticipated production change, which ultimately allows them to plan and manage wastewater recycling to achieve the aim of waste hierarchy.

Zero landfill

Given the importance of the ongoing issue of PIE and other related chemical contamination of aquatic life, plants and foods, the pharma industry in all sectors has been sought in general to promote near zero landfill via reusing, recycling and related recovery practices in collaboration with both internal and external waste consultants, as revealed in the interviews and reports. It was clear in the investigation that especially majority of the leading innovative pharma companies have set their main goal to reduce landfill to zero soon and some of them have already achieved this goal. For instance, one company (In – 04) reported that it has successfully diverted all wastes to recycling and reuse and has already achieved the goal of zero landfill in 2013, a similar finding is demonstrated by one of the interview respondents (B – site 2).

Evidence of such waste diversion was also seen in the generic and bio pharma sector, though comparatively to a lower extent than innovative. For instance, a generic company (Gn – 06) reported that it has diverted its wastewater by 97% (through incineration) from landfill. Another bio pharma (B – 18) also reported that about 22 metric tons of wastes are diverted annually from one of its sites, which is equivalent to a 90% wastewater diversion rate for that site and has saved related disposal costs.

It was also found that effective pre-treatment of hazardous wastes prior to discharging them into environment is one of the key green practices behind the goal of zero landfill. The aim of this pre-treatment of wastes is to reduce toxicity to a minimum level or to an acceptable level set by the regulator (e.g., as per local environmental standard if relevant) as highlighted in the interviews. It was also revealed in the reports and interviews that the process of this typical pre-detoxification of wastewater is termed as ‘autoclave’ across the industry. While

innovative pharma has extensively applied autoclave, generic and bio pharma have applied it at a moderate level.

It was however also evident in the study that generic and bio pharma in general have adopted varieties of advanced purification methods and technologies to deal with toxic wastewater. These purification methods and technologies can be chemicals, physical or biological or a combination of them as revealed in the study. Process wastewater is continuously tested and purified prior to final discharge into the fresh water. For instance, one of the companies (B – 19) reported that they treat discharged water applying such purification processes (e.g., membranes process) and remove metal-containing wastewater before releasing it into surface water. The company has further reported that they also assess the impact of the water they discharge on the ecosystem by using the whole effluent toxicity (WET) test in order to monitor the water quality of rivers and seashores where their effluent is discharged.

Similarly, another generic company (Gn – 15) also used a similar purification process (e.g., using membrane bioreactor technology) which has ultimately enabled them to recycle back and reuse (for cooling purposes in the process) a large proportion of wastewater purified. Another bio pharma company (B – 11) used nanofiltration technology to separate API compounds before the process wastewater is released to the treatment plant. They also use another technology called UV advanced-oxidation system, which has enabled the manufacturers to eliminate APIs from wastewater effectively.

Appendix 16: Drug wastes reduction related lean activities taken by the downstream stakeholders

- ✓ **Blister pack reminder**

Additionally, some other pharmacists interviewed also mentioned the ***'blister pack reminder'*** for a specific group of patients (e.g., elderly patients, patients with dementia etc) to increase drug adherence. As per the interviews and CCG reports, this aspect has explained how the pharmacies help elderly people or people with dementia to take their medication effectively on time without any error. The investigation also highlights that this practice is of great importance as the number of elderly patients is increasing in the UK and this practice would not only help them to take their medication efficiently and effectively but it also help reduce the unnecessary environmental loading of unused/expired drugs. As revealed in the interviews, pharmacists are actively engaged with elderly patients who are on regular

multiple medications but not able to remember or cannot identify drugs. Some of the pharmacy respondents also explain that these types of patients are provided with 'Dossette box' preps where each drug is popped out from the original blister pack and organises in different compartments within the box according to daily/weekly dosage requirements. The GPs and patients interviewed have also confirmed this practice. It was clear from the investigation that this not only improves patient safety but also improves adherence, reducing stockpiling and unwanted returns.

The use of blister pack reminder to optimize drug waste reduction has also been evidenced in both CCG reports and pharmacy service reports. For instance, one of the leading pharmacies (Ph - 06) has highlighted that they have implemented 'monitored dosage system' for those patients who struggle to remember to take their medicine. The pharmacy report has also highlighted how they communicate with the patient about this service saying – ***"If you have trouble remembering to take your medicines, we can supply them in a monitored dosage tray to help you to take your medication at the right time"*** Another clinical commission group report (CCG – 08) also mentioned the usage of blister packs for the terminally ill and /or elderly patients by the pharmacies and care homes.

Ensure effective and efficient stock management

The majority of pharmacists outlined this practice to reduce unnecessary drug waste. It was revealed in the interviews that usage-history of drugs and stock rotation based on fast moving / slow moving drugs, weekly stock (expiry) check, pharmacist personal experience about categories of demand are some of the key measures used by pharmacists to keep the stock at an optimum level. For instance, one of the pharmacists interviewed (N) explained that though their internal inventory management system projects automatic demand for the items needed based on historic usage, they always review and consider the most recent trend and use their common sense prior to purchasing drugs. Some other pharmacist respondents also mentioned that they always make sure they have received long date products from their suppliers. As per their SOPs (Standard Operating Procedure) they periodically check expiry date of products to follow FIFO. However, another respondent (K – store 1) highlighted that the stock expiry check interval varies from community to hospital pharmacy. While hospital pharmacies check stock every six months, the community pharmacy checks every month, as explained by another respondent (N).

Ensure effective and optimum purchase of OTC drugs by patients to reduce unnecessary stockpiling

It was revealed in the investigation that, due to OTC market competition and huge marketing communications for life style drug products (e.g., vitamins) and other basic symptoms related drugs, ready availability and easy accessibility through self-medication decisions, OTC consumption is exponentially increasing. Therefore, there is a tendency for drug stockpiling at consumers' homes due to having lower control over OTC purchase. This study has revealed that though the pharmacists promote OTC drugs they also take some essential measures to ensure effective and optimum purchase of OTC drugs by patients to reduce unnecessary drug wastes.

For instance, it was identified that pharmacies always follow a certain procedure to do this. For instance, one of the respondents (L) highlighted that they have a program called 'Responding to symptoms' which is used as a guideline to deal with OTC customers to advise and encourage the patients to choose most effective drugs. So, the pharmacists must intervene in detail prior to selling a particular OTC drug.

However, as revealed in the study, in some cases it is very difficult to control OTC drug usages. For instance, one of the pharmacy respondents (N) explained that as it may sometimes happen that a group of teenagers/people come separately and buy painkillers or some other drugs, and later on stockpile them for misuse. The respondent has also mentioned that each pharmacy member always strictly ask each patient who is this medication for, the respondent continued saying: ***"We always advise not to buy too much or not too take over dosage- it's harmful for you"***

However, though the majority of pharmacists confirmed promoting and encouraging patients to become rationale OTC drug users, some pharmacists still have concerns and highlighted that when it comes to whether the patient is taking appropriate medicine or not, they can only advise them how to do it in a proper manner. For instance, one of the respondents (L) contributed to the topic saying **"*Whether they are taking appropriately or not, it is kind of out of our hands, unfortunately. We do advise them in the most appropriate manner, and we do not know the rest"*** Unfortunately, the level of consideration of this kind of patient encouragement is low now.

- ✓ **Reduce drug usage by focusing on underlying reason of the disease rather than symptoms only**

It is also revealed by the GPs interviewed that they always focus on underlying reasons rather than treating symptoms only. They have also stressed that evidenced-based treatment is the key to their daily practice. 'Medication Optimization during prescribing where necessary' has become a norm in their daily practice, whilst at the same time they ensure safety, efficacy, and quality, as explained by one of them. For instance, one of the GPs (P) exaplained that this kind of rationale prescribing practice or ethical prescribing practice is built upon effective guidelines or standard operating procedure and best practice to follow. The respondent has also highlighted that ***'...the way you prescribe you don't misuse the drugs, you don't use wrong medication, you don't use the wrong dosage, you monitor for their side effects, and also monitor their risks, work mutually with patient …"***

- ✓ **Not issuing bulk supply**

It was also evident in the study that excessive supply of drugs was avoided whenever necessary and possible to do so to optimize drug usage. It was revealed by the GPs interviewed that as part of the medicine optimization and drug waste reduction agenda across NHS, they are instructed not to issue bulk supply whenever appropriate. The respondent further mentioned that GPs are actively following this and do not normally issue more than a one-month supply at a time for longer term or life-long treatment. They also keep an eye on the quantity of acute medication while prescribing for short term symptoms like cold cough or anything simple. So, they prescribe limited quantity for them.

However, as revealed in the interviews, it is important to highlight here that this drug optimization practice is applied on a case by case basis and cannot be generalised for all drugs. The study also reveals that there are certain groups of drugs (e.g., warfarin, oral chemotherapeutic drugs etc) that are not generally issued for more than one month, while some certain groups of drugs such as for the treatment of blood pressure, diabetes, certain heart condition etc can be given for more than one month but obviously with doctors' satisfactory evidence and related concerns. For instance, a few of the pharmacy respondents (e.g., N, K – store 1) outlined a few example (see Table 4.28) cases when drugs are not normally supplied in bulk quantity and not more than a one month supply due to the related dependency factors, such as the requirement of periodical diagnostic (e.g., blood tests) tests. On top of this the respondent also outlined two more important reasons for which bulk supply

is not given: firstly, for patients who are at the end of life, and secondly, sudden side effects may occur and drugs may therefore be changed for patients.

Table 4.28 Examples of some groups of drugs that cannot be given bulk supply to optimize drug wastes (Source: Interviews)

Disease treated	Examples drugs	Reason for not issuing bulk supply (not more than a month)
Blood clots	Warfarin	Regular observation: Blood test is required prior to give next supply
Cancer	Capecitabine; methotrexate	Regular observation: blood test, weight, liver condition etc are tested prior to give next supply
Severe acne	Isotretinoin	Give supply based on pregnancy test

- ✓ **Prescription Review Reporting**

Prescribing Review Reporting (PRR) has emerged as another important sub practice of prescribing practice. As revealed in the study, PRR is a process of continuous monitoring of prescriber's prescribing habits. This monitoring is done by the practising pharmacist in the GP. So, every quarter they bring a report to the GP practice and show who is prescribing what and how much, as explained by one of the GP consultants (O) interviewed. The respondent also highlighted that this evaluation is not only done to comply with regulation but also to seek the opportunity of how to optimize drug usage. The respondent has also mentioned the PRR as an academic as well as cost saving exercise.

- ✓ **Consider AMR while prescribing**

As per the interviews, what and how the prescribers consider the issue of AMR in their daily prescribing practice was explained. Given the severe issue of AMR, the investigation reveals that the healthcare professionals are continuously receiving prescribing advice from local expertise/microbiologists about the sensitivity of certain microorganisms (e.g., virus, bacteria, protozoa etc) as part of Antimicrobial Stewardship program. For instance, one of the GPs (O) interviewed has highlighted that they have been given educational materials, leaflet, news

bulletins and standard operating procedures (e.g., clear evidence of bacterial or viral infection, mandatory review etc) while prescribing antimicrobial related drugs (e.g., antibiotic). The level of consideration of the practice is very high which can also be externally validated by the publication of 'Antimicrobial Prescribing and Stewardship Competencies' by Public Health England in 2013, and 'Antimicrobial Stewardship Toolkit For English Hospital' published in 2015. The Antimicrobial Stewardship is a five-year strategic program guided by the department of health to deal with the ongoing issue of antimicrobial resistance developed by the inappropriate prescribing and use of antibiotics. According to the 'Antimicrobial Prescribing and Stewardship Competencies' report (2013), '***Antimicrobial stewardship initiatives aim to improve the prescribing of all agents, whether they target bacterial, viral, fungal, mycobacterial or protozal infections***''

As per the reports, the key message of the stewardship program is *Start Smart* (Do Not Start antibiotics in the absence of clinical evidence of bacterial infection) and *Then Focus* (Clinical Review and decision at 48 – 72 hours). It was also revealed that even though the driver for this program is patient safety rather than environmental safety, the evidenced based prescribing optimization and control of using antibiotics through proper education and awareness among the prescribers has eventually reduced the environmental loading of antibiotics in the water and food cycle.

Consider drug substitution or alternative therapies (where possible)

As emerged in the study, this green aspect provides the scopes of drug substitutions or alternative therapies to reduce the environmental loading of drugs. This green practice will have great importance, as it will reduce the amount of drug substances entering the water cycle via human excretion, which is the biggest source of contamination as reported by the respondent GPs interviewed. Though there is huge potential for reducing drug usage by prescribing alternative therapy, the study reveals a low level of consideration of this practice due to the lack of proper guidance, resources, legislation and leadership in this area of practice. As the GPs or prescribers must follow the NICE guidance on what to prescribe, and what not to prescribe, for a certain disease, they are currently considering prescribing physiotherapy.

For instance, one of the GPs (Q) mentioned that alternative therapy is still a way forward but not considered to too great an extent. Another GP (O) provided similar evidence. The concept of alternative therapy has moved forward to deal with chronic disease management, which

was not discussed in the existing literature. For instance, patients who have chronic back pain are prescribed for physical exercise instead of medication, as mentioned by both GPs (O, Q) interviewed. It was also highlighted by one of the respondents (O) that - "***.....these cohorts of patients can be benefitted from hydro pool, exercise classes, meditation, yoga, things like that. So, this is something they tried in varieties of NHS trusts".*** Unfortunately, this type of alternative prescribing practice is still very limited and the process of referral from GPs for prescribing these alternative services is still not universally available throughout the country, as revealed in the interviews. For instance, one of the GPs (O) outlined that "***at the moment they are in their infancy but there is some appetite to do this".***

The GP referral system is not available for types of physical activities apart from physiotherapy as highlighted by the GPs interviewed. The finding can also be partially validated by one of the reports published by NHS Health Scotland and highlighted by the GPs. This report has revealed another form of alternative therapy which is termed as 'Green Prescription'. Green prescription is a scheme which includes aspects of physical activity in outdoor settings with strong natural environment components (e.g. greenspaces, paths, parks, nature reserves and countryside) and which have some type of referral mechanism from health care practitioners as reported in the NHS Health Scotland report published in 2010. The report has also revealed that Primary care referral schemes were more likely to be mainly walking schemes while secondary care referral schemes were more likely to be horticulture, or conservation or green gym activities.

