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Greening the Pharmaceutical Supply Chain

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ABSTRACT

The pharmaceutical sector is critical from a life-saving perspective. However, it also poses significant environmental challenges due to large consumptions of non-renewable materials and energy, as also extensive by-product and waste generation. Addressing these issues is paramount, though surprisingly, research on it has largely been theoretical, fragmented and incomplete. These shortcomings are sought to be addressed in this work where a comprehensive green supply chain management (GSCM) framework for the sector is first developed through a systematic literature review. It is then empirically assessed and validated for UK's pharmaceutical sector through 47 interviews and analyses of 112 corporate environmental reports that covered all key stakeholders. Innovative and Bio-pharma players were found to be at the forefront of the greening efforts with generic players lagging behind. High levels of solvent recycling, AI-based drug design, and emphasis on Ecopharmacovigilance were observed for the Innovative players. The key drivers for greening were found to be regulatory pressures (e.g., f-gas, ERA, IED) and cost saving potential, with their influence being particularly greater for the Innovative players. Similarly, complex marketing authorization process, high investment requirements, lack of green culture and time pressure were revealed as the key barriers to greening. On the downstream side, lack of environment-related regulatory guidance on prescribing and contradictory regulatory guidance on disposing unused/expired drugs were identified as factors having a significant impact on the environmental loading of drugs. Overall, the study findings can help assess the green readiness of the sector, as also develop stakeholder-specific policy interventions and support mechanisms to increase green adoption.

1 | Introduction

The pharmaceuticals sector is known to significantly harm the environment. There is excessive waste generation, estimated to be 25 to 125 times the weight of the drugs produced, totalling 18 million tons annually. This waste runs off into the environment, contaminating the food and water cycles (Roschangar 2018; Slater et al. 2010). Not surprisingly, around 160 different active pharmaceutical ingredients (APIs) have been detected in surface and groundwater at levels considered unsafe (Kummerer 2009). Excessive waste generation also leads to lower resources' productivity incl. on energy, as well as unnecessary consumption of non-renewable petroleum-based feedstock (e.g. organic chemicals), which is a key input in around 90% of the products (Clark, Breeden, and Summerton 2010). Significant greenhouse gas emissions are also a concern due to extensive use of carbon-intensive chemicals, and the energy-intensive nature of the pharma production, storage, transportation and retailing operations (CPI 2022). With increasing life expectancy and greater access to drugs, all of these problems can only worsen with time. The need to green the pharma sector has therefore become critically important (Sabat, Krishnamoorthy, and Bhattacharyya 2022).

One approach could be to borrow ideas from other sectors where significant green or GSCM-related work has been done such as manufacturing (e.g. Pinto 2020), automotive (e.g. Vanalle et al. 2017), electronics (e.g. Huang, Borazon, and Liu 2021), construction (e.g. Balasubramanian and Shukla 2017), textile and apparel (e.g. Wu, Ding, and Chen 2012), food retailing (e.g. Petljak et al. 2018) and mining (Kusi-Sarpong, Sarkis, and Wang 2016). However, the nature of products, supply chains, manufacturing processes and technologies differ significantly across sectors, as do the characteristics of customers, stakeholders, competitive and regulatory environments and cost structures. Consequently, their key GSCM aspects – specifically the nature of green practices, the cost and performance implications of these practices, and the drivers and barriers to greening – are also likely to vary. To get an in-depth, realistic and practitioner-oriented knowledge and understanding of greening for a sector therefore, a sector-focussed approach is necessary (Sarkis, Zhu, and Lai 2011; Choi et al. 2016).

The pharma sector happens to be unique in several ways (Shah 2004; Wang and Jie 2019): a) Its predominant focus is on efficacy against disease, quality and safety rather than green attributes; b) It has to manage conflicting requirements given what is environmentally better, e.g. what improves a product's/drug's biodegradability compromises its stability/medical efficacy; c) It needs to meet stringent regulations across all supply chain stages from design to retailing; c) Hazardous, difficult-to-avoid chemicals are an intrinsic part of its processes; d) It causes much more severe as well as longer-lasting health and other environmental damage; e) Its product's (drug's) development success rates are highly unpredictable, and which also require huge investments and consume significant resources; f) Its products (drugs) are also typically patented with a limited patent life; and g) Its industry structure is highly complex, where, besides Innovators who develop and patent drugs, a large segment operates in the off-patent space competing on cost (called generics), with another one referred to as Biopharma using alternative technology (biosynthesis), rather than the conventional chemical synthesis. Incorporating green practices in such an environment characterised by high uncertainty, contradictory requirements, stringent multi-stage regulations, diverse environmental considerations and significant time and cost pressures makes it particularly risky and complex, and also substantially different from other sectors', thereby necessitating a separate investigation (Koenig et al. 2019).

While some previous work has been done on GSCM in pharma, it is largely limited, superficial and fragmented. Only a few empirical studies have been done, and therefore, practitioner-level insights and nuanced understanding is limited. Importantly, this (limited) empirical work is also narrowly focussed on specific stakeholder/s (incl. specific industry segments), supply chain stages and green themes. For examples, studies have considered particular stakeholders such as manufacturers (either Innovators, e.g. Schneider, Wilson, and Rosenbeck 2010; or Generics, e.g. Raju et al. 2016; or non-specified, e.g. Bade et al. 2023), or pharmacies (e.g. Latif, Boardman, and Pollock 2013), or doctors (e.g. Soete et al. 2017) with no study considering all of them together. Some important ones such as Biopharma manufacturers, and waste management and water treatment companies have also been missed. Studies have similarly been selective on supply chain stage/s by considering Drug manufacturing (API) (e.g. Schneider, Wilson, and Rosenbeck 2010), Drug manufacturing (formulation) (e.g. Bade et al. 2023), or Drug use and disposal (e.g. Khan and Ali 2022). No study was found to have considered drug design, a key stage, or all of the stages together. This was seen for green themes also, with studies mostly considering pairs of themes (e.g. green practices and green barriers, e.g. Watson (2012); or green practices and cost-related performance impacts, e.g. Soete et al. 2017) rather than all of the themes together. Such a fragmented approach has meant a lack of holistic understanding of the trade-offs/synergies/inter-relationships between supply chain stages, stakeholders and green themes that could be exploited to maximise the effectiveness, efficiency and reach of GSCM in pharma.

Finally, at an individual green theme level too, the limited number of empirical studies does not inspire confidence that all key aspects within each (e.g. all key practices for green practices, or all key drivers for green drivers) have been uncovered/understood for pharma. Those covered are also not discussed at an individual stakeholder level, or assessed from a strength/intensity perspective, being largely descriptive instead. Consequently, it is unclear which green practices are implemented more/less intensely, which green drivers and barriers are stronger/weaker, and which cost and environmental performance impacts are greater/lower for individual stakeholders in pharma. The lack of knowledge at this detailed level hinders managers from taking precise, tailored decisions that could provide more optimal GSCM-related outcomes.

Overall, the lack of comprehensiveness and depth from multiple perspectives may be undermining the efficiency and effectiveness of the industry-wide greening efforts in pharma, and which forms the motivation for this study that aims to: 1) Develop a comprehensive, GSCM application framework for the pharma industry consisting of green supply chain practices, the drivers and barriers associated with their implementation, and the benefits realised from them; and 2) Assess the applicability and validity of the framework in a real-world setting. While covering these objectives, the following research questions (RQs) are sought to be answered:

RQ1. What key green supply chain practices (GSCP) are implemented by pharma sector stakeholders?

RQ2. What drives or motivates them to implement these practices?

RQ3. What key barriers or challenges they face in implementing these practices?

RQ4. What impact do these practices have on their cost and environmental performance?

Answering these questions would provide a more holistic understanding of the interactions/interplay between green drivers, green barriers, green practices' implementation, and the cost and environmental performance impacts (of the green practices) thereby enabling better GSCM-related managerial actions. For example, which drivers and barriers to work on,

to increase application of which green practices, to make improvements on which cost and environmental performance measures of interest. Such a comprehensive approach is not seen in any previous GSCM study on pharma. Moreover, the understanding on each of drivers, barriers, practices and performance impacts will be gained at an individual stakeholder level, and cover all key stakeholders, supply chain stages and industry segments (i.e. Innovators, Generics and Biopharma). This understanding in each case will also be from a strength/theme perspective, with the green practices additionally understood through the prism of the green chemistry-oriented MET framework (M = *Materials, E* = *Energy* and T = *Toxicity*). Such an in-depth and integrated perspective, which again is not seen in any previous study, enables the GSCM-oriented managerial actions to be more precise and comprehensive. For example, actions could be considered at individual stage/stakeholder level, or across multiple stages/stakeholders with the implications on other stages/stakeholders also considered to make them more optimal. Finally, all of this understanding is developed through a rigorous empirical approach involving a large number of industry respondents and reports that is lacking in previous GSCM empirical studies on pharma. The fact that the UK, a key global hub for drug design and development (ACS, GCI 2019) was considered as the setting for the investigation provides further strength to the empirical findings. The study therefore makes a significant contribution to the understanding GSCM in pharma at multiple levels that can be useful to researchers and practitioners alike.

The rest of the paper is structured as follows: The next section explains the research framework, while Section 3 reviews the existing literature for developing the GSCM framework. Section 4 describes the research methodology and the setting considered. In Section 5, the findings are discussed as per the research objectives. We conclude in the last section, where the theoretical and practical implications, limitations and suggestions for future research are covered.

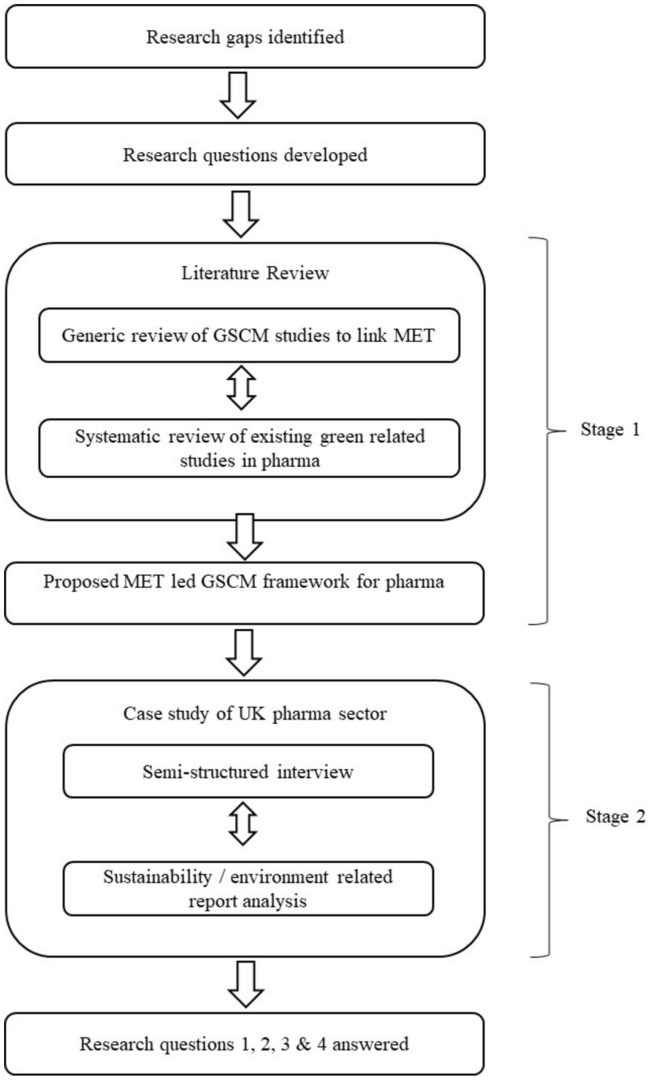

FIGURE 1 | Research framework.

2 | Research Framework

Figure 1 below presents the research framework used which can be seen to consist of two main stages: (a) The literature review stage used to develop the MET-led GSCM framework, and (b) the case study stage where the UK pharmaceutical sector is used to assess the applicability of the framework. These stages are discussed in detail in the following sections.

3 | Literature Review and Development of the Pharma GSCM Framework

Before delving into the literature, it is important to first understand the structure of the pharmaceutical supply chain, the interactions among the stakeholders and the importance of incorporating green practices at each stage supply chain. Figure 2 presents a blueprint of the pharmaceutical supply chain and its environmental implications.

As shown in the figure, the first stage in a pharma supply chain is drug design and development, a difficult process associated with high failure rates exceeding 90% (Bountra, Lee, and Lezaun 2017).

The extent of resource wastage and the associated environmental consequences are, therefore, huge. Thereafter, the journey from drug discovery to its marketing authorization is also quite protracted, typically spanning 10 to 15 years, with significant cost implications ranging from half a billion to a billion dollars (Taylor 2015). Such drug-related research and development (R&D) activities are the focus of most Innovative pharma companies, who then obtain patent rights and charge high prices during the patent period. The generic pharma sub-sector, on the other hand, focuses on producing off-patent drugs and typically competes on cost. Finally, the biopharma sub-sector produces biotechnology-based drugs that involve minimal use of chemicals.

