Valorization of End-of-Use Medicines in the Pharmaceutical Industry - A Circular Economy Perspective

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Abstract

Almost everybody requires medication at some point in their lives. The Pharmaceutical Industry is fundamental to human life and well-being playing a crucial role as a medicines' provider. Moreover, the market has experienced significant growth in recent years leading, inevitably, to a considerable growth of waste. Therefore, the sustainability of this industry has received growing attention from policymakers, organizations, and consumers. However, several barriers affect the adoption and development of sustainable supply chain initiatives contributing to waste growth throughout the process.

Accordingly, this dissertation aims at creating solutions, tailored to the Portuguese reality, in order to implement the circular economy concepts in end-of-use medicines. To achieve this, it is necessary to comprehend the circular economy, its practices in the pharmaceutical industry and understanding the wastes along the supply chain. Therefore, a characterization of the pharmaceutical industry and a comprehensive literature review on circular economy and sustainability within this industry are going to be performed. Also, a case study in a Portuguese company will be explored and also a survey made to the Portuguese population in order to propose accurate and feasible solutions.

The results proved that there is a long path to be done nevertheless with some strategic changes, it is possible to leverage the current initiatives and defining new ones. The strict legislation under which the pharmaceutical industry works could be, in fact, lighten and also partially changed without compromising the medicines' quality and minimizing waste, turning this industry more sustainable.

Keywords: Circular Economy; Medicines; Pharmaceutical Industry; Pharmaceutical Supply Chain; Sustainability

Resumo

Toda a população necessita de medicamentos nalgum momento das suas vidas. A Indústria Farmacêutica é fundamental para a vida e bem-estar do ser humano, desempenhando um papel crucial como fornecedor de medicamentos. Com o envelhecimento da população, tem-se verificado um crescimento do mercado levando ao aumento de desperdício. Consequentemente, a sustentabilidade tem recebido especial atenção dos decisores políticos, organizações e consumidores. No entanto, a cadeia de abastecimento farmacêutica está sujeita a várias barreiras que afetam a adoção e desenvolvimento de iniciativas sustentáveis, contribuindo para o crescimento dos resíduos ao longo de todo o processo.

Esta dissertação tem como objetivo identificar soluções, adaptadas à realidade portuguesa, a fim de minimizar o desperdício e integrando a economia circular no fim de vida dos medicamentos. Para tal, é necessário compreender os conceitos de economia circular, as práticas nesta indústria e os resíduos presentes ao longo da cadeia de abastecimento. Assim, será efetuada uma caracterização da indústria farmacêutica e uma revisão literária sobre a sustentabilidade e economia circular. A fim de propor soluções precisas e viáveis, será aplicado um caso de estudo a uma empresa portuguesa assim como será analisado um inquérito distribuído pela população portuguesa.

Os resultados provaram que, apesar dos esforços, existe ainda um longo caminho a percorrer em relação a este tópico. Com algumas mudanças estratégicas, será possível alavancar iniciativas em curso e definir novas medidas para reduzir o desperdício. A legislação rígida que atualmente vigora em Portugal poderia ser aliviada e adaptada, sem comprometer a qualidade dos medicamentos.

Palavras-chave: Cadeia de Abastecimento Farmacêutica; Economia Circular; Indústria Farmacêutica; Medicamentos; Sustentabilidade

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List of Abbreviations

AESGP: Association of the European Self-Care Industry

AHP: Analytical Hierarchy Process

AICEP: Agência para o Investimento e Comércio Externo de Portugal

API: Active Pharmaceutical Ingredient

APIFARMA: Associação Portuguesa da Indústria Farmacêutica

BLGN: Bluepharma Genéricos

CAGR: Compound Annual Growth Rate

CLSC: Close-Loop Supply Chain

CSCM: Circular Supply Chain Management

EFPIA: European Federation of Pharmaceutical Industries and Associations

ERA: Environmental Risk Assessment

EU: European Union

FDA: Food and Drug Administration

FLASC: Fast Life Cycle Assessment of Synthetic Chemistry

FLW: Full-Line Wholesalers

GDP: Good Distribution Practices

GMP: Good Manufacturing Practices

GSK: GlaxoSmithKline

GSCM: Green Supply Chain Management

IED: Industrial Emissions Directive

IFPMA: International Federation of Pharmaceutical Industries and Associations

IMI: Innovative Medicines Initiative

LCA: Life Cycle Assessment

MAH: Marketing Authorization Holder

NHS: National Health Service

PMI: Process Mass Intensity

REACH: Registration, Evaluation, Authorization, and Restriction of Chemicals

R&D: Research and Development

SIGREM: Sistema Integrado de Recolha de Embalagens e Medicamentos

SSCM: Sustainable Supply Chain Management

VSM: Value Stream Mapping

WHO: World Health Organization

1.Introduction

1.1 Problem Contextualization

During the last decades, the Circular Economy has been receiving greater attention from the more diverse industries and companies, recognizing sustainability as an important aspect to traditional business (Fogarassy & Finger, 2020). The Pharmaceutical Industry is no exception. The sustainability of this industry has been growing attention from the different stakeholders: consumers, policymakers, and organizations (Milanesi et al., 2020). However, it has some particularities. In fact, pharmaceutical companies have very stringent guidelines and regulations (Faisal, 2015). They must follow specific legislation from the manufacturing to the products' end-of-life, which may hinder the adoption of sustainable practices and increases the wastage throughout medicines' life cycle.

Moreover, medicines produced by pharmaceutical companies are then distributed and used by humans. Therefore, such industry is crucial to ensuring life-saving products and services to society, making them indispensable to people's health and well-being. Their availability to the population is a priority in most EU member states, in which, on average, about two thirds of the expenditure is financed by the government (Vogler et al., 2011). This proves the significant role of the state in medicines dispensing.

In fact, it is a sector that differs from the usual physical goods supply chains due to the importance, their maintenance way, and the regulatory requirements they must meet to guarantee their quality (Settanni et al., 2017). Unlike a "normal product," if the medicine is broken, it cannot be "repaired". When a consumer no longer needs a medicine, it cannot be easily passed on and reused by other consumers (such as a computer), which may cause more waste. The products and services provided in this industry have several impacts not only on people but also on the environment in different ways (European Commission, 2019). These may include expired or unused medicines, inappropriate distribution by pharmacies or drug companies, or even improper disposal of surplus medicines.

The pharmaceutical industry is growing rapidly, improving the research and development of medicines; however, the proper execution of supply chain activities (Faisal, 2015) and the integration of circular economy concepts in this sector is essential to minimize the generation of massive pharmaceutical waste, which is harmful to the environment and directly impacts human health. Therefore, the goal of this study is to identify the significant causes of waste by analyzing how the different entities that integrate the pharmaceutical supply chain are responsible. It also aims at proposing different solutions, taking into consideration the Portuguese reality, in order to integrate circular economy concepts in this industry, turning the supply chain more sustainable while minimizing waste. The focus will be on the downstream part of the supply chain, i.e., where the final product is already made.

It is worth mentioning that, in order to taper down into the Portuguese reality and have practical and close insights on this topic, a case study applied to a Portuguese pharmaceutical company, Bluepharma Genéricos (BLGN), will be studied to draw conclusions about it. The Portuguese market regulation in Portugal is very strong: Vogler et al. (2012) places Portugal among the countries with the largest number of legislative actions, together with Spain, Greece, and Iceland.

1.2 Master Dissertation's Objectives

The aim of this work is to study the current situation of circular economy in the pharmaceutical industry in order to understand the market and analyze what is being made by the industry regarding this topic. In addition, this dissertation also has the objective of proposing solutions, applied to the Portuguese context and reality, while integrating the circular economy principles.

The master dissertation seeks to provide the following objectives: (1) Problem identification: characterization and analysis of the pharmaceutical industry and investigation of sustainable actions and practices in this industry; (2) State of the art on the circular economy, sustainable supply chains with emphasis to the pharmaceutical sector; (3) Definition of the research methodology: describe each step of the methodology; (4) Understanding the Portuguese reality (both regarding the industry and the consumers) in order to propose solutions to turn the pharmaceutical supply chain more sustainable and circular; (5) Derive conclusions and suggestions for the future.

1.3 Master Dissertation's Structure

The following master dissertation is composed of six sections, detailed next:

Chapter 1 presents an introduction over the dissertation, which includes a contextualization of the problem analyzed and sets the main study's goals.

Chapter 2 provides a complete characterization of the pharmaceutical industry and market analysis. It is detailed how the industry and its supply chain operates. Additionally, a brief description of the circular economy concept is provided as well as its integration within the pharmaceutical context where a benchmarking of the actions undertaken by pharmaceutical companies is presented. The chapter ends with the problem characterization.

After the problem has been identified, a theoretical analysis is essential. Thus, **chapter 3** gives a comprehensive state of the art on circular economy and sustainable supply chains. Also, a literature review relating their principles and methods with the pharmaceutical sector is presented, discussing what has been explored in this area while identifying possible gaps that exists in the literature, which will be the purpose for conducting this work.

Chapter 4 describes the methodology to be implemented throughout the master thesis in order to meet the objectives previously defined. Different methods and processes will be presented with the correspondent theoretical basis.

Chapter 5 comprises four main sections, corresponding to the four steps identified in the research methodology. Therefore, it is provided a presentation of the outcomes obtained from each phase alongside with brief discussion and the development of solutions taking into consideration the Portuguese reality.

Lastly, **Chapter 6** includes the final and major conclusions of the project as well as a brief reflection on the further work to be developed, regarding the circular economy in the Portuguese pharmaceutical industry.

2. Pharmaceutical Industry

This chapter characterizes the pharmaceutical industry, and it is divided into four sections. Section 2.1 provides an overview of the pharmaceutical industry and its importance: first, globally, then looking into Europe and finally some highlights of this industry in Portugal and how it is represented. Section 2.2 presents the complex supply chain of pharmaceuticals. The pharmaceutical path involves many entities and processes. Consequently, different types of waste are generated, which is progressively turning into a key environmental concern, and therefore, pharmaceutical waste is also discussed in section 2.3. Then, in section 2.4, the concept of circular economy is introduced, and it is linked with the pharmaceutical sector. The chapter finishes with a description of some circular economy opportunities and activities undertaken by this industry. Lastly, section 2.5 characterizes the problem, which will be the focus of this work.

2.1 Market Characterization

2.1.1 Economic Sector Overview

Almost everybody requires medication at some point in their lives. People globally depend on pharmaceutical products and innovation for their health. Through its role as a provider of medicines and vaccines, the pharmaceutical industry is not only saving lives but is also contributing to economic welfare. Societal welfare and economic growth are built on the foundations of having a healthy and thus productive population (Sustainalytics, 2019). Therefore, this industry is fundamental to human life and well-being and has an important responsibility to provide reliable, effective, and safe medicines (WHO, 2006). The benefits of responsible use of pharmaceuticals for human health are recognized; however, there is a flip side of these substances They can also create adverse effects on the environment and human health via the environment when discharged, either through consumption or as unused products (Deloitte, 2016). The market has experienced significant growth in recent years, and the total global pharmaceutical market was valued at US$1.25 trillion in 2019, in comparison to US$390 billion, from 2001 (Statista, 2020). Consequently, worldwide prescription drug sales are expected to see a Compound Annual Growth Rate (CAGR) of 6.9% from 2018 to 2024. It is projected to rise from US$900 billion in 2019 to US$1.2 trillion by 2024, as represented in Figure 1.

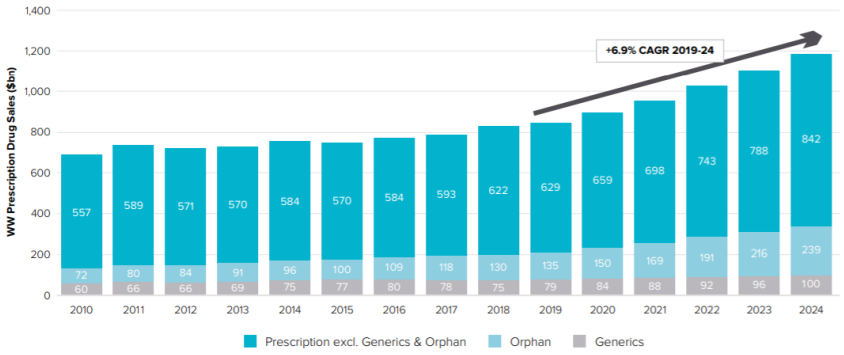


Figure 1: Worldwide Total Prescription Drug Sales- 2010-2024 (Evaluate Ltd, 2019)

In dollar terms, such growth puts worldwide pharmaceutic revenues at US$900 million in 2020 – a large sum but modest relative to total healthcare spending (Evaluate Ltd, 2019). Moreover, the pharmaceutical segment of rare diseases is gaining market, accelerating drug approvals. Besides this, there are additional reasons for the sales growth expected for the pharmaceutical sector, such as demographics (population is growing and aging) as well as innovation (The Business Research Company, 2018). The global population is expected to grow from 7.6 billion in 2020 to 8.5 billion by 2030 and 9.7 billion by 2050 (United Nations, 2019). It is also aging rapidly; by 2030, the total number of people aged 60 or over globally is projected to have risen to 1.4 billion- 16% of the world's inhabitants- from 901 million in 2015- 12% of the world's inhabitants (United Nations, 2015). In fact, older people typically consume more medicines than younger people- in five people aged over 75 take at least one prescription product, while 36% take four or more (PwC, 2007). Ensuring that adequate and appropriate health care is available to growing numbers of older people is a challenge shared by countries worldwide. Moreover, overall life expectancy is projected to increase from an estimated 73.7 years in 2018 to 74.7 years by 2023 (Deloitte, 2019). Therefore, if people are going to live longer, a need for more medicines to be accessible is foreseeable. In addition, biotechnology is contributing to the pharmaceutical industry by advancing new strategies and techniques to prepare medicines, diagnose, and treat many types of diseases products (Roche, 2008). Therefore, pharmaceutical companies use biotechnology for manufacturing drugs and pharmacogenomics derived from living organisms- biopharmaceuticals. By contrast, the "traditional" pharmaceuticals involve chemical and synthetic processes (McKinsey & Company, 2014). According to EUROSTAT data, the pharmaceutical industry and biotechnology is the sector with the highest ratio of R&D investment to net sales, as it is represented in Figure 2.

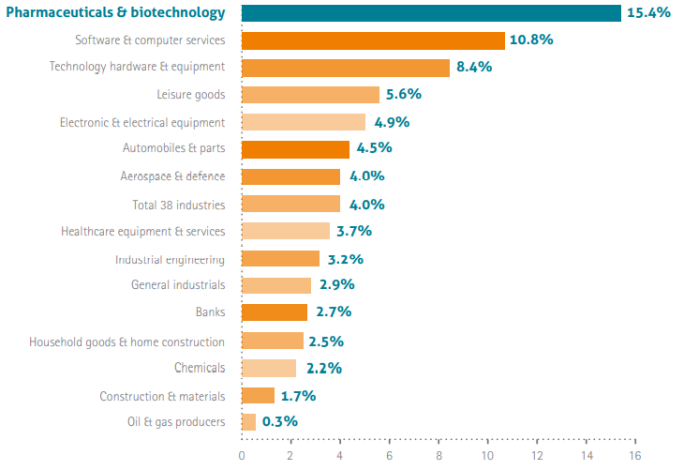


Figure 2: Ranking of industrial sectors by overall sector R&D intensity in 2019 (EFPIA, 2020a)

In fact, investing in biotechnology R&D has generated better returns than the pharma-industry average (McKinsey & Company, 2014). Therefore, the biopharmaceuticals market is growing fast and developing, and it is expected to continue for the future. In 2017, the global market accounted for US$186 million and was expected to reach US$526 million by 2025 (Allied Market Research, 2020).

Therefore, due to advances in science and technology, the pharmaceutical industry is developing research into innovative treatments and medicines contributing to patient well-being (EFPIA, 2020a). In conclusion, the pharmaceutical industry is a key asset not only to scientific and medical progress but also to the economy globally, including the European and Portugal market.

2.1.2 Pharmaceutical Industry in Europe and Portugal

The quantities of pharmaceuticals sold on the European market have grown quickly, both in terms of volumes of sales and numbers of Active Pharmaceutical Ingredients (APIs). Nowadays, more than 3000 APIs are on the market (European Commission, 2019). The Pharmaceutical Market in the EU values €183 million, positioning Europe as the second biggest pharmaceutical market globally, with Germany, France, Italy, United Kingdom, and Spain as the top 5 countries. However, in comparison to the globe, this represents a low value. In 2019 North America accounted for 48.7% of world pharmaceutical sales compared with 22.9% for Europe (EFPIA, 2020a). Medicinal products are advancing; however, there are challenges. The regulation of drugs involves rigorous standards and a complex regulatory environment. Governments generally fix prices and distribution margins, and VAT rates differ significantly from country to country in Europe (PwC, 2012). Portugal is a member of the European Union, and despite its relatively small dimension, it has an interesting market size. In 2018, the pharmaceutical market was valued at €3.890 million (APIFARMA, 2018), which has been increasing, since 2013, as shown in Figure 3.

Figure 3: Total pharmaceutical market in Portugal (in € million), 2010-2018 (APIFARMA, 2018)

Portugal represents about 2% of the EU pharmaceutical market. Moreover, Portugal is a net importer of pharmaceutical products since most multinational companies do not have production sites in Portugal, but mainly commercial offices. As observed in Figure 4, Portugal still has a trade deficit in Pharmaceutical related products. In 2018, pharmaceutical products and raw materials imports amounted to €2.636 million, while exports amounted to €979 million.

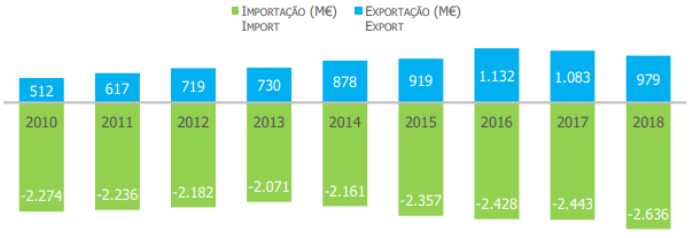


Figure 4: Pharmaceutical Trade Balance in Portugal, 2010-2018 (APIFARMA, 2018)

In order to increase the level of exports of pharmaceutical products, a public-private partnership between 14 national pharmaceutical groups and companies, AICEP, a business development agency, the Portuguese Association of the Pharmaceutical Industry (APIFARMA), and INFARMED, the national authority for medicines (which are going to be described above) set up the Strategic Project for the Export and Internationalization of the Portuguese Pharmaceutical Industry (PharmaPortugal, 2018). Given the quality of research infrastructures, Portugal is a competitive supplier of specialized scientific, technological, and analytical services however, although the quality, compared to other countries in Europe, the investment in R&D is significantly low: 100 million € vs. 5000-6000 million € from UK, Switzerland, or Germany (APIFARMA, 2018). Nevertheless, Portugal has the potential to become a

specialized center for pharma R&D and turn Portugal into a competitive player in the research, development, and manufacturing of products and services of high added value related to health (Health Cluster Portugal, 2020).

Portugal's pharmaceutical industry is dominated by multinationals, most of which import finished products. However, Portuguese companies are internationally recognized as high-quality suppliers of medicines, having high standards of quality and being able to produce and supply several products (PharmaPortugal, 2018). As mentioned before, an important Portugal authority significant to note is INFARMED, the national authority for medicines and health products, which carefully analyzes the value-added of each drug against the preexisting range of treatments, both from a therapeutic and a relative price standpoint. (INFARMED, 2016). Moreover, INFARMED plays a significant role regarding the reimbursement and market access of medicines, as it is the entity responsible for guiding the relevant procedures and proposing decisions to the Minister of Health. Its power also covers pricing and market access (The Law Reviews, 2020). APIFARMA, the Portuguese Association of the Pharmaceutical Industry, represents about 120 companies, and it is responsible for the production and marketing of medicinal products for human and veterinary use, vaccines, and in-vitro diagnostics. It contributes not only to the socioeconomic development of the pharmaceutical sector and the country but also to the improvement of health in Portugal (APIFARMA, 2020). Also, APIFARMA has international relationships and cooperates with different identities, such as EFPIA- European Federation of Pharmaceutical Industries and Associations- which represents the research-based pharmaceutical industry operating in Europe. However, every medicine on the market will have a long and complex pathway throughout its lifecycle. The approval of drugs for placement on the Portuguese market is governed by rules and procedures of the European regulatory system as well as by national policies based on scientifically objective criteria, safety, efficacy, and protection of public health (The Law Reviews, 2020). Due to the strict regulation and legislation, including in Portugal, waste created throughout the pharmaceutical supply chain is significant, representing a topic to which attention must be given.

2.2 Pharmaceutical Supply Chain

The pharmaceutical supply chain is defined as a "combination of processes, organizations, and operations involved in the development, design, and manufacturing of useful pharmaceutical drugs" (Singh et al., 2016). In other words, it is the means through which prescription pharmaceuticals are manufactured, available, and accessible to patients. It is a complex system involving the participation of a wide range of stakeholders which play different roles throughout the supply chain: manufacturers, wholesalers, distributors, health agents (hospitals, clinics, pharmacy chains), customers as well as regulatory agencies and research organizations (The Health Strategies Consultancy LLC, 2005). Also, the challenge of manage this supply chain increases due to short product life cycles, the increased outsourcing, the continuous advances in information technology which raises the variety of products, and also the high uncertainties in demands and capacity planning (Singh et al., 2016). Pharmaceutical companies are responsible for the organizational, operational, and value-adding activities needed to manufacture medicines and making them available to the final users (PwC, 2011).

As it is represented in Figure 5, the pharmaceutical supply chain has two principal stages: manufacturing and distribution. Generally, pharmaceuticals are originated in manufacturing plants, packaged, and finally distributed. The distribution is direct to providers or via a distributor, with providers ultimately selling or providing the drugs to the patients (Infosys Knowledge Institute, 2020).

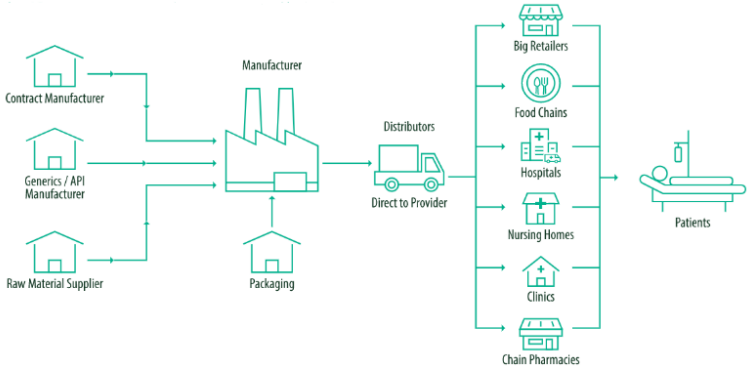


Figure 5: Pharmaceutical Supply Chain (Infosys Knowledge Institute, 2020)

The pharmaceutical manufacturing industry distinguishes brand manufacturers from generic manufacturers. Brand manufacturers produce finished goods in self-owned facilities or via third-party manufacturers. Most brand manufacturers dedicate a portion of their expenses to the scientific research and development of new drug therapies. On the other hand, generic drug manufacturers typically do not develop new drug therapies but instead manufacture generic compounds that compete directly with the originally patented version of the drug product once the patent has expired (The Health Strategies Consultancy LLC, 2005). Therefore, a generic drug is a drug with the same API, pharmaceutical form, and dosage, and with the same therapeutic indication as the original brand name drug, which served as a reference (FDA, 2017). The pharmaceutical industry also makes another distinction regarding the manufacturing step: the primary manufacturing and the second manufacturing:

- **Primary manufacturers** are responsible for producing required APIs, including either several chemical synthesis and separation stages to create the complex molecules or fermentation and purification in case of biochemical processes (Shah, 2004). API is the term used to refer to the biologically active component of a drug product that generates a desired pharmacological effect (WHO, 2011).
- **Secondary manufacturing** focus on taking the API already produced and adding excipients- also called inactive ingredients- which are all the other substances without pharmacological effect (Pharmaceutical Excipients, 2021). Therefore, the excipients are formulated in combination with APIs to manufacture finished pharmaceutical products. These manufacturers are not only responsible for further production processes with different technology levels but also for the **packaging**; this means finalizing the products in SKU form (Zahiri et al., 2017).

Both manufacturing stages may involve contract manufacturers, who do not have their own product portfolio but produce either key intermediates of active ingredients or final products by providing outsourcing services to other companies. This outsourcing process is a source of complexity in the supply chain. Still, it is also convenient as research-oriented companies concentrate on the discovery and development activities and rely on third parties' manufacturing competencies (Shah, 2004).

The packaging process is crucial to ensure the formulation protection against the environment to enhance its shelf life and conserve its content (WHO, 2002). Regarding this aspect, it is also important to refer the existence of three types of pharmaceutical packaging used by drug manufacturers.

- The **primary packaging** is the most important since it has a direct contact with the product (WHO, 2002). Usually, the materials used in this type of packaging are blister strips and pet bottles since they are made of nonreactive substances such as aluminum and PVC.
- Then, the packaging external to the primary packaging is the **secondary packaging**. It provides the additional physical protection necessary to ensure product safety and also the information about product name, properties, etc.
- Finally, **tertiary packaging** is important to keep the product safe during shipping and transportation (Swiftpak, 2020).

Packaging is the final step of the secondary manufacturing process before the distribution of finished goods. The distributors purchase pharmaceutical products already manufactured and distribute them to a variety of customers, including pharmacies, hospitals, clinics. Sometimes the pharmaceutical manufacturers manage the distribution directly to the pharmacy and hospital chains (The Health Strategies Consultancy LLC, 2005). As we can see and is represented in Figure 5, pharmaceuticals are submitted to different stages and processes. Owing to the unique nature of these products and their critical role in meeting global health challenges, this market is heavily regulated. Not only are the prices controlled to ensure accessibility and affordability but also the quality of both new and existing pharmaceutical products (Chen et al., 2020a). Moreover, throughout the value chain, from the R&D and manufacturing processes to the distribution and consumption, emissions and waste are produced. These have an impact on ecosystems and human populations. Legislations are increasing, and pharmaceutical companies have been more focused regarding this topic by evaluating the safety and efficacy of the chemical compounds, assessing the environmental impacts of the different processes, and also finding new ways of managing the waste (Bio Intelligence Service, 2013) - as it will be described in the next sections.

2.3 Pharmaceutical Waste Management

Companies' operations generate waste throughout the whole process, from chemical waste to expired or no longer needed pharmaceuticals. Pharmaceutical waste is not one single waste stream but many distinct waste streams that reflect the complexity and diversity of the processes that comprise pharmaceuticals. It includes not only expired and contaminated pharmaceutical products but also drugs and vaccines that are no longer required (Bio Intelligence Service, 2013). Different types of pharmaceutical wastes carry different types of risks and are governed by different sets of regulations (WHO, 2006). Pharmaceutical waste can be characterized either as hazardous- dangerous or potentially harmful to human health or the environment- and non-hazardous waste, this is, waste that is not governed by laws nevertheless must be disposed of properly. About 5 to 10% of pharmaceutical products can be classified as hazardous waste (Stericycle, 2004). Hazardous wastes pose a greater

risk to the environment and human health than non-hazardous waste and thus require a stricter control regime. The classification into hazardous and non-hazardous waste is based on the system for the classification and labeling of dangerous substances, which ensures the application of similar principles over the whole life cycle of materials. EU has some properties which classify hazardous waste as explosive, oxidizing, flammable, irritant- skin irritation and eye damage, toxic, carcinogenic, corrosive, infectious, mutagenic, sensitizing, and eco-toxic (European Commission, 2018). Waste is generated throughout the product's life cycle and residues of pharmaceuticals can enter the environment at all stages during production, use, and disposal. Understanding the life cycle impacts of any medicine is vital to understand the environmental and wastage created across the entire range of activities (AstraZeneca, 2019).

API Production/Formulation (1st Manufacturing):

Pharmaceuticals may end up in the environment due to effluents from manufacturing facilities being a source of pharmaceutical pollution. Responsible environmental management requires controlling the amount of APIs entering the environment (Sanofi, 2020a). The API is generated from the chemical synthesis, fermentation- production and separation of medicinal chemicals such as antibiotics and vitamins from microorganisms, and extraction- manufacture of botanical and biological products by the extraction of organic chemicals from vegetative materials or animal tissues (EPA, 1978). Regarding these processes, the main pharmaceutical hazardous waste consists of solvents and aqueous streams used in chemical syntheses - such as volatile organic compounds, which typically are industrial solvents. These compounds have a high vapor pressure, low water solubility and may contribute to air emissions. Once in the environment, they react with sunlight to create photochemical smog that is both carcinogenic and toxic to humans (EPA, 1978). EU legislation regarding manufacturing includes Good Manufacturing Practices (GMP): related to APIs production; Industrial Emissions Directive (IED): associated with emissions limit values (IED); and Regulation on the Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) to improve the protection of human health and the environment from the risks of chemicals. Also, incentives for the development of green medicinal products, such as extending data protection or patent duration for this type of products have been promoted (Bio Intelligence Service, 2013).

Packaging (2nd Manufacturing):

Although pharmaceutical packaging represents a very small percentage of waste, its disposal may cause problems for the environment (WHO, 2002). Pharmaceutical companies use many types of packaging for the medicines and vaccines they sell, and it requires the use of different raw materials. Environmental problems result from the methods used for waste disposal and will depend on the type of packaging waste concerned. It can include uncontaminated waste (paper, cardboard, glass, plastic) and also contaminated waste, for example, waste that has been in contact with blood, radioactive products, or cytotoxic products (WHO, 2002). In each country, specific regulations govern packaging, for example, acceptable concentration levels of certain heavy metals in packaging and the collection and recycling of packaging materials (Sanofi, 2020b). Moreover, the European Commission made directives regarding the packaging and packaging waste placed on the European market, setting targets

(Directive 94/62/EC) for the different materials recycling. The directive aims at harmonizing national measures concerning this topic and improving the quality of the environment by preventing the production as well as reducing the impact on the environment- promoting reuse and recycling instead of its final disposal (European Commission, 2020).

Usage/Disposal:

The pharmaceuticals that end up in surface and ground waters through end-of-life disposal or patient excretion also represent a significant environmental risk (EFPIA, 2017). Medicinal products may be indirectly released into the environment from waste treatment facilities, including incinerators, landfill sites, or wastewater treatment plants, as represented in Figure 6.

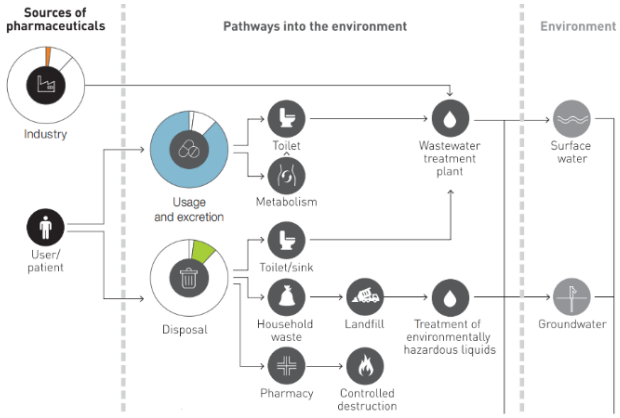


Figure 6: Different sources and pathways of pharmaceutical in the environment (EFPIA, 2017)

According to AstraZeneca, 88% of pharmaceuticals in the environment can be attributed to patient use and excretion of drugs (AstraZeneca, 2015). Pharmaceutical waste cannot be disposed of like conventional waste and requires special handling due to its dangers. Therefore, proper collection and disposal of pharmaceutical waste can contribute to reducing the impact of pharmaceuticals in the environment (Health Care Without Harm, 2013) while also minimizing waste by reusing it. In the EU, legislation under the waste framework embraces take-back schemes for unused and expired human medicinal products since 2004 (Bio Intelligence Service, 2013). Portugal has a national collection system for unused pharmaceuticals called SIGREM – Sistema Integrado de Recolha de Embalagens e Medicamentos fora de uso. This system covers household pharmaceutical waste, including veterinary pharmaceuticals, pharmaceutical packaging produced during industrial or distributor activity, and packaging from health providers (MedsDisposal, 2020). Pharmaceutical waste and pollution management is a challenge that concerns most stakeholders, which implies precise waste monitoring and tracking throughout the value chain. Proper waste management in the pharmaceutical sector involves preventing waste, reducing the quantity of hazardous waste generated by substituting hazardous process ingredients, or recycling/reusing whenever it is possible (Sanofi, 2020c). As we could see, decisions involving the supply chain, such as the sourcing of raw materials, packaging, and pharmaceuticals disposal, have potential negative impacts on the environment and can create unnecessary waste. To enhance the long-term sustainability of their supply chains, different measures and approaches are being taken, especially focusing on the promotion of reusing, recycling, and other forms of recovering the different types of materials. These activities contribute to the transition towards a circular economy- as it will be described in the following section (European Commission, 2020).