Ensure effective and efficient usage of drugs

This practice has emerged from drug administration and management in Hospitals (wards) and care homes. As reveal in the study, a significant part of drug supplies is administered in hospital and care home settings. For instance, it reveals (CCG – 08) that £50 million worth drugs are disposed by care homes every year which represents 17% of the total prescription medicine wastage in England each year. Care homes with elderly people, especially those who have reached the end of life stage are one of the key sources of drug wastes in the community as highlighted in the interviews. For instance, one of the care homes managers (S) highlighted the extent of their drug wastes saying "… ***20 kilos of each container and 20 of them are going back every month for disposing"*** so 400 kilos of drug waste is recorded every month in that particular care home. It was also highlighted that drug non-adherence is a significant problem in care homes. For instance, some care home managers interviewed (R &

S) have explained that many elderly people simply refuse to take medication on time. Some other respondents also highlight that though the care workers try to encourage them to take medication on time, they are not allowed to force them as explained by the respondent. One of the respondents (R) exemplified the type of non-adherence saying ***"… as we popped up and put them in a cup and these medicines are disposed as we cannot reuse for them and it happens every day"*** . Table 4.29 below shows the key scopes of drug wastes in care home settings identified from the study.

Table: 4.29 Key scopes of drug wastes in Care homes with elderly people (Source: Interviews)

- ✓ Over prescribing by the GPs or other prescribers
- ✓ Changing dosage frequently so ending up with unused stock
- ✓ Patient dying before completing their drug cycle
- ✓ Sudden changing dosages form (e.g., Tablet to syrup) due to inability of the patients to shallow
- ✓ Patient deliberately refusing to take medication on time
- ✓ Medications opened in the morning to be administered cannot be reused in the evening (if refused to take in the morning)

As revealed in the investigation, given such amount of drug wastes some local CCGs have ensured that patients' medications in the care homes are regularly reviewed by GPs and pharmacists. For instance, one of the CCG (CCG - 08) has reported that they have conducted 1,792 medication reviews between 2008 & 2012 under a medication review project and this has suggested a total of 5,913 medication changes, which eventually saves £218,241 which would have been wastes. However, it was clear in the investigation that such medication review projects have not been sought as a general scenario across the care homes due to the lack of direction and resources and budgets allocated for each CCGs. Apart from this, some other practices, which are discussed in the subsequent sections, are adopted by the local CCGs to ensure effective use of drugs as came out in the study.

- ✓ **MAR (Medicine Administration Record)**

As per the interviewees, given such severe drug wastes scenarios in the care homes, two key approaches were undertaken: MAR chart and periodic patient review. It was revealed in the interviews that care homes follow a medication administer chart, called a MAR (Medicine

Administration Record) chart to track and trace patient medication from box opening to final disposal. This chart is predominantly a paper document, though some care homes use electronic versions of it. As per the respondents, care workers fill in patients details (e.g., name, date of birth, allergic info etc) and medication administration details such as name of medication, dose, type of formulation (e.g., syrup, tablet, capsule etc), time of drug administration, reason for not administering etc in detail on the MAR chart. A few of the respondents also highlight that this document is kept secure for regulatory purpose (e.g., CQC audit). According to the respondents, this MAR chart has helped care workers to liaise with GPs and or pharmacies to keep track record of medication which has ultimately helped the pharmacies to issue medication effectively and efficiently. For instance, one of the care home managers (R) explained that pharmacies have been able to optimize their drug supplies using a MAR chart. For instance, if a patient refuses to take a particular dosage / formulation it is recorded on the MAR and the information is sent to either GPs or pharmacies to review prior to the next supply. However, another respondent (S) has highlighted that though a MAR chart is a good indication of drug usage traceability it is currently not being reviewed to such an extent by the regulatory authority for the purpose of drug waste reduction.

The investigation revealed that, on the other hand, in hospital (ward) settings the key drug wastes originating from patients are: not using their own medication during admission, no track and trace of medication between admission within different hospital departments and errors in drug preparation by the ward nurses and non-adherence. For instance, one of the respondents (Q) from hospital stress that ***"sometimes patient is prescribed drugs while they are in hospital but when they are discharged they never come back to collect the drug anymore so that a wastes***". It was also evidenced in the interviews and reports that similar types of drug chart or MAR charts are used in hospital as well to track and trace each drug dispensed. Table 4.30 shows the key initiatives that are taken by hospital (wards) to reduce drug wastes.

Table 4.30 Key approaches taken by hospital words for reducing drug wastes (Source: Interviews and reports)

- ✓ Track and trace of each drug supply using MAR charts
- ✓ Follow guidelines (SOPs) for preparation of drugs (e.g., mixing of antibiotic or other drugs)
- ✓ Consider Medicine optimization scheme: 'Green Bag Scheme', 'My medication passport'

- ✓ **Patient counselling and education**

As per the interviews, patient counselling and education prior to medication dispensing have been sought as one of the prime focuses of pharmacists as part of their ongoing regular operational activities. As per some pharmacist respondents, in general, pharmacists reinforce the key mechanism of a prescribed drug about how it works inside the body, possible side effects, number of dosages to be taken, and possible negative health consequences for not adhering to some prescribed dosages such as antibiotic dosage prior to dispensing. For instance, one of the pharmacist managers interviewed (K – store 2) has outlined that irregular dosage not only induces drug wastes but also incurs extra healthcare costs, and concern for patient safety. Another pharmacy respondent (L) adds to the topic highlighting that "***If they take regular dosage they don't need extra medication because they will have relieved from past medication''*** Therefore, patient counselling and education on regular dosage is the key to reducing drug non-adherence.

The GPs who participated in the study also agreed that they are actively engaged with the patients and take special consideration on patient education about their medication. It was also revealed in the interviews and CCG reports that as drug waste reduction is directly correlated with decreasing patient non-adherence, patients must understand why they are taking medication. The related importance can also be manipulated by quoting from one of the GP's (O) statement: ***'.....medicine waste reduction is a big agenda in hospital or even in the community. There are multi-factorial costs for it. The clinicians are doing – they probably doing as a rule of thumb, but you got to be able to ascertain whether patients are understood''***

- ✓ **Reduce drug usages by introducing trial package and disease alteration strategy**

It was revealed in the interviews that not for all diseases but, in particular, for those border-line diseases there is greater chance of avoiding longer term medication. In doing so patients are given a smaller quantity and limited experimental medication (actual drug substances and/or non-medication therapies such as exercises, diets etc), which were termed as trial package by the GPs. Though there are a few resource based limitations to introducing trial packages, the GPs interviewed were agreed on having high levels of involvement with this practice, where the patients are given a week or month or smaller fraction of trial medication

prior to treating long-term disease. For instance, one of the GPs (O) highlighted that the trial package was initiated with a belief to alter the disease or change the condition in the future. The respondent continued saying, specifically, that it is true for the patients with border line long term disease such as blood pressure, diabetes etc. The GPs interviewed stated that they do not straightaway start medication, rather they give patients time to alter the disease and then see whether they can improve it. One of the GP respondents (O) explained ***"all those borderline stuffs, they will have 3 to 6 months to alter, some people are successful, because they do take on board, they can free for sometimes from drug use''***

It was also evident in the interviews that targeted and personalised interventions are also strongly suggested to alter borderline disease by using accurate trial packages considering patients' age, sex, historical health condition etc. For instance, one of the CCG reports (CCG -17) outlined that the traditional trial-and-error prescribing approach induced drug waste. It also provides an example highlighting that while 'warfarin' is an effective treatment for blood clots, there can be 40-fold differences in the dosage required by patients. So, trials start one after another to end up with the correct dosage of the drug. Therefore, it is worth considering more targeted and personalised interventions with patients to alter borderline disease, where the disease alteration rate is comparatively higher than entering a trial-and-error prescribing phase – as explained by the GPs interviewed.

- ✓ **Training and education for prescribers and related healthcare professionals**

It was also evidenced in the investigation that education programs for healthcare professionals have become another important source to control practice. The study reveals that GPs and pharmacists are receiving varieties of education programs and tools such as e-learning, newsletters, case studies, professional training, posters and leaflets etc. aiming to increase their knowledge on how to optimize drug usage and reduce drug waste. As explained by one of the GPs interviewed (O), GPs and other related healthcare professionals receive monthly medicine optimization newsletters called 'Prescribing Matters' which demonstrate the current issue of medication waste and related advice for prescribers (e.g., advice on medication review). The respondent has further explained that the newsletter also publishes some extreme cases to learn from.

It was also reported (CCG -04) that the GPs and other prescribers also receive e-learning opportunities for repeat prescription management and electronic repeat dispensing (eRD) guidance for GPs and pharmacists. GPs and/or other prescribers also must complete

mandatory training, for instance, the antimicrobial prescribing and stewardship competencies, prior to starting prescribing antibiotics or other related drugs for infectious disease. They are also provided with medicine waste posters and leaflets regularly.

- ✓ **Medicine optimization scheme: 'Green Bag Scheme'**

Green Bag Scheme was selected as a voluntary approach to dealing with drug waste reduction and safe and effective use of drugs. It was evidenced in the interviews and reports that the scheme was developed and is currently being practiced by some NHS trusts across the country. It was revealed that the key message of this green bag scheme is also linked to the ongoing drug waste reduction campaign. As per the some of the CCG reports (e.g., CCG – 25), for instance, the core concept of a 'Green Bag Scheme' is to encourage patients to bring their own medications (PODs –patient own medication) during hospital admission carrying in a bag which is labelled clearly with the patient's details (e.g., patient's hospital number). As a result of this practice, hospital wards can reuse patient's own medication rather than redispensing them a new pack and thus reducing unnecessary stockpiling at the patient's home. It was further reported (CCG – 35) that though the bags do not have to be green, they must be easily identifiable bags which can be used for transporting medicines between and around care settings. As patients' own drugs are most of the times lost due to movement between wards, the POD under the green bag scheme ensures that drugs also move with patients across wards to reduce unnecessary dispensing of drugs when moving between wards, as revealed in the CCG reports. The report has further explained, for instance, that the bags can be used from home to hospital, hospital to homecare or brought into the community pharmacy for medication review purposes. It was also reported that the scheme has been continuously supported and promoted by the GPs, CCG, and community pharmacies across the country. For instance, the GPs and CCG in Brighton and Hove are actively promoting green bags to improve medicine safety and reduce waste (NHS Newsletter, 2017). It was also reported that all pharmacies in Brighton and Hove have supplies of the green bags, and they have also been publicised to local patient groups and care homes.

It was also reported (CCG – 25) that Green bags are offered when conducing MUR or NMS, or patients that may be admitted to hospital in an emergency e.g., with COPD, or patients who tell the pharmacists / GPs they are going into hospital for a planned procedure, delivery frail and elderly patients, or care home supply. It was further highlighted in the report that the successful green bag scheme depends on the involvement of all relevant healthcare

stakeholders such as hospital trusts (acute, community, mental health), ambulance service, and community pharmacy, CCGs, GP practices, Care Homes and others. However, the level of implementation of this scheme by individual care settings, such as in hospital in acute or mental, GPs, care homes, pharmacies are still unknown.

- ✓ **Medicine optimization scheme: 'My medication Passport'**

'My Medication Passport' is another medication optimization tool revealed by the study. It was also identified in the CCG reports and interviews that a lack of effective communication among the GPs, hospitals, care homes and community pharmacies about medication changes (e.g., stopping medication / dose reduction) is one of the crucial issues in the NHS for increased levels of drug waste. As per the interviewees and reports, whenever a patient transfers between care settings there is a risk that information about their medicines is not transferred or inaccurately transferred. This new scheme of 'My Medication Passport' is of great importance to deal with the issue as highlighted in the reports. As per the report interpretations, 'My medication passport' is a paper printed document or an electronic mobile app which stores all medication info including changes of doses and/or medication for a patient. For instance, it is reported (CCG – 08) that patients or patients' carers or patients' relatives are normally responsible for updating this passport by hand. It also includes some other additional info such as: info about the patient, info about the patient's GP/other healthcare professional, list of medicines the patient cannot take and the reason why, list of patients current medicines, changes made to current medicines and reason why, other medical info such as vaccination, screening, etc. It was also reported that the paper version passport is available to all healthcare professionals for distributing to the patients. The popularity of this tool is continuously increasing across the country. In line with medical intervention, this scheme has also been used as one of the key drugs optimization tools across some CCGs. However, the key reason for slow adoption of this practice across all CCGs could be operational barriers and lack of capacity.

Appendix 17: A greener roadmap of managing disposal of unwanted drugs

- ✓ **Promote unwanted drug returns to pharmacy:** ***Ensure effective and efficient collection of unused / expired drugs from patients for safe disposal***

The investigation reveals that different actors in the downstream use and disposal phase contribute in various ways, and in varying levels, to ensure effective and efficient collection of unused / unwanted drugs wastes from consumers or patients. The subsequent section presents how each actor has acted on it as emerge in the study.

Role played by pharmacies and GPs

The majority of the pharmacies investigated collected unused /expired or unwanted drugs from patients, and then disposed of them safely via licensed waste management companies. It was revealed in the interviews that as part of the standard operating procedure (SOPs) and good practices, pharmacies keep records of successful waste destruction or treatment reports provided by the waste vendors. As per some respondents, the patients do not necessarily have to be from their nominated pharmacy from where they normally collect their medication. Rather, pharmacies take any unwanted /unused/expired drugs from any patients or consumers, predominantly from the local area. The majority of the pharmacies interviewed stated that collection of unwanted / unused / expired drugs from customers is one of the key services they provide. This is also termed 'drug take back scheme' or 'patient return scheme'.

