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AN ANALYSIS OF THE PHARMACEUTICAL INDUSTRY PAIN POINTS - THE CASE OF ITALY

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Abstract

This study identifies the problem areas of the pharmaceutical industry in three European countries: Belgium, Italy, and Portugal. It examines the disparities in healthcare systems between the countries and what difficulties they are experiencing in becoming more patient-focused.

Some issues are common to the countries. Yet, they are weighed differently according to the country's characteristics, mainly economic power. The pharmaceutical industry in Italy is a robust and significant sector, with a strong emphasis on research and development, adherence to stringent regulatory standards, global market presence through exports, and active engagement in collaborations to drive innovation.

In general, these countries are making progress in prioritizing patients, paving the way for personalized medicines and better disease management. These developments promise substantial benefits in treatment outcomes.

Keywords: Healthcare; Italy; Pharmaceutical Industry;

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1. Introduction

The pharmaceutical sector finds itself at a crucial turning point, oscillating between a long-standing, product-driven system, and the requirement to change direction and shift towards a patient-centered model. The need for these changes is reflected in all aspects of healthcare around the world, echoing an implicit call for a fundamental reorientation to prioritize the well-being and empowerment of patients. Thus, rethinking the pharmaceutical industry towards a patient-centered approach is not just a suggested improvement, but an important and necessary change.

In this context, several challenges arise that highlight the challenges and barriers to the patient-centric requirement: the first of these challenges and issues lies in the variety of pricing strategies, a unique scenario in which profitability often coincides with patient accessibility and availability.

Reimbursement processes applied in healthcare systems perpetuate the divide between the availability of medicines and accessibility for patients. The rigorous and delayed approval of medicines, although designed to guarantee safety and efficacy, can delay critical treatments, which hinders patients' access to products.

Furthermore, the industry faces the dilemma between innovation and regulation, where the demand for innovative therapies often conflicts with the strict regulatory frameworks governing their development and implementation. At the same time, ensuring treatment adherence represents a challenge for pharmaceutical companies, which involves patient education, behavioral interventions, and support structures for them.

Patents, designed to encourage innovation, end up creating barriers by restricting the proliferation of generic alternatives, preventing patients from accessing more affordable treatments once a medicine's exclusivity period has elapsed. Knowledge gleaned from diverse research efforts illuminates the multifaceted nature of these challenges, emphasizing the need for the pharmaceutical sector to move toward patient-centered models. This imperative transcends mere corporate restructuring – it embodies an ethical obligation to put patients at the forefront of healthcare innovations and solutions.

The pharmaceutical industry's patient-centric transformation embodies an inflection point – an intersection where ethical imperatives converge with strategic imperatives, where the trajectory of healthcare advancement turns on the industry's ability to overcome these challenges. varied.

As this document develops, it is intended to promote a discussion between those based in the countries of Belgium, Italy and Portugal.

The main aim of this project is to understand the pain points faced by the pharmaceutical industry in three different countries, through literature and interviews.

2. Literature Review

2.1 Approval of Medicines

In a risk-averse industry, it is necessary to have tight rules regarding medicines. Ensuring that the drugs, and devices, are safe while easing the course of innovative therapies as rapidly as possible through the investigative process to public use (Norman, 2016), is the core goal of all the players involved in this process.

The two regulatory steps that a drug needs to take before it is approved and enters the European market are **clinical trial application** and **marketing authorization application**.

For the clinical trial application, the drug progresses have a sequential path that needs to be divided into three steps. The first step is the application. In this step, the manufacturer can submit it within one, or more states, to manage clinical studies each state designated with its particular regulatory body that defines the approvals.

In the second step, the manufacturers face clinical trials, that are split into three phases (Norman, 2016, 401):

I. **"Phase 0 and 1 Trials:** a small number of healthy subjects, clarify pharmacology and dose range.
II. **Phase II Trials:** several hundred patients with the target condition, to determine dose/response relationship.

III. **Phase III trials:** several hundred to several thousand patients to show safety and efficacy."

After these steps, the medicine faces the four pathways that a drug approval can take:

I. **Centralized procedure:** manufacturers acquire a marketing authorization that is credible throughout Europe. The timeline for this process is 210 days (about 7 months), since it considers the European Medicines Agency (EMA) opinion and then, submitted to Commission for final approval.

II. **Mutual Recognition procedure:** posterior to approval in a single state, the manufacturer can apply for mutual recognition in all countries through EMA. With the marketing authorization in the **Concerned Member States (CMS)** other than the **Reference Member State (RMS)**, the one before where the medicine was approved. An identical dossier is submitted to all EU member states where the pharmaceutical company applies for marketing authorization and, after the decision of one member state to evaluate the product, the state notifies the others to whom the application has also been submitted. The process can take 390 days (about 1 year).

III. **Nationalized Procedure:** the manufacturer only has marketing authorization in one state. To have this authorization, it is essential for the pharmaceutical company to submit it to the competent authority of the chosen country. The procedure can last 210 days (about 7 months).