2.4. Contribution of the Pharmaceutical Sector in Circular Economy

As represented above, EU is already playing an active role in pharmaceutical waste and activities that enhance the reuse and the recycling of different materials. In fact, the planet has finite boundaries, and in the linear economy model of production and consumption, the wastes generated through extraction and production of the goods and the post-consumption products generate pollution and eventually end up either in a landfill or are dispersed and contaminate the environment (Sauvé et al., 2016). Therefore, to prevent this from happening, the focus of any industry should be minimizing waste. Instead of today's take–make–dispose linear model of production where products are manufactured, used, and discarded, the circular economy is a system where the products of today may also be the raw materials of tomorrow (McKinsey & Company, 2016) this means, the "waste" from one process should be the input for another. The circular economy is restorative by design—using and reusing natural capital as efficiently as possible and finding value throughout the life cycles of finished products (McKinsey & Company, 2016). According to The Ellen MacArthur Foundation "formed to inspire a generation to rethink, redesign and build a positive future", three majors principles govern the circular economy: optimize resources by circulating products and components, reusing them as much as possible (closing cycles); preserve, regenerate and enhance natural systems (therefore reducing environmental impacts) and also design out waste and pollution (Ellen MacArthur Foundation, 2012). However, this concept will be thoroughly detailed in the following section. By engaging the circular economy approach, the pharmaceutical industry has an opportunity to ensure access to sustainable supplies of raw materials and energy in a resource-constrained world while also building a more sustainable and competitive business model (EFPIA, 2020b). There are already some contributions of the pharmaceutical sector in a circular economy focused on the Action Plan. Entities such as EPFIA and IMI play important roles in addressing this subject. IMI is the world's largest public-private partnership in health in the life sciences. It is a partnership between European Union- represented by the European Commission- and the European Pharmaceutical Industry- represented by EFPIA (IMI, 2020). Circular Economy Action Plan has identified that up to 80% of products' environmental impacts are determined at the design phase (European Commission, 2020), which highlights the importance of circularity in pharmaceutical research and development. Although its significance and consequent opportunities for growth and resource efficiency, due to the regulatory approval process for pharmaceuticals, it is currently very challenging to introduce innovative changes to enable circularity. It should be carefully balanced for not compromising the quality of the products (EFPIA, 2020b). Therefore, there are several opportunities and challenges that the pharmaceutical industry can address in a circular economy perspective throughout the value chain:

1st Manufacturing

In the design phase, choosing sustainable materials such as renewable, recycled, or low impact materials is fundamental to not only avoid using fossil-based materials and reduce carbon footprint, as well as leverage circular material flow and maximize product lifetime (Sanofi, 2020d). For example, using bio-based materials can lower the environmental impact creating future demand for sustainable products. These materials are derived from plant and animal-based sources. However, companies must take into consideration that bio-content is sourced to avoid ethical concerns regarding food scarcity and

deforestation (Novo Nordisk, 2020). Moreover, turning waste into secondary raw materials is also an opportunity for the pharmaceutical industry to minimize the environmental impact while moving to a circular approach. This approach is already widely adopted across the industry, especially for solvents, water, and packaging materials (EFPIA, 2020a). Regarding solvents, choosing the least toxic ones, reducing their quantities in industrial processes, and recycle them whenever possible are principles of green chemistry that companies are already actively applying (Sanofi, 2020d). Green chemistry focuses on making industrial chemistry safer and cleaner while also giving more consideration to how energy could be used more efficiently while generating economic benefits (EPA, 2017). Recovery and reuse of specific solvents, reactants, intermediates, and API are possible with the guarantee that accurate procedures exist for the recovery, and also the recovered materials meet all requirements for the intended use. Regular use of secondary raw materials is a challenge due to the high quality and purity requirements for medicines (WHO, 2006). On the other hand, recycled and recovered materials which do not comply with pharmaceutical quality requirements might be used for new purposes by different industrial sectors. This can be done by strong circular economy partnerships and active collaboration across sectors (Ellen MacArthur Foundation, 2012). As it has been mentioned, pharmaceutical products must have the lowest environmental impact over their intended lifetime. The product lifetime can be improved by making Life Cycle Assessments (LCA). This method helps to identify the most significant contributors to the environmental impact of a product, including raw materials, production, use, and waste management (Deloitte, 2016). Also, the development of an Environmental Risk Assessment (ERA) to evaluate the environmental impacts and potential risks during the development of new drugs contributes to the evaluation of the potential environmental risk (EMA, 2006). The extensive drug development process determines the appropriate dosage to cure patients while not over-prescribing and reducing the number of materials used, minimizing the waste. Moreover, the pharmaceutical industry is also increasing its focus to prevent disease and provide cures rather than long-term treatment of symptoms with the associated resources usage and thus saving and reducing them (EFPIA, 2020b).

Packaging (2nd Manufacturing)

Efforts are being made regarding reducing packaging (i.e., reducing the volume and weight of packaging materials) and eliminating the unnecessary and redudant protection of medicinal products. For example, minimizing the bulk of packaging by using multiple dosage containers rather than single-use containers (WHO, 2002). The use of environmentally friendly packaging is being considered: recyclable or degradable packaging made of renewable and biodegradable materials. These materials contribute to the development of sustainable pharmaceutical packaging while reducing the environmental impact of the disposal. Materials such as aluminum have been extensively recycled for many years. Recently, paper, glass, and plastic materials have joined the list of recyclable packaging materials. However, materials that have been in contact with toxic or highly potent drugs require special consideration (Singh et al., 2011). Some plastic materials cannot be recycled and are therefore incinerated. This method is regarded as the best available for the elimination of contaminated packaging because it significantly reduces the volume disposal (WHO, 2002). Moreover, the pharmaceutical industry has been executing extensive research into packaging to extend the shelf life of a product and minimize waste generation.

In general, extending the lifetime of products will lower the environmental impact by the reduction in product loss, but this must be evidenced, for example, by life cycle analysis (Deloitte, 2012).

Usage/Disposal

Currently, many products end up in landfills, which is a waste of resources and may be a cause of pollution. Pharmaceutical companies must take responsibility for the end-of-life of their products. Therefore, they are exploring the possibilities to design products, so it is easy to recycle valuable materials at their end-of-life (Novo Nordisk, 2020). Also, patient education programs to raise awareness on the importance of responsible end-of-use disposal of medicines have been established in many countries. In this way, improper disposal of unused pharmaceuticals is avoided. Moreover, there are take-back programs and establishing incentives to ensure that unused or outdated products are returned by retailers and others in the supply chain (Roche, 2020a). In conclusion, new ways of turning waste into resources, prolonging the life of products, and changes to consumer behavior are important key factors to move the pharmaceutical industry towards a more circular economy. However, its implementation is easier with the cooperation of industries as well as joint work with all the supply chain identities to ensure resource efficiency and sustainability (EFPIA, 2020a). The table in Appendix A represents a detailed analysis of the activities performed by five companies: GlaxoSmithKlein (GSK), Roche, Sanofi, AstraZeneca, and Novartis. According to Dow Jones Sustainability Indices, a global ranking published annually, these are the 5 Europe sustainability leaders in 2020, under the category "Pharmaceuticals" (S&P Global, 2020). The indices are determined by a complete assessment of long-term economic, environmental, and social criteria, which take into account general and industry-specific sustainability trends. The table is organized to better understand what the industry leaders are doing throughout their supply chain in order to be more sustainable and cope with a circular economy. The first manufacturing was divided into two columns: the process design, more related to the green manufacturing, and the production process itself and the product design. As it can be observed, all these companies are aligned with green manufacturing processes, reducing the use of hazardous substances and selecting the least toxic solvents. Regarding the product design, all recognize the need for the development of "greener" medicines trying to design products that cause less environmental burden. The second "main" column describes the efforts of these companies to reduce the environmental impact of their packaging, including programs to reduce packaging size and weight as well as setting limits on packaging-related waste. The column "patient use and disposal" emphasizes the responsible management of unused pharmaceutical products. Companies are trying to share responsibility for all relevant stakeholders. Most of them have established take-back programs for a number of key products and programs dedicated to consumer's education. Also, faced with a significant increase of waste that is generated throughout the supply chain, these companies have developed strategies to address this issue. Proper waste requires reuse, recycling, and energy and water recovery in order to optimize resource efficiency. However, despite these activities undertaken by some international sustainable pharmaceutical companies, in Portugal, small efforts are being made regarding this topic. In fact, circular economy in the pharmaceutical industry is not an “urgent issue" (Bluepharma 2020, Bial 2020).

2.5 Problem Characterization

Over the past years, circular economy has increased the attention from diverse industries and companies demanding transforming business processes into sustainable, close-loop resource systems (Fogarassy & Finger, 2020). The pharmaceutical industry is no exception, and the sustainability of this industry has been a focus from the different stakeholders: consumers, policymakers, and organizations. A paradigm shift of applying circular economy principles to achieve sustainable manufacturing is accepted by different manufacturing industries, including the pharmaceutical manufacturing industry, which has started to look into resource loops, such as drug ingredients, solvents, energy consumption (Ang et al., 2021). However, despite the fact that this industry plays a vital role in the structure of each country by providing medicines and vaccines with a direct impact on the population's quality of life, the complexity and particularities of this industry, as well as the strict regulations that are subjected to, represent an obstacle to implementing a circular economy throughout its supply chain. Therefore, wastage during medicines' life cycle increases, having social, environmental, and economic impacts. Accordingly, it is necessary to understand how the different entities that integrate the supply chain are responsible for the waste and realize what are the critical issues in order to integrate the circular economy concepts. Thus, the objective of the study is to identify the significant causes of waste and problems along the pharmaceutical supply chain and propose different solutions/scenarios in order to implement circular economy concepts in this industry and consequently to reduce the waste present along the supply chain. Moreover, in order to have a practical and close insight on this topic regarding the reality we are inserted, the Portuguese one, a case study applied to a Portuguese pharmaceutical company, BLGN, will be studied to draw conclusions about it and tailor the solutions to the Portuguese context.

2.6 Chapter Conclusions

The Pharmaceutical Industry has a direct impact on people's lives, not only because it contributes to their well-being in terms of health and quality of life but also because it is one of the most relevant sectors for the economy at a global level, playing a key role for national healthcare systems in most countries. Due to the unique nature of pharmaceutical products and their critical role in global health, the quality of medicines must be guaranteed. Therefore, the pharmaceutical market is heavily regulated, forcing pharmaceutical companies to meet regulatory requirements in terms of quality standards and price regulation/legislation. Moreover, an aging world population and the significant growth in the global pharmaceutical sector in recent years are raising awareness of the need to pursue sustainable development and a circular economy throughout the supply chain. Relevant examples demonstrate how the most sustainable pharmaceutical companies are addressing this topic and the activities that can be undertaken by the industry to reduce waste and turn this industry more circular.

3. State of the Art

This chapter provides state of the art about research on circular economy, sustainability in supply chains, and how these terms are addressed in the pharmaceutical industry. In section 3.1, the concept of circular economy is presented as well as its most relevant established definitions. In section 3.2, the concepts of sustainable supply chain management, closed-loop supply chain, and reverse supply chain are presented and linked with each other in order to understand the global picture of a sustainable supply chain. Moreover, the integration of circular economy in sustainability will be introduced since these two concepts have several aspects in common, and their distinction is still not explicit. Then, in section 3.3, a thorough literature review was conducted mainly to understand which subjects related to sustainability were addressed in the pharmaceutical supply chain. The fundamental principles are presented, and the main aspects of sustainability in manufacturing and waste disposal/management are detailed. In the end, the concept of reverse supply chain in this industry will be addressed, and the association with sustainability will be explicit, and a few words will be made regarding circular economy and sustainability in the pharmaceutical industry.

3.1 Circular Economy

The idea of the "circular economy" is not new. Its roots came from a variety of "schools of thought"; therefore, it cannot be traced back to one single date or author (Ellen MacArthur Foundation, 2012). The circular economy as a concept has its antecedents in broader historical, economic, and ecological fields and, in recent years, scholars from different fields have conducted a wide variety of researches on this topic in order to reduce the environmental problem (Murray et al., 2017). Therefore, its concept has been refined throughout the time as a result of academics, thought leaders, and businesses and developed by the different schools of thought (Ellen MacArthur Foundation, 2012), as it is going to be described.

The introduction of the actual concept "circular economy" is associated with Pearce and Turner, in 1990, who built their theoretical framework on previous studies of the ecological economist Kenneth Boulding, as mentioned in different studies, namely Su et al., (2013); Ghisellini et al., (2016); Geissdoerfer et al., (2017); Andersen (2007) and Murray et al., (2017). Boulding introduced the concept of closed systems- where success is achieved by minimizing the throughput from "factors of production," in contrast to open systems with infinite resources and predicted a future economy that would consider limits for both inputs and outputs in production and consumption processes (Cesari & Jarrett, 1967). In fact, the open and closed systems presented reflect the characteristics of what we consider today as linear and circular economies, respectively (Rizos et al., 2017). He was the first to combine economics and science and presented a warning about the deterioration of the environment as a result of human actions (Shen et al., 2020). Industrial Ecology also contributed to the circular economy concept being considered as a school of thought (Andersen, 2007). This term emerged from the "consciousness of the intimate and critical relationships between human actions and the natural world" (Ehrenfeld & Gertler, 1997, p.68) and aimed at looking at the industrial system as a whole, integrating notions of sustainability in economics and environmental systems. This approach represents a way to exploit products and

resources, including waste, better while achieving energy and materials optimization. It emphasizes the benefits of recycling residual waste, creating closed-loop processes in which waste serves as an input, thus eliminating by-products that are undesirable (Andersen, 2007).

Although key topics in Industrial Ecology, such as closed-loop material and energy, have been underlying, it was Stahel and Mulvey who first referred to a closed-loop economy (Murray et al., 2017). The focus of this concept is improving products' durability designing upgradable products with a long-life span. The reuse and life extension of goods with the available resources and without extra-consuming are key topics to address waste reduction and resource conservation (Stahel, 1994). Stahel coined the term "Cradle to Cradle" in 1970 (Ellen MacArthur Foundation, 2013). However, it was later popularized by the architect McDonough and the chemist Braungart, contributing significantly to framing the concept of circular economy. This concept focuses on recycling and reuse (keeping valuable materials in circulation) and emphasizes the role of product design as an enabler for a closed-loop material cycle. It distinguishes two types of materials that can be optimized through the design of products, manufacturing processes, and supply chains: biological and technical materials (McDonough and Braungart, 2002; (McDonough et al., 2003), as it is going to be detailed below. Also, there is a distinction between "cradle-to-grave" flows of materials and cyclical and "cradle-to-cradle," marking a difference in resource flow patterns that characterize linear and circular models (Braungart et al., 2008). Since the first formal use of the circular economy term by Pearce and Turner, there have been various attempts to define the circular economy influenced by several concepts (Rizos et al., 2017) and, although research has increased in the past years, no unified definition has been recognized due to the complexity of this concept (Korhonen et al., 2018). A number of authors have provided resource-oriented definitions and interpretations. Appendix B summarizes some circular economy definitions. As it is represented, although the term "circular economy" has been linked with a range of meanings and associations by different authors, they generally have in common the emphasis given to the need to create closed loops of material flows, reduce the consumption of virgin resources and it is associated with harmful environmental impacts (Rizos et al., 2017). The definition and key principles presented below are grounded on the Ellen MacArthur Foundation.

Characteristics and Key Principles of Circular Economy

As it was perceived, the concept of circular economy is broad and provides interactions among economic, environmental, technological, and social aspects of a process (Ghisellini et al., 2016). It represents the most recent attempt to conceptualize the integration of economic and environmental activities in a sustainable way (Murray et al., 2017). In order to have a global understanding of the circular economy, Ellen MacArthur Foundation created the butterfly diagram exhibited in Figure 7.

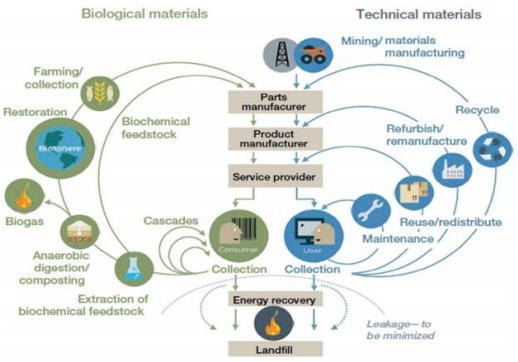


Figure 7: Outline of a Circular Economy (Ellen MacArthur Foundation, 2012)

It starts with the extraction of resources. These resources can be biological or technical, depending on their nutrients and characteristics. The **technical cycle** (in blue) involves the management of stocks of finite materials. In this cycle, materials are reused, remanufactured, and recovered, replacing the resource consumption. Technical nutrients are commonly synthetic or mineral materials that have the potential to remain safely within a closed-loop system (McDonough & Braungart, 2002; Ellen MacArthur Foundation, 2012; Ghisellini et al., 2016). The aim is to extent their value through many products' life cycles. The **biological cycle** (in green) includes the flows of renewable (biological) materials. Biological nutrients are biodegradable materials, i.e., natural/plant-based materials, that can be safely returned to the natural environment after use to feed biological processes since they do not introduce a hazard to living systems (McDonough & Braungart, 2002). In the end, when the product is no longer suitable for its initially intended purpose, the product has two possible destinations: can initiate the circular path through the recovery activity or can be collected to initiate the disposal and landfilling process.

Ellen MacArthur Foundation has also created three fundamental principles of circular economy, associated with each step:

Principle 1: Preserve and enhance natural capital by controlling finite stocks and balancing renewable resource flows. This principle stresses the importance of selecting resources wisely and chooses processes and technologies that use renewable resources. It refers to the importance of the design phase finding solutions to prolong the service life of products while also avoiding waste discharge in landfills: "Products are designed for a cycle of disassembly and reuse" (Ellen Macarthur Foundation, 2012; Ghisellini et al., 2016).

Principle 2: Optimize resource yields by circulating products, components, and materials in use at the highest utility at all times in both technical and biological. This principle introduces materials' reclassification into "technical" (such as metals and plastic) that are made to be reused at the end of their lifecycle and "nutrients" which "can return safely to the biosphere or in a cascade of consecutive uses" (Ellen Macarthur Foundation, 2012). Key strategies for increasing the circularity of resource flows include switching to longer-lasting products, remanufacturing, reuse, and redesigning products with less material which allows successive closed loops flows of material (Geissdoerfer et al., 2017). Therefore, this principle is directly linked to the concept "cradle to cradle".

Principle 3: Foster system effectiveness by revealing and designing out negative externalities This principle includes reducing damage to systems and areas (food, mobility, shelter, health, etc.) as well as managing externalities such as land use, pollution (air, water, and noise pollution), and toxic substances reducing the environmental problems caused by the linear economy (Ellen MacArthur Foundation, 2015). Circular economy aims to reduce negative externalities by redesigning the industrial structure in an ecological way (Su et al., 2013) in order to enhance the resilience of the economic system (Ghisellini et al., 2016).

Moreover, another core content present in the definitions exposed in Appendix B is the resource flow and "3R's principle": Reduce, Reuse and Recycle (Zhijun & Nailing 2007; Ghisellini et al. 2016). Circular economy mainly emerges in the literature through these three central values (Ghisellini et al., 2016). The 3Rs are essentially the foundation for green manufacturing derived in the 1990s from lean

manufacturing, which is based on 1R: Reduce (Jawahir & Bradley, 2016). The 3R aims to optimize production by utilizing reduced natural resources, producing minimum pollution, emissions, and wastes.

Some authors, such as Joshi et al. (2006), Jayal et al. (2010), Jawahir & Bradley (2016), Kane et al. (2018), extend their view and reinforce the importance of the inclusion of a 6R-methodology rather than 3R in the circular economy conceptualization, introducing three more elements: Redesign, Recover and Remanufacture. At the product level, there is a need to move beyond traditional 3R in order to form sustainable manufacturing (Jayal et al., 2010). This 6R approach offers a closed-loop, multiple-product life-cycle system as the basis for sustainable manufacturing minimizing the environmental burden of a product in the whole life cycle (Joshi et al., 2006). Later, a new framework, 9R, based on more circular economy strategies was created by Potting et al. (2017), where strategies in terms of increasing power to achieve circularity were emphasized. This is a more comprehensive scope, including the addition of Repair, Refurbish and Repurpose. Most of these "R's" are represented in Figure 10, in the diagram. The 9R-list are briefly explained as follows:

R0- Refuse: It refers to making a product redundant by abandoning its function or offering the same function with a radically different product (Potting et al., 2017). Refuse can also extend to the use of certain materials or production processes to make the economy more circular (Morseletto, 2020).

R1- Rethink: According to Potting et al. (2017), this principle refers to "make product use more intensive (e.g., through sharing products, or by putting multi-functional products in the market)." However, it has a broader connotation because it includes the re-elaboration/reconceptualization of ideas, processes, concepts, uses, and post uses of a product (Morseletto, 2020).

R2- Reduce: It aims to minimize the consumption of virgin materials, energy, water as well as emissions and waste flows. Improvements made on production efficiency may enhance the resilience of the economic systems and reduce environmental externalities (Su et al., 2013; Ghisellini et al., 2016).

R3- Reuse: This element can be defined as the second or further use of a product or a component that can fulfill its original function. It refers to the "reuse of a product at other facilities after its initial consumption rather than letting it become toxic waste" (Zhijun & Nailing, 2007) while maintaining its function and identity (Jayaraman, 2006). The reuse of goods means an extension of the utilization period through the design of long-life goods, reducing the flow of materials while using them in the subsequent life cycles (Stahel, 1994; Ghisellini et al., 2016; Jawahir & Bradley, 2016; Mosoletto, 2020).

R4- Repair: This principle refers to the reparation and maintenance of a defective product so it can be used with its original function (Potting et al., 2017). It is also making a broken product operational again through fixing and replacing failed parts (Jayaraman, 2006) and can be done by different actors, with or without the change of ownership (Reike et al., 2018).

R5- Refurbish: It means restoring an old product and bring it up to date, upgrading its function. Generally, it does not include disassembly, but replacement of parts (Mosoletto, 2020) and refurbished products are brought back to specified quality standards or satisfactory working (Jayaraman, 2006).

R6- Remanufacture: Also called second-life production, implies using parts of discarded products in a new product with the same function by re-processing the already used products. The aim of remanufacturing is to extend the life cycle of the product using minimal resources (Jawahir & Bradley, 2016; Morseletto, 2020; PwC 2020).

R7- Repurpose: This principle refers to the use of parts of the discarded product in the formation of a new product, with a different function and for an alternative purpose (Potting et al., 2017; Morseletto, 2020). This concept is used to a lesser extent, and some authors seem to mean the same using the concepts "fashion upgrading" (Stahel, 2010) or "part reuse" (Den Hollander and Bakker, 2012).

R8- Recycle: According to European Union, recycling of waste is defined as "any recovery operation by which waste materials are reprocessed into products, materials or substances whether for the original or other purposes" (Eurostat, 2014). Recycling means closing the loop between post-use waste and production (Stahel, 1994; Jawahir & Bradley, 2016; Ghisellini et al., 2016).

R9-Recover: This principle refers to the "process of collecting products at the end of the use stage, disassembling, sorting and cleaning for utilization in subsequent life-cycles of the product" (Jawahir & Bradley, 2016). It relates to several conversion processes related to solid waste otherwise disposed for landfill or burned without heat recovery. Through recovery products can be reused, refurbished, remanufactured, and redesigned, valuing the "waste" that was produced (Morseletto, 2020).

The 9R framework represents a priority order (Potting et al., 2017), and it is generally divided into three main loops: "short loop", "medium loop", and "long loop". In the first loop, refuse (R0), rethink (R1), and reduce (R2) are the most desirable forms of circular economy, as the resources are mitigated from the start (Ang et al., 2021). In the medium loop, the principles reuse (R3), repair (R4), refurbish (R5), remanufacture (R6), and repurpose (R7) are associated with product lifespan extension and lower frequency of resource consumption. It is important to refer that a product cannot be subjected to these treatments (R3-R7) simultaneously (Morseletto, 2020). Recycle (R8) and recover (R9) are in the long loop of the framework, emphasizing waste/ material recycling and energy recovery. They have the lowest priority and are mostly related to the traditional waste management and landfill (Ang et al., 2021). Under this framework, the circular economy aims to keep both types of materials at their highest utility and value at all the time through careful design, management, and technological innovation (Rizos et al., 2017). Through promoting the adoption of closing-the-loop production patterns within an economic system, circular economy aims to increase the efficiency of resource use, with the particular focus on urban and industrial waste, to achieve a better balance and harmony between economy, environment, and society (L. Liu et al., 2017). As it will be represented in the following sections, in order to integrate circular economy in any industry, it is necessary to have a sustainable supply chain.

3.2 Sustainable Supply Chain Management

3.2.1 Definition and Context

Sustainability awareness has increased over the last decades among governments, different industries, and the general public. Policymakers worldwide have integrated sustainability initiatives into industrial

development in order to promote it. In fact, sustainable development and social responsibility have become increasingly important strategic issues for companies of virtually every industry (Fiksel, 2006).

Therefore, Sustainable Supply Chain Management (SSCM) has become an integral part of a corporate strategy, being defined as "the strategic, transparent integration and achievement of an organization's social, environmental, and economic goals in the systemic coordination of key inter-organizational business processes for improving the long-term economic performance of the individual company and its supply chains" (Carter & Rogers, 2008, p. 368). They emphasized that, to have an optimized supply chain in the direction of sustainability, it has not only to be economically beneficial but also lead to a significant change in social and environmental impacts.

Moreover, Kuik et al. (2011) stressed the importance of including post-use operation and management to extend the product lifecycle along a supply chain. This requires an alternative disposal option (to reduce product disposal landfill) on consumer products and further product recovery options to increase its utilization value. Thus, it is provided a holistic view of the SSCM framework based on 6R (reduce, recover, redesign, reuse, recycle, remanufacturing) in order to rectify waste minimization along a supply chain and increase product utilization (Kuik et al., 2011). While traditional supply chain management focuses only on economic viability, such as reduced cost, short lead time, and high service level, with sustainability, companies are increasingly drawing their attentions on environmental impacts rather than economic goals (Low et al., 2016).

Additionally, due to the revolution in green manufacturing, Green Supply Chain Management (GSCM) concepts have become a strategic process enabling companies to create competitive advantage (Sivaprakasam et al., 2015). Concerns about environmental sustainability practices into the development of new products have become a central focus, particularly in terms of cleaner production and green supply chain, including greener manufacturing methods, i.e., new products that pose a lower environmental risk, recyclable packaging, and waste recycling (Zahiri et al., 2017). Therefore, when designing and evaluating production and consumption systems, sustainability performances such as resources and energy usage efficiency, effective manufacturing, distribution, and consumption carbon footprints, waste management, and reverse logistics valuations are taken into consideration (Sarkis & Zhu, 2018).

Within this context, the concept of reverse supply chain also has its importance. Reverse supply chain management is an extension of the traditional supply chains, which involves the effective and efficient management of activities to return products or materials in order to recapture their value or to dispose them properly. It embraces activities including reverse logistics- the process of retrieving the goods such as transportation, warehousing, and distribution - as well as recovery options such as repair, remanufacturing, refurbishing, or recycling (Prahinski & Kocabasoglu, 2006). It is also observed that reverse supply chain operations, unlike forward ones, are more complex and prone to a high degree of uncertainty, turning reverse flows, therefore, one of the most challenging supply chain activities. It affects collection rates, the availability of recycled production inputs and capacities in the reverse channel (Biehl et al., 2007; Shukla et al., 2011).

The literature on supply chain management reverse flows is associated with terms such as Sustainable Supply Chain Management (SSCM), Green Supply Chain Management (GSCM), and Closed-Loop Supply Chain (CLSC) (Kumar & Satheesh Kumar, 2013; Khan et al., 2021). A CLSC is an integration of the original forward supply chain with the reverse supply chain for product returns when they are managed in a coordinated way, mutually influencing each other. Therefore, as also represented by Govindan et al. (2015), reverse flows and CLSC have mutual interrelations. Nonetheless, reverse flows do not necessarily involve closed loops since it largely depends on the type of the targeted product and its complexity (Xie & Breen, 2012). Consequently, reverse supply chains are either open-loop or closed-loop. While recycling can often be described as an open-loop system because the products are not returned to the original producer but can be used in other industries, reusing components or even the product as a whole is typically closed-loop (Genevose et al., 2017). CLSC deals with the practice of taking back products from customers and returning them to the original manufacturer for the recovery of added value (Sasikumar & Kannan, 2008). Therefore, reverse supply chains add complexity to any supply chain management and affect several organizational activities due not only to new coordination issues but also to the uncertainties that exist regarding quality, quantity, and timing of product returns (Genovese et al., 2017). Additionally, a reverse logistic network is a costly and challenging project, especially for sectors where there is a high level of unpredictability in the supply chain and a highly regulated industry, such as in the pharmaceutical sector (Singh et al., 2016).

3.2.2 Integration of Circular Economy

Circular economy is seen as a new business model expected to lead to a more sustainable development and a harmonious society (Geng & Doberstein, 2008). Organizations are concerned about environmental and social performance (in addition to economic results), giving increasing importance to sustainability in their supply chain management and operations practiced (Walker et al., 2014). Remarkably, the concepts on green and sustainable supply chain management have been developed in parallel (although there are some fundamental differences in principles) to the circular economy discourse, which has been propagated in the industrial ecology literature and practice for a long time (Genovese et al., 2017).

On the one hand, SSCM seeks to integrate environmental concerns into organizations by minimizing materials' flows or by reducing unintended negative consequences of production and consumption processes (Srivastava, 2007; Sarkis & Zhu, 2018). On the other hand, as described by McDonough & Brangaurt (2002), circular economy pushes the frontiers of environmental sustainability. The underlying idea is transforming products in such a way that there are workable relationships between ecological systems and economic growth. This is achieved by lengthening product life and/or “looping” the product or its constituent materials back into the system to be reused.

Therefore, Genevose et al. (2017) emphasized that integrating the core principles of circular economy within GSCM may offer advantages from an environmental point of view. Nonetheless, the implementation of circular supply chains may be challenging from an economic perspective. However, despite often being used in similar contexts, the concepts of sustainability and circular economy are used in different situations and with different purposes. In fact, both are global in their nature, worrying

about the world in future generations, sharing concerns with the current state of technology, industrial production, and consumption. However, while circular economy seems to prioritize the economic systems with primary benefits for the environment, sustainability was initially conceptualized as holistically treating all three dimensions, i.e., economic, environmental, and social aspects, in a balanced way (Geissdoerfer et al., 2017).

Also, J. Liu et al. (2018) investigated the relationship between GSCM and circular economy and concluded that both aim to improve environmental and economic performance; however, future researches to discuss the conceptual and theoretical linkage of these two theories are needed, as well as the most appropriate methodologies and tools that can help apply and advance theories in both fields. In most of the studies, GSCM can be regarded as an organizational element to support circular economy practices and as an important unit of action towards circular economy.

Throughout the years, as supply chains become more complex, circular has been a base in helping address environmental sustainability concerns. SSCM and circular economy require effective performance measurement to help them progress. Therefore, Alkhuzaim et al. (2021) evaluated Emergy Analysis as an emergent and valuable technique that can be used in sustainability and circular development at various levels differentiating it from other conventional measures such as financial payback analysis in its capability to incorporate the donor-side value of the environment.