As per the interviews, in this type of pharmacy collection process, pharmacies do not have any external waste collection points either via their own initiative or via a third party waste collection vendor. However, it was also evidenced that pharmacies promote this service through word of mouth, such as informing and motivating patients to bring back their unused/expired/unwanted drugs to the pharmacy for safe disposal. For instance, one of the respondents (O) highlighted that they sometimes provide patient leaflet which highlights how the patients should manage their drugs and what they should do when they have unused/unwanted/expired drugs.

It was also found that, in the event of a drug recall, pharmacies are very active in collecting those recalled drugs from customer zones via word of mouth, such as informing them during face to face interventions, leaflets, posters etc. In addition to pharmacies, GPs or local CCGs or hospital trusts have also promoted this 'unwanted drug return to pharmacy' service through increasing awareness among the people as evidenced both in the interviews and reports. For instance, some of the CCGs have participated in a nationwide drug waste reduction campaign. One of the key messages of the campaign is to motivate people to return their unwanted medicine to their pharmacy for safe disposal as outlined by one of the CCGs (CCG - 01). It was also revealed in the CCG reports that patients were communicated to

mostly via leaflet, posters, and bus adverts (between 38% - 56%). A few of the communications (3%) were also made via traditional radio adverts or radio shows to promote collection of unused drugs from the patient zone.

Role played by local council

As local councils play a crucial role in collecting, segregating and treating final household waste, either using their own facilities and/or outsourcing other licensed waste vendors, the study investigated how they respond to promoting safe disposal of unwanted drugs in households. Less than half of the local councils interviewed have reported that they have taken any special considerations for managing household unwanted drugs. This is presented in Table 4.35.

Table 4.35 key considerations taken by local councils to promote collection of unwanted household drugs (Source: Interviews)

Key considerations taken by local councils to promote collection of unwanted household drugs:
✓ **Arrange separate collection** of clinical waste including household drugs (for free of charge) ✓ **Reporting to the householder** for separate collection if found (immediately by the collection crew) either in the recycling bag or inside the domestic waste bag ✓ **Self-Medicating Waste Issue Report** (or Self Medicating WIRE) - third party waste collector (work in liaison with local council) who collects patients self-medicating wastes including unused medication upon a collection request made by the patient ✓ **Encourage patients via council website** communication to return their unwanted medicines to the local pharmacy

Interestingly and more importantly, the majority of local councils do not feel any pressure, or they feel it is not their sole responsibility to ensure collection of household drugs separately, as they think this is the responsibility of pharmacies and hospitals. For instance, one of the respondents (LC -16) from a local council highlighted that ***"Un-used/surplus medication should go back to the pharmacy or GP who (should) have special collection arrangements to get it destroyed safely"***

- **Effective and efficient segregation of drug wastes & handover to licenced waste vendors**

As per the interviews, improper segregation of waste is not only a difficult state for the waste treatment companies for treating the waste using a particular technology, but is also an environmental burden. It was also highlighted by the respondents that inappropriate or wrong segregation of wastes incur significant disposal costs. For instance, incineration of hazardous drug wastes (e.g., cytotoxic drugs) costs five times higher than incineration of other non-hazardous drugs wastes as reported by one of the waste vendors (T) investigated. Therefore, segregation of wastes or categorize waste in right container is not only key for safe and responsible disposal but also key for economical reasons. The subsequent sections present the roles played by pharmacies, GPs, hospitals, and waste vendors in managing drug waste segregation.

Role played by Pharmacies

Though pharmacies follow their own SOP (Standard Operating Procedure) for collection and segregation of unwanted drugs, monitoring and managing patient return of unwanted drugs can be a challenging task. For instance, sometimes patient returns contain other types of wastes (e.g., metals, plastics etc) other than unwanted drugs and it is not always possible for pharmacy staff to physically check the patient return, as highlighted by some of the respondents (e.g., respondent L). As per the pharmacy respondents, once patients return their unwanted drugs to the pharmacy, they are segregated and placed in the right coded or coloured bins, for instance, yellow bin for hazardous (e.g., cytotoxic) drugs wastes which need to go to special permitted and licenced incineration plants. To allow correct segregation, some of the respondents (e.g., respondent N) explained that the patients are requested to unseal their bags and put unwanted drugs into a tray (called patient return tray). Then pharmacy staff segregate each drug by group of wastes such as tablets and capsules go into one bin, a separate bin for aerosol products, another separate bin for creams/ointments products and another separate bin for cytotoxic or hazardous drugs, as revealed by most of the pharmacy staff.

As evidenced in the study, however, some pharmacies have taken a slightly different approach (e.g., use declaration form while returning) to tackle this segregation issue for effective collection of unwanted drugs from patents. For instance, one of the pharmacy managers (K store 2) highlighted that they give a special card (termed as **Unwanted**

Medicine Card) to the patients to fill in prior to collecting their unwanted drugs. This card is served as evidence of patients' consent with their signature, which confirms that the returned pack does not contain any substances (e.g., chemicals, batteries, metals, plastics etc) other than unused/expired/unwanted drugs. A similar approach was suggested as standard practice by the PSNC as part of their service operations management as revealed in the interviews.

As part of collection process, the use of this typical consent card is also evidenced in the pharmacy service reports. For instance, one of the pharmacy services reports (PSR – 02) outlined that this card has helped pharmacies to manage segregating unused medicine waste by using the right colour coded sack and right code with consignment notes. This type of organised source segregation has eventually helped the waste treatments companies to treat those unwanted drugs using the correct methods and avoiding producing complex waste streams as highlighted by the respondents as well. Unfortunately, the 'Unwanted Medicine Card' approach is still not widely used.

It was also evidenced in the interviews that there is another type of drugs called controlled drugs or CD drugs (e.g., some strong pain killers such as morphine, methadone etc) which also require a special segregation process. They are legally controlled because misuse of these drugs (e.g., addition to methadone) is catastrophic to human health as highlighted in the study. As these groups of drugs are legally controlled in terms of limited, restricted and supervised usages and disposal, pharmacies use special kits, termed denature kits, where the unused returned CD drugs are kept to initially destroy their chemical functionality and recorded under supervised pharmacists, as explained by one of the respondents (N). Then the denature kits are kept in separate container.

Role played by Hospital and care homes

In the case of hospitals and care homes, effective and efficient waste segregation is the key to managing hospitals and care homes' drug wastes responsibly. As revealed in the study, hospitals and care homes had similar approaches to waste segregation. For instance, they have also developed their own standard operating procedures (SOPs) derived from the Healthcare waste Management guided by department of Health in the community pharmacies, as mentioned by one of the pharmacists (L). They separate waste inhalers, controlled drugs (CD) drugs, and solid/liquid drugs and/or separate hazardous / non-hazardous. As according to the Waste Framework Directive it is illegal to mix hazardous and non-hazardous waste, the efficient waste segregation procedure is used strictly by all

healthcare waste producers, as reported by the two respondents from two waste management companies (T and U) who regularly handle pharmaceutical wastes from hospitals, clinics and local pharmacies. That is why a robust SOP which follows different colour codes (red, yellow, green, pink) with special notes (e.g., hazardous, non-hazardous) on each pack of wastes is used as reported by one of the pharmacists who has also worked for a hospital pharmacy (N).

Role played by Waste vendors

As seen in the interviews and reports, when it comes to ***waste vendors,*** finally, the process of segregation is much more robust and clear. Both EWC and the colour code system are continuously being advised by the waste vendors interviewed for safe and responsible drug waste management. The concept of EWC and colour coding were also cross checked and supported by pharmacies, hospitals, and care homes. The study reveals that waste vendors follow EWC (European Waste Catalogue) codes prior to collecting waste from the source. As stated by the respondents, it was also reported by the Health Technical Memorandum by the Department of Health that the healthcare waste producers must adhere to this **EWC** by law for segregating and labelling the right waste category in the right container with a written description note about the waste, adequately labelled with an unique six digit code for each type of waste. As per the reports, for instance, household medicines returned to a community pharmacy should be coded as: cytotoxic and cytostatic medicines: 20-01-31* and other medicines 20-01-32, as reported. (*) An asterisk at the end of a code means the waste is hazardous. For instance, one of the waste vendors (T) highlighted that they always visit and audit the waste site as per the EWC code and their waste spec sheet. The spec sheet for the audit also contains the history of the wastes, materials types, process of initial segregation, for instance if it is being mixed with other wastes or not, as explained by the waste vendor. This is how they segregate waste either in the customer zone (predominantly) or in their own sites. It is also clear from the vendors interviewed (e.g., T) that though it is not a legal requirement, the majority of the healthcare waste producers (e.g., hospital, pharmacy) use a **colour code system** at the source for segregating the right waste in the right container more efficiently. Table 4.36 presents such key colour codes used for segregating drugs wastes as revealed in the study.

Table 4.36 Examples of drugs wastes segregation as per colour code used by hospitals, pharmacy, and care homes (Source: Interviews and reports)

Colour code / container	Type of drug wastes
Black	domestic (Municipal) waste stream which may undergo landfill / incineration / energy from waste process
Yellow	type of hazardous wastes (not cytotoxic or cytostatic) which requires disposal by incineration
Purple	cytotoxic and cytostatic waste which require incineration in a suitably permitted or licensed facility;
Blue	medicinal wastes (non-hazardous) which require incineration
Denature kits	CD (controlled drugs) – e.g., methadone, morphine, opium etc

Role played by the Local councils

As people have a tendency to throw their unwanted drugs into the household bins, local councils and their outsourced waste vendors could play a crucial role when collecting and segregating the household wastes. However, the investigation reveals that a very few councils have special arrangements for drug waste segregation from household wastes. For instance, one of the local council respondents (LC - 12) has highlighted that pharmaceutical wastes generally fall within the definition of hazardous clinical waste and as such, should be collected separately from other household waste. The respondent further stressed that ***"the Council's Clinical Waste Collection contractor, 'X' Ltd provides an on-request service without charge for this via Essentia Community Services***" which partially ensures appropriate segregation of drug wastes separately from household waste. However, some other local councils reported that the unwanted drug wastes contained in the household garbage are generally not segregated or separated from the general garbage. For instance, one of them outlined that '***Pharmaceutical waste in the general non-recyclable waste stream is likely to go undetected unless in large quantities as this waste is not manually sorted at any point either by our own crews or by the operator".*** The reasons for not doing it are also identified below (see Table 4.37).

Table 4.37 Key reactions and / or reasons local councils do not have any special arrangement or special segregation while collecting household wastes (Source: Interviews)

- **Responsibility issue** (e.g., this is pharmacies responsibility than local council)
- **Waste legislation issue** (e.g., unwanted household drug wastes is classified as non-hazardous)
- **Operational issues** (e.g., lack of resources to segregate unwanted drugs from household garbage)
- **Lack of understanding of the related environmental impact** (e.g., presence of unwanted drugs waste into household waste stream is not an issue)

✓ Consider safer and greener drug waste disposal option

As revealed in the study, waste vendors have predominantly been sought to treat drugs wastes in two ways: high temperature incineration with energy recovery and low temperature incineration with/without energy recovery. As per the respondents, unwanted drugs which are cytotoxic and/or cytostatic are considered highly hazardous and undergo high temperature incineration with an energy recovery process, while the other category of drug (any drug without cytotoxic / cytostatic) undergoes low temperature incineration. Table 4.38 shows the different categories of drug wastes and their treatments options available that emerged from the study.

Table: 4.38 Treatments available for categories of unwanted drugs wastes (Source: Interviews and reports)

Drug category	Segregation	Types of disposal
Cytotoxic / cytostatic	Yellow container	✓ High temperature (around 1000ºC - 1110ºC) incineration with energy recovery ✓ Zero landfills of by-products: Recycle of incinerated ash

Drug category	Segregation	Types of disposal
All other drugs without cytotoxic / cytostatic	Blue container	✓ Low temperature (~ 900ºC) incineration with or without energy recovery ✓ Zero landfills of by-products: Recycle of incinerated ash Exception: some vendors treat them on high temperature with energy recovery
CD (controlled drug)	Denature kits	

As part of responsible waste disposal, the majority of waste vendors employ byproduct (originated in the incinerators) diversion from landfills through recycling. For instance, one of the waste vendors (T) reported that in both cases of low or high temperature incineration, 10 to 15% of weight (of original wastes) remains as byproducts (bottom ash) which then is recycle as metal or glass materials to avoid landfills. However, some waste vendors have not yet reach 100% landfill diversion of incinerated byproducts. For instance, one of the respondents (V) highlighted that some of the byproducts (incinerated ash) are still of environmental concerns as they end up in landfill. It was also evident that the incineration process also produces excessive amount of heat and steam, which are used to power steam turbines and this produces electricity to supply locally. For instance, one of the waste vendors (T) reported that they have generated 37-megawatts of electricity from one of their clinical incineration plants.

Appendix 18: Case examples of some marketing authorization challenges to adopt green

Example 01: marketing authorization challenges to adopt continuous manufacturing into existing process

As revealed in the study, a complex marketing authorization process was identified as one of the top barriers for adopting continuous process into the existing process of a drug. This barrier was predominantly felt by generic companies and a few innovative companies. For instance, one of the respondents (B – site 2), a sustainability and utility manager responsible for an API production plant from a leading innovative pharma, stressed that it is always challenging to obtain regulatory approval for making a change to the existing manufacturing process. While the responded was further asked the scope of continuous manufacturing for the existing API in the market (which around 3000 APIs), the respondent clarified that they

all would need to apply for a new licence from the regulatory body for changing their manufacturing process and they would need to show an equivalence process, which ultimately would lead to quite a long wait and considerable cost, as it would require a new plant and new equipment for the new process. Similarly, another respondent, a senior principle environmental scientist (C) from one of the leading innovative pharma, also contributed to this thread saying: ***"... ... you need to get the approval from the FDA, so that's one of the crucial barriers for moving to continuous or from batch process"***

It was also evidenced in the interviews that generic pharma could adopt automatic cleaning equipment into the existing batch process to make it semi-continuous, which ultimately aims to save cleaning raw materials (e.g., solvents). However, as revealed in the study, even such a small change is not so straightforward, and it would require external regulatory validation. This is because this change could have potential impact on the quality of end products. For instance, one of the respondents (G) from a generic production plant, explained why they cannot apply automatic equipment cleaning for some products, though automatic equipment cleaning is more eco-friendly, using fewer chemicals than manual cleaning process. The respondent highlighted that it would require further validation (from the regulatory body) of the new automatic cleaning equipment introduced in the process.