With regard to pharma manufacturing, it is split into two stages: The Active Pharmaceutical Ingredients (APIs) production stage, and the formulation stage. The formulation stage is where the API is mixed with excipients through mechanical and chemical processes to form tablets, capsules and syrups. The drugs

are then shipped downstream to local hospitals, clinics and pharmacies, the role of pharmacies being to dispense drugs to patients based on doctor/prescriber prescriptions. Doctors, pharmacists and patients play a critical role in the effective use and disposal of unused/expired drugs that typically accumulate through ineffective prescribing, dispensing and use. As per estimates, more than 50% of the drugs prescribed globally are wasted (WHO 2003; Mudgal et al. 2013). Also, inappropriate drug disposal (10%) is the second largest contributor to environmental contamination from drugs after patient excretion (88%), and manufacturing discharge (2%) (AstraZeneca 2017). Finally, waste management and wastewater treatment companies play a reactive role in managing the environmental loading of drugs by segregating waste, and applying advanced waste management technologies.

3.1 | Systematic Literature Review Process

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used for the literature review (see Figure 3 for details).

The main databases and the search strings (with Boolean logical operators) used to identify and categorize the studies are provided in Table 1. Most relevant publications were journal articles, which were supplemented by a selection of book chapters in areas where journal articles were scarce.

After an initial search that yielded a broad spectrum of studies, a more selective screening narrowed the pool to 178 articles that covered the 2000 to 2023 period. Thereafter, use of NVIVO software's 'frequency' and 'Text Search Query' functions enabled a more precise assessment of the papers' relevance to our research, and helped in further narrowing the pool to 105 studies. We then conducted a thorough, full-text review of each paper to assess if they covered any of our core topics of drug design and development, drug manufacturing and drug use-and-disposal. This helped us finalise the selection to 24 studies. To expand and enrich our corpus, an additional 14 studies were identified through a meticulous examination of backward and forward citations. Ultimately, this rigorous process resulted in a curated collection of 38 studies that were deemed suitable for an in-depth assessment.

3.2 | Literature Review Findings and Gaps

Table 2 presents the synthesis of the shortlisted articles where the several gaps are clearly evident. Only a few empirical studies appear to have been done, which is not surprising given the pharma industry's secretive nature, and the consequent difficulty in data collection. These (few) empirical studies also appear to have mostly focussed on specific aspects: select stakeholders, select single/dual supply chain stage/s and select combination of green themes from among green practices, drivers, barriers and cost and environmental performance impacts. No study has covered all key stakeholders, supply chain stages and green themes that could provide a holistic understanding of GSCM for pharma. There are also important omissions, with important stakeholders such as Biopharma manufacturers, and waste management and water treatment companies not considered by any study. Finally, there is a lack of assessment of the strengths/intensities of the green themes—only two studies have considered this, and that too in relation to green practices' application only, not the others. A comprehensive understanding of the strengths/intensities of all the green themes together could enable a more precise/effective prioritisation and tailoring of the GSCM-related actions.

Overall, the lack of a comprehensive and holistic understanding of GSCM in pharma is clearly apparent, though when considering all of the findings from the different studies together, they provided us the relevant strands for a MET-based GSCM framework. They also helped highlight the roles of the different stakeholders in the greening of the pharma industry.

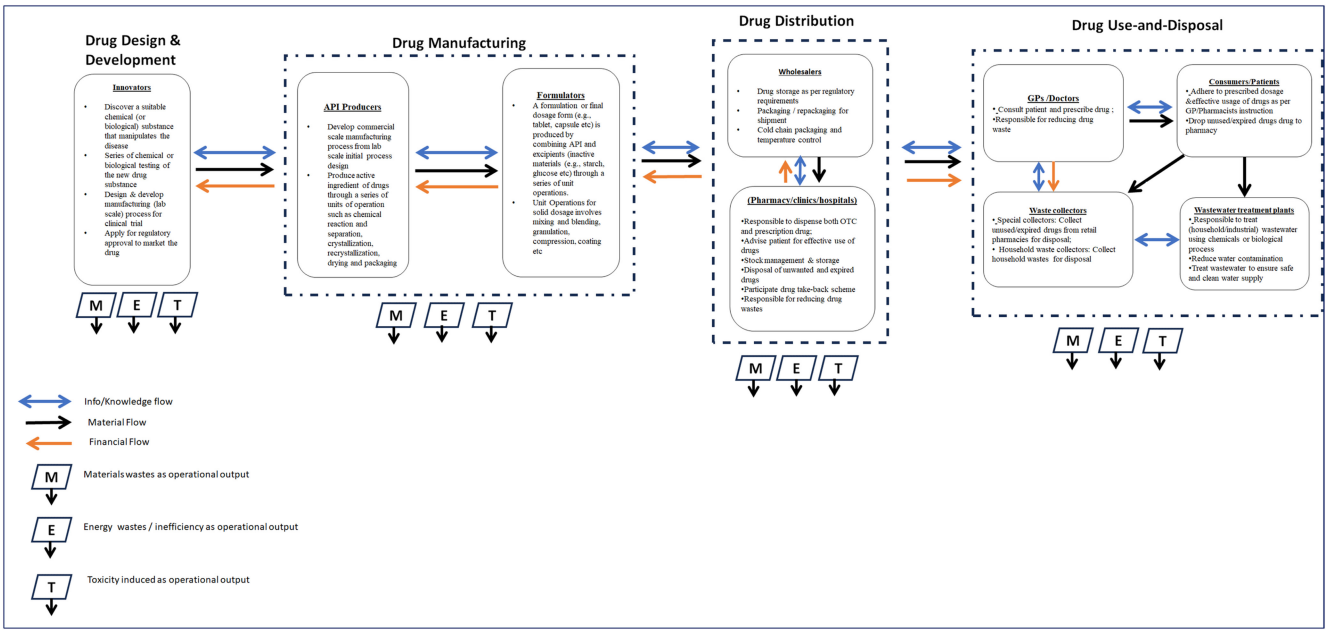

FIGURE 2 | Pharma supply chain with key stakeholders, their interactions, and the relevance of MET.

3.3 | Components of the GSCM Framework

This required conceptualising the MET-related GSCPs across the key supply chain stages. The literature review enabled us to develop the core MET-related practices in three areas: drug design and development, drug manufacturing and drug use-and-disposal. We then identified the relevant drivers and barriers to understand the opposing pressures stakeholders face to implement GSCP. Finally, we captured the performance benefits of implementing GSCP, especially from a cost and environmental perspective. Thus, the core components of the framework are green practices, green drivers, green barriers and green-related performance impacts. These are discussed in the following sub-sections.

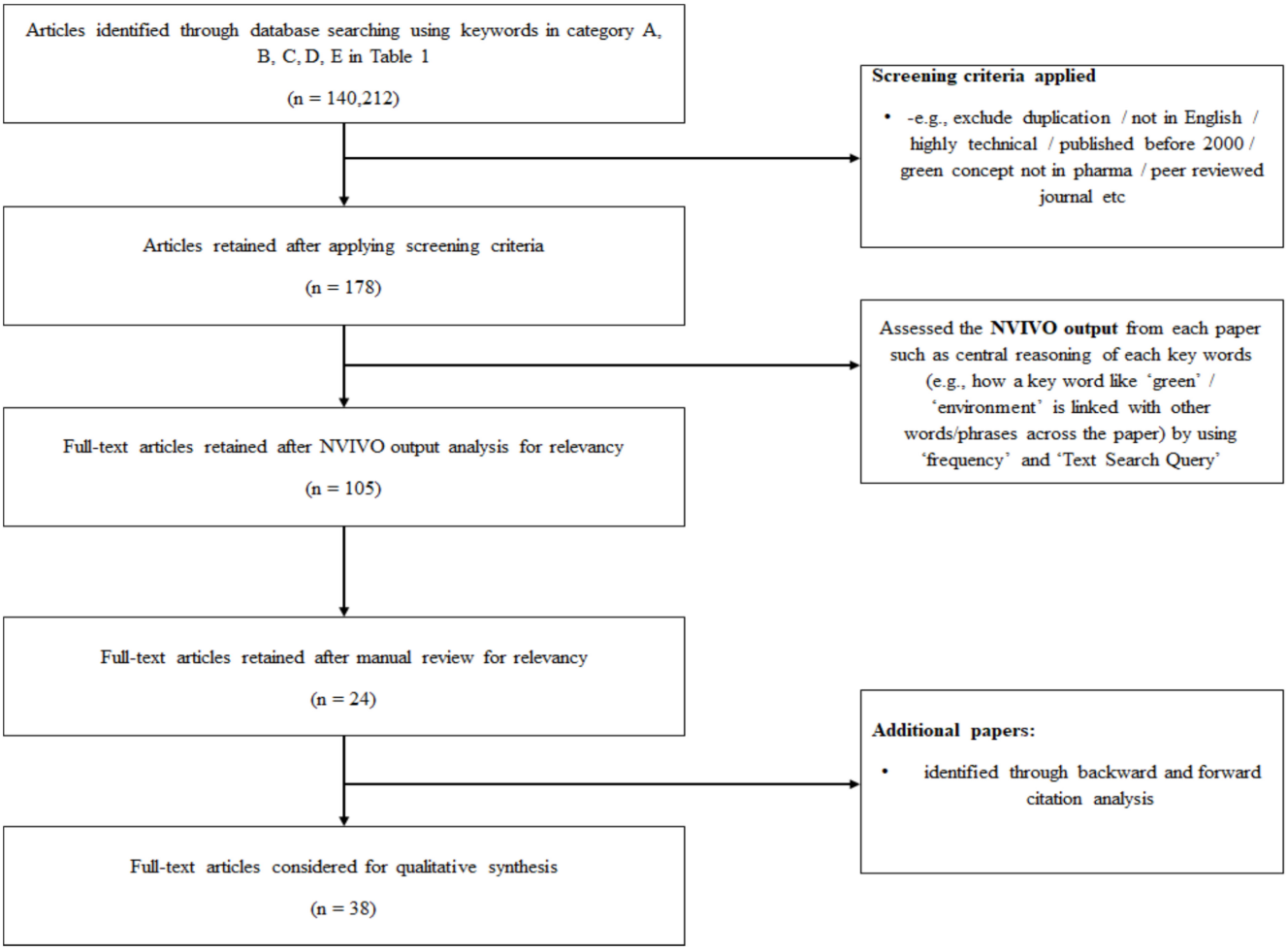

FIGURE 3 | Systematic review of green supply chain-related studies in the pharma sector.

TABLE 1 | Key databases and the search strings with Boolean logical operators used.

Database	Search strings with Boolean logic operator
Scopus (A)	"(Green OR sustainable) AND pharma", "Green" AND "Pharma" AND "Supply Chain", "Green AND manufacturing AND pharmaceutical AND sector", "Green AND Supply AND chain AND Pharmaceuticals"
ScienceDirect (B)	"Green Supply chain AND Pharma", "GSCM AND Pharmaceutical", "(Green AND Pharmaceutical) OR Supply Chain", "(Green AND drug AND manufacturing) OR pharmaceutical sector", ("Disposal and drug") OR "environment", "(Green OR sustainable) AND pharma"
Emerald (C)	"Green AND supply AND chain AND pharmacy"
Google Scholar (D)	"(Green OR sustainable) AND pharma", "drug use AND disposal AND environment"
SpringerLink (E)	"(Environment OR sustainability) AND pharma", "(Green OR sustainable) AND pharmacy"

3.3.1 | Green Supply Chain Practices (GSCP)

This section conceptualizes the GSCP across key supply chain stages, specifically design & development, manufacturing and use-and-disposal.

Green Drug Design and Development. Drugs are designed and developed in a way as to have lower toxicity, and lower material and energy-related impacts across their lifecycle (Clark, Breeden, and Summerton 2010; Leder, Rastogi, and Kummerer 2015). To reduce material-related impact, greener substances, such as biocatalysts are used (Challener 2016; Milanesi, Runfola, and Guercini 2020), though this requires strong coordination among upstream medicinal scientists and chemists (Clark, Breeden, and Summerton 2010). Digitizing the drug discovery process, including through High-Throughput Screening (HTS) and software-led focused libraries, can also dematerialize the process by reducing the requirement of raw materials for initial lab testing (Clark, Breeden, and Summerton 2010). The use of process metrics, such as Process Mass Intensity (PMI) for specific drug processes (Jimenez-Gonzalez et al. 2011; Ang et al. 2021), adopting the quality by design principle and designing combined drugs with two or more APIs (Ding 2018), can also lower the material-related impacts.

For improvements on the energy front, process-centric energy assessments in the early phase of drug development, and validation of energy-efficient equipment systems are useful (Clark, Breeden, and Summerton 2010; Slater et al. 2010). On the other hand, bio-based drug development can reduce water toxicity (Watson 2012). Drug processes can also be designed as to use fewer volatile organic compounds (VOCs), and thereby reduce air toxicity such as from greenhouse gases (Jimenez-Gonzalez et al. 2011). However, it is predominantly innovative pharma companies that have adopted these practices, with generic and biopharma ones lagging behind (Watson 2012). Also, most of these practices are used for new drugs, rather than those already on the market (Clark, Breeden, and Summerton 2010).