Overall, although the literature analysis indicates few academic researches with direct references to circularity in supply chains, its characterization still remains a marginal journey in the field of supply chain operations. The concept of Circular Supply Chain Management (CSCM) was defined by Batista et al. (2018) as harmonized forward and reverse supply chains through the incorporation of value creation aspects from products, by-products, and useful waste flows through a prolonged life cycle that improves the three dimensions of organizational sustainability. CSCM research has gained impetus in recent years, which is proven by the increasing number of publications since 2018. Since the research on this topic is at the beginning stage, the actual focus is more on case studies, conceptual and theoretical aspects, while the application of quantitative research methodology is lacking. Moreover, the studies made are based on the automobile and electronics industries. Therefore, due attention to other sectors such as healthcare, packaging, and pharmaceuticals was still not given so far (Lahane et al., 2020).

3.3 Pharmaceutical Sustainable Supply Chains

3.3.1 Key Aspects

The pharmaceutical supply chain, in which products are produced, transported, and consumed, is complex since it requires the participation of different stakeholders and has a variety of specific features (that are different from the other industries), such as the high cost, comprehensive research and development and a high level of regulation throughout the supply chain, creating some significant and unique management challenges (Xie & Breen, 2012).

Activities of the pharmaceutical industry have been the subject of growing attention in terms of sustainability. The awareness to include this topic in the business factor has become necessary for

pharmaceutical companies (Low et al., 2016).The pharmaceutical industry is growing rapidly in terms of upgrading the research and design within the industry. However, the execution of supply chain activities in this sector generates huge pharmaceutical waste, which is harmful to the environment and directly impacts human health (Faisal, 2015).

Although the primary goal of the pharmaceutical supply chain is to build the necessary inventory to supply the right medicines to health care systems at the right time, at the right place (Settanni et al., 2017), with the increasing awareness of sustainability over the past decades, this topic has been incorporated in the pharmaceutical industry (Zahiri et al., 2017).

According to Chaturvedi et al. (2017), to achieve sustainability in pharmaceutical manufacturing, a holistic approach throughout the entire product life cycle is required. They focused their attention on Indian pharmaceutical production and assigned to Indian law the definitive role of promoter of a successful application of green chemistry, indicating mandatory guidelines to achieve sustainability for all functional elements involved in the supply chain. Ding (2018) also pointed that a more sustainable pharmaceutical supply chain should be implemented to match future operations and management of pharmaceutical products throughout their life cycle. He depicted how techniques of Industry 4.0 may influence the current implementation of sustainable pharmaceutical supply chain (manufacturing, logistics, procurement and consumption in healthcare sectors, and household waste disposal), as it will be detailed in the next section.

There are many ways for pharmaceutical materials to influence the environment, including expired or unused medicines, inappropriate distribution by pharmacies or drug companies, disposal of surplus medications in household sewage, and improper disposal of pills or capsules by patients. Increasing pressures on environmental, economic, and safety issues have emphasized the need to implement GSCM in pharmaceutical businesses (A. Kumar et al., 2019; Shakeri et al., 2020). Therefore, A. Kumar et al. (2019) used an Analytical Hierarchy Process (AHP) for prioritizing the potential risks in adopting green supply chain initiatives in the pharmaceutical sector in the Indian context. A benchmark model was also presented to company managers and government authorities to effectively developing and managing green initiatives in line with sustainable development goals in the pharmaceutical industry. Milanesi et al. (2020) also studied sustainability in the pharmaceutical industry. Existing businesses and management studies on sustainability were reviewed and analyzed, and it was concluded that environmental sustainability had become a central focus of the academic world, particularly in terms of cleaner production, green supply chain, and green materials. However, despite this growing interest, literature is lacking in providing a systemic picture of the status of sustainability in the pharmaceutical industry.

The increased complexity of management is also affecting pharmaceutical companies, in which the need to ensure the balance between environmental, economic, and social sustainability, as well as to control expenses, has led to the introduction of an economic logic into the management of sustainability issues (Milanesi et al., 2020).

3.3.2 Sustainability in Manufacturing (1st and 2nd manufacturing)

Prior to the manufacturing process, pharmaceutical manufacturers should select the most suitable raw material suppliers that highly comply with environmental and social responsibility (Xie & Breen, 2012; Low et al., 2016). Pharmaceutical manufacturing covers i) API preparation; ii) primary product formulation; and iii) secondary pack processing (Fine et al., 2005).

In the product formulation, a significant volume of solvents is used. One way of achieving a greener production process is by evaluating solvent use and replacing it with a greener, more ecological wherever possible (Jiménez-Gonzalez et al., 2004). Practices such as solvent recovery and recycling are limited owing to the potential risk of cross-contamination and the high level of purity required, which can incur in an increased recovery cost. The computer-aided solvent selection tools enable managers to identify alternative solvents with fewer lab experiments, thus using the most suitable and eco-friendly solvent for different processes (Gernaey et al., 2012). Moreover, the focus when designing pharmaceutical products is more on safety and quality. Therefore, not any potential environmental substitutes can be used for the main API. However, medicines can still be designed to be more eco-friendly with higher efficacy under lower doses, containing less detrimental excretions or longer shelf life (Xie & Breen, 2012). To evaluate the environmental and social impacts incurred, Low et al. (2016) propose the AHP technique to select credible suppliers and outsourced manufacturers. This technique takes into account traditional criteria such as cost, quality, service, risk management, as well as regulatory compliance (social responsibility), and green purchasing.

After the API manufacturing, the focus is on making product packaging recyclable, thus making pharmaceuticals more eco-friendly. Emissions generated during this process depend on the type of packaging (Raju et al., 2016). Raju et al. (2016) performed a study comparing PVC blister packaging and aluminum blister packaging. It was concluded that the former performs better in most of the impact categories considered. In addition, the appropriate packaging design of medicine influences the logistic efficiency: poor quality may damage the product throughout the supply chain: transportation, storage, or on the retail shelf (Xie & Breen, 2014). Ding (2018), as mentioned before, investigate how Industry 4.0 can be applied in the sustainable pharmaceutical supply chain paradigm. The emerging technologies based on Industry 4.0 such as Internet of Things, Internet of Services, Smart Factory enable manufacturers to upgrade from batch-based mass production to agile, smart, and sustainable continuous production, with close-loop and online quality management. In addition, pharmaceutical manufacturers equipped with new technologies can significantly reduce GHG emissions, energy use, water wastage, as well as improve the raw material and by-products management (Li & Hamblin, 2016). Moreover, apart from manufacturers, the other entities involved in the pharmaceutical supply chain (distributors, healthcare providers, pharmacies) should also upgrade their services and technologies to accompany the demands of the future Pharma 4.0, including technologies from more innovative logistics (Ding, 2018).

Measuring in 1st & 2nd Manufacturing

Leonard & Schneider (2004) concluded that, for achieving sustainability in pharmaceutical companies, measuring, monitoring, and continuous improvement among all the processes and departments are

requested. They suggest an alignment between integrated sustainability initiatives and business goals so that the different activities are controlled in the three dimensions (environmental, social, and economic) just like the traditional business drivers.

Throughout the last decades, a variety of green metrics have been developed to guide the design of chemical and pharmaceutical processes while addressing environmental damages related to the different methods during the product life cycle (Jiménez-González et al., 2013). The American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable, created in 2005, selected Process Mass Intensity (PMI) as the key parameter to quantitively evaluate how environmentally sustainable a continuous process is (Gernaey et al., 2012). It is defined as the ratio between the quantity of raw materials involved in the process (including water) and the amount of product (API), both expressed in terms of mass. However, given the need for a lifecycle-based approach, researchers were concerned that these metrics could miss relevant factors that would be addressed by a more comprehensive LCA. In addition, PMI does not include specific concerns regarding the environment, people's health, or even the safety of the materials used or waste produced (Jiménez-González et al., 2013). By contrast, the LCA methodology offers "more holistic green metrics" to estimate the footprint of any product or process. It was designed in order to assess the environmental impact of a product in all stages of its life: from raw materials through production and use to end-of-life treatment and disposal or recycling- cradle to grave (Jiménez-González & Overcash, 2014).

Nevertheless, mass metrics such as PMI or its inverse mass efficiency are an indispensable intermediate step to estimate LCAs footprint (Jiménez-González et al., 2013). With the aforementioned tools, an important step was taken towards environmental sustainability assessments of pharmaceuticals. Also, a distinction can be made between process-oriented indicators such as E-factor, PMI, and lifecycle-based metrics, for example, Carbon Footprint (De Soete et al., 2014). As mentioned above, through the LCA method, the environmental impact and the energy used in different products or processes during the life cycle can be evaluated and also estimated according to CML 2001 impact assessment, for example. CML 2001 is the most widely applicable impact assessment method classifying lifecycle inventory results into midpoint categories such as climate change, acidification, and human toxicity (De Soete et al., 2014; Raju et al., 2016).

De Soete et al. (2014) demonstrate that different packaging of the same bioequivalent products may affect the drug adherence of patients. The size of pharmaceutical packaging should encourage customers to use the product completely, therefore, minimizing waste generation in households. Dhaliwal et al. (2014) used this metric to compare the environmental impacts of two packaging options offered by GE Healthcare: a polymer bottle and a traditional glass bottle. Also, Raju et al. (2016) compared two different types of packaging of tablets viz., PVC blister and aluminum blister packaging through LCA, quantifying the resource consumption, emissions, and the resulting environmental impacts throughout the supply chain. However, according to Cespi et al. (2015), although the application of LCA to the chemical sector is not new, its usage in the pharmaceutical area is still not a widespread practice. Moreover, they refer the lack of inventory data for many chemicals creates a considerable barrier to

more extensive implementation of LCA for pharmaceuticals. Raju et al. (2016) also mention that only a limited number of LCA studies are related to pharmaceutical drug manufacturing.

Therefore, there have been growing concerns over the environmental impact of pharmaceuticals. GSK developed FLASC (Fast Life Cycle Assessment of Synthetic Chemistry), a web-based tool to quickly screen synthetic routes to APIs at an initial stage in research and development. It is a cradle-to-gate methodology that includes the organization of LCI data associated with the manufacture of the materials used in specific synthesis (Sheldon, 2018). Nonetheless, despite recent efforts of some drug companies to integrate green principles into their production processes and drug designs, the utilization of LCA to measure progress remain far from standard practice. Moreover, a review of available pharma-LCAs revealed a certain inconsistency and heterogeneity in their methodology choices, emphasizing the need to develop product category rules in order to harmonize and facilitate the use of this metric in the pharmaceutical sector (Emara et al., 2018).

3.3.3 Sustainability in Waste Disposal/Management

As mentioned above, pharmaceutical supply chain activities generate significant pharmaceutical waste, which is costly and harmful to the environment while having a direct impact on human health. Therefore, taking actions in order to reduce the level of preventable waste is important (Xie & Breen, 2012). Pharmaceutical waste can be classified into three categories: Hazardous waste, Non-Hazardous waste ad Chemo waste. It may include solvents used in the formulation, expired drugs, patients' discarded personal medications; waste materials containing excess drugs (syringes, bags, vials, etc.); waste materials containing chemotherapy drug residues, and can (Pratyusha et al., 2012). Although medication retrieved from patients cannot be integrally re-used, it must be correctly disposed of. Unlike other products, expired or waste drugs have almost zero salvage value; therefore, they need to be inspected and sorted before being destroyed or properly disposed of (Xie & Breen, 2012; Kwateng et al., 2014)

In order to facilitate safe disposal, Xie & Breen (2012) emphasized the importance of channels through which expired or unwanted medicines return to manufacturers. These return services (made from logistics providers or wholesalers) have the strategic objective of removing excessive storage of medication at home while reducing the environmental burdens from inappropriate disposal methods. However, their research also shows that customer compliance in returning the medicines is low, which becomes a setback in developing effective healthcare waste management in the pharmaceutical supply chain. Generally, the standard applied disposal approaches include incineration, deep burial, landfill, and sewer (Kwateng et al., 2014; Sreedhar et al., 2018). Only small quantities of unused medicines collected by take-back programs are intact, with good efficacy, and within a useful date-use (Department of Health, 2011). For example, according to Kongar et al. (2015), in US households, 90% of unused or unwanted drugs are discarded in the garbage and water streams. Therefore, it is highlighted the importance of encouraging and educating customers to participate in take-back programs. However, the active programs in recycling are negatively influenced by the lack of commercial value in waste medicines. In fact, the most feasible fraction that can be recycled and reused are their packages and containers; however, pharmaceutical packaging wastes are majorly composed of plastics and metals,

which are difficult to recycle (Sreedhar et al., 2018); Weraikat et al., 2016b). Due to the hazardous nature of expired and unwanted medicines, there is more pressure to effectively green the pharmaceutical supply chain and properly dispose of these medications. Most waste medicines do not have accurate end-of-life (Ding, 2018).

Regarding waste management, Veleva et al. (2017) analyzed current waste reduction goals and data on different disposal methods of eight biotech and pharmaceutical companies, including GSK, Biogen, Novartis, and Johnson & Johnson. It was concluded that all of them rely predominantly on recycling, energy recovery, and incineration to reduce waste instead of source reduction through changes in manufacturing and supply chain practices. Moreover, regarding the indicators used to measure waste practices, this study demonstrates that, despite the existence of standardized guidelines, reporting of waste data differs significantly, which makes it difficult to effectively compare companies' waste reduction practices and identify opportunities for improvement. Also, according to Milanesi et al. (2020), waste management is one of the concerned areas that remain unexplored and may represent opportunities for future research.

To sum up, several aspects need to be taken into account to have a sustainable pharmaceutical supply chain. Moreover, the pharmaceutical industry is increasingly employing reverse logistics in their supply chain activities (Narayana et al., 2019) in order to turn them more sustainable, as it will be described in the next section.

3.3.4 Pharmaceutical Reverse Supply Chain

Reverse flows for the expired/unwanted medications are incorporated in the forward logistics network, in which medicines are produced by the pharmaceutical manufacturer, transported by the logistics providers to pharmacies, and finally are consumed by patients or buyers. As represented, a pivotal resource to ease product recycling is a reverse logistics network. Logistics providers or wholesalers have a crucial role in this process: collect medicines from the community pharmacy and transport them to manufacturers for suitable places for disposal (Xie & Breen, 2012). Xie & Breen (2012) believe that the participants in the pharmaceutical supply chain are expected to reduce medication waste by integrating environmental practices into their activities. For this, a reverse logistics system needs to be incorporated. Therefore, in their report, a formulation of an integrated green pharmaceutical supply chain model is presented with a focus on top management commitment, supplier certification and cooperation- that involves the communication of clean production and green packaging- , customer cooperation, and eco-design (the design of products that consume less new materials by adopting reusable or recyclable materials, and reduce the use of hazardous components).

Comparatively with the forward supply chain, the reverse one has irregular information. The different flow of materials and the data unpredictability led to the challenge in forecasting the reverse logistics activities. Moreover, reverse logistics in pharmaceuticals works differently from the other industries: returned pharmaceuticals are seldom repaired or resold. There are many aspects to be taken into account, such as the need for accurate tracking and visibility, batches and expiry control, proper storage and disposal, anti-counterfeiting. Only through a declaration to regulatory authorities and adequate

documentation can recalled pharmaceuticals be taken back, which is both costly and time-consuming (Kabir, 2013).

Also, the process of reverse logistics packaging has a significant influence on it. Package-related wastage needs to be processed, taking into consideration package sizes, shapes, and materials. The waste can be attributed to the oversized or inappropriate packaging that can hardly be emptied and recycled (Xie & Breen, 2014). Moreover, leftover or expired pharmaceuticals can adversely affect the environment and human health if not disposed of properly. Kongar et al. (2015) emphasized the need to address this topic and proposed an RFID-based information technology infrastructure that would provide real-time data visibility by tracking end-of-life pharmaceutical products using reverse logistics operations. This approach aims to improve communication throughout the supply chain as well as the overall performance of the reverse logistics system. Weraikat et al. (2016b) proposed a bonus-sharing scheme between the producer and several third-party logistics players to coordinate the collection and recycle of expired or unwanted medicines. This scheme was extended to include incentives to customers in a tri-party coordination-negotiation model (producer-3PL-customer) to return medications to the reverse channel for disposition that includes a donation to needy markets (Weraikat et al., 2016a)

Furthermore, although, recently, the collection and disposal of unwanted medications in households have raised an increasing amount of attention, there is little work on building an effective reverse logistics system (Hua et al., 2019). Hua et al. (2019) proposed a reverse logistics with a points-exchange incentive scheme and advertising. This system provides benefits for both pharmacy retailers and manufacturers since the formers are willing to advertise more and pharmacy retailers are willing to collect the unwanted medicines from householders. In the end, products are collected and returned to their sources.

Additionally, Narayana et al. (2019) studied the market dynamics that influence the performance of reverse logistics practices and sustainability aspects of the Indian pharmaceuticals industry. This study emphasizes the need for products to be disposed of safely using take-back programs as a sustainable practice. By reducing incineration/landfill, disposal and environmental costs may decrease, and this is achieved by investigating initiatives at a holistic level and associating reverse logistics. In fact, reverse flows of medicines are a complex process due to the extended nature of the pharmaceutical supply chain, the diversity of stakeholders, and strict regulations. It consequently hinders the adoption and the support of sustainable supply initiatives throughout the chain, from the raw material procurement and upstream production processes until the final use of medicines (Viegas et al., 2019).

“Sustainability” was the main word applied in this section; however, several notions are also involved and used in the circular economy concept. Both terms are increasingly gaining influence in today’s world, but the relationship between the concepts is not made explicit in the literature (Geissdoerfer et al., 2017). In the next section, a review of the literature regarding both terms within the pharmaceutical industry will be presented.

3.3.5 Integration of Circular Economy in the Pharmaceutical Supply Chain

The focus of existing sustainable practices of the pharmaceutical industry relies on resource consumption and waste generation, but it misses a vital step the closing the resource loops through the adoption of the concept of circular economy, such as drug ingredients, solvents, and energy consumption to improve the manufacturing sustainability (Ang et al., 2021).

Therefore, Ang et al. (2021) introduced the PM9R framework to meet the multiple inputs from academic research into a singular matrix to ease circular economy implementation in the pharmaceutical industry. For every R (Refuse, Rethink, Reduce, Reuse, Repair, Refurbish, Remanufacture, Repurpose, Recycle, Recover), it was exposed alternative chemistries or processes based on the literature. It was concluded that research publications are mainly in the area of alternative chemistry, especially about pharmaceutical manufacturing design, while publications related to existing pharmaceutical manufacturing processes and waste treatment processes are significantly less.

Moreover, Silvestri et al. (2021) also highlighted how sustainability and circular economy are strongly related to the concept of green chemistry. And green chemistry has a central role in the pharmaceutical sector (Chatuverdi et al., 2017). In fact, in terms of green chemistry, pharmaceutical is the most studied sector. The implementation of green principles such as reduction or the elimination of waste, hazardous materials, and the use of renewable material may have beneficial effects. The concept of sustainability is implicit and relevant to green chemistry. Also, green chemistry can represent the main driver for the circular economy (Silvestri et al., 2021). Sheldon (2018) showed that both sustainable production and circular economic perspective could be reached through a chemical production based on biological raw materials, as well as reducing waste through a more effective energetic use.

Moreover, Viegas et al. (2019) focus their research on reverse flows of end-of-life medicines and have associated circular economy and reverse logistics with GSCM as they keep green principles, such as wastage avoidance, in the supply chain. Circular economy was additionally linked with CLSC, as it seeks the maximum circulation of goods throughout the supply chain in order to avoid waste. It was concluded that, in the pharmaceutical supply chain literature, circular economy is not explicitly referenced. Nevertheless, the idea of circularity or CLSC is presented as the reuse and return of medicines. Under GSCM principles, the returns of medicines for correct disposal (reverse logistics), or for reuse (circular economy), are both associated with waste avoidance. However, broad research on qualitative aspects of medicines reuse and wastage is scarce (Bekker et al., 2017; Walker et al., 2014). In the context of end-of-life medicines, reusing becomes increasingly relevant, as significant quantities of medications that are not yet expired are leftover in houses, pharmacies, warehouses, hospitals. Therefore, opportunities for circularity lie mainly in the way patients and health professionals manage and value medicines that can be reused under careful supervision (Viegas et al., 2019).

To conclude, circular economy has been adopted in various sectors of the economy: from manufacturing to construction and packaging as well as waste management. However, as referred in Mhatre et al. (2021), “pharmaceuticals, medicine, and chemicals” is one of the sectors with the least number of case studies in the literature, which represents a challenge to overcome in the literature.

3.4 Chapter Conclusions

The circular economy concept was created as an alternative to the traditional linear economy of make-use- dispose and aims to keep the resources in use for as long as possible, extracting the maximum value from them when in use, then recovering and reusing products and materials. Companies are putting an increased effort into the development and implementation of these practices. The pharmaceutical supply chain is no exception, and its attention regarding this topic is growing, focusing on the development of medicines to patients with minimal environmental impact and increasing the sustainability of the processes throughout the products' life cycle. However, the pharmaceutical industry, due to its importance, has strict regulations to follow, and the reuse of medicines and closing loops cannot be a common practice due to its inherent risks, yet literature review on how to overcome these barriers was not done.

The literature review has revealed some gaps. First, a clear distinction between sustainability and circular economy in the pharmaceutical industry is not available. The relationship between the two concepts is not made explicit in the literature. Second, regarding the few studies integrating the pharmaceutical sector and circular economy, the majority address the upstream part of the supply chain. In fact, the downstream part of the supply chain (use/disposal dimension, where the final product is already made) regarding sustainability remains poorly explored and qualified when compared to the manufacturing dimension. Based on the literature gaps, the following research question will be answered: What circular economy solutions can be suggested in the downstream part of the pharmaceutical supply chain?

4. Research Methodology

This chapter describes thoroughly the methodology, which will be followed throughout the dissertation. It will be divided into four sections, corresponding to the four major steps that will be developed. It will be employed a multi-methodology approach in order to focus attention and use different methods on the relevant aspects of each phase (Mingers and Brockslesby, 1997). Figure 8 illustrates the generic steps of the methodology that will be applied, and each phase will be further explained.

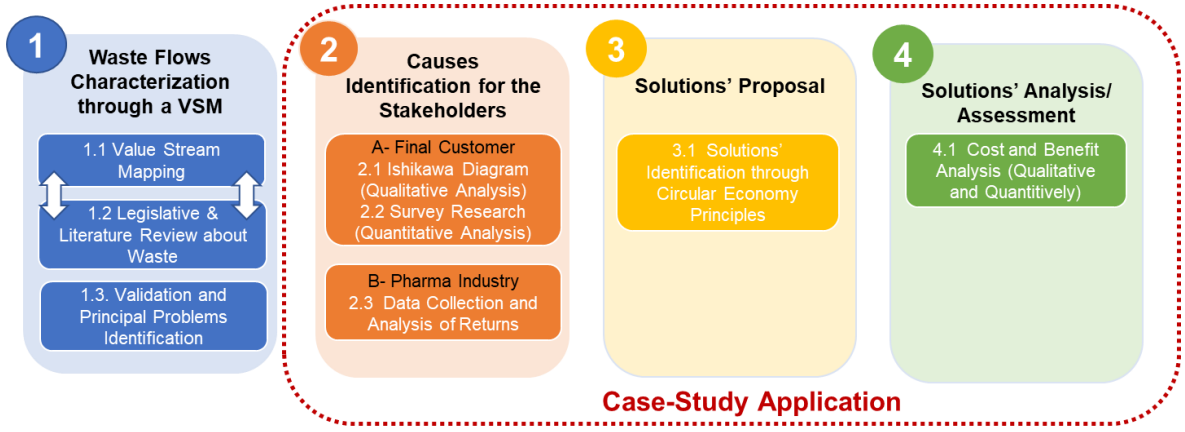


Figure 8: Proposed Research Methodology

Step 1- Waste Flows Characterization through a VSM

The main goal of this phase is to clearly represent the different waste flows throughout the pharmaceutical supply chain. For this, an extended and adapted form of the Value Stream Mapping (VSM) will be depicted. To complete this phase, steps 1.1 and 1.2 are essential to construct the VSM and collect information about waste characterization. Thus, they will be realized simultaneously in order to understand how the map is going to be made as well as how it is going to be filled. Having accomplished the global picture of wastes present along the supply chain, step 1.3 is crucial to validate the information and identify the principal problems. The VSM carried was based on the methods created by Rother (1999) while adding environmental and resource wastes from the Environmental Value Stream Mapping- E-VSM- from EPA (2009). Although the principal aim of VSM is to identify industrial waste in manufacturing systems (Torres Jr. and Gati, 2009), currently, it can be drawn for the entire supply chain providing a broader picture starting with raw material and ending with the customer (Kurdve et al., 2015). To develop the VSM, four steps will be followed.

Phase I- Supply Chain Mapping: for this step, it is necessary to define the different supply chain entities and represent their relational links while mapping the sequence of the main processes for the supply chain.

Phase II- Drawing the standard symbols: it is essential to understand which symbols are going to be represented in the VSM. Following Rother (1999), the icons that are going to be used are represented in Figure 9. It is important to mention that the conventional VSM approach maps both: material and information flows (such as lead time). However, in this case, the information flow icons will not be addressed since the primary goal is to depict the general supply chain.

Figure 9: Material flow icons

- Truck icon + broad arrow: indicate the movement of finished goods to the consumer.
- Inventory: not used in the manufacturing part, but it is important to draw on the map the places where the inventory accumulates to capture its location.
- Push arrow: the material movement that is pushed by the producer, not pulled by the customer. Processes are produced according to a schedule, so there is a transfer of material from one process to the next by push.
- Process Box: indicates a process in which the material is flowing. Since drawing one box for every processing step would make the map extensive and the manufacturing part is not the priority, the process box is used to indicate one area of material flow: ideally, a continuous flow.

Phase III- Drawing the environmental and material wastes: EPA's proposal is to adapt the environmental issue in VSM structure, analyzing material consumption in the manufacturing. However, in this case, analyzing the product in its final stage is also important. Therefore, not only the key non-product outputs that result from each manufacturing process are going to be drawn (as the conventional E-VSM) but also the key final-products waste from other entities along the supply chain. This is going to be done by using different colored lines to show the different waste flows. Figure 10 summarizes the different icons that will be used that were adapted from the EPA (2009). In green, the environmental boxes; in blue are the final product waste, i.e., the medicines waste, and in orange/yellow are the other type of wastes that exist due to the manufacturing and packaging processes. In order to complete these boxes, the information collected in step 1.2 will be necessary.

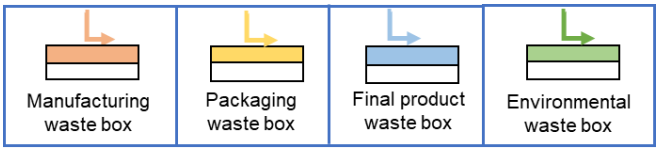


Figure 10: Adapted EPA icons

Phase IV- Scope Definition: although a generalized view of the entire supply chain for this master thesis, it is also to be delineated a clear frontier where the focus will be. To propose this scope, it is necessary to take into account what was reviewed in the literature review. As it was seen, the circular economy in the pharmaceutical industry has already been studied in some contexts. Thus, the strategy delineated will be to focus the study on the areas that have fewer studies: the topic on the integration of the downstream part of the supply chain (end-of-use/life medicines) with circular economy. Hence, it makes sense to define the scope of the work on the basis of the gaps found in the literature on circular economy and this industry, found in the state of the art chapter.

After understanding and defining the scope, step 1.2 follows it and explains the data collection performed through the literature review made (giving more emphasis to the scope previously defined). The

literature review is the selection of available documents on the topic, which contain information, data, and evidence from a particular angle (Flick, 2009).

Therefore, this step aims to deepen the knowledge and comprehension about the different waste flows as well as to fill, in a more precise way, the VSM that is going to be made. As so, two different types of sources are going to be used:

1) **Legislation documents** on waste at a EU level to learn what is considered waste by law. Legal instruments that lay down the principles, directives, regulations are going to be read and analyzed using the official website of European Union law, the Eur-Lex. Also, legal documents of WHO are going to be used. For this, it is important to understand where the waste information is taking place and then which of the information is applied throughout the pharmaceutical supply chain.

2) **The literature review** focused on the final product of pharmaceutical waste in order to gather information about it. The search of relevant material was performed through online journals, libraries, and databases, e.g. Direct Science, Google Scholar, Research Gate, PubMed TM, Scopus TM using the keywords "medicines", "medication", "drugs", "unused", "waste", "disposal", "management", "regulation", "legislation", "Europe", "garbage", "handling" and making combinations such as "pharmaceutical waste", “medicines wastage” "pharmaceutical supply chain", "pharmaceutical waste management", “medicines disposal”, “unused medicines”. Both academic and non-academic materials have been employed, and most of the articles were read. However, the papers analyzed and studied in-depth were selected based on three elements: 1) the selected documents were published after 2006 in order to achieve greater proximity with actual reality; 2) documents of the European Union (as the UK was part of EU until 2020, it was included on it). Also, studies involving both random and convenience samplings were included as well as studies employing various types of survey instruments (such as telephone questioning, interview with participants and mailed questionnaires).

Having accomplished the general picture of the VSM, the next phase (step 1.3) aims at validating the diagram while also defining the most critical problems in the light of the scope previously determined. For this, a type of semi-structured interview is going to be carried, the Expert Interviews, where the interviewee is integrated into the study as a representing group and has capacities as experts in a certain field of activity, as discussed by Meuser & Nagel (2002).

Expert interviews can be used for i) exploration/orientation in a certain field in order to generate a hypothesis, or for developing a theory about an issue; ii) collect context information complementing insights coming from other methods, exploring interview's opinion about the topic (Bogner & Menz, in Flick 2009). As so, the interviews will be used to simultaneously validate the VSM done in the previous step as well as defining the principal problems and wastage present in the map. Like any other type of research methodology, semi-structured interviews are also supported by a theoretical basis. They can be described as a balance between predefined open-ended and unstructured questions, allowing not only to explore systematic data but also permitting new ideas to emerge during the interview (Flick, 2009).

According to Flick (2009), an interview guide is developed, and it contains open questions followed by hypothesis-directed and confrontational ones. The formers can be answered on the basis of the interviewee's immediate knowledge and therefore include explicit opinions. Hypotheses-directed questions make implicit knowledge more explicit since these questions are oriented to the scientific literature about the issue. Confrontational questions "respond to the theories and relations that the interviewee has presented up to that point in order to critically re-examine these notions" (Flick, 2009, p.157). Therefore, the interview should follow the three steps presented in Figure 11:

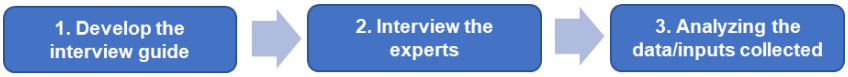


Figure 11: Semi-structured interview process

The interview is divided into two sections, with a total of 6 questions. The first one is focused on the expert's opinion about the VSM, and it aims at validating the map. The second section introduces the principal problems regarding waste throughout the pharmaceutical supply chain. This expert interview guide can be found in Appendix C.

Concluding, from this methodology step, after the development and validation of the adapted VSM, a clear idea of the different types of waste along the supply chain will be available, as well as the identification of the most critical problems, in order to focus our attention on them.

Step 2- Causes Identification for the Stakeholders

It is important to mention that, in the next steps (steps 2, 3, and 4), the focus will be the Portuguese market, and, in some phases, it will be applied a case study methodology to a Portuguese pharmaceutical company, BLGN. Although step 1 was a qualitative analysis done on a European level, it is now important to tapper down to the reality of Portuguese consumers and market, so the universe analyzed be the same in order to propose coherent solutions.

Having identified the principal problems, this step aims at understanding the main causes that lead to the principal problems identified. It is crucial to recognize what the root cause of a given problem is, underlining the contributing factors or causes of a system in order to propose and develop sustainable solutions or actions. However, since there are different stakeholders involved (the final consumer and the industry itself), it was decided to employ different methodologies for each one in order to address their needs in separate forms. Therefore, this section is divided into two main subsections (A and B). Steps 2.1 and 2.2 focus on the final consumer stakeholder (A), while step 2.3 is regarding the pharmaceutical industry stakeholder (B).

A popular tool to identify potential causes is the Ishikawa Diagram (also known as the cause-and-effect diagram or fishbone diagram), which is going to be carried in step 2.1 and later, in step 2.3. This technique is based on constructing a diagram that clearly shows the relations and interdependences between factors, assigning them into different categories (Ishikawa, 1985). The analysis consists of four phases:

Phase I- Problem Identification (Effect): it consists of identifying major existing problems and select one for the analysis.

