Green Pharma Supply Chain: A review of existing practices and future directions

Abstract.

Purpose - The pharmaceutical industry is facing significant pressure to tackle antimicrobial resistance (AMR). Other ecological, societal, and regulatory pressures are also driving the industry to 'go green.' While such a (green) transition could be possible through appropriate green practices' implementation, present understanding about it is superficial and vague. A key reason is the lack of green practices'-related studies on pharmaceuticals, and which are also insufficiently comprehensive. This knowledge gap is sought to be addressed.

Design/methodology/approach - A systematic literature review (SLR) was conducted with seventy-three carefully selected articles then subjected to thematic content analyses for synthesising the relevant themes and sub-themes.

Findings – Seventy-six operational-level green practices covering all key stakeholders across the drug lifecycle were identified. It was revealed that designing drugs having accelerated environmental degradability is important for combatting AMR, and that redesigning existing drugs is more resource-intensive than developing new ones with regards to enhancing eco-friendliness. Additionally, that there is considerable cost-saving potential in solvent recycling and flexible manufacturing, though both practices are not commonly used at present. With regards to green-related barriers, the stringent quality requirements for drugs, and therefore the risks in making green-oriented modifications in them, and the time-consuming and costly regulatory approvals were found to be the key ones.

Practical Implications – The operational green practices' framework developed for individual pharmaceutical supply chain stakeholders could help practitioners in benchmarking, modifying, and ultimately, adopting green practices. The findings could also assist policymakers in reframing existing regulations such as Good Manufacturing Practices or GMP-related to promote greener drug development.

Originality/value - This work is the first systematic attempt to identify and categorise operational-level green supply chain practices across stakeholders in the pharmaceutical sector.

Keywords – Green Supply Chain Practices (GSCP), Drug, Antimicrobial Resistance (AMR), PIE (Pharmaceuticals In the environment).

Highlights:

- Biodegradability of drugs is more important than environmental degradability.
- Flexible manufacturing process design (or quality by design) reduces resource wastage.
- Ecopharmacovigilance is effective in combating PIE and AMR-related issues.
- Upstream and downstream coordination is key to greening pharma operations.
- Costly and time-consuming regulatory approval is a key barrier to greening pharma processes.

Abbreviations/Nomenclature:

- PIE - Pharmaceuticals in the Environment
- AMR - Antimicrobial Resistance
- GMP - Good Manufacturing Practice
- FDA - Food and Drug Administration
- MHRA - Medicines and Healthcare products Regulatory Agency
- EMA - European Medicine Agency
- API - Active Pharmaceutical Ingredients
- GDP - Good Distribution Practice
- PAT - Process Analytical Technology
- CMO - Contract Manufacturing Organisations
- CRO - Contract Research Organisations
- GLP - Good Laboratory Practice
- NGOs - Nongovernment Organisations
- PSNC - Pharmaceutical Services Negotiating Committee

1. Introduction

Environmental degradation has intensified demands for a safer planet. Here, the role of the pharmaceutical industry is particularly critical. For example, the industry accounts for roughly 52 megatons of carbon emissions (Belkhir, 2019). Also, more than 90% of its raw materials inputs such as organic chemicals come from non-renewable petroleum feedstock (Clark *et al*., 2010). There is also tremendous waste generation, estimated to be 25-100 times the drug weight (Roschangar *et al*., 2017). Pharmaceutical pollutants also contaminate water and food cycles and cause antimicrobial resistance (AMR) that could lead to up to 10 million deaths and more than US$100 trillion in costs by 2050 (Kummerer, 2009; Johnson & Johnson, 2017). Not surprisingly therefore, the term 'Pharmaceuticals in the Environment' (PIE), that encapsulates the industry's role in pollution, climate change, and unsustainable natural resource exploitation has come to be commonly used (Vatovec *et al*., 2021).

The wide range of environmental challenges demand a comprehensive understanding of green practices across each of the lifecycle stages, and for individual pharmaceutical sector stakeholders (Balasubramanian *et al*., 2017). However, such an understanding is not evident from the previous literature which appears to predominantly focuses on specific supply chain stages and/or sustainability aspects. For example, Milanesi *et al*. (2020) focus on clean production, green materials, green human resource management, and reverse logistics. Similarly, Ding's (2018) review is predominantly on how Industry 4.0 technologies can assist the pharmaceuticals sector in improving sustainability, while Kazancoglu et al. (2022a) design a supply chain network considering carbon emissions and particulate matter. As a result, it is unclear what green practices are associated with a drug across its lifecycle stages, and what if any trade-offs/complexities exist across these stages. Similarly, it is unclear which green practices are appropriate for dealing with PIE, and which for protecting the natural resources.

One approach to addressing the knowledge gap could be through borrowing of ideas from other sectors. However, the pharmaceutical sector is significantly different because its products (drugs) have life-and-death implications and consequently face stringent regulations at all stages of their lifecycle, and also because most are developed after a long and expensive R&D process and enjoy extended patent protection. Incorporating green practices in pharmaceuticals is therefore much more challenging and requires a separate investigation.

The aim of our investigation is therefore to develop a comprehensive understanding of Green Supply Chain Practices (GSCP) in the pharmaceutical sector and highlight key research gaps and agendas to promote GSCP in the sector. The specific research questions (RQs) sought to be answered are:

RQ1. What green practices could protect natural resources from pharmaceutical operations?

RQ2. What green practices could reduce the adverse impact of pharmaceutical products (drugs) on the environment?

RQ3. What green practices could make pharmaceutical operations more environmentally friendly?

This investigation, which is based on a structured literature review, represents the first comprehensive exploration of operational-level GSCP in pharmaceuticals, where individual drug lifecycle stages and key stakeholders are also considered. A related stakeholder-level GSCP framework was also developed which is adaptable, and could be applied to different pharma industry contexts. Besides industry players, insights from the work would also be useful to regulators such as FDA and MHRA.

The rest of the paper is structured as follows. Section 2 provides a brief overview of the pharmaceutical supply chain including key stakeholders, while Section 3 details the structured literature review (SLR) methodology used. Section 4 then explains the descriptive and thematic findings pertaining to the research questions. Discussion on the findings and directions for future research are presented in Section 5. Finally, Section 6 concludes the paper and summarises its contributions.

2. Pharmaceutical Supply chain stages and key stakeholders

Figure 1 presents the supply chain stages. Here, drug design and development can be seen to be a part of the pharmaceutical supply chain as the candidate drug (termed API or active pharmaceutical ingredient) is manufactured for laboratory and clinical trials (Taylor, 2015). Only after successful clinical trials does an API get authorisation for large-scale manufacturing (Clark *et al*., 2010).

At the manufacturing stage, API is produced in bulk at a separate facility. The API is then supplied to the formulation plant where it is mixed with excipients and additives (e.g., colour, glucose, etc) to form a drug in tablet, capsule, or syrup form (Taylor, 2015). These drugs are then shipped to hospitals, pharmacies, and clinics from where they are sold/supplied to patients/end users (Rees, 2011).

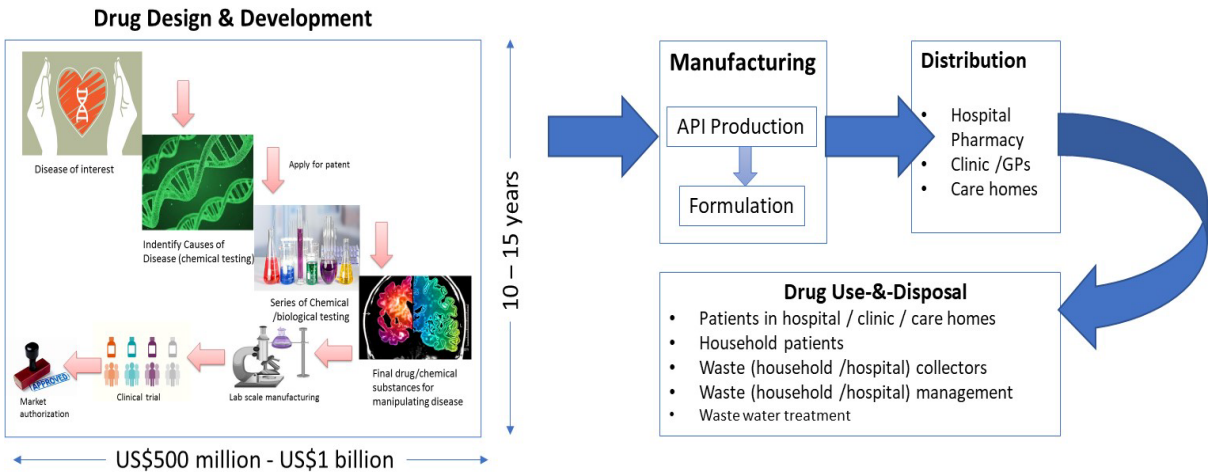

Fig. 1. A typical pharma supply chain (Source: Authors; Image source: Google image)

The pharma supply chain consists of upstream and downstream parts where drug producers such as Innovative, Generic or Biopharma companies constitute the upstream part. Innovative pharma companies focus on developing and patenting new drugs. On expiry of the patent, the drug becomes generic (Rees, 2011). Generic pharma companies then take over and manufacture and sell these drugs while ensuring adherence to efficacy, quality, and safety standards. Intense competition limits the pricing power of these companies whose success is based on volumes. Finally, Biopharma companies produce drugs using biotechnology and bio-based active materials, where no/limited amount of chemicals are used, though consumption of energy and water is substantial (Ho, 2010).

On the downstream side, the key stakeholders are doctors, pharmacists, patients, waste management vendors, and wastewater treatment companies who, collectively, play a reactive role in dealing with PIE (Vollmer, 2010). Doctors' prescribing practices, pharmacists' drug dispensing processes, and patients' adherence/non-adherence to drug prescriptions play a critical role in the effective use and disposal of drugs (Vollmer, 2010). The role of waste management companies is to collect unused/expired drugs from pharmacies, hospitals, clinics, and households, and dispose them as per specified waste management procedures. Similarly, wastewater treatment companies collect industrial wastewater and/or wastewater from other businesses/local households and treat them as per local environmental agency requirements. Waste management and wastewater treatment companies both play a reactive role in dealing with the environmental loading of pharmaceuticals (Kummerer, 2009).

