Sustainable guidelines for pharmaceutical research & development:

Enhancing environmental sustainability in drug development.

Thesis report

26 August 2024

Name: Koen Boon **Leiden ID**: s1682792 **Delft ID**: 5669375
MSc: Industrial ecology **Word count:** 18749

Supervised by:
First supervisor name: Dr. Glenn A. Aguilar-Hernandez
Organisation: Leiden University, Department: Institute of Environmental Sciences (CML)

Second supervisor name: Dr. Linda Kamp
Organisation: Technical University Delft, Department: Technology, Policy and Management

Table of Contents

Abstract

The pharmaceutical industry presents complex challenges and opportunities for environmental sustainability. Despite strict regulations ensuring medication quality and safety, there is a clear disconnect between pharmaceutical and sustainability guidelines. Guidelines, frameworks and regulations for pharmacy do not cover environmental sustainability sufficiently, while those for sustainability are insufficiently applicable to pharmaceutical development.
This thesis examines the global, international, and regional regulatory structures in pharmaceutical development from an environmental sustainability perspective. By evaluating the current practices in pharmaceutical R&D and operations, and modern environmental standards, this study offers a novel perspective by aligning pharmaceutical and sustainability guidelines, providing recommendations for enhancing environmental sustainability throughout the full pharmaceutical life cycle.

Through literature review of 142 sources including 55 on guidelines, regulations, frameworks and standards related to pharmaceutical development (such as ICH, EMA, FDA) and sustainability (such as SDGs, WHO), along with 60 journal and research articles along with 3 expert interviews, the current state of environmental practices in pharmaceutical development was evaluated. This revealed significant structural issues, with most pharmaceutical guidelines not aligned with modern environmental standards. For example, one of the ICH guidelines is 19 years outdated while being active and recently verified, and current practices often focus on minimal compliance.

Results from this study indicate there is significant potential for improving environmental sustainability through practices like lean manufacturing and life cycle analysis (LCA) starting from the earliest stages of drug development and operations as these have an existing structure for life cycle management which currently does not include environmental considerations. The existing structure requires an environmental risk assessment only for the active pharmaceutical component but ongoing research is looking into expanding on this as well.

Key recommendations include: 1. Harmonising global pharmaceutical guidelines with modern sustainability standards and more regular updates. 2. Establishing specific environmental impact indicators and metrics for pharmaceuticals and packaging, adapting chemistry frameworks like SSbD and green chemistry principles to pharmaceuticals. 3. Incorporating LCA methodology in life cycle management and early drug development, along with development of a dedicated database for pharmaceutical environmental impacts. 4. Enhancing collaboration to bridge knowledge gaps and improve transparency between regulatory bodies, industry, and environmental scientists. These recommendations can facilitate a systemic shift toward long term sustainability in pharmaceutical development.

1. Introduction

1.1 Background

The pharmaceutical industry is an integral part of modern healthcare, and the COVID pandemic highlighted its importance as it rapidly researched and developed a vaccine in response. In 2017 the global pharmaceutical industry contributed "one percent of global GDP or about the GDP of the Netherlands"(Ostwald et al., 2020). Upon closer inspection, the projected revenue of pharmaceuticals is $1.1trillion (Statista, 2024a). In comparison, the projected revenue of passenger cars for 2024 is $2.0 trillion (Statista, 2024b). According to Ledley et al., (2020), the net earnings (as a fraction of revenue) of pharmaceutical companies are significantly higher (13.8% vs. 7.7%) compared to non-pharmaceutical companies. Although it provides a clear positive contribution in terms of healthcare and economy, the opposite can be said for its environmental contributions. For example, in 2019, the pharmaceutical industry produced a 55% higher CO2 equivalent per $1 million revenue generated compared to the automotive industry (Belkhir & Elmeligi, 2019; Richie et al., 2020; Jayasree, 2022), and its carbon footprint is expected to triple by 2050 at the current rate (Jayasree, 2022; Statista, 2024a; Statista & Tiseo, 2024). The carbon footprint in this example is based on both direct and indirect CO2 emissions owned or controlled (scope 1 and 2 emissions) by companies or entities directly (Belkhir & Elmeligi, 2019; Soete et al., 2017).

1.2 Current State

There are very strict guidelines for pharmaceutical development (Abraham, 2009; Haleem et al., 2015; European Medicines Agency [EMA], 2024b; The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH], 2024), and state-of-the-art frameworks focused on, for example, quality-by-design (QbD) (Kumari et al., 2024; EMA, 2024c; EMA, 2024d) and (safe) and sustainable by design (SSbD)(European Commission [EC] et al., 2022a; EC et al., 2022b). The sustainable development goals (SDGs) framework is among the most well-known (Hajian & Jangchi Kashani, 2021; United Nations [UN], 2024a). But, for example, drugs are only mentioned directly in goal 3; good health and wellbeing (Domingo-Echaburu et al., 2021). Historically, the pharmaceutical industry has been resistant to change due to factors such as legislation, intellectual property concerns, financial competitiveness, and the viability of large-scale implementation (Silvestre, 2023). These issues are multifaceted and very complex in terms of scientific, technical, and societal challenges. In terms of scientific and technical challenges, there has been slow progress towards actual implementation of environmental sustainability in both research & development (R&D) and general production (Wynendaele, et al., 2021). As for social challenges these primarily include environmental concerns regarding biodiversity and reliable healthcare (Chen, E. Y. H. et al., 2023).

Sustainability is defined here as: "Meeting the needs of the present without compromising the ability of future generations to meet their own needs" (Brundtland, 1987; Oxford English Dictionary [OED], 2023; UN, 2024c; Virtanen et al., 2020). And second, sustainable practices are

broadly defined here as 'measures with the clear intention towards reducing unnecessary waste or environmental impact'. A comprehensive overview of additional sustainability terminology and principles can be found in Glavič & Lukman (2007). Additionally "standards is the preferred term for mandatory norms, accompanied by enforcement or certification mechanisms" (Picciotto, 2005).

Current sustainability efforts often emphasise recycling and circular economy principles to reduce waste, such as policies to incentivize proper waste disposal or the return of unused medication for re-packaging/distribution (Huang et al., 2015; Suhandi et al., 2023) and supply chain resilience (Yaroson et al., 2021). From the perspective of the 3 R's 'Reduce, reuse, Recycle' (Holt, 2018; Mostafa & Peters, 2017), there is attention towards possibilities for reuse and recycling of unused medication, but this remains a debated topic (Paut Kusturica et al., 2017). Circular economy is a model more focused on a resource efficient economy with the intention of reducing environmental impact (Suhandi et al., 2023). However, drug safety and efficacy concerns hinder the adoption of sustainable practices regarding reuse and recycling for both packaging and medication. Storage conditions can be compromised, and contamination risks are high in case of pollution both from and to the environment (Fatima et al., 2024). Additionally, the supply chain's reliability remains a critical challenge due to the large variety and limited availability of compounds required for production (Chen, Z., 2024; Suhandi et al., 2023). There are often limited or no alternatives to certain types of medication nor viable alternative methods of production, and only some chemical-based medication can be broken down into its components (Soete et al., 2017; Agbenyega, 2010; Becker et al., 2022) further limiting options for sustainable practices.

1.3 Research Gap

Despite the increasing attention towards sustainability, the pharmaceutical industry remains focused on compliance with safety and quality standards, while environmental sustainability is often an afterthought. Comprehensive guidelines and practical examples specifically including, or aimed at, environmental sustainability and sustainable practices in pharmaceutical development appear to be very limited or absent at first glance, and information is fragmented (Emara et al., 2018; Wynendaele et al., 2021). While current research focuses on the environmental impact of waste from pharmaceutical manufacturing and post-market stages, there is limited academic work addressing prevention rather than mitigation of waste in a systematic way. Although there are some initiatives towards managing roles and responsibilities of stakeholders (The European Federation of Pharmaceutical Industries and Associations [EFPIA], 2024), there is increased pressure on manufacturers as these are often held accountable, however there remains a critical gap in the systematic structure. These are especially absent in the initial stages of pharmaceutical research and development (R&D) and its guidelines and regulations, perpetuating the minimal compliance and mostly voluntary initiatives rather than structural improvements in the area of environmental sustainability.

This thesis contributes to the literature and ongoing interests in innovation of pharmaceutical

development, by conducting an in-depth analysis that compares pharmaceutical guidelines and environmental guidelines and frameworks as well as current practices. It highlights how sustainability can be embedded systematically from the initial stages of pharmaceutical R&D with implications for the later stages as well, which has not been sufficiently explored in previous studies. The focus is on the current procedural guidelines and regulations for pharmaceutical development & operations and their ability to facilitate sustainable innovations and modern environmental standards.

1.4 Research Objectives and Questions

The aim of this study is to explore the potential for integrating environmental sustainability more systematically into pharmaceutical research & development and operational practices. By addressing gaps in the current regulatory landscape and assessing its effectiveness at promoting environmental sustainability, this research seeks to provide recommendations that can be implemented by researchers, regulatory bodies, and industry stakeholders. The focus is on evaluating both existing guidelines and current practices, identifying areas of improvement, and proposing strategies to embed environmental sustainability across all stages of drug development. The primary research question is:

"How can environmental sustainability be better incorporated in pharmaceutical development and operations?" By approaching this in a systematic way using the existing structure of guidelines and regulations, it is expected that areas of improvement can be identified to significantly enhance environmental sustainability in earlier stages of development, impacting all aspects of production and operational practices down the line (Wynendaele et al., 2021). To achieve this, three sub-questions have been formulated.

Research questions to answer the main question:

1. What are the current regulations and guidelines for monitoring material use during drug development and operational practices?
2. To what extent are sustainable research practices considered in drug development?
3. What is required to better incorporate environmentally sustainable methods in drug development and operational practices?

1.5 Relevance

From a holistic perspective, the contrast between the economic and environmental aspects of the pharmaceutical industry highlights its significance. Current efforts, which focus on recycling, policies regarding waste disposal, and returning leftover medication, primarily address medication already produced and on the market as mentioned in the background. This reactive approach suggests the need for a more fundamental, proactive strategy. By examining how environmental sustainability can be integrated from the earliest stages of drug development it could yield significant long term improvements in sustainability. This study

aims to shift the focus from mitigation to prevention, potentially reducing environmental impact before production is upscaled.

1.6 Context and Contribution of This Study

This study is a thesis done as a requirement for the master of science (MSc) Industrial Ecology (Lifset & Graedel, 2015). Defining the concept of 'industrial ecology' (IE) as 'the study of material and energy flows through industrial systems' this master consists of different disciplines and an interdisciplinary perspective is taken in this study as well. The concept of sustainability is also a central aspect of the master. IE combines conceptual frameworks and theories often from a systems perspective in an attempt to bridge gaps between individual fields and is closely linked to innovation.

This study contributes to the field of IE by focusing on the existing regulatory structure in the form of procedural guidelines and regulations for the pharmaceutical industry from the perspective of environmental sustainability. The central focus is on pharmaceutical development as this aspect is most closely linked to innovation. Also it provides a way of using the existing regulatory structure to systematically improve the integration of environmental sustainability from the earliest design stages. Improvements in development stages will affect the full life cycle of pharmaceuticals and its associated environmental impacts.
By studying the current state-of-the-art in pharmaceutical research & development, operational practices in pharmacy, modern environmental standards and practices and then evaluating the ability of the current guidelines and regulatory structure to facilitate adoption of sustainable innovations in pharmacy, this study contributes a novel perspective by aligning pharmaceutical and sustainability guidelines and frameworks and providing recommendations on how to enhance environmental sustainability in drug development with implications for the full life cycle of pharmaceuticals.

1.7 Thesis Outline

This thesis is structured into 6 chapters with the content covering different aspects of environmental sustainability and how to enhance environmental sustainability in pharmaceutical development and operations, with additional focus on design. Chapter 1 is the current chapter and explains the background, including the problem, societal and scientific challenges, and relevance of this study. Chapter 2, the theoretical background, elaborates on important concepts, and perspectives including variations and context, serving as a foundation for reasoning in this study. Following this, chapter 3 is the methods. In chapter 4, results, findings from both the literature and interviews are presented, and organised according to the research questions into subchapters. Chapter 5 focuses on interpretation and scrutinising results, limitations, and aspects to consider both within and outside the scope of this study. Suggestions about actions that can be taken will be provided here. Finally, Chapter 6 summarises the research, reflects on implications, and considerations for future research directions.

2. Theoretical background

This chapter outlines the theoretical background that guides this study, providing a foundation for understanding the integration of environmental sustainability into pharmaceutical development and operational practices. First some key terms are explained. Some terms are used interchangeably across literature and are further defined or provided in context to avoid ambiguity in this study. In the case of 'drugs, medication, and pharmaceuticals' most literature uses these terms interchangeably and this study does as well as variations in this term were deemed acceptable.

2.1. Life Cycle Assessment (LCA):

LCA provides a methodological framework for assessing the environmental impacts associated with all stages of a product's life cycle (cradle-to-grave), from raw material extraction impacts (cradle) to manufacturing (cradle-to-gate) and then operational use until disposal (gate-to-grave) (Hauschild, 2018; Jacquemin et al., 2012). It helps identify opportunities for reducing the environmental footprint of products or for comparing alternatives, and can be included in process design and optimization (Jacquemin et al., 2012). Although an LCA is not conducted in this study, LCA studies are an important aspect to be considered during literature search as they provide means to identify or even quantify environmental impacts and areas of improvement. The terminology 'cradle-to-gate' is used to describe the entire pharmaceutical development process rather than a single product in this study. LCA is often closely related to the circular economy principles which are used as a model for supply chain aspects of environmental sustainability, most of this relates to the 3 R's reduce, reuse, recycle (Holt, 2018; Mostafa & Peters, 2017).

2.2. Pharmaceutical Development Phases

This study primarily focuses on providing recommendations that can be applied to the cradle-to-gate stages of the pharmaceutical development trajectory (which usually takes 4-6 years), aligning with FDA guidelines (The United States Food and Drug Administration [FDA], 2018). These phases are:

- **Discovery (Phase 1):** Initial research and identification of potential drug candidates.
- **Pre-clinical research (Phase 2):** In vitro and in vivo testing to assess safety and efficacy.
- **Clinical trials (Phase 3):** Testing in human subjects to evaluate drug performance.
- **Market approval (Phase 4):** Regulatory review and approval for market entry.
- **Post market approval.** All aspects of use and disposal, and post market surveillance.

2.3. Pillars of Sustainability

As the concept of sustainability developed across different fields, several concepts emerged such as the 'three pillars' concept (social, economic, environment) which emerged from different fields, stating these 3 pillars need to be balanced to achieve sustainability. This concept

can be considered a dominant framework for defining and operationalizing sustainability, many variations are based on this framework and the terms are often used loosely (Purvis et al., 2019; Barbier, 1987; Brundtland, 1987; Elkington, 1998; Slaper & Hall, 2011; Loviscek, 2021; Larivière & Smit , 2022) Variations include 'Environmental, social, governance' (ESG), and 'people, profit, planet' (3P, or Triple bottom line, TBL). Each of the pillars is clarified here to avoid ambiguity.

- **Environmental Sustainability**
  Definition: Environmental sustainability refers to the responsible interaction with the natural environment to avoid the depletion or degradation of resources, ensuring that ecosystem services are maintained for future generations.
  Key Focus Areas: It includes the conservation of natural resources and use of renewable resources when possible, reducing waste and pollution of air, water, and soil, protecting biodiversity, and mitigating climate change. The goal is responsible consumption and to preserve the environment's ability to support life and provide essential resources for human society, one example is circular economy models to reduce waste.
- **Social Sustainability**
  Definition: Social sustainability is concerned with maintaining and improving social quality, including equity, diversity, quality of life, and social cohesion. It focuses on the relationships between people, communities, and society at large.
  Key Focus Areas: This pillar addresses issues such as human rights, education, health care, labour rights, community development, and cultural preservation. Its goals are to ensure that all people have access to basic needs, can live in a healthy environment, and participate in decision-making processes (governance) that affect their lives. Most of these aspects are applied through policies and practices.
- **Economic Sustainability**
  Definition: Economic sustainability involves practices that support long-term economic growth and stability (resilience) without negatively impacting social, environmental, and cultural aspects of the community by taking ethical principles into account. It seeks to ensure that economic activities are viable and equitable in the long run.
  Key Focus Areas: It includes efficient use of resources, innovation, job creation, and fair distribution of wealth. Economic sustainability aims to create a stable economy that provides opportunities for all, while not compromising the environment or social equity. It also includes sustainable management, corporate responsibility.

The three pillars (environmental, social, and economic) are interdependent, and achieving sustainability requires a holistic approach that balances the needs and impacts across all three pillars. Failure to address any one pillar can undermine efforts in the others, as each pillar supports the overall stability and health of the system. The environmental sustainability pillar is central in this thesis while focusing on pharmaceutical development, emphasising how environmental sustainability can be better integrated into drug development phases. Although for analytical purposes the three pillars can be clearly separated, to address the interdependence of the environmental pillar, the other two pillars are considered based on their relation to

environmental sustainability as well, as decisions made regarding social and economic sustainability directly influence how environmental sustainability is implemented within the pharmaceutical industry. For this purpose regulatory, academic, business, and social perspectives are acknowledged for their influence on environmental outcomes.

3 Methodology

This section is aimed at providing a concise overview of all the different steps taken to answer the research questions in a way that is reproducible. In addition it describes how data is collected and processed, and justification of the decisions made regarding how to process and collect data.

3.1 System Boundaries and Scope

The system boundary is limited to environmental sustainability in pharmaceutical development, with a primary focus on pharmaceutical research and development (R&D) and operations. The research scope emphasises recommendations for drug development phases 1, 2, and 3 (FDA, 2018), which cover the pre-market approval stages and are more uniformly defined globally. These phases are selected as they encompass the largest range of procedures relevant to environmental sustainability. Findings regarding phase 4 (market approval) and post-market approval activities are studied in relation to the research scope and objectives, but are not the main focus of this study.

In this context, the research examines guidelines, practices, and recommendations that are generally applicable to environmental sustainability in pharmaceutical development. However, specific chemical processes, synthesis steps, proprietary processes, or guidelines for individual classes or groups of medications are excluded from the scope due to the wide variability and specificity of these processes unless they have broad applicability or relevance to environmental sustainability.

The study prioritises regulatory and material aspects of R&D, with a focus on material and equipment use within operations if detailed information is available. Relevant areas of study include procedural guidelines, procurement, waste management, and other operational practices that impact environmental sustainability. Guidelines, standards, and articles available in the public domain are prioritised to maintain transparency. For the public domain this includes resources accessible via Google Scholar, Google, and semi-public availability using institutional access, specifically through Leiden University (LU) and Delft University of Technology (TUD). Through TUD the NEN-connect service was used, which provided access to standards such as ISO.

Throughout the study, regulatory, academic, business, and social perspectives are analysed across literature to explore various factors influencing environmental outcomes. These perspectives serve as the foundation for the recommendations provided in the results and discussion sections, where the focus is narrowed to specific recommendations for different groups of stakeholders aimed at better implementation of environmental sustainability within pharmaceutical development.
Procedural guidelines and regulations for pharmaceutical development are a central focus for

recommendations as these provide a way of using the existing regulatory structure to systematically improve the integration of environmental sustainability.

Regarding geographical and spatial boundaries, the inclusion criteria for guidelines prioritise those that are global, international, or regional in scope over national or company-specific guidelines, ensuring applicability across different regions and in broader context.
The research favours more extensive, detailed, and complete guidelines over generic ones, as they offer a more thorough basis for cross-comparison. More recent guidelines are also preferred to ensure relevance. All guidelines, regulations, and standards are assessed based on if they are currently in use. Exclusion criteria include national or company-specific guidelines unless they offer unique insights or have broad applicability to multiple contexts.
The recommendations provided in this research are assumed to be applicable to pharmaceutical development in general, unless otherwise specified in the limitations section. Additionally, outdated guidelines that have been superseded are excluded, unless they remain in widespread use (conditional exclusion criteria). This approach ensures the relevance and comprehensiveness of the findings across diverse regulatory and operational contexts. This global approach is intended to make the findings relevant to a broad audience (researchers and entities working in pharmaceutical development regardless of region), encompassing diverse regulatory and operational contexts.

3.2 Research approach

This section provides a concise overview of the research approach. A flow diagram (Figure 1) is included to visually represent the stages of the research process, aligning each stage with the corresponding sub-questions.

An essential tool within the theoretical background is the Life Cycle Assessment (LCA) methodology, which is used to assess the environmental impacts of processes and operations across various stages. LCA is an internationally standardised methodology that quantifies environmental impacts associated with all phases of a product's life cycle, from raw material extraction through manufacturing, usage, and disposal. In this research, LCA provides a structured way to evaluate pharmaceutical development processes, helping to identify areas where environmental sustainability can be better integrated, particularly in the early research and development (R&D) phases. This structured approach ensures consistency across the stages of analysis and helps connect findings to the study's overall objective of enhancing environmental sustainability. Other frameworks are also considered depending on literature findings, however LCA is an example of state-of-the-art framework for sustainability regarding environmental impact of materials and provides a good starting perspective to identify what information is required for assessing environmental sustainability.