Phase II- Causes Categorization: the next phase is to decide how to categorize the major causes of the problem by brainstorming generic categories. The formulation of the traditional Ishikawa is based on the 5M+E method (manpower, methods, machinery, materials, management, and environment), where these are considered the main sources of causes of accidents in manufacturing systems and are placed on the oblique axes of the diagram. However, in this case, since the problem in hands is not related to the production, other categories are going to be used.

Phase III- Brainstorming all the possible causes of the problem: in this step, the question "why does this happen?" must be asked, and each answer, i.e., each specific cause, is assigned to the appropriate category and is placed in the horizontal axes. Causes can be written in more than one category if related to different categories.

Phase IV- Fishbone Diagram Construction and Analysis: construction of the diagram showing the relationships between the different causes.

For the causes' categorization and the brainstorming phase, the literature review of the articles identified in the previous step was used in order to gather information about the topic and make the basis of the analysis. However, as it was mentioned before, the aim is to taper down to the Portuguese reality. Therefore, the brainstorming was then discussed with an expert in the field of supply chain and sustainability and also a specialist of the pharmaceuticals' area in order to confirm the literature review findings and investigate whether they make sense considering the Portuguese reality. Therefore, the fishbone diagram will be used to identify the principal factors that can be pointed as the potential causes for the effect identified.

After 2.1 being completed, step 2.2 follows it where a survey is going to be carried to analyze the Portuguese consumer behavior and, once again, understand the root causes for the waste. This method was chosen as it allows to gather standardized information from a large sample of participants in a very cost-effective way. As referred by Evans & Mathur (2005), online surveys are a useful and flexible tool when it is needed to collect different types of information, compare results from different respondents while having a large sample easy to obtain.

Therefore, this survey aims to 1) understand consumer behaviors on unused medicines that they maintain at their homes as well as point the main reasons for keeping them, 2) assess consumers' actions on disposal medicines and how willing the Portuguese population is to return their no longer needed medicines in pharmacies and 3) understand respondents' environmental and social consciousness and their engagement in activities that are better for the environment and human health. Based on the work by Ball (2019), the survey should follow the four steps presented in Figure 12.

Figure 12: Survey process

The survey design phase is characterized by the definition of its main characteristics, the information to be explored, the sample selection, and the questions diversity (since online surveys enable many types of questions). The survey was developed in an electronic format using the Google Forms platform.

Also, to initiate the survey, and before asking participants to answer any questions, an introductory page explaining the purpose of the research, the identity of the researchers, and giving some details of the project's structure should be presented. The survey is divided into two sections with a total of 20 questions. The first section is focused on consumer behavior related to unused/unwanted medicines. It also addresses respondent's environmental and social consciousness and perceptions about this topic. Therefore, this section aims at understanding the current Portuguese citizen's awareness and practices concerning unused/unwanted medicines, with the focus on the disposal method. It also aims to identify and explore respondent's attitudes, perceptions, and motivations regarding possible solutions that are going to be suggested in the third step of this master's dissertation to minimize this type of waste. The second section focuses on the respondent's demographic information.

Having briefly explained the content of the survey, its design can be found in Appendix D. Note that the original survey was distributed in Portuguese in order to gather more answers. All the questions were mandatory and there were also conditional display questions and that is the reason for having created in the formulary 5 sections - as it is possible to see in Appendix D.

The step that follows is the testing and validation phase. In order to assure the survey's effectiveness and accuracy, the survey's validation is going to be performed by an expert in sustainability and supply chain, and also tested by a specialist in the pharmaceutical industry who works in BLGN. In this way, the content will be validated, ensuring the questions are focused on the topic to be addressed and guaranteeing the questions posed imply the desired outcome.

After having the survey completed and approved, the data collection phase starts. The surveyed sample shall not be biased, i.e., not representative of any region or group, to reasonably understand the attitudes of consumers and their behavior. To ensure this, the survey will be distributed to different groups of people either through different social platforms (Facebook, WhatsApp, and LinkedIn). Like any other type of research methodology, surveys are also supported by a theoretical basis. In this case, the survey is going to be based on a study made by Dias-Ferreira et al. 2016 where the authors already studied the characteristics and perceptions of Portuguese participants on salient concerns. Also, the literature review previously analyzed also served as a basis. Hence, the table below, Table 1, summarizes the references or justifications that support the content of the survey's questions, the type of question, and its aim.

Note that the questions' numbers (first column) were not shown to the respondents- but here each question is numbered, so it is possible to clearly identify each one of them. Then, the data analysis follows to summarize the information that have been collected in order to achieve the goals previously mentioned, partitioning responses based on the relevant characteristics.

Table 1: Survey questions' references, types, and objectives

Question	Type of Question	Objectives	References
Consumer behavior and perceptions related to unused/unwanted medicines			
1.	Multiple Choice	Identify if respondents have leftovers and its range	Perrson et al. 2009
2.	Multiple Choice	Identify their nature (prescriptive or not)	Coma et al. 2008
3.	Multiple Choice	Evaluate the reasons for having medicines at home	Dias-Ferreira et al. 2016; Perrson et al. 2009
4.	Multiple Choice	Identify magnitude range of expired medicines	Alnahas et al. 2020
5.	Yes/No	Evaluate respondents' knowledge for returning medicines to the pharmacy	Dias-Ferreira et al. 2016
6.	1 to 5 scale	Evaluate respondents' perception on the importance of returning pharmaceuticals	Bond et al. 2006
7.	Multiple Choice	Identify the type of disposal	Dias-Ferreira et al. 2016
8.	Multiple Choice	Identify reasons behind the disposal method	Dias-Ferreira et al. 2016
9.	Multiple Choice	Identify the returning frequency	Bungau et al. 2018
10.	Multiple Choice	Identify the returning reasons	Dias-Ferreira et al. 2016
11.	Multiple Choice	Identify respondents' motivations to return	Dias-Ferreira et al. 2016
12.	1 to 5 scale	Evaluate respondent's level of engagement to a bag solution	Perrson et al. 2009; Dias-Ferreira et al. 2016
13.	1 to 5 scale	Evaluate level of engagement to return more often medicines if having fiscal incentives	Ruhoy & Daughton 2008
14.	1 to 5 scale	Evaluate respondent's level of engagement to donations/redispensing	Bekker et al. 2018b; MacRae et al. 2016
15.	Yes/No	Understand if respondents are in favor of unit dosing dispensing	Coma et al. 2008; Bekker et al. 2018b
16.	1 to 5 scale	Evaluate respondent's level of engagement to redispensing	Mackridge & Marriott 2007
Consumer Data			
17.	Multiple Choice	Identify age gap	Hughes et al. 2016
18.	Multiple Choice	Identify level of education	Hughes et al. 2016
19.	Multiple Choice	Identify household members	Hughes et al. 2016
20.	Multiple Choice	Identify household children members	Hughes et al. 2016

After analyzing the consumer dimension, step 2.3 focuses on the pharmaceutical industry in Portugal. Therefore, analogously to the previous step, the final purpose of this procedure is to gather information about pharmaceutical waste.

As mentioned before, this part of section 2 analyzes in detail a company (BLGN) data. Hence, in order to manage this process, the research methodology employed will be a case-study analysis. The case study is an analytical research strategy that investigates a current trend within its real-life context, based on an empirical investigation (Yin, 2003). Generally, case studies are the preferred strategy for "why" or "how" questions, relating theory with the field of investigation. This method can capture the procedures in an exact and detailed way while being able to fully use other methods (Flick, 2009).

It is going to be performed aiming to i) collect the data- identify and collect information about returns; ii) analyze the data- categorize and sort the material given to systematize and consolidate the data gathered and iii) explore the main causes for the returns, understand which are preventable in order to draw our attention on them and understand where the focus of the proposals should be. The complete analysis is going to be presented in section 5.2. Moreover, according to Eisenhardt (1989), the case

study methodology approach can be used to generate theory. The resultant theory is often empirically valid since the evidence gathered may be qualitative, quantitative, or both, guaranteeing the reliability of the findings.

Therefore, analysing the data from BLGN, the final goal is to understand and explore the principal reasons for them to happen while identifying the associated wastage. Once again, in order to have a deeper knowledge and understand the root causes of the problems identified, the qualitative tool carried on step 2.1, the Ishikawa Diagram, will again be used. The four phases previously identified: Problem Identification (Effect), Causes Categorization, Brainstorming and the Fishbone Diagram Construction will be followed. However, in this case, the categories of the traditional Ishikawa based on the 5M+E method will be applied. Moreover, the causes' categorizations and brainstorming will be done with interviews.

In conclusion, from the accomplishment of steps 2.1, 2.2, and 2.3 and by analyzing both stakeholders with different tools, the output will be a conceptualized idea of the main and critical causes of waste in order to propose different solutions for their change.

Step 3- Solutions' Proposal

Given the identified principal root causes, the next step is thinking about possible solutions for some of the addressed problems, taking into account the circular economy principles. Once again, the solutions and recommendations that will be given will have in consideration the Portuguese context.

Therefore, step 3.1 aims at identifying different solutions, in which, there may be (or not) the consideration of different scenarios. According to Nielson & Karlsson (2007), scenarios are used for predicting, exploring, and anticipating the future. Hence, the aim of this step is precisely to develop and identifying these possible paths. Following the research of O'Brien & Meadows (2013) and adapting it to this master thesis context, scenario planning will be proposed. A scenario planning process can be organized into three phases:

- **Preparatory phase**: it provides specific issues and factual details about the current situation based on data as well as general theoretical aspects of the situation. The purpose and focus are agreed upon, and the logic of the topic in question is understood.
- **Development phase**: it involves the development of the scenario narratives themselves
- **Use phase**: where the scenarios are used for their intended purpose. It is organized into three key activities in relation to supporting strategy development: understanding the implications of the scenarios, developing strategic options, and evaluating strategic options.

The first phase was accomplished with the previous steps of this master thesis. Therefore, in step 3.1, it is going to be made, simultaneously, the development phase and part of the use phase. As such, the analysis goes through a first step of creating different scenarios to minimize waste (the development phase), while also analyzing and understanding the implications of the proposed scenarios. A remark should be done about the word "scenarios" in the context of this master thesis. There will be solutions where scenarios may not exist. However, the same reasoning will be applied since scenarios are, in

general terms, coherent and plausible stories, described in words and numbers (Swart et al., 2004) that aim at opening the future by creating possible pathways.

Therefore, the development phase will represent the description of each solution (or scenario, if it is the case), while the use phase will concern the implications of the solutions, the possible barriers and necessary incentives in order to turn the solutions feasible and concrete. The evaluation part will be made in the next section, through a cost and benefit analysis. Also, it is important to mention that, to propose these scenarios, besides the knowledge and information found in the previous steps, the solutions will follow the circular economy principles identified in the literature review chapter. Moreover, these solutions will be designed together with pharmaceutical experts in order to ensure their feasibility.

Step 4- Solutions' Analysis/Assessment

At last, the final part of the dissertation is the assessment of the different proposals created in the previous step. For this, a qualitative analysis of the benefits and trade-offs found will be performed for each of the players involved, in step 4.1. An economic evaluation (quantitative analysis) will also be carried out for the proposals whenever data regarding costs can be used. For that, a cost and benefit economic analysis will be employed, using monetary units. If it is not possible to quantify the economic burden, just a qualitatively analysis will be done.

The cost and benefit analysis aims at identifying and valuing the impacts of a project (or, in this case, of the proposed solutions) in terms of their effects, comparing the positive (benefits) with the negative ones (costs). According to Boardman et al. (2011), the first four basic steps of a cost and benefit analysis process are: definition of the project; decision on whose cost and benefits are counted for; selection of the measurement and measuring the appropriate costs and benefits (data collection) and estimation of the outcome of cost and benefits. Therefore, throughout this step, different variables and their components will be identified for computing the model alongside with the characterization and data collection process for each variable's component. The data for the solutions that are feasible to do so will be collected from BLGN and therefore, the extrapolation for the whole Portuguese market will be performed.

5. Results and Discussion

This chapter is divided into four main sections, each corresponding to the principal steps described in the previous section. Therefore, section 5.1 presents the VSM with the various types of waste present throughout the pharmaceutical supply chain. Then, section 5.2 analyses the causes for the different problems identified in the previous section. In section 5.3, using the information collected, different solutions and actions will be proposed and discussed. Finally, section 5.4 presents a cost and benefit analysis

5.1 Waste Flows Characterization through a VSM

In this section, the VSM is presented along with relevant considerations and the information obtained from the legislative and literature review about waste. Pharmaceutical waste may be present in any of the common physical forms: solids, liquids, and gases. The waste can be categorized in several ways depending on the source, physical state, hazard, security, handling, and disposal (Castensson, 2008).

The process of development of the VSM was obtained following the steps described in the methodology. The waste and disposal problem starts with the production of the API and finishes with the final disposal of the pharmaceutical product. Therefore, the main entities are manufacturing, distributors, and the final consumer. The study will be focused on the distribution to the end-of-use/life phase, since it was a gap found in the literature review. The manufacturing phase has already been explored in various studies, which recognize the important role of circular economy. However, the downstream part of the supply chain, focusing on the final product and the link between this and circular economy concepts has only been subject to a minority of studies. Hence, both the legislative and literature review, although comprehensive, will have its emphasis on the final product itself.

5.1.1 Legislative and Literature Review & VSM

As aforementioned, it is necessary to understand the kinds of waste that may be found throughout the supply chain. Figure 13 represents the three types of waste that will be present in the VSM: regarding the manufacturing phase (both API production- in light orange- and packaging- in yellow) as well as the final product transported from the wholesaler to the final consumers. For this reason, the output of each phase can gather either non-product and/or final product waste. Moreover, the environmental wastes are present during all the processes, as it is illustrated in Figure 13, in green. Therefore, they will be briefly mentioned and also be represented in the VSM, without so much detail.

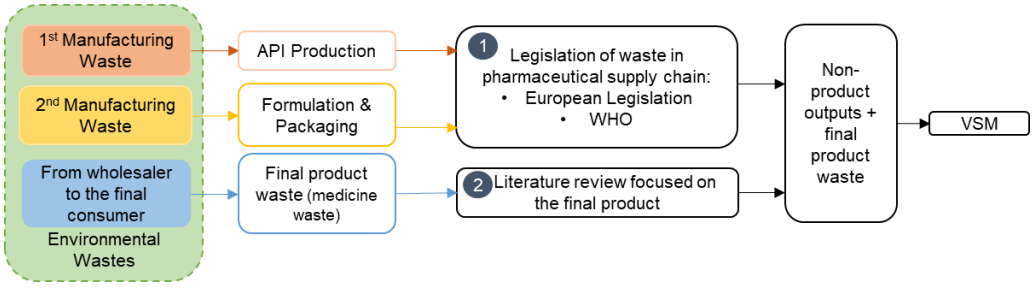


Figure 13: Guidelines to the construction of the VSM

Starting with the legal documents for the pharmaceutical waste (represented by number 1 in Figure 13), in the EU, waste management planning is based on three directives that describe the responsibilities:

- Directive on waste (75/442/EEC) + amendments
- Directive on hazardous waste (91/689/EEC)
- Directive on packaging and packaging Waste (94/62/EC)

The Directive on waste (75/442/EEC) points to requirements for all types of waste unless they are specifically regulated by other directives. The EU defines waste as "any substance or object which the holder discards or intends or is required to discard" (EU, 2006). Regarding the two first directives mentioned, a hierarchical list of waste descriptions is included in a Commission Decision (2000/532/EC). This list is divided into 20 main chapters, and pharmaceutical waste categories are defined in chapters: 7 (Wastes from organic chemical processes), 15 (Waste packaging materials), 18 (Wastes from human or animal health care and/or related research, except kitchen and restaurant wastes not arising from immediate health care), and 20 (Municipal wastes; household waste and similar commercial, industrial and institutional wastes, including separately collected fractions). Also, there is information on WHO documents. Therefore, Table 2 summarizes the different flows present in the supply chain entities that will be represented in the VSM. Any waste marked with an asterisk (*) is considered as hazardous waste pursuant to Article 1(4), first indent of Directive 91/689/EEC on hazardous waste.

Table 2: Waste categorization and type associated with each pharmaceutical entity/phase

1st Manufacturing	**CD (2000/532/EC) - Chapter 7 (Wastes from organic chemical processes- pharmaceuticals)**	
	* Aqueous washing liquids and mother liquors	
	* Organic halogenated solvents, washing liquids and mother liquors	
	* Other organic solvents, washing liquids and mother liquors	
	* Halogenated still bottoms and reaction residues	
	* Other still bottoms and reaction residues	
	* Halogenated filter cakes, spent absorbents	
	* Other filter cakes, spent absorbents	
	* Sludges from on-site effluent treatment containing dangerous substances	
	Sludges from on-site effluent treatment other than mentioned	
	Wastes not otherwise specified	
2nd Manufacturing: Packaging (Raw Materials + Final Product)	**CD (2000/532/EC) - Chapter 15 (Waste packaging materials)**	**Final Product - WHO (2002)**
	Paper and cardboard packaging	- Boxes - Labels - Display Units - Leaflets
	Plastic packaging	- Closures - Bags - Bottles - Tubes
	Metallic packaging (e.g aluminium)	- Collpasible Tubes - Blisters - Rigid Cans - Foils - Pressurized Container - Needles
	Glass packaging	- Ampoule - Bottles - Vials - Syringes
	Mixed packaging	- Closures, including plungers (rubber)
From Wholesaler to Final Consumer	**CD (2000/532/EC) - Chapter 18 (Wastes from human/animal health care)**	**Medicines Waste - WHO (2002) + Literature review**
	Sharps	Expired/Almost expired medicines
	* Waste whose collection and disposal is subject to special requirements in view of the prevention of infection	Damaged medicines
	Waste whose collection and disposal is not subject to special requirements in view of the prevention of infection	Household leftovers & accumulation
	*Cytotoxic and cytostatic medicines	Improper disposal
	Medicines other than those mentioned above	Over-stocking
	CD (2000/532/EC) - Chapter 20 (Municipal wastes)	Returns
	*Cytotoxic and cytostatic medicines	
	Medicines other than those mentioned above	

As denoted in the table above, regarding the manufacturing phase (in light orange), the list included in the Commission Decision (2000/532/EC) refers to wastes from organic chemical processes in chapter 07, more precisely subsection 07 05, includes wastes from manufacture, formulation, supply, and use (MFSU) of pharmaceuticals. Concerning the formulation packaging (in yellow), i.e., the second manufacturing, waste is classified by the European List of Waste in chapter 15 - Packaging waste, among others. Depending on the type of packaging one is referring to different materials are used, as represented in Figure 14.

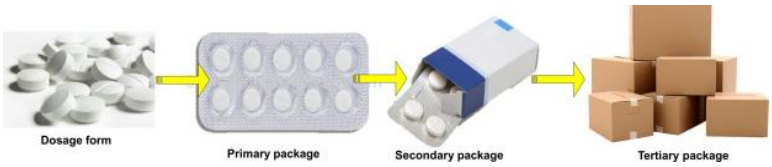


Figure 14: Package of pharmaceutical products (adapted from Amarji et al., 2018- Book Dosage Form in Design)

For the primary packaging, which is the smallest unit of distribution, it can be used blisters, bottles, vials (WHO, 2002). However, in Europe, at the industry level, pharmaceutical blisters represent the leading segment, with 85% of solid drugs packed in this medical packaging (Sudden, 2019). The types of materials authorized as primary packaging, and therefore directly having contact with the medicine, are specified by the European Medicines Agency (EMA, 2005). This agency has guidelines for plastic packaging materials that meet the active substances - "Guideline on plastic immediate packaging materials". In order to group the primary package, boxes and cartons are used as a secondary pharmaceutical packaging. One shall not forget that leaflets (that exist inside the secondary package) also represent a type of waste when the medicines are no longer needed. Finally, tertiary packaging bulk handling, warehouse storage, and transport shipping typically are in the form of pallet loads: barrel, container. From the distribution phase to use/end-of-life medicines, the wastage present is already in the final product form. This waste can have considerable implications both economically, due to the financial loss, and environmentally, when disposed of incorrectly such as directly in the environment (Bekker et al., 2018b).

After manufacturing, distributors, such as wholesalers, take responsibility for storage and/or further distribution to pharmacies. Given their critical role, pharmaceutical wholesalers operate under strict legal frameworks such as the Directive 2001/83/EC relating to medicinal products for human use, recently updated by the Directive 2011/62/EU regarding the prevention of falsified medicinal products to enter into the legal supply chain as well as the guidelines of Good Distribution Practices (GDP) - EU Directive 2013/C 343/01. According to the GDP, medicinal products can only be returned to saleable stock if the products are in their unopened and undamaged secondary packaging, are in good condition and have not expired. Otherwise, they need to be disposed of. Bear in mind that, even though a simple fall can lead to a damage package, it does not mean that the medicine itself is waste and unsuited for its initial purpose- this is an important nuance, which will be addressed later.

The waste from the final product is listed on the European Waste List mentioned above, in chapter 18- Wastes from human or animal health care and in chapter 20- Municipal wastes; household waste and similar commercial, industrial and institutional wastes, including separately collected fractions (European Commission, 2004). As represented in Table 2, in blue, waste medicines are considered non-hazardous, except for cytotoxic and cytostatic medicines. The medicines considered hazardous

wastes are practically cytotoxic and cytostatic medicines. Cytotoxicity means that the drug will directly harm or kill cells, and cytostatics are drugs used to block the growth of cancer cells. Cytotoxic drugs do not specifically affect cancer cells but all dividing cells (Backhaus et al., 2008). Moreover, according to WHO (1999), pharmaceutical waste also includes "expired, unused, spilt, and contaminated pharmaceutical products, drugs, vaccines, and sera that are no longer required and need to be disposed of appropriately". Thus, any medicine stored in a household without the intention of being used, returned to a pharmacy or disposed of properly (e.g., through waste collection places) or improperly (e.g., via household garbage) can be considered waste.

The above Table 2, gathers the different type of wastes that will be present in the VSM. The different colors of the table (which represent the different phases of the supply chain) will match the colors that will be present in the VSM. Regarding environmental wastes, the EU waste management policy incorporates the preventive and precautionary principle to ensure a reduction in waste's negative effects on human health and on environment, especially to reduce the hazardous substances in waste. Pharmaceuticals may end up in the environment due to effluents from manufacturing facilities, medicines consumed by patients and then excreted, and the improper disposal of unused and expired medicines.

In fact, the presence of an increasing number of pharmaceuticals in the environment can be detected with an improvement in analytical tools. Depending on the substances and where they are found, they may be present in very low concentrations in various environmental matrices such as wastewater, surface water, ground water and even in drinking water. A major study by the WHO concluded that at current levels of exposure in drinking water, adverse effects on human health are very unlikely. Concerns have been raised, however, on the potential long-term environmental effects especially with certain classes of pharmaceutical products such as hormonal substances or antibiotics (WHO, 2012).

During the first manufacturing phase (i.e., the production process), pharmaceutical chemicals, although in small quantities, may be released into the environment during manufacture use and disposal of excipients and APIs. Therefore, production facilities need to follow environmental standards in order to manage and minimize potential emissions of APIs in wastewaters and effluents. Therefore, the EU provides guidance for manufacturers on GMP to ensure a consistently high quality of the medication without compromising the environment. Three legal instruments lay down the principles and guidelines of GMP in the EU:

- Regulation No. 1252/2014 and Directive 2003/94/EC applying to active substances and medicines for human use;
- Directive 91/412/EEC applying to medicines for veterinary use;
- Directive 2001/83/EC and Directive 2001/82/EC lay down related provisions.

There is also a guideline on the results of an environmental risk assessment (ERA) of medicinal products (EMA, 2006). Its assessment is a legal obligation required for any new pharmaceutical marketing authorization and must be performed to evaluate and limit potential adverse effects of medicines on the environment. This involves conducting studies to evaluate the environmental fate of the API and assess

its potential toxicity to relevant environmental species. Moreover, the ERA also assesses the risk to both surface water and groundwater for every use.

Concerning the packaging materials, they also consume resources, although they represent a small percentage of waste. Its disposal can also cause problems for the environment: they impact the environment through pollution caused by incineration and landfills (WHO, 2002). No pharmaceutical packaging is reused, but the outer packaging of pharmaceuticals is usually an uncontaminated material (similar to domestic waste: paper, cardboard, glass, plastic) that can undergo recovery or recycling together with empty non-hazardous pharmaceutical packages. Disposal methods will vary but should always be following the national legislation. For example, a major environmental issue affecting particular types of pharmaceutical products concerns the chlorofluorocarbon (CFC) propellants, and the threat they pose to the ozone layer (WHO, 2002).

From the wholesaler to final consumer, there are environmental issues regarding the emissions produced by transporting medicine products around the countries. Moreover, the final consumer has also a role in this matter: flushing unused drugs into sewer systems, throwing them in the garbage or not treating household waste in an environmentally responsible way constitutes a gateway into the environment contributing to environmental pollution. The proper and safe disposal is essential. Directive 2004/27/EC (amending Directive 2001/83/EC) on the Community code relating to medicinal products for human use consider the precautionary and safety measures to be taken for the disposal of waste products, together with an indication of potential risks presented by the product to the environment. EU member states are obliged to ensure that appropriate collection systems are in place for medicinal products that are unused or have expired. The use of incineration as a disposal method is regulated in the EU by Directive 2000/76/EC on the incineration of waste and, although being the safest option, this method has also the drawback of releasing pollutants. However, this is handled by regulations stipulating limit values on the emission to the atmosphere. Also, the temperature of the gases in the process should be at stipulated values depending on the waste content. Therefore, the environmental wastes will be resumed: wastewater, emissions who leads to air pollution and waste heat (energy).

The second part of this section is the literature review regarding the final product waste, as shown in Figure 13. Therefore, Table 3 presents the articles of the studies analyzed regarding medicines' end-of-life at a European level, including their disposal methods. Analyzing the different studies, the types of disposals of the pharmaceutical waste considered are the ones represented in Table 3 (in the last column, in blue). Inappropriate drug disposal behavior includes throwing unused drugs into the garbage waste, sink, toilet, etc. The improper disposal of unwanted medicines represents a source of pharmaceutical pollution. By contrast, there is also the option of returning medicines to pharmacies, which is the proper way to dispose of. However, as it is represented, the disposal of pharmaceuticals by garbage is the most common method in many countries. For example, as it is described, a Serbian study revealed that 88% of participants disposed their unused drugs in the garbage or toilet (Kusturica et al.,

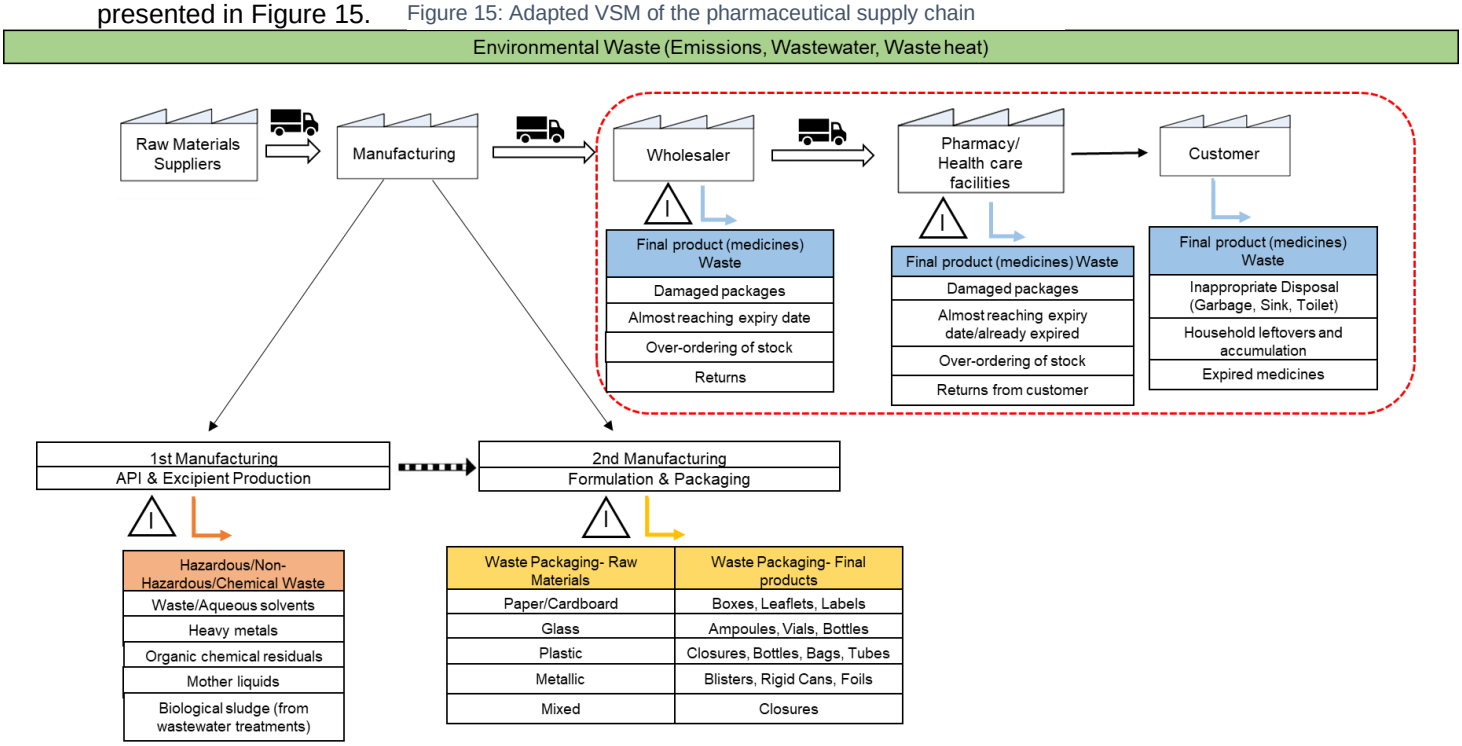
2012). Another study performed in Ireland reported that the majority of the participants disposed of their unused drugs through inappropriate ways, mainly household waste, sink, or toilet (Vellinga et al., 2014).

Table 3: Studies in European Countries on the different disposal method

Country	Study	Aim	Most Commonly Reasons for Waste	Disposal Methods		
				Return to pharmacy	Garbage	Toilet or sink
Sweden	Ekehdal et al. 2006	Interviews with patients **returning** medications to pharmacies in Sweden	**1**. Passed expiricy date **2**. Patient's death **3.** Condition improved/resolved			
	Person et al. 2009	To learn about what the general public does with **unused prescription drugs** and their attitudes regarding this issue		43%	3%	
United Kingdom	Bound et al. 2006	To investigate the **household disposal of unused and expired pharmaceuticals** as a source of pharmaceuticals in environment			**63.2%**	11.5%
	Mackridge and Marriott 2007	To analyze all **medicines returned** from patients to community pharmacies and GP surgeries in Eastern Birmingham	**1**. Patient's Death **2.** Clearout of old/expired medicines **3.** Medication changed			
Germany	Gotz and Keil 2007	To clarify to what extent consumers in Germany **dispose of unused medicines**		**29%**	6.5%	11%
	Alnahas et al. 2020	Local survey conducted among students from university and their families regarding **disposal of expired medicines**		15.9%	**72.7%**	3.4%
Spain	Coma et al. 2008	To study the amount of **unsued drugs** by doing and analyzing a cross-sectional questionnaire on 38 community pharmacies	**1**. Passed expiricy date **2.** Condition improved/resolved **3.**Patient's death			
Serbia	Kusturica et al. 2012	To investigate the **storage and disposal habits** for medications of the population in the South Backa District of Serbia		4%	**88%**	
Malta&Ireland	Fenech et al. 2013	To understand the **current disposal practices** and the relevance of the various routes of unused medicines entry into the environment		<10%	**57% liquids; 68% pills**	28% liquids; 14% pills
Portugal	Dias-Ferreira et al. 2016	To study on **pharmaceutical waste generated at households** in Portugal and exploring people's attitudes and risk perception	**1.** Expected future use **2.** Not expired **3.** Over-prescription	69% *good-answer effect		
Netherlands	Bekker et al. 2018b	Cross-sectional study to assess patient **medication returned to pharmacies** and possibilities for redispensing unused medications	**1.** Patient's death **2.** Condition improved/resolved **3.** Passed expiricy date			
Poland	Rogowaska et al. 2019	Two studies conducted to estimate the problem of **collection and disposal of expired/unused pharmaceuticals** with different purposes			68% (1st survey); >35% (2nd survey)	
Romennia	Manea et al. 2020	Assess the attitude of pharmaceuticals consumers in Bucharest towards their management and their **disposal after the expiration date**		2.4%	**>79%**	

However, people returning medications to pharmacies was a common disposal method according to a Swedish survey made in 2007 (Persson et al., 2009). Sweden has a long tradition of the system to return unused drugs to a pharmacy and not to throw the leftover drugs in the garbage or flush it down the drain. This is accomplished by disposal awareness campaigns. Also, according to some studies made for returned drugs, the most commonly reported reasons for wastage is passed expiry date; condition improved/resolved; patient's death (Coma et al., 2008; Ekedahl et al. 2006; Bekker et al. 2018b). Therefore, with the information presented and based on Table 3, it was possible to design the VSM presented in Figure 15.