A detailed perspective on the stakeholders and operations at different supply chain stages, along with their environmental impacts is presented in Figure 2. It is pertinent to highlight that the entire pharma supply chain is highly regulated. For example, regulatory agencies such as the FDA (Food and Drug Administration), the EMA (European Medicine Agency), and the MHRA (Medicine and Healthcare products Regulatory Agency) authorize the marketing of drugs in USA, EU, and UK respectively, after scrutinising their safety, quality, and efficacy across the entire life cycle (Taylor, 2010).

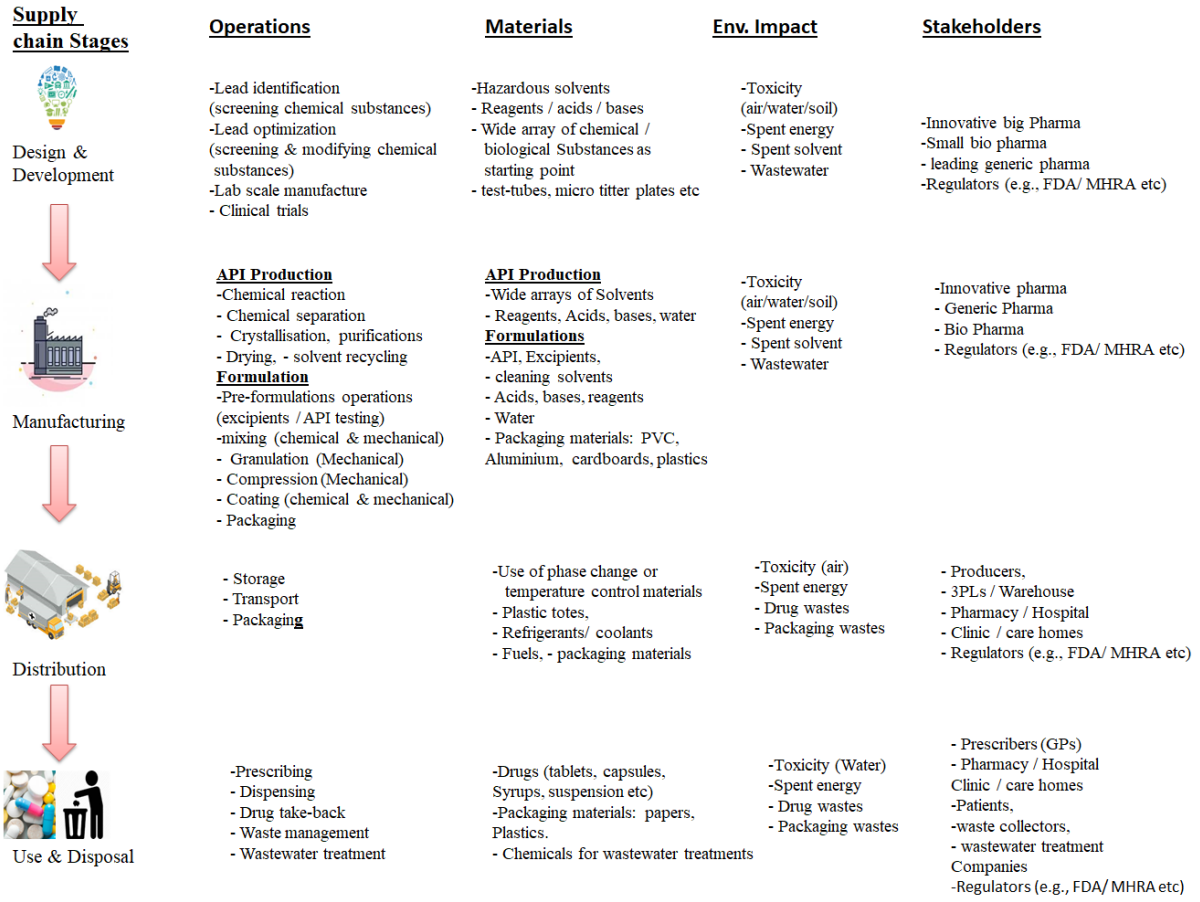

Fig. 2. Pharma supply chain stakeholders, operations, and environmental impacts (Source: Authors; Image source: Google image)

3. Methodology

A systematic literature review (SLR) was used to uncover, collate and synthesise green practices in the pharma sector. SLR is known to enrich the understanding of a topic (Ahmad *et al*., 2022), and is an objective, reproducible, and replicable process that enables reliable and valid inferences to be made (Badi and Murtagh, 2019). In particular, we followed the PRISMA four-phase model (Moher *et al*., 2010) as presented in Figure 3. With regards to databases, Scopus, ScienceDirect, Emerald, Google Scholar, and SpringerLink were considered as they are known to provide high-quality research articles (Tseng *et al*., 2019).

The list of keyword searches used is shown in Table 1. They were applied in two phases where, after searching papers in the first phase, we got ideas for the second phase that continued till the end of search. The SLR took six months to complete.

A set of screening criteria were applied to filter the papers obtained from the database search. The review considered papers published in English between 2000 and 2023. The year 2000 was chosen because green-related innovation including green chemistry initiatives in pharma first emerged that year. The papers considered were predominantly from peer-reviewed

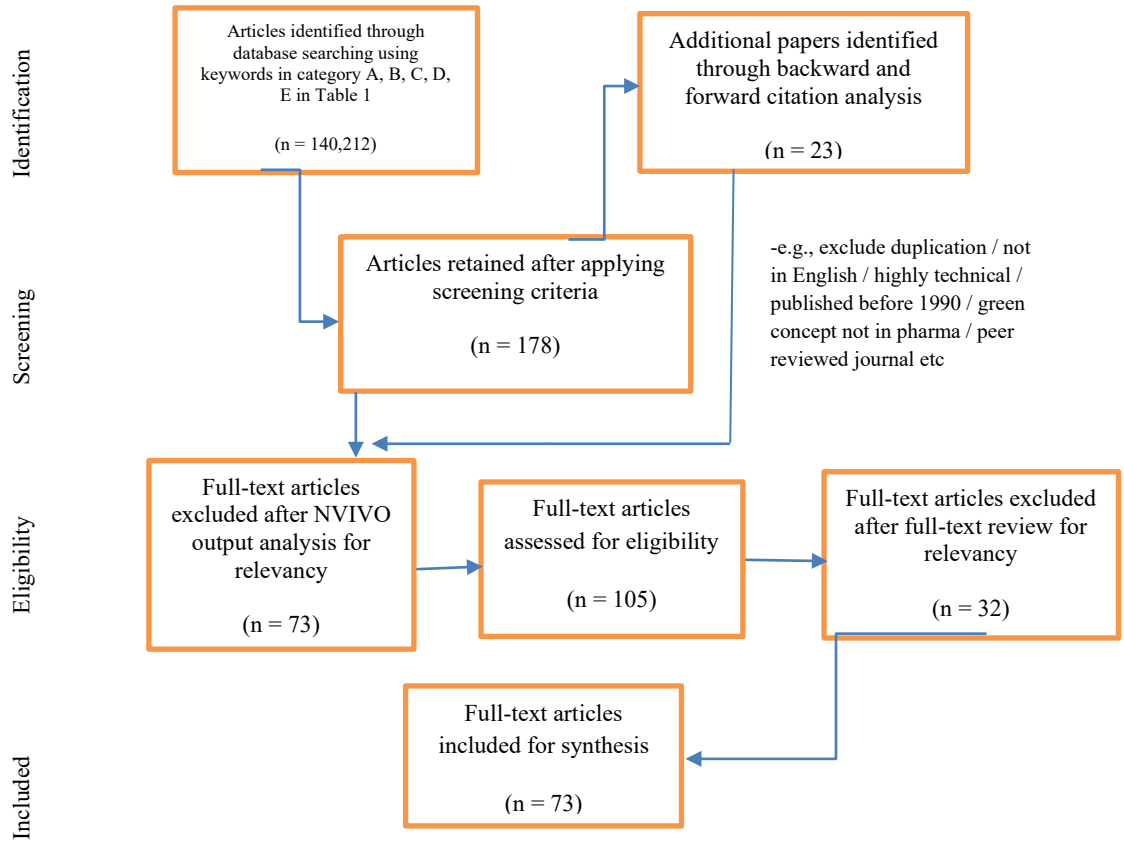

Fig. 3. The PRISMA four-phase model used for data collection (Adapted from Moher *et al*., 2010)

Table 1. Key databases and relevant keywords applied (source: Authors).

Database	**Keywords**	**Category**
Scopus	'Green and Pharma', 'Green manufacturing in pharmaceutical sector', 'Green Supply chain and Pharmaceuticals'.	A
Science Direct	'Green Supply Chain and Pharma', 'GSCP in Pharmaceutical'; 'Green Pharmaceutical Supply Chain', 'Sustainable Pharmaceutical Supply Chain', 'Green manufacturing in pharmaceutical Sector', 'Disposal of drug and Environment'	B
Emerald	'Green supply chain management and pharmaceutical sector'	C
Google Scholar	'Green and sustainable pharma'	D
Springer Link	'Environment and sustainability and pharma', 'Green and sustainable pharmacy'	E

journals, though, for topics such as green pharma purchasing, green distribution, and green drug design where these were not available, book chapters were considered. Finally, technical papers, as also those not solely focussed on pharma were avoided. 178 papers were retained after applying these screening criteria.

Subsequently, each paper was assessed using NVIVO where 'frequency' and 'Text Search Query' functions were used. This involved analyses such as the most occurring word/s, and central reasoning of each keyword (e.g., how a keyword like 'green'/'environment' is linked to the other words/phrases in the paper). This resulted in the exclusion of 73 papers.

Finally, each of the remaining 105 papers underwent a full-text review to further assess their relevance. This led to the exclusion of an additional 32 papers, leaving 73 papers for detailed analysis. This comprehensive review process, involving both subjective (e.g., full-text review) and objective (e.g., NVIVO output analysis) elements, increased the validity and reliability of the investigation (Gough *et al*., 2017). Subsequently, information was extracted from each of the papers and subjected to thematic content analysis. Such an approach enables an objective and systematic assessment of documented texts and ensures that replicable and valid inferences can be made from the texts to their use-contexts (Krippendorff, 1980; Neuendorf, 2002).

4. Research Findings: Analysis and Synthesis

4.1. Descriptive statistics from the review

This section covers knowledge generation on GSCP in pharmaceuticals, as per the distribution of relevant papers across time and geographies, their focus areas, their methodologies, and their publication outlets.