Green Drug Manufacturing. This involves manufacturing API and formulations in a way that minimizes material, energy, and toxicity-related impacts not only in this stage, but also subsequent ones of distribution, use, and disposal. The review suggests use of continuous mode of manufacturing (Plumb 2005; Slater et al. 2010; Ding 2018), reuse and recycling of raw materials (e.g. solvents) (Teunter et al. 2003; Perez-Vega et al. 2013), and application of lean approaches for dematerializing the manufacturing process. In contrast to continuous manufacturing, batch operations require more energy, and also generate more waste as cleaning with solvents is required between batches. With regard to solvent reuse and recycling, it is both less intensive, and has also only recently been introduced in pharma (Perez-Vega et al. 2013). No wonder, its recycling rate in the sector is only 50%. The adoption of energy-efficient technology, and plant-specific energy management programs (Clark, Breeden, and Summerton 2010; Ding 2018) have also been found to be useful from an energy conservation perspective.

Sustainable raw material management programs, such as green solvent selection guides (Sheldon 2010; Slater et al. 2010; Bade et al. 2023), in-house standard operating procedures to manage toxic gases (Slater et al. 2010), monitoring and controlling the environmental toxicity of drug substances (known as Ecopharmacovigilance) (Taylor 2010), and responsible waste management (Perez-Vega et al. 2013) can all detoxify manufacturing operations and are important with regards to addressing the PIE and AMR challenges. The degree of adoption of these practices though varies across stakeholders. While most innovative pharma companies have adopted many of these practices, only a few, such as solvent recycling, have been adopted by generic pharma, and that too only on a trial basis (Watson 2012).

Green Drug Use-and-Disposal. This refers to drugs being prescribed, sold, used, and disposed in a manner that minimizes their material, energy and toxicity-related impacts. Downstream entities, such as patients, prescribers, and drug retailers (e.g., pharmacies), play a critical role here (Vollmer 2010; Tat and Heydari 2021). As per the literature, a range of lean approaches such as medical intervention in drug usage (Latif, Boardman, and Pollock 2013), and drug reuse and recycling (Mackridge and Marriott 2007; Ruhoy and Daughton 2008) can optimize the prescribing, dispensing, and use of drugs, thereby minimizing related material waste. Inappropriate prescribing, dispensing, and drug use are all serious problems currently costing the NHS around £300 million annually (NHS Waste Management Campaign 2017). Coordination problems among prescribers, dispensers, hospitals, and patients are also known to cause drug wastage (Vollmer 2010; Smale et al. 2021), and which can be addressed by digitizing their interactions. Finally, environmental toxicity can be mitigated by offering drug take-back services for their safe and responsible disposal (Glassmeyer et al. 2009; Vollmer 2010).

3.3.2 | Drivers of Green Supply Chain Practices' Implementation

The pharma sector is being pressurised by both internal and external sources to adopt GSCP. The review highlighted regulatory and stakeholder pressures as the key external drivers, with cost savings and top management commitment identified as the main internal ones.

External Drivers. Regulations like the Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH) (Clark, Breeden, and Summerton 2010), and the Environmental Risk Assessment (ERA) (Taylor 2010) tend to promote the adoption of green practices. For instance, pharmaceutical companies that produce or import large quantities of raw materials in the EU (e.g., intermediate pharmaceuticals greater than a ton per year) must comply with the REACH requirements. This regulation encourages producers to consider greener substances and avoid hazardous ones in the early drug design phase. The result is both a less toxic drug being produced, as also less toxic by-product generation in the process. Similarly, Innovators involved in drug discovery and development are required to perform an ERA for newly developed drugs. This can force them to consider bio-based drug development, where the environmental risks are considered to be lower. Regulations on industrial emissions, particularly those involving greenhouse gases and F-gases can also inspire green innovations in the sector

TABLE 2 | Summary of key GSCM-related studies in the pharma sector.

				Supply chain stages covered				Green themes covered					Strength/intensity of green themes				
Study	Country setting	Methodology	Stakeholder/s covered	Drug Design	Drug Manufacturing - API	Drug Manufacturing - Formulation	Drug Use and Disposal	Green Practices	Green Drivers	Green Barriers	Cost-related performance impact from green practices	Environment-related performance impact from green practices	Green practices' application	Green drivers	Green barriers	Cost-related performance impact from green practices	Environment-related performance impact from green practices
Teunter et al. (2003)	Germany	Qualitative case study (empirical)	Pharma manufacturers (innovators)		✓			✓	✓								
Plumb (2005)	General	Conceptual	Pharma manufacturers (innovators)		✓	✓		✓		✓		✓					
Mackridge and Marriott (2007)	UK	Quantitative case study (empirical)	Pharmacy/ Hospital				✓	✓			✓						
Ruhoy and Daughton (2008)	USA	Conceptual	Hospital/ Healthcare Institutions				✓	✓									
Glassmeyer et al. (2009)	USA	Conceptual	Pharmacy/ Hospital				✓	✓									
Vollmer (2010)	Europe	Survey (empirical)	Pharmacies				✓	✓	✓	✓							
Breen, Xie, and Thiaray (2010)	UK	Conceptual	Pharma manufacturers (unspecified type) & distributors				✓	✓									
Schneider, Wilson, and Rosenbeck (2010)	Global	Content analysis (empirical)	Pharma manufacturers (innovators)		✓			✓									
Kummerer (2010)	General	Conceptual	Pharma manufacturers (innovators)	✓				✓				✓					
Sumpter (2010)	Germany	Conceptual	Pharma manufacturers (innovators)	✓				✓				✓					
Clark, Breeden, and Summerton (2010)	Germany	Conceptual	Pharma manufacturers (innovators)	✓	✓	✓		✓	✓	✓							
Sheldon (2010)	General	Conceptual	Pharma manufacturers (innovators)		✓			✓									
Slater et al. (2010)	General	Conceptual	Pharma manufacturers (innovators)		✓			✓	✓	✓	✓	✓					

(Continues)

TABLE 2 | (Continued)

				Supply chain stages covered				Green themes covered					Strength/intensity of green themes				
Study	Country setting	Methodology	Stakeholder/s covered	Drug Design	Drug Manufacturing - API	Drug Manufacturing - Formulation	Drug Use and Disposal	Green Practices	Green Drivers	Green Barriers	Cost-related performance impact from green practices	Environment-related performance impact from green practices	Green practices' application	Green drivers	Green barriers	Cost-related performance impact from green practices	Environment-related performance impact from green practices
Taylor (2010)	Germany	Conceptual	Pharma manufacturers (unspecified type)	✓	✓		✓	✓	✓	✓		✓					
Castensson and Ekedahl (2010)	Global	Conceptual	Pharmacies, doctors and patients				✓	✓		✓							
Jimenez-Gonzalez et al. (2011)	General	Conceptual	Pharma manufacturers (innovators)		✓			✓			✓						
Watson (2012)	Global	Survey (empirical)	Pharma manufacturers (innovators and generics)		✓			✓		✓			✓				
Boltic et al. (2013)	Serbia	Experimental (empirical)	Pharma manufacturers (generic)			✓		✓			✓	✓					
Perez-Vega et al. (2013)	General	Conceptual	Pharma manufacturers (innovators) and waste management companies		✓			✓			✓						
Latif, Boardman, and Pollock (2013)	UK	Observations and Interviews (empirical)	Pharmacies				✓	✓			✓						
Daughton and Ruhoy (2013)	USA	Conceptual	Doctors				✓	✓		✓							
Daughton (2014)	USA	Conceptual	Doctors				✓	✓		✓							
Leder, Rastogi, and Kummerer (2015)	General	Conceptual	Pharma manufacturers (innovators)	✓				✓		✓		✓					
Raju et al. (2016)	India	Quantitative case study (empirical)	Pharma manufacturers (generic)			✓		✓				✓					
Challener (2016)	General	Conceptual	Pharma manufacturers (innovators)	✓				✓			✓						

(Continues)

TABLE 2 | (Continued)

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Study	Country setting	Methodology	Stakeholder/s covered	Drug Design	Drug Manufacturing - API	Drug Manufacturing - Formulation	Drug Use and Disposal	Green Practices	Green Drivers	Green Barriers	Cost-related performance impact from green practices	Environment-related performance impact from green practices	Green practices' application	Green drivers	Green barriers	Cost-related performance impact from green practices	Environment-related performance impact from green practices
Soete et al. (2017)	Belgium	Interviews and survey (empirical)	Pharma manufacturers (unspecified type), hospitals, pharmacies, doctors, NGOs		✓	✓		✓			✓						
Chaturvedi et al. (2017)	India	Conceptual	Pharma manufacturers (unspecified type)		✓			✓				✓					
Veleva and Jr (2017)	India	Content analysis (empirical)	Pharma manufacturers (innovators and generic)		✓	✓		✓	✓	✓			✓				
Ding (2018)	General	Conceptual	Pharma manufacturers (innovators)		✓	✓		✓				✓					
Koenig et al. (2019)	General	Conceptual	Pharma manufacturers (innovators), contract manufacturing & contract research organisations			✓		✓		✓							
Milanesi, Runfola, and Guercini (2020)	Generic	Conceptual	Pharma manufacturers (unspecified type)		✓			✓			✓	✓					
Alshemari et al. (2020)	General	Conceptual	Distributors, pharmacies and patients				✓	✓									
Tat and Heydari (2021)	General	Conceptual (modelling based)	Pharma manufacturers (unspecified type) and pharmacy				✓	✓			✓						
Khan and Ali (2022)	General	Interviews (empirical)	Pharma manufacturers (unspecified type)				✓		✓	✓							
Ang et al. (2021)	General	Conceptual	Pharma manufacturers (unspecified type)		✓			✓									

(Continues)

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Study	Country setting	Methodology	Supply chain stages covered					Green themes covered					Strength/intensity of green themes				
			Stakeholder/s covered	Drug Design	Drug Manufacturing - API	Drug Manufacturing - Formulation	Drug Use and Disposal	Green Practices	Green Drivers	Green Barriers	Cost-related performance impact from green practices	Environment-related performance impact from green practices	Green practices' application	Green drivers	Green barriers	Cost-related performance impact from green practices	Environment-related performance impact from green practices
Smale et al. (2021)	General	Conceptual	Pharma manufacturers (unspecified type), distributors, doctors, pharmacies			✓	✓	✓		✓							
Hirst (2022)	General	Conceptual	CDMO (contract design & manufacturing organization)	✓				✓		✓							
Bade et al. (2023)	Germany	Content analysis and interviews (empirical)	Pharma manufacturers (unspecified type)			✓		✓		✓							

(Clark, Breeden, and Summerton 2010). Finally, environmental sustainability, and specifically PIE, may drive downstream customers such as hospitals and clinics to pressurise drug producers to produce greener drugs (Sumpter 2010; Clark, Breeden, and Summerton 2010).

Internal Drivers. The principal internal driver for implementing green practices appears to be the cost savings they generate. For example, Innovative and generic pharma companies are both motivated to pursue solvent recycling because of its high return on investment (Teunter et al. 2003; Perez-Vega et al. 2013; Soete et al. 2017). Solvent recovery also has huge potential given that solvents account for roughly 80–90% of the total process mass in a typical pharma manufacturing operation (Slater et al. 2010). For biopharma companies, though, solvent use is minimal (Clark, Breeden, and Summerton 2010). On the downstream side, distributors such as hospitals and pharmacies are known to adopt waste reduction approaches to minimise costs. Finally, in view of PIE and AMR, pharma sector's top management is increasingly focussed on developing a green and sustainable culture (Watson 2012; Soete et al. 2017). For instance, many innovative pharmaceutical companies have developed in-house green chemistry training programs, and developed incentives to increase environmental awareness among its workforce.

3.3.3 | Barriers to Green Supply Chain practices' Implementation

Understanding the hindrances to the adoption of green practices is also important (Clark, Breeden, and Summerton 2010). The key external barriers include a complex drug market authorization process, an unclear and weak regulatory guidance, and a lack of demand for green products, while high investment costs, operational challenges, cultural issues, and a lack of (green-related) training and education are identified as the key internal ones.

External Barriers. Each stage in a drug's lifecycle is stringently scrutinized by appropriate regulatory bodies (e.g., the FDA in the US, MHRA in the UK, etc.) before grant of marketing authorization. Also, any subsequent product/process modifications require a time-consuming and expensive revalidation and reapproval process (Plumb 2005; Slater et al. 2010; Koenig et al. 2019). However, given the large number of off-patent APIs in the market (more than 3000), such a revalidation process is needed if any meaningful impact is to be made on the environmental front (Clark, Breeden, and Summerton 2010). For generic pharma, which is dominant in this off-patent API space where cost efficiency is paramount, this regulatory approval-related barrier would be particularly critical.

Additionally, current regulations pertaining to GLP (or good laboratory practice) and GMP (or good manufacturing practice) still primarily focus on a drug's safety, quality, and efficacy, rather than its green attributes (Clark, Breeden, and Summerton 2010). Other local regulations are also unclear/conflicting with regard to how to address PIE and AMR during the drug use-and-disposal phase (Vollmer 2010; Daughton 2014).

Internal Barriers. Large investment requirement for research and development (Clark, Breeden, and Summerton 2010), and in

particular, for green process innovation (Taylor 2010; Veleva and Jr 2017) is a significant hurdle to developing green API's. Generic pharma companies, which typically have limited resources, and are also cost focussed, may struggle to make these investment commitments (Veleva and Jr 2017; Khan and Ali 2022) Another factor could be that the long-term benefits and return on investment from green process development (e.g., converting batch to continuous process) are still unclear.