Figure 15: Adapted VSM of the pharmaceutical supply chain



The VSM starts with the raw materials suppliers which gather and deliver the products necessary to the manufacturing. As aforementioned, the manufacturing comprises APIs and excipient production (1st manufacturing), as it is represented in the process box, and then the formulation and packaging (2nd manufacturing). Therefore, the drugs, which are manufactured in bulk, are formulated into various dosage forms such as tablets, syrups, and lotions. Then, the formulated products are packaged in appropriate containers. The production of pharmaceuticals involves a series of steps, often involving several different companies and production sites, in order to produce a finished pharmaceutical product. The APIs may be assembled into pills at special formulation plants, with packaging taking place at yet other sites. From the 1st manufacturing to the 2nd the materials are pushed by the producer. After having the medicines in their final form, wholesalers distribute to the pharmacies and health care facilities who, ultimately, dispense them to the final customers. Also, there are materials and medicines' inventory in the manufacturing, wholesaler, pharmacies entities (represented with a "I" in the triangle).

The main wastes of each phase are present in the different wastes box. The environmental box, in green, is included throughout the supply as it was already mentioned. At each stage, pharmaceutical waste enters the environment however, since it is not the core of the thesis, are just briefly mentioned. The red dashed circle is the scope previously defined. The focus is going to be on the downstream part of the pharmaceutical supply chain when the medicine is already produced. A remark should be done about the packaging materials waste of the final product that, although not represented in the medicines' boxes (in blue), also exist and represent a waste stream.

Being the wastes already identified, the next step is to understand, via small interviews, which of them are more urgent.

5.1.2 Interviews Main Findings

This section summarizes the significant answers and information from the expert interviews in order to validate and deepen the analysis with specialized inputs about the industry.

The selected four experts work within the pharmaceutical industry and, since the scope is the downstream part, wholesalers and pharmacists were both interviewed. Therefore, these interviewees have given to this work real perceptions about the Portuguese market - which is important since the solutions that will be presented are going to be applied to the Portuguese context and reality. Within the scope of wholesalers, the two interviewees work in companies that are leaders in Portugal: one from a Portuguese multinational pharmaceutical company (expert 1), and the other is a leading distributor and wholesale company in Portugal (expert 2). Both sell and distribute medicinal product, however for different entities, as it is going to be explored below. The other two interviewees (expert 3 and 4) are pharmacists. The first three questions investigate the experts' opinion about the VSM presented collecting feedback about it while the other questions have the objective of understanding the critical problems within the scope previously defined (i.e., the downstream part of the supply chain, represented in the VSM through the red circle) in order to derive conclusions about where the main focuses of this thesis will be.

• **Experts' opinion about the VSM**

All the specialists validated the VSM stating that, in terms of scheme, it is very complete: "The main types of waste are represented and in a precise way" (expert 1). The categories that were identified are accurate and, although in a global form, they include the most important types of waste. Expert 4 considered that the categories represented are inclusive and he does not remember of more.

The experts pointed out that, in terms of entities represented, they may vary according to each country: "the world of wholesalers is very complex and, although the aim is distributing and selling medicines, there are different entities doing it", state expert 2. Moreover, he also underlined that, although Europe is divided into a series of distinct national markets, medicinal products are generally distributed via the following distribution path: manufacturer to (pre-wholesaler) to pharmaceutical full-line wholesaler (FLW) to pharmacy to the consumer. "The pre-wholesaler and pharmaceutical full-line wholesaler can be aggregated in the wholesaler since the type of medicines waste is the same. Also, in Portugal the FLW is called "armazenista" (expert 1).

Experts 3 and 4 also called attention to this topic: "the wholesaler entity represented in the VSM can be disaggregated" and mentioned that making it on "a European basis, it represents the European reality, in a simplistic and general way".

Therefore, if we wanted to apply to the Portuguese context, the supply chain entities would be as they are represented in Figure 16.

Figure 16: Pharmaceutical supply chain entities applied to the Portugal context

The entity added was the Marketing Authorization Holder (MAH). The MAH is a company or other legal entity authorized to market a medicine in one or several EU members and has ultimate responsibility to ensure that the product placed in the market is safe, effective for use and produced according to the Good Manufacturing Practices. This entity is allowed to distribute and sell their medicines.

In Portugal, a very common situation is the MAH being a separate company from the manufacturer. Hence, the large majority of MAH companies are not directly engaged in the manufacture of medicinal products themselves but are crucial to distribute and store medicines.

Therefore, the link between the manufacturer and FLW (the "armazenista") can be made directly through the MAH or through an intermediary, the pre-wholesaler. Figure 16 represents this process.

Pharmaceutical pre-wholesalers act as logistic service partners for pharmaceutical manufacturers or MAH and are highly specialized providers of supplies to other wholesalers. They can be seen as the prolonged arm of manufacturer and/or MAH (depending on if these two entities are the same) and use their own storage facilities to store their stocks, while also providing services, such as product packaging and labelling for national markets, warehousing, storage and distribution. For example, BLGN, a MAH

licensed for the distribution of products, has its own facilities to store and sell the products directly to the pharmaceutical FLW.

Concluding, the VSM was validated by the experts and the categories of waste were accurate and comprehensive. The suggestions made do not change the global picture of the VSM previously sketched since it intends to represent the European reality trying to be comprehensive in a simplistic and general way, in terms of entities.

- **Questions about the existing problems according to the experts' experience**

The different respondents identified problems related to their field area, given their expertise and knowledge.

Both experts 1 and 2, being wholesalers identified returns as one of the critical problems in the industry. They further specified that legislation is very complex and strict, which obliges companies to create waste that, in fact, is not necessarily "waste". Expert 1 also highlighted that the problem with returns also meets the categories of "expired medicines" and "damaged packages", depicted in the VSM: "during the processes carried by the wholesalers, which involves warehousing and distribution of medication stocks to pharmacies, medication waste can derive as a consequence of the expiry date and damaged boxes". Moreover, expert 2 emphasized that Portuguese consumers "have a problem with the right disposal. I think they are aware of the benefits of returning medicines to the pharmacy however they do not do it, keeping too many medicines at home".

Specialists 3 and 4 have outlined their perception on wrong disposal of the final consumers, considering a critical issue that people do not have the habit to return the non-used packages: "people think that the only pharmacies' purpose is to buy medicines". Expert 3 further mentioned: "the categories regarding the consumer entity, written in the VSM, are closely related given that the household accumulation and storage lead to having expiry medicines at homes which may lead to the inappropriate disposal". Expert 4 corroborates this point of view and also clarified that the problem of expired medicines within the pharmacies is not critical since this is a problem for the MAH or pre-wholesalers given that "they are the ones who acquire the full batches to further distribute according to the market needs on a short period of time".

Regarding the main challenges faced by companies and the industry, all respondents pointed out the legislation topic. Expert 1 highlighted that the problem of returning begins with the definition of what is considered to be waste. It seems that the problem and the harm begin, in first place, when there are so many legal restrictions. For example, the expert pointed out that, in Portugal, any product whose shelf life ends in 6 months can no longer be in the market and cannot be donated: "this is not wise, and the legislation should be adapted to consider some cases where donations could be possible".

So, from the interviews it is possible to conclude that the most critical issues are the ones related to returns (once they include unnecessary waste such as damaged boxes and waste concerning expiry date), the household accumulation and the type of disposal by the end-consumers. It is, thus, important

to analyze the reasons why consumers accumulate this type of waste at home, as well as to explore the problem of the returns of the companies, the damaged boxes and expiry date issues.

However, this implies the involvement of two stakeholders that have different points of view, that should be analyzed separately since it represents two different perspectives related to different stakeholders.

Therefore, as represented in Figure 17, from the consumer's perspective it is necessary to understand the household accumulation and type of disposal and, from the industry companies, explore the issues with damaged packages and expiry date which also meet the returns problems. The critical waste problems mentioned were concluded having in consideration the interviews performed to Portuguese experts inserted in the Portuguese context- for that reason this is the reality which is going to be explored in the following sections.

Figure 17: Critical waste pointed by expert interviews

As such, the next step is exploring the root causes of these issues by analyzing the consumer behavior through a survey and studying the returns of the Portuguese company, BLGN.

5.2 Principal Causes Identification

After having the scope and the main problems defined, this section intents to identify the causes of the main problems pointed out above. As aforementioned, the main problem impacting the stakeholders (A- final consumer and B- industry) involved will be analyzed separately.

A. Final Consumer Stakeholder

5.2.1 Ishikawa Diagram

The problems identified concern waste from unused medicines resulting in household storage, as well as their accumulation and disposal method.

Taking into account the literature review of the previous step, it is possible to identify a variety of factors throughout the supply chain entities, from manufacturer to patient, contributing to this problem.

- Manufacturers may produce unnecessarily large packages (over-sized medication package) with quantities that exceed the amount required for treatment (West et al., 2014). Patients consume a portion of the medicine supplied in oversized medication packages, and this leads to waste.
- Pharmacists are not always allowed to split packages into smaller quantities and thus dispense excessive amounts to the patient that eventually go unused and wasted (Bekker et al., 2018a). Also, many pharmacy chains have promotions that encourage increased purchase of certain medications by offering lower prices for example, for additional over the counter medications. The larger supply stored in their homes increases the quantity of unused medication.
- Prescribers may prescribe medications for a longer period than the patient actually needs. It is important to highlight that imprudent or inappropriate prescribing, including over-prescribing or mis-prescribing, leads to larger than needed dose quantities or longer than needed durations. All of these can contribute to the accumulation by the patient of unused medications, financial waste, and

harm to the environment (Bekker et al., 2018b). There may also be a lack of communication between the prescriber and the patient: while one may believe they have explained the disease and the medicine's mechanism of action in reality, the patient may not understand the information regarding the treatment/medication prescribed.

- Finally, medication waste may occur at the patient level too.
  - Therapy changes have found to be a frequently reported cause of medication waste by patients (Coma et al., 2008; West et al. 2014; Mackridge & Marriot 2007; Braund et al. 2008).
  - Also, side effects, unsatisfactory treatment responses, or early discontinuation during medication use may lead to therapy changes that may result in excess of dispensed medication (Coma et al., 2008; Braund et al., 2007; Ekhedal et al., 2006). For example, patients may have side effects caused by medications, and therefore may stop using them. There are cases where a patient recovers sooner than expected or experiences a change in her/his condition which leads to a change in medication. Remaining older medication is, therefore, wasted. Likewise, patients may decide they do not really need the medication due to misjudgment of their health status or change their beliefs on medication effectiveness and choose another therapy.
  - Moreover, forgetfulness has a role in missing doses of medications and, therefore, may also be a cause for medicines are stockage. Patients will, therefore, keep the remaining amounts for later use, discard them with the household garbage or return them to pharmacies.

After discussing the points presented above with the experts and applying the causes founded to the Portuguese market and reality, it was possible to illustrate, in Figure 18, the main causes for the type of waste concerning the final consumer, via a Fishbone Diagram.

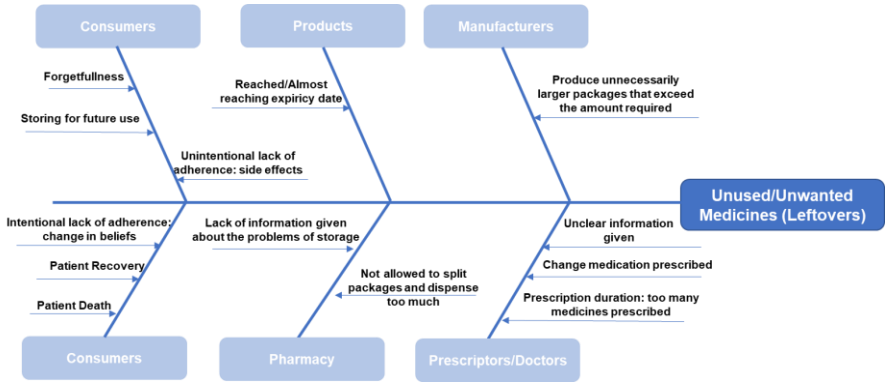


Figure 18: Fishbone diagram for unused/leftover medicines

As it is represented, although the waste occurs on the patient level, i.e., the ultimate responsibility is at the patient, causes may rely in other entities. The reasons represented in Figure 18, will serve as the basis to some of the survey's questions, more precisely, in the ones intended to understand why Portuguese people accumulate their medicines at home (both unused/unwanted). To this end, the analysis can be deepened in order to draw some conclusions about the critical and priority causes. Moreover, as pointed out in the literature review, the disposal method is also a main topic that will be addressed in the survey.

5.2.2 Survey Research

Following the proposed methodology, and in order to deepen the analysis to the Portuguese reality, a survey was designed and presented to Portuguese population. The survey responses were gathered online, and a total of 570 responses were achieved. The sample is a convenience one and it is not representative of any region or group in specific.

In order to characterize the sample, it is necessary to analyze the demographic information and the household characteristics, therefore Table 4 summarizes this information. As it is represented, the majority of the inquired belongs to the 18-30 age gap (42%) and 31-55 (34%). Also, the sampled population has a high education level since 86% has a university degree.

Regarding household (household represented all the persons who occupy a housing unit), more than half of the participants were living with less than 4 household members. Moreover, 78% of the households have less than 2 children.

Table 4: Demographics and household characteristics of the survey respondents (N=570)

Gap Age			*Level of Education*			*Household Members*			*Children in Household*		
	N	*%*		N	%		N	%		N	%
< 18	1	0%	**Secundary High School**	63	11%	**1**	53	9%	**0**	195	34%
18-30	239	42%	**University (BSc, MSc, PhD)**	492	86%	**2**	124	22%	**1**	98	17%
31-55	191	34%	**Professional Course**	15	3%	**3**	131	23%	**2**	153	27%
56-70	88	15%				**4**	142	25%	**3**	80	14%
+71	51	9%				**5**	71	12%	**4**	25	4%
						+5	49	9%	**+5**	19	3%

Focusing the first questions of the survey, which focused on the household medicines, Figure 19 represents the quantity of unused/unwanted pharmaceuticals stored at home.

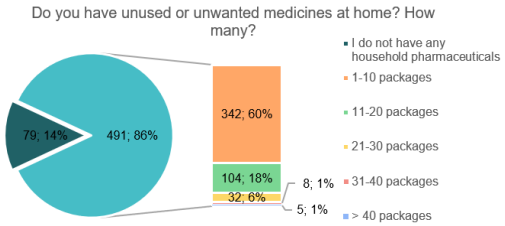


Figure 19: Distribution of respondents regarding household medicines

Participants declaring not having unused drugs at home were 79 (14%), while regarding those having unwanted medicines, the most common answer was having 1-10 packages (342 persons). Considering all the responses, there is a tendency for having unused or unwanted medicines stored at homes. This reality may cause an inadequate disposal of drugs, increasing risks to public health and the environment.

Analyzing these medicines and as it is presented in Figure 20, from the 389 respondents who declared having expired medicines at home (which corresponds to 79% of the population), 95% have between 0 and 50% of the medicines expired. Highlighted by these questions there is the need to pay attention to the expired medications.

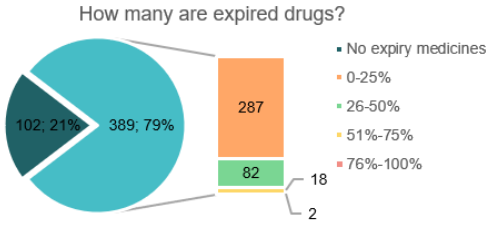


Figure 20: Household medicines validity

Also, as it was concluded through the fishbone diagram, unused pharmaceuticals are kept at home for several reasons and Figure 21 represents the respondent's reasons. It is important to denote that for

this question, several answers were possible to be chosen since, different medicines, may have different reasons for storing them. The most cited ones (approximately 68%) was within expiry date and expected future use (even if no use is expected in the near future). This introduces a large time gap between acquisition and discarding which influences medicines wastage.

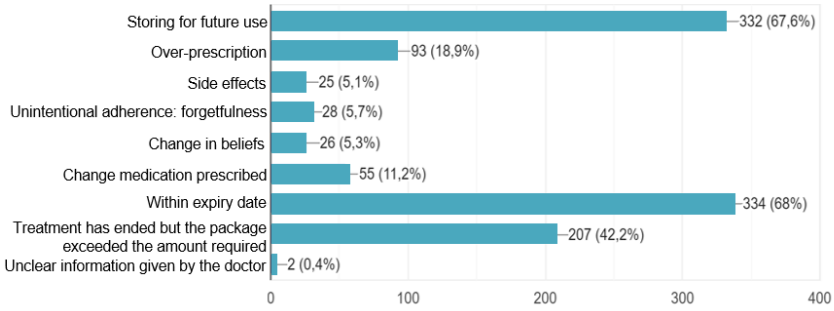


Figure 21: Respondents' main reasons for storing unused/unwanted medicines at home

A total of 207 respondents (42%) stated that the treatment has ended but the package exceeded the amount required and 93 persons (20%) of answers related to over-prescription i.e., too many pharmaceuticals, which after being bought were stored at home. Therefore, the number of pills contained in each package is an issue, since the patient consumes a portion of the medicine supplied and stores the rest and this eventually leads to waste. The gap between the shelf life and the actual obsolescence date leads to storage, reuse or disposal of pharmaceutical products.

Regarding the disposal of unused/unwanted medicines, the purpose of the question was to find how respondents handled with these pharmaceuticals and their motivations and perceptions regarding this topic. Figure 22 represents in which percentage do the respondents dispose of their unused or unwanted pharmaceutical products and their packaging. Throwing to the sink/toilet is the least common option, for every percentage of the waste. According to the sample, 92% do not use this mean at all, meaning respondents throw medicine exclusively to garbage or return it to the pharmacy, or use a combination of the different means (in different proportions). Similarly, no respondent (0%) use the toilet as mean to throw their medicines. Given these insights, it is possible to conclude sink/toilet is not a significant mean in the analysis of the medicine's end-of-life.

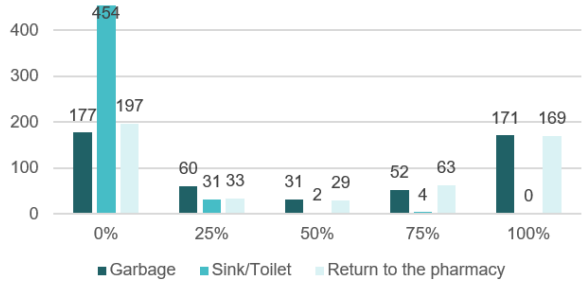


Figure 22: Respondent's behavior related to unused/unwanted medicines disposal

Approximately the same number of people dispose 100% of their unused pharmaceuticals in the garbage or return to the pharmacy, even though, according to the sample, using exclusively garbage for medicine disposal is the most preferred behavior out of all the possible behaviors (171 respondents rely exclusively on garbage, being the highest probability among all behaviors (35%)). Thus, the most preferred mean of disposal is garbage, with 64% of respondents using garbage to throw their medicine, exclusively or in combination with other means, despite returning to pharmacy also being a common

practice (60%). The result of 60% of the people returning to the pharmacy (either exclusively or combining different types of disposals) can have some reserves: Figure 22 might be overrated because, even though by assuming that behavior, which showcases the awareness of such practice, it is not irrelevant to consider that the respondents might not actually have that practice. Regarding this question, a final conclusion can be extracted concerning the combination of different types of disposals.

According to the sample, respondents prefer only relying in one type of disposal over using a combination of several means to throw their medicine. As it is represented in Figure 23, more than 70% of respondents use exclusively one method of disposal.

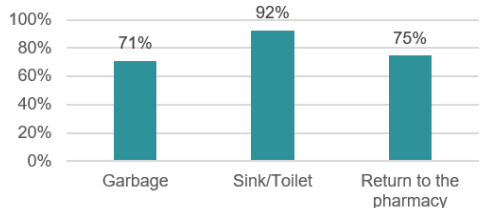


Figure 23: Probability of respondents to take 0% or 100% of their medicines to exclusively one type of disposal

From a changing behavior strategy, it is therefore easier to make people shift behaviors as, for instance, if they use the garbage to throw their medicines, if they start returning it to the pharmacy, chances are higher to rely solely on pharmacy to dispose their medicine and not having a combination of different means.

Regarding the respondent's perceptions of returning medicines to a pharmacy, Figure 24 shows that, 346 respondents which corresponds to 70% of the answers to this question, realize that pharmaceuticals can be returned to a pharmacy for the appropriate disposal and nearly 50% voted with 5 points regarding the perceived value on this topic, with only 13% attributing between 1 and 2 points. This proves that most people are conscious about the right type of disposal and its importance.

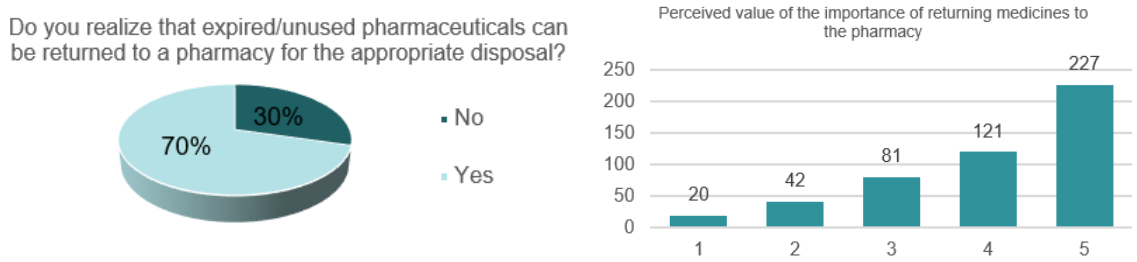
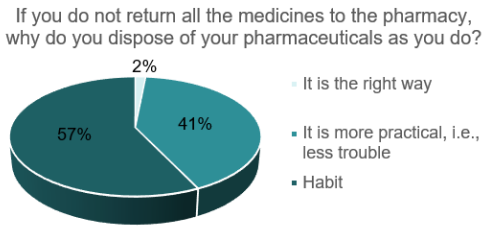


Figure 24: Respondent's perceived value on the right disposal (N=491)

As stated above, 251 respondents (51% of the people who answer this question) do not return their unused or unwanted medications and instead resort to inappropriate means of disposal (toilet, sink or garbage). Question number 8 of the survey, represented on Figure 25, helps to understand the reason behind people make the wrong type of disposal. Of those discarding in other ways rather than returning to the pharmacy, few considered that the destination chosen was the most adequate (2%), reinforcing the trend seen previously of returning to the pharmacy being perceived as the right thing to do.



The justifications for not discarding at the pharmacy were mainly pragmatic reasons (it is more practical to do in some another way), and established routines, which can be hard to change although the need for this shift to occur is important.

Figure 25: Respondents' motivation on dispose of their medicines as they do (N=491)

Regarding question number 9, Figure 26 depicts the return frequency of the respondents. 39% (191 participants) had never returned medicines to the pharmacy while almost half of them return just once or twice a year. Therefore, the most common answers given were "never" and "once a year" which makes the frequency rate low.

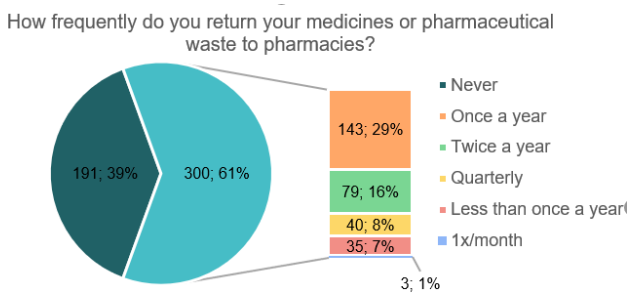


Figure 26: Respondent's frequency rate of returning medicines to the pharmacy (N=491)

For the 300 persons who, at some rate, return medicines to the pharmacy, the chart in Figure 27 represents the reasons behind doing so. In this question, the respondents could, once again, give multiple answers, when a patient returns several different medicines, there may be different reasons for the different medicines being returned. The main reason cited (208 participants- 89,3%) was that the medicines had already expired. Other reasons ranged from having already improved (so no more explicit benefit arises from keeping pharmaceuticals- 70 respondents) to house-cleaning. Few stated changes in therapy or that there had been adverse drug reactions.

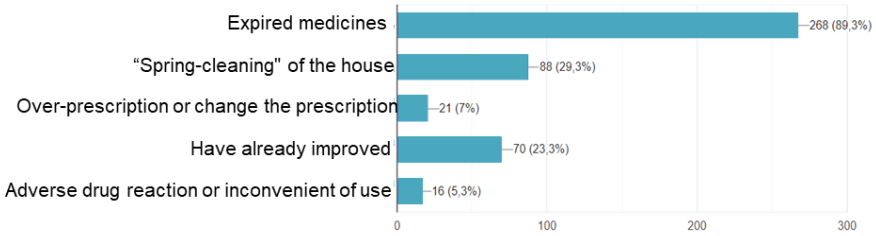


Figure 27: Reasons to return unused medicines

When asked about the motivations behind retuning to the pharmacy, the most frequent answers were "to recycle or reuse the materials" (56%) and to "protect the environment and public health" (71%). Therefore, the awareness previously concluded is also emphasized by this environmental sensitivity.

Despite awareness of environmental and public health impacts caused by the presence of these pharmaceuticals wastes in the environment, the vast majority of population eliminates them thought household sewage. Given this reality, it is important to emphasize the implementation of enlightening campaigns that inform users about the correct procedures for the deposition of these wastes.

The next figures depict the respondent's answers from questions 12 to 16. These questions were included in the survey in order to understand the perceptions and consumer openness regarding some ideas/solutions that will be presented in the following section. Figure 28 represents the respondents answers of question 12. If special bags were provided, the majority of the individuals would possibly dispose of their medicines in the pharmacy, more often. Nearly 65% of the respondent's voted with 4 and 5 points regarding this topic. The use of a box to store pharmaceutical waste is not a common practice in Portuguese households however if this becomes more widespread it could help change routines and incentivize more people to return household pharmaceutical waste to the pharmacy. In the absence of such service, patients end up retaining medicines within their household for a longer period of time.

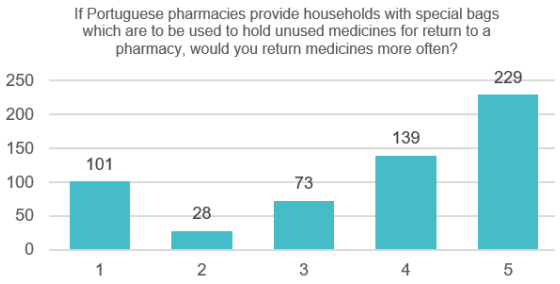


Figure 28: Respondent's level of adherence of special boxes to store pharmaceutical products at home

Also, 67% of the sample which is being analyzed voted with 5 points regarding the probability of returning more often if financial incentives were given for example a possible reimbursement system for the drugs which were returned or even a discount in the next prescriptive medicines bought in a pharmacy. Answers to this question is represented in Figure 29 as well as answer to question 14 (graphic on the right). Question 14 was made to explore the possibility of donations, to minimize waste and trying to give other destination for the medicines. 412 respondents (72%) voted with 5 points which means that people are open to donations and want to avoid the pharmaceutical wastage.

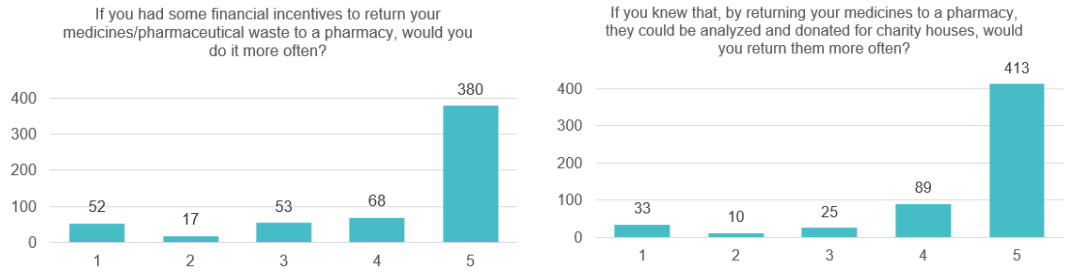


Figure 29: Respondents' answers to questions 13 and 14

Regarding unit-dosing, Figure 30 shows that 82% of the participants would be interested on going to a pharmacy and buy just the quantity prescribed or even the number of pills they wanted for a certain occasion. Unit-dose dispensing could minimize the quantity dispensed since it would ensure that all the medicines dispensed would be consumed.

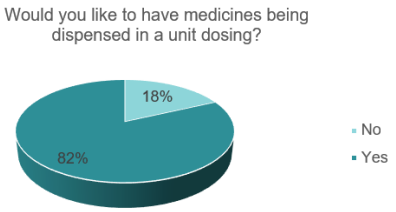


Figure 30: Respondents' preference on unit dose dispensing

Finally, the last graphic of these questions, in Figure 31, shows that, of the 570 people who completed the survey, more than a half (52%) were not willing to buy and use medicines that were stored in another patients' home, punctuating only 1 or 2 points. Therefore, this is not a "valid" option for the majority of the participants.

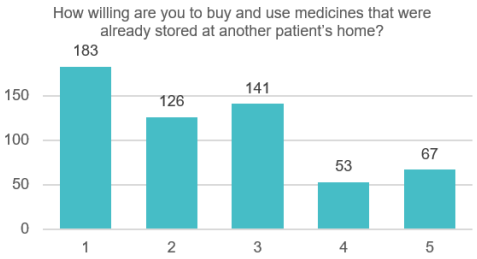


Figure 31: Respondents' willingness to buy use medicines that were already stored at another patient's home

To deepen the analysis made to the survey responses, some answers were crossed between different questions to provide a more detailed study regarding the inquirers' preferences. The most relevant observations and data gathered is presented as follows:

- Although most of the of the respondents acknowledge that pharmaceutical products could be return to the pharmacy, there is a relationship between this and the gap age, as it is represented in the Figure 32. People between 18-30 years old are less aware that returning pharmaceutical waste to the pharmacy is actually an option.

Figure 32: Relationship between gap age and right disposal awareness

For this reason, more information campaigns are necessary to inform and educate the population on the appropriate and secure disposal of medicines: the need to have more information reaching the younger age group concerning the benefits of returning pharmaceutical waste to the pharmacy is clear. The success of drug take-back programs depends on efficient campaigns influencing them to take the right attitudes. In this way, it is no surprise that the attitude of returning medicines to the pharmacy was exhibited more significantly in >30 age group while the attitude of never returning medicines to the pharmacy is recurring in the younger people, as it is represented in Figure 33.

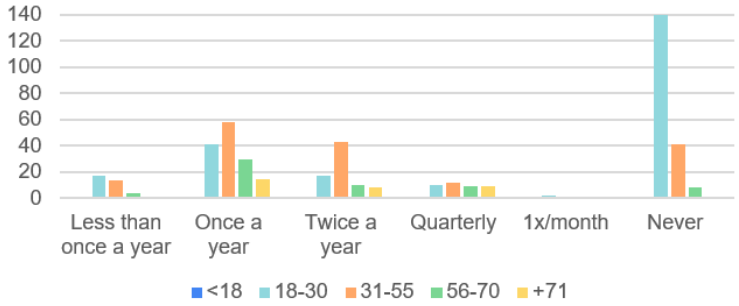


Figure 33: Relationship between age group and returning to the pharmacy frequency rate

- Also, household with children have more stocked pharmaceuticals at home. The number of packages between 11-20 or 21-30 have risen from having no children or having more.
- In the same line, household with more members have also more medicines. However, the tendency is that the bigger the house, the least frequent is the disposing to the pharmacy (in proportion). The percentage of never returning increased with the number of household members while delivery in three in three months (quarterly) decreases. This happens because, probably, bigger families have more things to do, being easier to use other means to dispose of their medicines. Once again, these habits should be changed with information to sensitize people to do the right choices.