Though the generic concept of GSCP can be traced back to the early 1990s (Zhu and Sarkis, 2006), their relevance for pharmaceuticals began being discussed only from 2000 onwards, when green chemistry technology first emerged. Figure 4 shows the publication pattern of papers on GSCP in pharma. As can be seen from the figure, interest in this subject was limited and inconsistent between 2000 and 2008. However, thereafter, interest picked up and remained high through 2017, but has been stagnant/declining since then. The latter could be due to the complex nature of the subject involving different kinds of chemists, engineers, pharmacologists and management experts. Another factor could be the difficulty in accessing data for research as the pharmaceutical sector tends to be secretive.

Secondly, GSCP concepts involving pharma have mostly been discussed in multi-disciplinary publications (see Table 2). Also, coverage of green pharma concepts in mainstream operations and supply chain journals has been minimal. A total of 36 journals have published 66 papers, with a further 13 chapters published in three books: *Green and Sustainable Pharmacy (7)*, *Green Chemistry in the Pharmaceutical Industry* (2), and *Green Logistics* (4).

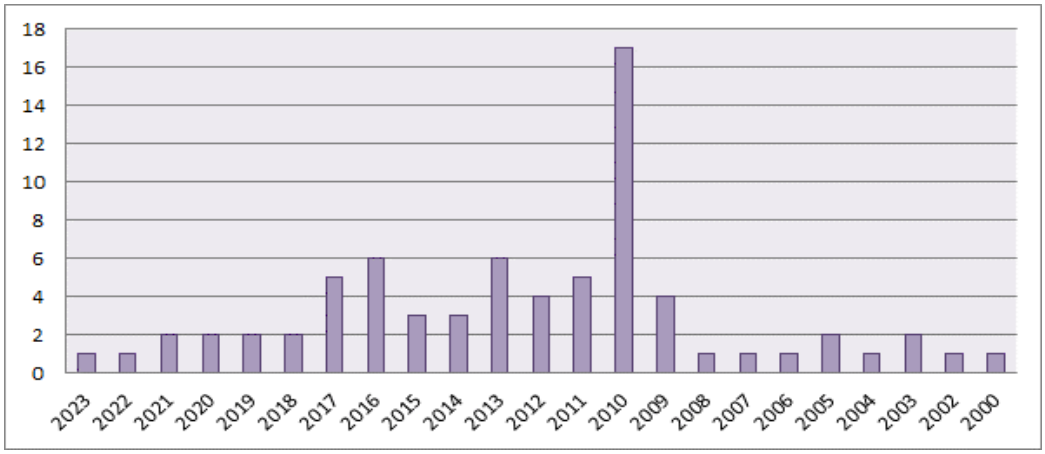

Fig. 4. Distribution of papers on GSCP in pharma over the years (Source: Authors)

Table 2. Papers published on GSCM in pharma across journals and books (Source: Authors).

Journal/Book Title	No. published
Journal of Cleaner Production	7
Green and Sustainable Pharmacy	7
Green Chemistry	4
Supply Chain Management: An International Journal	4
Green Logistics	4
Science of the total environment	3
Journal of Environmental Management	3
Organic Process Research & Development	3
Environment International	2
Green Chemistry in the Pharmaceutical Industry	2
Benchmarking: An International Journal	2
The International Journal of Logistics Management	1
Pharmaceutical Technology	1
International Journal of Production Economics	1
European journal of operational research	1
Operations Research for Health Care	1
International Journal of Supply Chain Management	1
Transport Research Part D	1
Computers and industrial engineering	1
Journal of Public Health	1
Chemical Engineering Research and Design	1
Drug Invention Today	1
EcoHealth	1
Econometric Institute Research	1
Environmental Health Perspective	1
Expert Review of Clinical Pharmacology	1
Green Chemistry Letters and Reviews	1
Green chemistry, a pharmaceutical perspective	1

Patient Education and Counselling	1
Perspectives in Science	1
Systematic Reviews in Pharmacy	1
Process Safety and Environmental Protection	1
Social Science & Medicine	1
Sustainable Chemistry and Pharmacy	1
The American Journal of Managed Care	1
Environment, Development and Sustainability	1

The review also revealed a dearth of studies on developing countries, with more focus being on the developed ones (see Figure 5). UK, USA, Germany, and India are the four countries where maximum studies appear to have been done. One reason could be that many companies from these regions became members of the pharma green innovation society known as ACS GCI (American Chemical Society's Green Chemistry Institute) Pharmaceutical Roundtable.

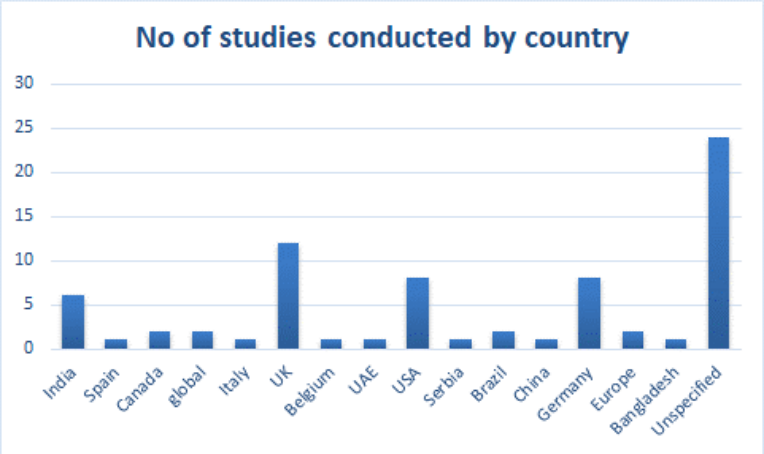

Fig. 5. No of studies conducted by country (Source: Authors).

The review revealed the use of a wide variety of methods (refer to Table 3) including those based on conceptual and expert reviews (27%), case studies (14%), and surveys (11%). Some studies have also used specific quantitative approaches such as LCA (1%) and system thinking (1%).

Table 3. Key research methods applied (Source: Authors)

Research Method Applied	**Percentage of Papers**
Case Study	14%
Mix Method	1%
Operations research	1%
Interview	7%
Life Cycle Analysis (LCA)	1%
Literature Review	5%
Mathematical Modelling	4%

Secondary (company documented data)	6%
Survey	11%
Sustainability report	1%
System thinking	1%
Conceptual & expert review	27%

From an environmental perspective, the key operations and supply chain-related areas that have been covered are downstream supply chain/distribution, manufacturing, and reverse supply chains/logistics (refer to Figure 6).

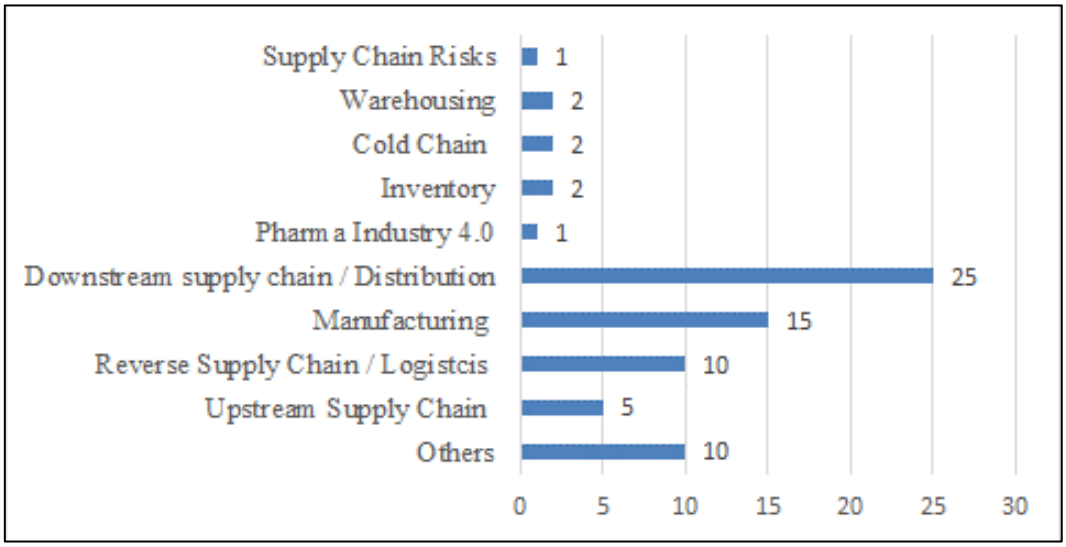

Fig. 6. Operations and supply chain focus areas of studies (Source: Authors)

With regards to studies based on literature review, they were found to be fragmented across a wide domain such as medicinal science and process chemistry (upstream), and formulation science and waste management (downstream).

4.2. Scopes of GSCP in pharma

The review revealed a collection of green ideas and practices, but with limited empirical support. These include for example, cleaner production (Milanesi *et al*., 2020), drug design based on green raw materials such as bio-based enzymes (Leder *et al*., 2015), green solvent selection (Chaturvedi *et al*., 2017; Veleva *et al*., 2018), solvent recycling (Teunter *et al*., 2003), drug take-back (Vollmer, 2010), reverse logistics (Narayana *et al*., 2014; Weraikat *et al*., 2016) and eco-prescribing (Daughton, 2014). They gave us the initial contours of green supply chain management in pharma; however, the operational aspects remained unclear. For instance, when Milanesi *et al*. (2020) highlight cleaner production, it is debatable whether this implies solvent recycling, or continuous manufacturing, or something else (Clark *et al*., 2010). Similarly, when Leder *et. al.* (2015) suggest environmental biodegradability as a core drug design aspect, others highlight how this can be problematic from a drug bioavailability, and therefore efficacy perspective (Taylor, 2010; Sumpter, 2010). Likewise, when Ding (2018) highlights longer shelf-life to be a consideration in drug design, others suggest how this could be environmentally

negative as it would require more chlorinated substances to be used. These considerations also vary across innovative, generic, and biopharma. Finally, while some researchers (e.g. Clark *et. al*., 2010; Veleva *et. al*., 2017) emphasise green manufacturing to protect natural resources from pharma operations, others (e.g. Sumpter, 2010; Leder *et al.*, 2015) want to have a separate focus on practices to deal with the PIE impact.

This lack of clarity and conflicts motivated us to conceptualise an overall scope of GSCP (refer to Figure 7) where green practices are split into three areas: *green practices for the protection of natural resources from pharma operations*, *green practices for reducing the adverse impact of pharma products (drugs) on the environment,* and *other operational green practices*. The subsequent sections advance knowledge on each of them.