As per some other interviewees, the requirement of internal quality assurance to demonstrate the safety and efficacy of the changed process (batch to continuous) is also crucial prior to applying for costly regulatory validation. For instance, one of the respondents (C) explained the significance of such internal quality assurance of the redesigned process. The respondent highlights that there are lots of considerations on the stability of the drug molecule, such as the reaction time, that going through limiting steps, they would also have safety related issues; and the process of going through the quality issues, in terms of credibility and stability of the products at particular stages, materials and other activities, may have to be huge in establishing whether they could do continuous production – that's the concerns for them now. It was also stressed by the respondent about internal validation that – ***"... you make sure you haven't introduced anything which is not verified for safety and quality"***

Example 2: marketing authorization challenges to adopt solvent recovery into the existing process

It was also revealed in the interviews that the complex marketing authorization process has also impeded many generic and in some cases a few innovative companies to redesign or

modify the existing process to adopt solvent recovery. As per the respondents, only if the regulatory body is happy that there is no impact on product quality due to recycling, reusing or reprocessing solvent, then they will grant a licence to do it. It was also revealed that there were lots of wastes generated from the process, the industry called them faulty batches, due to internal quality failure. The majority of the respondents also highlight that if manufacturers want to reprocess those faulty batches, they would have to go through the long regulatory paperwork to get the approval to do it, and only if the regulatory body sees they have not compromised product quality and efficacy. For instance, one of the respondents (G), a production manager from a generic company, shared an incident of batch failure due to quality discrepancies. The respondent further explained that after first-time filtration (a unit operation during API production) of the product they found some discrepancies. So, if they wanted to redo the filtration process again to achieve the standard quality to avoid wastes and related time and costs, they would need to have permission from the regulatory body again to do it, as explained by the respondent. It was also revealed that if the regulatory body relaxed the relevant documentation process with cost estimation and a quicker approval process, this could significantly reduce waste, save significant amountsof money and save significant amounts of resources.

Another respondent (B site – 2), a sustainability and utility manager from a leading innovative pharma, also explained how quality requirements for regulatory approval have become a barrier for them to thinking about the solvent recovery in the process. The respondent has highlighted that it would be very difficult for them to meet the quality specifications (from the regulatory body) of the solvent required for a process for reuse. It was also outlined by the respondent that some of the final washing stages (as part of API production) are regulated to be fresh solvents, which is operationally difficult to achieve.

It was also found that to achieve external regulatory validation, it is initially important to meet and convince the internal quality requirements for solvent recovery. For instance, it was highlighted by one of the respondents (B site- 1), an EHS manager from a leading innovative pharma, that it is quite hard for them to reuse materials from one production line to another new production process due to the stringent quality requirement of the site. Similarly, another respondent (A) also explained why they are not able to adopt recovery practices due not to convince the internal quality assurance team. The respondent has also outlined that the challenges for them is to work with their quality assurance people to assure the quality of recycling or reusing solvent is high enough so they can reuse them in a new production

process. The respondent has further stressed that for the quality assurance team, quality is the key here for a drug product production and it is better not to distract from quality by adopting recovery practice.

It was also evidenced in the study that bio pharm has felt this barrier to a lesser extent than generic and innovative pharma due to having very limited scope of recovery in the bio process. A few of the bio pharma have also been unable to convince the internal quality team about recycling. As per the study, generally, the recovery process in bio pharma operations is rare due to complex equipment engineering and uncertainty in product quality. For instance, one of the respondents (F site – 2) explained that though some of their main components are water-based media and this would never be difficult to recycle, as part of sterility assurance strategy the process has to go through extra processing and have extra packaging, which actually leads to the difficulty of adopting reusing/recycling/recovering practice across the cell development process.

Example 03: marketing authorization challenges to adopting green packaging

As revealed in the study, pharma packaging, especially primary and secondary packaging, ensure the product stability and integrity during storage and transportation. Hence, pharma packaging requires maintaining stringent quality specifications, such as traceability, product purity, efficacy, effectiveness, tempering, protecting microbial contamination etc, as highlighted in the interviews and reports. It was also understood that any post marketing changes into packaging materials or packaging design (e.g., resizing) could have a significant impact on drug stability, safety and efficacy. As per the respondents, companies are required to submit a regulatory validation to demonstrate the safety, quality and efficacy for the changed packaging system, which has ultimately impeded the companies (both innovative and generic equally) to adopt green packaging option. For instance, it was evidenced from a respondent, a senior supply chain leader from a generic pharma manufacturing plant (E – site 3), that they have felt regulatory challenges to redesigning the pharma packaging system for green credentials. For instance, the respondent explained that there is less scope for applying green practice in pharma packaging, as they cannot change the manufacturing specification after regulatory approval and if they want to do so, they would have to redo all relevant product stability experimentation, which is costly and time consuming. The respondent has further highlighted into this thread: ***"... it would be very difficult for you to redesign process specification, you can't just change packaging material because you had lots of series of***

trial previously to fix that material; you have to redo all stability testing, you will need to do you know all shelf life testing... ... ..."

However, it was also revealed in the study that convincing the internal quality team prior to submitting proposed packaging change to the regulatory body is also critical and challenging. This is because in case the of packaging the main concern is quality rather than environmental criteria. For instance, one of the respondents (H) outlined that in packaging they could use glass instead of aluminium foil, but the glass is so heavy and expensive. Additionally, as identified in the interviews and reports, it is important to highlight here that different drug substances are stable in different forms of packaging contact. For instance, if it is a sterile product, it is mandatory to consider product stability first over the environment, as explained by the respondent. Again, the respondent provided another example, eye drops, which rely more on plastics because the drops have less interaction with the plastics and are more stable inside plastic. So, different drug formulations have different levels of stability to different types of packaging materials, as highlighted by the respondent. So, it is difficult to combine product stability and environmental criteria of packaging materials together to convince internal quality, as outlined by the respondent. Another respondent from a generic pharma (E – site 3) also highlighted that packaging materials are critical, as product stability could be influenced by the green materials of the packages. The respondent has further stressed that "… ***changing material in packaging need lots of money and stability work; maintaining stability of drugs could be crucial barrier while using different green packaging materials"***

The reason why this barrier has only been faced by the manufacturers is also clear. The majority of the process changes, regardless of environmental related ones, arise during the commercial manufacturing phase as revealed by the study. This is because the process is better understood as time passes and therefore green innovation and related process streamlining activities (e.g., solvent recycling etc) happen during the commercial manufacturing phase rather than the R&D phase. For instance, one of the respondents (A), a senior environmental specialist from a leading innovative pharma highlighted that though the company has lots of environmental considerations during the drug design and developmental phase, it is always a risk to get the development done rapidly. As developing related process knowledge (e.g., understand the impact of solvent recycling on product quality etc) during the R&D phase is a time consuming and costly process, the manufacturing phase is the key stage to demonstrate knowledge-based process change.

Appendix 19: Evidence of uncontrolled drug wastes from high concerned patient groups

- ✓ ***Patients in End of Life care***

After interviewing the pharmacist managers, care home managers, and GPs, it emerged that drug wastes from patients in end of life care is difficult to control due to frequent hospital admissions and lack of communication (in terms of patient medication) between different hospital departments. In addition, their prescription is also reviewed by multiple healthcare groups, such as community pharmacists, community nurses, GPs, nutritionists, physiotherapists etc, and because of this there are lots of drug interactions and frequent prescription changes, which lead to unused drug waste at the end. However, the trade-off between 'admit them to hospital /frequent GP visits to their home/care homes' and 'final drug wastes' is still not evaluated or ignored, as highlighted by a number of the respondents. One of the respondents (N) however also highlighted that it would apparently be costlier if frequent GP visits / hospital admissions were considered to review the patient (aims to optimize drug usage).

Some strong case examples have also helped the understanding of the severity of the challenges. For instance, one of the care home mangers (S) interviewed stated that this group of patients in care homes is more than 80% and as such the waste is huge. The care home manager (S) also comtributed to this thread saying ***"In care homes most of the patients are dyeing before complete the cycle".*** The respondent also highlighted the example that sometimes GPs prescribe 12 capsules of antibiotic but in reality after three days that antibiotic does not work, so the doctor changes the medication again before the cycle and induces drug wastes. This is just one example but there are many similar cases that are faced every day. Another care home manager highlighted that this group of patients most of the time do not want to take their medication on time even though the care workers encourage the patients to take them. The respondent outlined their challenges in this regard saying: ***"We try to encourage them to take on time, but we cannot force them. As we popped up and put them in a cup and these medicines are disposed of as we cannot reuse for them".*** The respondent has also highlighted that this is an everyday scenario for them.

- ✓ ***Patients with dementia***

As per the interviews, patients with dementia are another group of patients who do not adhere to the drug prescribed. As emerged in the study, the majority of pharmacists have identified this group of patients who are not being recruited and reviewed regularly under the MUR scheme. Even though this group is under the MUR scheme, the non-adherence just cannot be controlled, as highlighted by both GPs and pharmacists. This is because the majority of this group of patients forget to take their medication on time and this non-adherence requires further prescription and drug wastes as highlighted by the pharmacists (e.g., N, O).

- ✓ ***Patients with multiple complex morbidity***

As revealed in the study, patients with complex morbidity who are prescribed with several different (more than five to ten) types of drugs is another group of patients who also show a significant proportion of drug nonadherence. Most of the respondents (GPs and pharmacists) have highlighted that this non-adherence was due mainly to actual adverse drug interactions or due to a fear of drug interactions and related side effects. As per a few respondents, this is because the patients in this group have multiple chronic diseases and as such, they must take multiple drugs at a time. This is also termed polypharmacy in the healthcare sector, as was revealed in the study.

It was also highlighted in the study that the increasing trend of polypharmacy in the UK is overwhelmingly very high. For instance, it was reported previously that the average number of prescription item prescribed for each patient has increased by 53.8% between 2001 and 2011 (Duerden et al., 2013). This study reveals that though polypharmacy can be useful for some patients, it has been identified as one of the key challenges for optimizing drug wastes in most of the cases. Both GPs and pharmacists have strongly agreed on two aspects here: first is frequent medication changes due to drug – drug interaction and side effects, and, second is the fear among the patients of drug-drug interaction and side effects. Both aspects are reasons for not taking drugs as prescribed, leading to frequent drug non-adherence. For instance, one of the GPs (O) highlighted this saying: ***The trouble is lots of elderly and we have significant proportion of people with dementia, multiple complex morbidity patients they don't know or they forget or pile up drugs"***

Appendix 20: Evidence on key GHG emission related measures and related performance impacts

- ✓ ***Reduction of scope 1 emission***

As revealed in the study, scope 1 emission was used to measure a particular plant's emission originating from direct operational activities of that plant, such as running combustion process for ignition of chemical reaction, solvent separation, crystallization, purification, drying, and/or emission from formulations operations. It was evidenced from the interviews that the majority of the respondents from innovative pharma highlighted that they are actively considering this measure for assessing plant level GHG emissions. Some of them also highlighted that this was because the managers are accountable to report on these measures to the divisional manager towards achieving carbon emission targets.

As discovered in the interviews and reports, having such measures in place, companies across the industry were also driven to capture the related environmental impact. In the case of scope 1 emission reduction, it was clear that all stakeholder companies reported improvement of saving scope 1 emission with varying levels. As evidenced in the study, the majority of the innovative companies significantly improved their Scope 1 emission performance through applying green practices, such as reducing raw materials usages, recycling, reusing of inhalers products and redesign pack size. For instance, as per the reports, one of the innovative companies (In – 08) had reduced scope 1 emission by 21% globally (as of 2017) since 2010 against their internal targets of 20% reduction by 2020 and 80% reduction by 2050. Another innovative company (In – 01) reported 50,000 tonnes of scope 1 carbon emission savings since 2010 from just applying green packaging (e.g., optimized blister pack size). The majority of the interviewees also agreed to such savings.

Table 7.3 also highlights some related environmental improvements across the industry as identified in the reports. The middle row in the table shows the actual emission benefits captured (what), which key green practices were attributed to achieving this level of improvement (how) and what was the key motivation to do that (why).