Limitations:

- Subjectivity of the answers: as mentioned above, answers to the questions regarding disposal habits and attitudes are self-reported in nature and some respondents may not have been telling the truth. It cannot be confirmed whether respondents actually put into practice what they answered.
- The sample of households included in the study was relatively small and this study cannot guarantee that just 1 person per household answered the survey, so perhaps people from the same household had responded with different answers.
- The study had probably reached more people in Lisbon, so it might not cover all the regions in Portugal thus, not reflecting the sociological and geographical diversity in the country. Moreover, the availability of medications in rural and urban areas differ, as well as the education and habits of the people including with medication disposal behavior. Therefore this study may not be inclusive.

Final conclusions of the survey:

- People have the tendency to stock accumulate unused and/or expired medications in their homes. In this study, this tendency was confirmed, since 86% of the respondents stated that they had unused/unwanted medications at home and 80% of the respondents have expired medicines. The common reason to possess medicines is storing for future use. However, if they are not used, these medicines will eventually reach their expiry date and end up in the garbage.
- It was also found that, among the consumers who have medication leftovers, although the vast majority is aware of the correct way to dispose of unused and/or expired medicines, most proceed incorrectly, putting them in the regular garbage, sink or toilet. This can be justified by laziness and old habits. It is, therefore, important to facilitate this process while give more information and guidance in order to get people more sensitive to this topic and remind them the importance of the medicines' right disposal.
- It was also pointed as a common reason for having stockpiled medicines, the number of medicines in each package, that exceed the necessary. There is, therefore, a need for increased cooperation between health systems and the pharmaceutical industry to decrease waste accumulation.
- Finally, this study also shows that some practices would make people return more often their pharmaceutical wastage, which could reduce the accumulation of medicines, change their disposal behaviors, and consequently reduce the harmful impacts on the environment and public health. Some of these practices and suggestions will be pointed out on section 5.3.

B- Pharmaceutical Industry Stakeholder

5.2.3 Analysis of the returned medicines sample from BLGN

In order to study and understand the pharmaceutical wastage within pharmaceutical industry, data from BLGN, a Portuguese MAH, was collected. The study was conducted with data from 2019 and the sample analyzed included all the returns that arrived at this company. It is important to remember that the medicines' returns handled in this section, never left the closed circuit of the medicine, i.e., they were never sold to the consumer. In this context, these returns belong to FLW and pharmacies. In Portugal,

it is forbidden to return to the industry medicines that were already sold to the final consumers which means that, all the household pharmaceutical waste discussed previously, is under the responsibility of VALORMED which collects, transports to sorting facilities, from where it is sent for recycling (e.g., cardboard packaging) or for incineration (e.g., pharmaceutical residues; contaminated packaging).

Information about the price, products from each return, quantities of the medicines were retrieved from BLGN' database. The value of the medicines content was determined at the pharmacy retail price, i.e., the public selling price in 2021. The main reason for choosing this type of price was that retail prices of each company are standard across pharmacies and, unlike purchasing prices, do not vary according to special bonuses issued by pharmaceutical agents. Each stakeholder obtains a share of profits from drug sales as such, in order to compare different perspectives, the retail price was the best one. Table 5 has general information about the sample which is going to be further analyzed. In 2019, there were 5 484 returns however only 2% of them were from pharmacies. The remaining were from FLW. The number of packages returned is 18 157 which corresponds to 231 different products, representing 159 468€.

Table 5: General information about the sample

No of returns	No of packages returned	No of products	Total value
5 488	18 157	231	159 468 €

With the data given, two Pareto analysis were made: on the number of packages and on the value, represented in euros (i.e., the retail price). Figure 34 represents this analysis where it can be observed that, approximately 80% of the waste, is due to the following categories: "expiry date" and "others" (which represent 30% of the causes). However, within "others" category, there are multiple reasons and none of them are relevant for the waste considered in this dissertation making this category not relevant for the analysis. Hence, the focus will be on the expiry date returns and on the following most relevant category after "others", i.e., "damaged materials". This is consistent with what was concluded about the critical issues in the expert interview, supporting this problem.

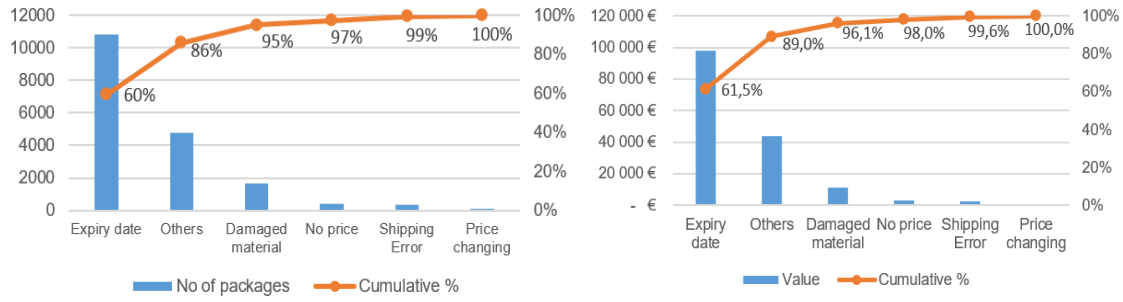


Figure 34: Pareto on packages (left) and on value (right) of the reasons for the returns

Notably, these are the two reasons (out of six), represented in the database, that effectively generate waste since the other reasons pointed can return to the market (if there is no price, the industry can put it; a shipping error can be solved and if the price has changed, there is also a way to put these medicines on the market). It is worth mentioning that approximately 60% of the packages returns is due to expiry date issues. However, it was decided to take the damaged packages into account given the urgent need of adapting the legislation.

Therefore, by tapering our analysis to these two reasons that generate waste, there are 307 returns with a total of 12440 packages and 109 384€ of total waste value. For that reason, the values presented from now on are regarding the two principal causes of waste identified (damaged materials and expiry date). As represented in Figure 35, almost 90% of the packages are waste because of expiry data issues.

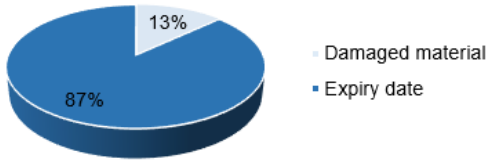


Figure 35: Percentage of packages according to the effectively waste returns analysis

Figure 36 represents some characteristics from the products of the sample. Regarding the packages' size, normally, there are two different options: the small and the large package and the vast majority (92%) of the waste is represented by the small ones. Most of the small packages, which can also be called, "test packages" (in Portuguese "embalagens teste") are imposed by law to be produced for drugs intended for long-term treatment/chronic therapies (packages up to 20 units). As such, the majority of the medicines that have large packages will necessarily have a small package associated. It is important to denote that the actual number of pills packaged depends on the medication itself. For example, the large package of alprazolam corresponds to 60 pills and the small has 20 pills while pantoprazole, has 56 pills on the large package and 14 on the small one. The size of the packages can be also an issue in the industry. In fact, for a medicine to be in the market, it must have a small package manufactured although doctors usually prescribed the large ones and the rotation of these packages in the market is significantly low. Therefore, a considerable pharmaceutical waste is created because of this obligation.

Moreover, regarding the type of medicines, there is a distinction between medicines to treat chronic diseases and acute ones. Broadly speaking, acute medicines treat diseases that are limited in their duration (e.g., the flu), while chronic, on the other hand, are long-lasting and the conditions may be worsen over time. In the sample, as depicted in Figure 36, 66% of the packages are from medicines to treat chronic diseases while 34% are for acute ones.

	% of packages
Damaged material	**13%**
Large package	13%
Expiry Date	**87%**
Large package	79%
Small package	8%
Total	**100%**

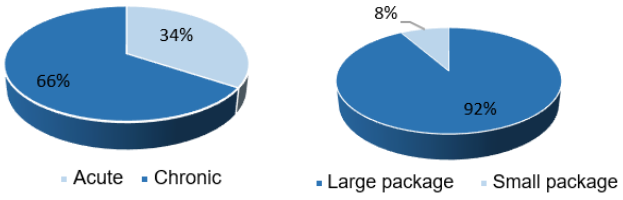


Figure 36: Sample's characterization regarding the number of packages

It is interesting to observe also in Figure 36 that there are no waste regarding damaged material of small packages. This is due to the volume of sales of these boxes, which is significantly low when comparing to large packages (as explained before). Therefore, if these medicines have no rotation, they are not in constant circulation, therefore, they do not get damaged because they are not moved within the warehouse.

Analyzing the types of medicines in the sample, the Anatomical Therapeutic and Chemical (ATC) classification system was used and retrieved by BLGN database. This classification of the WHO divides the active substances into different groups regarding to the organ on which they act and their

therapeutical, pharmacological and chemical properties. Drugs are classified in groups at five different levels (WHO, 2021).

Table 6: Quantity of medicines packages according to ATC classification

ATC Classification		% of packages
J01	Antibacterials for systemic use	19%
C09	Agents acting on the renin-angiotensin system	11%
C10	Lipid modifying agents	10%
A02	Drugs for acid related disorders	10%
-	Other	6%
N05	Psycholeptics	5%
C01	Cardiac therapy	4%
M01	Antiinflammatory and antirheumatic products	4%
G04	Urologicals	4%
A10	Dugs used in diabetes	4%
N06	Psychoanaleptics	4%
R05	Cough and cold preparations	4%
N03	Antiepileptics	3%
…	…	…

Table 6 shows the number of packages of each ATC 2nd level classification. This level represents the therapeutic subgroup. The most common type of the sample analyzed was that pertaining to the antibiotics (20%), closely followed by medicines belonging to coronary diseases (C09 and C10). The most common are, curiously, essential, and recurring medicines that humans need. Antibacterials for systemic use are the common antibiotics that people need. Besides that, for example, during 2020, in Portugal, the therapeutic classes that lead the sell out in value, i.e., that lead the sales from pharmacy to the final consumer, were A10 (Drugs used in diabetes), B01 (Antithrombotic agents), N06 (Psychoanaleptics), C10 (Lipid modifying agents), C09 (Agents acting on the renin-angiotensin system) (HMR, 2020).

Moreover, it is also important to emphasize that, the amount of waste is not only a burden to the industry but also to the final consumers and to the state. The Portuguese NHS is in charge of the reimbursement of some medicines and medical devices, i.e., it covers a percentage of the costs of some medicines. Medicines that receive upfront reimbursement of the pharmacy sale price by the NHS generally fall within one of four rating bands, i.e., four rating groups: Band A - 90%; Band B - 69%; Band C - 37%; Band D - 15%, as represented in Table 7. These scales vary according to the therapeutic indications of the drug, its use, the entities that prescribe it, and also the increased consumption for patients suffering from certain pathologies.

Table 7: Percentage of packages and total values paid by NHS and user co-payment for each reimbursed category

Reimbursed Category		% of total value	% of packages
A (90%)	*NHS*	70%	11%
	User	30%	
B (69%)	*NHS*	49%	32%
	User	51%	
C (37%)	*NHS*	29%	32%
	User	71%	
D (15%)	*NHS*		
	User		
Non-reimbursed (0%)	*NHS*	-	25%
	User	100%	

Table 7 details the percentage of packages as well as the percentage of values paid by NHS and the user co-payment by the reimbursed category. There are no medicines being reimbursed at a 15% rate and the most common rates are 37% and 69%. In this sample, as it is illustrated in Figure 37, the state subsidizes the cost of 91% of the medications of the sample, which represents 75% of the total number of packages. As we can see, the state has a key role on medicines subsidies.

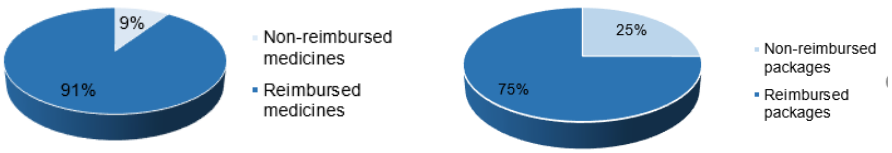


Figure 37: Reimbursed and non-reimbursed percentage of medicines (left) and number of packages (right)

Analyzing the medicines waste caused by expiry date issues, it is necessary to understand the reason behind the significant number of packages concerning this category. As it is represented in Figure 38, approximately 24% of the items had, in fact, expired. Therefore, 76% of the packages could still be reused as they were not yet expired, and their high quality can be assured.

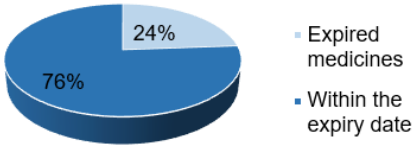


Figure 38: Sample's expired medicines

This type of waste occurs because Portuguese FLW do not accept products with less than 6 months from expiry date. Therefore, since this is the accepted date within the Portuguese pharmaceutical industry, BLGN accepts expiry date returns whenever products have their shelf life less than 6 months. It is important to refer that, although the stipulated data is 6 months, according to Ministerial Order no 348/98: "8.4.1 - Products that are two months from their expiry date or have already passed their expiry date should be separated from useable stock and should not be sold or supplied but returned immediately to the supplier. If the product is not in stock, it must be stored in a clearly separate area so as not to be sold by mistake or contaminate other goods".

Analyzing the category of damaged materials, this type of returns occurs if the products damaged in the transportation have visible damages and are recorded in the transporter's guide. However, damaged occurred in 75% of the returns, only takes place in the secondary packaging being the medicine itself intact and in proper conditions to be administered. The problem here refers to the secondary packaging and the legislation. Being BLGN a marketing authorization holder, Decree-Law 135/95 of June 9, determines that this type of stakeholders is obliged to comply with the principles and norms of GDP where, according to the guidelines, based on Article 84 and Article 85b(3) of Directive 2001/83/EC): "Medicinal products which have left the premises of the distributor should only be returned to saleable stock if all of the following are confirmed: (i) the medicinal products are in their unopened and undamaged secondary packaging and are in good condition; have not expired and have not been recalled (…)" Moreover, as concluded from the expert interviews, the damaged packages apart from the returns are also relevant, i.e., the damaged boxes that did not come from returns but instead were smashed during the operations in the warehouse. This also represents waste that is going to be recycled or incinerated, although being in perfect conditions to be administered. The same might occur with the internal waste coming from the expiry date issues. Therefore, to deepen the analysis of the internal reasons, the database with the waste deriving from internal reasons was also analyzed, relating to the year of 2019. Table 8 depicts the five reasons present in the database with the percentage of packages originated by each one.

Table 8: Description of internal reasons for waste and the percentage of waste accordingly

Internal reasons	Description	% of packages
Expirying date	Products whose expiry date is less than 6 months	70%
Supplier returns	Medicines returned to the respective supplier (asked by the supplier)	16%
Damaged material	Products that were damaged during the operations inside BLGN's warehouse	10%
Complaints to the suppliers	Non-conforming products that require a complaint to the supplier	3%
Medicines recalls	Recall of one or more defective batch(es) of a medicine from the market or prohibition of supply. Medicines are collected due to INFARMED orders: to perform on going stability studies; product quality assurance: parameters out of specification; the dosage changes, etc	1%

The internal reasons cover, for example, complaints to the suppliers and also returns asked by the suppliers. Once again, the expiry date issues represent a significant proportion (70%) of the total waste. Moreover, 10% of the waste packages are regarding products that were damaged during operations inside BLGN's warehouses. In order to know more about the reasons why packages can be damaged, the fishbone diagram in Figure 39 was made together with the warehouse supervisor from BLGN.

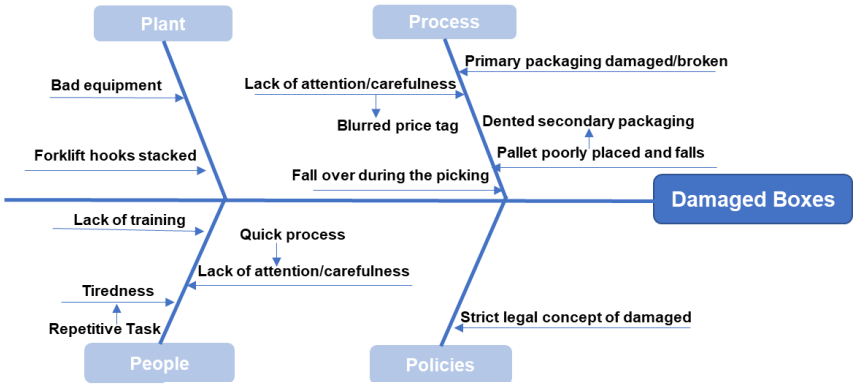


Figure 39: Fishbone diagram on damaged boxes

According to the fishbone depicted, four major reasons can be described. One of the reasons could be related to the facility, either due to inadequate equipment or problems with the hooks. Other two reasons are related to people and processes which, according to the expert insights, are the critical categories that lead to a damaged package. Within these categories, the main issues for people concern the lack of training or attention and repetitive task and the main issues for processes are related to a wrongly done processing or to a lack of rigor when following procedures. A final reason is regarding policies which due to a strict policy to classify what is a damaged material can deeply influence the weight of the other reasons towards the described outcome. Therefore, the problem of the legislation is, once again, present in the internal causes why damaged packages cannot be reused and therefore represent a waste source to the pharmaceutical industry.

Final conclusions of the analysis:

- The critical problems for the majority of waste that occur is due to legislation obligations. The need to return medicines cannot be completely eliminated since it mainly occurs due to expiry date or having primary packaging indeed damaged which are things that cannot be totally avoided. However, as it was confirmed, several packages are unnecessarily considered waste. Therefore, it should be the possible to reuse these types of packages instead of mandatorily send to be destroyed.
- Regarding expiry date, the main problem relies with the 6 months stipulated by the current processes of the industry.
- Regarding damaged boxes, which, although less common than expiry date issues, represents a significant amount of waste when extrapolating for the whole pharmaceutical market.

This section pointed out the causes of the problems previously identified either at industry and consumer level. Therefore, in the following section some suggestions are going to be made in order to minimize the waste while turning the pharmaceutical supply chain more sustainable.

5.3 Solutions' proposals

Given the identified root causes of the problems and the analysis made throughout this master dissertation, it is now possible to make some suggestions and propose solutions to reduce the pharmaceutical wastage, either at the consumer and the industry level, in a holistic form bearing in mind the Portugal context.

One strategy to achieve a sustainable medication policy is via the circular economy concept which is, as it was mentioned before, very broad and that employs multiple approaches to manage resources and minimizing waste. Therefore, the aim of this section is to link the solutions and actions proposed with the circular economy concepts (where the basic principles rely on the 9R) while describing those solutions. When considering the application of circular economy principles to the pharmaceutical supply chain, the best methods for reducing pharmaceutical wastage in the downstream part of the supply chain include reducing, reusing, and recycling the materials and the final product, with the minimization of waste set as a priority.

Figure 40 presents some solutions for the Portuguese reality (represented by the black circles) as well as their integration within the pharmaceutical supply chain, which includes the consideration of forward and reverse flows. The arrows of different colors represent the different flows.

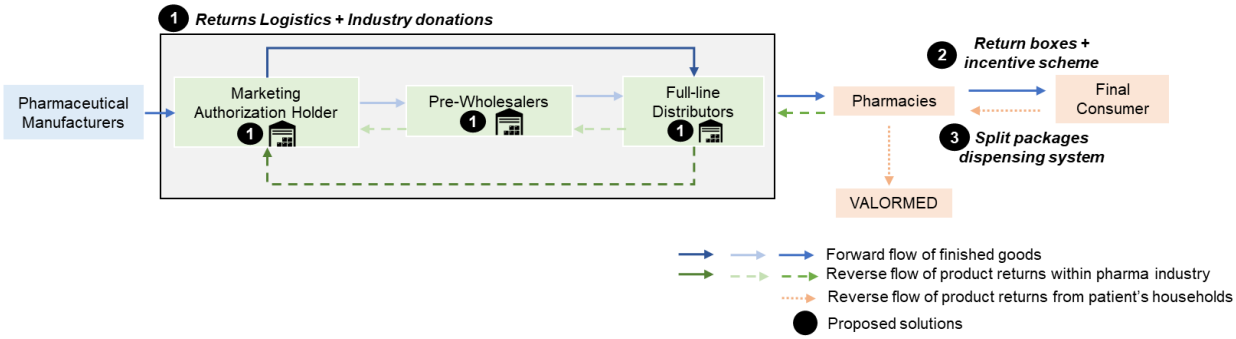


Figure 40: Generic structure of the solutions proposed in the Portuguese pharmaceutical supply chain

- **Forward flow**, represented in two tones of blue, can have two paths depending on which entity is considered.
  - After manufactured, medicines are transported to the MAH (sometimes the MAH and the manufacturer are the same entity)
  - After the MAH, there are two possible paths:
    - From the MAH directly to FLW (represented in dark blue), when the MAH has the capacity to store their medicines in their own warehouses (this is the case of BLGN);
    - Or, from MAH to pre-wholesalers (who stock the products) and from these to FLW (in light blue);
  - Then, the FWL supply the pharmacies, and these dispense medicines to the final consumers.
- The **reverse flow** is represented in dashed arrows (in the two tones of green and in orange):
  - The dashed arrows in orange represent the medicines returned to the pharmacy from consumer's households. These are mandatory collected by VALORMED for correct disposal.
  - In green it is showed the reverse flow of the products that were never sold to a consumer, i.e., never left the internal circuit of the pharmaceutical industry. Depending on which entity is

responsible for the return, there the reverse flow ends. Similarly to what happens in the forward flow, medicines can be transferred directly from the FLW to the MAH if no intermediary is necessary (represented in dark blue) or via a pre-wholesaler (in lighter green)

As it is also represented in Figure 40, three solutions are going to be proposed throughout the supply chain: **1) Returns logistics + industry donations**: the aim is to create space in the warehouses where the industry "waste" would be managed to be donated. This solution also includes an online platform where social institutions and the whole pharmaceutical market would be in contact to facilitate the medicines redistribution; **2) Return boxes + incentive scheme**: sustainable cardboard boxes delivered by pharmacies to end-consumers in order to incentivize them to return more often unwanted/expired medicines; **3) Split packages dispensing system:** a new way of dispensing in pharmacies where packages could be split on smaller units which would turn the dispensing method tailored to the customers' needs (and according to what doctors prescribed). Each solution is going to be described below, thoroughly

Solution 1: Returns logistics + industry donations

Description

As concluded in the previous section, up to the present days, the Portuguese market does not consume medicines with less than 6 months of shelf life. There are medicines (both for chronic or acute use), that effectively generate waste due to the rules that are imposed either by law, or by the industry which protects itself from being forced to have medicines that cannot be sold. This unnecessary medicine waste can be present either on MAH, pre-wholesalers or FLW warehouses. Therefore, the proposed solution aims at having, in each player's facility and warehouse, their own space for the products which, due to the legislation requirements, are considered "waste" and cannot be placed in the market to be sold. The proposal is to redistribute these medicines to the people in need and stimulate the use of drugs which did not enter in the commercialization circuit, but are in full therapeutic and safety conditions. In fact, currently, it already exists a similar concept called the "Medicines' Bank" created to promote the access of people who need medicines, especially supporting the elderly with low income (APIFARMA, 2012). However, in practice, there are a significant amount of products that would be suitable for this purpose yet, because of the actual norms, it is not leveraged. For example, medicines with less than 6 months of shelf life are not included. Moreover, it does not include the FLW.

In the previous section, as revealed by the case study of BLGN, it was concluded that this waste comes mainly due to expiry date issues (medicines that are not effectively expiry but according to the industry practices they cannot be sold) and damaged materials (that accidentally fell off and the damage relies only on the secondary packaging, not compromising the quality of the medicine). Although the expiry date accounts for almost 90% of the cases, it was decided that the damaged materials could also be explored and considered. Moreover, these "waste" products can be originated from two different movements, as it is represented in Figure 41, since each warehouse may gather:

Figure 41: Facility's inputs and outputs

- Each facility's own waste created due to regulations and that cannot be sold for the following supply chain entities (the internal waste).
- Products that were returned by other entities. As aforementioned, these returns do not consider the ones from the final consumers. The returned products can be sent back either to FLW, MAH or pre-wholesaler warehouses, depending on each case and on who is responsible for it. One must not forget that if a product was returned is because the entity in question wants to be financially reimbursed, thus the reverse flow will "end" on the agent in charge for the reimbursement.

Therefore, the goal of this proposal is to extend these medicines' use-life, while reducing the waste. As such, industry donations are the most feasible option. In fact, donations can improve the access to medicines from people in need while reducing pharmaceutical waste. Discarding medicines indiscriminately mean wasting the opportunity to distribute to the ones who cannot afford them. However, poor coordination can hinder the efficacy of this proposal. For this reason, in order to complement this solution, an online platform should be used with a complete database where social institutions and pharmaceutical industry would be connected. By connecting participating entities, it aims to reduce medicine wastage that otherwise would be destroyed. This would guarantee a match between real needs of the society and availability on the industry, avoiding waste. In fact, the Medicines Bank has already developed a similar platform which, according to the experts, is user friendly and fulfills its purpose. As such, this platform is a sharing "marketplace" for the pharmaceutical industry and social institutions that creates transparency in the supply and demand for medicines. However, once again, this sharing platform is exclusively meant for medication that was never issued to the consumer and has always remained under the strictly controlled storage conditions legally imposed.

A remark should be done about the consumer's donations. The possibility of individual donations was also put into the equation, i.e., the possibility of this online platform also aggregates the medicines that consumers return to pharmacies, however it was discarded. It is not possible to guarantee that these returned medicines are in their fully and storage condition and one must not forget that medicines are not simple commodities. Therefore, in order to reuse these medicines' returns, strict quality control and safety monitoring measures are needed to ensure the appropriateness of medications for reuse. Such procedures include monitoring by specialists to confirm the capacity and limit any risk of damage, contamination, or infection. This would represent a significant cost since the process of inspecting the drugs requires, namely, chemical, stability, temperature, safety tests. The inherent costs are extremely expensive and do not compensate for a few packages. Moreover, it would be a burden for pharmaceutical companies in terms of time (besides the costs).

Implementation of the solution

Although the management and the process are going to be decentralized, i.e., the system is based on the "individual" responsibility of each player for their products, information would be shared in a centralized platform to reduce the burden of each wholesale distributor. Each player would control its reverse process and its waste since it has already developed warehouses and the equipment necessary for the appropriate storage. Besides these players have all the know-how needed to handle with

pharmaceutical products. As such, it will be only necessary to reorganize the layout of the warehouses to create a “evident space” for these products.

Figure 42 presents an example of a possible process that could be followed in the warehouses. The process activities should start with the collection of products which would be sorted in two categories. These categories were chosen through the BLGN case study analysis. This analysis allowed us to conclude that products returns mainly occur when products are reaching the expiry date or when there are damages in the secondary packaging. Although donations for people in need is the more explored route, the possibility to donate to veterinary centers (after the necessary changes in Portuguese legislation) or resale to lower-income countries when materials are damaged (by repackaging them) could also be considered. A remark should be done about this suggestion which is not going to be studied and explored in detail. Up to date, it is not allowed to sell or donate human medicines to animals. However, there are some human medicines which can be administered to animals (although maybe in different dosages). For example, Pepcid AC (famotidine), Tagamet HB (cimetidine), Aspirin, Claritin (loratadine), Zyrtec (cetirizine), Benadryl (diphenhydramine) (Vetstreet, 2011).

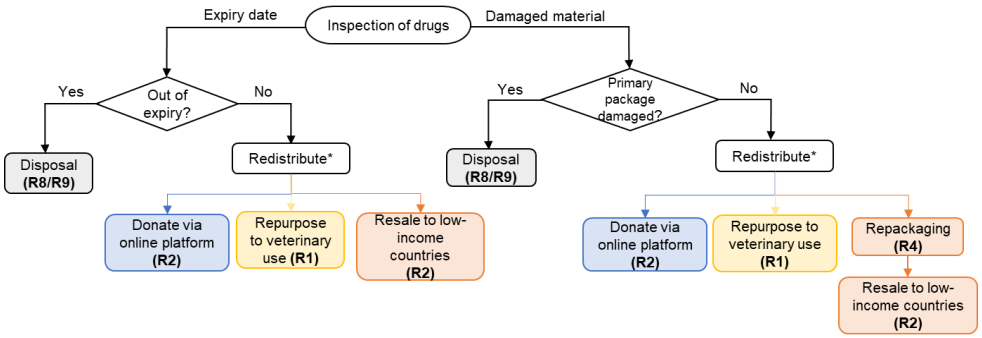


Figure 42: Diagram of an example of a possible evaluation and redistribution of drugs

This suggestion would involve a lot of legislative changes and a change in the current system nonetheless it would be another way to reduce medicines waste. As such, Figure 42 depicts an example of a possible way of organizing the inspection process. After being inspected, it should be decided whether they are eligible and/or more suitable for reuse (donations), repaired for being sale to low-income countries, repurpose to veterinary use and/or proper disposal. One the one hand, if the drugs are classified into the “expiry date” category and their validity has already passed, they will be correctly disposed of. Therefore, the recycling (R8) or incineration (linked with R9- proper treatment for energy recovery) is guaranteed since each player is responsible for the destruction of its own waste (for example, by outsourcing a company to do the sustainable waste management). On the contrary, i.e., if the products are within their shelf life, it could be possible to choose between three options: reselling at lower prices to low-income countries (R2), donate the products (R2) or repurpose to veterinary uses (R1). On the other hand, if the category is “damaged material” and the drugs within the primary package are not intact, they are immediately discarded, since it implies the deterioration of the product. If the problem is with the secondary packaging and the quality of the medicine is not compromised, the three options explained above should be also considered. However, in the case of reselling to lower income countries, since the secondary package is damaged, it should be repaired first (R4) which, in this context, means repackaging (in order to bring them back into the economy). If it is a small damage

perhaps the option of donating to a social institution or repurpose the medicine to a veterinary center is possible. This was an example of a possible evaluation however, when confronting this idea with industry experts, it was concluded that the repackaging was unfeasible. Theoretically, one could consider repackaging from a technical point of view, however this process is economically unrealistic. In fact, repacking a dozen boxes involves the same procedures as thousands of boxes, and the costs associated with the analysis and product release components are also the same. Thus, repackaging could have been a possibility but, due to the economic component, it is not a valid solution. Moreover, it was also considered the possibility of repackaging damaged boxes inside the facilities of wholesalers and MAHs since they have in their facilities secondary package cardboard surplus. However, the industry experts emphasized that there are products whose surplus packages are not inside their facilities turning the logistic of having to ask for more empty packages time-consuming.

Since we were talking about damages that only occurs in the secondary packaging (and just the “small” damages), it would only implies removing blisters from the damaged package and placing them in a new one. However, this option is also unfeasible, since the guaranty of the drug traceability is effectively the manufacturing process. In this context, everything that comes out of this process is already subject to human error. The MAH (or the wholesale distributors) may not be authorized to repackage the product, it must be done by the entity that has the secondary packaging activity registered at INFARMED. And, because they are registered, they must guarantee all the processes that ensure that there are no changes in batches or in the dosage. This is the difficult part of making repackaging simpler and easier. There are several imposed regulations, which turns this also an unfeasible option. Therefore, one should seriously begin to allow the redistribution of packages that have acceptable damages as donations. Thus, the creation of regulated documents with certain rules could be applied.

Therefore, when evaluating this proposal in the next section, the will focus only on donations to social institutions and its efficient and safe operations, having as a basis the current Medicines Bank and comparing the costs and benefits between the actual model and the proposed one. The comparison between the actual Medicines Bank process and the proposed one is represented in Table 9.