3.2.1 Overview of the Research Phases

The research is divided into three stages, each corresponding to one of the sub-questions, with further elaboration provided in their respective sections. The overall process aims to integrate

environmental sustainability more systematically into pharmaceutical R&D practices by evaluating existing guidelines, methods, and practices.

1. **Stage 1: semi-systematic review of guidelines (addressing sub-question 1)**
   The first stage of the research (represented in figure 1 as stage 1) involves a semi-systematic review of literature (Snyder, 2019). This stage focuses on identifying and evaluating guidelines related to pharmaceutical development, with a specific emphasis on guidelines that incorporate or affect sustainability. This review includes both **general sustainability guidelines** and **pharmaceutical development guidelines**. The purpose is to gain a comprehensive understanding of the existing regulatory framework and its relevance to environmental sustainability in pharmaceutical R&D. More details on the review process and literature search strategy are provided in section 3.3.
2. **Stage 2: review of sustainable practices and interviews (addressing sub-question 2)**
   In the second stage (Stage 2 in Figure 1), the literature review expands to include sustainable methods and practices currently used in pharmaceutical development, with a focus on how these practices relate to environmental sustainability. Alongside the literature review, semi-structured interviews are conducted with three experts who work in fields closely related to pharmaceutical development and/or sustainability. The interviews aim to validate findings from the literature review and provide practical insights into the real-world application of sustainability in pharmaceutical development. These interviews are discussed in more detail in section 3.4.
3. **Stage 3: cross-comparison and development of recommendations (addressing sub-question 3 and main research question)**
   The third stage (stage 3 in figure 1) involves the **cross-comparison** of findings from both the literature review and interviews. This step focuses on identifying challenges, and opportunities in current practices and guidelines. The findings are then used to develop recommendations for improving environmental sustainability in pharmaceutical development, particularly during the R&D phases. Section 3.5 provides a detailed explanation of the methodology used for cross-comparison and synthesis of findings.

3.2.2 Visual Representation of Research Phases

Figure 1 (Flow Diagram) provides a visual summary of the research stages and how they connect to the sub-questions. This figure helps clarify the flow of the research process and the sequential steps taken to address the research questions.

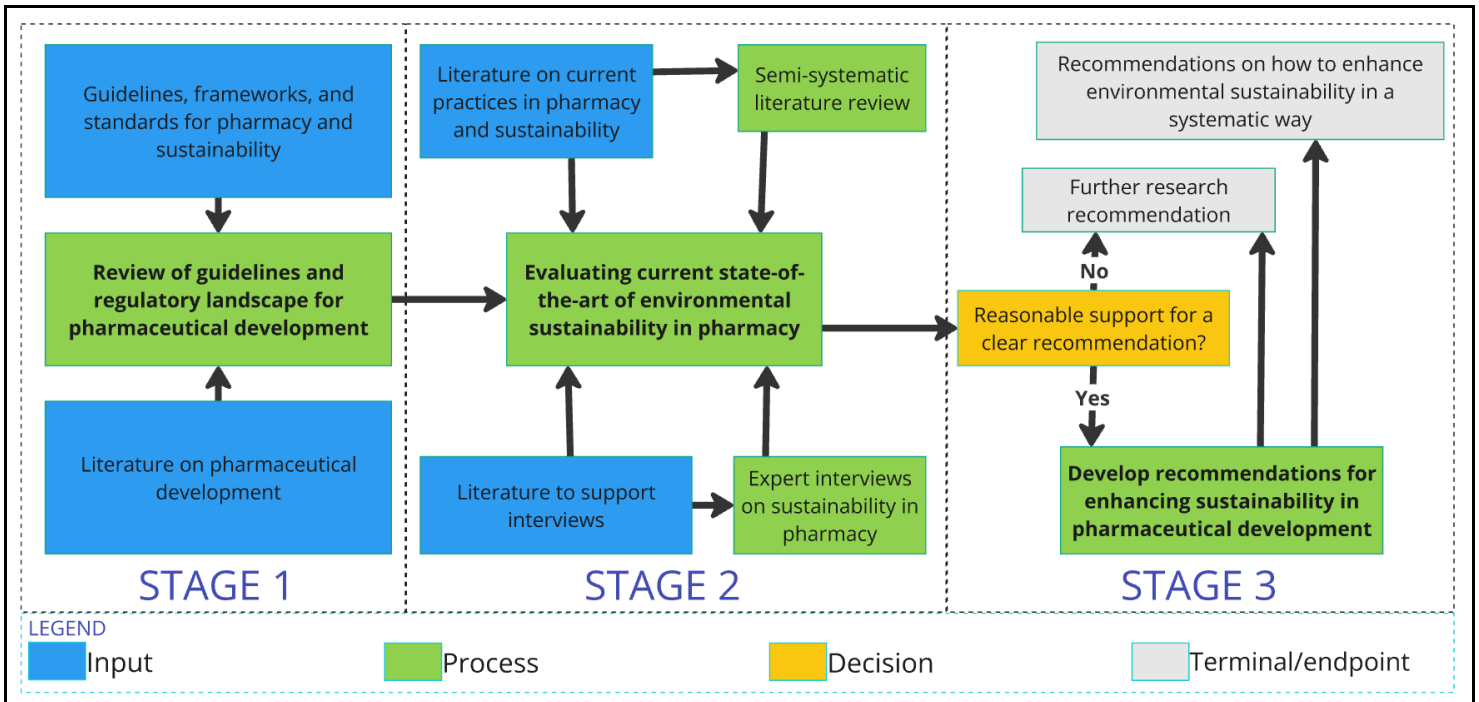

Figure 1: Research flow diagram. The research approach is visualised here with a simplified overview of steps, each vertical section of stages corresponds with a research sub-question. The figure aims to show how the questions and steps in the report are connected, starting with literature and guidelines. Then followed by further literature review, interviews, and comparison, and finally a comparative analysis where the quality and quantity of information is assessed to determine if there is reasonable support for recommendations. Recommendations and results are iteratively refined at each stage with primarily literature studies as input.

3.3 Description of Literature Search Strategy

The literature search strategy was designed to ensure a comprehensive review of existing research and guidelines related to environmental sustainability in pharmaceutical development. The initial approach was guided by a semi-systematic methodology (Snyder, 2019), allowing flexibility in identifying relevant guidelines, frameworks, and research articles. As the search progressed, the scope expanded to include grey literature, given the fragmented and diverse nature of available sources, and snowball sampling was applied to obtain literature sources from within other literature identified. Due to the semi-systematic nature and snowballing, the general approach and criteria are described here.

3.3.1 Search Methodology

The primary databases and sources used included:

- **Google Scholar**: This was the primary database for identifying academic literature.

- **Google**: The regular google search engine was used to search for and navigate to sites of official regulatory authorities and organisations, as well as broadening the search into less academic sources and grey literature.
- **Institutional access**: Using student access through **Leiden University** (LU) and it's community network (ULCN) account, and **Delft University of Technology** (TUD), additional sources were retrieved when necessary through university libraries and catalogues to access specific articles, books, and journals that require subscriptions.
- **NEN-connect**: This specialised service provided by TUD was used to access all official ISO standards related to environmental management and pharmaceutical R&D operations.

The search strategy followed these three simple steps: Initial search, filtering, and screening on relevance, these steps are further described here.

1. **Initial search**: Systematic searches using a set of predefined terms were conducted to identify relevant guidelines and literature. Variations of these terms were also employed to capture a wide range of sources related to environmental sustainability in pharmaceutical development and aspects thereof.

3.3.2 Search Terms Used

The following search terms were applied during the initial literature search, some variations in the term pharmaceutical, drug, and medication were used interchangeably, attention was paid to words with different spelling in british english (for example rigor vs rigour) as these can yield different results:

Pharmaceutical industry, Pharmaceutical industry R&D, Pharmaceutical development guidelines, Sustainable pharmaceutical development, Green supply chain, Environmental sustainability in pharmacy, Green chemistry, Green chemistry in pharmaceutical industry, Environmental sustainability guidelines for pharmacy, Green chemistry and sustainability, Sustainability metrics in pharmaceutical industry, Green manufacturing, ISO standards pharmaceutical R&D, ISO 14001 environmental management, Challenges and recommendations for environmental sustainability, Triple bottom line framework, Life Cycle Assessment (LCA) pharmaceutical products, UN definition of sustainability, Sustainable by design framework, Sustainable pharmacy, Pharmaceutical packaging, Pharmaceutical operations, Pharmaceutical management guidelines, Quality by design framework, ICH guidelines, EMA guidelines, WHO guidelines pharmaceutical development, WHO guidelines healthcare, Sustainable development goals and pharmacy, Global reporting initiative, Environmental indicators for pharmaceuticals, Environmental indicators for chemicals, methodological rigour, methodological rigor.

Further searches were done based on snowballing of literature and some terms within the initial findings, primarily to find specific guidelines and standards after the initial search.

2. **Filtering results**: Filters were applied to prioritise recent publications (primarily from 2020 onward), ensuring the literature reviewed was up-to-date and relevant. These filters were removed or adjusted depending on the relevance of results found. Important events include the Paris agreement in 2015 (UN, 2015) which affected global attention on sustainability also in regulations, and the COVID-19 pandemic (2019>), which increased attention to healthcare, and pharmaceutical development.
   Filters Used: *None*, *Since 2020*, *Since 2015*, *Since 2017*, *Since 2019*. The none filter means the search includes publications from any year.
3. **Screening for relevance**: Results were screened based on titles and abstracts, based on relevance to the scope, mainly aspects related to pharmaceutical development, environmental sustainability, material aspects of pharmaceutical development and operations (procedures, procurement, waste management, material use). Further inclusion and exclusion criteria are provided here, inclusion criteria were applied more loosely than exclusion criteria due to the broad nature of information.

Additionally, a focused search within literature and guidelines was done using the following terms to find relevant sections after initial screening: Sustainability, sustainable, environment, environmental, ecology, ecological, impact, emission, material, recourse, waste, practical, practice, practical, application, applied, applicable.

Inclusion criteria applied to screening:

1. Guidelines, frameworks, and articles discussing environmental sustainability in pharmaceutical R&D or operational practices. Preference for international, regional, and global guidelines.
2. Publications emphasising sustainable use of materials, waste management, and operational practices in pharmaceutical development. Older publications and sources from <2020 are included for consistency and compared to in-use practices, as historical information and studies can be persistent when the practice or guideline it applies to is still in use.
3. Recent publications, primarily from 2020 onward, that reflect the current state of sustainability efforts and novel developments.
4. Grey literature and non-peer-reviewed sources when relevant to regulatory and operational practices, or when providing useful perspectives. Primarily relevant for snowballing to trace back to scientific literature origins if provided.

Exclusion criteria:

1. Older or outdated guidelines and standards superseded by recent updates, unless they are still in use.
2. Articles and sources focused solely on chemical processes without broader relevance to environmental sustainability or pharmaceutical development, or too specific-use case articles that are not sufficiently applicable beyond their case.
3. No specific search into national or corporate guidelines was done to focus on general applicability based on scope. National-level guidelines or corporate guidelines without

international or cross-regional relevance are excluded with the exception if they provide unique insights into pharmaceutical development or sustainability, or implementation of practices.
4. Older publications on operations, practices, and frameworks that are no longer in use at present, AND have been clearly replaced, been integrated, or transitioned into more novel or recent methods. Unless both criteria are met, older publications are included as in-use practices are assumed to depend on technological and financial factors on a national or corporate level, as well as being affected by time lag between discovery and implementation.
5. Guidelines and literature on medication for veterinary use are not directly studied, the focus is on medication for human use. Based on the scope, if encountered veterinary guidelines or regulations are briefly compared to the human equivalent for similarity, but will further be excluded from mentioning.

3.4 Description of interview design

3.4.1 Background and purpose of interviews

The purpose of the interviews is to gain insights into how environmental sustainability is currently being implemented in pharmaceutical development and operations in practice. The input was used to improve our understanding of the existing state of sustainability efforts, and highlight challenges and opportunities for improvement most relevant to the present. This information is compared to findings from literature and used to develop recommendations for enhancing environmental sustainability in pharmaceutical development.
The interview findings and literature are compared to see the relation between theory and practice, and this addresses the second sub-question: "To what extent are sustainable research practices considered in drug development?".

3.4.2 Selection of Interviewees

Interviewees were selected based on their expertise and roles in relation to the pharmaceutical industry, or specific relation to (environmental) sustainability guidelines or research. The preferred target group is people involved in regulatory affairs, and/or environmental sustainability, and a required inclusion criteria was having any expertise with- or working in a role related to- drug development. Interviewees were screened based on research, work, or study background, and asked for confirmation if they had expertise on this topic. A more generic sampling method with directional search was used to identify key stakeholder groups, including regulatory officials, sustainability consultants, researchers, and others, to ensure a diverse range of perspectives and comprehensive understanding of the current practices and challenges in different practical areas. Due to time constraints the amount of interviews was limited to 3, a brief overview of interviewee details is presented in table 1. Snowball sampling was applied, asking recommendations for potential interviewees throughout existing connections and asking people to forward the invitation.

Table 1: Interviewee details. Brief overview of the organisations, roles and functions, and relevant experience to pharmaceutical development and/or environmental sustainability. Further details about the interview questions are available in appendix B, specific identifying information and interview transcripts are only available on request.

Type of organisation	Role/function	Relevant experience	Additional remarks
Community pharmacy	Head pharmacist	26 Years as pharmacist	In-text: Interview 1. Details: Appendix B1 (On request)
Hospital, hospital pharmacy	Head of the oncology department, also responsible for department logistics	5 Years pharmacist, 5 year specialisation hospital pharmacist, 3 year specialisation as clinical pharmacologist	In-text: Interview 2. Details: Appendix B2 (On request)
University	Post-doc researcher	5+ years in environmental engineering and industry, 2 years on specialisation in LCA and emerging technologies	In-text: Interview 3. Details: Appendix B3 (On request)

3.4.3 Interview procedures

Semi-structured interviews were designed based on initial literature findings, to allow for flexibility in exploring various aspects of the research questions while maintaining a consistent framework for comparison. An interview guide was developed, consisting of four open-ended questions designed to get detailed responses about current regulations, sustainable practices, and potential improvements in the integration of environmental sustainability in drug development. Interviews are conducted preferably online via video platforms and audio-recorded for transcription purposes with participants' consent to ensure accurate and efficient data collection. The interview guide, which includes detailed questions and preliminary information provided to interviewees, is available in the appendix (Appendix B). The numbered questions 1 to 4 were asked, and sub-questions A to D were only asked for directional information if considered insufficiently covered.

3.5 Comparative assessment

This section focuses on comparison of findings across the three stages of the research approach as described in figure 1. The purpose of this section is to describe how the different elements are

combined to answer the main research question in chapter 4.4. The information obtained from literature studies across different stages of the research is comparatively evaluated, the research sub-questions are answered using chapters 4.1, 4.2, and 4.3.
Thematic analysis is employed in the literature study in 4.1 to identify common themes and patterns across sources, first the different guidelines, academic research articles, interviews, and other literature are categorised. Secondly, the information is qualitatively and if possible quantitatively assessed based on the frequency of key terms such as LCA and green chemistry to see how often certain problems are mentioned and to see if certain problems are persistent across different sources or regions. And thirdly, results are qualitatively evaluated for any potential underlying causes or possible correlation as well, for example the distribution of topics before 2015, after 2020, or between these years.
Regarding the process, the literature is studied and guidelines, literature, and interviews are assessed to uncover gaps or areas for further investigation not yet clearly defined by other literature. In section 4.3.2 suggestions are provided specifically based on problems identified in literature with the help of insights from literature and interviews. This approach enabled a robust understanding of how environmental sustainability is currently addressed in practice and what steps can be taken to enhance better implementation in pharmaceutical development.
Chapter 4.4 synthesises the information to answer the main research question based on the different chapters and identified themes, to provide more specific recommendations, the intention is to provide recommendations primarily intended for researchers across different fields that want to implement environmental sustainability including but not limited to pharmaceutical development.

4. Results

A brief overview is given here on how the results section is structured. First the general findings and results from the literature search are described in 4.1 (stage 1 of the research approach), followed by a more detailed review of current guidelines, regulations, frameworks, and standards that are applicable or relevant to pharmaceutical development is provided in 4.2 further backed by literature from 4.1 and by insights from interviews (corresponding with stage 2 of the research approach). Chapter 4.3 focuses more on areas of improvement including challenges and opportunities specifically for enhancing environmental sustainability in pharmaceutical development, based on literature from 4.1 and interviews as well, and further synthesis of recommendations is done based on observations made in this study (stage 3 of the research approach), the main research question is also addressed here.

4.1 Literature search results

This section contains the results from the literature search including overviews of the findings and some generic observations. As mentioned before by Wynendaele et al. (2021) there are challenges in integrating sustainability in early pharmaceutical R&D due to the fragmented guidelines and regulations, similarly, Becker et al. (2022) provides a case study demonstrating how the life cycle of APIs lacks integration with environmental sustainability principles during the manufacturing process. These are just 2 examples of fragmented information, which was a recurring theme across several sources. More detailed observations based on certain types of literature and observed trends are discussed in chapters 4.2 and 4.3. An overall observation is that most problems and recommendations identified in literature are also rather generic or specific for a part of pharmaceuticals like APIs but practical improvements are still lacking. A comprehensive overview of findings from the literature search are presented in table 2. It includes literature on aspects relevant to environmental sustainability in pharmaceutical development, focusing on diverse aspects like guidelines, regulations, frameworks, standards, and operational practices. On average at least 5 screened research articles yielded 1 relevant reference, already accounting for duplicates in searches, for specific focused searches and snowballing through literature lists, after the initial semi-systematic approach, an average of 4 sources were screened for relevant non-article references. A minimum of 632 sources were screened but an exact count was not kept for snowballed sources. The **142** references used in this report were deemed relevant after screening. The relevant literature spans a variety of source types identified including articles from journals, governmental and organisational pages, corporate pages and reports, and other sources categorised as 'other'. The different types of sources provide various insights into aspects related to sustainability and pharmacy in general as well. Records were excluded primarily if they lacked relevance to the pharmaceutical sector or sustainability, or if they were outdated and had been replaced by more current guidelines. Additionally, sources were excluded if they focused solely on specific chemical processes without broader application to the regulatory framework or sustainability practices, most green chemistry sources were included specifically due to their broader application potential. This

ensured that only directly applicable and currently relevant records were used in the final analysis.

Within the journal articles category, there is a balanced mix of open access and institutional access articles. One observation is that open access articles tend to focus on broader sustainability applications because they are often geared towards general dissemination and are intended to promote broader awareness on topics like green chemistry and LCA. In contrast, institutional access articles frequently include detailed studies and in-depth analyses, likely because these are often funded by specific research institutions or industry collaborations, which have access to proprietary data and are more targeted towards professionals in the field. On the other hand, government and corporate reports provide critical insights into regulations and frameworks. These include contributions from national and international governmental organisations, EU agencies, and corporate stakeholders like the European Medicines Agency (EMA) and the International Council for Harmonisation of Technical Requirements (ICH), each emphasising the need for pharmaceutical practices to adapt to evolving environmental standards. Notably, reports from the Dutch Ministry of Health (2020) and EMA (2024) focus specifically on regulatory frameworks for reducing the pharmaceutical industry's environmental impact, with clear guidelines on emissions (more generic environmental impacts) and risk assessments for medication also being present in international regulations (very specifically focused on medication or it's active components as also mentioned in Becker et al (2022), not so much other aspects).

Table 2. Literature search results overview. This table includes an overview of all the literature found during the literature study and after screening. Details are provided on the types of literature in addition to generic key themes or topics that stand out also in relation to the scope (environmental sustainability and/or pharmaceutical development and operations related elements). Literature from preliminary search for identifying the research gap has been included in the categories. The main purpose is to provide quantitative information.