Table 7.3 Highlights of some key environmental impact related to scope 1 emission (Source: reports)

Key performance sub measures	**Highlights of some Key environmental improvements**	**Stakeholder reported the benefit & source of evidence**
Reduction of scope 1	What? - 3 million metric tonne of co2 emission expected to be eliminated.	(In – 01)

Key performance sub measures	Highlights of some Key environmental improvements	Stakeholder reported the benefit & source of evidence
emission	How? - apply greener process for a product called 'Lyrica' Why? - target of waste reduction	
	What? - 3 million tons of CO2 emissions from 2007-2020 (estimated) How? - apply solvent recovery project Why? - target of waste reduction	(In – 03)
	What? - saved carbon dioxide emissions equivalent to taking 5,199 cars off UK roads. How? - apply recycling, reusing of inhaler products Why? - target of waste reduction	(In – 02)
	What? - CO2 emissions are saved by 50,000 tones co2e since 2010. How? - redesigning pack size. Why? - Packaging waste reduction	(In – 01)
	What? - 600,000 tons of CO2 emissions saved during production lifecycle. How? – materials reduction (water, zinc, plastics bottle) Why? – Materials cost reduction	(In – 05)
	What? - 30% energy efficiency improvement over the last 10 years How? – improve emery efficiency (materials based) of API manufacturing process Why? – Internal environmental target	(In – 05)
	What? – Reduced approx. 490 tons of CO2 emission per annum How? – Green packaging (replace plastic drum with paper fibre drum for OTC drug) Why? – Promote sustainable packaging	(Gn -04)
	What? – Expected reduction of 3,500 metric tons of CO2 equivalent emissions in 2018 How? – apply resource conservation measures (mainly from water reduction activities) Why? – Materials cost reduction	(B – 01)

Key performance sub measures	Highlights of some Key environmental improvements	Stakeholder reported the benefit & source of evidence
	What? – estimated 14,000 tons of carbon dioxide reduction per year (equivalent to taking 7,300 cars off the road) from manufacturing plant How? – Renewable source of energy – site specific wind turbine installation Why? - Reduce scope 2 emission and electricity purchase costs	(In – 08)
	What? – 16,700 tons of greenhouse gas (GHG) emissions reduced in 2017 How? – apply energy efficiency projects Why? - Reduce scope 2 emission and electricity purchase costs	(Gn -03)
	What? – Reduced 100 MT CO2 e GHG emissions by three months through saving 95,856 kWh of electricity How? – Energy efficiency project (replace chilled water-cooled compressor with an air cool one) Why? – Energy reduction	(Gn -04)
	What? – Reduction of 128 metrics tons of CO2e How? – Energy kaizen (site boiler upgrading) Why? – Energy reduction target	(B – 23)

- ✓ ***Reduction of scope 2 emission***

As evidenced in the study, scope 2 emissions were used to measure the amount of carbon emitted from purchased (indirect) energy in terms of gas or electricity for the plant operations. It was evidenced from the interviews and reports that almost all stakeholders were seen to consider scope 2 emission reduction measure to improve energy related emission performance from their operations. As revealed in the study, the majority of the respondents attributed this to the corporate environmental pressure for achieving energy related carbon reduction targets. However, some of the generic and bio pharma were seen to consider scope 2 emission only, rather than scope 1 emission.

It was revealed in the study that almost all stakeholders reported related performance improvement though at varying levels. The majority of innovative pharma investigated had

reduced scope 2 emissions significantly through applying a variety of energy efficiency practices. For instance, it was reported by one of the innovative companies (In -08) that it had consumed 25% of total energy from renewable sources, which significantly reduced related scope 2 emission. It also estimated a reduction of 14,000 tons of energy emission per year from installing wind turbines across the manufacturing sites. However, generic and bio pharma almost equally reported the medium level of improvement. It was also observed in the study that in most of the cases both generic and bio pharma reported scope 2 performance improvement from applying varieties of energy kaizen / energy efficiency projects (e.g., boiler upgrading and energy efficient equipment), while innovative companies reported improvement mostly from installing renewable sources of energy. For instance, one of the generic companies (Gn – 03) had reduced 16,700 tons of scope 2 emission in 2017 from just applying energy efficiency projects (without any renewable energy projects). Similarly, one of the bio pharma (B – 23) had reduced 128 metric tons of scope 2 carbon emission from applying varieties of energy kaizen projects (e.g., equipment/machineries upgrading).

Table 7.4 also highlights some related environmental improvements across the industry as identified in the reports. The middle row in the table shows the actual emission benefits captured (what), which key green practices was attributed to achieve this level of improvement (how) and what was the key motivation to do that (why).

Table 7.4 Highlights of some key environmental impact related to scope 2 emission (Source: reports)

Key performance measure / sub measures	**Highlights of some Key environmental improvements**	**Stakeholder reported the benefit & source of evidence**
Reduction of scope 2 emission	What? – estimated plant energy efficiency by 80% and reduce related carbon emission How? – renewable source of energy supply using CHP Why? – Reduce scope 2 emission and electricity purchase costs	(In – 04)
	What? – estimated 14,000 tons of carbon dioxide reduction per year (equivalent to taking 7,300 cars off the road) from manufacturing plant How? – Renewable source of energy – site specific wind turbine installation Why? - Reduce scope 2 emission and electricity purchase costs	(In – 08)

Key performance measure / sub measures	Highlights of some Key environmental improvements	Stakeholder reported the benefit & source of evidence
	What? – 16,700 tons of greenhouse gas (GHG) emissions reduced in 2017 How? – apply energy efficiency projects Why? - Reduce scope 2 emission and electricity purchase costs	(Gn -03)
	What? – Reduced 100 MT CO2 e GHG emissions by three months through saving 95,856 kWh of electricity How? – Energy efficiency project (replace chilled water-cooled compressor with an air cool one) Why? – Energy reduction	(Gn -04)
	What? – Reduction of 128 metrics tons of CO2e How? – Energy kaizen (e.g., site boiler upgrading) Why? – Energy reduction target	(B – 23)

- ✓ ***Reduction of VOCs emission***

As revealed in the study, the majority of the respondents from the innovative pharma outlined measuring VOCs in their process. They have also highlighted that they use this measure because most of their processes are significant sources of VOCs. Some of the interviewees also highlighted that they also have internal targets on reducing VOCs emissions. For instance, one of the respondents (B – site 2) explained - ***"We also have environmental restriction on VOC emission; we also take measures to minimize VOCs during recovering process of used solvents".*** The measure was also used by some of the bio pharma and only a few generic pharma. The majority of these companies attributed their internal environmental goal to using this measure.

It was also evident that VOCs emission-related performance impact has also been captured across the industry. The majority of the innovative companies showed significant positive performance by reducing VOCs emissions from the production process by applying green chemistry practices. For instance, one of the innovative pharma (In – 07) measured both halogenated and non-halogenated VOCs emission to assess the effectiveness of existing green activities (e.g., redesign existing process for using lower impact substances) to reduce

related VOCs impact on environment. It was observed that though non-halogenated VOCs emission from the production process had increased by almost double within the last four years (between 2010 to 2014), the use of halogenated VOCs (which is predominantly responsible for GHG emission contribution) had decreased by almost half within the same period.

In the case of bio pharma, a medium level of improvement was observed. Some of the bio pharma reported significant improvement of VOCs (mainly halogenated) emission from the manufacturing sites. For instance, one of the bio pharma (B – 11) had reduced 99% of VOCs since 1992 across all its manufacturing sites through reduced use of halogenated substances during manufacturing. Interestingly, though some of the generic pharma adopted VOCs reduction activities, very few generic pharma were seen to measure performance and report improvement.

The related performance impact is presented in Table 7.5, which shows in detail what impact has been observed, how it is achieved and what the key drivers behind it are.

Table 7.5 VOCs emissions measures and related performance impact across the industry (Source: reports)

Key performance measure / sub measures	**Highlights of some Key environmental improvements**	**Stakeholder reported the benefit & source of evidence**
Reduction of VOCs consumption	What? – Estimated reduction of VOCs by 50% by 2020 from the base year 2003 level How? – Redesign production process with lower impact chemicals (e.g., avoid methanol) Why? – Promote Sustainable production	(B – 19)
	What? – 21.3 % VOCs is reduced by one year How? – Redesign production process with lower impact chemicals (e.g., avoid methanol); apply equipment operation procedure. Why? - Promote Sustainable production	(In – 09)
	What? – Total VOCs emission is increased by 57.1% from 196 tons in 2010 to 308 tons in 2014. But halogenated VOCs are reduced to almost half, i.e., from 15 tons in 2010 to 8 tons in 2014.	(In – 07)

Key performance measure / sub measures	Highlights of some Key environmental improvements	Stakeholder reported the benefit & source of evidence
	How? – Increased usage of non-halogenated products Why? – Either no alternative found / not known for increased non halogenated emission; optimize production process for eliminating / less use of halogenated products results lower level halogenated emission	
	What? – Halogenated VOCs reduced by almost 45.6% from 103 tons in 2013 to 56 tons in 2017; Non halogenated reduced by 61.4% for the same period How? – Optimize production process for lower VOCs impact Why? – GHG emission reduction target	(In – 05)
	What? – 99% of VOCs reduction since 1992 (across all manufacturing sites). How? – Reduce use of halogenated substances Why? – Strong internal environmental target	(B – 11)
	What? – Reduced by about 35% VOCs emission in 2011 compared to 2008 How? – Solvent recovery practice Why? – Internal environmental targets	(B – 19)
	What? – Significant reduction of VOCs since 2016 How? – VOCs containing residues (generated from solvent recovery) was used as alternate fuel in cement plants Why? – Internal goal of VOCs reduction	(Gn – 04)

- ✓ ***Reduction of ODS emission***

As revealed in the study, this measure was widely used across the industry due to the regular and continuous usage of coolant materials across the pharma operations. It was also revealed that both innovative and bio pharma were seen to report significant overall improvement, while generic pharma was shown to have a comparatively lower level of improvement. As per the interviews, the majority of the innovative companies, especially those who produce inhaler products, have used this measure to keep tracking the improvement against their internal goals. For instance, one of the respondents (A) also outlined that they must

continuously measure the emission of ODS, as they have been producing fluorinated inhaler products, which have significant negative impacts on the environment. They keep tracking the amount of ODS, as they are looking for alternatives for testing and reducing the ODS impact.

As per the study, innovative companies have significantly reduced ODS from their operations. For instance, one of the innovative companies (In – 05) recorded zero ODS emission in recent times (2017), while it had measured 0.4 tons (CFC R11 equivalent) of ODS substances in the facility in 2013. This significant performance achievement is attributed to the adoption of relevant green activities such as complete phase out of CFC refrigerants and considering natural refrigerants etc. In most cases they were seen to phase out ODS from their operations. Similarly, it was revealed in the reports that bio pharma companies have also reduced ODS significantly from their operations. For instance, one of the bio pharma were seen to reduce their operational ODS by 40% in 2016 against their internal goal of 95% reduction by 2020. The related performance impact is presented in Table 7.6 which shows in detail what impact has been observed, how it is achieved and what the key drivers behind it are.

Table 7.6 ODS emissions measures and related performance impact across the industry (Source: reports)

Key performance measure / sub measures	**Highlights of some Key environmental improvements**	**Stakeholder reported the benefit & source of evidence**
Reduction of ODS (Ozone Depleting Substance) emission	What? – ODS emission is reduced by 46.3% from 82 kg in 2016 to 44 kg in 2017. How? – CFC refrigerants completely phased out; use chlorine free HFCs; natural refrigerant (e.g., ammonia) Why? – Promote green chemistry based manufacturing or green manufacturing	(In – 05)
	What? – Reduction of 6350 pounds of ODS refrigerant How? – Lean operations (leak detection, repair, replace with natural refrigerant) Why? – achieve GHG emission target	(Gn – 20)
	What? – ODS emission is reduced by 33.4% within two years (2015 –	(In – 08)

Key performance measure / sub measures	Highlights of some Key environmental improvements	Stakeholder reported the benefit & source of evidence
	2017) How? – Phasing out ODS related substances Why? – F-gas related regulation	
	What? – ODS emission is reduced by 87.5% within four years (2010 – 2014) How? – Phasing out ODS related substances Why? – Sustainable manufacturing	(In -07)
	What? – ODS contained in equipment is reduced by 75% from 7794 kg in 2010 to 1934 kg in 2017; ODS released from equipment is reduced by 75.2% from 214 kg in 2010 to 53 kg in 2017 How? – Use green alternative Why? – Promoting green manufacturing	(In – 02)
	What? – ODS emission is increased by more than double from 2.02 tons in 2014 to 4.84 tons in 2016, though 14.2% reduction from 2015 How? – Not known Why? – Not known	(Gn – 03)
	What? – Reduced by 40% in 2016 having an internal goal of 95% reduction by 2020 How? – Reduce use of ODS substances Why? – Internal environmental goal	(B – 21)

However, in the case of generic pharma, as evidenced in the interviews and reports, the performance improvement was comparatively very low. This is because though some of them are agreed on the importance of using this measure, the majority of them are still in the planning stage to replace ODS from their operations. For instance, it was evidenced in the interviews that two (G, H) of the respondents from generic pharma highlighted that they payed particular attention to measuring ODS emission, as they are extensive users of CFC-based refrigeration systems. Though they are thinking of using ammonia-based chillers, the impact of ammonia on the product quality is still a massive concern. That is why ODS

measures are very important for them. One of the generic pharma (Gn - 03) reported a slight improvement (14.2% reduction in 2016 from 2015) on ODS reduction from their operations, though this apparently increased over three years in average between 2014 and 2016 (see Table 7.6).

- ✓ **'GHG emission measures by sales volumes' and 'GHG emission measures per employee'**

As revealed in the study, some companies relate the function of carbon emission to their sales revenues and employees to better capture the importance of reducing carbon emission from the pharma process. For instance two of the companies, one from innovative pharma (In – 09) and another from bio pharma (B – 24), reported that it is more effective to measure the carbon emission impact by dividing the total plant emission by the total sales volume, which has also been termed *eco-efficiency*.

However, some other companies have outlined that the emission measures are effective while considering the emission impact per employees. For instance, some of them have measured how many tons of carbon emissions were induced from one employee. One of the bio pharma reports (B – 25) highlighted that ***"We have also estimated our total CO2 emissions and have indicated our "environmental intensity" on a per employee basis, an important indicator of our activity".*** Another of the bio pharma (B – 11) recorded a 29% reduction in carbon emission per employee from 2013 to 2018. Regarding this typical measure, the company further highlighted that ***"Every employee is personally responsible for mitigating harmful impacts of the Company's operations on the environment"***

- ✓ ***GHG emission measure per production unit***

As revealed in the reports, some bio pharma companies have measured GHG emission per production unit. For instance, one of the bio pharma (B - 04) reported the carbon emission measure as 'total kg of carbon emission generated per production line'. As per some of the respondents, this could be one of the rudimentary approaches for the greening pharma process as well as meeting demand from the downstream customer for green API. For instance, the NHS could have been provided with specific carbon emission performance for each API production, as explained by the respondents.