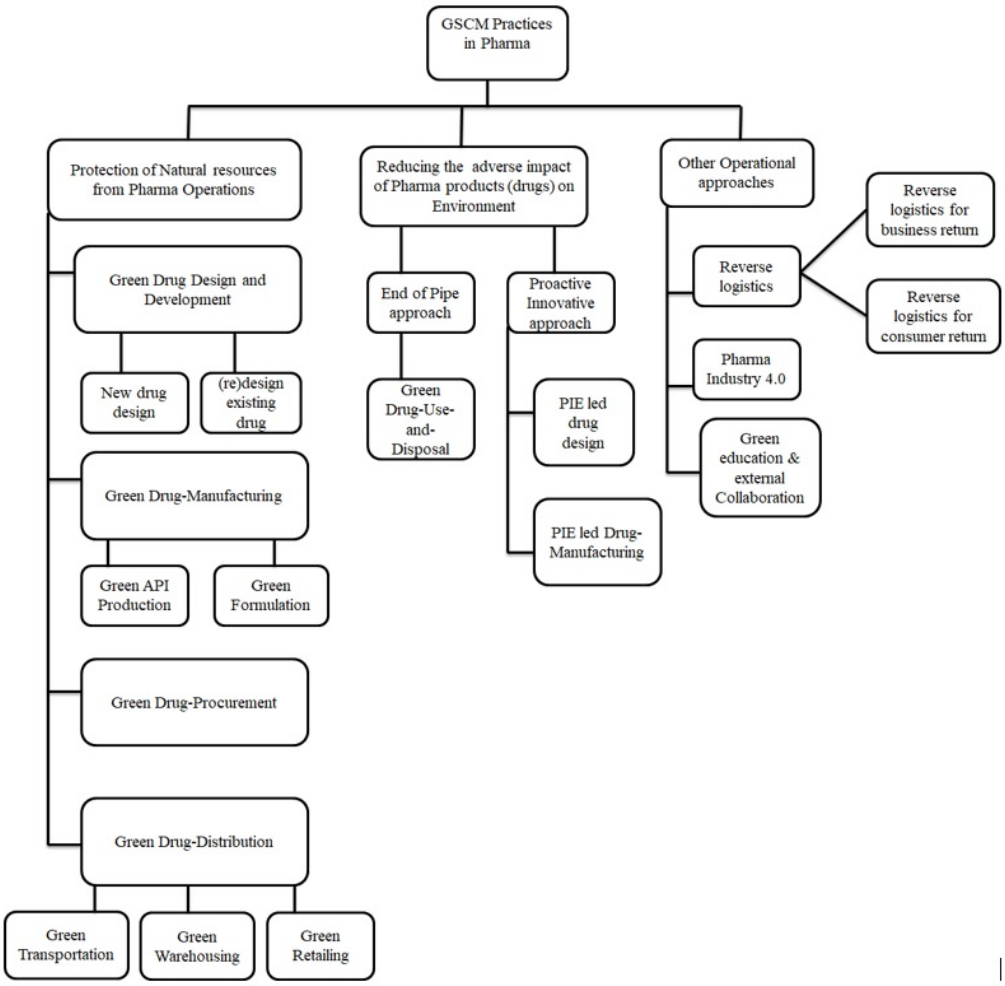

Fig. 7. A conceptual framework of GSCP in the pharmaceuticals sector (Source: Authors).

4.2.1 Protection of Natural Resources from Pharma Operations (RQ1)

This section advances our understanding of green practices that deal with the degradation of natural resources and related pollution from pharma operations. Here, four practices, specifically green drug design and development, green drug manufacturing, green drug procurement, and green drug distribution were identified. Further, based on the review, detailed practices and sub-practices were identified under each, which are presented in Tables 4 to 7.

These tables also present the key life cycle stages considered during design as also the related stakeholders. They also highlight the importance given to each sub practice; also, the extent of explanation provided on each which was determined through analysis of the 'text search query' output from NVIVO as also the researchers' judgment.

4.2.1a Green drug design and development

The review revealed five design and eleven sub-design practices across the drug life cycle (refer to Table 4). The table reveals that some green design practices such as AI-led drug design for material reduction, design to increase renewability, formulation packaging design for lower environmental impact, and combined drug design for dematerialization are rated as highly important, though the extent of explanation provided on them is quite limited. It is also unclear why the adoption of these practices by generic and biopharma is lower than that of innovative pharma. Finally, although green drug design's positive environmental impact on other drug lifecycle stages such as formulation, transportation, storage, and use-and-disposal is apparent, it still requires empirical validation.

The review suggests that drug process can be designed to use less material and energy throughout the entire lifecycle. The implications of this for the manufacturing footprint as well as the associated cost savings are significant (Clark *et al*., 2010; Perez-Vega *et al*., 2013). Similarly, using chemicals with known druggability can significantly reduce the requirement for solvents and other testing materials during the discovery process (Clark *et al*., 2010). Furthermore, a flexible manufacturing process design allows producers to include all possible process variations in the early regulatory submission (Slater *et al*., 2010) thereby reducing material waste considerably during the commercial manufacturing phase.

Potential energy consumption can also be a factor in the drug process selection. For instance, use of hazardous substances during drug discovery and development lowers cost and increases throughput (Moscrop, 2018), but can also significantly increase hazardous wastewater generation during manufacturing that requires (greater) energy for treatment (Clark *et al*., 2010). Such lifecycle impacts need to be considered during the drug process selection.

The solvent used is one of the key determinants of a process's overall effluent toxicity level. For example, use of eco-friendly solvents such as Methanol instead of DCM (Dichloromethane) early in the design phase could significantly reduce toxic waste generation and related disposal costs during the commercial manufacturing phase (Perez-Vega *et al*., 2013). Given that more than 80% of raw materials in drug manufacturing involve the use of solvents, this practice can significantly impact the manufacturing phase (Perez-Vega *et al*., 2013). However, the viability of making such process changes across different therapeutic drug classes still needs to be assessed.

A bio-based process design could significantly enhance renewability in pharma manufacturing (Challener, 2016). However, currently, the metal-based approach involving use of metals such as palladium, where the natural availability is limited, is prevalent (Chem21, 2020). Though redesigning to a bio-based process is possible, and which has immense potential, the scope of doing so and the associated challenges are still unknown.

Table 4. Concepts of Green drug design and development in Pharma (Source: Authors)

Green Drug Design and Development			Stakeholders			Level of importance	Extent of explanation	Study
Key green design practices	**Life cycle impact considered during design**	**Sub-green design practices**	**Innovative Pharma (In)**	**Generic Pharma (Gn)**	**Bio Pharma (Bio)**			
Design for Material Reduction	Drug design, discovery & development process	Design drug discovery process applying AI to reduce testing materials use (ND)	In			H	a	Clark *et al*., 2010
	Manufacturing, use-and-disposal	Design manufacturing process for less by-products formation (ND* + RD*)	In			H	c	Sumpter, 2010; Veleva *et al*., 2017; Jimenez-Gonzalez *et al*., 2011; Kummerer, 2010; Watson, 2012;
		Design combined drug for dematerialization (RD)		Gn		L	a	Ding, 2018
		Design process for flexibility in quality (RD)		Gn		H	a	Slater *et al*., 2010; Ding, 2018
	Distribution: Packaging, storage, transportation	Design drug for longer shelf life (ND)	In			M	a	Ding, 2018
		Design (secondary) packaging to use recyclable materials (ND)	In			H	b	Ding, 2018
Design for Energy efficiency	Manufacture	Design and develop manufacturing processes for the least energy consumption by evaluating alternative processes (ND)	In			H	b	Clark *et al*., 2010

Green Drug Design and Development			Stakeholders			Level of importance	Extent of explanation	Study
Key green design practices	**Life cycle impact considered during design**	**Sub-green design practices**	**Innovative Pharma (In)**	**Generic Pharma (Gn)**	**Bio Pharma (Bio)**			
Design for toxicity reduction	Manufacturing, use-and-disposal	Design manufacturing process (of API) to use substances (e.g., solvent) with lower env. Impact (ND+RD)	In			H	c	Perez-Vega *et al.*, 2013; Clark *et al.*, 2010
	Manufacturing	Design formulation packaging with lower env. Impact (ND+RD)	In			L	a	Raju *et al.*, 2016
Design for Biodegradability	Use & disposal	Design and develop drug substances to increase environmental biodegradability (ND +RD)	In			H	c	Leder *et al.*, 2015; Kummerer, 2010; Sumpter, 2010
Design for Renewability	Manufacturing	Design process to use renewable raw materials (RD)	In			M	a	Challener, 2016

ND - New Drug Design; RD - Redesigning existing drug; AI – Artificial Intelligence; H -high, M – Medium, L – Low; a – limited explanation, b – moderate explanation, c – detailed explanation

4.2.1b Green drug-manufacturing

It was found to be one of the most discussed operational green practices whose aim is to minimise the adverse environmental impacts in a typically two-stage pharma manufacturing process. A total of fourteen sub-green practices under four key green practices were identified. The detailed concept of green drug manufacturing is presented in Table 5.

As can be seen from the table, though most sub-practices are rated as highly important, the extent of explanation provided and the associated understanding is quite limited. Similarly, the explanation provided for generic and biopharma pharma is also quite limited. Previous literature also appears to predominantly cover green practices in upstream API production with the downstream formulation segment ignored. There is also a dearth of empirical evidence on how green API synthesis has a positive environmental impact on other drug lifecycle stages.

Inefficiencies cost the pharma industry 50 billion dollars annually (Roschangar, 2018), and therefore, material reduction-related practices are important. Here solvent recovery gets the highest priority, but the review revealed this to be the case primarily in API production at Innovative Pharma. This could be because such a recovery in Bio and Generic pharma requires complex engineering, and is costly (Teunter *et al.*, 2003; Veleva and Jr, 2017).

Table 5. Concepts of Green drug-manufacturing in Pharma (Source: Authors).