Source Type	**Total: 142**	**Details**	**Key Themes Identified**
Journal and research Articles	60	**Open Access (32):** (Al-Awamleh et al., 2022; Ashiwaju et al., 2023; Azim & Hasan, 2013; Barbier, 1987; Chen, E. Y. H. et al., 2023; Daughton & Ruhoy, 2009; Domingo-Echaburu et al., 2021; Donyai et al., 2021; Glavič, & Lukman, 2007; Gupta & Jain, 2013; Hardjono & de Klein, 2004; Henry & Lexchin , 2002; Holt, 2018; Yaroson et al., 2021; Jamwal et al., 2021; Sengar & Tripathy, 2012; Ostwald et al., 2020; Moermond et al., 2022; McRae et al.,	**Since 2020:** Green chemistry, Biodegradable packaging **Since 2015:** More articles on Life Cycle Assessments (LCA) **None:** Pre-2015 trends focus on foundational

		2021; Loviscek, 2021; Ledley et al., 2020; Larsson , 2014; Kittery & Miettinen , 2023; Huang et al., 2015; Mostafa & Peters, 2017; Noori et al., 2020; Rockström et al., 2009; Toklu & Hussain, 2013; Villanueva et al., 2024;Virtanen et al., 2020; Slaper & Hall, 2011; Lifset & Graedel, 2015) **Institutional Access (28):** (Becker et al., 2022; Belkhir & Elmeligi, 2019; Chen, Z. et al., 2024; Crespo-Gonzalez et al., 2020; Crespo-Gonzalez et al., 2021; Dong & Hauschild, 2017; Haleem et al., 2015; Hay et al., 2014; Eskandari et al., 2022; Mishra et al., 2021; Narayana et al., 2012; Milanesi et al., 2020; Lau, 2016; Mamiya et al., 2020; Davies et al., 2006; Jones et al., 2022; Ögmundarson et al., 2020; Fatima et al., 2024; Larivière & Smit , 2022; Kumari et al., 2024; James & Magee, 2016; Jacquemin et al., 2012; Elkington, 1998; Nieminen et al., 2020; Suhandi et al., 2023; Snyder, 2019; Soete et al., 2017; Wynendaele et al., 2021)	guidelines and concept descriptions to some extent.
Government/ Corporate sources ***Note: assigned category is based on what was deemed most applicable but might not be completely accurate.**	60	**Government and authority sources(40):** (EMA, 1997; EMA, 2000; EMA, 2006; EMA, 2008; EMA, 2020; EMA, 2023; EMA, 2024a; EMA, 2024b; EMA, 2024c; EMA, 2024d; EMA, 2024e; Dutch Ministry of Health Welfare and Sport, 2020; National Institute for Public Health and Environment [RIVM], 2016; RIVM, 2022a; RIVM, 2022b; Lee et al., 2017; The Center for Drug Evaluation and Research [CDER]. FDA, 2020; FDA, 2024; EC, 2024a; EC, 2024b; EC, 2024c; EC, 2024d; Rijksoverheid, 2023; Directive (EU) 2022/2464; EC et al., 2022a; EC et al., 2022b; EC et al., 2023; Electronic Code of Federal Regulations[eCFR]. FDA, 2024; Organisation for Economic Co-operation and Development [OECD], 2023; ICH, 2024; UN, 2015; UN, 2024a; UN, 2024b; UN, 2024c; The Environmental Protection Agency [EPA],	**Since 2020:** Focus on compliance with new environmental laws, stricter regulations, and frameworks (Green Deal for example) gradual shift towards more environmental sustainability mentioned, but practical application examples are still behind. Significant time lag in adaptation of some guidelines. **None:** No significant themes

		2013; EPA, 2015; World Health Organization [WHO], 2020; WHO, 2023; WHO, 2024a; WHO, 2024b) **Corporate sources(9):** (EPD International, 2024a; EPD International, 2024b; EPD International, 2024c; The Royal Pharmaceutical Society [RPS], 2023; RPS, 2024; Cisneros, 2022; Statista & Tiseo, 2024; Statista, 2024a; Statista, 2024b) **Non-governmental organisation source (11):** (Health Care Without Harm **[**HCWH] et al., 2019; The International Organization for Standardization [ISO], 2023; ISO, 2022; ISO, 2017; ISO, 2016; ISO, 2015a; ISO, 2015b; ISO, 2006a; ISO, 2006b; Dutch Environmental Database [NMD], 2024; Silvestre, 2023)	pre-2015
Non-Profit Organisation Reports	8	(The Global Reporting Initiative [GRI], 2024; The World Economic Forum [WEF], 2022; Australian Pharmacy Council [APC], 2020; (EFPIA), 2024; Fédération Internationale Pharmaceutique [FIP], 2021; FIP, 2022; Brundtland, 1987; Agbenyega, 2022)	
Other Sources	14	**Book chapters (6)** (Abraham, 2009; Hauschild, 2018; Hajian & Jangchi Kashani, 2021; Emara et al., 2018; Scherer, 2000; Paut Kusturica et al., 2017) **Other sources (8) including books, company pages, grey literature, and uncategorised sources.** (Tietje & Brouder, 2009; Kaylor, 2023; Danzon, 2014; Schuhmacher et al., 2016; Siegert et al., 2019; Picciotto, 2005; OED, 2023; International Federation of Pharmaceutical Manufacturers and Associations [IFPMA], 2024)	

4.2 Current guidelines, regulations, frameworks, and standards for pharmaceutical development.

An overview of current guidelines, regulations, frameworks, and standards is provided (4.2.1 and 4.2.2) relating to the full process of, and important aspects relating to pharmaceutical development. These sections cover the first sub-question **"What are the current regulations and guidelines for monitoring material use during drug development and operational practices?"**
The objective was getting a comprehensive oversight of guidelines relating directly or under consideration also indirectly to pharmaceutical development and sustainability in pharmacy. Table 3 contains a brief overview of the references and the amount of guidelines and frameworks identified to answer the research question, mainly aimed at quantitative information. These guidelines, detailed in appendix A, focus on key aspects of pharmaceutical development, including guidelines specific to material use or management and operations, and their relation to environmental sustainability. Sections of the guidelines are referenced by chapter or page to ensure clarity when relevant. This chapter includes a brief overview of the findings from appendix A.

Table 3. Brief overview of guidelines, regulations, frameworks, and standards identified in the literature study. For the elaborate overview including full names, and details on relevant sections refer to Appendix A. Do note the official publication year is posted rather than just the most recent update year of the guideline, all guidelines mentioned here are currently in effect at the time of writing.

Type of Literature	Total Count (55)	Pharmacy related (Appendix A, table 1) (Total 28)	Sustainability related (Appendix A, table 2) (Total 27)
Guidelines	17	**(12 guidelines)** - FDA Guidelines (2) (FDA, 2020; CDER. FDA, 2024) - EU Guidelines (EC, 2024d) (contains 4 relevant guidelines: Volume 3, Volume 4, Volume 9, Volume 10) - ICH Guidelines (6) (EMA, 1997; EMA, 2000; EMA, 2006; EMA, 2008; EMA, 2020; EMA, 2023)	**(5 guidelines)** (WHO, 2020; Lee et al., 2017; OECD, 2023; EPA, 2013; EMA, 2024a)
Frameworks/Regulati	38	**(16 standards)**	**(22 standards)**

ons/Standards *Note the other colum states standards, but also contain frameworks and regulations, more details are in Appendix A.		- HACCP (Haleem et al., 2015) -Quality risk management (QRM) (WHO, 2023) - 7 additional WHO standards (WHO, 2024a; WHO, 2023). - (Annual) Product Quality Review (APQR/PQR) (Cisneros, 2022) - ISO 9000:2015 (ISO, 2015a) - ISO 17025 (ISO, 2017) - ISO 15189 (ISO, 2022) - ISO 13485:2016 (ISO, 2016) - ISO 15189:2022 (ISO, 2022) - Process Analytical Technologies (PAT) (FDA, 2004)	-SDGs (UN, 2024a) -Planetary boundaries (Rockström et al., 2009) -EPD (EPD International, 2024a) -PCR (EPD International, 2024c; NMD, 2024) -ISO 14025(ISO, 2006a) -ISO 14040 (ISO, 2006b) -SSbD (EC et al., 2022a; EC et al., 2022b) -ISO 14001 (ISO, 2015b) -ISO 14000 Series (ISO, 2023) -CSRD (EC, 2024b; Directive (EU) 2022/2464) -ESRS (EC, 2024b; EC et al., 2023) -(GRI, 2024) **(contains 5 specific standards)** -BREFs (EC, 2024a) -RCRA (EPA, 2015) -TBL (Elkington, 1998;Loviscek, 2021) -UNGC (UN, 2024) -PIE (EFPIA, 2024)

4.2.1. Pharmaceutical and sustainability guidelines

In pharmaceutical development, there are many existing guidelines covering specific details and types of medication, the focus here is on guidelines relevant to pharmaceutical development or contain some mention of material aspects, as material use considerations are often directly related to design, operational efficiency, and waste. These are central to evaluating sustainability practices in the pharmaceutical industry, making it essential to the analysis of existing guidelines.

Pharmaceutical guidelines, such as those provided by the International Council for Harmonisation (ICH), the World Health Organization (WHO), and various national regulatory bodies on international levels, predominantly focus on the technical and procedural aspects of drug development (based on table 3 and appendix A. Pharmaceutical guidelines are rigorous in

ensuring drug quality, safety, and efficacy but fall short in addressing environmental sustainability. While it is known and confirmed here that existing guidelines do not directly incorporate sustainability in pharmaceutical development, this study provides a novel comparative analysis of how environmental frameworks can be integrated within the pharmaceutical guidelines. The contribution lies in offering a systematic approach to aligning overlapping areas between guidelines and frameworks, a gap that previous studies have not explored in depth. Based on observation of the different guidelines, regulatory decisions and enforcement are often left to national or regional authorities (see appendix A, table 1 for more detailed assessment), while there are also international routes for approval of pharmaceuticals. This leads to potential alternative routes for market approval that facilitate minimal compliance as there is no clear assignment of responsibility regarding environmental considerations beyond the bare minimum, even if some structure exists at national or regional level.

In comparison, the sustainability guidelines with applicability to pharmaceutical development, also described in table 3 and in detail in appendix A table 2, are not necessarily specific to pharmaceutical development. These guidelines cover a wide range of principles and standards aimed at promoting environmental sustainability across various industries, including but not specific to the pharmaceutical industry. Most guidelines and standards are formulated by organisations such as the United Nations (UN), the Global Reporting Initiative (GRI), and the International Organization for Standardization (ISO), with documents like ISO 14001 (Environmental Management Systems) being particularly relevant as most guidelines for pharmacy are centred around management aspects, often focused on quality, efficacy, and safety.

Unlike pharmaceutical-specific guidelines, sustainability guidelines offer a more comprehensive approach to environmental issues, addressing aspects such as resource efficiency, waste management, and pollution prevention. However, the challenge lies in their broad applicability, which often leads to a lack of specificity when applied to the pharmaceutical sector. While these guidelines provide a robust framework for environmental management, they may not fully account for the unique challenges associated with pharmaceutical development, such as the environmental impact beyond that of active pharmaceutical ingredients (APIs) (Becker et al. 2022) or the life cycle management of pharmaceutical products. Also, due to the complexity and variety of regulatory literature required to navigate to find what is applicable in practice to pharmaceuticals, this decreases transparency. This is caused by the fact there are guidelines and standards for pharmaceuticals at global, international, and regional levels, each which are often derived from guidelines at a different level and there is also interaction between some guidelines, on top of that there can be a significant time lag in updates between guidelines. Key findings identified after comparison between guidelines, frameworks, and literature, are described here.

Key Findings from Guidelines and Supporting Literature

Some of the key findings based on the guidelines and frameworks with additional support using literature sources are:

1. International and global guidelines have significant time lag and can use standards that are even more outdated, for example ICH Q7 (EMA, 2000) has not been updated since its publication 24 years ago. Another example is ICH Q10 (EMA, 2008) was last updated in 2014 and currently legally effective, while it still uses the ISO 9000:2005 standard which has been replaced in 2015 by ISO 9000:2015. (ISO, 2015a) This means that besides the guideline itself being 10 years old, the actual time lag with the standard is 19 years behind the present. As several other guidelines and frameworks build upon the ICH guidelines it was observed that no additional changes or mentions are made, which implies these problems are most likely inherited when adopted elsewhere, with the rapid pace of pharmaceutical development it can be clearly stated the pharmaceutical guidelines (at least at international and global level) are insufficiently adaptable to keep up with rapid drug development.

2. There are guidelines and frameworks with significant potential for application to pharmaceuticals and their development already, but nearly all of these are not sufficiently applicable to pharmaceuticals yet without significant adaptation. For example guidelines and frameworks specific for chemicals, their manufacturing, and their waste management towards being more environmentally sustainable such as the SSbD framework (EC et al., 2022a; EC et al., 2022b) and the green chemistry principles(EPA, 2013) and green manufacturing, but it is not sufficiently applicable to pharmaceuticals yet. There are ongoing efforts to adapt frameworks and some cases where frameworks can be partially applied to waste and materials, but one aspect that makes this complicated is the need for a more clear set of indicators specific for pharmaceuticals (Becker et al., 2022;) also to better detect or monitor pharmaceuticals in the environment such as ground water, currently only the environmental risk assessment (ERA) (EMA, 2024a) focused on active pharmaceutical substances ending up in the environment directly (the specific information requirements for the ERA are in appendix A, table 1). This is also related to antimicrobial resistance (AMR) (Davies et al., 2006) and relevant as it is not clear how pharmaceuticals can impact the environment after being metabolised and small concentrations still end up in the environment this way and through traces from packaging or use (Fatima et al., 2024; Daughton & Ruhoy, 2009; Ashiwaju et al, 2023).

3. There appear to be significant efforts and willingness in both researchers and pharmaceutical practitioners to improve environmental sustainability, also in pharmaceutical development. Interview 2 mentions environmental sustainability is becoming a more regular agenda point during congresses which also indicates the growing interest to become more environmentally sustainable in the pharmaceutical industry, but that pharmacy practitioners also have insufficient information to implement changes directly. Meanwhile interview 3 mentions that environmental researchers and LCA experts also want to map the environmental impacts of pharmaceutical manufacturing and operational practices (phase 2 and 3), but also due to intellectual property concerns more detailed data on this can be seen as a 'black box' for those not directly included in the process, or this data is just not available at all due to lack of case studies into environmental impact of operational practices and environmental impacts of the production process (Interview 2; Eskandari et al., 2022). There are some attempts to innovate or include environmental impacts or environmental sustainability policies and regulations by regulatory authorities as well, for example suggestions on how to improve some guidelines for

example ICH E6 (R3) (EMA, 1997) revision document published in 2023 (reference number EMA/553381/2023 Rev.1, more detail in Appendix A, table 1) proposes to include the following changes on drug development for next update: "Add environmental impact of trials (travel, shipments, waste, resources) to the guidelines" in several cases these initiatives focus on healthcare in general (Rijksoverheid, 2023) and some include roadmaps specific for pharmacy (FIP, 2022) or to implement (Mamiya et al., 2020) or adapt (FIP, 2021; IFPMA, 2024) sustainable development goals for pharmaceuticals, this does however remain a challenge (Silvestre, 2023) as currently in the SDGs drugs are only mentioned directly in goal 3; good health and wellbeing (Domingo-Echaburu et al., 2021). Out of 169 targets, the only targets that mention drugs/medication/pharmaceuticals are target 3.5 focused on reducing substance abuse and 3.b providing affordable access to medicines and vaccines. By focusing on development of better indicators for pharmaceuticals these can be integrated in existing guidelines and frameworks such as the SDGs..

At the same time some concerns arose from interviews (interview 1) which states that there are some guidelines but "nobody gets up for those, because there are no sanctions or controls" and compares it to 'statiegeld' which is a system of depositing empty drinking cans or bottles for a small cash return for example 5 or 10 euro cents per can. They explain it is similar because people still throw them away rather than make use of the deposit system because the process of depositing cans is very slow, there is a lack of motivation or pressure and people do not consider the environmental benefits or money worth their time, while it does provide a benefit for those that were already looking for ways to be more environmentally friendly. Also mentioned in interview 2, when the costs of for example wages or operating costs are higher than the returns from more environmentally friendly alternatives this becomes a financial barrier to adopt more sustainable practices. The time lag in pharmaceutical guidelines has a similar effect, that in combination with lack of enforcement of environmental considerations in many cases limits innovation and initiatives and maintains the status quo around minimal compliance with regulations. Interview 1 also mentioned 'not in my backyard' for comparison that even if people state an interest in improvements this often stops when it requires them to take action, which can be applicable when commercial interests of companies are involved.

4. Another critical finding is the need to consider the full life cycle of pharmaceutical products during development. In several guidelines such as ICH life cycle is mentioned but not from an environmental perspective but often management perspective. This study emphasises that environmental sustainability should be integrated from the earliest stages of product design, including considerations for packaging and waste reduction (Haleem et al., 2015; Interview 1; Interview 2; Interview 3). Life cycle assessment (LCA) can play a vital role in identifying potential environmental impacts and exploring alternatives that minimise waste and resource use throughout the product's life (Chen, Z. et al., 2024; Fatima et al., 2024). This approach aligns with broader sustainability practices but requires more specific application within the pharmaceutical industry. Identified literature on LCA is mentioned in more detail in 4.2.2 but also a key theme across the full study due to the relevance to the study context.

4.2.2 Current State of Environmental Sustainability in Pharmaceutical Development

Environmental sustainability has become an increasingly important topic across various industries, driven by global commitments such as the Paris Agreement of 2015 (UN, 2015), which emphasised the need for all sectors to reduce their carbon footprint and environmental impact (Dong & Hauschild, 2017; Azim & Hasan, 2013). This chapter aims to address the second sub-question "**To what extent are sustainable research practices considered in drug development?**"

A significant portion of the literature identified in 4.1 discusses environmental sustainability through guidelines, frameworks, and regulations, including the application of life cycle assessments (LCA), and the complexity of pharmaceutical waste management in terms of recycling or reuse (McRae et al., 2021). This section primarily builds on 4.1 with more specific focus on articles and trends in literature.

Thematic trends from literature on sustainable practices and materials are shown in table 4. These literature findings highlight shifts in industry practice towards more environmentally sustainable considerations. Earlier sources focus more on foundational guidelines, such as the ICH Q7 for Good manufacturing practice (GMP) (EMA, 2000) and ICH Q12 for life cycle management (EMA, 2020) without any significant contributions into environmental considerations, these persist regardless of time period, and are more specific to guidelines.

Table 4. Thematic trends on sustainability topics based on frequency of key terms in literature. Thematic trends based on publication dates show common topics related to material use and environmental sustainability, these sources do not include guidelines or frameworks. The sources can overlap in topics, however the total of unique sources is 26.

Key topics	Total sources	Main observation	Sources
'Green(er) chemistry, synthesis, and manufacturing.	11	7 out of 11 sources on this are from 2020> with the remaining 4 closer to 2015 than 2020.	(Agbenyega, 2022; Becker et al., 2022; Fatima et al., 2024; Kaylor, 2023; Lau, 2016; Milanesi et al., 2020; Mishra et al., 2021; Moermond et al., 2022; Soete et al., 2017; EPA, 2013; Larsson , 2014).
Biodegradable or more sustainable packaging, and recycling options	8	Another large portion of sustainability literature is on with 7 out of 8 sources	(Ashiwaju et al., 2023; WEF, 2022; Donyai et al., 2021; Holt, 2018; Kaylor, 2023; Milanesi et

for medicinal packaging.		being 2020> The remaining source 2015>	al., 2020; Nieminen et al., 2020; Noori et al., 2020)
Related to LCA	10	Sources related to LCA are diverse and overlap significantly with other key topics. These are described in more detail in the text.	(Dong & Hauschild, 2017; EPD International 2024a; Hauschild, 2018; Jacquemin et al., 2012; Ashiwaju et al., 2023; Becker et al., 2022; Chen, Z. et al., 2024; Emara et al., 2018; EC et al., 2022b; Siegert et al., 2019; Ögmundarson et al., 2020)

Regarding life cycle assessment (LCA) across several guidelines 'life cycle management' is mentioned, however this is not from an environmental perspective like LCA. Specific literature identified in 4.1 regarding LCA is rather diverse, with 10 different sources identified, some are sources specific to LCA and for example indicators for environmental sustainability or generic environmental sustainability in industry (4) (Dong & Hauschild, 2017; EPD International 2024a; Hauschild, 2018; Jacquemin et al., 2012) some focus packaging of pharmaceuticals (Ashiwaju et al., 2023) while some focus specifically on LCA in context of (bio)chemicals and/or pharmaceuticals **(6 sources) which are the most relevant to this thesis** (Becker et al., 2022; Chen, Z. et al., 2024; Emara et al., 2018; EC et al., 2022b; Siegert et al., 2019; Ögmundarson et al., 2020) For example, Becker et al. (2022) and Chen, Z. et al. (2024) examine the role of sustainability in pharmaceutical production, highlighting both achievements and areas needing further improvement, such as the need for harmonised LCA methodologies specifically for pharmaceuticals, and the lack of databases on pharmaceuticals suitable for LCA.

4.3 Areas of improvement.

To briefly describe the content in this subchapter, areas of improvement in pharmaceutical development and operations identified during the literature study in 4.1 are described here. It includes sections focusing on identified challenges (problems, obstacles, and barriers etc) in 4.3.1 and opportunities (recommendations, solutions, and strategies etc) in 4.3.2, the identified challenges and opportunities from literature are not necessarily limited specifically to drug development and/or environmental sustainability but the focus is on problems that are specific to, or strongly impact environmental sustainability in pharmaceutical development in line with the scope of this study. This also aims to address the third sub-question "**What is required to**

better incorporate environmentally sustainable methods in drug development and operational practices?"
This chapter focuses more on specific examples from literature, while supplementing them with expert interviews and additional literature. Recommendations based on overarching themes, problems, and solutions are described in 4.4.