Table 9: comparison between the actual Medicines Bank scenario and the proposed one

	Actual Scenario	**Proposed Scenario**
Online platform	INFARMED	INFARMED
Donor entities	MAH	MAH Pre-wholesalers FLW
Donate medicines with shelf life < 6 months	No	Yes
Donate damaged packages	No	Yes
Transportation costs	MAH	State

INFARMED would continue to be in charge of the online platform management, identifying the donor entity, information of the quantities of each medicine made available, and the respective social institution. One of the differences rely on the possibility of not only MAH but also pre-wholesalers and FLWs to donate their medicines since all these entities have internal waste (e.g., damaged packages from operations inside their warehouses). Moreover, the shipment of traded goods would be organized in a safe, GDP compliant manner to guarantee safety and quality at every stage however, the state would cover this cost. As such, this would not be a burden for pharmaceutical companies and they would have more incentives to embrace this initiative. Moreover, as aforementioned, damaged packages if in compliance with certain criteria and medicines with shelf life of less than 6 months would be possible.

The feasibility of this solution relies on some assumptions, such as: i) regulated donations more flexible: the adoption and adaptation of Portuguese laws in order to facilitate the redistribution of drugs to people in need or social institutions (charity houses, foster houses, etc.). This would mean the authorization to donate medicines with less than 6 months of validity and ii) the concept of damaged material and the obligation to dispose of these products. It should be possible to donate the medicines whose integrity is not compromised. As it can be perceived, one of the barriers to this solution is the operational and logistics complexity. All logistics involved need to be managed and planned. Also, the efficiency is crucial to prevent medicines reaching out their expiry date. It is also crucial to have an efficient database supporting accurate information flows, relationship management with charity houses, inventory and transport management.

To conclude, this solution suggests some critical changes to the Medicines Bank which encompasses a centralized systematic approach to establish an efficient and reliable reverse logistics system for pharmaceutical products to overcome some waste that, effectively, is not waste. Therefore, the model is designed to give priority to unexpired medicines by donating them.

Solution 2: Return boxes + incentive scheme

Description

At the pharmacy level, another proposal includes delivering reusable cardboard boxes to the consumers, which will serve as household recycling bins for the collection of expired or unwanted medicines as well as their empty packaging. As concluded by the survey, the accumulation of unwanted medicines represents a problem for pharmaceutical waste. Moreover, respondents believe that it is desirable to return unused household medicines to a collection point, which indicates that the use of these boxes would be a well-received and beneficial idea. As such, it would be a complement of the take-back program that already exists, promoted by VALORMED to incentivize people to make the domestic collection of medicine residues and returning them to a pharmacy. As it was mentioned throughout this master thesis, the collection schemes, also called drug take-back programs, provide a safe method of disposing of drugs that helps to prevent medicines being disposed of inappropriately (flushed down the toilet or sink, or thrown out with household garbage). In this way, this solution could also be seen as an awareness campaign besides being a way to remember people to right dispose of their medicines. It would be easier if they have a specific place at their homes to put the unused/expired medicines, just adding one more recycling bin, apart from the plastic and cardboard that people probably already have. The key to translating knowledge into action is to make the action easy, continue using pharmacies as collection points, and promote routinely and continuously the importance of proper medication disposal.

Moreover, this solution also proposes a points-exchange incentive to form a more effective system for collecting unwanted medicines. As mentioned, consumers stock their medicines even if they do not need them anymore. As such, to incentivize their returns, whenever individuals return their unwanted medicines to the pharmacy, they would obtain points for this delivery. The practice of giving incentives for collecting unwanted products was also suggested and studied by some researchers as it was mentioned in the state of the art (Wereikat et al., 2016a; Hua et al. 2019). The exchange offer (or called trade-in) is an incentive, and it refers to when a consumer purchases a new product and can give back

the same old goods to vendors for a discount. The accumulation of these points achieved by the packages returned in the pharmacy can be redeemed, by a certain proportion, into cash vouchers that can be used to have discount in some products (over-the-counter medicines). These exchange points also serve to encourage people to change their old habits. As concluded by the survey, more than 70% of the respondents use just one method of disposal. Therefore, from a changing behavior strategy, if they begin to only dispose of their medicines by going to a pharmacy, chances are higher of not having a combination of other different (incorrectly) means.

Implementation of the solution

This solution should be ensured by VALORMED. In terms of process in the pharmacies it would be as follow: whenever a consumer goes to a pharmacy to buy some medicines, the pharmacist would ask if he/she already had this box. This would create awareness among consumers and the pharmacist would give advice on proper drug disposal. Then, consumers store all the medication waste in these boxes. When they are full or whenever the consumer wishes to, the aim is to return the box to a pharmacy and ask for its contents to be placed in the VALORMED container. This would promote the adequate recycling of the products.The box would be reused so people would bring it back to fill again (beginning to have this practice as a routine). Regarding the exchange points, each costumer would have a cardboard card where the exchange-points would be accumulated. After the cardboard being complete, they would have a discount in a pharmaceutical product. In this solution, pharmacists would be key actors since they are the ones with a direct contact with the consumers. They need to be aware of this practice and encourage end-consumers to right dispose of their medicines, therefore educational programs would be also beneficial. A remark should be made regarding this solution: in 2018 and 2019, VALORMED promoted a similar initiative with sustainable bags, however it did not reach all families/households. It is necessary to boost this initiative and spread it all over the country. Cultural attitudes such as this one need time and persistence to succeed in a long term. Pharmacists have a key role in this solution therefore without their knowledge and willingness to spread the word and ask for this return bags, this solution cannot succeed. People need to be constantly reminded to return their medicines to the pharmacy.

Solution 3: Split packages dispensing system

Description

As highlighted by the survey, one of the reasons that justifies the accumulation of medicines at households is the excess of medicines bought when compared to the real needs. Most of the times the package exceeded the amount required for the treatment prescribed. Therefore, this creates unnecessary waste, since the patient consumes a portion of the medicine supplied and stores the rest that eventually reach out the expiry date. This proposal suggests the fragmentation of medicines' packages in the pharmacies, dispensing only the medication needed according to each prescription. By dispensing only the right quantity, unnecessary waste and the accumulation of medicines will be avoided, and it will ensure that patients do not take more medicines than the prescribed. With the splitting, the user is prevented from keeping medicine leftovers at home, reducing the possibility of

adverse effects and intoxications, derived from self-medication. In addition, there is less environmental impact resulting from the disposal of medicines.

Implementation of the solution

The fractioning procedure would be carried out in pharmacies, under the responsibility of the pharmacist. In order to ensure the safety of the process, the packaging should allow for their subdivision, ensuring the characteristics of the original form of the product, i.e., without breaking the primary packaging (as it is represented in Figure 43), preserving the identification data and the same characteristics of quality, safety and efficacy of the original packaging.

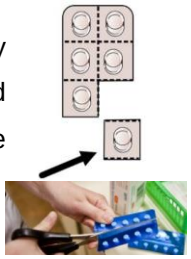


Figure 43: Primary package fractioned (Avisa 2021b; PSNC, 2021)

The pharmacies should have a specific area for the splitting and the adequate equipment for doing it. Therefore, the pharmacist should be responsible for ensure the quality and safety of the dispensing of medicines in individualized quantity, which takes place under his responsibility, supervision and control and guarantee that the patient is informed about the dispensing of medicines in individualized quantities. These quantities will be put on a bag (such as the one represented in Figure 44), with a label which can be printed directly on the packaging, containing standardized information, and parts to be filled manually or computerized to customize the information: name, active ingredient concentration, number of batch, expiry date. Different medicines require different packages in order to avoid mismatches between drugs.

Figure 44: Bag with individualize medicines or split package (Anvisa 2021a)

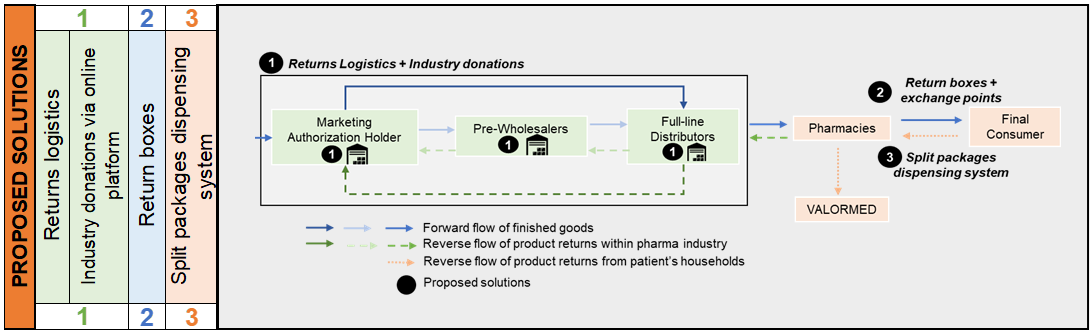
Therefore, the main steps of this fragmentation process would be: 1) Prescription evaluation by the pharmacist; 2) Subdivision of the drug package into smaller fractions from its original packaging to meet the prescribed quantity or the therapeutic needs of the consumer, when exempt from the prescription; 3) Packaging of the fractionated units in a bag provided by the pharmacy, containing the medicine's information; 4) Return of the remaining units to the original packaging to be fragmented for the next consumer; 5) Labeling of the packaging destined for direct dispensing to the user, containing the information required. Regarding the leaflet, people who buy more than one package, for example one package and a half, receive the information in the leaflet included in first entire package. However, for the ones who buy less than one package, the pharmacists should indicate where to find it online, in case of need. Regarding prices, the price charged to the consumers would be a percentage of the total package.

A remark should be done about the two different types of blisters: i) the blisters that are prepared for single doses which not only have a "break" between each pill, but also each pill has the variable product data printed on it, i.e., the expiration date and the batch. Consequently, in the case of this type of blister, by splitting the packaging and detaching one pill, for example, it will never lose the crucial information; ii) the other blisters have the variable data printed but in the corner of the blister, so when cuting the blister, only a part has this information. In that case it is necessary to ensure that the variable data is on both parts since this information is essential and cannot be omitted. Therefore, this solution should only be applicable to the first type of blisters.

The feasibility of this solutions relies on the assumption that Portuguese legislation is adapted in such a way that it allows the dispensing on pharmacies in this splitting packages. This will need regulated documents, rules and clear guidelines to be delivered to pharmacies as well the appropriate and timely training of pharmacists. Moreover, doctors should be aware of this practice to begin to prescribe the quantities in terms of number of pills instead of number of packages.

The aim of all of these proposals is to minimize the pharmaceutical waste, ensuring the implementation of circular economy principles, and supporting sustainability in the pharmaceutical supply chain, taking into account the Portuguese context. Therefore, Figure 45 summarizes each solution's objectives and links them to the 9R principles. In the center of the matrix is represented the figure previously described as a reminder of the solutions. This matrix links each solution (1,2, and 3) with the 9R principles as well as the main goals/what is leveraged with each solution. The matrix is read as follows: each solution (in green, blue and orange) is connected, through the dots of the respective colors, to the 9R principles (in the top of the matrix) as well as to their benefits (in the bottom of the matrix). For example: the solution of the sustainable boxes (in blue) is linked with the following Rs (represented with the blue dots): reduce, recycle and recover and leverages the pharmaceutical wastage in the following ways: prevents/avoid unnecessary waste/environmental damages; raises awareness of environmental or social issues, etc.

				9R PRINCIPLES (applied to end-of-use medicines)	
●	●			**R0** Refuse	Consumers buy/use less; Preventing the use of medicine waste
●	●		●	**R1** Rethink	Repurposing medicines for veterinary use; Make medicines use more intense
●	●	●	●	**R2** Reduce	Reduction of medicines wastage (industry donations, reselling); New ways of dispensing
●	●			**R3** Reuse	Reclamation of discarded medicines which are still in good conditions (e.g., individual donations)
●				**R4** Repair	Repair of defective materials which are still in good use (e.g., repackaging)
●		●		**R8** Recycle	Processing of materials in waste disposal
●		●		**R9** Recover	Generation of energy from waste materials in waste disposal



				GOALS / BENEFITS
●		●	●	Prevents/avoid unnecessary waste/environmental damages
●	●		●	Reduces pharmaceutical wastage by extending medicine's use-life/by distributing less quantity (including packages)
●				Enables medicines reuse while guaranteing their quality
●				Facilitate repackaging of goods
	●			Optimizes distribution chains and products
	●			Guarantees the math between supply and social institution's needs
		●	●	Raises awareness of environmental or social issues
		●	●	Reduces accumulation of unnecessary medicines at households
		●		Increases the probability of people returning to the pharmacy
			●	Tailors the medicines dispensed to patient's needs

Figure 45: Solutions linked with 9R principles and the according goals/benefits

To adapt the generic 9R framework into working practices for the end-of-use/end-of-life medicines, there is a need to consider a new perspective for each “R”. There are R’s whose applicability regarding this context is difficult, as such, not all of them were possible to propose an adapted concept due to how specific and niche this area is. For example, unlike final products in other industries, such as the electronic product chains, where market value can be recovered, expired medicines have no market value and cannot be brought back. Therefore, since the first four loops (R0-R3) exist close to the consumer and the core part of this master thesis is on the medicine itself, the linkage and solutions proposed were focused on these R’s. The practices to promote the reduction of waste creation, to enhance the reuse of medication when legal and possible and recycle products clearly supports the circular economy philosophy. However, this philosophy only succeeds if all the stakeholders of the pharmaceutical chain contribute to minimize the medication waste. The multiple causes of pharmaceutical waste listed in the previous sections imply that no single intervention is sufficient to overcome the problem, requiring a variety of approaches. A remark should be done about the “R’s” that are not present in the matrix (refurbish, remanufacture, repurpose). In fact, the first two R’s mentioned resemble one another. Therefore, in the context of end-of-use medicines, they can be used as synonyms. In theory, refurbish appeared as superior or more desirable option prior to remanufacture. In the context of end-of-life/use medicines, it does not have a direct application being more adequate in the manufacturing phase (e.g., the reclamation of solvents or waste heat) or when the final product of a certain industry is a large multi-component product, and some components are replaced or repaired. The concept of repurpose may have the same meaning of rethink since we are not transforming defective medicines into other products with different functions (which is outside of the end-of-life/use process). In the following section, an analysis of these solutions is going to be made, bearing in mind the stakeholders involved.

5.4 Solutions’ Analysis/Assessment

Given the proposed solutions, this section aims at assessing the benefits and trade-offs of implementing each solution, separately: a qualitative analysis will be made for each solution however, for the first one, a more in-depth quantitative analysis with BLGN’s data is going to be carried.

Solution 1: Reverse logistics + industry donations

Starting with the first proposal, Table 10 analyses the overall benefits and disadvantages for the different actors of the solution regarding the new scenario (in contrast to the Medicines’ Bank).

Table 10: Qualitative analysis of solution 1

	Pharma market	State	Final consumer
Benefits	• transportation costs to social institutions eliminated • integration of this initiative into the social responsibility strategy • reduce disposal costs • promotion of their products	• spare the reimbursement cost of the medicines that otherwise would have to be bought. • the reduction of waste disposal (incineration/recycling) contributes to the fulfillment of the established environmental goals	• free access to medication • quality life improvement
Drawbacks	• alocattion of human resources to sort and manage the process • disregard of the core activities	• transportation costs • the legislative changes require a task force involving all the stakeholders	

The **pharma market (MAH, pre-wholesalers and FLW):** the transportation costs to social institutions will be eliminated however, the "burden" of logistics and the possible need to allocate human resources to sort and manage the process in an accurate way can be seen as a drawback. In fact, the flow of products will be significantly higher therefore there the need to allocate more people to control this task might be a possibility. In addition, this may lead to some core activities disregard. Companies can also integrate this initiative into their social responsibility while also promoting their products, although in a freeway.The **state** will also have gains with this scenario, although being now in charge of the transportation costs. However, this cost may be important to encourage companies to participate more actively in this initiative. The state should invest in this measure given the return of this investment: by reducing prescriptions, the state would save in reimbursing such prescriptions. Regarding **the final consumer**, both social institutions and patients will only benefit from this solution since they have access to the medicines that otherwise they could not afford thus contributing to their quality of life.

Based on the previously analysis, this section will characterize the costs and benefits of the first solution, in a quantitative analysis. Two different scenarios are considered: (1) the Actual Scenario (AS), i.e., the extrapolation of the benefits and costs for the current system of the Medicines Bank and (2) the Proposed Scenario (PS) where products that are still in good conditions, although unable to be sold in the "normal" market, could be donated. Both scenarios will be evaluated with the data retrieved from BLGN and their participation in Medicines Bank in 2020. Also, benefits and costs will be assessed regarding stakeholders who have an active participation on this solution. In terms of costs, the variables that will be used to measure these processes monetarily are the following:

- **Transportation Costs (C_T)-** since the products are already in each facilities' warehouses, the distribution costs result in the transportation from the warehouse to each social institution. Thus,

$$C_T = \sum (C_{1i} * Q_{Ti}) * 12 \quad (1)$$

Where, C_{1i} refers to the unit transportation charge per delivery (to a social institution) per month and Q_{Ti} refers to the number of deliveries per month.

Data Collection: to determine the parameters of transportation costs, a BLGN excel was analyzed.

- **For the AS**, it was found that during a year the average number of monthly deliveries to social institutions is approximately 6, having months with 1 request and others with 20, for example. The unit cost per delivery is approximately 5€.
- **In the PS**, the distribution costs are attributed to the state and, assuming that the unit cost per delivery remains the same (5€), it was estimated that the number of deliveries per month are around 14. This estimation was based on the number of social institutions. In the AS, the 6 deliveries/month was taking into account the 50 institutions that were active and used the platform to request medicines to BLGN. However, for this new scenario it was considered that the number of social institutions who actively participate in this initiative may increase to 150. Therefore, assuming a linear relationship, if, with 50 institutions, there are 6 deliveries/month; with 150, there is going to be 14 deliveries/month.

- **Disposal Costs (C_D)-** companies that need to have their products destroyed, incur in this disposal costs since they pay to other companies to rightly disposed of pharmaceutical medicines. Thus, these costs can be calculated as follows:

$$C_D = \sum (C_{2i} * Q_{Di}) \quad (2)$$

Where, C_{2i} refers to the costs for dispose of a unit package of waste (including transportation to the facility); Q_{Di} refers to the quantity of packages to be disposed of.

Data Collection: taking into account BLGN data, the unit cost of sending pharmaceutical products to their destruction is of 0,16€/package.

- **For the AS**, the quantity donated was 2 283 packages.
- **For the PS**, the quantity of items considered that could also be donated was 14 178.
  As mentioned in the last section, the percentage of damaged boxes suitable for donation is approximately 75%. Curiously, the packages that do not passed the validity date were 76%.

Consequently, it was assumed 75% as the rate percentage of packages suitable to be donated in both categories (damaged material and expiry date), as represented in Figure 46.

		Total packages		Packages possible to donate
Internal Waste	Damaged material	778		584
	Expiry date	5 685	75%	4 264
Returns Waste	Damaged material	1 636		1 227
	Expiry date	10 804		8 103
	Total	18 903		14178

Figure 46: Total number of packages possible to be donated regarding the different waste causes

Therefore, the final total for the PS is 2 283+14 178=16 461. Moreover, it is worth mentioning that the match between supply and demand, i.e., the match between the quantities requested by social institutions and the quantities effectively distributed in 2020 was 99% (retrieved from BLGN data). Therefore, it was assumed in the AS that, with a large variety of products and a larger number of social institutions, the rate would be 100%. It is worth mentioning that there are no testing and classification costs once the medicines never leave the close circuit of the industry. Moreover, it was decided that, for this situation, the holding costs were not worth to be mentioned. Although companies have to store the collected medicines until they can be transported to the according social institutions', concerning the whole cost scenario the attributed costs to management and holding is residual. Similar reasoning was made regarding the labor costs. Both assumptions were approved by BLGN expert.

In terms of benefits, the quantifiable benefits of this solution will be calculated regarding the avoided waste, i.e., how much the entities involved would spare with the avoided waste.

- **Economic Value of Avoided Waste (A_W)-** this revenue includes the saved costs for the state and the end-consumer. Calculation of avoided financial cost is as follows:

$$A_W = \sum (C_{3i} * Q_{Wi}) \quad (3)$$

Where, C_{3i} refers to the average cost per package of "waste" and Q_{Wi} refers to the quantity items i doable.

Data Collection: regarding the number of packages, for the AS is 2 283 and for PS (as aforementioned) 16 460. Assuming as average cost per package at NHS: 12,47€ in retail price and NHS expenditure

8,04€ (i.e., the market price for the state reimbursement for each package sold), the average user co-payment price is 4,43€ (INFARMED, 2019).

- **Avoided Cost for the Disposal** (A_D) - It is possible to "save" from not having to destroy the medicines, i.e., by avoiding their destruction. This revenue can be calculated as follows:

$$A_W = \sum (C_{4i} * Q_{Di}) \quad (4)$$

Where, C_{4i} refers to the costs for a unit package disposal and Q_{Di} refers to the quantity of packages i to be disposed of.

Data collection: for the AS, the amount of packages not disposed in a year is, once again, 2 283 and 16460 for the PS. The cost of transport and disposal per package is 0,16€.
There is also a humanitarian variable that cannot be quantifiable. The access to quality medicines is fundamental to maintaining and improving people's health. A reliable supply chain of essential medicines can save lives, reduce morbidity, and improve life quality.

Extrapolating the data for the whole Portuguese pharmaceutical market, the number of packages of BLGN represents 1% of the pharmaceutical market. The number of BLGN's packages delivered to the market was 2,1 million and, according to the report of Health Market Research, the whole pharmaceutical market accounts of 262 million packages. Considering all the data collected and these two scenarios, the results obtained can be observed in Table 11, and in more detail in Appendix E.

Table 11: Cost and benefit analysis for the pharmaceutical market in thousands Euros (€)

	AS			PS		
	Companies	State	Final consumer	Companies	State	Final consumer
Total Costs	263 €	0 €	0 €	0 €	900 €	0 €
Total Benefits	37 €	1 836 €	1 011 €	263 €	13 234 €	7 292 €
B-C	-226 €	1 836 €	1 011 €	263 €	12 334 €	7 292 €

As such, for the AS, companies have more costs than benefits. However, for the proposed scenario, they will clearly have more benefits than costs since transportation costs would be the state's responsability and the number of social institutions actively participating on this initiative will have a significant growth. Moreover, the state will have more savings derived from the increase number of packages that will be donated. The final consumer will also increase their savings in 86%. A remark should be done about the extrapolated data. The extrapolated results did not take into consideration both pre-wholesalers and FLW internal waste once it cannot be found. Therefore, the gains from the proposed solution would be increased, for the three main entities represented.

A remark should be done in terms of environmental impact: it is not possible to say that this solution can reduce X tons of waste because the avoided waste, although a good measure of environmental impact, should be complemented with others, such as, a LCA in order to find if the whole cycle (including the emissions during the transportation) is, in fact, more viable. This analysis has also others limitations, such as:

- The sample analyzed is only for generics since BLGN only sells this type of medicines. However, the average market prices considered were retrieved from INFARMED data which takes into consideration all types of medication (generics and non-generics).

- The considered data refer only to one year, which may not be representative.
- The online platform maintenance cost was not taken into consideration, since the platform is functioning well, therefore the costs will be the same both in the AS and the PS.
- The holding costs were not included (as explained above), which, in some way, may biases the results.

Solution 2: Return boxes + incentive scheme

Table 12 summarizes the overall benefits and disadvantages of this solution for the different actors.

Table 12: Qualitative analysis of solution 2

	Pharmacies	Final consumer
Benefits	● increase in sales caused by people going to the pharmacy and exchanging points ● boost customers' loyalty to the participating pharmacies	● contribution to a better environment ● discounts on the purchase of goods at the pharmacy
Drawbacks	● allocation (albeit in a small percentage) of customer service time to the accounting of returned packaging and respective points on the card	● the inconvenience of storing medicines at home and having to go to the pharmacy to return them instead of throwing in the trash

With the points exchange incentive scheme, it is expected that the pharmacies in which the points will be swap, will enhance their sales. However, a setback that can be pointed out is related to the increase of the time spent with each customer. From the consumer point of view, although the “inconvenient” of having to go to the pharmacy more regularly in order to return their medicines, there are advantages related to the possibility to benefit from the discounts on goods bought at the pharmacies. Moreover, taking into account the natural attitude of people, this scheme could boost customers’ loyalty to the participating pharmacies. In fact, customers who adhere to this system will choose whenever possible, to go to the adherent pharmacies to get more points and then be able to exchange them for products with discounts. This may also attract more customers who, in addition to buying the necessary medicines, will be able to use the points and discounts to buy other products, thus increasing the sales of these pharmacies. Thus, any cost that pharmacies might have by needing to allocate additional human resources to serve the public could be offset by the potential increase in customers and sales. Moreover, this proposal does not involve great expenses because it could, in a pilot project, take advantage of the loyalty card and the respective gift catalog of the Portuguese Pharmacies. The delivery of medicines’ packages, as explained in the previous section, benefit from points that would be accumulated in the card to be later exchanged for discounted products or a cash value that could be used in a purchase.

A remark should be done regarding the benefit of the end consumer of contributing to a better environment, pointed out in Table 12. In fact, the principal aim of this proposal is providing benefit for the environment since it stimulates the collection of unwanted medicines. Delivering these boxes, as mentioned before, contribute to remind people of the need to collect and deliver medicines waste that have already expired or are no longer used, for the correct disposal. In fact, as mentioned in the state of the art, concern is increasing about the harm the medicines do to human health and the environment. As such, incentivizing people to properly dispose of their household pharmaceutical waste can

contribute to reduce the impact of pharmaceuticals in the environment. Protecting the planet is of everyone's responsibility and each one of us can play an active role protecting the environment and achieving a better world. These health and environmental concerns are increasing because it is foreseen that the situation will be worse in the future given the expected increase in the use of medicines due to a growing and aging world population. As aforementioned, many pharmaceutical substances have been found in various water bodies, including in drinking water supplies such as analgesics, anti-inflammatory drugs, antibiotics, etc. Pharmaceuticals that are designed to interfere with our hormone system and are active at very low concentrations, such as endocrine active pharmaceuticals, anti-cancer treatment drugs because they have the potential to cause cancer, and antibiotics because they have the potential to promote resistance, are of particular concern (Health Care Without Harm, 2013). The development of antimicrobial resistant the most serious threat posed by pharmaceutical product residues in the environment to humans. Therefore, this measure pretends to prevent the wrong disposal while contributing to the safe recycling and incineration of pharmaceuticals, contributing to a more circular economy. According to VALORMED's CEO, the circular economy will be the main innovation challenge driving the next decades and "the collection of expired medicines in pharmacies is fundamental to be correctly destroyed, avoiding environmental contamination of water and land". The contribution of the pharmaceutical industry in the environmental aspect is, in fact, of extreme relevance, since the hundreds of tons of waste that are annually collected can be now recycled or energetically recovered, avoiding their disposal in landfills and a significant decrease in contamination with medicines (Expresso, 2021).

In conclusion, this proposal invites both pharmacies and consumers to engage in activities that will have, in medium/long term advantages, although in the first phase they may require an increased effort, in order to achieve successful results. At a time where people, in general, are aware of environmental issues and everyone is hearing the words "sustainability" and "circular economy", this system begins by calling for a massive distribution of boxes to customers so they can have a place at home to put expired or unused/no longer needed medicines. At a first glance, it may seem that storing and returning medicines to the pharmacy may be an inconvenience for users and may hinder the success of this solution, but the truth is that, it not only contributes to the environmental protection, but also it involves discounts on products sold at the pharmacy, which can be an incentive to increase community involvement.

Solution 3: Split package dispensing system

Finally, Table 13 depicts the pros and cons regarding the split package dispensing system.

Table 13: Qualitative analysis of solution 3

	Pharmacies	Final consumer	State
Benefits		● contributing to a better environment ● avoid having to take unnecessary medicines at home, having to store them, and having to return them so often	● do not have to reimburse so many medicines
Drawbacks	● increase of time handling the medication amount needed by the user ● re-evaluation of stock identification inside the pharmacies	● cost allocated to the bags (if needed)	

This system is already used in several countries for different reasons. From the research done on the international situation there can be several reasons for the existence of this system: saving resources (in some Africa countries), avoiding waste (in more developed countries like the USA) or due to lack of medicines or situations of extreme poverty in which people cannot afford to buy a full box of medicines (developing countries). Also, in England and Brazil this is a common practice. It has not been used in Portugal particularly due to legal reasons: the government and health authorities do not consider this a safe and reliable procedure. The Medicines Statute (Decree-Law no. 176/2006, of 30th August) states, in Article 5, that the use of medicines should be carried out with due regard for the principle of rational use of medicines, in the interests of patients and public health. The rational use of medicines exists when patients receive medicines appropriate to their clinical needs, at doses and periods appropriate to individual particularities, at low cost to them. Therefore, we can assume that rational use involves avoiding waste and preventing users from having access to an excess of medicines, which could lead to unnecessary or wrong consumption of certain medicines in certain specific situations (self-medication). Self-medication is a serious public health problem. One of the biggest risks of the incorrect use of medicines is that inappropriate and excessive doses are taken, which can lead to undesirable side effects. One should not forget that the same medicine, in a similar dosage, taken over the same period of time by two different people with similar diagnoses, can have different results.

As represented in Table 13, this proposal essentially favors the user, who will not need to keep unneeded medication, and the state, which will see its level of co-payments reduced. For the pharmacies there is no additional value with this proposal. In fact, pharmacists will increase the time spent dispensing the right number of medicines for each customer. Moreover, a reorganization of stocks' identification is going to be need as well as strict guidelines to be followed by pharmacists. By only receiving the amount necessary for the treatment prescribed by the doctor, the consumer no longer stores the excess medication at home and consequently do not have the urgent need of delivering the empty packages to the pharmacy. The consumer may have, however, an additional charge: the cost of the bag whenever a package needs to be split in order to deliver the right quantity to the patient. On the other hand, regarding the benefits, the non-inconvenience of having to return the medicines to the pharmacy so often can be pointed out as well as the contribution to a better environment (since, once again, this solution reduces the waste of unnecessary medicines at home).

In conclusion, all the above interventions and the three solutions presented seem promising for reducing medication waste. However, it seems that the main barrier which hamper their implementation is the nation's legislation and reimbursement systems which influence how medications are prescribed, dispensed, and collected at the pharmacy. Furthermore, legislation could be challenging to the implementation of waste-reducing activities. Therefore, a revision of the legislation in order to turn allow some changes and turn this industry more sustainable is needed.

6. Final Conclusions and Future Work

The pharmaceutical industry is of significant relevance since it directly impacts people's lives, contributing not only to their well but also because it plays a pivotal role for national healthcare systems. Moreover, an aging world population and the significant waste growth of the pharmaceutical sector in recent years are raising awareness of the need to pursue sustainable and circular economy practices. The literature review revealed that little work has been presented regarding the pharmaceutical industry and circular economy and that few studies integrate this concept with the downstream part of the pharmaceutical supply chain, comparing with the manufacturing dimension. Therefore, it was decided to explore the situation where the medicines were already produced and focus on their end-of-use, diving into the Portuguese reality in order to propose solutions feasible of being implemented to reduce the waste present in this sector.

For the purpose of this work, a general VSM was mapped, and, after some expert interviews, it was possible to understand that there was an urgent need of minimizing the waste regarding medicines household accumulation and their inadequate disposal as well as the use of medicines that, inside the industry, are considered waste but, in reality, are in high quality and could be administered to anyone. In this way, two main stakeholders were identified: the pharmaceutical companies and the final customer. Regarding the first one, it could be seen, given the example of BLGN, a Portuguese MAH where the case study of this dissertation relied, that there is a lot of potential that can be leveraged towards sustainability. Through the characterization of this company, its data and experts' knowledge, it was possible to conclude that there are a lot of medicines unnecessarily considered waste. The current Medicines of Bank initiative does not include this type of waste however, if medicines with an expiry date of less than 6 months or damaged packages (where the damage do not compromise the quality of the primary package) could be also donated, not only companies but also the state and the final consumer would increase their net benefits. From the scenario analysis presented in the previous chapter, it is possible to conclude that the resulting solution shows significant improvements for all the entities covered. This is possible due to state incentive on the transportation between companies and social institutions. As such, this solution contributes to a bigger humanitarian cause: the access to quality medicines to maintain and improve peoples' health and life quality while reducing morbidity.