However, only a few innovative and generic companies have sought to apply this API specific carbon emission measure. The related performance impact has also been captured in

the reports. For instance, one of the innovative pharma (In – 05) measured an API based CO2 emission. It reported that its AI API (Anti-infective API) production line produced 2 to 3 times lower carbon footprint compared to other AI API in the industry. Hence this product has been considered as 'low carbon product' by the company across its global sites. Another example can be taken from one of the generic pharma (Gn – 07), which reported scope 1 emission (direct emission from production process) from an intravenous product called 'Viaflo 1 Litre Intravenous Solution'. It reported that the direct emission from production of the product is 30%. It also highlighted that the product's overall emission reduced by 33% in two year from 2014 to 2016.

Appendix 21: Materials related performance measures and relevant performance impact

- ✓ ***Reduce Process Mass Intensity (PMI)***

The majority of respondents from innovative pharma have strongly advocated the use of PMI, as they strongly believe that this measure has not only reduced raw materials input, but also energy and waste related costs. For instance, one of the respondents (C) highlighted that, being a micro-level green measure, PMI provides a process specific result and therefore, the process chemists have lots of alternative options for streamlining the process for lowering the PMI value. The respondent also outlined that they have already set PMI targets for some of their products based on projected sales of the products within their portfolio. It was also highlighted by one of the innovative pharma (In – 03) that ***"We have completed a PMI assessment for 47% of our development portfolio in respect of the API synthesis".*** The company further highlighted that PMI was one of the rudimental corporate targets for the last decade to demonstrate organisational impact in the product pipeline. Though low in number, there were still significant materials savings reported by the companies. For instance, one of the innovative pharma (In - 08) reported a 17% reduction of PMI in 2017 against the target of 20% reduction by 2020. Examples of some related performance impacts have also been highlighted in Table 7.8. The importance of this measure can also be assessed when the company (In - 08) highlights that ***"The team uses PMI as a key internal metric to measure and track raw material use efficiency rate and identify improvement opportunities"***

Table 7.8 Highlights of some PMI measure related environmental impact across the pharma industry (Source: Reports)

Key performance measure / sub measures	Highlights of some Key environmental improvements	Stakeholder reported the benefit & source of evidence
Process Mass Intensity (PMI)	What? – PMI is reduced by 17% by 2017 against the target of 20% reduction by 2020 How? – Identify opportunity to streamline process by tracking raw materials (e.g., solvent, reagents etc) use efficiency rate during process development Why? – Promote green and sustainable chemistry or MET practices	(In – 08)
	What? – PMI is decreased by 22% across the product portfolio during API production in 2017 How? – apply green chemistry principles or MET practices Why? – Promote green chemistry or MET practices	(In – 03)
	What? – 57% reduction in PMI for a product developed to treat a rare disease neurological disease How? – Process efficiency improvements Why? – Promote process innovation for resource efficiency	(B - 12)

However, it is revealed in the study that the concept of PMI is still not widely popular in generic pharma and bio pharma. As per the majority of the respondents, they still do not have such kinds of PMI for the bio-based production process, as it is difficult to measure bio-based input rather than chemical-based input raw materials. For instance, one of the respondents (A) has outlined that they are trying to develop a PMI for bio-based production so they could control the amount of water usage. Some of the respondents have also highlighted that this kind of API for the bio-based process would be a very efficient and effective approach for the bio pharma industry, as this industry consumes water considerably.

- ✓ ***Amount of Water reduction***

Water is one of the biggest natural resources employed in pharma operations. A typical manufacturing site consumes 79% of water for cooling purposes (e.g., cooling tower or cooling reaction chamber to reduce access heat from the process) and 21% for actual production purposes, as outlined in the reports (e.g., Gn – 05). Given such significant

potential of water footprint, the measure of water reduction has been popular across all three industry stakeholders. The majority of respondents from innovative pharma, almost half from generic pharma and two thirds of bio pharma respondents have strongly advocated measuring the amount of water consumed or reduced by means of assessing different kaizen projects. The respondents from innovative pharma and generic pharma equally highlighted that as part of kaizen projects they measure how much water they have saved from different recovery (e.g., reuse, recycling etc) activities. While demonstrating the importance of measuring the amount of water reduced or saved, one of the respondents (B – site 1) from a leading innovative pharma highlighted that –***"... ... for water, we try to come with project, to reduce the water use because there is plenty of water that we use as part of cleaning of vessels and we try to come up with idea and suggestions to improve".*** Similarly, another innovative pharma also (In – 17) committed to reduce water consumption by stressing that ***"we have site-based targets based on production volume and water scarcity, with plans for a 5% improvement by 2023 against a 2017 baseline"***

Driven by the measurement of water reduction, bio pharma companies have also sought to undertake proactive measures to save water, as bio pharma is one of the biggest sources of water consumption. Most of them have also reported significant improvement. For instance, one of the bio pharma (B – 09) has measured that they are expecting to save a significant amount of water (approx. 53000 cubic meters) by undertaking water efficiency projects, such as installing low flow facet aerators across its all manufacturing sites. The company has stressed this performance impact highlighting that "***we expect to save 53,000 cubic meters, equating to approximately 21 Olympic swimming pools of water per year".*** Some examples of water reduction measures and related environmental performance impact are presented in Table 7.9.

Table 7.9 Some key highlights of water reduction related performance impact across the industry (Source: Reports)

Key performance measure / sub measures	**Key environmental benefits captured**	**Stakeholder reported the benefit & source of evidence**

Key performance measure / sub measures	Key environmental benefits captured	Stakeholder reported the benefit & source of evidence
Water reduction	What? – Reduce water consumption by 12% in a year How? – Adopt water efficiency project Why? – To maintain continuous improvement	(Gn – 20)
	What? – 20,000 litres of water savings from a single plant annually How? – Water monitoring system installation Why? – Meet Energy reduction goal	(B – 18)
	What? – Expected more than 100,000 m3 water savings in a year How? – Water efficiency projects (e.g., recycling, reusing etc) Why? – Reduce water footprint	(In – 15)
	What? – Estimated water reduction by 20% by 2030 How? – Energy efficiency projects (e.g., Green TSO – technical ad supply operations project) Why? – Reduce water footprint	(B – 02)
	What? – 60% less water consumption to clean equipment for manufacturing How? – Design combined drugs (e.g., SYMTUZA) Why? – Sustainable drug production	(In – 08)
	What? – Water consumption has increased by 3% from 2012 to 2014 How? – Increased liquid (injecTable medicine) production in some sites Why? – Water efficiency target	(In – 04)
	What? – 40% water savings within a site in a year How? – Install vacuum toilet flushing system, flow-controlled taps, recycle toilet flushing water Why? – Water reduction target	(In – 11)
	What? – 58% water consumption reduced by 2017 from 2010 level, while target was 40% by 2020 How? – apply water efficiency projects (e.g., automatic wash in place for equipment, high pressured spray gun for cleaning process areas, water audit etc)	(Gn – 04)

Key performance measure / sub measures	Key environmental benefits captured	Stakeholder reported the benefit & source of evidence
	Why? – Achieve energy target	
	What? – expected water savings 80 million gallons per year How? – Water efficiency projects (e.g., recycling, reusing, reducing) Why? – Reduce water footprint specially in water scarcity regions	(B – 21)
	What? – water savings by 33% of total water used within a year (2016 to 2017) How? – water recycling and reusing Why? – Meet Energy savings target	(B - 17)

It was also evidenced from the reports that some generic and bio pharma companies have related the function of water measurements to employees for better control. For instance, one of the generic pharma (Gn - 03) measured that water usages per employee had been reduced by 5% from 184.71 m^3 in 2012 to 180.48 m^3 in 2016. Some of the innovative companies considered further sub measures to calculate the total amount of water consumption within a site. For instance, one of the leading innovative pharma (In 05) reported how they had measured total water reduction. The report outlined that the company measured the following different micro level sub measures:

- 'water used for cooling',
- 'water used in process for washing',
- 'water used for sanitary purpose',
- 'water used in boilers',
- 'amount of water reused'
- 'Amount of water recycled' etc.

It was observed in the study that these micro level water measures were vitally important to ensure appropriate management and control of water usage across the manufacturing plant. Another two innovative pharma companies (In – 01; In – 02) also used these types of micro

level measures. As per the reports, these companies also added another important dimension of measurement - water usage by sources (e.g., municipal water, surface water/ground water etc) - so as to protect natural water imbalance and related ecosystem disruption due to drought. Compared to innovative and bio pharma, generic pharma used less extensive micro level water measures. As the bio process is water exhaustive, a similar approach but further robust measures have been evidenced in the bio pharma companies. For instance, almost half of the bio pharma company reports have carefully considered the factors of:

- 'source of water',
- 'water conservation',
- 'sales versus water use', and
- 'Water usage per employee' into their measures.

✓ ***Amount of raw materials (e.g., API, excipients, solvents, packaging waste etc) use / save / reduces***

This measure simply evaluates the total amount of raw materials (e.g., solvents, reagents, excipients and packaging materials) usage, savings or reductions across the manufacturing site. As per the respondents, this differs from PMI in such that it considers plant-wide raw materials use rather than process centric input and output materials. This measure was a moderately influential measure and almost equally applied in both the innovative and generic pharma sectors, especially for measuring solvent usages, as they are the costliest raw materials in pharma. Driven by this measure, companies across the industry have sought to measure related performance impact. In the case of innovative pharma, significant savings in raw materials, especially solvents and packaging materials, were achieved through applying green chemistry practice or MET. For instance, one of the innovative pharma (In – 01) has reported savings of 11000 gallons of byproduct solvents through a solvent recycling and reusing project for cleaning site equipment. In the case of bio pharma, they were seen to report medium level performance. As per the majority of the interviewees, they saved both solvents and packaging materials more than any other raw materials in the process. However, the majority of generic pharma reported more packaging related savings than any other raw materials like solvents. Table 7.10 presents some of the key examples of performance impact that came out of the reports.

Table 7.10 ‘Amount of raw materials use/save/reduce’ as a measure and its performance impact (Source: reports)

Key performance measure / sub measures	**Key environmental benefits captured**	**Stakeholder reported the benefit & source of evidence**
Amount of raw materials use / save / reduce	What? – reduce use of organic solvents by 20% during API synthesis process step and reduces 1000 litters solvent by products per kg of output during purification step to produce a drug for treating neurological disorder How? – Develop a greener (water based) process and avoid use of organic solvents (e.g., methanol, ethanol etc); it reduces number of chemical reactions to 60 from 80. Why? – Promote green chemistry or MET practices	(B – 12)
	What? – Save 89% of solvents from the commercial manufacturing process of Sildenafil How? – Develop greener process by eliminating toxic and highly volatile solvents in API synthesis process; reduce solvents uses to 4 types from 10 different types Why? – Sustainable product innovation	(Gn – 04)
	What? - reduced solvent usage; - reduced process waste; - 99% solvent recovered. How? - applying waste kaizen projects; - solvent recovery projects. Why? - cost effectiveness; - environmental concern	(In – 03)
	What? - reducing the number of chemical by-products that are typically discarded by more than 25 percent. How? - apply solvent recovery project Why? - target of waste reduction	
	What? - reduced consumption of packaging materials (aluminium foil) by 30% How? - redesigning the pack size Why? - Packaging waste reduction	(In – 01)
	What? - cut by 80% volume of water and zinc that were used to sending to waste, and 21.5 million fewer Tablets and 850,000 fewer plastic bottles have been produced for use in clinical trials	(In – 02)

Key performance measure / sub measures	Key environmental benefits captured	Stakeholder reported the benefit & source of evidence
	How? – Apply green chemistry or MET practices Why? – Promote sustainable pharma manufacturing	
	What? – recover and reuse 66.4% of ethanol consumed in production process in a year How? – Solvent recovery (via onsite distillation tower) Why? – Materials cost reduction	(B – 24)
	What? – solvent use reduction by 42% How? – Apply continuous manufacturing Why? - promote green manufacturing	(In – 02)
	What? – reduce secondary packaging volume: 32% less paper board and 68% less plastics for a product called Neulasta How? – Redesign packing system Why? – Promote Green packaging	(B – 09)

Appendix 22: Findings on Energy related performance measures and relevant performance impact

- ✓ ***Total Energy use, amount of energy purchased, and total use of energy generated onsite***

Given the key importance of carbon reduction targets and energy cost reduction, companies across the industry have measured energy consumption from different sources such as gas, electricity, biomass, renewable, non-renewable, local onsite production etc for inclusiveness and completeness of the measure. The majority of respondents from innovative pharma highlighted that they measure total energy used in the plant, where half of them stated that they also measure two different sources of energy generated: "amount of energy generated onsite (e.g., using CHP)", or "energy generated from waste" for instance, and "amount of energy purchased". A few of them also outlined that they separately measure the contribution from renewable sources of energy such as solar panels.

Table 7.12 also highlights some related environmental improvements across the industry as identified in the reports. The middle row in the table shows the actual emission benefits captured (what), which key green practices was attributed to achieve this level of improvement (how) and what was the key motivation to do that (why).