IV. **Decentralised procedure:** pharmaceutical companies can put in an application for concurrent approval in more than one country, but this applies to products that "have not yet been authorized in any EU state and do not fall under the mandatory centralized process" (Norman, 2016, 401). The evaluation report is planned by the Reference Member State (RMS) and takes into consideration observations made by the Concerned Member States (CMS) and the authorization should be a match between RMS and CMS. The time to have the procedure done is 210 days (about 7 months).

Pharmaceutical companies face crucial problems related to the approval of medicines. These problems vary from issues related to costs to uncertainty. Here, we expose five problems that have an impact on pharmaceutical companies:

I. **Extended and expensive timelines for development:** is time-consuming and the discovery and regulatory approval of new drugs. The long timelines lead to several development costs delaying the introduction of innovation to the market.

II. **High development costs:** the development of a new drug has a few phases related to preclinical and clinical trials, regulatory submissions, and post-market surveillance. These phases need high investment in development and can impact a company's profitability and prevent investment in R&D.

III. **Uncertainty in clinical trials:** in phase III, there's a high risk of failure. Issues related to safety, efficacy, and others, can guide trials to failure, backlogging the process of development of new drugs.

IV. **Regulatory requirements:** it is demanding to meet EMA requirements for safety, efficacy, and quality. To meet these standards, it is time-consuming for pharmaceutical companies. Also, the introduction of new and innovative therapies may be challenging for the actual regulatory frameworks.

V. **Regulatory agency workload:** each agency has a high number of applications and, at the same time, limited time to review all applications. The time constriction has an impact on pharmaceutical companies that cannot move on without their authorization.

2.2 Innovation

The existence of a patent system in the pharmaceutical industry perfectly aligns with the value of innovation. The profits emerging from patent protection motivate pharmaceutical companies to invest in R&D and, as a result, they offer a wider range of new medicines to patients. However, it is important to analyze the interaction between innovation and its effect on generic competition.

To begin with, there are various types of pharmaceutical patents, depending on the drug they protect. The lifetime of pharmaceutical patents is limited to the country and is different from other industries due to the gap between **the statutory patent term**, approximately 20 years following the filing of the patent application, and the **effective patent term**, whereby companies guarantee the quality and

effectiveness of the drug. This is because a company files for a patent well in advance of conducting clinical trials to evaluate the drug's safety and efficacy. As a result, the effective patent period after the drug's final approval is typically seven to twelve years, which implies that by the time the product is available on the market, the patent is close to expiring (Mandal, 2023). This highlights the difficulty of pharmaceutical companies to enjoy the full benefits of having market exclusivity on their invention and to truly compensate for the huge R&D expenses and the risk involved in new drug discovery (Upadhyaya, 2023). On one hand, without patent extension, some companies may be more inclined to discontinue their products because margins are no longer attractive, and rather prefer to free up their production capacity to produce higher value-added products. On the other hand, extending the patent monopoly gives companies the possibility to avoid generic

competition, whereby rivals enter the market and produce generic drugs, driving down prices, and thus stealing demand from the patented company. This highlights the tradeoff between innovation and competition, and the use of "evergreening" strategies (Nawrat, 2019). For instance, pharmaceutical companies request secondary patents by making minor changes to the first invention, which don't necessarily bring additional therapeutical improvements to patients, but only serve to keep generics off the market. This suggests that companies rely on the use of patents as a defensive strategy, which allows them to keep prices high by limiting the launch of generic drugs, restraining themselves from competition, and extending their market monopoly without necessarily fostering innovation in R&D (Nawrat, 2019). Overall, this emphasizes that there is an unbalance between protecting the rights of innovators and the right of patients to obtain accessible brand-name drugs.

2.3 Outcome and Value Measurement

The Institute for Healthcare Improvement describes these measurements as a substantial piece of testing and implementing changes. They contribute to improving patients' experience in care and, the population's health, reducing cost per capita, and clinician and staff burnout. At the same time, this important metric also contributes to revealing areas in which interventions could help improve care,

identify new variations of care, provide evidence about patients, and compare the effectiveness of treatments and procedures.

Even though the measurement of outcomes and values seems to be a good path for healthcare, there are some issues concerning pharmaceutical companies and these measurements. The first is the diversification of healthcare systems. This diversity gives each state the role of prioritizing the healthcare aspects that they think best suit their country. So, it is complicated for companies to establish a standardized outcome that can be applied to all countries. The impact on the budget is crucial to address since some healthcare systems may prioritize cost containment over comprehensive outcome measurement. A lack of resources may be allocated to outcomes research.

Access to patient information is protected by regulations such as the General Data Protection Regulation (GDPR), which imposes strict requirements on how organizations share patient information (this can be applied, for example, to hospitals sharing patient information with pharmaceutical companies). For pharmaceutical companies to acquire access to patients' information they need to have patient consent, the data need to be limited and anonymized, or used pseudonyms, and the company is obligated to implement appropriate security measures to protect confidentiality, integrity, and availability of data. Sometimes it is difficult for pharmaceutical companies to have permission for patients' information. Yet, access to this information through measurement of outcomes and value will help pharmaceutical companies to conduct more effective research and development, based on patient's needs.

Evaluating short-term and long-term outcomes can be challenging. Although short-term outcomes are quicker to measure, the long-term have more impact and require effort to collect data.