Operational complexities pose additional challenges. Given the diversity of drug formulations (e.g., solid tablets, liquids, inhalers, etc.), a one-size-fits-all approach is difficult. The complexities and incompatibilities in technology, machinery calibration, and setup, along with the lack of environment-related data, and the short market lead time requirements are some of the operational challenges associated with green implementation (Clark, Breeden, and Summerton 2010; Taylor 2010; Slater et al. 2010). Ensuring that drugs are safe and effective to use, while also minimising their wastage during the use-and-disposal phase is also challenging (Daughton and Ruhoy 2013).

Finally, cultural barriers are evident in the industry's struggle with the managerial mindset and an unwillingness to redesign cleaner processes (Slater et al. 2010; Ding 2018). Managers fear deviating from established processes delivering safe and effective drugs due to patient and regulatory-related risks. The emphasis on MET-oriented training is also limited. While some innovators (e.g., Pfizer, Novartis etc.) pay attention to it (Watson 2012), most generic ones do not. The latter's principal focus instead is on developing process standards as per patented drug formula, where a GMP-focussed training is more appropriate.

3.3.4 | Performance Benefits From Green Practices' Implementation

Practitioners, policymakers, and academic researchers working on pharma supply chains are increasingly demanding evidence of performance improvement from green initiatives (Teunter et al. 2003; Henderson, Constable, and Jimenez-Gonzalez 2010). Here, innovative pharma companies appear to have realised greater cost savings from green adoption than generic and biopharma ones (Watson 2012).

The review revealed a significant potential for reducing Scope 1 and Scope 2 greenhouse gas emissions, as well as volatile organic compounds (VOCs), and ozone-depleting substances (ODS) through green processes (Watson 2012; Slater et al. 2010). Significant reductions in requirements for input materials, and associated cost savings have also been reported through related process changes, as also through the use of relevant performance measures such as process mass intensity (PMI) (Jimenez-Gonzalez et al. 2011). For example, Pfizer could double the yield of an API in Zoloft through a MET-led process change. This also resulted in a 20% to 60% reduction in raw material requirement, and a significant reduction in hazardous waste generation (Slater et al. 2010).

By both reducing hazardous waste generation, as well as recycling it, the environmental burden from drug discharges into the environment, such as in the form of PIE and AMR, could be reduced (Kummerer 2009; Slater et al. 2010; Clark, Breeden, and Summerton 2010). One such high potential opportunity is through the use of green solvents which have been found to significantly reduce hazardous by-product generation during the early drug design phase (Slater et al. 2010; Leder, Rastogi, and Kummerer 2015). Recycling of by-products, incl. of solvents, has also been noted to be profitable. For instance, the German pharmaceutical company Schering AG could save approximately DM 25 million annually (around 8.5% of its production cost) through solvent recycling and reuse (Teunter et al. 2003).

Overall, enhanced returns on investment from green projects (Clark, Breeden, and Summerton 2010), along with cost savings through raw material and energy efficiency improvements (Teunter et al. 2003; Soete et al. 2017), water efficiency improvements (Slater et al. 2010), finished drug reuse/recycling (Mackridge and Marriott 2007), and patient intervention strategies (Latif, Boardman, and Pollock 2013) have been reported. With regard to the extent of improvement in energy performance, it can vary as per the investment/commitment to green energy.

3.4 | Proposed GSCM Framework for the Pharma Industry

Figure 4 shows the proposed GSCM framework for pharma. Central to the framework are the various MET-related GSCPs. Antecedents of GSCP are the Internal and External drivers and barriers, while the outcomes of GSCP are captured through Environmental and Cost performance impacts. Previous studies have found such frameworks to be useful in greening their investigated industries (Balasubramanian and Shukla 2020; Balasubramanian, Shukla, and Chanchaichujit 2020).

4 | Research Methodology

Given the nature of the research questions, and the complexity of the investigated phenomenon, our knowledge creation process followed Burrell and Morgan's (1979) subjective interpretivism. It is known to provide an in-depth understanding of a phenomenon within a specific context, and is considered appropriate when complex meaning cannot be understood through observation and measurement alone, but must be interpreted (Bille and Hendriksen 2023; Wieland, Tate, and Yan 2024). The 'what', 'why' and, 'how' of green practices' application by the pharma sector to improve (its) environmental and/or economic performance was ontologically vague and lacking in clarity. Through subjective interpretivism, a deeper understanding of each green theme/sub-theme individually, as well as together was possible.

An abductive logic, which utilizes both deductive and inductive reasoning (Kovács and Spens 2005) was followed. Since existing theories could not fully explain how green chemistry interacts with GSCM principles in a new context such as pharma, abduction was used to both apply, as well as advance the framework through continuous, iterative interactions between real-life observations and GSCM theories (Dubois and Gadde 2002).

4.1 | Case Study Approach

We adopted a case study approach, which is appropriate for investigating a contemporary phenomenon in a real-life context. It is particularly useful where the boundaries between phenomenon and context are not clearly evident (Yin 2009). Given the lack of adequate empirical insights on GSCM in pharma, it is appropriate for this study. Specifically, an explorative single-case study of the UK pharma supply chain was considered, as it represents a critical and unique case for green adoption (Yin 2009; Rymaszewska, Helo, and Gunasekaran 2017). The UK is home to some of the world's leading pharma innovators, including AstraZeneca, GSK, Novartis, and Pfizer, which are involved in both research & development as well as application of green practices. Interesting insights could be gained from these companies on their green-related experiences and accomplishments. Secondly, UK's pharma sector is the largest sectoral contributor to greenhouse gas emissions in the country (16% of total) that need to be urgently reduced to meet the country's emissions target (Kyoto Protocol 1998). There is also pressure to address the AMR challenge by 2040 (UK Department of Healthcare and Social Care 2019). UK therefore serves as an interesting country context for examining how green requirements are being responded to and adapted to by the pharma sector. The key learnings from there would also be relevant to pharma sectors around the world facing similar challenges.

Within this case study, an embedded case approach with multiple units of analysis (e.g., drug manufacturing firm, retail pharmacy, hospital, GP, local council, etc.) was used (Yin 2009; Balasubramanian et al. 2023) as each stakeholder within the pharma supply chain had to be covered. Data was collected through interviews and from corporate environmental reports (refer to Table 3 for details). Data collected through such multi-methods are known to provide more valid and trustworthy insights (Saunders, Thornhill, and Lewis 2016).

4.2 | Data Collection: Interviews

Companies were contacted via email and phone, with only knowledgeable and managerial-level employees targeted for the interviews (Voss, Tsikriktsis, and Frohlich 2002). In-depth semi-structured interviews where then conducted with 47 participants from across the pharma supply chain covering both upstream and downstream ends. These participants were chosen through purposive sampling to mitigate the risk of extreme particularism, and to investigate the diversity of approaches (Theodorakopoulos, Ram, and Kakabadse 2015). The sample size was deemed adequate as data saturation was achieved in terms of quality, richness, quantity and replication (Tracy 2010; Fusch and Ness 2015). Each interview lasted 45 min to an hour, with the exception of some that were asynchronous online interviews. Questions were posed as per the interview protocol with the focus being on the 'what', 'how' and 'why' of the green practices' implementation, the green drivers, the green barriers and the green-related performance impacts. Additionally, internal research/performance reports, annual reports, departmental reports and web links etc. provided by the respondents were used as a supplement.

4.3 | Data Collection—Company Reports

Next, content analyses of 112 environmental-related reports were done with the relevant information compiled, coded and analysed. The sampling process involved selecting all available reports that published environmental-related information and covered at least one or two environmental aspects, such as climate/CO2 emissions, energy use, water/material use, eco-friendly drug disposal, etc.

Companies were chosen from a database created by the researchers that considered a wide range of industry sources for inputs. We selected the pharma companies using a combination of well-known sources such as ABPI (Association of British Pharmaceuticals Industry), BGMA (British Generic Manufacturing Association), eMC (Electronic Medicines Compendium), HAD (The Healthcare Distribution Associations UK), PAGB (Proprietary Association of Great Britain), Dow Jones Sustainability index database and GRI (Global Report Initiatives). We used NHS Service websites (https://www.nhs.uk/nhs-services/) for selecting pharmacies and Local CCG (Clinical Commissioning Group). We also used Oscar-research (https://www.oscar-research.co.uk/datasheets/carehomes) for care homes. UK Gov (Waste water treatment in the United Kingdom - 2012 (publishing.service.gov.uk) and UKWIR for water companies. Local councils were selected using (List of councils (publishing.service.gov.uk)).

4.4 | Data Analysis

The interview data and report content allowed us to creatively assess empirical evidence vis-à-vis the initial theoretical framework in line with our abductive approach (Kovács and Spens 2005). The information from the interviews and reports was categorized and coded as per the principles of thematic content analysis. Initially, we deductively categorized the first-order themes based on the initial framework. Then we adopted an inductive approach to categorize the second-and third-order themes/subthemes to thoroughly conceptualize each green practice. For example, the concept of green drug design was fully understood by establishing five sub-themes related to materials, two sub-themes related to energy, and two sub-themes related to toxicity. A similar approach was applied to explore each component (e.g., green practices, drivers, barriers and performance) in the initial framework. A combination of manual and software (NVIVO 12 Pro) approaches was used, providing an effective and efficient way to interpret each theme and sub-theme, while also ensuring rigour (Yin 2009). Such an approach has been used by other researchers in the past (e.g. Hofer, Cantor, and Dai 2012).

Finally, findings pertaining to each green practice, driver, barrier, and performance impact were rated as 'Low', 'Moderate', or 'High' as per the evidence gathered. The related evidence was gathered both through manual analysis, as well as from the NVIVO output (e.g., text search queries, frequency, and central reasoning of keywords). The information/insights from reports and interviews were also cross-checked with each other to get a rich perspective on each research question.

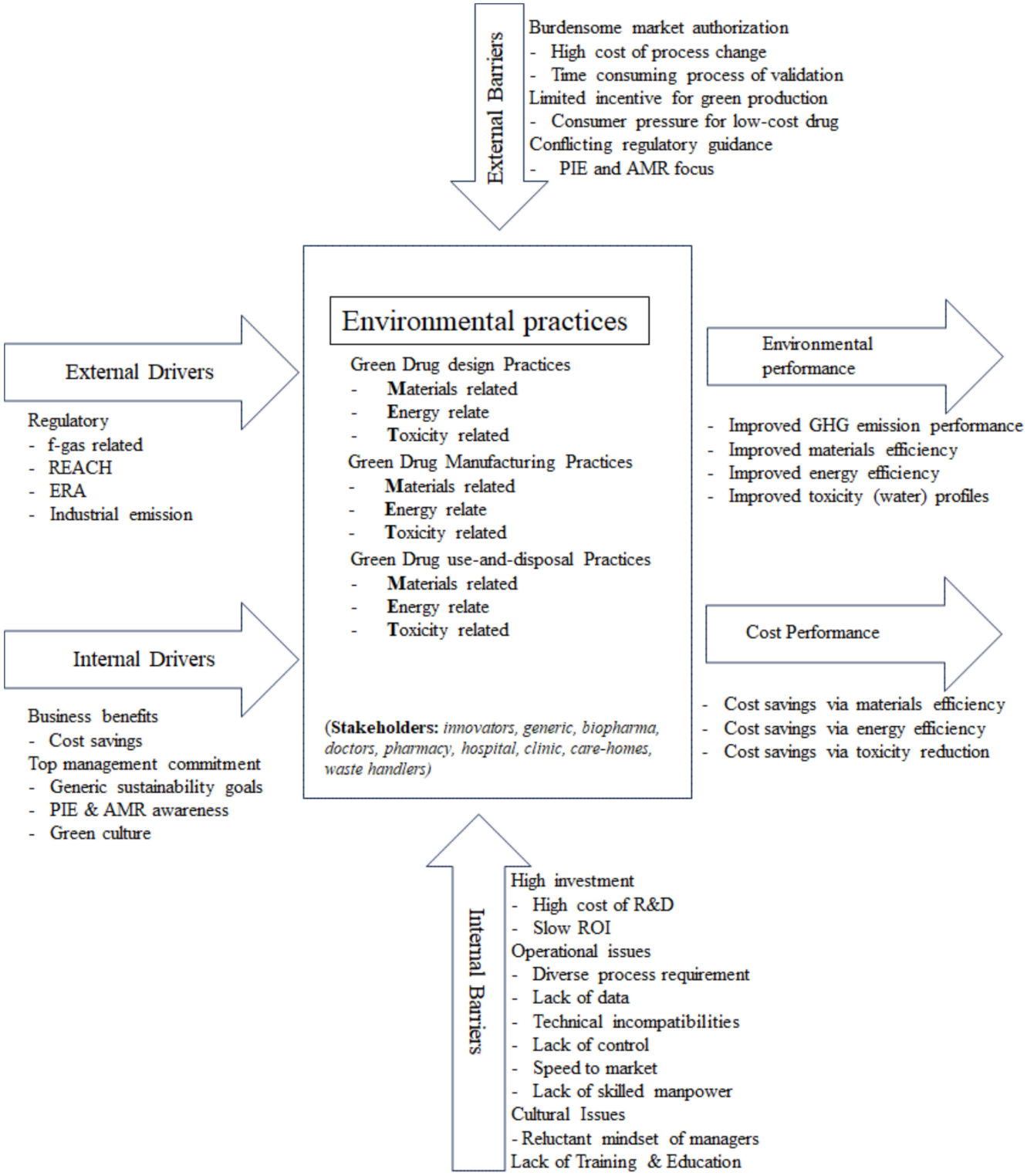

FIGURE 4 | GSCM framework for Pharma sector.