4.3.1 Challenges

This section identifies several key challenges specific to environmental sustainability in pharmaceutical development and operations, which will also be addressed in 4.3.2 with more specific solutions. The integration of environmental sustainability within pharmaceutical development and operations remains complex, as already identified in 4.2.1 the regulatory framework and existing guidelines for pharmaceutical development are outdated to some extent while being interconnected on national, regional, international, and global levels. This can also contribute to the system being resistant to changes (Silvestre, 2023; Kittery & Miettinen , 2023) as implementation of changes would require other guidelines to adapt to the change as well, based on interview 1 this can play a role when there are many stakeholders that benefit or profit from the current state as these might prefer keeping the current system. The complexity and diversity of regulations and for example the option to either get market approval at the EU level (EC, 2024d) or at national level while there can be overlapping and sometimes contradictory regulations at the global, international, and regional levels creates confusion and operational inefficiencies (Glavič & Lukman, 2007; Hay et al., 2014; Ashiwaju et al., 2023) making it difficult for companies to navigate and comply with them effectively. This regulatory complexity can deter businesses from pursuing sustainability initiatives, especially in the absence of strong economic incentives or clear penalties for non-compliance (Hay et al., 2014; Domingo-Echaburu, S, 2021). There are also cases of market failure regarding pharmaceuticals due to a competitive market linked to patents and intellectual property legislation, and financially strong competitors, informed decisions on environmentally sustainable options also becomes harder (Al-Awamleh et al., 2022).

Some additional challenges specific to environmental sustainability in pharmaceutical development is the need for industry-specific sustainability guidelines that address the unique environmental challenges of pharmaceutical development, such as managing the ecological footprint of APIs, reducing waste and emissions, and enhancing resource efficiency throughout the drug life cycle. The siloed nature of academic research means that environmental scientists, chemists, and pharmaceutical researchers often work in isolation, rather than combining their expertise to develop more sustainable pharmaceutical processes (Crespo-Gonzalez et al., 2020). This lack of collaboration extends to the interaction between academia and industry, where the potential for practical application of sustainable research is often not fully realised in pharmacy (Hay et al., 2014) this 'disconnect' is also noticeable when comparing the pharmacy guidelines with the sustainability guidelines as these seem to have been developed to be more independent from each other. As mentioned in interview 3, there can also be many different steps, sometimes up to 50 during drug production, and combined with complex terminology

associated with some of these processes and chemical reactions it can be complicated for researchers outside the field to navigate pharmaceutical literature due to complex terminology (Jones et al., 2022).

Additionally, financial and technological concerns also play a significant role in strategies and decision making in pharmaceutical development. As stated by Schuhmacher et al., (2016) “New drugs serving unmet medical needs are one of the key value drivers of research-based pharmaceutical companies” however although this fits in with sustainability, in some cases less financially strong stakeholders or developing countries might not have the option to choose for more environmentally sustainable alternatives when these have increased costs, either in operational practices or because it requires a higher level of technology and infrastructure (Jamwal et al., 2021; Narayana et al., 2012), these issues can be present at both corporate level or national level (Danzon, 2014). For the same reason pharmaceutical development favours development of medication that is either more likely to succeed in approval or has a lower investment cost, or is more profitable (Henry & Lexchin , 2002). As mentioned in interview 2 and by (Hay et al., 2014) the price of medication plays a significant role with for example oncolytic medication (cancer medication and for example chemotherapy) being among the most expensive type of medication it has a high initial (early stage) approval rate but a lower chance of reaching market approval which means high investment cost and high risk.

Based on operational practices by practitioners (pharmacists and other healthcare providers) at the consumer side identified through interview 1 and interview 2, bulk manufacturing, shipping, and packaging can lead to increased waste downstream as medication needs to be repackaged in a way it can be provided to the consumers, this can mean over the total life cycle of medication, bulk production and packaging can lead to increased negative impact for the full life cycle. Another obstacle related to this for stakeholders is the concern that reducing medicinal waste leads to a paradox that this might increase the carbon footprint of production, this also applies to the potential reuse of medication with the requirement that reuse must have a lower environmental impact than potential created waste or impact if simply unused and disposed of (Donyai et al., 2021; Paut Kusturica et al., 2017; McRae et al., 2021). This can again also play a role regarding financial concerns with medication that is cheaper to produce than to potentially recycle, for expensive medication like oncolytics this is however clearly beneficial, this can be interpreted as a challenge regarding feasibility of reuse or recycling, these considerations can provide additional insight during drug development.

A lack of awareness and expertise among pharmaceutical professionals regarding environmental sustainability, can also hinder the industry's ability to adopt more sustainable practices. For example the RIVM. (2016) tries to address these by increasing practitioners' awareness regarding the impacts of pharmaceutical waste, how to reduce waste during operational practices, and how to better manage pharmaceutical waste.

4.3.2 Opportunities

In this section opportunities are described based on the identified challenges, these are mostly based on literature but also include additions based on cross-literature findings.
Connecting this section back to the different challenges identified in 4.3.1, regulatory authorities at international and global level can improve their collaboration with research institutions and other stakeholders at national and corporate levels to create a more comprehensive oversight of requirements between the different levels (Kaylor, 2023; Toklu & Hussain, 2013) additionally, to provide a counter argument regarding implementation of changes requiring other guidelines to adapt to the change as well, this is also an opportunity as this can also be used to push more environmentally sustainable practices through to other guidelines.

Interview 2 also mentions operational practices aimed at reducing waste specifically for health care providers, oncologists (those that administer oncolytics), and other practitioners in hospitals or other healthcare environments. It also mentions practices regarding dose bending (always round down) and dose rounding (focused on specific dosages) and trying to avoid having to open a new container when only 5% of the contents is needed and the rest would need to be discarded, as the price of one dosage container for oncolytics can be several thousand euros. The third practice it mentions is vial sharing, where multiple patients receive their treatment at the same time to avoid having leftover medication, interview 2 mentions a specific example where in some cases different dosages can have the same price which does not promote sustainable practices and can increase waste unnecessarily.
A decision by the hospital and associated pharmacies from interview 2 in switching to 100mg dosages of oncolytics rather than 500mg dosage reduced waste by 80% in the entire region for one specific type of oncology medication. These operational practices in oncology settings highlight how sustainability can be integrated into drug administration, providing practical insights that can be applied to broader pharmaceutical development. By considering sustainability at the design and dosage level, as emphasised in Interview 2, this research finding offers a clear recommendation for reducing waste in pharmaceutical practices, which aligns with the overall goal of enhancing environmental sustainability in pharmaceutical development.
This also highlights the importance to include considerations during the design and development of medication to provide dosages more tailored to the specific needs of patients. Following up on this, interview 2 stated that in metrics this meant 1 ton euro's every 8 months is wasted less due to the application of the specific oncology medication, and that in theory they could also translate this to something like carbon footprint to get a comparable metric, however this order of magnitude is unknown so money savings was used as metric, because there is not enough knowledge about environmental indicators or terms used within the pharmaceutical industry, as for example carbon footprint is relatively new in pharmacy or healthcare and information is usually combined for different areas (HCWH et al., 2019) , it does not say much yet as there is no comparison because there is no clear scale for comparison, practitioners and researchers still need to better develop indicators for this. This type of information can however

be relevant for LCA researchers as mentioned in interview 3 to develop better indicators on environmental performance.

Linking this back to the initial problems regarding the need for industry-specific sustainability guidelines that address the unique environmental challenges of pharmaceutical development, the existing pharmaceutical guidelines do provide requirements for life cycle management, though not from an environmental perspective. This creates an opportunity to directly integrate sustainability through tailored standards or indicators by connecting guidelines on life cycle management to LCA. Specifically as identified in section 4.2.2 there are existing indicators and frameworks for chemicals already partially applicable to pharmaceuticals, as well as some LCA methodology for both chemicals and pharmaceuticals (Chen, Z. et al., 2024) which has potential to be directly connected to life cycle analysis in pharmacy guidelines. The different sources do state more comprehensive environmental indicators for pharmaceuticals need to be developed, interview 3 is used to provide a more comprehensive overview of ongoing developments, in interview 3 it is stated that currently studies are ongoing on electricity/energy consumption and chemical consumption of specific equipment, this is one example of how to assess the environmental impact of operational practices and procedures.

Those are some of the main obstacles so far in current practices, as there is little information which is further backed by literature (Eskandari et al., 2022) stating indicators for lean manufacturing in pharmaceutical industry are also required (which to some extent is also relevant to indicators for LCA), and states significantly more operational studies need to be done as there is almost no information on them. This also brought to attention that in this study although there are some practical examples of sustainability guidelines and frameworks, few clear examples on practical application of specifically pharmaceutical (development) guidelines was observed in the current literature (Kumari et al., 2024) this information is expected to be more available at organisational or manufacturer levels which are outside the scope, however based on the current findings from literature this information might not be available at all (Eskandari et al., 2022).

According to Crespo-Gonzalez et al. (2021) sustainability should also be included better in pharmaceutical services. Going back to interview 3, ecotoxicity and human toxicity concerns matter a lot in the development of environmental indicators for pharmaceuticals. Most LCA studies (on pharmaceuticals) focus on single stages in LCA rather than the full cycle. As stated in the interview “From LCA practitioners point of view, they focus on the drug itself.” This also corresponds with the literature analysis so far, especially concerning the guidelines for pharmaceutical development. It is also mentioned there is lots of data missing that is required for a proper LCA due to how complicated drugs are, the amount of steps taken is too hard to track als there could be 50 steps, and biopharmaceuticals can be even more complex. Additionally it is currently hard to find a reliable database for LCA as the standard database mentioned (Ecoinvent) has insufficient information to map processes for pharmaceuticals. Even if LCA on the pharmaceuticals themselves is not possible yet with the current information, it is mentioned they can still include this in guidelines better for other aspects such as better monitoring of operational practices, and packaging (Siegert et al., 2019), and this could also

apply to other single use/disposable equipment, one goal identified for the Netherlands for example (Rijksoverheid, 2023) on more sustainable operational practices is switching to reusable equipment, with "The ambition is that at least 20% of (medical) devices will be reusable by 2026.".

Further linking the earlier literature from 4.2.2 on packaging, during drug development alternative types of packaging should already be considered. Especially with more focus towards more long term (environmental) sustainability, bioplastics do not rely on fossil fuels which are increasing in price overtime (Holt, 2018) in addition to considerations that although the initial materials for bioplastics and polymers (Nieminen et al., 2020) might have more initial cost compared to traditional packaging plastics and glass or metal, they have significantly lower operating costs due to less energy being required for processing the materials. Such considerations should be included in pharmaceutical development during design considerations before potential upscaling of manufacturing, as this provides a potential tradeoff in the long term regarding costs, this would also require more case studies into operational practices, for example as mentioned in interview 3 and by Eskandari et al., (2022) energy and chemical consumption by a factory.

4.4 Recommendations for Enhancing Environmental Sustainability in Pharmaceutical Development

Based on the analysis of the existing guidelines, frameworks, regulations, and standards in 4.2 and areas for improvement in 4.3 discussed in earlier sections, several core elements and recommendations are identified for better integrating environmental sustainability in pharmaceutical development. These findings are used to answer the main research question "How can environmental sustainability be better incorporated in pharmaceutical development and operations?" These recommendations are built on the findings from the literature study, particularly the evaluation of challenges and opportunities, and build on the key themes observed, specifically related to guideline adaptability, operational inefficiencies, and sustainability practices. This chapter focuses on a holistic perspective rather than specific problems and the recommendations might not specifically state they are for environmental sustainability in pharmaceutical development. However, the recommendations were determined to be the most essential following steps to facilitate better incorporation of environmental sustainability in pharmaceutical development.

1. Harmonisation of Pharmaceutical Guidelines and Standards

A recurrent issue identified across sections 4.2 and 4.3 is the outdated and inflexible nature of international and global guidelines for pharmacy, in particular the ICH guidelines being the most practical and extensive guidelines for pharmaceutical development, yet some contain sections and standards that have not been updated significantly in years or even decades in some cases. These outdated standards impede progress toward innovative technology and sustainability by relying on practices that do not reflect modern environmental concerns and

efforts, or advancements in green chemistry and research. Furthermore, because many pharmaceutical frameworks are derived from these guidelines in most cases problems are inherited. Their lack of timely updates perpetuates the inflexibility of sustainability efforts across the entire sector.

Recommendation:
First of all it is recommended to include a periodic review process for updating guidelines similar to how the ISO updates most standards every 5 years, particularly global ones like the ICH, to ensure alignment with the latest developments in research as well as environmental standards. Additionally it is recommended to establish mechanisms for international regulatory bodies to regularly consult with experts in (environmental) sustainability, and life cycle assessment (LCA) which would allow guidelines to evolve more in line with scientific advancements and broader developments in chemistry and healthcare practices. The development of harmonised LCA methodologies for pharmaceuticals could provide a vital role to create a uniform system for assessing environmental impacts in the pharmaceutical sector. Better cooperation with entities on a national level to increase transparency across regions is also advised. Alternatively, within the guidelines good manufacturing practices (GMP) are the most consistent as a requirement, if the guidelines for GMP were to include environmental sustainability more explicitly this could have a significant impact on the entire pharmacy sector without having to adapt all other guidelines directly. Additionally most of the ICH and pharmacy guidelines have a list of required roles to be included in most management guidelines, directly including environmental scientists in this section to include them in the decision making process can also provide a clear way to shift towards more environmentally sustainable practices.

2. Integration of Environmental Indicators in Drug Development

While there are existing sustainability guidelines for the chemical industry (e.g., SSbD framework by the EU and green chemistry principles by the EPA), these are not yet sufficiently tailored for the pharmaceutical sector. Currently, drug development often overlooks the post-market approval environmental impact of pharmaceuticals, especially in terms of waste management and API (Active Pharmaceutical Ingredient) residues in water systems which do have to include an environmental risk assessment (ERA) but only specific for the active pharmaceutical components. Moreover, although life cycle management is mentioned in pharmaceutical guidelines, it is not from an environmental perspective, which creates a significant gap in addressing the full environmental life cycle of drugs. These aspects also based on literature indicate that pharmaceutical development is more driven to get medication onto the market quickly to reduce development costs and increase profits, while the current pharmacy guidelines do not provide any incentive or motivation for organisations to go beyond the bare minimum for compliance with regulations in most cases.

Recommendation:
Develop industry-specific environmental indicators that address the unique challenges of pharmaceutical development. These could focus on areas such as the ecotoxicity of APIs, energy

consumption in manufacturing, and waste management practices from a design perspective during development. For example, adapting the LCA methodology to pharmaceuticals should involve comprehensive environmental information to track the impact of pharmaceutical production, distribution, and post-consumer waste. Additionally, it is important to include sustainability metrics in existing guidelines for drug approval. Metrics like carbon footprint, water usage, and resource efficiency could be integrated into pharmaceutical life cycle management frameworks to ensure that drugs not only meet efficacy and safety standards but also minimise environmental harm throughout their life cycle.
More specific examples would include improvements on the environmental risk assessment (ERA). The ERA currently requires specific details on 1. Expected environmental exposure 2. If components are non-natural (naturally occurring), 3. If they are biodegradable, and 4. It is also checked if there is an existing ERA for the active substance. Expanding the ERA for example with indicators more specific for environmental impacts using point 2 and 3 across the full life cycle based on active substances can be a systematic way to improve regulations on pharmaceutical wastewater as well (RIVM, 2016; RIVM, 2022a; RIVM). These can help provide more details on expected environmental exposure for example with detection of trace pharmaceuticals in (waste) water and sewage, and could be beneficial for identifying specific waste streams and targets for filtering or prevention.

For other impacts related to energy, water, and material consumption, the production steps of the pharmaceuticals and operational practices in manufacturing can provide relevant information for LCA by adding monitoring tools to specific equipment and facilities. These can be directly used with sustainability metrics to assess considerations regarding energy, water, and materials holistically on a detailed level, rather than grouping these as a 'black box' with only input and output. For example in packaging considerations this allows comparing savings on energy or water consumption between different materials and helps make design choices during the design part of development on operating practices before upscaling. This can facilitate a shift towards long term over short term benefits from the perspective of the full life cycle. This can be integrated into the current guidelines on life cycle management.

3. Cross-Sector Collaboration and Knowledge Exchange

One of the key barriers identified is the segregated nature of pharmaceutical research and the lack of transparency for those outside (and inside) the field of pharmacy due to the complexity and interactive elements and intellectual property concerns. This leads to a lack of integration of sustainability expertise in drug development. Furthermore, as highlighted in the challenges in 4.3.1, there is a disconnect between academia and industry, with slow progress towards combining sustainable research practices and modern environmental practices into practical pharmaceutical applications. The transition of innovations from theory to practice in the pharmaceutical industry is slow as the regulatory aspects make it complicated to adjust existing and proven manufacturing methods due to the rigorous requirements, and manufacturing methods can also be patented or not publicly disclosed.
Based on interview 2 and 3 more transparency and discussion of operational strategies between

researchers from both pharmacy and sustainability and pharmacy practitioners, can directly affect adoption of sustainable practices during operational practices and drug development. Interview 2 mentions a clear example where direct caregivers and those administering and prescribing medication communicated more directly with patients about remaining dosages rather than just providing a full prescription at set intervals, reducing waste from overprescription. The interview mentions this example was brought up during the European Congress of Clinical Pharmacology and Therapeutia (EACPT), a congress for pharmacy practitioners, which raised the concern about the cost of extra work hours by caregivers compared to the price savings from reduced prescription waste. They clearly stated for oncolytics as the medication costs thousands of Euros the benefits clearly outweighed the costs but for more regular medication it might not be cost effective and that this requires more research.

Recommendation:
Based on information from interviews and literature, encourage cross-disciplinary collaborations by creating platforms where environmental scientists, chemists, and pharmaceutical researchers can share knowledge and develop joint projects that incorporate sustainability from the early stages of drug development. Regulatory bodies should also collaborate with academic institutions to pilot programs that integrate sustainability research into practical applications for pharmaceuticals, such as the adoption of biodegradable packaging materials or more energy-efficient manufacturing processes.

Additionally, public-private partnerships can serve as a model for integrating sustainability across the sector. Initiatives like the Green Chemistry Initiative for Sustainable Development Goals (SDGs) could benefit from better collaboration with pharmaceutical companies to apply their principles to pharmaceutical operations as well, although some adapted versions of the SDGs for pharmaceuticals were identified, developing clear targets for pharmaceuticals to be included in the existing SDG framework would potentially be more impactful. Expert researchers in environmental sustainability and LCA could assist with developing better reference scales for the environmental impacts and for example carbon footprint of waste reduction as mentioned in interview 2, as there are financial numbers and metrics as well as values on waste reduction and cost savings, but without a scale or reference these say nothing on their own. Collaboration to develop a clear comparison for such metrics will provide a way to quantitatively evaluate impacts beyond just the financial savings, and provide better comparison information in a broader sustainability context, such as the planetary boundaries.

4. Addressing Regulatory Complexity and Streamlining Approvals

As identified in the challenges in 4.3.1, the regulatory landscape is fragmented, with overlapping or conflicting regulations at national, regional, and global levels. This complexity creates operational inefficiencies, making it difficult for companies to comply with environmental standards while also meeting pharmaceutical regulatory requirements. The option to pursue market approval at either the EU or national level, compounded by differing regulations, adds to this confusion and may deter companies from adopting more

environmentally sustainable practices and only focus on minimal compliance also mentioned in interview 1. There are additional concerns when considering developing countries and aspects related to minimum costs and requirements relating to the technological infrastructure. In some cases there might not be clear regulations on a national level either for pharmaceutical development or they can potentially be circumvented. As mentioned in more detail in section 4.2.2, the current regulatory structure only includes life cycle management and a single environmental risk assessment for the API. Life cycle assessments (LCA) are currently applied inconsistently and not required at international and global level, while often only focusing on single phases or processes according to interview 3. Often this is also in the post-market phase rather than during early-stage R&D.

Recommendation:
To resolve the fragmented regulatory landscape, regulatory bodies should work towards streamlining approval processes by creating a unified framework that includes both pharmaceutical safety and environmental sustainability criteria. This could involve combining approvals for pharmaceutical products with mandatory environmental assessments that ensure drugs are developed with sustainability in mind (beyond just an ERA of the medication). Such a system could be modelled on the **EU's Strategic Environmental Assessment (SEA) Directive**, which mandates environmental impact assessments for large-scale projects, applied to pharmaceutical innovations and the stages of drug development. This is not just focused on decisions but also includes considerations regarding the process. The SEA requires public consultation and participation, in the case of pharmaceutical development this could include environmental sustainability researchers and experts, confidential information can be handled with the use of NDAs. The SEA also requires more detailed consideration and study of alternatives, which is an important aspect that is often not given enough attention in pharmaceutical development due to strong preference for traditional and common practices. This also overlaps with some of the recommendations for guideline revisions suggestions as mentioned in 4.2.1 to include more information on impacts of resource acquisition, transport, and energy of specific trials rather than the full process alone.