Green Drug-Manufacturing Practice		Stakeholders			Level of importance	Extent of explanation	Study
Key Green manufacturing practices	**Sub green practices** (Applies to API / Formulations)	**Innovative Pharma (In)**	**Generic Pharma (Gn)**	**Bio Pharma (Bio)**			
Material reduction	Run continuous mode of manufacturing (API)	In			H	c	De Soete *et al.*, 2017; Ding, 2018; Chaturvedi *et al.*, 2017; Jimenez-Gonzalez *et al.*, 2011; Plumb, 2005; Watson, 2012
	Recycle solvent (API)	In			H	a	Veleva *et al.*, 2018; Teunter *et al.*, 2003;
	Reduce water consumption in the manufacturing process (API +F)	In	Gn		H	b	Veleva *et al.*, 2018; Li and Hamblin, 2016
	Use of recyclable (secondary) packaging content (API+F)	In	Gn		H	a	Ding, 2018

Green Drug-Manufacturing Practice		Stakeholders			Level of importance	Extent of explanation	Study
Key Green manufacturing practices	**Sub green practices** (Applies to API / Formulations)	**Innovative Pharma (In)**	**Generic Pharma (Gn)**	**Bio Pharma (Bio)**			
Energy efficiency	Consider process-based energy kaizen (API)	In			H	a	Schneider *et al*., 2010;
	Run energy-efficient processes using computer-based process simulation (API)	In			M	a	Jimenez-Gonzalez *et al*., 2011
Toxicity reduction	Reduce VOC emission from process (API + F)	In			H	b	Schneider et al., 2010;
	Use solvent with lower environmental impact (API)	In			H	c	Veleva *et al*., 2018; Chaturvedi *et al*., 2017; Kummerer, 2010; Watson, 2012
	Reduce the generation of wastewater from the process (API)	In			H	b	Veleva *et al*., 2018
	Avoid toxic packaging materials (e.g., PVC) (API)	In			H	a	Schneider *et al*., 2010;
	Recycle toxic wastewater (API)	In			H	b	Chaturvedi *et al*., 2017
	Consider the hierarchy of waste management (API)	In			H	a	Veleva *et al*., 2018
Renewability	Use renewable content in secondary packaging	In	Gn		H	a	Ding, 2018
	Use Renewable energy (API+F)	In	Gn		H	a	Chaturvedi *et al*., 2017; Li and Hamblin, 2016;

ND - New Drug Design; RD - Redesigning existing drug; F -Formulation; H -high, M – Medium, L – Low; a – limited explanation, b – moderate explanation, c – detailed explanation

With regards to the manufacturing process, continuous processes are environmentally better than batch ones (Slater *et al*., 2010, Perez-Vega *et al*., 2013). This is because batch operations require cleaning of equipment in-between batches that increases energy and solvent requirement, and also causes more wastage (Plumb, 2005; Slater *et al*., 2010). However, the extent and scope of continuous manufacturing in biopharma and generic pharma require more exploration. The few studies done on the latter indicate continuous mode of manufacturing to be limited to tablet coating (Boltic *et al*., 2013) and wet granulation (De Soete *et al*., 2013). With regards to technology application, digital technologies (e.g., PAT – Process Analytical Technologies) are able to continuously monitor and control the process parameters thereby ensuring lower energy consumption. Process-centric historical performance data (energy-related) can also be input into computer-based simulation models to identify and run the most energy-efficient processes (Jimenez-Gonzalez *et al*., 2011).

To enable effective detoxification of the drug manufacturing process, a green solvent database can be developed for the API manufacturers. This database can be based on the PBT (Persistence, Bioaccumulation, and Toxicity) data available for solvents together with the accumulated experience of chemists and chemical engineers (Clark *et al*., 2010; Perez-Vega *et al*., 2013). Importantly, the criticality of using green solvents in tablet formulation is even greater given that 80% of the drugs produced globally are in that form (Plumb, 2005). One approach could be to swap organic solvents used in tablet coating with water solvents. However, this would require costly and time-consuming regulatory approvals to check/confirm that the safety, efficacy, and quality of the tablet is not compromised.

4.2.1c Green drug-procurement

Inappropriate procurement-related choices could lead to adverse environmental consequences such as GHG emissions and waste generation. With greater outsourcing, this cause of environmental degradation has increasingly come to the fore (Zhang, 2011). A total of three green practices and nine sub-green practices were identified here (refer to Table 6).

As can be seen from the table, while most sub-green practices are rated as highly important, the scope and extent of empirical evidence provided on them is quite limited. Additionally, the review revealed deficiencies in purchasing habits that cause significant wastage: for example, the upstream R&D operations' purchase/consumption of substantial amounts of solvents and other raw materials during early drug discovery. Similarly, at the downstream end, care homes demanding vast quantities of drugs for multimorbidity patients, most of which goes waste. The review also indicated green purchasing's positive environmental influence on other lifecycle stages such as storage and use-and-disposal, though this requires empirical validation.

Other ideas advanced by scholars include formulators purchasing APIs from suppliers with lower carbon footprint as per the purchasing specification sheet (Clark *et al*., 2010). API suppliers can also be provided with Standard Operating Procedures (SOPs) or manufacturing guidelines to meet the environmental footprint requirements of downstream customers like hospitals, pharmacies, or clinics (Ding, 2018). A green labelling system for API suppliers has also been proposed where they could disclose relevant environmental footprint such as the amount of waste produced per kg of the final drug produced (Roschangar *et al*., 2015). However, this could mean additional packaging or labelling processes which some drug ingredients could be sensitive to. This therefore requires more empirical exploration on a case-by-case basis across different classes of drugs. Similarly, empirical evidence on whether hospitals (e.g., NHS in England) and/or pharmacies demand green API is also needed (Clark *et al*., 2010).

4.2.1d Green drug-distribution

Pharmaceutical distributors are continuously confronted with tackling greenhouse gas emissions and waste generated from their distribution operations (McKinnon and Edward, 2010). For example, the cold chain distribution system typically used consumes significant amounts of energy and packaging materials. Also, the wooden pallets that are used may

Table 6. Concepts of Green drug-procurement in Pharma (Source: Authors)

Green Drug-Procurement Practice			Procurement stages and related stakeholders		Level of importance	Extent of explanation	Study
Key Green Procurement practices	**Life cycle impact of drugs considered**	**Sub green practices**	**Upstream (Manufacturing)**	**Downstream (Distribution)**			
Green Specification	UAD	Product content requirements for green (e.g., lower carbon footprint of API)		H/C	H	a	Clark *et al.*, 2010
	M	Provide SOPs or manufacturing guidelines to the suppliers	AP	F	H	a	Ding, 2018
	M	Use green labelling: (e.g., label drug pack with amount of wastes generated per kg of final API produced)	AP		H	a	Roschangar *et al.*, 2015
Green Supplier Development	M	Collaborate with suppliers for green sourcing	AP	F	H	b	Xie and Breen, 2012
	M	Supplier certification for green credentials	AP	F	L	b	Xie and Breen, 2012
	M	Env. Audit of suppliers	AP	F	H	b	Ding, 2018
Internal Purchasing Operations	UAD	Consider Vendor Managed Inventory		H/C	M	a	Daughton and Ruhoy, 2011
	UAD	Responsible prescribing		H/C	H	c	Daughton and Ruhoy, 2011
	UAD	Consider Internal Environmental Purchasing Program		H/C	M	b	Vatovec *et al.*, 2013

M - Manufacturing, UAD - Use-and-disposal, AP - API Producers, F - Formulators, H/C - Hospital / Clinic; H -high, M – Medium, L – Low; a – limited explanation, b – moderate explanation, c – detailed explanation

contaminate the drugs and cause additional waste generation (Hardisty, 2011). The practices and sub-practices associated with green drug distribution are presented in Table 7.

As can be seen from the table, most sub-level green practices are rated as highly important. However, the explanation provided and the understanding about them is quite limited. For

example, it is important to explore how passive packaging, which typically involves the use of phase change materials like dry ice and insulation materials (e.g., polystyrene, polyurethane, etc) could be improved from an environmental perspective. An alternative is to use active packaging, which though eco-friendly, is more expensive. However, further studies are needed to understand the detailed scopes and limitations in adopting it.

Table 7. Concepts of Green drug-distribution in Pharma (Source: Authors)

Green Drug-distribution Practice			Stakeholders	Level of importance	Extent of explanation	Reference
Key Green distribution practices	**Life cycle impact of drug considered**	**Sub green practices**				
Green Transportation	D-T	Consider co-loading or shared-user networks	AP, F	M	a	Piecyk, 2010
	D-T	Consider a Greener Mode of transportation (e.g., air to sea)	AP, F	H	a	Taylor, 2010
	D-T	Eco-driving program for drivers	AP, F	L	a	Taylor, 2010
	D-T	Consider GHG emission target from fleet	AP, F, W	H	a	Taylor, 2010
	D-T	Use smaller & more efficient vehicle	W/LP	H	a	Taylor, 2010
Green Packaging	D-T	Consider active (greener) packaging configuration for transporting TTSPPs		H	a	Taylor, 2010
	D-T	Use energy-efficient refrigerants	F, W/LP	H	a	Taylor, 2010

Green Drug-distribution Practice			Stakeholders	Level of importance	Extent of explanation	Reference
Key Green distribution practices	**Life cycle impact of drug considered**	**Sub green practices**				
	D-T, D-R D-W, UAD	Use reusable and recyclable packaging *(e.g., reusable blanket in passive packaging; replace wooden pallet with plastic one)*	W/LP	H	b	Taylor, 2010; Hardisty, 2011
	D-W, D-R	Reduce packaging materials		H	b	Taylor, 2010
Green Cold chain management	D-T	Reduce temperature excursion-related wastes by using PCMs *(Phase Change Materials for precise temperature control)*	W/LP	H	a	Shanley, 2016
	D-W, UAD	Use a time-controlled temperature monitoring system to reduce related wastes	W/LP	H	a	Shanley, 2016
	D-W	Use energy-efficient materials handling equipment	W/LP	L	a	Marchant, 2010

D-T = Distribution - Transport; UAD = Use-and-disposal; D-W = Distribution - Warehouse; D-R = Distribution - Retail; AP = API producers; F = Formulators; W = Wholesalers; W/LP = Wholesalers / Logistics Provider; H -high, M – Medium, L – Low; a – limited explanation, b – moderate explanation, c – detailed explanation

With regards to transportation of pharmaceutical products, the related decisions are complex and multifaceted due to the need to follow GMP and GDP regulations. Scholars have suggested operational practices such as modal choice, intermodal transport, alternative fuel, packaging design, vehicle utilisation, and eco-driving to improve the environmental footprint (McKinnon and Edwards, 2010; Ubeda *et al*. 2010; Leal Jr and D'Agosto, 2011; Dekker *et al*. 2012).