To ensure methodological rigour, we followed the techniques suggested by Rowley (2002), Baskarada (2014), and Beverland and Lindgreen (2010). For construct validity, we developed an initial research framework and created a chain of evidence using interviews, reports, and other relevant secondary data for each sub-unit of the case study, triangulating evidence from multiple sources (Yin 2009). Although the effect is minimal, internal validity was ensured by studying the similarities and differences between different sub-units (e.g., green adoption approaches and motivations across Generic, Biopharma, and Innovative pharma). For external validity, we applied the replication logic across different sub-units, and established how such sub-units represent the case under investigation. Finally, reliability was ensured through the use of a standardized interview protocol, and the inclusion of multiple units of analysis.

5 | Findings and Discussions

The findings are presented for each of the core components of the framework in Tables 4, 5, 6 and 7. Here, green practices' adoption, green drivers, green barriers and green performances' impact, as well as each's categorisation in 'low', 'medium' and 'high' terms can be seen.

5.1 | Adoption of Green Supply Chain Practices (RQ1)

The findings reveal varying levels of GSCP adoption among stakeholders, shaped by the complexity and diversity of pharmaceutical operations. Overall, Innovative and Biopharma companies were found to outperform the Generic ones on green adoption. Generic pharma though also has a significant role to play on the environmental front given its large market share and production volume. However, the costly and time-intensive nature of the regulatory approvals needed post green-related product/process changes is a big challenge for these players as they also need to be cost-competitive to succeed. The sections below discuss each of the key GSCPs from a MET perspective.

5.1.1 | Green Drug Design and Development Practices

As indicated in Table 4, the scope and development of green drug design strategies in the pharmaceutical industry are both promising and unique. Its contribution was highlighted by a leading pharmaceutical player, who noted "... a 71 percent reduction in solvent use, a five-fold increase in throughput, and a 40 percent reduction in operating time ..." when developing a new drug based on green principles for secondary hyperparathyroidism. However, the industry's overall movement towards adopting green drug design practices is still limited. This (limited) movement is also primarily by innovative and biopharma companies, with generic pharma companies lagging behind.

Evidence suggests greener substances, particularly biocatalysts, to have a significant positive environmental impact on the drug lifecycle. This is in the form of reduced input material and energy requirements, and less toxic waste generation during the production and disposal phases. Here again, innovative and biopharma companies were found to be more likely adopters. Generic pharma players too could use biocatalysts by redesigning their manufacturing processes, and realise associated benefits. However, their engagement with it was found to be limited and considered only on a case-by-case basis because of regulatory approval-related challenges, financial investment return-related uncertainties, and biocatalyst availability issues.

To reduce the overall toxicity of drug substances, medicinal scientists and process design teams were found to have largely eschewed the use of chemicals of concern (such as Benzene and Dichloromethane) in the early drug design phase. Nonetheless, some respondents expressed reservations about developing more biodegradable drugs to reduce environmental toxicity as their bioavailability – and consequently, their medical efficacy – could be compromised in the process (Clark, Breeden, and Summerton 2010; Milanesi, Runfola, and Guercini 2020).

Innovative pharmaceutical companies were also found to use various AI and digital technologies such as focused library screening (for example, DNA-encoded libraries), in-silico chemical screening, nanotechnology, and laboratory information management systems (LIMS). These technologies have accelerated drug design and development activities, and reduced the need for expensive chemical testing, and related raw material requirements such as of solvents, reagents, and reactants. For instance, a research scientist from site B-3 emphasized the shift from random to focused-library screening: *"... things are being streamlined to be specific to avoid shooting in the dark; we streamline things so that there will be a particular drug target ..."*. PMI-led manufacturing design process was also observed to be a key design practice for the Innovators. They were also found to adopt other material reduction-oriented green practices at medium to high levels, such as designing drugs with flexible quality requirements (also termed as quality by design), and designing combined API drugs. Some Innovators also choose processes based on energy evaluation, and install energy efficient equipment, though this is not widely practised due to the additional time and regulatory costs involved.

5.1.2 | Green Drug Manufacturing Practices

As can be seen in Table 4, a continuous mode of manufacturing, solvent recycling, and eco-pharmacovigilance have garnered significant attention from the industry due to their demonstrable environmental benefits. The extent of adoption of these practices ranges from low to medium. However, it varies considerably across different product portfolios due to the diverse requirements of processes, time, demand, throughput, equipment, and engineering process complexities, as per the interviewees.

Further, it was revealed that some innovative pharma facilities have combined API production and formulation into a single continuous process, thereby enabling the production of a drug from initial synthesis to its final form, such as tablets. More commonly though, API production and formulation happen separately. Most innovative pharma and some generic pharma respondents also revealed that Process Analytical Technology (PAT) integration into continuous production has enabled them to learn, control, and optimize process parameters (e.g., reaction time, throughput, temperature, pressure, etc.) in real-time. This has resulted in savings in solvents, water, and other raw materials, and reduced the generation of hazardous by-products. Additionally, it has also improved process throughput and reliability, product quality, and scale of operations, while reducing labour costs (Plumb 2005; Slater et al. 2010). For example, as per a Biopharma respondent: *"Continuous manufacturing (e.g., flow chemistry) allows scientists to scale up and down easily, achieve significant energy and waste reductions, and improve safety."* Continuous formulation's usefulness from a cost and environmental standpoint was also found to be well appreciated. For instance, a generic pharma player reported that their new continuous formulation process for one of the product portfolios could reduce API

TABLE 3 | Summary of primary and secondary information sources.

Primary source: Interview				Secondary source: Reports			
S. No	Code	Interviewee	Stakeholder company	No of reports assessed	Stakeholder company	Code	Types of reports
1	A	Senior Environmental Specialist	Innovative pharma	16	Innovative Pharma	In – 1, 2, ... etc.	Environmental/ sustainability/CSR
2	B – site 1	EHS Manager		20	Generic Pharma	Gn – 1, 2, ... etc.	
3	B – site 2	Sustainability and Utility Manager		25	Bio Pharma	B – 1, 2, ... etc.	
4	B – site 3	Lab Scientist		12	Pharmacy	P – 1,2, ... etc.	Service report*
5	C	Senior Principal Environmental Scientist		42	CCG*	CCG – 1,2, ... etc.	STPs* report
6	D - site 1 (R&D)	Strategic Business Development Manager		**Total report = 112** CCG* – NHS Clinical Commissioning Group STPs* – Sustainable Transformation Planning (only collect drug use and disposal related data) Service report* – Pharmacy service reports (only collect drug disposal related data)			
7	D - site 2	Supply Chain and Quality Operations Executive					
8	E - site 1	EHS Manager	Generic Pharma				
9	E - site 2	Manufacturing Engineer					
10	E - site 3	Senior Supply Chain Leader					
11	F - site 1	Head of Quality					
12	F -site 2	Principal Scientist					
13	G	Production Manager					
14	H	Production Manager					
15	I	Senior Scientist	Bio pharma				
16	J - 1	Lab Manager					
17	J –2	Quality Assurance Manager					
18	K – store 1	Pharmacy Manager	Pharmacy (Community)				
19	K – store 2	Pharmacy Manager					
20	L	Pharmacy Manager	Pharmacy (Hospital)				
21	M	Service Development Pharmacist	NGO (Community pharmacy)				
22	N	Senior Pharmacy Technician	Pharmacy (Hospital)				
23	O	GP	CCG (GP)				
24	P	GP					
25	Q	Senior Nurse	CCG (Hospital)				
26	R	Care Home Manager	Care home				
27	S	Care Home Manager					
28	T	Environmental Compliance Advisor	Clinical waste management				
29	U	Environment Advisor					
30	V	Project Manager	Water company				
31	W	Environmental Government Manager	Water company				

(Continues)

TABLE 3 | (Continued)

Primary source: Interview				Secondary source: Reports			
S. No	Code	Interviewee	Stakeholder company	No of reports assessed	Stakeholder company	Code	Types of reports
32	LC – 01	Information Officer	Local council (waste management)				
33	LC – 02	Information Officer					
34	LC – 03	Waste Contract Manager					
35	LC – 04	Information Governance Officer					
36	LC – 05	Corporate Services Officers					
37	LC – 06	Head of Corporate Services					
38	LC – 07	Technical Assistant					
39	LC – 08	Information Access Officer					
40	LC – 09	Information Governance Officer					
41	LC – 10	Interim Assistant Director of Public Space					
42	LC – 11	Information Governance Officer					
43	LC – 12	FOI & Complaints Manager					
44	LC – 13	Customer Feedback Manager					
45	LC – 14	Compliance Support Manager					
46	LC – 15	FOI & DPA officer					
47	LC – 16	Information Governance Officer					

requirements by 80 to 90% compared to traditional batch processes. They also reported lower waste generation, and yields exceeding 97%. These findings are consistent with those of Soete et al. (2017), and Watson (2012). Surprisingly, despite these benefits, the adoption of continuous formulation within generic pharma remains low.

The importance of solvent recycling during manufacturing was also highlighted. According to the interviewees, while the initial investment in solvent recycling is high, the payback period can be as short as two years. For example, an innovative pharma (In – 14), reported annual savings of 5600 tons of solvents (constituting 76% of its solvent usage) through solvent recovery projects. These environmental outcomes resonate with the findings of Teunter et al. (2003), and Perez-Vega et al. (2013). However, the specific characteristics of solvent recycling and reuse (e.g., recovery processes, types of solvents, recovery purposes, etc.) differ across companies. While Innovative pharma companies primarily focus on organic solvent recycling projects, generic and biopharma companies typically recycle purified distilled water from their processes, citing difficulties with equipment engineering and product quality concerns with organic solvents.

Collaboration between upstream process developmental scientists, engineering teams, and downstream waste treatment vendors was found to be effective in reducing material-related waste. Lean projects such as process optimization, digitization of batch process records, leak detection, and automated machine failure detection were also seen to be adopted across the sector at medium to high levels. Majority of the Innovators and some Biopharma players were also found to execute a wide range of energy kaizen projects such as ZAP (Zero Accidental Promotion), and energy auditing.

Continuous monitoring, and control of environmental toxicity of drug substances, i.e., eco-pharmacovigilance, was found to be a significant practice among Innovative pharma to address concerns on PIE and AMR. Though predominantly aimed at new drugs, it is also important for existing drugs (~3000 APIs) in the market, most of which are off-patent and fall within the purview of generic pharma. Eco-pharmacovigilance by generic pharma, however, is unfortunately low, which should not be the case given their large drug production volumes, and associated significant contributions to PIE. Finally, monitoring and controlling API discharge from manufacturing process is also critical to reducing environmental toxicity.

5.1.3 | Green Drug Use-and-Disposal Practices

Given the large and growing drug consumption, how effectively the drugs are used, and how effectively the unused or expired ones are disposed of, could have significant environment toxicity-related consequences. It was revealed that relevant practices are mostly considered for the new drugs being developed, rather than the existing ones in the market, which is problematic.

Prescribers (e.g., doctors), dispensers (e.g., pharmacists), patients, local healthcare providers (e.g., NHS), hospitals, care homes, and drug waste vendors were noted as the key stakeholders for this stage. As can be seen from Table 4, among others, prescribers' prescribing habits, consistent prescription

monitoring, regular interaction with patients, prescribing alternative drug therapies, and digital prescribing and dispensing, significantly reduce drug waste generation, and the associated environmental loading.

Most pharmacists and doctors were found to agree that routine patient interventions (e.g., Medicines Use Review (MUR) and New Medicine Service (NMS)) improve adherence to drug regimens and reduce drug wastage. For example, adjusting drug dosages, or discontinuing drugs early based on the severity of the side effects is part of the MUR service. One pharmacy manager (K – store 1) emphasized, *"We can optimize, or reduce the full use of the medication they are on, or determine if any other changes need to be made to further optimize their treatment"*. Drug take-back programs for unused or expired drugs, as well as incinerating them to generate heat and ash, were also identified as important practices.

The integration of digital technologies (e.g., Electronic repeat dispensing (eRD), Electronic Prescribing Service (EPS), EPS prescription tracker, and patient care summary record, etc.) and the real-time capability to check, modify, and track prescriptions and dispensed drugs have greatly enhanced communication between prescribers, dispensers, and patients. Such digitization in downstream patient and medication management has greatly reduced drug wastage by preventing errors, duplication, and miscommunication during the transfer of patients across services. However, summary care records were found to be not fully synchronized across systems, compromising their effectiveness. For instance, patient records may not be updated when they are admitted to a different care facility than their usual one, or patient records may not be promptly revised to reflect movements across different care settings. Addressing such gaps could improve drug administration management, ultimately enhancing the effectiveness and efficiency of the care system. Finally, energy-efficient refrigeration systems (e.g., digital temperature loggers, and absorption refrigeration) for storage, along with energy recovery from high temperature incineration (primarily by waste vendors) were identified as the key energy- efficiency practices.