5. Incentivizing Sustainable Practices

A common theme across the literature is that companies face limited economic incentives to pursue sustainability, especially when compliance with environmental regulations does not lead to immediate financial benefits and potential increased cost. Moreover, the lack of strong enforcement mechanisms for environmental guidelines further weakens the push for innovation and adoption of greener practices. As enforcement of guidelines is relatively weak and mainly just compliance based, incentives are more likely to yield results. Several examples related to this for example from interview 1 and 2 also mentioned in 4.2.1 that incentives rather than enforcement mainly depend on voluntary implementation such as with the statiegeld example. There is a growing interest as identified in literature especially for manufacturers to improve environmental performance, but stronger incentives to make sustainable alternatives

more financially competitive is more reliable to facilitate innovation. This would also provide motivation to go beyond minimal compliance, which would be required if the pharmaceutical industry is going to attempt to achieve carbon neutrality by 2030 based on the European green deals.

Recommendation:
Introduce economic incentives for pharmaceutical companies to adopt sustainable practices. This could take the form of tax breaks, subsidies, or fast-tracked approvals for drugs developed using sustainable methods and broader environmental assessments. In regions where sustainability standards are less strict, incentivizing practices such as green manufacturing, renewable energy use, and reduced packaging waste by reducing costs would promote voluntary adherence to higher sustainability standards.

Incorporating eco-labeling for pharmaceuticals, similar to the system used for consumer goods, could also provide a market incentive by making it easier for consumers and healthcare providers to choose more environmentally friendly products, this is also relevant as literature also mentions lack of awareness while consumers choices can be a significant driver towards sustainable alternatives when they can make more informed decisions. In addition to this, regulatory authorities should make more specific and clearer goals for improving environmental sustainability within a certain time range by also setting clearer terms for transitioning from incentives and motivational approaches towards more enforcement measures to ensure the pharmaceutical industry transitions overtime rather than maintaining the current state.

6. Improving Data Availability and Technological Adoption

Finally, one of the most pressing challenges identified is the lack of comprehensive environmental data on pharmaceuticals. The absence of reliable databases hinders the ability to conduct complete LCAs, especially for biopharmaceuticals, which are even more complex to track through multiple life cycle stages. This is separate from the indicators, but still relates to metrics also mentioned in interviews, by measuring the amount of medication in mg or ml for example the quantified information can indicate how much medication is left as waste, this can then be connected to other metrics such as CO2 equivalent. This example is based on interviews 2 and 3. Often it is just converted to money as a proxy because there is insufficient information on indicators as well or lack of a scale to compare it to. At present without more comprehensive information even if the carbon footprint is calculated, without a scale or reference it is just a number that says almost nothing.

Recommendation:
There needs to be significant investment in the development of data infrastructure for pharmaceuticals. This includes expanding LCA databases to capture the full environmental impact of drug production, transportation, and disposal during the different drug development phases. This allows for better evaluation of alternatives in operational practices and packaging in the long term. Developing digital tools that allow for the real-time monitoring of

environmental indicators, such as carbon emissions or water usage, would also help pharmaceutical companies track their progress in meeting sustainability targets during phase 2 and 3. Measurements of energy, water, and chemical use during operations are also relevant but currently not very present in literature yet, interviews also mention this needs to be monitored more. A more specific recommendation based on information from LCA literature and interviews is for researchers to focus on improving databases for LCA such as Ecoinvent, together with information from databases like ChEMBL and PubChem and similar databases on chemicals and medication, data for specific pharmaceuticals and their active substances can already be found due to unique registry numbers. Expanding the information in the chemical database with environmental impact data or adding detailed impacts derived from processes during drug development to ecoinvent can provide valuable insights during phase 2 and 3 into how operational practices can be adjusted to lower environmental impacts, before these get upscaled for mass production after market approval.

5. Discussion

This study explored how environmental sustainability can be better integrated into pharmaceutical development by examining the current state of guidelines, frameworks, and operational practices. The findings indicate significant gaps in existing guidelines, particularly

in their adaptability to the rapid pace of pharmaceutical innovation and their lack of focus on the full life cycle of products. The study also highlighted the potential for collaboration between stakeholders to develop specific environmental impact indicators and identified operational practices that could enhance sustainability. However, the study also revealed limitations in current research and the need for more regulatory and financial support to drive sustainable practices in the industry.

5.1 Interpretation and Discussion of Results

This section describes additional interpretation and discussion of results, the focus in this section is emphasis on results. This research advances the field of industrial ecology and pharmacy by offering a comprehensive comparative analysis between pharmaceutical and environmental guidelines, identifying the disconnects and synergies between these frameworks. By doing so, it not only addresses the literature gap but also contributes recommendations that can be adopted by various stakeholders to improve sustainability across the drug development lifecycle, from research to manufacturing and as well as post-market activities. The following sections discuss specific recommendations and results in more detail.

Collaboration for Environmental Impact Indicators

This research confirms the critical need for collaborative efforts among regulatory bodies, academic institutions, and pharmaceutical companies to develop environmental impact indicators specific to pharmaceuticals. Collaboration can start at the level of current research initiatives and extend to policy-making. The main contribution of this study is emphasis on the fact that the pharmaceutical industry lacks standardised environmental indicators despite the clear environmental risks, and the existing fragmentation in research and practice makes progress slow. Becker et al. (2022) and Dong & Hauschild. (2017) contributes to this conclusion, but it is important to state there is a clear necessity for a framework that allows stakeholders to integrate these indicators into drug development processes effectively. A structured, collaborative approach between the mentioned stakeholders could close the gap that currently is not sufficiently covered by the existing environmental risk assessment for pharmaceuticals, especially regarding specific APIs and their life cycle impacts.

Inadequate Adaptation of Guidelines

One of the most significant insights is how outdated guidelines and standards such as ICH Q7 (EMA, 2000) or the reliance on obsolete standards like ISO 9000:2005 hinder the pharmaceutical industry from adopting environmentally sustainable practices. While the literature acknowledges the need for updated frameworks, this analysis highlights the inflexibility of regulatory bodies as a key barrier to sustainable pharmaceutical development. By stressing the time lag in updating these standards (as noted in the ICH Q10 example), this research pinpoints a crucial area where environmental sustainability can be embedded directly into guideline updates. This analysis is specific and novel because it not only critiques the outdated nature of the guidelines but also emphasises the importance of dynamic regulatory processes to adapt to

rapid changes in pharmaceutical development.
One reason for the persistence of outdated guidelines, as highlighted in Section 4.3.1, is the high cost associated with regulatory overhauls and adapting to newer sustainability frameworks. Implementing updated guidelines using for example the SSbD framework (EC et al., 2022a) or Green Chemistry principles (EPA, 2013) specifically adapted to pharmaceuticals would require significant investment in research, operational restructuring, and employee training, which many companies may view as a financial burden. Moreover, political drivers and industry lobbying often favour maintaining the status quo, particularly when the current regulations allow companies to operate without making major investments without clear financial returns, like in the case of environmental concerns. In many cases, the status quo is also maintained due to the long approval cycles for new regulatory measures, where currently pharmaceutical companies prioritise short-term profitability over long-term sustainability, as mentioned in Section 4.3.2.

Life Cycle Considerations in Pharmaceutical Development

Suggestions to better include Life Cycle Assessments (LCA) practices goes beyond the current application of life cycle management in pharmaceutical guidelines, suggesting that environmental sustainability should be considered throughout the entire product life cycle, from design to disposal. The gap identified here is the lack of comprehensive LCA databases for pharmaceuticals, as current systems (e.g., Ecoinvent) are insufficient for mapping the complexity of pharmaceutical products (Chen, Z. et al., 2024). This contribution is key because it highlights the missing infrastructure for accurately measuring and mitigating the environmental impacts of drug development. Moreover, the findings emphasise that pharmaceutical development must evolve to incorporate environmentally specific LCAs rather than focusing solely on quality control. By proposing this shift, an attempt is made to directly address the research gap by suggesting that full life cycle monitoring could become an integral part of regulatory requirements, thus leading to more sustainable production processes.

Leveraging Operational Practices for Sustainability

The integration of indicators also for Lean Manufacturing into pharmaceutical operations represents a practical opportunity to enhance environmental sustainability, yet it is not thoroughly applied in the sector. This finding is valuable because it challenges the industry to rethink its current operational models. The emphasis on resource efficiency as a core aspect of Lean Manufacturing is directly linked to reducing environmental impact (Gupta & Jain, 2013). However, commercial pressures and drivers such as short-term profit focus deter companies from fully adopting these systems. At the same time considerations regarding more sustainable operational practices should be made (RPS, 2023; RPS, 2024; Holt, 2018; Nieminen et al., 2020)although there are very few studies into operational practices have been done so far (Eskandari et al., 2022; interview 3) and in general literature on practical application of guidelines also seems absent. One example specific for long term considerations is on non-traditional materials like bioplastics and polymers, although these have a slightly higher initial material cost, they require significantly less energy to process. This contributes to the ongoing

discussion on the long-term economic and environmental benefits of sustainability measures. By focusing on long-term value creation, companies can align their sustainability goals with profitability, thus overcoming the short-term focus that often dominates decision-making in the pharmaceutical sector. To enhance this point, regulatory bodies can provide more incentives for such practices through financial support programs or subsidies or eco-labels, thus creating a stronger incentive for pharmaceutical companies to adopt sustainability as a core operational principle.

Regulatory and Financial Support for Sustainability

A major insight from the study is the lack of regulatory enforcement and financial incentives to encourage sustainable practices within the pharmaceutical sector. This issue goes beyond compliance—it reflects the regulatory barriers that prevent companies from investing in environmentally friendly technologies. This analysis offers a specific insight: government intervention is necessary to create the economic conditions for sustainability (EC et al., 2022b). This is applicable to the pharmaceutical industry in general while it has the most impact on considerations during drug development regarding the design of the product (drug and packaging) and implementation of more environmentally sustainable operational practices. Furthermore, incentives or eco-labels can help with designing a regulatory framework not only to enforce compliance but also to reward innovation in sustainable development. The introduction of tax incentives, subsidies, and eco-certifications for pharmaceutical products could address the financial concerns currently preventing widespread adoption of green technologies and better inform consumers as well.

5.2 Implications

Implications for the Pharmaceutical Industry

The implications of this research are significant for both the pharmaceutical industry and environmental sustainability. One of the major implications is that the development of environmental impact indicators will enable more informed decision-making and environmental risk management. This study contributes a novel perspective by suggesting that the pharmaceutical industry needs to move beyond traditional safety and efficacy concerns and financial focus (Scherer, 2000) and incorporate environmental sustainability as a core part of the drug development process, rather than more reactive approaches commonly practised.
The implications for the industry are clear: without proactive and systematic integration of sustainability in guidelines and development, the pharmaceutical industry risks falling behind both regulatory expectations and consumer demands for greener products compared to other industries. The study also highlights the need for innovation in how companies approach product life cycle management, which can lead to operational improvements on environmental impact from a holistic perspective better including water and energy perspectives rather than only from a recourse and material perspective.

Implications for Sustainability in Pharmacy

This study adds depth to the existing literature on sustainability in pharmacy by emphasising the need for industry-specific guidelines that account for the unique environmental challenges of pharmaceutical development. Findings suggest that the pharmaceutical industry should not rely on generic sustainability frameworks; instead, tailored approaches are necessary to address the complex environmental footprint of pharmaceuticals, especially regarding the disposal of pharmaceuticals and post-consumer waste. Additionally, pharmaceutical development

Operational Strategies

From an operational standpoint, the research highlights several strategies that could significantly enhance sustainability efforts in practical application. The most pressing recommendation is the incorporation of environmental sustainability principles into GMP. Implementing sustainability within GMP could involve establishing cross-industry partnerships between pharmaceutical companies and regulatory bodies, as well as environmental researchers. For instance, pharmaceutical companies could collaborate with international regulatory agencies like the FDA and EMA to update existing GMP protocols, while also engaging environmental experts to integrate LCA and Lean Manufacturing principles, similar to how the SSbD framework in chemical industries was developed through cross-sector partnerships (Section 4.3.1). At a higher level, this could involve forming global working groups that include key stakeholders from regulatory agencies, industry leaders, and academic institutions to ensure the practical implementation of environmental sustainability goals. These working groups could be modelled after initiatives like the Green Chemistry Initiative, which fostered cross-collaboration between public and private sectors (section 4.1), or like the Eco-Pharmaco-Stewardship (EPS) initiative aimed at development of better tools for potential environmental risks and improved ERA (EFPIA, 2024).
As GMP is a globally mandated guideline, the addition of environmental metrics to GMP could drive industry-wide adoption of sustainable practices in a systematic way, rather than as a voluntary initiative like these 2 initiatives. Indicators for Lean Manufacturing principles and LCA methodologies, focusing on resource efficiency and waste reduction could provide a practical solution for pharmaceutical companies aiming to adopt environmental sustainability. Findings suggest that integrating these strategies into GMP will require a shift from a short-term profit driven mindset to one that prioritises long-term sustainability goals. However, this shift has the potential to yield significant financial benefits through cost savings and regulatory compliance in the long run for the industry as a whole.

5.3 Limitations and Future Research

This study has several limitations that impact the generalizability and robustness of its findings.

One significant limitation is the relatively narrow scope of stakeholder engagement. The study only contains three interviews and insufficient stakeholder perspectives from literature to properly support multiple stakeholder perspectives. Case studies on operations (Eskandari,

2023) or literature on stakeholder perspectives (Tietje & Brouder, 2009) are also lacking, which constrains the range of perspectives represented. A more extensive and diverse group of stakeholders from different fields such as regulatory bodies, academic researchers, industry professionals, and environmental agencies, would have provided a more nuanced understanding of the challenges and opportunities in integrating environmental sustainability into pharmaceutical development. For instance, engaging with government authorities and legislators could have offered deeper insights into regional policies and their practical application (Hardjono & de Klein, 2004; Dutch Ministry of Health, Welfare and Sport, 2020). Similarly, more input from academic researchers and academic institutions could have provided more information on state of the art ongoing innovations and educational initiatives as literature suggests this can be lacking in pharmacy education as well (Chen, E. Y. H. et al., 2023; APC, 2020). Discussions with manufacturers and practitioners working in development would have better captured the complexities of implementing sustainability practices in pharmaceutical R&D and production processes (Nieminen et al., 2020; Chen et al., 2024). A more focused study into more specific recommendations for certain groups of stakeholders in specific domains (governmental, business, academic) and case studies in specific regional or national structures would be good follow up on this study, as the level of detail in this study is limited to international or regional level.

Further research recommendations on this would be improved by collaboration between research institutions, corporations, and other organisations. Educational research is often more publicly accessible while corporate research is often more confidential, but has high potential for improvement by directly including researchers or specialists focusing on environmental sustainability aspects of drug development during the process as stated in interview 3 as well. Bridging this gap in data transparency could be achieved by facilitating the inclusion of educational researchers in corporate research using NDA's, or with dedicated job positions for environmental specialists in drug development.

Another limitation stems from the study's theoretical background, which was adapted to fit the diverse nature of the literature covered. While this provides a useful structure for the context at the foundation of the analysis and improves robustness of diverse findings, its application may not be entirely robust or reliable across all perspectives and applicability to specific regional examples can be limited. The perspectives to evaluate the business and social/governmental pillars were based on existing frameworks (Villanueva et al., 2024; James & Magee, 2016) that relies on domains instead of pillars of sustainability, but it may not fully account for the complexities of each domain, particularly in the rapidly evolving field of pharmaceutical development. This limitation suggests that more scientifically rigorous evaluations using domains or from the perspective of the environmental pillar, potentially including quantitative studies, could be better suited to specific areas identified for improvement, such as more focused studies on, and development of, environmental impact indicators and the practical application of guidelines in pharmaceutical settings which has strong potential for future research and more direct application of environmental sustainability in pharmacy.

The scope of the literature review is another notable limitation. The study focused primarily on widely applicable guidelines and frameworks for pharmaceutical development with some more specific focus on international scale, potentially overlooking those specific to certain regions, sectors, or types of pharmaceutical products. For example, national, corporate, or not included regional guidelines may offer unique insights into how environmental sustainability is addressed within different regulatory contexts as regulations and legislation are enforced on this level, yet these were not thoroughly explored due to their complexity and limited area of application found in academic literature specific for environmental sustainability (Sengar & Tripathy, 2012; EC et al., 2022a; ISO, 2023) more detailed research into regulations at the level of national regulatory organisations (Sengar & Tripathy, 2012) would be among the most useful to support the findings in this study.

Furthermore, the literature study due to its focus on information primarily found in the public domain for transparency may have missed less generalised or public guidelines and standards directly applicable to educational institutions and corporate practices, which are also mainly regulated on national, regional, or organisational level, where significant innovations and often early implementations of sustainability measures are occurring. This omission could lead to an incomplete understanding of the current state of environmental sustainability in pharmaceutical development at the organisational level. In a broader context, as the main focus in literature study was general applicable sustainability guidelines and guidelines specific for pharmaceutical development, some guidelines more focused on general healthcare practices with relevance to the scope might have been omitted due to narrowing the scope. The applicability of recommendations to guidelines and regulations outside the scope of this study needs evaluation on a per case basis as these are not uniformly defined.

Additionally, it is acknowledged that different guidelines and regulations mostly by the same authorities for medicinal products in veterinary use rather than for human use were observed during literature study. These were further excluded after brief comparison to the human equivalent; it is assumed recommendations are also applicable to medicinal products for veterinary use, sometimes it is even stated directly that guidelines or regulations apply to both, as there is overlap in generic guidelines and practices for pharmaceutical development.

6 Conclusions

The integration of environmental sustainability into pharmaceutical development requires a concerted effort from all stakeholders, supported by updated regulatory frameworks, industry-wide adoption of best practices, and a commitment to innovation. While the pharmaceutical industry has made strides in some areas, it lags behind other sectors in fully embracing sustainability. By adopting the strategies and recommendations outlined in this study, the

industry can align more closely with global sustainability goals, ensuring that future pharmaceutical development is both effective and environmentally responsible.

Focusing back on the initial research questions:
1. **What are the current regulations and guidelines for monitoring material use during drug development and operational practices?**
This study finds that while current pharmaceutical guidelines, such as ICH and WHO, rigorously address drug safety and efficacy, they lack explicit guidelines for environmental sustainability. There is minimal attention to life cycle management and other aspects from an environmental perspective, with gaps in material use and environmental impact monitoring that do not extend beyond the immediate safety concerns of the drugs. This is among the most important findings as it provides a way to connect environmental sustainability practices through LCA almost directly to the existing regulatory structure at global and international levels.

2. **To what extent are sustainable research practices considered in drug development?**
The study reveals that sustainable practices, such as green chemistry principles, sustainable design, and LCA, are applied in a limited capacity and mainly post-market. Although some recent efforts aim to integrate these practices earlier in the development process, this is not yet widely adopted, and most international and global guidelines do not mandate sustainability considerations in the design phase at all beyond the minimal environmental risk assessment. The chemical industry has more innovative practices towards sustainability which can potentially be adapted for pharmaceuticals but is not sufficiently done at present. Guidelines, practices, and operations for pharmaceutical development are far behind modern environmental concerns.

3. **What is required to better incorporate environmentally sustainable methods in drug development and operational practices?**
This research identifies the need for updated and harmonised guidelines that incorporate environmental impact indicators, life cycle assessments, and the integration of sustainability principles into GMP and drug development. Additionally, stronger collaboration between regulatory bodies, industry, and environmental scientists is essential for making significant progress towards overcoming some long standing barriers in the pharmaceutical industry.

In summary, when focusing on the main research question "H**ow can environmental sustainability be better incorporated in pharmaceutical development and operations?**"
The study concludes that environmental sustainability can be better integrated into pharmaceutical development through 1. The harmonisation of global pharmaceutical guidelines

with sustainability guidelines and national pharmacy regulations, and more regular updates considering innovative practices. 2. The establishment of more specific environmental impact indicators for pharmaceuticals, and establishing reference cases for environmental metrics 3. The incorporation of LCA methodology into life cycle management and early drug development stages including better monitoring of environmental impact from operations, and development of a database specific for environmental impacts from specific synthesis methods and active substances in pharmaceuticals. These recommendations can facilitate a systemic shift toward long term sustainability in pharmaceutical development.

References

The format used is American Psychology Association (APA) 7th edition.