Table 7.12 Highlights of some key environmental impact related energy efficiency measures (Source: reports)

Key performance measure / sub measures	**Highlights of some Key environmental improvements**	**Stakeholder reported the benefit & source of evidence**
Total energy used	What? – Total energy used is reduced by 2.4% from 2015 to 2017; non-renewable sources reduced by 15.2 % and renewable sources increased by ten times by 2017 from 2015. How? – Energy efficiency program (e.g., employee training, energy kaizen projects etc) Why? – Energy reduction goal	(In – 08)
	What? – Total energy consumption reduced by 3.4% from 2016 to 2017 How? – Energy efficiency programs Why? – Responsible manufacturing	(In - 12)
	What? – Consumption is increased by 4% from 2014 to 2017 How? – Increased production volume Why? – New market expansion	(In – 10)
	What? – Consumption reduced by 14.5% within ten-year time (2007 – 2017) How? – Energy conservation Why? – Energy reduction target	(B – 09)
Total use of energy purchased	What? – total purchased energy (in terms of gas, electricity, biogas, diesel etc) reduced by 2.5% by 2017 from 2015 How? – Increase onsite energy generation Why? – Energy reduction goal	(In – 08)
Total use of energy generated	What? – total onsite energy generated (from co-generation, wind, solar PV, biomass etc) reduced by 2.8% from 2015 to 2017	(In – 08)

Key performance measure / sub measures	Highlights of some Key environmental improvements	Stakeholder reported the benefit & source of evidence
onsite	How? – Not known Why? – Not known	
	What? – Onsite energy generation increased by 3% within two years How? – Energy efficiency project (e.g., Solar panel, PV, CHP etc) Why? - Increase renewable source of energy	(In – 03)
	What? – Onsite generation increased by 52% from 2016 to 2017 How? – using solar panel Why? – Energy efficiency target	(B – 02)

Driven by these different forms of energy measures, companies have reported related performance impact (shown in Table 7.12). For instance, one of the innovative pharma (In – 08) reported that their total purchased energy (in terms of gas, electricity, biogas, diesel etc) had reduced by 2.5% by 2017 from 2015 through energy efficiency programs and increasing onsite energy generation programs to achieve the strategic energy reduction target. The study also reveals that though companies have sought to increase onsite renewable energy generation (e.g., CHP, biomass etc) significantly, the amount of total energy consumption on average has been improved at a very slow (see Table 7.11) and low amount (not so drastically) as opposed to individual energy targets. Indeed, in some cases it has increased slightly and failed to meet year on year energy targets. For instance, one of the innovative companies (In – 10) reported that their overall energy consumption increased by 4% within three years, from 2014 to 2017, due to increased production volumes.

However, in the case of a number of bio pharma, the companies have dealt with business expansion and production volumes in such a way that they have still been able to decrease energy consumption through adopting more energy efficiency projects and onsite generation of renewable energy. For instance, one of the bio pharma companies (B – 09) reduced its energy consumption by almost 15% in ten years still having expanded its production in multiples sites. As revealed in the study, in the case of generic pharma, though overall they

have reduced energy consumptions (medium level), they are still far behind in onsite energy production compared to other stakeholder companies.

- ✓ ***Amount of energy saved from conservation & efficiency improvements***

The study reveals that all three industrial sectors (innovative, generic and bio pharma) have paid attention almost equally to adopting this measure to save energy. Successful energy savings from applying varieties of energy conservation or energy efficiency or energy kaizen projects have been observed thoroughly in the study. It was revealed in the interview that the majority of innovative companies measure the progress of all relevant energy saving activities using energy kaizen projects. For instance, one of the respondents (B – site 1) outlined that they measured how much energy they had saved from energy kaizen or energy saving programs, for instance, 5% energy savings from onsite waste recovery projects from the previous year. However, it is important to highlight here that process specific energy usage measurement is still not available. For instance, one of the respondents (B – site 2) highlighted the limitation of measuring energy used for a specific process. The respondent explained that though the process specific energy measurements are assumed to be undoubtedly helpful and effective measures for the operations managers to adopt more green chemistry practices, total energy input and output measure within a particular process is still underdeveloped and a lot more research is required to understand the transformation of energy within a process. Similar evidence was gathered while exploring environmental reports. For instance, one of the innovative companies (In – 05) estimated 80% energy savings from tri-generation technology adoption in their sites. Some more examples of related performance impact across the industry are presented in Table 7.13

Table 7.13 Highlights of some key energy efficiency-based measure and related environmental impact across the pharma industry (Source: Reports)

Key performance measure / sub measures	**Highlights of some Key environmental improvements**	**Stakeholder reported the benefit & source of evidence**
Amount of energy saved from conservation & efficiency	What? – 30% savings of electricity from manufacturing sites How? – 100% LED lighting and motion sensor lighting Why? - Achieve Energy reduction target	(In – 11)

Key performance measure / sub measures	Highlights of some Key environmental improvements	Stakeholder reported the benefit & source of evidence
improvements	What? - 50 GWh of electricity savings within a year How? – Consider energy efficiency programs Why? – Energy savings target	(Gn – 03)
	What? - 95,856 kWh of electricity savings within three months How? – Apply water savings project (e.g., replace water cooled compressor with air cooled one) Why? – Energy savings target	(Gn – 03)
	What? – 30% energy efficiency achieved from a single production process (e.g., production process of AI API) How? – Redesigned process for energy efficiency Why? – Green manufacturing	(In – 05)
	What? – 50% energy savings achieved How? – Apply RCM (Resource conservations measures) Why? – Energy reduction target	(B – 01)
	What? – energy consumption is reduced by more than 16% How? – Apply CI project Why? – Energy reduction target	(B – 05)
	What? – Reduced energy consumption by 31.7% from 41000 KW/hr to 28000 Kw/hr within manufacturing site How? – Consider energy monitoring system Why? – Achieve energy reduction target	(B – 18)

Generic and bio pharma also measure the amount of energy saved from conservation and efficiency improvements at almost equal pace with innovative pharma (see Table 7.11). For instance, almost half of the generic pharma respondents explained that they had undertaken extensive energy efficiency projects (e.g., leak detection programs, LED lighting, replacing old process equipment and machineries with more energy efficient ones, employees energy related behavioural modification strategy etc) across the plants and they compared the energy

savings before and after implementation of those energy kaizen projects. For instance, one of the respondents (G) strongly agreed to undertake machine reliability checks on regular intervals (e.g., beginning of the process and end of the process) to improve energy performance, especially when machines are run 24/7.

In addition to these three key measures, another four measures have been identified in the reports: Total electricity consumed per production unit, Total Electrical Energy per Sales (GJ/million sales), Total Electricity usage per employee and Total gas usage per employee. All these measures are used by bio pharma and only one of these measures – Total electricity usage per employee - is used by generic pharma. It is evidenced in the report that compared to innovative and generic companies, bio pharma has been sought to relate the functions of sales revenue, employees, and specific production units for measuring energy usage. As per the reports, instead of using macro-level generic energy usage, it is more impactful when the energy usage is linked to micro-level per sales or per employee or per production unit for better energy management. However, the operational viability and cost benefits of macro-level versus micro-level energy measures is still not known.

Appendix 23: Findings on waste measures and related performance impact

- ✓ ***Amount of wastes (hazardous) generated***

As per the findings, this has been one of the simplistic measures for assessing waste efficiency. This measure was predominantly used by innovative pharma and some generic and bio pharma. It was evidenced from the interviews that the majority of respondents outlined that they are actively measuring the types of wastes produced in the production plant as per the waste reduction goals. This measure helped the companies to identify the scopes of reducing hazardous waste generation in the process. As revealed in the study, both innovative and bio pharma reported significant improvement in hazardous waste reduction driven by their internal hazardous waste reduction goal. For instance, one of the innovative companies (In – 08) reported a 7.29% reduction in hazardous wastes generated within a two year period (2015 – 2017). Another bio pharma (B – 22) reported a 49% reduction in hazardous wastes in two years through applying green chemistry principles. Unfortunately, as revealed in the interviews, there was very low scope of reducing hazardous wastes in the generic pharma process, as the majority of them work on already approved off-patent processes, and less

choice for using alternative solvents. Therefore, overall performance improvement is low in generic pharma. A wide range of related performance impact across the industry is also captured in Table 7.15.

Table 7.15 Examples of hazardous waste related performance impact across the industry (Source: reports)

Key performance measure / sub measures	Key environmental benefits captured	Stakeholder reported the benefit & source of evidence
Amount of wastes (hazardous / non-hazardous) generated	What? – production of hazardous wastes decreases by 1% within a year How? – Use of lower environmental impact solvents Why? – Promote green chemistry	(In – 04)
	What? – 49% hazardous waste reduction within two years period (2015 to 2017). How? – Waste reduction in early development through establishing green team; non-hazardous is increased due to increase production Why? – Identify and mitigate waste reduction opportunities	(B – 22)
	What? – 51% hazardous wastes reduced by 2016 against the goal of 60% reduction by 2020 How? – Apply site specific lean and six sigmas to improve process efficiency and reduce defects and waste generation Why? – Promote green production	(B – 21)
	What? – 1454 pounds of hazardous wastes reduced in a year from a product (the name of the product was not known) How? – Recycling of aerosol cans (Isopropyl alcohol aerosol cans) which used to be treated as hazardous wastes Why? – Waste reduction target	(B – 23)
	What? – 86.7% decrease in hazardous wastes generation in a year How? – apply waste kaizen program: in liaison with local waste vendor the company has classified waste into 45 separate streams for the best treatment option Why? – Promote responsible waste management and cost reduction via waste recovery	(In – 01)

	What? – Hazardous wastes decrease by 30% between (2011 – 2016) How? – Consider lower impact chemicals Why? – Improve waste efficiency	(Gn – 03)

- ✓ ***'Measure toxicity level of waste'***

Under the hazardous waste streams, companies have also been sought to measure the toxicity level of the hazardous wastes generated in the industrial effluents. This measure is of greater and particular interest for the manufacturers to adhere to the regulatory requirement of discharge limits of wastewater through assessment of the toxicity level of the wastewater.

As revealed in the study, this measure is used to assess the performance of toxicity reducing related practices and/or activities, such as how much toxicity has been reduced from a manufacturing plant through reducing usage of hazardous toxic chemicals, or through treating the toxic wastewater from the plant, or through undertaking environmental risk assessment programs for safe discharge of effluent into the environment. As revealed from the investigation, this measure has been identified as one of the key environmental performance measures because the pharma companies are placed under considerable pressure from local government to meet water quality legislation. As per the majority of the interviewees, this is also important due to companies' top management's environmental commitment towards saving aquatic contamination that leads to disrupted local ecosystems.

The study reveals that this measure has been used in two phases of operations – one phase is during usage of raw materials (e.g., amount of hazardous raw materials used/saved) in the manufacturing process and the other phase is during the treatment of manufacturing effluents (e.g., amount of API discharge into the environment, amount of toxic substances released into the aquatic environment which may have a negative impact on aquatic life, as well as water quality). Therefore, two sub measures were identified in the study:

- ❖ ***Assessment of effluents discharged into the water*** and
- ❖ ***Amount of toxic/hazardous raw materials reduced/saved/eliminated.***

- ❖ ***Assessment of effluents discharged into the water***

In terms of assessing the effluents, the majority of the pharma companies investigated were considering different micro-level measures, such as BOD (Biological Oxygen Demand) - a measure used to evaluate the quality of river water and industrial wastewater; COD (Chemical Oxygen Demand) – which measures organic pollutants levels in the water, high COD loads can reduce the oxygen in water bodies; TSS[13] (Total suspended solids), amount of substances such as API, phosphorous, nitrogen, etc discharged into the water, reduced/eliminated for demonstrating the level of water quality. As revealed in the study, a lower level or safety threshold (the level which is safe for drinking water, as well as safe for aquatic life) of BOD, COD and TSS in the discharged water is expected to be achieved by the companies. It was also revealed that the discharge limit was set by the local water regulatory bodies. As per the majority of the respondents, the discharge limit also depends on various factors such as types of operations, types of chemicals used in the process, daily limit, or monthly limit etc. Table 7.16 shows a typical limit for the biological and natural extraction process as per the reports. The subsequent section discusses each of these measures.

Table 7.16 Typical limit of BOD, COD and TSS for biological and natural extraction process (Source: reports)

Toxicity measures	Discharge limit per day (mg/L)	Discharge limit per month average (mg/L)
BOD	35	18
COD	228	86
TSS	58	31

COD and BOD

The study reveals that the majority of the respondents from innovative pharma have used BOD and COD as part of their effluent assessment. As per most of the respondents, companies carry out these measures because they must comply with local and national water

[13] TSS – Total suspended solid are solids in water that can be trapped by a filter. TSS can include a wide variety of material, such as silt, decaying plant and animal matter, industrial wastes, and sewage. High concentrations of suspended solids can cause many problems for stream health and aquatic life (http://bcn.boulder.co.us/basin/data/BACT/info/TSS.html)

quality requirements set by the local/national water authority. Hence, these micro-level measures are crucial for demonstrating better water quality. For instance, one of the respondents has highlighted that they have a separate specialist contractor who is specialized in assessing effluent quality to assess both COD and BOD on an ongoing basis.

As revealed in the study, driven by the regulatory requirements, all stakeholder companies almost equally prioritize COD /BOD measures for assessing water quality. For instance, one of the innovative companies (In – 09) reported a 14.2% increase in BOD efficiency by 2016 from the base year of 2010, meaning that the company has now improved its discharged wastewater quality, which will have lower impact on aquatic life due to having lower levels of BOD in surface water. Similarly, some bio pharma reported that they maintained BOD and COD levels well below the permitted discharge level by improving hazardous materials efficiency. For instance, one of the bio pharma (B – 22) explained that ***"the improvement in materials use efficiency has also helped to reduce the BOD levels".*** In response to the performance impact of BOD and COD from manufacturing plants, another innovative pharma (In – 15) reported that the number of regulatory limit breaches reduced to 23 in 2017 from 42 in 2016, which is predominantly due to the improvement in BOD and COD levels. Another generic pharma (Gn – 07) highlighted that their COD efficiency level had improved by 4.16% from 24 mg/L in 2015 to 23 mg/L in 2017, while the average performance of BOD was 9.3 mg/L within same period.