5.2 | Drivers of Green Supply Chain Practices (RQ2)

Insights on green drivers could enable them to be more effectively leveraged for the green transition. Table 5 summarises all relevant drivers identified in the study.

5.2.1 | External Drivers

Formal regulations such as those related to fluorinated gases (F-gases), Registration, Evaluation, Authorisation, and Restriction, of Chemicals (REACH), Environmental Risk Assessment (ERA), and drug take-back, emerged as the key external green drivers. As per most innovative pharma respondents, these regulations were a key factor in their adoption of green practices in R&D and manufacturing. However, this was the case for only a few generic and biopharma companies. With regard to specific legislations, F-gas-related legislation was revealed to be one of the most critical. For instance, the industry is under increasing pressure to explore alternative designs to replace CFC-based inhalers whose production has become a subject of parliamentary scrutiny. In response, one of the companies (B – 21) was found to have established an internal target to reduce ozone-depleting substances by 95% by 2025. Similarly, some of the generic pharma companies (e.g., Gn – 04, Gn – 02) have decided to refine and optimize their F-gas-related cooling and refrigeration systems to comply with related regulatory requirements.

REACH was found to be another important regulation. It was the motivation for a majority of innovative and biopharma companies to reduce the use of hazardous substances (e.g. toxic solvents) during the R&D process. As per one Innovative pharma company (In – 07): "Companies in the pharma industry are particularly affected with regards to registering intermediates due to REACH." These companies are therefore adopting greener substances and technologies (e.g., more in-silico than in-vitro methods during discovery) so that the toxicity of the drug as well as the intermediates produced is lower. On the other hand, generic players have a narrow scope for producing pharma intermediates given that they: 1) Hardly do any new drug development; and 2) Primarily produce those versions of APIs (off-patent), whose intermediates have already been approved by REACH. As such, pressure on account of REACH is somewhat limited for these players.

The ERA regulation is particularly relevant for Innovators who discover, develop, and patent new drugs, with its principal aim being to manage and control PIE and AMR. It was found to have significantly influenced almost all of the Innovators to invest in different PIE-related projects. For example, driven by ERA, one innovative pharmaceutical company (In – 02) has invested in artificial intelligence and machine learning (e.g., cheminformatics, bioinformatics, etc.) to assess early environmental impacts of specific drug substances and their intermediates. Similarly, others have been motivated by ERA to develop a Persistence, Bioaccumulation, and Toxicity (PBT) database for new and existing APIs in the global market. Drug take-back legislation has also motivated downstream stakeholders (e.g., pharmacy, GP, hospitals etc.) to promote different kinds of collection programs to ensure that unused/expired drugs are safely disposed.

5.2.2 | Internal Drivers

Cost savings, and the resultant high return on investment (ROI) from solvent recovery and continuous manufacturing were found to be the key motivators for pharmaceutical companies to adopt these green practices during the early drug development phase. Innovative pharma players were found to particularly encourage developmental scientists and chemists to create and refine drug processes that enhanced solvent recovery. As per one of the interviewees: "*I guess the main driver is finance. Raw materials are relatively cost-effective—relatively low compared to our total income; profit margins are generally quite high.*" This finding aligns with Slater et al.'s (2010) previous observations regarding solvent recovery.

According to the interviewees, the return on investment (ROI) from continuous processes surpasses that for batch ones. Not

TABLE 4 | Summary of MET-related Green Practice Adoption Assessment of UK Pharma sector. (M—Materials; E—Energy; T—Toxicity).

	Innovative	Generic	Biopharma
Green drug design & development practices			
Design and develop manufacturing process to use greener substances (M)	**High** – Mostly designed to use greener substance (e.g., biocatalysts) for new drug; redesigned existing process to use biocatalysts for reducing byproducts in mass production	**Low** – Mostly limited scope to redesign existing process; few of them replace biocatalysts with metal one	**High** – Mostly designed process to conduct greener (enzyme-based) operation to optimize biochemical reaction in living organisms; limited scope with existing drug process
Design drug discovery process to dematerialize (M)	**High** – Mostly digitized (e.g., automation, 3D virtual image of chemical interactions, HTS) lab testing to replace actual chemicals testing; some designed nano particle-based formulation;	**Low** – Few adopted LIMS to streamline R&D related materials	**Medium** – Some used automated quality test; used LIMS; used 3D virtual image to identify therapeutic target;
Design process to consume less raw materials by applying process metric (e, g., PMI) (M)	**High** – Mostly developed process using PMI to save raw materials in manufacturing phase	**Not considered** – As mostly follow patented process	**Not considered** – Due to complex process equipment & engineering
Design drug manufacturing process for flexibility in quality (M)	**Medium** – Some of them documented quality variations (e.g., purity, stability etc.) in the early regulatory submission to reduce unwanted wastes during mass production	**Low** – Few of them plan to document such quality variations; costly process of regulatory approval;	**Not considered** – As difficult and challenging to enrich early process knowledge.
Design combined drug (e.g., use multiple active substances) for material efficiency (M)	**Medium to High** – Designed formulation which contains multiple APIs for multiple therapeutic effects.	**Not considered** – Costly regulatory burden	**Not considered** – Complex manufacturing process and incompatibility of APIs within formulation
Design and develop manufacturing process for least energy consumption by evaluating alternative process (E)	**Low** – Few developed alternative processes based on energy input/output simulations; assessed/predicted energy requirements for continuous or batch process;	**Not considered** – Lack of time and cost to produce such process level data; not felt the benefit of doing so	**Not considered** – Engineering difficulty to track such unit level assessment
Design and develop manufacturing process by installing and validating energy efficient equipment system (e.g., reaction vessel) (E)	**High** – Mostly validated thermal oxidation equipment & heat exchangers in the process;	**Low** – Few replaced old process equipment with new energy efficient one (especially heating and cooling process)	**Medium** – Some replaced stainless-steel reaction vessel with 'single-use' process technology
Design and develop bio-based drug process to reduce water toxicity (T)	**High** – Mostly developed process to increase biodegradability of drugs; conducted ERA; solvent selection guide; predicted toxicity level of a process using software;	**Low** – Focus more on biodegradability of drug for safety and quality than environmental degradability	**High** – Mostly designed process to use biological sourced starting materials; solvent selection guide;

(Continues)

TABLE 4 | (Continued)

	Innovative	Generic	Biopharma
Design and develop drug process to reduce air toxicity (T)	**Medium** – Some designed inhaler products to replace CFC with HFA for lower GHG emission impact	**Low** – Some validated VOC absorbing filters in separation process (e.g., chromatography)	**Low** – Validated VOC filters and replaced fluorocarbon containing process equipment with less impact substance;
Green drug manufacturing practices			
Run continuous mode of manufacturing (M)	**High** – Mostly adopted continuous process of API production; some aligned API with formulation into once continuous process; mostly used PAT; not applicable for all API;	**Medium** – Some adopted only continuous coating and tabletting; API and excipients are continuously added to blending;	**Low** – Few adopted continuous fermentation and extraction process;
Recycle and reuse solvents (M)	**High** – Mostly recycled to extract useful raw materials (e.g., low graded solvents) from byproducts; mostly used recovered solvents for cleaning;	**Low** – Few recycled purified distilled waters rather than solvent; recovered complex byproducts;	**Medium** – Some used recovered raw materials for cleaning equipment to save costly solvent; applied computer simulation;
Consider green collaboration for materials efficiencies (M)	**High** – Mostly collaborated and shared process data among the upstream and downstream managers to optimize the process;	**Low** – Internal team collaborated with external process experts;	**Not considered** – Very limited scope of process optimization due to complex equipment engineering and safety;
Consider lean operations for materials reduction (M)	**High** – Mostly adopted water reduction related lean activities; paperless batch process record (eBPR); mostly reduce QC test of incoming materials via strategic suppler relations;	**High** – Mostly adopted water and packaging reduction related lean; used e-version of medication guide; digitize QC process;	**Medium** – Mostly adopted water reduction related lean activities via waterless cooling/closed loop cooling; eBPR;
Consider energy efficient technologies (E)	**High** – Mostly used HVAC air conditioning; LED lighting; water cooling than mechanical cooling; CHP/CCHP etc.	**Medium** – Automatic cleaning; water cooling; HVAC; energy efficient motors, compressors, and guns in packaging	**Low** – Few insulate piping; heat recovery technology; install steam boiler than biomass boiler;
Consider energy management program (E)	**High** – Mostly adopted energy kaizen and CI related program (e.g., ZAP, 'Britest Tool' etc.)	**Low** – Few adopted energy kaizen and CI related program (e.g., 'Britest Tool' etc.)	**Medium** – Some applied lean. Six sigma, energy kaizen to optimize process;
Consider greener chemical (e.g., solvent) management (T)	**High** – Train employee how to reduce hazardous solvents use; reduce toxic-byproduct formation;	**Medium** – Eliminated VOCs and/or other toxic volatile chemicals from the production;	**Medium** – Track and trace of the chemicals of high concerns;
Monitor and control environmental toxicity of drug substances (ecopharmacovigilance) (T)	**High** – In most cases conduct ERA (Environmental Risk Assessment) of API	**Low** – Some of them followed site specific API discharge management guidance;	**Low** – Few of them followed API discharge guidelines; participated PIE program;

(Continues)

TABLE 4 | (Continued)

Green drug use-and-disposal	Pharmacy	GPs	Hospitals	Care-homes	Waste handlers/ Local council
Consider lean operations for optimized prescribing, dispensing and usages (M)	**High** – Medical intervention program; monitor prescribers' prescribing habit; patient counselling;	**High** – Rationale prescribing; disease alteration strategy; reduce bulk supply; prescribe alternative therapy;	**Medium** – Reuse of drugs; drug waste reduction projects: green bag scheme; my medication passport;	**Medium** – Regular medicine review; monitor MAR chart; Patient review;	Not relevant
Consider digital technologies for optimized prescribing, dispensing and usages (M)	**High** – Mostly adopted electronic prescribing system; online summary care record to streamline the communication between patients, pharmacy, and prescribers;	**High** – Electronic repeat prescription dispensing; shared online summary care record;	**Not considered** – System incompatibility and decentralised operations	**Not considered** – System incompatibility and decentralised operations	Not relevant
Energy efficient refrigeration system & temperature control (E)	**Low** – f energy efficient refrigerators system; built in insulation system with refrigerators; manual or automatic temperature log;	**Not considered** – As very low volume of storage	**Low** – 'Absorption drug refrigerator' uses waste heat (e.g., hot water) from an external source	**Low** – Manual or automatic temperature log; energy efficient refrigerators	Not relevant
Energy recovery from drug incineration (E)	Not relevant	Not relevant	Not relevant	Not relevant	**High** – Recover energy from high temperature (>1100 °C) drug incinerators
Safe & responsible management of unused/expired drugs (T)	**High** – Drug takeback scheme; follow SOP; appropriate segregation of drugs in the point of collection;	**Low** – Some GPs participate in drug take back scheme;	**Medium** – Promote drug collection from patient via leaflet, posters, and bus adverts;	**Medium** – Follow (SOPs) derived from the Healthcare waste Management guided by department of Health in the community pharmacies	**High** – High temperature Incineration; recycle of incinerated ash; participate in drug take back;

surprisingly therefore, not only innovative pharmaceutical companies, but a few biopharma ones also, have considered continuous manufacturing during early process development. For instance, an innovative pharma company (B – site 2) noted that despite the substantial upfront cost of continuous manufacturing, the associated ROI exceeds that of batch processing due to the savings in (expensive) solvent usage.

Cost savings from waste diversion (i.e., waste to beneficial use) was found to be another important green driver, and one that is motivating a majority of innovative pharma companies. For example, one innovator (In – 01) could save over a million dollars annually through a 'waste to clean' initiative, which reduced the need for purchasing high-purity solvents during the R&D process.

Some downstream stakeholders (e.g., pharmacies) were found to be driven by monetary incentives to promote projects such as MUR, while others such as hospitals adopted a wide range of drug waste reduction practices to manage the surge in healthcare costs. Overall, the majority of pharma companies, especially the Innovators feel that they have a huge responsibility towards the environment and the wider community, and which is why they have instituted environment targets, such as zero landfill.

5.3 | Barriers to Green Supply Chain Practices (RQ3)

Knowledge of barriers to green practice adoption is important as practitioners and policymakers can then focus their attention to mitigate them. Those for the pharma sector are summarised in Table 6.

5.3.1 | External Barriers

The barriers identified include complex marketing authorization for drugs, lack of standardisation in equipment and engineering, patient-related challenges, unregulated drug waste, and ambiguous regulations regarding drug prescribing and waste management.

The regulatory marketing approval process for drugs is particularly complex and protracted. This means any minor green-related change in the design space, or even major ones such as transitioning from batch to continuous processing, or substituting with greener solvents requires significant time and money to secure regulatory reapproval for marketing authorization. This barrier was found to disproportionately influence generic pharma given their lower financial strength, and significant cost focus. A respondent from generic pharma (F site – 1) succinctly expressed this dilemma as: *"...if you want to change, it would be an expensive regulatory submission to get that change approved, plus years of stabilisation work."* These insights regarding regulatory barriers not only corroborate, but also build on similar issues identified previously (e.g., Slater et al. 2010; Koenig et al. 2019).