To assess the end-consumer stakeholder, a survey was performed, and, henceforth, it was concluded that the peoples' habits need to be changed. It could be seen that a lot of waste is still being made mainly because people put their medicines in their household garbage and only a small part is returning 100% of those products to the pharmacies. One of the conclusions concerns consumers' education by encouraging them to return their pharmaceuticals to the pharmacy, through an incentive scheme with points-exchange. The effectiveness of this action is mainly dependent on the awareness of the society. Moreover, although the activity of dispensing concerns mainly prescribers and pharmacies, the accumulation of unnecessary medicines occurs at the patient level. Therefore, another solution proposed was the split package dispensing system. This activity is very important and aims at reducing medication waste, combating the number of medicines' surplus at households. This would be a preventive action that would eliminate the waste prior to disposal.

The medicines' value chain is very complex and includes a lot of stakeholders so it is not easy to create thorough solutions benefiting all stakeholders at the same time reducing waste during the whole path. However, with this solution, some paths become clearer. A conclusion that can be taken from this work is that there are some already good practices going that can still be leveraged and increase their scale so the impact of such practices can be even enlarged, and sustainability improved overall. One must not forget to take also into consideration the crucial role of the government and its regulations that hinder all this process. It is clear that, due to the unique nature of pharmaceutical products and their critical role in global health, the quality of medicines must be guaranteed. As a direct consequence, the market is heavily regulated, forcing pharmaceutical companies to meet regulatory requirements regarding quality standards and strict laws. However, there are some measures that could be lighten and would not compromise the medicines' quality. Therefore, it is also proposed, to work lightening some regulations (for example, in terms of validity and damaged packages).

Therefore, the implementation of the concept of circular economy in the end-of-use medicines has still a long path but one thing is crucial: companies, academia, and regulatory authorities should work side by side, in a closely ecosystem. Although this is a profitable industry, the planet has finite resources and this should concern everyone, with no exception. Cooperation of all stakeholders is a prerequisite to ensure the success of efforts to promote circular economy and sustainability. Health authorities could have a pivotal role in motivating shareholders to take their responsibility, but to facilitate this, medication waste must be seen as a priority in everyone's agendas. The results and knowledge of this analysis can be used by governments to improve the regulations of the pharmaceutical industry and lighten some measures and policy decisions in order to minimize waste while also moving to a more sustainable industry.

Finally, four main areas for future research are suggested. First, a quantitatively process should be performed to assess the split package dispensing system. Regardless of the "good-will" of this measure and its importance, it is necessary to quantify its economic benefits, which involves a new legal framework and changes in the activities of the various stakeholders. Moreover, a LCA analysis should be performed to environmentally measure all the solutions. Second, the possibility of having an established link between veterinary and human medicine. It would be opportune to evaluate the possibility of pharmaceutical companies being able to also donate drugs that are currently only for human use to animals. This would require an autonomous process, but it could avoid waste, as these drugs would be disposed of more quickly, avoiding the excess of expired medication that is treated as waste. Synergies could be created and the development of standardized procedures or methodologies to, somehow, "reuse" medicines to humans for animals. Third, a similar economic analysis for the first solution should be made but this time including both pre-wholesalers and FLW. Lastly, a thorough study of the regulations and the concrete role of government to analyze the possibility and impact of the change of specific regulations and common practices among the pharmaceutical world towards a greater sustainability.

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Appendix A: Activities Undertaken by the Sustainable European Leaders

Sustainability Leaders (Europe)	1st Manufacturing		Packaging (2nd Manufacturing)	Patient Use and Disposal	Waste Management
	Process Design (API Production and Formulation)	Product Design			
GLAXOSMITHKLEIN (GSK) (GSK, 2019a; GSK, 2019b)	Implemented an ERA program across all manufacturing sites to ensure a safe discharge and to minimize the risk of any APIs entering the environment	Ellipta Device: dry powder inhalers (DPIs) with new technologies- don't release greenhouse gas emissions	Plans to reduce plastic packaging, making it recyclable, and exploring how GSK can increase the use of recycled plastic content	Take-back program "Complete the Cycle": inhaler recycling scheme	"By the end of 2020, we aim for 100% of our sites to send zero waste to landfill. This avoids harmful environmental impacts from landfill and keeps materials, such as solvents, in circulation for use in new products."
	GSK is part of the AMR Industry Alliance that concerns about antimicrobial resistance. The link between manufacturing discharges and antibiotic resistance patterns is not well understood; however, GSK recognizes the importance of managing effluent discharges responsibly: "By 2020, we will have established science-led, risk-based targets for discharge concentrations of antibiotics"	GSK has developed a new pump for Flonase/Sensimist, which reduces the amount of plastic used in the device by 12%	GSK aims to remove PVC from all vaccines packaging by the end of 2020		In the US, labs are outfitted with the latest technology for R&D, and they also create more concentrated amounts of regulated medical lab waste. An example of beneficial disposal is this lab waste stream, instead of being incinerated, is being treated and turned into park benches and bricks.
	GSK also entered a collaboration under the Innovative Medicines Initiative (IMI), aimed at speeding up the development of better and safer medicines for patients and the environment. The focus of the project is on developing in silico tools to predict environmental risks of pharmaceuticals in their pipeline		The project 'rightsizing' looks at ensuring each package is no larger in terms of volume, weight, and thickness than it needs to be in order to fulfill its function of protecting the product. For example, by increasing the number of tablets contained within each foil blister strip from four to six, the foil consumption and overall pack size were reduced. This resulted in a reduction of CO2-equivalents emissions		By embracing Green Principles, GSK is working with processes that need less material and produce less waste and is implementing a new wastewater treatment system
	GSK embraces "Green Chemistry" to minimize the potential environmental impact of its chemistry throughout the pipeline: (1) choosing solvents less toxic that can be recovered and recycled in an energy-efficient way (and develop methods to do it); rather than disposed of by incineration. (2) monitor chemicals of particular concern or high risk to remove from manufacturing processes if necessary. When elimination or substitution is not possible, appropriate and, responsible risk management approaches are adopted		As a purchaser of commodities (paper, pulp, palm oil), GSK is committed to deforestation-free sourcing by 2030. GSK is working with the Roundtable for Sustainable Palm Oil- a global initiative promoting the production and use of sustainable palm oil - to develop an internal sourcing standard for palm oil and its derivatives. GSK regularly assess its supply chain against internal standards and with the Rainforest Alliance to audit and assure paper packaging along the supply chain		GSK wants to increase recycling and find ways of diverting waste and other resources they no longer need to organizations that can use and benefit from them. GSK is sharing best practice across its network and encouraging collaboration, both across internal sites and with other businesses
	GSK is advancing its manufacturing through the introduction of new technologies and innovations that will help deliver higher quality medicines more effectively to patients (the aim is making medicines cheaper, faster, and with a smaller impact on the environment)				
ROCHE (Roche 2019, Roche 2020a, Roche 2020b, Roche 2020c)	New APIs are investigated for biodegradability and initial ecotoxicity during their development. An ERA is developed based on chronic environmental effects and advanced environmental fate data	Diabetes Care: redesigned the blood glucose monitoring strips and repackage them completely to improve material efficiency and reduce waste. The new innovative strip architecture resulted in a strip size that is 60% smaller than the prior version and has fewer components overall.	Roche is developing a new generation of packaging known as GenPack, which comes in two sizes and can accommodate up to ten vials with a single insert in one package. Clinics that normally accumulate a large number of vials will benefit from this: less packaging waste to manage and less consumption of packaging materials	Patients treated with any of Roche's biotechnological products metabolize them and generally do not excrete them into the environment	Roche has globally adopted the principles and practices surrounding waste management: (1) Avoid the use of environmentally harmful or toxic materials (e.g., eliminating the use of chlorinated solvents, heavy metals, etc.). (2) Reduce/Minimize the consumption of raw materials and the amount of waste generated in all business processes. (3) Re-use by-products and packaging materials. (4) Recycle, e.g., recovery and recycling of solvent mixtures, packaging materials, etc. (6) Down-cycle to a lower-value product
	A systematic program to optimize chemical syntheses of new APIs - the Roche Environmental Awareness in Chemical Technology (REACT)	Roche seeks to reduce the use of hazardous substances and materials and actively collaborates with other companies and organizations to develop and promote techniques for a sustainable product design.	The new design of "Diabetes Care" has reduced polyester usage and improved the packing density, allowing more products to be shipped on the skids and in tertiary containers. This also reduces the distribution cost and environmental impact	Roche participates in take-back programs in various countries to avoid improper disposal of unused pharmaceuticals	Roche has established an effective Safety, Security, Health, and Environmental protection (SHE) management system, including internal guidelines, Group directives, and auditing, to continuously reduce waste and the potential for negative impacts of operations.
	Roche manufacturing processes and facilities are designed and operated to ensure that, as far as practicable, the APIs are not discharged into the wastewater. All aqueous manufacturing emissions are treated in wastewater treatment plants, where a significant part of this waste is degradable and thus readily removed via biological mechanisms.	Roche is monitoring all biotechnological products and processes, although product residues from manufacturing processes are easily biodegradable overall and give no rise to environmental concerns.		Roche has a corporate initiative to reduce all remaining chemical wastes to landfill by 50% within 5 years using 2015 as the baseline (excluding construction and remediation wastes).	Roche thermally destroys waste by incineration with state-of-the-art flue gas treatment. As incineration significantly reduces the volumes, toxicity, and reactivity of potentially harmful wastes, it is Roche's preferred disposal method for organic and hazardous waste. Only inert materials such as incineration residues and clean building rubble or other wastes not suitable for incineration go to landfill.
	"Green Chemistry" principles are applied to reduce the raw material input, avoid or minimize the volumes of critical substances and minimize the consumption of resources in Roche's future manufacturing processes. Roche joined the "Green Chemistry" Pharmaceutical Roundtable of the American Chemical Society	Roche also supports the development of well-defined regulatory frameworks for the introduction and development of biosimilars and is actively engaged in stakeholder dialogue. This helps to ensure that there is a high and consistent level of public health protection			Each Roche affiliate has been given the challenge to step up efforts to avoid, reduce or recycle general wastes. Affiliates have been tasked to increase recycling rates for general waste and, when recycling is not possible, to incinerate general wastes for heat recovery as opposed to landfilling these types of wastes.
	Roche is actively engaged in a number of initiatives to better understand the PiE issue and to minimize the amount of our products that are released to the environment. Example: AMR Industry Alliance- tackling responsible manufacturing in the context of antimicrobial resistance (AMR).				
SANOFI (Sanofi 2020a, Sanofi 2020b, Sanofi 2020c, Sanofi 2020d)	Sanofi has developed tools to optimize the use of solvents in industrial processes (chemical synthesis, cleaning equipment, etc.) while minimizing their environmental impact: selecting the least toxic solvents; reducing the quantities of solvents used; promoting the use of recycled solvents	Sanofi has already implemented processes to rationalize the use of natural substances (animal/plant for API, excipients) and to develop alternatives to preserve resources. For example, Sanofi sells an antimalarial medicine based on artemisinin which is extracted from a plant called wormwood, grown mainly in Africa and Asia. To preserve this resource, Sanofi has developed an innovative alternative method to produce artemisinin based on a biological synthesis process that no longer requires using the natural resource	A comprehensive initiative to reduce the consumption of packaging materials was introduced in early 2013 for all solid forms of our products packaged in blisters made of PVC/aluminum and aluminum/aluminum	Sanofi has been engaged in initiatives to encourage the proper use of medicines, in particular by promoting information and education for healthcare professionals and patients.	Each Sanofi site has a waste hierarchy: Avoid waste production and reduce waste flow at the source; Reuse, recycle, and recover on-site or with selected validated providers; Incinerate, with energy recovery wherever possible; Send waste to authorized landfills as a solution of last resort, provided that the landfill complies with local regulations and control systems. Landfills should be audited on a yearly basis for hazardous waste landfilling and audited every three years for non-hazardous waste landfilling.
	Sanofi uses a KPPI (Key Process Performance Indicators) analysis tool for all its projects to guide chemists in the selection of synthesis routes, evaluate the critical parameters in terms of cost and HSE performances and allow a more targeted process improvement	Sanofi decided to switch (since 2018) to a new pipette for our syrups, combining a better dispenser system, a mono-material design (all PP (polypropylene) instead of PE (polyethylene) + PS (polystyrene)), and reduced weight.	Using pallet occupancy as the basis for logistics optimization, with a target pallet occupancy of over 85%; Defining common shipment volumes to help maximize pallet occupancy	In 2015, Sanofi developed a website for healthcare professionals and patients dedicated to the responsible prescription and consumption of antibiotics	Waste management program: "Be landfill-free" program to avoid landfill with targets of less than 3 % in 2020 and less than 1 % in 2025
	Sanofi has joined the ACS-Green Chemistry Institute -Pharmaceutical Roundtable to catalyze the implementation of green chemistry and engineering. Some initiatives include the assessment of PMI improvements for the production of key APIs and contribution to the current review of the solvent guide with members of the GCIPharmaceutical Roundtable		The new Vaxigrip packaging has been designed to be plastic-free, thanks to complete cardboard packaging. For this project, the current PVC blister has been replaced by a carton wedge. This new packaging halves the size of the box, which optimizes its storage and reduces its environmental footprint: reduction of the number of transportations needed (air, sea, and road) and CO2 per box		Waste management program: "3R (Reuse-Recycle-Recover)" program with a target >90 % of volumes recycled or recovered. They included in this program the avoidance of waste, especially hazardous waste. Focus: reuse and recover raw materials such as water and solvents as often as possible

	Sanofi joined the project CHEM21 of IMI in Europe. One objective is to use sustainable methodologies to the development of a more efficient and greener process for medicine molecules manufacture		Sanofi's ambition is to replace plastic trays with carton-made systems for secondary packaging, as far as possible in terms of acceptance by final users (medical staff and patients). This progressive approach has been started for Lovenox in the UK		Waste management program: "Performance & digitalization" program to standardize Sanofi processes, use partnerships with major waste companies and implement on sites apps.
	An Environmental Risk Assessment (ERA) is conducted to evaluate the environmental impacts during the development of new drugs. Also, Sanofi has implemented a voluntary program to evaluate its legacy products that were brought to market prior to the enactment of the ERA requirement. This program aims at increasing knowledge about the environmental fate and effects of their marketed products		Sanofi decided to conduct a Life Cycle Analysis (LCA) on a major typical product of its portfolio: a solid form product consisting of 30 tabs, 1 blister packaged in a folding box. This LCA gave the proportion of packaging in the overall environmental footprint of the product. Within the packaging, it also gives the respective contribution of each packaging material		Sanofi recycles industrial waste and also collects many types of waste (e.g., batteries, paper, plastic, ink cartridges) for recycling or recovery by local waste managers and seeks to develop innovative processes to recycle water required for drug manufacturing.
	Sanofi is also engaged in the Industry roadmap for combating Antimicrobial Resistance. Focus: develop and implement measures to reduce environmental impact from the production of antibiotics across manufacturing and supply chain; invest in the R&D of new antibacterial medicines and vaccines (to limit or prevent AMR)				Sanofi invests in technologies to improve wastewater treatment plants (WWTP) and minimize potential emissions of APIs in effluents but also seeks to limit effluent discharge upstream of the WWTP in order to reduce effluents at the source. The Group has implemented an environmental risk management strategy targeting pharmaceuticals in wastewaters.
ASTRAZENECA (AZ) (Astrazeca 2018, Astrazeneca 2019, Astrazeneca 2020)	AZ is aligned with green chemistry: developing manufacturing processes that use less energy and water, as well as fewer and less environmentally impactful chemicals	AZ is improving product design (using PMI) and process innovations to decrease waste by-products created during manufacturing	Better packaging solutions that reduce resource consumption and waste: decreasing size of the packaging, switching to recycled materials, and using materials that are readily recyclable	Patient education programs to raise awareness on the importance of responsible end-of-use disposal of medicines, and sharps takeback, in addition to contributing to the funding of collection schemes.	Waste audits and employee engagement at sites worldwide investing in the reuse and recycling of solvent wastes in order to reduce the need for raw materials
	AZ uses the metric Process Mass Intensity (PMI) to measure the efficiency in materials use. PMI is measured as kilograms of raw materials used to produce a kilogram of the final API. A PMI target is set for all drug molecules contributing to decreasing overall solvent/water consumption and waste from the laboratory.	Alongside its work to eliminate carbon emissions from its own operations, AstraZeneca also recognizes the direct link between reforestation and the impact it can have on both the climate and human health. Trees naturally remove CO2 and are essential to mitigate the effects of climate change. AZ partners with recognized reforestation organizations (One Tree Planted- and governments in a number of countries to plant 50 million trees over the next five years (2020-2025).	AZ piloted a project to optimize the packaging of tablets in blisters. This pilot redesigned packaging for a medicine used to treat high cholesterol using a new, higher-quality foil to develop a pack that uses 30% less material. The benefits identified during this pilot were: CO2 reduction, savings in material cost/year, increased productivity	Pilot project for mail-back of inhalers to support recycling in the US: AZ sends products to hospitals and clinics involving a huge amount of packaging. The original process used a box the size of a small table that had to be thrown away after delivery. AZ decided to work with its distribution partner to develop a new approach involving a returns process	Avoiding, Reducing, Reusing, and Recycling is their strategies to increase material efficiency and reduce waste.
	Global Green Labs initiative in partnership with the not-for-profit organization, My Green Lab aimed to learn about and assess lab practices with respect to better manage waste, energy, water, and chemicals (to improve environmental footprint)	In 2015, AZ selected some products for full LCA in order to improve environmental sustainability. For one of the cardiovascular, renal metabolic medicines, it was identified both a traditional batch process for a common synthetic intermediate and an alternative continuous process. The last one has superior environmental performance			One of the AZ team had a successful proposal in a competition, managed by UK Research and Innovation, to develop innovative solutions to eliminate plastic waste. Working alongside industrial, technical, and academic partners to advance new plastic recycling techniques, develop faster degrading plastics, and implement the circular economy
	Perform not only the ERA prior to the launch of any new drug, as well as, establish Environmental Reference Concentrations (ERCs) and Maximum Tolerable Concentrations (MTCs), which must not be exceeded for manufacturing discharges to the aquatic environment. They share it with key relevant suppliers so they can risk assess and manage emissions associated with the APIs they manufacture. AZ also conduct ecopharmacovigilance (EPV) to ensure that our ERAs and safe discharge concentrations remain up to date and reflect the latest science	AstraZeneca commits to launching its next-generation inhaler to treat asthma and chronic obstructive pulmonary disease (COPD) with minimal GWP (global warming potential) propellants by 2025. They expect the propellant used in the next generation pressurized metered-dose inhalers (pMDI) to have a GWP (carbon footprint) that is 90-99% lower than propellants used in older pMDIs.			At the Gaithersburg, MD, US site, 97% of biowaste is recycled. In Cambridge, various programs have targeted recycling of specific plastics: falcon tubes – potentially saving 21,000 tubes from incineration per year, bulk pack stripette recycling – saving approximately 19,000 single-use plastics per year
	In 2016, AZ also committed to Combating Antimicrobial Resistance, and it is co-funding the research to develop and establish approaches to define safe environmental levels for antibiotics entering the environment through drug production and patient use.				
NOVARTIS (Novartis 2018, Novartis 2019a, Novartis 2019b)	Performs ERA to evaluate the potential impacts of new medicines on human and environmental health during the R&D process before the products reach the marketplace	Life cycle assessment (LCA) of two BREEZHALER inhaled products to assess the carbon footprint. The evaluation included the whole product lifecycle, including the device, APIs, and the optional sensor.	Eliminate polyvinyl chloride (PVC) in secondary and tertiary packaging (by 2025) and reduce waste disposal by half versus 2016 levels. E.g., saving cartons through smaller packaging; instead of using PVC in syringe in the primary packaging, engineers designed a stable carton inlay.	Recommendations to dispose of any unused or expired products or waste materials in accordance with applicable legal and regulatory requirements	The aim is to prevent, reduce, recycle or use waste as an energy source before selecting safe disposal as an option. Waste prevention and reduction are always preferred to treatment, incineration, or disposal.
	Novartis minimizes discharges of active pharmaceutical ingredients from operations into the aqueous environment. They monitor potential emissions on an ongoing basis and take appropriate corrective action if necessary.	Novartis favor raw materials with a reduced environmental footprint and prefer materials from renewable sources if technically feasible and economically viable	Novartis currently assess the global plastic footprint and estimate that our factories generate around 2.5 tons of plastic annually, which is not recycled. So far, 90% of our manufacturing sites globally have eliminated PVC in secondary and tertiary packaging, including three sites in 2019		The waste target for 2020: to reduce total non-recycled operational waste relative to production quantities by 30% compared to 2010.
	Novartis is also a member of the Antimicrobial Resistance Industry Alliance (ARM), which aims to eliminate or significantly reduce antibiotic residues from the manufacturing	By 2030, they seek to be plastic neutral with all new products meeting sustainable design principles	To help ensure product package integrity, Novartis maintained a global network of 248 secondary packaging security verifiers in 77 countries, who performed 528 secondary packaging inspections of suspected falsified medicines in 2019		Novartis is actively exploring ways to recycle water. For example, they developed technology at a site in Turkey, which enables to treatment and reuse of wastewater in cooling towers. This technology was implemented at the second site in 2019 and is being considered for a further five.
	Novartis participates in Europe's largest public-private initiative IMI iPiE (Innovative Medicine Initiative on intelligent assessment of Pharmaceuticals in the Environment)				The majority of the solvents used are recycled. Solvents that are not recycled are either used as alternative fuels or are incinerated at waste facilities that recover the energy generated from combustion. The waste solvents reused at our sites constitute recycled input materials.

Appendix B: Circular Economy Definitions

Study	Definition
Geng and Doberstein (2008)	"Circular economy is understood to mean the realization of a closed loop of materials flow in the whole economic system, implying a closed-loop of materials, energy and waste flows."
Preston (2012)	"Circular economy is an approach that would transform the function of resources in the economy. Waste from factories would become a valuable input to another process – and products could be repaired, reused or upgraded instead of thrown away."
Su et al. 2013	"a traditional open-ended economy model developed with no built-in tendency to recycle, which is reflected by treating the environment as a waste reservoir"
Ellen MacArthur Foundation (2013)	Circular economy is "an industrial system that is restorative or regenerative by intention and design. It replaces the 'end-of-life' concept with restoration, shifts towards the use of renewable energy, eliminates the use of toxic chemicals, which impair reuse, and aims for the elimination of waste through the superior design of materials, products, systems, and, within this, business models''. The overall objective is to "enable effective flows of materials, energy, labour and information so that natural and social capital can be rebuilt''
EEA (2014)	Circular economy "refers mainly to physical and material resource aspects of the economy – it focuses on recycling, limiting and re-using the physical inputs to the economy, and using waste as a resource leading to reduced primary resource consumption''
European Commisson (2015)	"The circular economy is an economy where the value of products, materials and resources is maintained in the economy for as long as possible, and the generation of waste minimised"
Sauvé et al. (2016)	Circular economy refers to the "production and consumption of goods through closed loop material flows that internalize environmental externalities linked to virgin resource extraction and the generation of waste (including pollution)''.
Stahel (2016)	"A circular economy would turn goods that are at the end of their service life into resources for others, closing loops in industrial ecosystems and minimizing waste. It would change economic logic because it replaces production with sufficiency: reuse what you can, recycle what cannot be reused, repair what is broken, remanufacture what cannot be repaired"
Geissdoerfer et al. (2016)	Circular Economy is "a regenerative system in which resource input and waste, emission, and energy leakage are minimised by slowing, closing, and narrowing material and energy loops. This can be achieved through long-lasting design, maintenance, repair, reuse, remanufacturing, refurbishing, and recycling."
Jawahir & Bradley (2017)	"(…) reducing wasteful resources through effective design and implementation of products and processes for improved resource-efficiency with circular material flow involving recovery, reuse, recycling and remanufacturing of products"
Kohronen et al. (2018)	"CE is a sustainable development initiative with the objective of reducing the societal production-consumption systems linear material and energy throughput flows by applying materials cycles, renewable and cascade-type energy flows to the linear system. CE promotes high value material cycles alongside more traditional recycling and develops systems approaches to the cooperation of producers, consumers and other societal actors in sustainable development work"
Morseletto (2020)	Circular economic is "an economic model aimed at the efficient use of resources through waste minimization, long-term value retention, reduction of primary resources, and closed loops of products, product parts, and materials within the boundaries of environmental protection and socioeconomic benefit"

Appendix C: Expert Interview Guide

- **Expert's opinion about the framework**

1. Does the framework suit the pharmaceutical supply chain? What is your impression of it?

2. Which actions and practices would you add to the VSM? Which would you remove?

3. Which critics do you have about it? Why?

- **Questions about the existing problems according to the experts' experience**

4. Looking at the different phases (in the red circle), do you believe some are more critical than others and therefore need greater attention?

5. In your opinion, which aspects do you consider the highest priorities and must be further explored?

6. Which are the main challenges/problems faced by pharmaceutical companies in terms of minimizing waste?

Appendix D: Survey's Design

START

Consumer behavior on unused/unwanted pharmaceuticals

---Please read carefully before you start---

Thank you for your time in answering this survey. It should take approximately 4 minutes to complete. This survey supports a Master Thesis, "Valorization of Valorization of End-of-Use Medicines in the Pharmaceutical Industry - A Circular Economy Perspective," being pursued at Instituto Superior Técnico (IST). The present survey aims at understanding the consumer behavior of no longer needed pharmaceuticals and their disposal in Portugal. All the information will only be used for the matter of the present study. Thank you very much for your contribution.

Consumer behavior and perceptions related to unused/unwanted medicines

Section 1

Do you have unused or unwanted medicines at home? How many?

- From 1 to 10 packages
- From 10 to 20 packages
- From 20-30 packages
- From 30-40.
- More than 40.
- I do not have unused or unwanted medicines at home

If one of these answers were considered go to Section 2

If the last answer was considered go to Section 4

Section 2

How many are prescriptive medicines?

- 0-25%
- 26%-50%
- 51%-75%
- 76%-100%
- Honestly, I don't have any idea

Why do you keep unused pharmaceuticals at home? (You can select more than one option)

- Storing for future use
- Over-prescription, i.e., too many pharmaceuticals prescribed
- Unintentional adherence: forgetfulness
- Side effects so I stopped having the medication that was prescribed
- Intentional lack of adherence: change in beliefs
- Change medication prescribed
- Unclear information was given by the doctor
- Treatment has ended but the package exceeded the amount required
- Patient recovery

From the medicines kept at home, how many are expired drugs?

- 0-25%
- 26%-50%
- 51%-75%
- 76%-100%
- I don't have expired medicines at home

Do you realize that expired/unused pharmaceuticals can be returned to a pharmacy for the appropriate disposal?

- Yes
- No

Please indicate, from 1 (least important) to 5 (most important), your perceived value of the importance of returning medicines to the pharmacy.

Figure 47: : Perceived value of returning medicines to the pharmacy

For each handle/dispose option, in what percentage of the following options, do you dispose of unused or unwanted pharmaceutical products and their packaging (e.g. return to pharmacy: 50%; throw to garbage 50%)

Figure 48: Different ways to dispose unused

If you do not return all the medicines to the pharmacy, why do you dispose of your pharmaceuticals as you do?

- Habit
- It is the right way
- It is more practical, i.e., less trouble
- All my medicines are returned to the pharmacy

How frequently do you return your medicines or pharmaceutical waste to pharmacies?

- 1x/month
- Quarterly
- Twice a year
- Once a year
- Less than once a year
- Never

If one of these answers were considered go to Section 3

If the last answer was considered go to Section 4

Section 3

Why do you return medicines or pharmaceutical waste to the pharmacy? (You can choose more than 1 option)

- Expired medicines
- “Spring-cleaning" of the house
- Over-prescription or change the prescription (and they are within the expiry date)
- Have already improved, they are no longer needed (and they are within the expiry date)
- Adverse drug reaction or inconvenient of use (and they are within the expiry date)

If you return medicines to a pharmacy, what are your motivations to do so?

- To recycle or reuse the materials
- To protect the environment/public health
- Make home safer
- Precaution in general
- I think my medicines can be reused by someone
- Another reason

Section 4

If Portuguese pharmacies provide households with special bags which are to be used to hold unused medicines for return to a pharmacy, do you think you would return medicines more often/start to return your medicines/pharmaceutical wastage?

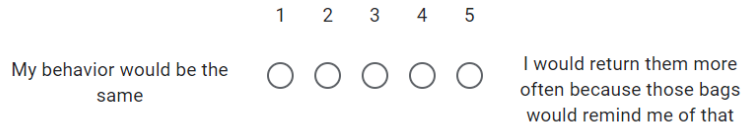

Figure 49: Importance of having special bags at home to return more often medicines to the pharmacy

If you had some financial incentives to return your medicines/pharmaceutical waste to a pharmacy, would you do it more often?

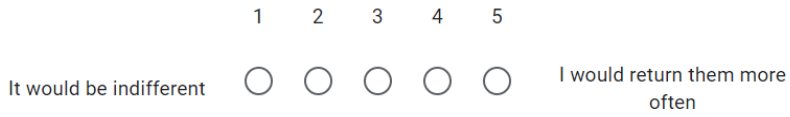

Figure 50: Importance of having fiscal incentives to return more often medicines to the pharmacy

If you knew that, by returning your medicines to a pharmacy, they could be analyzed and donated for charity houses, would you return them more often?

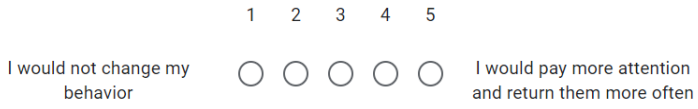

Figure 51: : Importance of donations in people’s behavior

Would you like the idea of going to a pharmacy and only buy the medicines you need instead of having to buy the whole package (i.e., would you like to have medicines being dispensed in a unit dosing)?

- Yes
- No

How willing are you to buy and use medicines that were already stored at another patient's home?

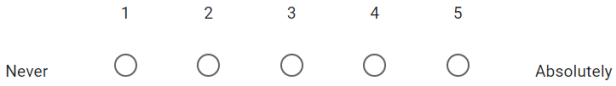

Figure 52: Respondents' willingness for re-dispensing

Consumer data

Section 5

What is your gap age?

- Under 18
- 18-30
- 31-55
- 56-70
- +71

What is your education level?

- Secondary High school
- University (Bachelor's, Master's, Doctorate degree)
- Professional Courses

How many members have your household?

- 1
- 2
- 3
- 4
- 5
- +5

How many children are currently living in your house?

- 0
- 1
- 2
- 3
- 4
- More than 5

Thank you for your time and contribution!

END

Appendix E: Cost and Benefit Quantitively Analysis

ECONOMIC COSTS AND BENEFITS

	ACTUAL SCENARIO (AS)			PROPOSED SCENARIO (PS)		
COSTS	**COMPANIES**	**STATE**	**CONSUMER**	**COMPANIES**	**STATE**	**CONSUMER**
Transportation Costs						
Number of deliveries	6 deliveries/month	-	-	-	14 deliveries/month	-
Unit cost	5€/delivery	-	-	-	5€/delivery	-
Total Transportation Costs	360,00 €	-	-	-	900,00 €	-
Disposal Costs						
Unit item disposal cost	0,16€/package	-	-	0,16€/package	-	-
Quantity of items disposable	14178	-	-	0	-	-
Total Disposal Costs	2 268,48 €	-	-	0,00 €	-	-
Total Costs	2 628,48 €	-	-	0,00 €	900,00 €	-
Total Costs for Pharma Market	262 848,00 €	-	-	0,00 €	90 000,00 €	-
BENEFITS (Cost Savings)						
Economic Value of Avoided Waste						
Quantity of items donable	-	2283	2283	-	16460	16460
NHS reimbursed	-	8,04 €	-	-	8,04 €	-
User-copayment	-	-	4,43 €	-		4,43 €
Total Value of Avoided Waste	-	18 355,32 €	10 113,69 €	-	132 338,40 €	72 917,80 €
Avoided Cost for the Disposal						
Unit item disposal cost	0,16€/package	-	-	0,16€/package	-	-
Quantity of items for disposal	2283	-	-	16461	-	-
Total Value of Avoided Disposal	365,28 €	-	-	2 633,68 €	-	-
Total Savings	365,28 €	18 355,32 €	10 113,69 €	2 633,68 €	132 338,40 €	72 917,80 €
Total Savings for Pharma Market	36 528,00 €	1 835 532,00 €	1 011 369,00 €	263 368,00 €	13 233 840,00 €	7 291 780,00 €