TSS (in terms of API assessment)

The study further reveals that as part of manufacturing effluents assessment companies have also used environmental risk assessment programs or PIE programs to assess the amount of API discharge into the aquatic environment, which is seen as an extended item for TSS. It was also clear in the interviews that though it was still not a part of water quality regulatory requirements, companies (especially innovative) were seen to measure it for two important reasons – firstly, it was a mandatory requirement for marketing authorization of drugs by FDA/EMA and secondly, it was a strong top management commitment to deal with PIE and AMR due to strong pressures from all levels of pharma stakeholders. For instance, one of the innovative pharma (C) respondents highlighted that they were measuring the amount of API discharge to improve and reduce the aquatic effluent toxicity along with BOD and COD in an ongoing basis. The process of how they measure and set limits for API discharge has already been covered in the fourth chapter under the green practice section. For instance, one of the

respondents from innovative pharma (B site 1) highlighted that they use a terminology called EHAC (Environmental Hazard Assessment Category) to categorise the toxicity levels of each API based on PEC/PNEC ration. The respondent highlighted that –***"we classify specific API under EHAC categories; so depending on how toxic how hazardous that material is we have this from EHAC from 1 to 5 how important from environmental perspective of that material".*** The responded further explained that driven by this measure the company has recently measured the toxicity levels of all its APIs in its existing product portfolios and identified 17 of them as hazardous whose discharge limit had already been set internally beyond the actual regulatory limit.

However, very few of the generic and bio pharma measured the API discharged amount from their sites as evidenced from both interviews and reports. For instance, one of the bio pharma (B – 11) highlighted that they evaluate their APIs, excipients, and other raw materials in line with the SHE (Safety, Health and Environment) perspective. For instance, they used safety datasheet included in the SHE to assess the risk of API or other raw materials use in the process, as the safety data sheet contains relevant hazards and waste disposal methods which are readily assessable by their employees. Some of the respondents from generic and one respondent from bio pharma highlighted that they use the measure of 'the amount of toxic chemicals (e.g., solvents) reduced/eliminated from the sites' and they do this due to the regulatory pressure from REACH. Additionally, this is because though API is out of REACH, the intermediates toxic by-products are not.

- ***Amount of toxic / hazardous raw materials reduced / saved / eliminated.***

Amount of wastes (hazardous) converted to beneficial use (e.g., waste to energy)

As revealed in the study, this measure was one of the key factors to ascertaining the cost benefit of responsible waste management. As found out in the investigation, it measures how much hazardous waste is re-processed for beneficial purposes such as how much is 'waste to energy' or how much is 'waste to compost'. In the majority of the cases, companies (especially innovative) have onsite waste to energy facilities, but some other companies have sent off their wastes to offsite waste energy plants.

Innovative pharma is the leader in applying it and in reporting the related positive environmental impact to date. For instance, one of the respondents (B – site 1) from a leading innovative pharma highlighted that their company is working towards achieving a target of

80% wastes to beneficial usages like converting waste to energy, or other beneficial use. The respondent also highlighted that they have employed an outside waste consultant who has provided a detailed breakdown of waste generated and, based on this breakdown, they are able to identify measures and fix the significant sources of wastes. The respondent commented: ***". ... so we have waste contractor who deals with this, and we know exactly how much paper, how much plastic how much pharmaceutical have been generated in each specific production area, we can track to see if any increase in the amount to try to understand the reason why there has been an increase.. ..."***

It was revealed in the study that the majority of innovative pharma are continuously working to reduce wastes across the manufacturing plant by applying several waste kaizen projects. Some of the respondents further highlighted that they were addressing this waste reduction in accordance with the guideline of waste hierarchy. Therefore, they measure waste reduction by applying all sources of waste treatments such as amount of waste they have recycled/reused/incinerated or landfill.

The study also reveals that driven by this measure, companies across the sectors have been continuously reducing their overall waste streams through converting wastes (both hazardous and non-hazardous) into beneficial usage, though some companies have put more focus on reducing hazardous wastes through avoiding higher environmental impactful chemicals from the manufacturing process. However, regardless of hazardous or non-hazardous waste streams, the companies, especially the innovative companies, have converted wastes into beneficial usages though the ratios of conversion from hazardous and non-hazardous are slightly different in some cases. For instance, it was evidenced that one of the innovative pharma (In – 08) reported that energy recovery from hazardous wastes had decreased by 25% within two years (2015 – 2017), while energy recovery had been increased by 3.4% from non- hazardous waste stream for the same period. As per the respondents, the reasons for this variation were multifaceted, such as types of products produced, and amount of wastes generated from products and processes etc.

The performance impact was also captured in the case of both bio pharma and generic pharma, though the overall performance level was low. In another example, a bio pharma company (B -12) showed increases in energy recovery from wastes. For instance, it recorded that (non-hazardous) waste to energy had increased by 50.6% from 793 metric tons in 2013 to 1195 metric tons in 2016. Some bio pharma also reported another form of beneficiary use:

waste to compost. For instance, one of the bio pharma (B -12) increased (non-hazardous) composted waste from 1435 to 3543 metric tons within same period. Similarly, a number of generic pharma reported energy recovery from hazardous waste. An example from a generic pharma (Gn – 07) showed that energy recovery from hazardous wastes increased by 163.4% in two years between 2015 –2017.

Amount of wastes (hazardous) recycled / reused / incinerated / landfill

As revealed in the study, the pharma companies investigated, especially innovative pharma, were seen to measure their hazardous wastes based on recycled amounts, reused amounts, incinerated amounts, and landfill amounts. It was also highlighted in the study that this measure was of great importance to track the progress of the management of hazardous wastes conversion rate, as the disposal of hazardous wastes is the key concern for pharma. The study also reveals that though this measure is applied across the industry with a moderate emphasis, innovative pharma apply it more than other sectors. The subsequent section also highlights some evidence from non-hazardous waste related performance in order to make a comparison.

It is evidenced that very few of the generic and bio pharma have measured levels of hazardous waste in treatment such as the amount of hazardous wastes incinerated/reused/recycled/land filled. Though both generic and bio have partially followed the waste hierarchy methods, the majority of them have not used all the relevant measures in each category (recycling/reuse/incineration/landfill) apart from recycling and incineration in a few cases, as found in the study. As per a few respondents, one of the reasons is that they do not feel such regulatory pressure to maintain hierarchy of wastes. Rather they adhere to regulatory discharge limits of API or amount of BOD, COD etc as explained by the majority of the respondents.

The study also reveals that both hazardous and non-hazardous waste recycling and reuse have significantly increased while incineration is decreasing gradually. For instance, one of the generic pharma (Gn -07) reported that its recycling rate had increased by 76% (of that 78% non-hazardous waste recycling and 60% hazardous recycling) in a year (2017) and the net income generated was 4.9 million US Dollars. Driven by this measure the company has adopted waste management optimization such as removing hazardous liquid wastes by adding a drum dryer for reusing wastes to allow recycle the rest of the contents. Similarly, another bio pharma has reported that 141 tons of plastics wastes generated from bio

manufacturing were recycled within a year (2017) through companywide manufacturing plastics waste management programs. Most of these plastics wastes are gloves, tubing, pipettes, and other related plastics. These wastes are taken to an external vendor who processes them into industrial-grade plastics which are used in benches, pallets, road curbs etc.

Interestingly, in many cases (especially in innovative pharma cases), it is evidenced that overall hazardous waste performance has significantly increased compared with non-hazardous waste. The performance breakdown on recycling, reuse, incineration, and landfill under hazardous and non-hazardous wastes from a leading innovative pharma (In – 08) is presented in Table 7.17, which shows the performance differences within the same period of operation. Some respondents from innovative pharma have also highlighted the key reasons for this difference, such as types of drugs manufactured within the time frame, amount and types of wastes by-products produced (as it differs from process to process), average production volume, and available cost modelling for wastes treatments within that time frame.

Table 7.17 Differences in the performance impact of hazardous and non-hazardous wastes treatment (Source: In – 08)

Types of Waste conversion	Hazardous wastes stream (% of change from 2015 to 2017)	Non- hazardous wastes stream (% of change from 2015 to 2017)
Recycle rate	(+) 9%	(+) 2.1%
Reuse rate	(+) 109.3%	(+) 2.4%
Landfill rate	(+) 66.6%	(+) 3%
Incineration rate	(-) 49.37%	(+) 21.5%

(-) = decrease; (+) = Increase

‘Zero landfill of hazardous wastes’ has also been identified in the study as another key measure for the pharma industry. As per the majority of respondents, this measure has helped the industry not only to stay ahead of reducing hazardous and toxic contamination of drug

substances but also to provide a strong cultural commitment across the industry for waste reduction and increased waste diversion.

In the case of innovative pharma, it was evidenced that majority of them reported significant improvements in reducing landfill of hazardous substances through strong internal commitment. For instance, one of the innovative companies (In – 05) had committed to eliminating their hazardous waste to landfill completely**.** The extent of applying this measure is significantly higher for innovative pharma than other sectors. The company further reported that ***"In 2007 we banned the practice of disposing of organic hazardous waste in landfills from all its operations worldwide and this commitment remains in place today".***

Some respondents from innovative companies also highlighted the zero landfill of hazardous wastes. Majority of them had strong internal goals to reduce hazardous waste to landfill. For instance, another respondent (B – site 2) from an innovative pharma also explained that they had used waste reduction measures across their production plant as they had strong corporate level waste management commitments, such as Zero to landfill, and therefore, they measured all sources of wastes including % of waste going back to beneficial use. Driven by this measure, many companies have decreased their landfill rate significantly against their internal target. For instance, one of the innovative companies (In - 06) reported that 42% of all its sites had sent off zero waste to landfill as of 2017, while the target was at least 50% of all its manufacturing sites to send zero waste to landfill.

Similarly, generic and bio pharma have contributed to this strong commitment of waste measure. For instance, one of the generic pharma (Gn - 07) highlighted that it has recently prevented 66% of wastes from landfill through a waste management project for one of its manufacturing sites. The company has also outlined that 30% of all its manufacturing sites have already achieved more than a 95% waste diversion rate as of 2017, against the target of achieving more than 95% diversion rate from all its manufacturing sites by 2020. Bio pharma has also shown significant progress on this. For instance, one of the bio pharma companies has reported a 79% increase in achieving a landfill diversion rate as of 2016, against the target of an 85% diversion rate by 2020.

Appendix 24: Findings on The Waste Legislation

The Waste (England and Wales) regulation 2011

It was revealed in the study that as per the hierarchy of waste legislation (the waste legislation 2011), the waste must be treated in a hierarchical order based on the capability, capacity and technical viability of the R&D and manufacturing sites in pharma. For instance, prevention is in the first order, then it is followed by re-use, then recycling if it cannot be reused, then follows the other recovery options (e.g., energy from waste) and finally follows disposal if all options failed in the top hierarchy. The key scope of the legislation in pharma is shown in Table 5.6 as revealed in the study.

Table 5.6 Key scopes of the waste (England & Wales) regulations 2011 in pharma (source: Interviews and Reports)

Key aspects of The Waste (England and Wales) Regulations 2011	
Examples of wastes	✓ Process wastewater (cleaning wastes) ✓ Hazardous solvent wastes (e.g., hazardous API discharge) ✓ Non-hazardous papers / plastics wastes
Key environmental impact of wastes	✓ PIE from hazardous process wastes ✓ Water, air, and land contamination
Key regulatory requirements	✓ Any business produces wastes must follow five stages of waste management hierarchy (prevention,>reuse> recycle>other recovery (e.g., waste to energy)> disposal) where prevention is the top priority and disposal is in the last resort, when technically and economically feasible.
Key consequences for not following the regulation	✓ Monetary penalty/ warning letter ✓ Suspension of environmental permit
Examples of green practice driven	**Green Manufacturing**: recycle and reuse solvent; wastes solvents to energy, avoid using of toxic and SVHCs related solvents etc

The investigation reveals that the majority of the companies highlighted this legislation as a driver to look for greener scope for processing their wastes. Regardless of sectoral differences, the majority of the companies had moved from lower stage to upper hierarchy whenever feasible. For instance, in particular, the majority of innovative pharma companies have adopted solvent recycling projects to save raw materials costs as well as to conform

with wastes legislation. For instance, one of the respondents (B – site 1) from a leading innovative pharma highlighted that inspired by the site waste management guidance built on waste hierarchy strategy, they have a target of zero landfills. Waste hierarchy based site waste management policy has encouraged them to eliminate wastes in the first instance (e.g., use greener solvents from solvent guide) and the respondent also showed the driving force of waste hierarchy legislation by explaining - "***If we can't eliminate waste then we try to find alternative to reuse the waste that we generate, or to recycle or to recover the waste with energy".*** The respondent further highlighted that one of their zero to landfill sites since 2014 has also achieved the target of converting 80% of the waste to beneficial use. The respondent believes that though cost savings is one of the drivers, waste legislation plays a key role in being in such a position in terms of managing their site wastes.

Similar cases were also evidenced in the environmental reports from other innovative pharma. For instance, one of the innovative companies (In -08) reported that driven by the hierarchy of waste management process, the company have been able to achieve a 74.7% waste diversion rate in 2017 compared with 69.3% in 2016. The company also has been motivated to recover zinc metals used in processing and has sent them for recycling and reuse. Similarly, the waste hierarchy has driven another company (In – 04) to introduce closed loop recycling for reusing materials in the process.

As came out from the study, though few bio pharma (e.g., B – 11, B – 18) were seen to be motivated by this legislation and were seen to adopt waste performance measures based on waste hierarchy to achieve their internal waste reduction goals, generic pharma showed the lowest level of motivation. This is due to the fact that when it comes to solvent wastes, which are the predominant and more concerned ones, generic companies still struggle to redesign their processes, as they would have to apply for a new regulatory licence to run a recovery project. For instance, one of the respondents (B – site 1) who runs a generic liquid production plant highlighted that though the company are aware of the hierarchy of waste legislation, the company still do not have viable scopes for running solvent recycling due to costs and regulatory burdens. Additionally, some other respondents from generic pharma further highlighted that the process of solvent recycling is technically and economically not feasible for them. A few of the respondents also commented that it is labour intensive and uses more extensive mechanical energies which require for recycling, the solvent to be returned into the system - so regenerating wasted solvent would be an energy intensive and costly process.

However, some of the generic companies were seen to apply recycling practices for packaging related wastes driven by the legislation.