The lack of standardized equipment and engineering was also recognized as a key impediment, such as for solvent recycling. As per the interviewees, the solvent recovery process is intricate and specific to each procedure, making the equipment and engineering solutions non-transferable across manufacturing sites.

The study also uncovered patient-related challenges, especially in managing medications for three groups of highly vulnerable patients, specifically, patients in end-of-life care, patients with dementia, and patients with multiple complex morbidities. The result is high drug wastage.

As per a Care home manager (S): *"In care homes, most of the patients are not completing their drug cycles leading to significant waste"*. Further, healthcare professionals, including general practitioners (GPs), highlighted the lack of regulatory guidance/legislation on prescribing with environmental considerations in mind (such as the impact on PIE), with the exception of antibiotics. For instance, while clinical guidelines for prescribing painkillers are clear, there is a lack of guidance on how it will impact the environment. Here it is important to mention about the Electronic Medicine Compendium (eMC), where the excretion profile of each API is covered. However, here again there is no regulatory guidance on how these profiles should be considered to ensure high medical efficacy, but low environmental impact. The Innovators also strongly felt lack of PBT data for off-patent drugs to be hampering their understanding and management of PIE issues.

The interviews also revealed ambiguities in legally classifying something as waste, and drug take-back legislation causing confusion. Waste vendors reported that patients often dispose of unused drugs with household waste, believing it to be the correct approach. This is because it has been tacitly accepted for a long time as being aligned with local waste collection policies. Interestingly, local councils do not consider pharmaceutical waste as a special category, with one council (LC – 09) commenting, "Special consideration is not given to pharmaceutical waste as we have not encountered it as an issue.".

5.3.2 | Internal Barriers

The key internal barriers identified are substantial investment requirements, time constraints, and employee reluctance.

While generic manufacturers acknowledge the resource-intensive nature of certain processes, and the need for optimization, financial and cost constraints often hinder the related changes. A respondent (C) pointed out that the strict cost constraints on generic drugs left little margin for investments in environmentally oriented process modifications. They stated, *"... there is little to motivate because the costs, the financial model for it, doesn't really support it."* Most generic players also strongly feel that the market is not yet ready to pay for the expensive green alternatives. These findings substantiate and reinforce the conclusions of Slater et al. (2010) and Plumb (2005).

Innovative pharma companies were found to strive to minimize the drug development time, so that they can maximise the time available for exclusive sales during the patent period (Taylor 2015). Similarly, generic pharmaceutical companies

TABLE 5 | Summary of MET related Green Drivers Assessment of UK Pharma sector.

Drivers of green drug design and manufacturing	Innovative	Generic	Biopharma
F – gas related regulation	**High** – More tax imposed on CFC based products; stringent regulatory fines; became parliamentary issue; driven to redesign CFC based products (e.g., inhalers);	**Low** – Comparatively low scopes to design and produce F-gas related drug products (e.g., inhalers) apart from cooling system	**Low** – Comparatively low scopes to design and produce F-gas related drug products (e.g., inhalers) apart from cooling system.
Industrial Emission Directive (IED)	**High** – Driven to redesign operations to maintain the discharge permit of VOCs/API discharge/hazardous organic chemicals etc.; driven to invest API detection technology;	**Medium** – Mainly dealt with formulation than API production, so, comparatively lower scopes of discharging VOCs/organic solvents/	**Medium** – Driven to adopt advanced technology & technique (waste hood with special absorbing filter, autoclave process etc.) to stay within permit;
REACH regulation	**High** – Significantly driven to adopt MET practice to reduce by-product/ intermediate chemicals production	**Low** – Low scopes of producing pharmaceutical intermediate products as they mostly involve formulation than API synthesis;	**Low** – Driven them to regular review of SVHCs (Substance of Very concerns); lower chemical based by products;
Environmental Risk Assessment (ERA) of Drugs	**High** – Mandatory requirement of regulatory approval; stringent control of API discharge level; Driven ERA project to enrich PBT database;	**Low** – Low scope of new drug approval; pressure from API suppliers to limit discharge;	**High** – Mandatory requirement of regulatory approval; Driven ERA project to enrich PBT database;
Cost savings opportunity	**High** – High ROI from solvent recycling, continuous manufacturing, energy efficient equipment etc.	**Low** – Cost reduction from waste valorisation, energy efficient equipment validation;	**Low** – Cost savings from water reduction projects
Internal environmental target	**High** – Strong internal environmental commitment; internal environmental policy; member of ACS GCI to promote MET practices; many green awards;	**Medium** – Strongly motivated to achieve internal goal of Zero land fill; few members of ACS GCI;	**Medium** – Incentives and awards for green innovations; internal environmental policy;
Community wellbeing and corporate responsibility	**High** – Strong ethical and corporate responsibility pressure to go green; many voluntary green measures;	**Low** – Few voluntary measures such as some energy efficiency activities;	**Low** – Few voluntary measures such as some RCM (Resource Conservation Measure);

Drivers of green drug use-and-disposal	Pharmacy	GPs	Hospitals	Care-homes	Waste handlers/ Local council
Drug Tabe-back legislation	**High** – Pressure from quality body (CQC), key contractor (NHS);	**Low** – Low scopes of unwanted drug collections;	**High** – Strong pressure from the NHS trusts to promote patient return;	**High** – Responsible to arrange safe disposal of drugs via authorized waste vendor;	**Low** – Not obliged for collection; only some voluntary collection;

(Continues)

TABLE 5 | (Continued)

Drivers of green drug use-and-disposal	Pharmacy	GPs	Hospitals	Care-homes	Waste handlers/ Local council
Monetary incentives	**Medium** – Extra income for medicine review service;	Not relevant			
High healthcare cost	**Medium** – Pressure from NHS to reduce unnecessary drug wastes;	**High** – Pressure from NHS for effective and efficient prescribing;	**High** – Strong pressure to reduce drug wastes related costs as drug is one of the key costs of NHS	**Medium** – Pressure from NHS to reduce unnecessary drug wastes;	Not relevant

typically aim to be the first to develop newly off-patented drugs. For both, time is of the essence. Such time pressure hinders consideration of greening in product and process design and development. This barrier's significance was highlighted by an interviewee (C), who noted: *"...there is difficulty ensuring a low environmental footprint in the developmental phase as the pressure is to develop the product quickly for the market."*

Finally, the reluctance of internal quality assurance teams to adopt green practices was found to be a significant barrier. The difficulty lies in ensuring that recycled or reused solvents meet the required quality standards for reintroduction into the process. This was conveyed by a respondent discussing the transition from batch to continuous processing: *"...the challenge would be working with our quality assurance people to ensure that the quality of recycling, or of the solvents being used, is high enough to re-enter the process."*

5.4 | Performance Benefits From Green Supply Chain Practices' Implementation (RQ4)

Performance implications of green practices is critical to determining the scope and viability of greening for a sector. These implications, especially the environmental and cost ones, are presented in Table 7.

5.4.1 | Environmental Performance

GHG emissions-related, materials-related (M), energy-related (E) and toxicity-related (T) performance aspects were found to be key to realising environmental sustainability in pharma.

GHG Emissions-Related. Significant emission reductions were observed through implementation of green practices. For instance, one of the innovative companies (In – 08) was able to reduce their Scope 1 emissions globally by 21% in a 10-year period from 2010 to 2017. It is now aiming for an 80% reduction by 2050. While innovative pharma showed large reductions in Scope 1 emissions, low to medium reductions were observed for generic and biopharma players, and which are in line with their respective green practice adoption levels. With regards to Scope 2 emissions, almost all stakeholders showed reductions, though to varying extents. In the case of innovative pharma, many players were found to have significantly reduced these emissions by adopting energy-efficient projects and technologies, such as the combined heat and power (CHP) technology.

With regards to volatile organic compounds' (VOCs') emissions, the majority of innovative companies were found to have reduced them through incorporation of green chemistry principles in their production processes. In fact, some biopharma companies have also reported substantial reductions in VOCs at their manufacturing sites. For example, one company (B – 11) could reduce its VOC emissions by 99% across all manufacturing sites since 1992 by reducing the use of halogenated substances during production. With regards to generic pharma though, while some companies have adopted VOC reduction activities, few have actually measured and reported it.

Materials-Related. Three key sub-measures are predominantly used here, specifically: Process Mass Intensity (PMI), amount of water reduction in plant/process, and the amount of raw materials used in the process/plant. PMI has become a popular material-consumption-related measure, particularly among innovators who have observed improvements in it. For example, one such company (In – 08) reported a 17% reduction in PMI in 2017. The significance of this measure is underscored by the company's statement that *"The team uses PMI as a key internal metric to measure and track raw material use efficiency rates and identify opportunities for improvement"*. Also, the return on investment (ROI) based on PMI is gaining traction from other stakeholders in the industry with the generic pharma sub-sector expecting to adopt it soon. For Biopharma, the development of PMI-based processes is more complex due to the intricacies of equipment choice, and the need for specialized engineering expertise. Overall these findings support and build upon previous assumptions about PMI's potential for material and energy savings (e.g. Jimenez-Gonzalez et al. 2011; Ang et al. 2021). Downstream reductions in material waste (finished drug) are also possible, driven by enhanced

TABLE 6 | Summary of MET related Green Barriers Assessment of UK Pharma sector.

Barriers of green drug design and manufacturing	Innovative	Generic	Biopharma
Complex marketing authorization process of greener drug (redesigned off patent)	**High** – Apply for a new marketing license for an existing drug is a costly, time consuming and uncertain process;	**High** – Fierce competition to reduce costs; no incentives to reapply for costly redesigning process;	**Low** – The streamlining activities for environmental benefits are rare when the product is already in the market;
High investment and costs	**Low** – Being innovators the investment in general is significantly high and low competition;	**High** – Huge capital expenditure for conducting relevant product stability testing;	**Medium** – Expensive operational and equipment engineering requirements.
Lack of green culture (Green Mindset)	**Low** – Some felt fears of external revalidation of process change; mostly innovative mindset to streamline process;	**High** – Mostly blamed the sceptical behaviour of internal quality team for not adopting green practices;	**Medium** – Employee reluctant to follow the best practice, e.g., follow right process of chemical measurements etc.
Lack of standardisation in equipment and processes	**High** – Solvent recovery process is complex and unique for each process; unique byproducts formation;	**High** – Mostly achieving reliability is difficult due to the diversified equipment systems in different process;	**Low** – Mostly used standardized 'single use technology' for delivering varieties of end products;
Time to market	**High** – Limited patent for exclusive sell right of the product; less time to explore alternative green process;	**High** – Fear of losing market share while the new greener process design may take extra 2 years or more;	**High** – Serious pressure to meet market demand due to the nature of products (e.g., vaccines); less time for greener validation;
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	
Lack of environmental education and training	**Low** – Mostly have in house green chemistry team who trains up scientist, chemists, chemical engineers, and related other employees	**High** – Mostly train up employees on how to adhere to GMP/GLP/GDP purely rather than focus on green education such as green chemistry education	
Lack of Demand for Green API	**Low** – Still not clearly understood what green measures (e.g., low energy/ low materials/low PIE impact etc.) the market are looking for	**High** – Markets for green alternatives (e.g., API with lower energy, materials, toxicity footprint) are limited	**Low** – Still not clearly understood what green measures (e.g., low energy/ low materials/low PIE impact etc.) the market are looking for

Barriers of green drug use-and-disposal	Pharmacy	GPs	Hospitals	Care-homes	Waste handlers/ Local council
Uncontrolled drug wastes from high concerned patient groups	**High** – 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				Not relevant
Lack of performance measures of patient interventions service (e.g., NMS/MUR)	**High** – No clear measures of how much drugs wastes prevented from those services				Not relevant

(Continues)

TABLE 6 | (Continued)

Barriers of green drug use-and-disposal	Pharmacy	GPs	Hospitals	Care-homes	Waste handlers/ Local council
Barriers of getting patient's consent for conducting medical intervention (e.g., MUR/NMS)	**Low** – Burdensome admin works s (e.g., DBS clearance, consent from patients etc.) to conduct medical intervention on the existing drug usages among some patient groups such as patient in care homes or in prisons.				Not relevant
Time constraints	**High** – Mostly felt lack of extra time to conduct regular medical intervention with patients to understand the effectiveness of drugs usages				Not relevant
Lack of regulatory guidance on environmental consideration in prescribing	Not relevant; majority deals with dispensing	**High:** Fear of defensive medicine; No guidance on how to consider drugs with lower excretion rate;			Not relevant
Contradictory regulatory guidance for disposing unused/expired drugs		Not relevant			High – Contradictory outlines of drug takeback and UK wastes legislation

drug regimen adherence facilitated by MUR, and relevant interventions by dispensers/prescribers. For instance, one of the respondents (L) pointed out that in more than 80% of cases, MUR lead to improved patient adherence due to their better understanding of how and why to take medications. Also, Clinical Commissioning Groups (CCGs) were found to significantly reduce drug wastage by using patients' own medications during hospital stays. For example, one of the CCGs (CCG – 25) estimated annual savings of around £3.6 million from just 40% of the admitted patients bringing their own medications prior to hospital admission.