Abraham, J. (2009). International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use. In C. Tietje & A. Brouder (Eds.), Handbook of Transnational Economic Governance Regimes (pp. 1041–1053). Brill | Nijhoff. https://doi.org/10.1163/ej.9789004163300.i-1081.897

Agbenyega, J. (2022). Green chemistry in the pharma industry: Sustainable pastures for those who innovate. CAS Division of the American Chemical Society. Retrieved 3 July 2024, from: https://www.cas.org/resources/cas-insights/green-chemistry-pharma-industry

Al-Awamleh, H., Alhalalmeh, M., Alatyat, Z., Saraireh, S., Akour, I., Alneimat, S., Alathamneh, F., Abu-Farha, Y., & Al-Hawary, S. (2022). The effect of green supply chain on sustainability: Evidence from the pharmaceutical industry. Uncertain Supply Chain Management, 10(4), 1261–1270. https://doi.org/10.5267/j.uscm.2022.8.002

Ashiwaju, B. I., Orikpete, O. F., Fawole, A. A., Alade, E. Y., & Odogwu, C. (2023). A Step toward Sustainability: A Review of Biodegradable Packaging in the Pharmaceutical Industry. Matrix Science Pharma, 7(3), 73. https://doi.org/10.4103/mtsp.mtsp_22_23

Australian Pharmacy Council (APC). (2020). Accreditation Standards for Pharmacy Programs. https://www.pharmacycouncil.org.au/resources/pharmacy-program-standards/

Azim, M. & Hasan, Z. (2013). Corporate sustainability reporting by pharmaceutical companies: Is it what it seems to be? Corporate Ownership and Control, 11, 754–765. https://doi.org/10.22495/cocv11i1c8art6

Barbier, E. B. (1987). The Concept of Sustainable Economic Development. Environmental Conservation, 14(2), 101–110. https://doi.org/10.1017/S0376892900011449

Becker, J., Manske, C., & Randl, S. (2022). Green chemistry and sustainability metrics in the pharmaceutical manufacturing sector. Current Opinion in Green and Sustainable Chemistry, 33, 100562. https://doi.org/10.1016/j.cogsc.2021.100562

Belkhir, L., & Elmeligi, A. (2019). Carbon footprint of the global pharmaceutical industry and relative impact of its major players. Journal of Cleaner Production, 214, 185–194. https://doi.org/10.1016/j.jclepro.2018.11.204

Brundtland, G. H. (1987). Our common future: Brundtland Report 1987. Retrieved 3 July 2024, from: https://www.are.admin.ch/are/en/home/medien-und-publikationen/publikationen/nachhaltige-entwicklung/brundtland-report.html

Center for Drug Evaluation and Research (CDER), & U.S. Food & Drug Administration (FDA). (2024). Environmental Impact Review at CDER. FDA. https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/environmental-impact-review-cder

Chen, E. Y. H., Forrester, C., McEvoy, A. M., & Singleton, J. (2023). Pharmacy students' perceptions on environmental sustainability in pharmacy education and practice. Exploratory Research in Clinical and Social Pharmacy, 12, 100366. https://doi.org/10.1016/j.rcsop.2023.100366

Chen, Z., Lian, J. Z., Zhu, H., Zhang, J., Zhang, Y., Xiang, X., Huang, D., Tjokro, K., Barbarossa, V., Cucurachi, S., & Dong, B. (2024). Application of Life Cycle Assessment in the pharmaceutical

industry: A critical review. Journal of Cleaner Production, 459, 142550. https://doi.org/10.1016/j.jclepro.2024.142550

Cisneros, L. (2022, November 15). Annual Product Quality Review (APQR / PQR) in Pharma: Importance, benefits & challenges. QbD Group. https://qbdgroup.com/en/blog/annual-product-quality-review-apqr-in-pharma/

Crespo-Gonzalez, C., Benrimoj, S. I., Scerri, M., & Garcia-Cardenas, V. (2020). Sustainability of innovations in healthcare: A systematic review and conceptual framework for professional pharmacy services. Research in Social and Administrative Pharmacy, 16(10), 1331–1343. https://doi.org/10.1016/j.sapharm.2020.01.015

Crespo-Gonzalez, C., Benrimoj, S. I., Scerri, M., & Garcia-Cardenas, V. (2021). Community pharmacists' perspectives about the sustainability of professional pharmacy services: A qualitative study. Journal of the American Pharmacists Association, 61(2), 181–190. https://doi.org/10.1016/j.japh.2020.11.004

Danzon, P. (2014). Competition and Antitrust Issues in the Pharmaceutical Industry. Retrieved 1 July 2024 from: https://faculty.wharton.upenn.edu/wp-content/uploads/2017/06/Competition-and-Antitrust-Issues-in-the-Pharmaceutical-IndustryFinal7.2.14.pdf

Daughton, C. G., & Ruhoy, I. S. (2009). Environmental footprint of pharmaceuticals: The significance of factors beyond direct excretion to sewers. Environmental Toxicology and Chemistry, 28(12), 2495–2521. https://doi.org/10.1897/08-382.1

Davies, J., Spiegelman, G. B., & Yim, G. (2006). The world of subinhibitory antibiotic concentrations. Current Opinion in Microbiology, 9(5), 445–453. https://doi.org/10.1016/j.mib.2006.08.006

Domingo-Echaburu, S., Dávalos, L. M., Orive, G., & Lertxundi, U. (2021). Drug pollution & Sustainable Development Goals. Science of The Total Environment, 800, 149412. https://doi.org/10.1016/j.scitotenv.2021.149412

Dong, Y., & Hauschild, M. Z. (2017). Indicators for Environmental Sustainability. Procedia CIRP, 61, 697–702. https://doi.org/10.1016/j.procir.2016.11.173

Donyai, P., McCrindle, R., Hui, T. K. L., & Sherratt, R. S. (2021). Stakeholder Views on the Idea of Medicines Reuse in the UK. Pharmacy, 9(2), Article 2. https://doi.org/10.3390/pharmacy9020085

Dutch Environmental Database (NMD). (2024). Product Category Rules (PCR). https://milieudatabase.nl/en/environmental-data-lca/information-for-life-cycle-assessment-lca-practitioners/product-category-rules-pcr/

Dutch Ministry of Health, Welfare and Sport. (2020). More sustainability in the health and care sector—Sustainable healthcare—Government.nl. Ministerie van Algemene Zaken. https://www.government.nl/topics/sustainable-healthcare/more-sustainability-in-the-care-sector

Elkington, J. (1998). Partnerships from cannibals with forks: The triple bottom line of 21st-century business. Environmental Quality Management, 8(1), 37–51. https://doi.org/10.1002/tqem.3310080106

Electronic Code of Federal Regulations (eCFR), & U.S. Food & Drug Administration (FDA). (2024). 21 CFR Part 25—Environmental Impact Considerations. Retrieved 3 July 2024, from https://www.ecfr.gov/current/title-21/part-25

Emara, Y., Siegert, M.-W., Lehmann, A., & Finkbeiner, M. (2018). Life Cycle Management in the Pharmaceutical Industry Using an Applicable and Robust LCA-Based Environmental Sustainability Assessment Approach. In E. Benetto, K. Gericke, & M. Guiton (Eds.), Designing Sustainable Technologies, Products and Policies: From Science to Innovation (pp. 79–88). Springer International Publishing. https://doi.org/10.1007/978-3-319-66981-6_9

EPD International. (2024a). Environmental Product Declarations. The International EPD System. Retrieved 3 July 2024, from: https://www.environdec.com/home

EPD International. (2024b). The EPD. Retrieved 3 July 2024, from https://www.environdec.com/all-about-epds/the-epd

EPD International. (2024c). The PCR. Retrieved 3 July 2024, from https://www.environdec.com/product-category-rules-pcr/the-pcr

Eskandari, M., Hamid, M., Masoudian, M., & Rabbani, M. (2022). An integrated lean production-sustainability framework for evaluation and improvement of the performance of pharmaceutical factory. Journal of Cleaner Production, 376, 134132. https://doi.org/10.1016/j.jclepro.2022.134132

European Commission (EC). (2024a). BAT reference documents | EU-BRITE. Retrieved 9 July 2024, from https://eippcb.jrc.ec.europa.eu/reference

European Commission (EC). (2024b). Corporate sustainability reporting—European Commission. Retrieved 9 July 2024, from https://finance.ec.europa.eu/capital-markets-union-and-financial-markets/company-reporting-and-auditing/company-reporting/corporate-sustainability-reporting_en

European Commission (EC). (2024c). Strategic Environmental Assessment —European Commission. https://environment.ec.europa.eu/law-and-governance/environmental-assessments/strategic-environmental-assessment_en

European Commission (EC). (2024d). Legal framework governing medicinal products for human use in the EU - European Commission. https://health.ec.europa.eu/medicinal-products/legal-framework-governing-medicinal-products-human-use-eu_en

European Commission (EC), Directorate-General for Financial Stability, Financial Services and Capital Markets Union. (2023). Commission Delegated Regulation (EU) 2023/2772 of 31 July 2023 supplementing Directive 2013/34/EU of the European Parliament and of the Council as regards sustainability reporting standards. Note: effective since 25 December 2023 intext reference (EC et al., 2023) Retrieved 9 July 2024, from https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32023R2772

European Commission. (EC) Joint Research Centre. (JRC), Caldeira, C., Farcal, L. R., & Garmendia Aguirre, I. (2022a). Safe and sustainable by design chemicals and materials: Framework for the definition of criteria and evaluation procedure for chemicals and materials. Publications Office of the European Union. https://data.europa.eu/doi/10.2760/487955

European Commission, (EC) Joint Research Centre. (JRC), Caldeira, C., Farcal, R., Moretti, C., Mancini, L., Rauscher, H., Riego Sintes, J., Sala, S., & Rasmussen, K. (2022b). Safe and sustainable by design chemicals and materials: Review of safety and sustainability dimensions, aspects, methods, indicators, and tools. Publications Office of the European Union. https://data.europa.eu/doi/10.2760/879069

European Federation of Pharmaceutical Industries and Associations (EFPIA). (2024). Pharmaceuticals in the Environment (PIE). https://www.efpia.eu/about-medicines/development-of-medicines/regulations-safety-supply/pharmaceuticals-in-the-environment-pie/

European Parliament, & Council of the European Union. (2022). Directive (EU) 2022/2464 of the European Parliament and of the Council of 14 December 2022 Amending Regulation (EU) No 537/2014, Directive 2004/109/EC, Directive 2006/43/EC and Directive 2013/34/EU, as Regards Corporate Sustainability Reporting (Text with EEA Relevance), EP, CONSIL, 322 OJ L (2022). Note: effective since 5 January 2023 intext reference (Directive (EU) 2022/2464) https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32022L2464

European Medicines Agency (EMA). (1997). ICH E6 (R2) Good clinical practice—Scientific guideline | European Medicines Agency (EMA). Current version and revisions. Most recent revision draft 2023. Reference Number: EMA/CHMP/ICH/167068/2004 Retrieved 3 July 2024, from https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice-scientific-guideline

European Medicines Agency (EMA). (2000). ICH Q7 Good manufacturing practice for active pharmaceutical ingredients—Scientific guideline | European Medicines Agency (EMA). https://www.ema.europa.eu/en/ich-q7-good-manufacturing-practice-active-pharmaceutical-ingredients-scientific-guideline

European Medicines Agency (EMA). (2006). ICH Q8 (R2) Pharmaceutical development—Scientific guideline | European Medicines Agency (EMA). Reference Number: EMA/CHMP/ICH/167068/2004 Last updated 2014. Retrieved 3 July 2024 from https://www.ema.europa.eu/en/ich-q8-r2-pharmaceutical-development-scientific-guideline

European Medicines Agency (EMA). (2008). ICH guideline Q10 on pharmaceutical quality system—Step 5. Reference Number: EMA/CHMP/ICH/214732/2007 Last updated 2014. Retrieved 3 July 2024, from https://www.ema.europa.eu/en/ich-q10-pharmaceutical-quality-system-scientific-guideline

European Medicines Agency (EMA). (2020). ICH Q12 Technical and regulatory considerations for pharmaceutical product lifecycle management—Scientific guideline | European Medicines Agency (EMA). Reference Number: EMA/CHMP/ICH/804273/2017 https://www.ema.europa.eu/en/ich-q12-technical-regulatory-considerations-pharmaceutical-product-lifecycle-management-scientific-guideline

European Medicines Agency (EMA). (2023). ICH Q9 Quality risk management—Scientific guideline | European Medicines Agency (EMA). Reference Number: EMA/CHMP/ICH/24235/2006 https://www.ema.europa.eu/en/ich-q9-quality-risk-management-scientific-guideline

European Medicines Agency (EMA). (2024a). Environmental risk assessment of medicinal products for human use—Scientific guideline | European Medicines Agency (EMA). Reference Number: EMEA/CHMP/SWP/4447/00 Rev. 1 https://www.ema.europa.eu/en/environmental-risk-assessment-medicinal-products-human-use-scientific-guideline

European Medicines Agency (EMA). (2024b). ICH guidelines | European Medicines Agency. Retrieved 3 July 2024, from https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/ich-guidelines

European Medicines Agency (EMA). (2024c) Quality by design | European Medicines Agency. Retrieved 3 July 2024, from https://www.ema.europa.eu/en/human-regulatory-overview/research-development/quality-design

European Medicines Agency (EMA). (2024d)Quality: Pharmaceutical development | European Medicines Agency. Retrieved 3 July 2024, from https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/quality-guidelines/quality-pharmaceutical-development

European Medicines Agency (EMA). (2024e)Scientific guidelines | European Medicines Agency. Retrieved 5 July 2024, from https://www.ema.europa.eu/en/human-regulatory-overview/research-development/scientific-guidelines

Fatima, T., Tauseef, I., Haleem, K. S., Naeem, M., Ul-Islam, S., Khan, M. S., Ul-Islam, M., & Subhan, F. (2024). Footprint of green synthesizing ingredients on the environment and

pharmaceuticals. International Journal of Environmental Science and Technology, 21(10), 7329–7340. https://doi.org/10.1007/s13762-024-05498-8

Glavič, P. & Lukman, R., (2007). Review of sustainability terms and their definitions. Journal of Cleaner Production, 15(18), 1875–1885. https://doi.org/10.1016/j.jclepro.2006.12.006

Global Reporting Initiative (GRI). (2024). GRI - GRI Standards English Language. https://www.globalreporting.org/how-to-use-the-gri-standards/gri-standards-english-language/ Retrieved 3 July 2024 from:

Government of the Netherlands (Rijksoverheid). (2023). C-238 GREEN DEAL: Samen werken aan duurzame zorg. [Green deal: working together on sustainable healthcare] Green Deal duurzame zorg. Retrieved 3 July 2024 from: https://www.greendeals.nl/sites/default/files/2023-01/C-238%20Green%20Deal%20Working%20together%20towards%20sutainable%20healthcare.pdf

Gupta, S., & Jain, S. K. (2013). A literature review of lean manufacturing. International Journal of Management Science and Engineering Management, 8(4), 241–249. https://doi.org/10.1080/17509653.2013.825074

Hajian, M., & Jangchi Kashani, S. (2021). 1—Evolution of the concept of sustainability. From Brundtland Report to sustainable development goals. In C. M. Hussain & J. F. Velasco-Muñoz (Eds.), Sustainable Resource Management (pp. 1–24). Elsevier. https://doi.org/10.1016/B978-0-12-824342-8.00018-3

Haleem, R. M., Salem, M. Y., Fatahallah, F. A., & Abdelfattah, L. E. (2015). Quality in the pharmaceutical industry – A literature review. Saudi Pharmaceutical Journal, 23(5), 463–469. https://doi.org/10.1016/j.jsps.2013.11.004

Hardjono, T., & de Klein, P. (2004). Introduction on the European Corporate Sustainability Framework (ECSF). Journal of Business Ethics, 55(2), 99–113. https://doi.org/10.1007/s10551-004-1894-x

Hauschild, M. Z. (2018). Introduction to LCA Methodology. In M. Z. Hauschild, R. K. Rosenbaum, & S. I. Olsen (Eds.), Life Cycle Assessment: Theory and Practice (pp. 59–66). Springer International Publishing. https://doi.org/10.1007/978-3-319-56475-3_6

Hay, M., Thomas, D. W., Craighead, J. L., Economides, C., & Rosenthal, J. (2014). Clinical development success rates for investigational drugs. Nature Biotechnology, 32(1), 40–51. https://doi.org/10.1038/nbt.2786

Health care without harm (HCWH). Karliner, J., Slotterback, S., Boyd, R., Ashby, B., & Steele, K. (2019). Health care without harm (HCWH) green paper 1. Health care's climate footprint. Noharm.org. Consulted on 03 July 2024 at:

https://global.noharm.org/sites/default/files/documents-files/5961/HealthCaresClimateFootprint_092319.pdf

Henry, D., & Lexchin, J. (2002). The pharmaceutical industry as a medicines provider. The Lancet, 360(9345), 1590–1595. https://doi.org/10.1016/S0140-6736(02)11527-3

Holt, C. (2018). Reduce, Reuse, Recycle – The 'three R's' of the waste management hierarchy and their impact on packaging. School of Architecture, Design and the Built Environment, 1-7. Retrieved 18 July 2024, from: https://citeseerx.ist.psu.edu/document?repid=rep1&type=pdf&doi=7e6af2134192e81f3655caf7fae8c4827df4eaf0

Huang, H., Li, Y., Huang, B., & Pi, X. (2015). An Optimization Model for Expired Drug Recycling Logistics Networks and Government Subsidy Policy Design Based on Tri-level Programming. International Journal of Environmental Research and Public Health, 12(7), Article 7. https://doi.org/10.3390/ijerph120707738

International Federation of Pharmaceutical Manufacturers and Associations (IFPMA). SDGS In Focus—Global Health Progress. (2024). Retrieved 3 July 2024, from https://globalhealthprogress.org/sdgs-in-focus/

International Pharmaceutical Federation (FIP). (2021). Sustainability in Pharmacy. FIP Development Goals. Retrieved 3 July 2024, from https://developmentgoals.fip.org/dg21/

International Pharmaceutical Federation (FIP). (2022). The FIP Global Roadmap 2030: Sustainable advancement for pharmacy worldwide. The Hague: International Pharmaceutical Federation; 2022. Retrieved 3 July 2024, from: https://developmentgoals.fip.org/globalroadmap2030/

International Organization for Standardization. (ISO) (2006a). ISO 14025:2006. Environmental labels and declarations — Type III environmental declarations — Principles and procedures ISO. https://www.iso.org/standard/38131.html

International Organization for Standardization. (2006b). ISO 14040:2006. Environmental management — Life cycle assessment — Principles and framework ISO. https://www.iso.org/standard/37456.html

International Organization for Standardization. (ISO) (2015a). ISO 9000:2015. Quality management systems — Fundamentals and vocabulary ISO. https://www.iso.org/standard/45481.html

International Organization for Standardization. (ISO) (2015b). ISO 14001:2015. Environmental management systems — Requirements with guidance for use ISO. https://www.iso.org/standard/60857.html

International Organization for Standardization. (ISO) (2016). ISO 13485:2016. Medical devices — Quality management systems — Requirements for regulatory purposes ISO. https://www.iso.org/standard/59752.html

International Organization for Standardization. (ISO) (2017). ISO/IEC 17025:2017. General requirements for the competence of testing and calibration laboratories ISO. https://www.iso.org/standard/66912.html

International Organization for Standardization. (ISO) (2022). ISO 15189:2022. Medical laboratories — Requirements for quality and competence ISO. https://www.iso.org/standard/76677.html

International Organization for Standardization. (ISO) (2023). ISO - ISO 14000 family—Environmental management. ISO. https://www.iso.org/standards/popular/iso-14000-family

Jacquemin, L., Pontalier, P.-Y., & Sablayrolles, C. (2012). Life cycle assessment (LCA) applied to the process industry: A review. The International Journal of Life Cycle Assessment, 17(8), 1028–1041. https://doi.org/10.1007/s11367-012-0432-9

James, P., & Magee, L. (2016). Domains of Sustainability. In A. Farazmand (Ed.), Global Encyclopedia of Public Administration, Public Policy, and Governance (pp. 1–17). Springer International Publishing. https://doi.org/10.1007/978-3-319-31816-5_2760-1

Jamwal, A., Agrawal, R., Sharma, M., Kumar, V., & Kumar, S. (2021). Developing A sustainability framework for Industry 4.0. Procedia CIRP, 98, 430–435. https://doi.org/10.1016/j.procir.2021.01.129

Jones, M., Ionescu, C. M., Walker, D., Wagle, S. R., Kovacevic, B., Chester, J., Foster, T., Johnston, E., Kuthubutheen, J., Brown, D., Atlas, M. D., Mikov, M., Mooranian, A., & Al-Salami, H. (2022). Biguanide Pharmaceutical Formulations and the Applications of Bile Acid-Based Nano Delivery in Chronic Medical Conditions. International Journal of Molecular Sciences, 23(2), Article 2. https://doi.org/10.3390/ijms23020836

Kaylor, A. (2023). 7 Ways to Increase Pharmaceutical Sustainability. PharmaNewsIntelligence. https://pharmanewsintel.com/features/7-ways-to-increase-pharmaceutical-sustainability