4.2.2 Reducing the adverse impact of Pharma products on the Environment (RQ2)

This section addresses the second research question. Here, key green practices and sub-practices to deal with contemporary issues of PIE (Pharmaceuticals in the Environment) and its impact such as on increase in antimicrobial resistance are covered. From an overall perspective, there are two main approaches: 1) An end-of-pipe approach such as green drug use-and-disposal; and 2) A proactive innovative approach such as PIE-oriented drug design and PIE-oriented drug manufacturing.

4.2.2a End-of-pipe approach (*Green drug-use-and-disposal)*

This approach focuses on two areas: *drug waste reduction from all possible sources*, and *safe disposal of unused and/or expired drugs* to minimise environmental loading (Vollmer, 2010; Clark *et al*., 2010). The key players here are GPs, pharmacists, patients, hospitals, clinics/care homes, drug waste collectors, and wastewater treatment companies. The nature of interactions and relationships between these players including the emphasis on reliability and responsiveness plays a key role in drug waste reduction as well as safe disposal of drugs. A summary of findings from the review on green drug use-and-disposal is presented in Table 8.

As can be seen in the table, most sub-green practices are rated as moderately or highly important, though, here again, the extent of explanation/understanding provided including empirical support is quite limited. With regards to the players, while local councils, special drug waste collectors, and wastewater treatment companies can play a key role in preventing drug waste from entering the water cycle, little is known about the actual practices. Likewise, while most studies focus on safe drug use and disposal, the detailed drug waste management approaches taken by individual stakeholders are yet to be explored.

Table 8. Concepts of Green drug-use-and-disposal in Pharma (Source: Authors)

Green Drug use-and-disposal Practice		Stakeholders	Level of importance	Extent of explanatio	Reference
Key green practices	**Sub green practices**				
Eco Pharmacy dispensing	Reduce unnecessary stockpile of drugs through patient intervention	Ph, P	H	b	Ruhoy and Doughton, 2008; Latif *et al*., 2011
	Reduce drug waste by digitizing the repeat prescriptions process	Ph	H	a	Daughton, 2014; Ruhoy & Daughton, 2008; Xie and Breen, 2012; Mackridge and Marriot, 2007
	Collection of unused/expired drugs for safe disposal	GP, Ph	H	c	Vollmer, 2010; Gotz and Deffner, 2010; Mackridge and Marriot, 2007; Ruhoy and Daughton, 2008; Glassmeyer *et al*., 2009; Kotchen *et al*., 2009; Peterson and Anderson, 2002
	Reuse of drugs which have not left the pharmacy premises and are in good condition	Ph in hospital	M	c	Ruhoy and Doughton, 2008; Glassmeyer *et al*., 2009; Pomerantz, 2004;
Eco-prescribing practice	Reduce drug waste through evaluating prescribers' prescribing habit	GP, Ph	H	c	Latif et al., 2011; Ruhoy and Daughton, 2008;
	Promoting drug substitution or alternative therapy where appropriate	GP	M	a	Daughton, 2014; Ruhoy and Daughton, 2008

Green Drug use-and-disposal Practice		Stakeholders	Level of importance	Extent of explanatio	Reference
Key green practices	**Sub green practices**				
	Selection of drugs based on AMR / PIE impact	GP	H	a	Daughton, 2003
	Reduce unnecessary drug waste through patient education on safe drug use	GP	H	a	Daughton and Ruhoy, 2011;
Safe & responsible disposal	Ensure safe disposal of drugs by proper segregation of drug wastes at sources	LC, WM	H	b	Vollmer, 2010
	Ensure safe disposal of drugs by promoting the drug take-back scheme	LC, WM	H	b	Glassmeyer *et al*., 2009; Vollmer, 2010; Gotz and Deffener, 2010; Kummerer. 2009;
	Ensure safe disposal of drugs through special local collection programs	GP, Ph	H	b	Daughton, 2003; Kotchen *et al*., 2009; Glassmeyer et al., 2009
Greener Waste Management	Apply high-temperature incineration for treating drug wastes	WM	H	b	Vatovec *et al*., 2013; Ruhoy and Daughton, 2008; Glassmeyer, 2009; Daughton and Ruhoy, 2011; Kummerer, 2009; De Campos *et al*., 2017
	Monitor the drug concentration in the oncoming wastewater	WWT	H	a	Comber *et al*., 2018
	Consider the hierarchy of waste management	WM	L	a	De Campos *et al*., 2017
	Consider advanced wastewater treatment technologies	WWT	H	b	Kummerer, 2009

GP - General Practitioners, Ph - Pharmacists, P - Patients, LC - Local Council, WM - Waste Management companies, WWT - Wastewater Treatment companies; H -high, M – Medium, L – Low; a – limited explanation, b – moderate explanation, c – detailed explanation

Several authors have emphasised how effective drug use and safe disposal practices for expired and unused drugs could significantly reduce PIE and AMR-related environmental burdens (Kummerer, 2009; Vollmer, 2010; Gotz and Deffner, 2010). This is especially because production of green API and use of bio-based drugs are not yet common. With regards to effective drug use, timely medical intervention/support to patients is needed so that they can take the right medication at the right time in the right quantities. Additionally, ensuring that they report back to their prescribers and/or pharmacists in case of any side effects. In such cases, to avoid wastage, recurring supply or dispensing of drugs in bulk can be avoided (McDonald *et al*., 2010; Latif *et al*., 2011). Scholars have found trial prescriptions and increased monitoring of patients to not only reduce drug wastage (from unwanted drugs), but also improve health outcomes and physician-patient relationships (Ruhoy & Daughton, 2008). This is already being done on a large scale in Sweden and Canada, and well appreciated there (Castensson and Ekedahl, 2010).

4.2.2b Proactive Innovative approach

This approach considers environmental impact data (e.g., Persistence, Bioaccumulation & Toxicity or PBT data) in the drug design and manufacturing phases to control the PIE impact. Two scopes were identified here: PIE-related drug design, and PIE-related drug manufacturing.

PIE related drug design (proactive)

This entails that a drug should be discovered, designed, and developed in a way as to completely/partially degrade when entering the environment through un-metabolized excretion or inappropriate disposal. Previous studies have mostly focused on how to increase the environmental biodegradability of drugs to deal with the issue of PIE and related increases in antimicrobial resistance. The key attempts are presented in Table 9 below.

Table 9. Review of literature focused on PIE-led drug design (Source: Authors).

PIE Led Drug design			Stakeholders			Level of importance	Extent of explanation	Reference
Key green design practices	**Stages of drug discovery & development**	**Sub-green design practices**	**Innovative Pharma (In)**	**Generic Pharma (Gn)**	**Bio Pharma (Bio)**			
Design for degradability	R&D: LI; LO	Design drug process to replace toxic (e.g., fluorinated or other halogens) chemicals with lower env. impact one	In			H	b	Sumpter, 2010
	R&D: LI; LO	Design discovery process for continuous modification of non-degradable parent drug substances to increase env. degradability	In			H	a	Kummerer, 2010; Leder *et al.*, 2015

ND - New Drug Design; RD - Redesigning existing drug; LI – Lead Identification; LO – Lead Optimization; H - high, M – Medium, L – Low; a – limited explanation, b – moderate explanation, c – detailed explanation

PIE related drug manufacturing (reactive)

It is considered difficult to enhance the (environmental) degradability property of a drug during the design phase due to non-availability of relevant environmental toxicity data (Kummerer, 2010). Assessing and controlling drug/API discharges from a plant during manufacturing therefore becomes critical. In this regard, Taylor (2010) has discussed a concept of eco-pharmacovigilance. It involves continuous monitoring and collection of relevant environmental

toxicity data of drugs post-market launch so that producers can take appropriate decisions on their API discharges. This could mean either reducing the API discharge levels and/or using advanced wastewater treatment technologies to reduce the API concentration levels before discharge.

4.2.2.2 Other operational approaches (RQ3)

This section answers the third and final research question where the scopes of reverse logistics, application of Industry 4.0 technologies, and green education, training, research, and external collaboration are covered.

Reverse logistics (RL)

This in the case of pharma involves collecting expired or unused drugs including those recalled from customer zones. The focus is more on safe disposal rather than financial gain (Xie and Breen, 2012; Weraikat *et al*., 2016). Categorisation can be in terms of: a) RL pertaining to Business Returns (BR); and b) RL pertaining to Consumer Returns (CR). The overall scopes of RL can be seen in Figure 8, while the sub-practices are presented in Table 10.

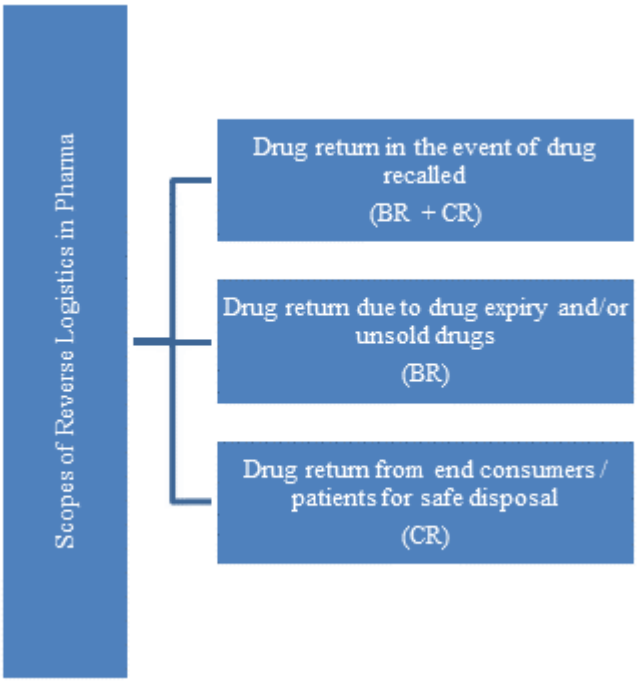

Fig. 8. Scopes of reverse logistics in pharma (source: Authors)

BR involves quick return in the event of a drug recall or a quality failure during storage and transportation (Kabir, 2013; Narayana *et al*., 2014). Such unexpected returns can be reduced through the application of six-sigma or other quality improvement approaches. It is also useful to correlate each return with the quality gaps encountered, and make related continuous quality improvements a part of the strategy.