Energy-Related. Total energy used, energy purchased, energy used that is generated onsite, and energy saved from conservation and efficiency improvement projects are the key measures used to assess energy performance. The innovators were found to be at the forefront in adopting them, and who also reported a positive impact on these. A significant positive improvement was sought through installing solar panel, PV, CHP and CCHP technologies onsite. For instance, one of the leading innovative pharma (In – 05) reported an energy efficiency improvement of 80% from projects such as solar panel, combined heat and power (CHP), and combined cooling, heating and power (CCHP).

Toxicity-Related. The amount of hazardous waste converted to beneficial use (e.g., waste-to-energy) was a key factor in determining the cost benefit of responsible waste management. Innovative pharmaceutical companies are leading the way in applying this practice, and in reporting the related (positive) environmental impact. A significant positive improvement from avoiding chemicals of environmental concern was also noted. For example, one of the innovative companies (In – 08) reported a 7% reduction in hazardous waste generation over a two-year period (2015–2017).

5.4.2 | Cost Performance

With regards to cost/economic measures, the return on investments (ROI) from green projects, the cost savings in raw material, disposal, and from energy and water efficiencies, and the cost of green production were identified. Most respondents from innovative pharma companies confirmed that a cost–benefit assessment of green projects (e.g., waste kaizen project, energy kaizen project, water kaizen project, etc.) was necessary before implementing them in practice. Hence, circular economy-led pharma operations' decisions are becoming a prerequisite for green and sustainable pharma (Ang et al. 2021; Alshemari et al. 2020). For example, the ROI projection of green projects (e.g., a solvent recycling project) involved one of the innovators (A) saving 342 tons in equivalent solvent costs over two years. The project allowed the site to recover and reuse solvents such as toluene, ethyl acetate,

TABLE 7 | Summary of MET related Green Performance Assessment of UK Pharma sector.

Environmental performance of green drug design and manufacturing	Innovative	Generic	Biopharma
GHG emission related	**High** – Significant reduction in scope 1 and 2 emission, e.g., 600,000 tons of CO_2 emissions saved during production lifecycle from materials reduction; reduced halogenated VOCs by almost half; phased out ODS substances reduction by 33.4% in 2 years; 21.3% VOCs is reduced by one year from greener process;	**Low** – Low improvement due lower greener adoption; a few reported increased due to increased level of production, e.g., Reduced approx. 490 tons of CO2 emission per annum from green packaging;	**Medium** – Few reported increased emissions due to new production line/plant installations; Expected reduction of 3500 metric tons of CO_2 equivalent emissions in a year from water reduction projects; 99% of VOCs reduction since 1992 (across all manufacturing sites);
Materials related	**High** – Significant reduction of PMI through MET adoption, e.g., 22% PMI reduction in a year; Most of the benefits only captured in the case of chemicals-based process; high level of water, packaging, solvents, and excipients savings; reduced WIP materials, e.g., 60% water savings from greener process; 99% solvent recovered;	**Low to Medium** – Not developed PMI as costly; high water reduction; significant solvent and tertiary packaging reduction; slight reduction in WIP materials; increased landfill, e.g., water reduction by 12% in a year; Save 89% of solvents from the commercial manufacturing process of a drug;	**Low to Medium** – PMI rarely developed; high water reduction; significant solvent usage reduction; High packaging reduction; slight reduction in WIP materials, e.g., 20,000 L of water savings from a single plant annually, e.g., recover and reuse 66.4% of ethanol consumed in production process in a year;
Energy related	**High** – Successful energy savings from energy kaizen projects and energy efficiency activities; plant wide energy reduction, e.g., 3.4% energy consumption reduction in a year from energy efficiency program; increased onsite energy production; 30% savings of electricity from manufacturing sites; 30% energy efficiency achieved from green process; waste to energy generation.	**Medium** – E.g., – saving 95,856 kWh of electricity by three months from energy efficiency projects; energy recovery from hazardous wastes;	**High** – E.g., consumption reduced by 14.5% within 10 years' time from energy conservation programs; Onsite generation increased by 52% in a year; 50% energy savings achieved from RCM;
Toxicity related	**High** – Significant reduction in hazardous byproducts, e.g., 86.7% decrease in hazardous wastes generation in a year from waste kaizen; improved quality of discharge; reduced regulatory breaches from 42 to 23 in a year through reducing toxic byproduct discharge; zero waste to landfill;	**Medium** – Hazardous wastes decrease by 30% in 5 years from using low impact substance; Waste diversion rate is more than 95%;	**High** – 49% hazardous waste reduction within two years period through green collaboration; Increased landfill diversion rate by 79% as of 2016 against the target of an 85% diversion rate by 2020;
Cost performance of green drug design and manufacturing			

(Continues)

TABLE 7 | (Continued)

Environmental performance of green drug design and manufacturing	Innovative	Generic	Biopharma
Cost saving from materials efficiency	**High** – Significant cost savings from solvent recovery and continuous manufacturing, e.g., estimated cost saving over £765,696 in a typical year through eliminating the need for expensive, high-purity solvents;	**Low** – Cost savings from waste disposal, e.g., Disposal cost has decreased by 8.6% in a year, cost savings up to £20,741 per annum per year from green manufacturing;	**Medium** – Significant cost savings mainly from water reduction projects, e.g., £1.2 million savings in a year;
Cost savings from energy efficiency	**High** – Significant cost savings from energy efficiency projects and energy kaizen, e.g., cost savings from 100% LED lighting and motion sensor lighting; savings from 30% energy reduction in green API manufacturing;	**Medium to High** -Significant savings from energy efficiency activities, e.g., – cost savings from 50 GWh of electricity savings within a year;	**Medium to High** -Savings mainly from energy efficiency projects. E.g., 31.7% energy reduction related cost savings from energy monitoring system;
Cost savings from toxicity reduction	**High** – Cost savings from expensive disposal, e.g., £0.3 million of savings from disposal in a year for a typical company; -Significant amount of hazardous waste were recycled in many cases; some profitable waste conversion from hazardous stream;	**Low** – Landfill reduction related cost savings; Low savings on solvent use due to low level of solvent recovery; costly incineration; only few reported hazardous wastes to energy production (off sites predominantly);	**Medium** – Less scope of recovery related savings; some savings from landfilling; increased hazardous disposal costs in some cases; few evidence of hazardous waste conversion related cost savings;

	Pharmacy	GPs	Hospitals	Care-homes	Waste handlers/ Local council
Environmental performance of green drug use-and-disposal					
Materials related	**High** – Improved drug wastes reduction; eliminate prescribing error; reduce issue of bulk supplies; paperless prescribing; Improved drug adherence;		**Medium** – Improved drug wastes via medical intervention, reuse of drugs, medicines management for patients etc.		**Low** – Rarely promote the drug take back;
Energy related	Not known		**High** – Improved energy performance via efficient refrigeration and automations;	Not known	**Medium** – Energy recovery from drug incineration;

(Continues)

TABLE 7 | (Continued)

Toxicity Related			**High** – Reduced drug load in environment as overall collection of unwanted drugs increased; improved temperature excursion related drug wastes;		**Low** – Low rate of waste diversion in council; reduce toxicity via bottom ash testing;
Cost performance of green drug use-and-disposal					
Cost saving from materials (drug waste related) efficiency	**Medium** – Reduce operational costs; cost savings from drug reuse;	Not known	**Medium** – Reduce operational costs; cost saving from drug reuse, e.g., £450 K savings each year through redispersing of unused drugs (ward/patient return)	Not known	Not relevant

and methanol. However, concerns have been raised by some innovative companies regarding the longer payback period for green adoption when considering the 'ROI of green projects' as a metric. For instance, one company (A) estimated a payback period of more than seven years, with additional staff hours required for redesigning existing processes to greener ones (e.g., batch to continuous processes).

The 'cost of green production' was also highlighted as a key green performance measure, particularly by generic pharma companies. Interviews revealed that the generic sector often projects a negative economic performance for green manufacturing due to the high costs associated with regulation-mandated changes in the process. This concern arises because, as one respondent (C) noted, *"the ROI assumes a different prediction when a process is changed"*.

6 | Conclusions

This study proposed a Green Supply Chain Management (GSCM) framework through a systematic review of the literature, and demonstrated its practicality utility and relevance for the UK pharmaceutical sector. The findings meet most of the requirements for framework validity, such as credibility, transferability, dependability, confirmability, fairness, and authenticity, thereby helping improve understanding, and stimulating and empowering action (Creswell and Miller 2000; Balasubramanian et al. 2021, 2023). The results confirm pharma as one of the most promising sectors for GSCM adoption. While the insights are particularly relevant to the UK, the framework and lessons learnt provide a robust foundation for practitioners and policymakers in other countries to consider and apply. The implications of the study are wide-ranging.

6.1 | Research Implications

The study is arguably the first attempt to develop a comprehensive GSCM framework for pharma, and test its applicability in a real-world setting. It examines operational-level green initiatives, the associated complexities, and the role each stakeholder plays in the transition towards sustainability, thereby addressing a notable gap in the literature. Moreover, it sheds light on green drug design and development, environmentally conscious manufacturing, and sustainable drug-use-and-disposal practices, particularly within the advanced UK pharma context. These insights may serve as benchmarks for economies at different stages of pharma development. Furthermore, the literature review synthesizes more than two decades of existing knowledge and establishes a new foundational understanding for future research in the GSCM domain, particularly within the pharmaceutical sector. The study is also arguably the first one to adopt the principles of green chemistry and map green practices at each supply chain stage through the MET framework (M = Materials, E = Energy and T = Toxicity). A GSCM framework underpinned by green chemistry provides a strong theoretical foundation for future researchers to adapt as necessary for diverse contexts.

6.2 | Practical Implications

The insights from the study will be particularly useful for practitioners. Stakeholders at any stage of the pharma supply chain will have knowledge of the green practices they can implement within their own stage, as well as what the environmental implications of those practices will be for their own, and subsequent stages. They will also have a sense of how easy and beneficial it was to implement a practice based on its strength/intensity of application revealed in the study (e.g. higher intensity will be indicative of easier and/or more

beneficial to implement). The resulting greater clarity on green practices, both in terms of the options available, as well as those to prioritise based on (higher) application levels, will help increase their adoption.

Practitioners could increase the green practices' adoption levels further by leveraging the insights on drivers and barriers (to greening) provided in the study; they could do this by strengthening the drivers, and/or mitigating the barriers. Here, they can also be selective by focussing on only a few high strength/intensity drivers, and/or barriers. The information on the strength/intensity of each driver and barrier provided at individual supply chain stage and stakeholder levels in the study could be utilised for this. Further impetus to green adoption can come from the clarity provided on the associated performance benefits. These benefits, which are identified in the study in cost and environmental terms, and at individual supply chain stage and stakeholder levels, with strengths/intensities also indicated, could serve as a powerful motivator for greening to the practitioners.

Finally, due to the detailed insights provided in the study, it is possible to relate the performance benefit desired (cost or environmental and their nature), to the nature of green practice/s to be implemented to generate that benefit, to the nature of green driver/s and/or green barrier/s to be strengthened and mitigated respectively to ensure implementation of those practice/s effectively. The result will be more efficient and effective greening. Hence, to summarise, the comprehensive, in-depth and precise knowledge of each of green practices' (application), drivers and barriers (to greening), and performance benefits (from greening) provided by the study can enable greater green practices' implementation across all supply chain stages and stakeholders, with the implementation also being more efficient, and with greater cost and environment-related benefits realised from that implementation.

6.3 | Policy Implications

The findings call for policymakers to take decisive action to facilitate the industry's green transition. These include:

- Regulatory bodies could streamline the approval process for environmentally friendly process changes, thereby promoting green-related innovations.
- Green principles could be incorporated into existing regulatory guidance for all supply chain stages and activities.
- Policymakers could balance the management of persistent, bioaccumulative, and toxic (PBT) substances against the redesign of off-patent drugs to prevent future health crises.
- Prescribing policies could be redesigned to consider the environmental impact of drug excretion, thereby guiding the prescribers towards more sustainable choices.
- Waste disposal guidelines could be reassessed to accurately reflect the hazards of improper pharmaceutical disposal, and thereby promote proper disposal practices.

6.4 | Study Limitations and Suggestions for Future Research

While the study makes valuable contributions, it is not without limitations. Although the proposed framework was developed on the basis of a systematic literature review, some of the relevant green supply chain practices, drivers, barriers, and performance impacts could have been missed. Similarly, the framework was applied and tested on only one country (UK). Future studies could therefore apply the framework in other country settings and test/validate its usefulness and applicability there.

Further, the key components of the framework were assessed only qualitatively, with the statistical/quantitative precision missing. Future research could therefore try to empirically validate the framework through quantitative, survey-based approaches. The extent of implementation of individual green practices, the intensity of individual green drivers and barriers, and the extent of the different performance impacts could all then be precisely assessed. Assessments of the causal links between green drivers, green barriers, and green supply chain practices' implementation, and between green supply chain practices' implementation, and the environmental and cost performance impacts could also then be possible.

Despite these limitations, the framework presented, and its application significantly advance our understanding of the complexities in adopting green practices within the pharmaceutical industry. It is expected that this work will encourage further research in this important area.

Conflicts of Interest

The authors declare no conflicts of interest.

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