Kittery, A., & Miettinen, M. (2023). Environmental considerations in the European Union's pharmaceuticals legislation: Key instruments and their challenges in addressing global manufacturing supply chains. Review of European, Comparative & International Environmental Law, 32(1), 77–91. https://doi.org/10.1111/reel.12488

Kumari, A., Aggarwal, G., & Kaur, A. (2024). Applications of Quality by Design in Pharmaceutical Product Development Lifecycle. In N. K. Jain & N. Bajwa (Eds.), Introduction to Quality by Design (QbD): From Theory to Practice (pp. 419–453). Springer Nature. https://doi.org/10.1007/978-981-99-8034-5_15

Larsson, D. G. J. (2014). Pollution from drug manufacturing: Review and perspectives. Philosophical Transactions of the Royal Society B: Biological Sciences, 369(1656), 20130571. https://doi.org/10.1098/rstb.2013.0571

Lau, L. (2016). Filling a greener prescription. Canadian Pharmacists Journal : CPJ, 149(4), 202–203. https://doi.org/10.1177/1715163516651244

Ledley, F. D., McCoy, S. S., Vaughan, G., & Cleary, E. G. (2020). Profitability of Large Pharmaceutical Companies Compared With Other Large Public Companies. JAMA, 323(9), 834–843. https://doi.org/10.1001/jama.2020.0442

Larivière, B., & Smit, E. G. (2022). People–planet–profits for a sustainable world: Integrating the triple-P idea in the marketing strategy, implementation and evaluation of service firms. Journal of Service Management, 33(4/5), 507–519. https://doi.org/10.1108/JOSM-01-2022-0033

Lee, D., Pulawska, G., & Morton, J. (2017). Implementation Guide for the Sustainable Development Goals (SDGs). Asia-Europe Foundation (ASEF). Retrieved 11 July 2024, from https://asef.org/publications/implementation-guide-for-the-sustainable-development-goals-sdgs/

Lifset, R., & Graedel, T. (2015). Industrial Ecology. In International Encyclopedia of the Social & Behavioral Sciences (pp. 843–853). https://doi.org/10.1016/B978-0-08-097086-8.91023-7

Loviscek, V. (2021). Triple Bottom Line toward a Holistic Framework for Sustainability: A Systematic Review. Revista de Administração Contemporânea, 25. https://doi.org/10.1590/1982-7849rac2021200017.en

Mamiya, K. T., John, C., Alnahar, S. A., Bader, L., & Bates, I. (2020). Achieving Sustainable Developments Goal 3 on health from global pharmacy workforce. Journal of Global Health, 10(2), 020350. https://doi.org/10.7189/jogh.10.020350

McRae, D., Gould, A., Price-Davies, R., Tagoe, J., Evans, A., & James, D. H. (2021). Public Attitudes towards Medicinal Waste and Medicines Reuse in a 'Free Prescription' Healthcare System. Pharmacy: Journal of Pharmacy Education and Practice, 9(2), 77. https://doi.org/10.3390/pharmacy9020077

Milanesi, M., Runfola, A., & Guercini, S. (2020). Pharmaceutical industry riding the wave of sustainability: Review and opportunities for future research. Journal of Cleaner Production, 261, 121204. https://doi.org/10.1016/j.jclepro.2020.121204

Mishra, M., Sharma, M., Dubey, R., Kumari, P., Ranjan, V., & Pandey, J. (2021). Green synthesis interventions of pharmaceutical industries for sustainable development. Current Research in Green and Sustainable Chemistry, 4, 100174. https://doi.org/10.1016/j.crgsc.2021.100174

Moermond, C. T. A., Puhlmann, N., Brown, A. R., Owen, S. F., Ryan, J., Snape, J., Venhuis, B. J., & Kümmerer, K. (2022). GREENER Pharmaceuticals for More Sustainable Healthcare. Environmental Science & Technology Letters, 9(9), 699–705. https://doi.org/10.1021/acs.estlett.2c00446

Mostafa, M. K. & Peters, R. W. (2017). Applying the three R's: Reduce, reuse, and recycle in the chemical industry. Journal of the Air & Waste Management Association, 67(3), 322–329. https://doi.org/10.1080/10962247.2016.1234421

Narayana, S. A., Pati, R. K., & Vrat, P. (2012). Research on management issues in the pharmaceutical industry: A literature review. International Journal of Pharmaceutical and Healthcare Marketing, 6(4), 351–375. https://doi.org/10.1108/17506121211283235

Nieminen, J., Anugwom, I., Kallioinen, M., & Mänttäri, M. (2020). Green solvents in recovery of aluminium and plastic from waste pharmaceutical blister packaging. Waste Management, 107, 20–27. https://doi.org/10.1016/j.wasman.2020.03.014

Noori, M. T., Bhowmick, G. D., Tiwari, B. R., Das, I., Ghangrekar, M. M., & Mukherjee, C. K. (2020). Utilisation of waste medicine wrappers as an efficient low-cost electrode material for microbial fuel cell. Environmental Technology, 41(10), 1209–1218. https://doi.org/10.1080/09593330.2018.1526216

Oxford English Dictionary (OED). (2023). Sustainability, n. Meanings, etymology and more | Oxford English Dictionary. Retrieved 3 July 2024, from https://www.oed.com/dictionary/sustainability_n

Organisation for Economic Co-operation and Development (OECD). (2023). OECD Guidelines for Multinational Enterprises on Responsible Business Conduct. Organisation for Economic Co-operation and Development. Available from: https://www.oecd-ilibrary.org/finance-and-investment/oecd-guidelines-for-multinational-enterprises-on-responsible-business-conduct_81f92357-en

Ögmundarson, Ó., Herrgård, M. J., Forster, J., Hauschild, M. Z., & Fantke, P. (2020). Addressing environmental sustainability of biochemicals. Nature Sustainability, 3(3), 167–174. https://doi.org/10.1038/s41893-019-0442-8

Ostwald, D. D., Cramer, D. M., Albu, N., & Tesch, J. (2020). The Global Economic Impact of the Pharmaceutical Industry. Available from: https://www.wifor.com/uploads/2021/06/WifOR_Global_Economic_Footprint_Study_September_2020.pdf

Paut Kusturica, M., Tomas, A., & Sabo, A. (2017). Disposal of Unused Drugs: Knowledge and Behavior Among People Around the World. In P. de Voogt (Ed.), Reviews of Environmental Contamination and Toxicology Volume 240 (pp. 71–104). Springer International Publishing. https://doi.org/10.1007/398_2016_3

Picciotto, R. (2005). The Value of Evaluation Standards: A Comparative Assessment. Journal of MultiDisciplinary Evaluation, 2(3), 30–59. https://doi.org/10.56645/jmde.v2i3.100

Purvis, B., Mao, Y., & Robinson, D. (2019). Three pillars of sustainability: In search of conceptual origins. Sustainability Science, 14(3), 681–695. https://doi.org/10.1007/s11625-018-0627-5

Rijksinstituut voor Volksgezondheid en Milieu (RIVM). (2016) Integrated approach reduces harmful effects of medicines in surface waters. Retrieved 3 July 2024, from https://www.rivm.nl/en/news/integrated-approach-reduces-harmful-effects-of-medicines-in-surface-waters

Rijksinstituut voor Volksgezondheid en Milieu (RIVM). (2022a). More attention needed for potential impact of drug waste on drinking water quality Retrieved 3 July 2024, from https://www.rivm.nl/en/news/more-attention-needed-for-potential-impact-of-drug-waste-on-drinking-water-quality

Rijksinstituut voor Volksgezondheid en Milieu (RIVM). (2022b). Pharmaceuticals in the environment | RIVM. Retrieved 3 July 2024, from https://www.rivm.nl/en/pharmaceuticals-in-environment

Rockström, J., Steffen, W., Noone, K., Persson, Å., Chapin, F. S. I., Lambin, E., Lenton, T. M., Scheffer, M., Folke, C., Schellnhuber, H. J., Nykvist, B., De Wit, C. A., Hughes, T., Van Der Leeuw, S., Rodhe, H., Sörlin, S., Snyder, P. K., Costanza, R., Svedin, U., … Foley, J. (2009). Planetary Boundaries: Exploring the Safe Operating Space for Humanity. Ecology and Society, 14(2), art32. https://doi.org/10.5751/ES-03180-140232

Royal Pharmaceutical Society (RPS). (2023). RPS to develop sustainability guidance for pharmacy teams. Retrieved 3 July 2024, from https://www.rpharms.com/about-us/news/details/rps-to-develop-sustainability-guidance-for-pharmacy-teams

Royal Pharmaceutical Society (RPS). (2024). Pharmacy's Role in Climate Action and Sustainable Healthcare. Retrieved 3 July 2024, from https://www.rpharms.com/recognition/all-our-campaigns/policy-a-z/pharmacys-role-in-climate-action-and-sustainable-healthcare

Sengar, G., & Tripathy, P. (2012). Pharmaceutical Regulatory Agencies and Organizations around the World: Scope and Challenges in Drug Development. PharmaTutor. https://www.pharmatutor.org/articles/pharmaceutical-regulatory-agencies-and-organizations-around-world-scope-challenges-in-drug-development

Scherer, F. M. (2000). Chapter 25 The pharmaceutical industry. In Handbook of Health Economics (Vol. 1, pp. 1297–1336). Elsevier. https://doi.org/10.1016/S1574-0064(00)80038-4

Schuhmacher, A., Gassmann, O., & Hinder, M. (2016). Changing R&D models in research-based pharmaceutical companies. Journal of Translational Medicine, 14(1), 105. https://doi.org/10.1186/s12967-016-0838-4

Siegert, M.-W., Lehmann, A., Emara, Y., & Finkbeiner, M. (2019). Harmonized rules for future LCAs on pharmaceutical products and processes. The International Journal of Life Cycle Assessment, 24(6), 1040–1057. https://doi.org/10.1007/s11367-018-1549-2

Silvestre, D. (2023). The difficult marriage of the pharmaceutical industry and the sustainable development goals. Retrieved 3 July 2024 from: https://sdgs.un.org/sites/default/files/2023-05/B49%20-%20Silvestre%20-%20The%20difficult%20marriage%20of%20biotech%20pharma%20and%20SDGs.pdf

Slaper, T.F., & Hall, T.J. (2011). The Triple Bottom Line: What Is It and How Does It Work? Indiana Business Review, 86(1), 4-8. https://www.ibrc.indiana.edu/ibr/2011/spring/article2.html

Snyder, H. (2019). Literature review as a research methodology: An overview and guidelines. Journal of Business Research, 104, 333–339. https://doi.org/10.1016/j.jbusres.2019.07.039

Soete, W. D., Jiménez-González, C., Dahlin, P., & Dewulf, J. (2017). Challenges and recommendations for environmental sustainability assessments of pharmaceutical products in the healthcare sector. Green Chemistry, 19(15), 3493–3509. https://doi.org/10.1039/C7GC00833C

Statista, & Tiseo, I. (2024). GHG emissions global chemical industry 2030. Statista. Retrieved 3 July 2024, from: https://www.statista.com/statistics/1343676/global-ghg-emissions-from-the-chemical-and-petrochemical-industry-by-scenario/

Statista. (2024a). Pharmaceuticals—Worldwide | Statista Market Forecast. Statista. Retrieved 3 July 2024, from https://www.statista.com/outlook/hmo/pharmaceuticals/worldwide

Statista. (2024b) Passenger Cars—Worldwide | Statista Market Forecast. Statista. Retrieved 3 July 2024, from https://www.statista.com/outlook/mmo/passenger-cars/worldwide

Suhandi, V., & Chen, P.-S. (2023). Closed-loop supply chain inventory model in the pharmaceutical industry toward a circular economy. Journal of Cleaner Production, 383, 135474. https://doi.org/10.1016/j.jclepro.2022.135474

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). (2024). ICH Official website: ICH. Retrieved 3 July 2024, from https://www.ich.org/page/ich-guidelines

Tietje, C., & Brouder, A. (Eds.). (2009). Handbook of Transnational Economic Governance Regimes. Brill Nijhoff. https://brill.com/edcollbook/title/14661

Toklu, H. Z., & Hussain, A. (2013). The changing face of pharmacy practice and the need for a new model of pharmacy education. Journal of Young Pharmacists, 5(2), 38–40. https://doi.org/10.1016/j.jyp.2012.09.001

United Nations (UN). (2015). The Paris Agreement. United Nations; United Nations. https://www.un.org/en/climatechange/paris-agreement

United Nations (UN). (2024a). THE 17 GOALS | Sustainable Development. (2024). Retrieved 3 July 2024, from https://sdgs.un.org/goals

United Nations (UN). (2024b). The Ten Principles | UN Global Compact. https://unglobalcompact.org/what-is-gc/mission/principles

United Nations (UN) (2024c). Sustainability. United Nations; United Nations. Retrieved 3 July 2024, from https://www.un.org/en/academic-impact/sustainability

United States Environmental Protection Agency (EPA). (2013). Basics of Green Chemistry [Overviews and Factsheets]. https://www.epa.gov/greenchemistry/basics-green-chemistry

United States Environmental Protection Agency (EPA). (2015). Resource Conservation and Recovery Act (RCRA) Regulations [Other Policies and Guidance]. https://www.epa.gov/rcra/resource-conservation-and-recovery-act-rcra-regulations

U.S. Food & Drug Administration (FDA). (2020). The Drug Development Process. FDA; FDA. https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process

Villanueva, D., Ong, A. K., & German, J. (2024). Machine Learning Methods Analysis of Preceding Factors Affecting Behavioral Intentions to Purchase Reduced Plastic Products. Sustainability, 16, 2978. https://doi.org/10.3390/su16072978

Virtanen, P. K., Siragusa, L., & Guttorm, H. (2020). Introduction: Toward more inclusive definitions of sustainability. Current Opinion in Environmental Sustainability, 43, 77–82. https://doi.org/10.1016/j.cosust.2020.04.003

WEF. (2022). 6 ways the pharmaceutical industry can reduce its climate impact. World Economic Forum. https://www.weforum.org/agenda/2022/11/pharmaceutical-industry-reduce-climate-impact/

World Health Organization (WHO) (2020) WHO guidance for climate resilient and environmentally sustainable health care facilities. ISBN: 978-92-4-001222-6 https://www.who.int/publications/i/item/9789240012226

World Health Organization (WHO). (2023). Quality assurance of pharmaceuticals: A compendium of guidelines and related materials, tenth edition. Volume 2. Good manufacturing practices and inspection. 2. Retrieved from https://ispe.org/sites/default/files/regulatory/2024/9789240086081-eng%20(1).pdf

World Health Organization (WHO). (2024a). WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-seventh report. Geneva: World Health Organization; 2024 (WHO Technical Report Series, No. 1052). Retrieved from: https://iris.who.int/bitstream/handle/10665/376607/9789240091030-eng.pdf?sequence=1

World Health Organization (WHO). (2024b). Guidelines: Norms and Standards for Pharmaceuticals. Retrieved 18 July 2024, from: https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/guidelines

Wynendaele, E., Furman, C., Wielgomas, B., Larsson, P., Hak, E., Block, T., Van Calenbergh, S., Willand, N., Markuszewski, M., Odell, L. R., Poelarends, G. J., & De Spiegeleer, B. (2021). Sustainability in drug discovery. Medicine in Drug Discovery, 12, 100107. https://doi.org/10.1016/j.medidd.2021.100107

Yaroson, E., Breen, L., Hou, J., & Sowter, J. (2021). Advancing the understanding of pharmaceutical supply chain resilience using complex adaptive system (CAS) theory. Supply Chain Management: An International Journal, ahead-of-print. https://doi.org/10.1108/SCM-05-2019-0184

Appendix

Appendix A: Guideline overview

This section includes the overview tables of guidelines, regulations, frameworks, and standards for pharmaceutical development that chapter 4.1 is based on.

Table 1: Overview of guidelines, regulations, frameworks and standards for pharmaceutical development. A holistic overview is provided to cover the full process of, and important aspects relating to pharmaceutical development. Integration of environmental sustainability elements is briefly assessed here. All aspects were assessed on being applicable to current practice, being the most recent version and/or being legally effective at present. Specific identifiers based on version differences are provided when available to ensure clarity also in case of interrelations between sources.

Guideline,	Aspects covering	Relevant	Assessment of integration for

regulations, frameworks, standards (and reference)	pharmaceutical development, material use, and operations.	perspective(s)	environmental sustainability
Guidelines for pharmaceutical development			
FDA Guidelines (FDA, 2020; Haleem et al., 2015; CDER. FDA, 2024)	**21 CFR Part 210** and **21 CFR Part 211** outline Good manufacturing practice (GMP) for drug manufacturing and processing. - Emphasis on risk management and modern quality systems.	Regulatory, Business	Includes risk management, indirectly supporting environmental sustainability through improved practices and technological advancements. -21 CFR part 25 regards Environmental Impact Considerations (eCFR. FDA, 2024) and as stated in (CDER., FDA, 2024) "specify that environmental assessments (EAs) must be submitted (in part 25.20) as part of certain new drug applications (NDAs), abbreviated new drug applications (ANDAs), applications for marketing approval of a biologic product, supplements to such applications, investigational new drug applications (INDs) and for various other actions, unless the action qualifies for a categorical exclusion (25.31)."
EU Guidelines (EC, 2024d)	- **Overview page of the EU legal framework governing medicinal products**, includes	Regulatory, Business	EU guidelines address quality control and compliance; indirect environmental considerations through GMP adherence and

	regulations and guidelines on GMP, clinical trials, and pharmacovigilance. - Covers various volumes related to human (volume 1) and veterinary (volume 5, further excluded) medicinal products. - Includes **at least** 4 relevant guidelines mainly linked through EudraLex in overview (EC, 2024d), which are **volume 3** for medicinal products in human use, **volume 4** regarding GMP, **volume 9** for pharmacovigilance/monitoring, and **volume 10** for clinical trials.		product lifecycle management mostly through increased efficiency and reducing waste. Also mention more specific regulations for different aspects directly. In some cases the EU guidelines rely on the ICH guidelines as well or are based on parts of these.
EMA and ICH Guidelines (Abraham, (2009; Haleem et al., 2015; EMA, 2024b; ICH, 2024) Specific reference numbers are provided as identifiers for transparency.	- Contains at least 6 relevant specific guidelines - Harmonises technical requirements for product registration across regions. Some guidelines are presented in an overview in (EMA 2024d) specific to quality in pharmaceutical development and	Regulatory, Business	-Promotes global standardisation; indirect impact on environmental sustainability through resource efficiency and safety measures. Across the different ICH guidelines, the only concern is the effect of the environment on medication during manufacturing and packaging, rather than the effect or impact of medication on the environment. The focus is on quality, safety, and efficacy in relation to the medication, and any clear relation to environmental

	(EMA, 2024e) for scientific guidelines (EMA, 2024e not counted in guidelines for pharmacy). - Focuses on efficient use of resources and safeguarding quality, safety, and efficacy. -**ICH E6 (R2)**, good clinical practice (GCP) regarding operational practices ((EMA, 1997) reference number EMA/CHMP/ICH/135/1995) last updated in 2016, effective at present. -**ICH Q7** Good Manufacturing Practice (GMP) ((EMA, 2000) CPMP/ICH/4106/00) -**ICH Q8 (R2)**, Scientific guideline for Pharmaceutical development ((EMA 2006) reference number EMA/CHMP/ICH/167068/2004) -**ICH Q9 (R1)** quality risk management ((EMA, 2023) reference number EMA/CHMP/ICH/24235/2006) -**ICH Q10** pharmaceutical quality		sustainability or sustainability in general appears absent. A short evaluation is done for each relevant ICH guideline, absent in context is used to describe not explicitly included or excluded, nor implied. -**ICH E6 (R2)** environmental sustainability is not explicitly mentioned, in context for **ICH E6** the 2023 update revision comments((EMA, 1997) **ICH E6 (R3)** reference number EMA/553381/2023 **Rev.1**) guideline proposes the following changes: On page 20 "Add environmental impact of trials (travel, shipments, waste, resources)", On page 46 "Add 12th principle: The processes, measures and approaches of the clinical trial should be implemented in such a way that the environmental impact/pollution is kept as low as possible." however the R2 version remains the current active version. -**ICH Q7** explicitly states "The Guide as a whole does not cover safety aspects for the personnel engaged in the manufacture, nor aspects of *protection of the environment*. These controls are inherent responsibilities of the manufacturer and are governed by

	systems (PQS) ((EMA, 2008) reference number EMA/CHMP/ICH/214732/2007). Also links to GMP and ISO standards (ISO 9000:2005) -**ICH Q12** Technical and regulatory considerations for pharmaceutical product lifecycle management - Scientific guideline ((EMA, 2020) reference number EMA/CHMP/ICH/804273/2017)		national laws." This implies exclusion of environmental sustainability considerations. -**ICH Q8 (R2)** environmental sustainability is absent in context. -**ICH Q9 (R1)** mentions "protect the environment (e.g., personnel, potential for cross-contamination) from hazards related to the product being manufactured." on page 24 in relation to hygiene in facilities, and "sustainable GMP compliance" on page 13. Environmental sustainability is only indirectly included through safety measures. - **ICH Q10** environmental sustainability is absent in context. -**ICH Q12** environmental sustainability is absent in context.
Guidelines for sustainability in pharmaceutical development			
WHO guidance for climate resilient and environmentally sustainable health care facilities. (WHO, 2020)	"Appropriate use of resources (in particular water and energy and sustainable procurement), and release of hazardous materials (biological, chemical, radiological), into their surrounding environment." (WHO, 2020)	Regulatory, Business	Direct focus on climate resilience and environmental sustainability.
Implementation Guide for the Sustainable Development			See SDGs.