Table 10. Concepts of reverse logistics in Pharma (Source: Authors)

Sub practices of reverse logistics	Stakeholder	Type of returns	Level of importance	Extent of explanation	Reference
Collect unused/expired drugs through collaboration and negotiation among participating stakeholders	Gn	BR	H	c	Narayana *et al*., 2014; Xie and Breen, 2012; Weraikat *et al*., 2016
Reduce drug return rate by optimizing inventory in the customer zone (e.g., VMI)	Gn, LP,P/H/C, LC	BR	H	c	Ritchie *et al*., 2000; De Campos *et al*., 2017; Kabir, 2013; Weraikat *et al*., 2019
Recycling of pharmaceutical stock for later re-use (e.g., drug donation)	P/H/C	CR	H	b	Ritchie *et al*., 2000; De Campos *et al*., 2017; Xie and Breen, 2014
Reduce the rate of unexpected drug return by avoiding temperature excursion in storage and transportation	In, Gn, LP	BR	L	a	Kabir, 2013

BR - Reverse Logistics for business return; CR- Reverse logistics for consumer return; P/H/C - Pharmacies/Hospital/Clinic; LP - Logistics Providers, LC - Local Council; In - Innovative pharma; Gn - Generic Pharma; ***H -high, M – Medium, L – Low; a – limited explanation, b – moderate explanation, c – detailed explanation***

CR require a collection infrastructure to collect unused and/or expired drugs from end consumers for safe disposal (Xie and Breen, 2014). Here Vendor Managed Inventory (VMI) could be used which would reduce waste due to expired drugs (Weraikat *et al*., 2019). However, consumers' voluntary participation in drug return after end-of-use or end-of-life is the main determinant for success (Ritchie *et al*., 2000).

The returned drugs that have not expired could be donated to countries struggling with healthcare affordability (Xie and Breen, 2014; De Campos *et al*., 2017). There is also a possibility of recycling unused/unexpired drugs (Ritchie *et al*., 2000), though this requires strong collaboration between upstream suppliers and downstream retailers (Tat and Heydari, 2021), and patients' willingness to use such drugs. At the moment, this is selectively done as per the discretion of hospital management (Suhandi and Chen, 2023). Large-scale application though is hampered by challenges such as ethical dilemmas, and lack of safety and quality assurance measures. Further detailed study is needed to investigate the scope and viability of such recycling of unused returned drugs, so as to realise its significant economic and environmental potential.

Pharma Industry 4.0

Industry 4.0 entails the application of different smart technologies to realise hyper-efficiencies in manufacturing (Ding, 2018; Kumar *et al*., 2020). While the orientation is predominantly economic, these technologies can also provide significant environmental benefits. Table 11 presents these technologies and their environmental benefits for pharma. As can be seen in the table, each technology (actually technology-driven green practice) is rated as highly important, though the extent of explanation provided is limited. Also, importantly, the scope of these technologies across different stakeholders and their motivation to adopt such technologies for environmental gain is unclear. However, a recent study by Chetthamrongchai and Jermsittiparsert (2020) noted the positive impact of robotic and AI technical knowledge and awareness on environmental performance.

Table 11. Scopes of Industry 4.0 in Pharma (Source: Authors).

Scope of industry 4.0 in pharma	**Stakeholders**	Level of importance	Extent of explanation	**References**
Material reduction through computer-aided drug discovery	In	H	a	Clark *et al*., 2010; Tucker, 2006
Reduce process wastes through web-based monitoring tools	In, Gn	H	a	Ding, 2018; Jimenez-Gonzalez *et al*., 2011; Slater *et al*., 2010
Reduce wastes in a cold chain through real-time data capture	LP	H	a	Shanley, 2016
Reduce drug waste through E-Prescription	Ph/H	H	a	Daughton and Ruhoy, 2011
Reduce resources through real-time data capture of the manufacturing process	Gn	H	a	Ding, 2018
Reduce drug wastes (non-adherence related) through wearable technology	Ph/H	H	a	Ding, 2018

Innovative Pharma (In); Generic Pharma (Gn); Distributor: Logistics provider (LP); Ph/H – Pharmacy/hospital; ***H -high, M – Medium, L – Low; a – limited explanation, b – moderate explanation, c – detailed explanation***

In terms of the actual technologies themselves, web-based process analytical technology (PAT) has enabled pharma companies to monitor and control processes 24/7, thereby avoiding unexpected waste and pollution (Slater *et al*., 2010; Jimenez-Gonzalez *et al*., 2011; Ding, 2018). Similarly, web-based temperature loggers are useful in monitoring and controlling temperature, humidity, and air pressure in cold chain management. Unexpected temperature

excursions and related wastages are therefore avoided (Shanley, 2016). Likewise, computer-aided drug design has enabled scientists and medicinal chemists to make more effective and efficient drug discoveries, and where the use of valuable resources is also minimised (Tucker, 2006; Clark *et al*., 2010; Taylor, 2015). Finally, the use of RFID and related digital technologies enable information from a complex web of stakeholders to be effectively managed thereby ensuring quick and successful return of recalled drugs (Ritchie *et al*., 2000; De Campos et al., 2017). Finally, counterfeit-drug-related waste can be reduced by adopting a proof-of-work-based blockchain across the supply chain stakeholders (Chandrasekaran *et al*., 2024). However, related design, latency, scaling up, security, data accessibility, and ownership issues need deeper understanding. Similarly, the overall environmental implication of such blockchain-based approaches also requires clarity.

Green education and external collaboration

Green practices, or more specifically green chemistry practices, can be promoted through building a learning culture across the organisation/industry. Details of related practices are provided in Table 12. As can be seen from the table, only Innovative Pharma and their CMO/CRO have sought to adopt these, with Generic and Biopharma far behind (Veleva *et al*., 2017). Further, the review reveals a lack of understanding of the scope of such education and green collaboration initiatives at an individual stakeholder level. There is also a lack of clarity on the associated drivers and barriers, especially for generic pharma players.

Table 12. Key education and external collaboration for promoting green practice in Pharma (Source: Authors).

Green related Education and external collaboration	**Stakeholders**	Level of importance	Extent of explanation	**Reference**
Training & conferences on Green chemistry practices	In	H	c	Veleva et al., 2018
Publish green metrics/related practices guide for the chemists	In	H	c	Schneider et al., 2010;
Green chemistry management program: metrics/targets/tools/recognition/external collaboration	In, CMO/CRO	H	c	Veleva et al., 2018; Leahy et al., 2013

In - Innovative. CRMO/CRO - Contract Research & Manufacturing Organizations / Contract Research Organization; ***H -high, M – Medium, L – Low; a – limited explanation, b – moderate explanation, c – detailed explanation***

Traditional education establishments are still far from incorporating key green practices, such as what, why, and how to consider materials, energy, toxicity, biodegradability, renewability, and pollution prevention in their curriculum. However, several pharma companies (especially Innovative Pharma) have developed in-house green chemistry training programs to raise green-related awareness among their workforce (Leahy *et al*., 2013; Veleva *et al*., 2018).

5. Discussion: Knowledge gaps and future research directions

The review provided us with a holistic understanding of green supply chain practices in pharma. It also advanced our knowledge of what green practices influence which functional area/s of the drug supply chain as represented in Table 13. Such a representation can be useful for practitioners to explore and define the role played by pharma stakeholders for a green transition. For instance, green API design reduces material and energy consumption during the commercial manufacturing phase (both API production and formulation) through optimisation of the reaction stages (Slater *et al*., 2010). It can also positively influence cost and environmental efficiency during storage, transportation, cold chain, and use-and-disposal operations (Clark *et al*., 2010). For instance, the appropriate choice of chemical compound(s) during design can lower the storage temperature requirement during distribution, thereby lowering the costs as well as the environmental consequences of refrigerated transportation and warehousing.

The R&D function's critical role in the adoption of a concurrent engineering process also emerged. This involves liaising with API manufacturers, formulators, transporters, and distributors. Such a process can define the requirements of a greener API that delivers sustainability across the supply chain. Additionally, the green-related innovation capability of the stakeholders is also key to sustainable drug (e.g., vaccines) supply chain (Kazancoglu *et al*., 2022b). However, existing reviews appear to have paid little attention to concurrent engineering processes and related innovativeness during the early drug design phase (Clark *et al*., 2010; Sumpter 2010). Future research could therefore explore this including the associated drivers and barriers.

As reflected in Table 13, the types and amounts of raw materials such as excipients/filler/binders used in a formulation primarily depend on the chemical and physical characteristics (e.g., melting point, solubility in water/ other chemical substances) of the API involved. Therefore, an API, with greener attributes such as being more water-soluble (to reduce water toxicity) will have a positive impact on the greenness of the formulation operations associated with it. Similarly, the type of excipients selected will have an impact on drug stability and shelf life. Likewise, the choice of granulation design such as dry/wet granulation will reduce the energy requirement during the commercial formulation stage.

The correlation between green practices' implementation and actual greenness realized and related economic benefits at each functional stage of the drug supply chain needs to be empirically assessed. Unfortunately, currently, there is only limited empirical support for such correlations (e.g., Teunter et. al., 2003, Watson, 2012). This is particularly important for green design and manufacturing practices identified as critical in process industries of this kind

(Kazancoglu *et al*., 2020). These correlations could also vary across processes for different therapeutic classes of drugs, given their use of different resources and raw materials. More work is needed on this aspect as well.

More environmentally biodegradable drugs offer a potential solution to PIE and associated AMR. However, developing such drugs is challenging given that the predominant focus currently is on medical effectiveness and safety, as also the speed with which they are developed (Kummerer, 2010). The drug discovery process is in any case uncertain, complex, expensive, and time-consuming. Further consideration of environmental degradability will make it even more challenging. Not surprisingly therefore, only a few attempts, and that too of a theoretical nature, have been made in the past (e.g., Kummerer, 2009; Leder et. al., 2015).

Table 13. The impact of green practices on each stage of the pharma supply chain

	Green API design *(Materials, degradability, Energy focus)*	Green formulation design (Material & energy focus)	Green (Primary) package design *(Renewability, materials, energy focus)*	Green API synthesis *(Continuous mode, solvent recycling)*	Green formulation *(energy & materials focus)*	Green Procurements *(Energy & materials contents requirements)*	Green transportation *(Less package, co-loading, energy efficient vehicle, eco-driving)*	Green storage (Temperature excursion related wastes, energy focus)	Green cold chain Packaging (Active Vs passive packaging, material & energy focus)	Green use-and-disposal (Drug waste reduction activities)
Drug design & development										
API manufacturing	↓↓			↓↓						
Formulation	↓↓	↓↓	↓		↓↓					
Procurement						↓				
Transportation	↓		↓				↓↓			
Storage	↓↓	↓	↓		↓	↓		↓		
Cold chain	↓								↓	
Use-and-disposal	↓↓	↓↓	↓	↓↓	↓↓	↓				↓↓

↓ - Indicates the positive environmental impact of green practices on the related supply chain stage.

↓↓ - Indicates both positive environmental and cost economic impact of green practices on the related supply chain stage.

However, we argue that while current (non-biodegradable) drugs are saving lives, they are threatening the existence of an entire generation of people in the future. Therefore, it is important to advance our understanding about incorporating environmental biodegradability into drugs without sacrificing their safety, quality, and efficacy. Also, the associated challenges for each of Innovator, Biopharma, and Generic pharma sub-sectors need to be assessed. It will also be useful to explore how medicinal chemists, process scientists, and chemical engineers could proactively consider energy, toxicity, biodegradability, renewability, and pollution prevention aspects for each material they use, and for each stage they follow during the R&D process.

Another issue is of existing APIs (~3000) in the market (Clark *et al*., 2010). A substantial proportion of these are generics whose environmental biodegradability aspects has mostly been ignored so far. However, as advanced analytical approaches are employed, more environmental

toxicity data (e.g., PBT) is expected to become available, which can be used to redesign these drugs to improve their toxicity profiles and biodegradability (Kummerer, 2009; Leder *et al*., 2015). However, uncertainty in such redesigning exercises such as materials exhaustive R&D operations, complex regulatory affairs, and costs could be a challenge. Future research should therefore explore the feasibility of redesigning existing drugs considering materials, energy, toxicity, biodegradability, and renewability. Future research should also investigate whether downstream players and relevant regulatory bodies (e.g., local council, local environmental agency, pharmacy, hospital council, etc) could collaborate on such redesigning initiatives, and what the nature of such a collaboration could be including consideration of practices and cost-benefit trade-offs.

Despite the environmental focus, many practitioners still find the use of certain chemicals of concern (e.g., chlorinated substances linked to global greenhouse emissions) during drug design to be economically beneficial. This is because they increase a drug's shelf life. There is an urgent need therefore to guide practitioners towards options that provide both a longer shelf life as also eco-friendliness. Innovators, generic, and biopharma producers could also develop an end-to-end vigilance process to initiate, monitor, and govern pharma (drugs) from market launch, through use, to end-of-life. The overall PIE impact for each class of drugs could then be assessed (Taylor, 2010). However, unfortunately, there is a dearth of research on such eco pharmacovigilance practices, and related challenges faced by stakeholders. Future research could therefore focus on this aspect.

While there is compelling evidence of resource conservation through continuous API manufacturing (Jimenez-Gonzalez *et al*., 2011; De Soete *et al*., 2017; Chaturvedi *et al*., 2017), it is unclear why the formulation process is still predominantly batch-oriented. Though there are some valid reasons for batching in formulation (e.g. regulatory requirements, special coating requirements), other economic and environmental aspects are less favourable. A comprehensive understanding based on multiple perspectives is therefore needed which only a few researchers have attempted to provide so far (e.g., Plumb, 2005; Slater *et al.*, 2010). Future research should therefore focus on the feasibility and scope of making the formulation continuous, as well as the associated drivers and challenges for stakeholders.

Pharmacy take-back programs could be an effective way to manage unused/expired drugs in households. Though some countries have made this a legal requirement for pharmacies, the nature of the return pattern and the associated economic and environmental benefits still need to be properly understood. Similarly, recycling unused/unopened drugs could significantly reduce drug wastage as well as conserve resources. While there has been some investigation on the scope of drug recycling (e.g., redistribution of unused/unexpired drugs), ethical and regulatory requirements continue to be a significant factor on which there has been much debate (Mackridge & Marriott, 2007; Ruhoy and Daughton, 2008; Suhandi and Chen, 2023). More investigations are therefore needed to understand the scope, viability, and acceptability of drug recycling; also, to conceptualise a related global standard operating procedure to influence the regulatory bodies.

With regards to reverse logistics (RL), the process used for collecting unused/expired household drugs is significantly different from that for drug recalls. Differences in the nature of the regulations, the extent of willingness to take part in such programs, and the nature of the infrastructure could explain this. Cost, quality, accuracy, information and knowledge flow, motivation of different actors, speed, volume, and flexibility could also be key determining factors. A comparative study could help understand the relevance of these factors for different reverse logistics contexts. The knowledge and experience gained from these studies can also help in combating the PIE issues in pharma, which are not discussed in sufficient detail in previous studies such as Vollmer (2010) and Weraikat *et al*. (2016).

The preceding paragraphs identified key research gaps in several important operational areas that are relevant to the greening of the pharma supply chain. These gaps as well as what future researchers should focus on are summarised below:

5.1 Lack of empirical evidence

The review revealed a significant lack of empirical evidence, both in general, as well as in several key areas. For instance, empirical support is lacking on the correlation between green practices and performance (cost and environmental) for individual stages of the pharma supply chain for different therapeutic drugs. Related empirical investigations could also be conducted on 'assessing the greenness of tablet design and manufacturing' or 'assessing the greenness of liquid product manufacturing' to gain a deeper understanding of the process variations and their relevance to green operations. Here use of case studies would be particularly useful. Further, empirical evidence is also needed on the drivers, challenges, and benefits of concurrent engineering in the early drug design and discovery phase.

5.2 Lack of holistic view

The review provided an incomplete understanding of GSCP because of a myopic perspective on the green adoption mechanism (e.g., solvent recycling only). Heterogeneous factors such as firm size and categories, product varieties – liquid formulation, tablet, old versus new drug development, and regulations which shape the overall green adoption capability across the pharma sector were not considered. All these therefore need to be comprehensively assessed in future studies. More studies are also needed to understand the challenges and benefits of improving the biodegradability of drugs across different therapeutic classes. The drivers, barriers, and performance benefits from adopting green supply chain practices for each of innovative, generic, and biopharma also need to be explored. More empirical case studies are also needed to understand the challenge/complexity of greening existing drugs.

5.3 Lack of focus on interdisciplinary research

Green drug production requires multifaceted skills and knowledge. However, unfortunately, only a few previous studies have sought to link traditional supply chain principles with the green engineering-related complexities of drug design and development. More interdisciplinary research that can operationalise the core principles and theory of green chemistry, engineering in pharma, and supply chain, is therefore needed.

5.4 Lack of focus on diverse healthcare contexts

As the overall healthcare service provisions shape the behaviour of each stakeholder (e.g., drug producer, pharmacy, doctors, drug waste vendors, regulators, etc), the green practices and related drivers, barriers, and performances for each could be significantly different from each other. Exploring such contextual differences is important for enriching our green pharma knowledge. Unfortunately, previous studies' focus has been narrow and selective. More studies are therefore needed to identify the key drivers, barriers, and successes of drug take-back and recycling programs across different healthcare contexts.

It is also important to compare GSCP across developed, developing, and underdeveloped countries. In fact, green adoption needs to be particularly explored across China and India which produce the lion's share of APIs globally and pose significant PIE threats. Future studies also require an understanding of the impact of current regulations (e.g., FDA GMP) on green practice adoption across different countries.

5.5 Lack of focus on Eco-pharmacovigilance studies

Regular eco-pharmacovigilance studies are important for dealing with PIE. Unfortunately, such studies are usually done for new drug producers, and are quite technical/scientific keeping the regulatory audience in mind. Future studies should therefore focus on integrating eco-pharmacovigilance output across each of the functional areas of the supply chain, particularly for generic pharma companies.

6. Conclusion

This study conducted an in-depth exploration of green practices at the operational level for each stakeholder across the pharmaceutical supply chain, which has not been previously attempted. The green practices were also conceptualised to develop a related framework that can be tested, modified, and applied in different pharma contexts. The operational-level green practices were identified in the following areas: green practices to address the impact of pharma operations on natural resources, green practices to address the impact of drugs on the environment, and other operational green practices. While this literature-based study followed a rigorous review-process, the studies included may not be exhaustive due to limitations of keyword searches and databases used. Still, despite these limitations, the study made major contributions which are as follows:

6.1 **Theoretical and research implications**

A detailed conceptual framework of GSCP in Pharma has been developed which is not seen in the previous literature. Also, which green practices influence which supply chain stage has also been clarified thereby providing a holistic understanding. Finally, the study fills a gap in the literature concerning an in-depth exploration of operational-level green practices, related complexities, and the role of each stakeholder in pharma's green transition.

6.2 **Practical Implications**

The study has given clear indications to pharma practitioners on how to gain a competitive advantage through environmental initiatives (e.g., savings through solvent recycling, PIE-related health costs, etc). More importantly, the findings can motivate them to work with internal quality teams and regulators to improve sustainability. For instance, while generic pharma pose a more immediate threat to the environment than innovative pharma, the costly and complex process of revalidating existing processes to incorporate green attributes discourages them from adopting those practices. Similarly, while innovative firms can afford some of the post-marketing process changes (e.g., batch to continuous) as part of their R&D investment, generic firms would struggle because of their limited budget (Watson, 2012). Biopharma on the other hand faces significant engineering-related challenges for green practice adoption such as continuous fermentation (Slater *et al*., 2010). Downstream entities such as drug dispensers, pharmacies, and doctors are also encouraged to optimise their drug use and disposal process to reduce drug wastage such as through digitization and eco-prescribing.

6.3 **Policy Implications**

The study results can help policymakers in understanding which stakeholders should be motivated, and which penalised from an environmental perspective. A revised policy can also be developed to motivate generic pharma to collect PBT data on their existing drugs and regulate associated API effluent discharges. Thus, the study provides important implications for regulators (e.g., EMA, MHRA, FDA, etc), and NGOs (e.g., PSNC in the UK) to improve the operational viability of green practices. It also draws attention to practical considerations such as excessive cost, time, and resource-consuming laboratory tests when redesigning off-patent drugs for green credentials which regulatory bodies should consider. For instance, regulators can streamline the validation/marketing approval of process changes. They can also incentivise the innovators (e.g., increase patent duration) and generic firms (e.g., give exclusive sales rights to the first green innovator) for green process development.

Existing GMP/GLP/GDP guidelines can also be updated for mandatory green practices wherever practically feasible and economically viable for firms. The scope of drug recycling under different scenarios could also be paid attention to by the local healthcare authorities in conjunction with industry to address the issue of PIE.

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