Goals (Lee et al.,2017)			
OECD Guidelines for Multinational Enterprises on Responsible Business Conduct (OECD, 2023)		Business	Clearly mentions sustainable development, provides guidelines on how enterprises, including pharmaceutical companies, should minimise environmental impacts, with a focus on pollution prevention, sustainable resource use, and overall environmental management. The 2023 version also adds recommendations on aligning with international climate and biodiversity goals.
Green chemistry principles (Soete et al., 2017; EPA, 2013; Agbenyega, 2022; Becker et al., 2022)		Regulatory, Business	
Environmental risk assessment (ERA) of medicinal products for human use - Scientific guideline (EMA, 2024a)	Requires a risk assessment and a hazard assessment specific for the active substances of the drug and nothing else		Concerns all aspects related to the environmental risks and potential hazards from exposing the environment to the drug directly or indirectly. The following identifying information is required for the ERA: "- CAS number - Molecular formula, molecular weight - Structural formula - Physico-chemical information on the substance that could influence test protocols used, e.g. highly lipophilic substances. - Information (one sentence) on the pharmacological profile, including whether the substance is an

			antibiotic, antiparasitic or endocrine active substance (EAS) (a tailored testing or specific assessment strategy will be needed, see section 4.3 ((in EMA, 2024a))"

Table 2: Overview of regulations, frameworks and standards for pharmaceutical development. A holistic overview is provided to cover the full process of, and important aspects relating to pharmaceutical development. Integration of environmental sustainability elements is briefly assessed here. All aspects were assessed on being applicable to current practice, being the most recent version and/or being legally effective at present. Specific identifiers based on version differences are provided when available to ensure clarity also in case of interrelations between sources.

Guideline, regulations, frameworks, standards (and reference)	**Aspects covering pharmaceutical development and material use**	**Relevant perspective (s)**	**Assessment of integration for environmental sustainability**
Frameworks, standards, and regulatory requirements for pharmaceutical development			
WHO norms and standards for guidelines (WHO, 2023; WHO, 2024b)	-Handbook on Good Manufacturing Practices (GMP) covering principles, starting materials, specific products, and inspection (WHO, 2023). - Norms and standards for pharmaceutical guidelines which are grouped into (1) development, (2) production, (3) distribution, (4) inspection, (5) quality	Regulatory, Business	Focuses on quality assurance and regulatory practices; indirect environmental impact through adherence to GMP through reduced waste and increased efficiency. Specific example mentions recommendations for environmental aspects for the prevention of antimicrobial resistance, and "prevent pollution of the external environment" (WHO, 2024b) (Page 14). These focus on the manufacturing environment. Also mentions "environmental monitoring" in

	control, (6) regulatory standards and (7) specific texts for prequalification of medicines (WHO, 2024a). **- There are at least 8 relevant standards by the WHO.**		Standard operating procedures and records (SOPs) (operational practices) on page 54 and also regard keeping records of, and monitoring decisions taken and keeping records of actions and decisions also for materials, ingredients, and packaging. -Quality Risk Management (QRM) which mainly replaces HACCP covers aspects like R&D, sourcing of materials, manufacturing, packaging, testing, storage and distribution (WHO, 2023) environmental sustainability is only indirectly included. -Quality Management Systems (QMS) are stated to "facilitate continual improvement and provide a sound basis for sustainable development to comply with statutory and regulatory Requirements" (WHO, 2024b, page 1220) SDGs and sustainable development are mentioned, but environmental sustainability is not explicitly mentioned. -Only focus mentioned on direct manufacturing and production environment, mention of contributing to the SDGs (WHO, 2024a; WHO, 2024b) but no clear mention of environmental sustainability anywhere, only implied (WHO, 2023; WHO, 2024a; WHO, 2024b).

Hazard Analysis and Critical Control Point (HACCP) **(**Haleem et al., 2015; WHO, 2023**)**	Risk assessment system originally for food safety, applicable to ensuring safety in pharmaceutical manufacturing, focuses on material handling across the full lifecycle. Replaced by Quality Risk Management (QRM) in more recent guidelines by WHO (WHO, 2023) still present in ICH Q9 (R1)	Business	Environmental sustainability is absent in context, only indirectly benefits from safety measures.
(Annual) Product Quality Review (APQR/PQR) (c)	-APQR/PQR is a regulatory requirement for documenting product quality. -It Involves analysis of process parameters, raw materials, and specifications and aims to improve product quality, process consistency, and compliance. -Includes verification of product performance and manufacturing process.	Regulatory, Business	The APQR/PQR process primarily focuses on ensuring product quality and regulatory compliance. Environmental sustainability integration is not explicitly addressed but could be considered in the context of process improvements and risk assessments related to environmental impacts.
ISO 9000:2015 (ISO, 2015a)	Quality management standards focusing on customer satisfaction and continual improvement.	Business	Environmental sustainability is not the primary focus; integration could be achieved through quality improvement initiatives. Section 3.7.4 on page 26 states: “Sustained success emphasizes the need for a balance between economic-financial interests of an organization and those of the social and ecological environment.” no further mention of aspects related to environmental sustainability.
ISO 17025 (ISO,	Standards for the	Business	Limited direct impact on

2017)	competence of testing and calibration laboratories.		environmental sustainability; improvements may be indirect.
ISO 15189 (ISO, 2022)	Standards for medical laboratory quality and competence.	Business	Environmental aspects not specifically covered; could integrate through broader quality management practices.
ISO 13485:2016 (ISO, 2016))	General requirements for the competence of testing and calibration laboratories	Business	Environmental aspects not specifically covered.
ISO 15189:2022 (ISO, 2022)	Medical laboratories Requirements for quality and competence	Business	Environmental impact not specifically covered
Process Analytical Technologies (PAT) (FDA, 2004; EMA, 2024c)	Technologies to understand and control manufacturing processes for improved quality. - Also mentions quality by design (QbD) aspects (EMA, 2024c; EMA, 2024d)	Business	Integration through improved efficiency; indirect benefits to environmental sustainability.
Frameworks, standards, and regulatory requirements for sustainability			

Sustainable Development Goals (SDGs) (UN, 2024a)	Drugs are only mentioned directly in goal 3; good health and wellbeing (Domingo-Echaburu et al., 2021). The only targets that mention drugs/medication/pharmaceuticals are 3.5 focused on reducing substance abuse. 3.b providing affordable access to medicines and vaccines. Neither are focused on material aspects.	Academic	Sustainability including environmental sustainability are at the centre of the SDGs. Includes 169 sustainability targets. The global indicator framework includes **231** unique indicators, of which 13 are used for multiple targets (EC et al., 2022a). -As mentioned, only 2 of these are directly related to pharmaceuticals, More specific focus on pharmaceuticals is absent at present, although generic recommendations for industries on being more (environmentally) sustainable still apply. - Some variations and databases developed by pharmaceutical organisations exist to better connect SDGs to the pharmaceutical industry (IFPMA, 2024; FIP, 2021).
Planetary Boundaries (Rockström et al., 2009)	The planetary boundaries regard all 'windows' where life remains possible, this includes material aspects related to recourse use to avoid overexploitation, and reducing waste to the environment.	Academic	Centred around all aspects of sustainability involved with maintaining life, such as different types of pollution, material use, and water use. -Although chemical pollution is specified and states "wide range of organic compounds of human origin" to be included, pharmaceuticals are not specifically included.
Environmental Product Declarations (EPD International, 2024a; EPD International	- Reports environmental performance of products (e.g., drugs, packaging) from a lifecycle perspective. - Uses LCA to evaluate environmental impacts.	Regulatory, Academic, Business	Enhances transparency and comparability of environmental performance data; supports assessment and communication of impacts for pharmaceuticals but does not mandate specific sustainable practices.

2024b)			EPD is a Type III Environmental Declaration based on ISO 14025.
Product Category Rules, (PCR) (EPD International, 2024c; NMD, 2024)	- Standardised guidelines for LCAs and creating EPDs. - Defines system boundaries, declared units, and impact categories. - Ensures consistency in environmental declarations.	Regulatory, Academic	Supports sustainability by standardising LCA processes, leading to consistent and comparable EPDs; ensures reliable assessment of environmental impacts for individual products. Do note for example pharmaceuticals and packaging are independent products.
Quality by design (QBD) (EMA, 2024c; EMA, 2024d)	Frameworks focused on quality of medication from a design perspective.	Regulatory, Business	Does not include focus on environmental sustainability, or generic sustainability, only focuses on quality.
ISO 14025:2006 (ISO, 2006a)	- Establishes principles and procedures for Type III environmental declarations for products. - Uses ISO 14040 series standards for LCAs of products (for example packaging). - Relevant for business-to-business and optionally business-to-consumer communication. - One example of practical application of this guidelines was found (Kumari et al., 2024)	Regulatory, Academic, Business	Provides a standardised approach for creating Type III environmental declarations, enhancing transparency and comparability of environmental impact data, including for pharmaceuticals.
ISO 14040 :2006 (ISO, 2006b; Hauschild, 2018)	-Evaluating the environmental impact throughout the drug's lifecycle.	Regulatory, Academic, Business	Provides a description of the principles and framework of LCA and its different phases Environmental management
Safe and Sustainable by Design	- Defines criteria and evaluation procedures for safe and sustainable	Regulatory, Social	Provides a comprehensive framework for assessing and designing safe and sustainable

Framework (SSbD) (EC et al., 2022a; EC et al., 2022b)	design of chemicals/materials. - Assesses safety, environmental, and socio-economic impacts. - Applies to design, development, and the full life cycle of chemicals and materials.		chemicals/materials; aligns with the EU Chemicals Strategy for Sustainability (CSS) and supports innovation towards greener alternatives.
ISO 14001:2015 (ISO, 2015b)	Standards for environmental management systems to reduce environmental impact.	Business	Directly applicable; focuses on integrating environmental practices into management systems. Environmental management system See sections 6.2.2
ISO 14000 Series (ISO, 2023)	Series of standards for managing environmental impacts, including ISO 14001.	Business	Provides a framework for integrating environmental sustainability across various aspects with a focus on environmental management.
Corporate Sustainability Reporting Directive (CSRD) (EC, 2024b; Directive (EU) 2022/2464)	Legislation for the EU requiring companies to "disclose information on what they see as the risks and opportunities arising from social and environmental issues, and on the impact of their activities on people and the environment." (EC, 2024b) which also applies to pharmaceutical companies including research & development. -The directive (Directive (EU) 2022/2464) has the document identifier "Document 32022L2464"	Regulatory, Business	The purpose of the CSRD is improving quality and corporate transparency to enhance comparability of sustainability information across the EU. This should enhance the ability of investors, consumers, and other stakeholders to assess the sustainability performance of companies. It also aims to support the EU's broader sustainability objectives, including climate goals and social responsibility. - Makes use of the ESRS standards (EC et al., 2023)

European Sustainability Reporting Standards (ESRS) (EC, 2024b; EC et al., 2023)	Regulations and requirements for what is included regarding stating the positive and negative material impacts of strategies and decisions by companies, including scope and severity, on people and environment, as also mentioned in the CSRD. - Requires inclusion of stakeholders affected by material processes. -The commission delegated regulation (EC et al., 2023) has the document identifier "Document 32023R2772"	Regulatory, Academic	- The three sustainability pillars are included here as "b) topical standards" and mentions this regulation **legally effective in force from the first of January, 2024.** Specifically mentions this is for companies in the EU. - Requires (qualitative) statements on the effects of material processes across the life cycle on people and the environment. The main focus is still on financial statements. - In section 5.2 (EC, 2024b) "With reference to policies, actions and targets, the undertaking's reporting shall include upstream and/or downstream value chain information to the extent that those policies, actions and targets involve actors in the value chain . With reference to metrics , in many cases, **in particular for environmental matters for which proxies are available**, the undertaking may be able to comply with the reporting requirements without collecting data from the actors in its upstream and downstream value chain" - Covers aspects including but not limited to pollution, biodiversity and ecosystems, water and marine resources, and business conduct. For example scope 1, 2 and 3 emissions (direct and indirect emissions by a company, or entities it has control over, or entities beyond its control.)

General Reporting Initiative (GRI) (GRI, 2024))	There are many GRI standards, the following **4 main standards** were identified that are applicable to pharmaceutical development and material use (and monitoring): **-GRI 102: General Disclosures** -GRI 102-9: Supply chain: Organisations should describe their supply chain, which is particularly relevant for pharmaceutical development in terms of sourcing raw materials and components. **-GRI 103: Management Approach** -GRI 103-1: Explanation of the material topic and its Boundary: Organizations must explain why a particular sustainability topic is material (i.e., important) and describe the boundary of where the impact occurs. -GRI 103-2: The management approach and its components: Details how the organization manages its material topics, including policies, commitments, and responsibilities. **-GRI 304: Biodiversity**	Academic	GRI Standards relevant to environmental sustainability cover a broad range of aspects across the full lifecycle of products from transparency and accountability, to material use and monitoring **the following 5 standards** are relevant for environmental sustainability and pharmaceutical development: **-GRI 301: Materials** -GRI 301-1: Materials used by weight or volume: Organisations should disclose the total weight or volume of materials used during the reporting period, distinguishing between renewable and non-renewable materials. -GRI 301-2: Recycled input materials used: This standard requires the disclosure of the percentage of recycled input materials used in the manufacturing process. -GRI 301-3: Reclaimed products and their packaging materials: This involves disclosing the percentage of products and packaging materials reclaimed by category. **-GRI 302: Energy** -GRI 302-1: Energy consumption within the organization: Details energy consumption by type, including renewable energy sources. -GRI 302-4: Reduction of energy consumption: Requires organizations to report initiatives to reduce energy consumption and the results of these initiatives. **-GRI 303: Water and Effluents**

	-GRI 304-2: Significant impacts of activities, products, and services on biodiversity: Disclose significant impacts on biodiversity in areas affected by the organization's operations, including material sourcing and production processes. **-GRI 308: Supplier Environmental Assessment** -GRI 308-1: New suppliers that were screened using environmental criteria: Report the percentage of new suppliers screened using environmental criteria, relevant for the procurement of materials in pharmaceutical development. -GRI 308-2: Negative environmental impacts in the supply chain and actions taken: Requires reporting on negative environmental impacts identified in the supply chain and the actions taken to address them.		-GRI 303-1: Interactions with water as a shared resource: Organizations must describe their water usage practices and impacts, including how they manage water in shared resources. -GRI 303-3: Water withdrawal: Disclose the total volume of water withdrawn by source. -GRI 303-4: Water discharge: Disclose the total volume of water discharged and the quality of the discharged water. **-GRI 305: Emissions** -GRI 305-1: Direct (Scope 1) GHG emissions: Requires reporting on greenhouse gas (GHG) emissions from sources owned or controlled by the organisation. -GRI 305-2: Energy indirect (Scope 2) GHG emissions: Disclose indirect GHG emissions from the generation of purchased electricity, heat, or steam. -GRI 305-5: Reduction of GHG emissions: Report the initiatives and achievements related to reducing GHG emissions. **-GRI 306: Waste** -GRI 306-1: Waste generation and significant waste-related impacts: Organizations need to describe the generation of waste and its significant impacts. -GRI 306-2: Management of significant waste-related impacts: Disclose how the organization manages waste-related impacts. -GRI 306-3: Waste generated: Requires disclosure of the total weight of waste generated.

			-GRI 306-4: Waste diverted from disposal: Report the weight of waste that has been diverted from disposal through various methods. -GRI 306-5: Waste directed to disposal: Report the weight of waste directed to disposal.
Best Available Techniques (BAT) Reference Documents (BREFs) (EC, 2024a)	BREF for the Manufacture of Organic Fine Chemicals, which includes pharmaceuticals, providing guidance on techniques to minimise environmental impact.	Regulatory	Focused on minimising environmental impacts of chemicals and pharmaceuticals from manufacturing practices.
Resource Conservation and Recovery Act (RCRA) (EPA, 2015)	Overall the RCRA contains several regulations for both storage and disposal of non-hazardous waste, hazardous waste, including but not limited to solid waste.	Regulatory	No specific mention of environmental sustainability, or sustainability in general. Does regard waste management but this is only indirectly addressing environmental sustainability.
Triple Bottom Line (TBL) framework (Elkington, 1998;Loviscek, 2021; Slaper & Hall, 2011**)**	Similar to the three pillars, focuses on people, profit, planet which is a generic overarching term, not specific to pharmacy and partially covers materials through planet.	Business	Planet is also the only aspect that covers environmental sustainability to some extent.
United Nations Global Compact (UNGC) (UN, 2024b)	Consists of 10 principles, grouped into human rights, labour, environment, and anti corruption. These principles are aimed at corporate sustainability and management in general. No specific	Business	Environmental principles listed as follows: - Principle 7: Businesses should support a precautionary approach to environmental challenges; - Principle 8: undertake initiatives to promote greater environmental responsibility; and - Principle 9: encourage the

	aspects regarding material use or pharmacy, however it applies to operational practices in general which can cover these.		development and diffusion of environmentally friendly technologies.
Pharmaceuticals in the Environment (PIE) (EFPIA, 2024)		Business, Academic	Eco-Pharmaco-Stewardship (EPS) initiative, on sharing responsibilities with stakeholders.

Appendix B: Interview Guide

Includes the preliminary information and detailed questions provided to interviewees.

The information document provided to interviewees includes a short background and the research questions. More important questions or aspects/important differences between questions are marked in bold. Interviewees have given permission to use this data for the thesis. The raw information from the interviews was transcribed, this information was processed into the results section. Interview contents and identifying information such as the names and organisation are available on request.

———

Interview preliminary information.

Background:
This study aims to explore how environmental sustainability can be better incorporated into pharmaceutical development and operations. We are interested in understanding the current operational practices, guidelines and frameworks, and material and equipment usage. Pharmaceuticals and chemical synthesis are outside the scope due to the large range of variations. The goal is to provide recommendations on how to make pharmaceutical development more (environmentally) sustainable by design.

The main research question:
"How can environmental sustainability be better incorporated in pharmaceutical development and operations?"

Purpose of the interview:
We seek to gain insights into how environmental sustainability is currently being implemented in pharmaceutical development and operations in practice. Your input will improve our understanding of the existing state of sustainability efforts, and highlight challenges and

opportunities for improvement. This information is compared to findings from literature and used to develop practical recommendations for enhancing environmental sustainability in the pharmaceutical sector.

QUESTIONS

1. How do you (your organisation) currently incorporate **environmental** sustainability in pharmaceutical development?

   Supporting questions:

   A. What **guidelines and frameworks** does your organisation follow to ensure environmentally sustainable practices within the pharmaceutical industry?

   B. Can you provide examples of sustainability initiatives or projects that your organisation has implemented in pharmaceutical production?

   C. How do you ensure that **environmental** sustainability is integrated into operational strategies, such as procurement, material usage, and waste management?

2. How do you measure or monitor the effectiveness of **environmental** sustainability efforts within operational practices?

   Supporting questions:

   A. When evaluating environmental sustainability only for non-pharmaceutical materials and equipment, how would you describe the current state? What metrics or methods do you use to evaluate or monitor environmental performance?

   B. Do you have more focused examples for procurement, material usage, or waste management?

3. What challenges and obstacles do you encounter in implementing environmental sustainability within pharmaceutical operations?

   A. How do you currently address these challenges and obstacles?

   B. In your opinion, what are the biggest challenges or obstacles?

4. In your opinion, how can environmental sustainability principles be better incorporated into the operations for pharmaceutical **production**?

    A. In terms of environmental sustainability performance, which aspects of pharmaceutical operations and development have the most potential for improvement?

    B. Looking ahead, what strategies or innovations do you envision to promote a more environmentally sustainable pharmaceutical sector?

    C. How would you describe the current efforts in environmental sustainability in pharmaceutical development and operations, specifically the relation between what **can** be done, what **is** being done, and what **should** be done?

    D. What improvements regarding environmental sustainability in the pharmaceutical sector would you (your organisation, or as an individual in your function) like to see the most?

5. Any further remarks or questions?

    A. Questions 1 and 2 are more aimed at the current state and structure and (guidelines for) operational practices in relation to environmental sustainability.

    B. Question 3 and 4 are aimed more towards obstacles and challenges, and potential areas for improvement on different scales.

    C. Any questions about the subject by the interviewee not directly about or beyond the interview questions?