According to Michael E. Porter (Porter, 2013), the outcomes that matter to patients are divided into three tiers:

Tier 1. Health Status achieved and retained: survival and degree of health or recovery.

Tier 2. Process of recovery and disutility or treatment process.

Tier 3. Sustainability of health: sustainability of health or recovery nature of recurrences and long-term consequences of therapy.

With the alignment of what is important to the patient in mind, pharmacies can try to reach the patient, creating medicines and accompanying solutions for the patient. For instance, nowadays, some smaller companies are creating devices to measure patient's values regarding a disease daily. Doing a partnership with these companies will allow pharmaceutical companies to have a closer relationship with the patient, creating loyalty with the end user. For diseases that need a medical device and medication, for example, if the smaller company provides the device and the pharmaceutical company the medication, the patient that uses the combination of both will create a relationship of proximity with the company and, when in need, search for their product. Also, the daily information on the disease will let pharmaceutical companies improve their products, preventing the failure of the same on phase III of the clinical trials, and avoiding refunds from the company. These will increase the company's profitability and their market share.

Being innovation a sensitive field for this industry, these partnerships will bring a robust database for the studies, bringing more value to the patient and, perhaps, more investment in these new innovative medicines.

As an example, the creation of H2O, a "multi-jurisdictional ecosystem to incorporate patient-reported and other health outcomes into health care decision-making across Europe. Focus on diabetes, cancer, and inflammatory bowel disease evaluating and selecting meaningful outcomes standards in a way that ensures broad acceptability among all stakeholders" (Stamm et al. 2021). This eco-system provides a digital tool for patients where "patient outcomes and their health care experience can be improved through the systematic capture and appraisal of their perspectives" (Stamm et al., 2021).

2.4 Patent System

Detailed analysis of the European pharmaceutical patent system

The European Patent Office (EPO) is an executive arm of the European Patent Organization, and examines European patent applications, to strengthen the global patent system through a centralized

and uniform procedure (European Patent Office, 2022). Currently, there are two kinds of patents available, namely national and European patents. When registering for patent protection in one or more European Patent Convention (EPC) contracting states, companies have the option either to pursue individual national procedures for each desired state or opt for the European route, a single process that grants protection in all designated contracting states. Securing a European patent typically costs three or four times more than obtaining a national patent (European Patent Office, 2022).

To begin with, obtaining a European patent is a lengthy procedure, typically it takes two to four years and encompasses two main phases. In the first stage, the applicant drafts a provisional application outlining the invention. Once the application has been filed, the EPO ensures compliance regarding filing, documentation, and formalities requirements of the EPC (Walker, 2023). Following this, the applicant submits a full non-provisional application, which initiates a **formal examination period** during which the EPO furnishes a search report and preliminary opinions on similar inventions to the applicant. An authorized International Searching Authority (ISA) conducts a comprehensive search for the most relevant prior art documents, assembling them into an International Search Report (ISR). This step helps to verify the application's adherence to patentability criteria. Meanwhile, the applicant may submit the Patent Cooperation Treaty (PCT) application to facilitate potential patent grants across 152 countries at a later stage (Walker, 2023). The second stage entails a regional and national **substantive examination**, whereby the EPO determines the potential grant of the European patent. The process can take a few months to five years. Following **publication**, the applicant is granted a set of national patents, and each state is responsible for validating the patent by its respective national legal requisites. After **validation**, a nine-month opposition period allows the applicant to request revocation of their patent. Simultaneously, if third parties contest the novelty of the invention, they may also oppose the patent at the EPO (Walker, 2023).

<u>The significance of patents in the Pharmaceutical Industry</u>

The pharmaceutical industry is one of the largest industries, with one the highest share of R&D spending. To recoup and protect investments involved during the R&D stage, drug patents play a fundamental role in providing incentives to pharmaceutical companies and promoting innovation.

First, patents provide inventors with a period of exclusivity, namely 20 years from the date of filing, whereby the government grants them the exclusive right to prevent others from manufacturing and selling their inventions. Also, it should be publicly disclosed, thereby contributing to the sharing of scientific and technical knowledge, and thus accelerating advancements in innovation (EFPIA, 2023). Unless the inventor gives any prior permission, such as through a patent license, only the holder of the patent is authorized to market the drug. This explains why pharmaceutical patents an important source of profit for the company are and contribute almost 80% of the pharmaceutical company's revenue (Walker, 2023). As a result, this allows pharmaceutical companies to make a profit out of their sales and recoup their investments (Upadhyaya, 2023).

Second, the adoption of a patent system helps pharmaceutical companies to foster innovation and growth. Patents are a crucial element of undistorted competition and enable companies to sustain higher prices. Hence, patented medicines are more expensive than generic medicines because they outweigh both the large, risky, and costly R&D investments for developing new prescription drugs and the low cost of imitation (Cockburn, 2015). This price differential prevents pharmaceutical companies from fearing generic competition which generally leads to a reduction in drug prices. Without patent protection, other companies would take advantage by making other firms undergo research without having to pay for it (Cockburn, 2015). Therefore, the existence of patents is crucial for safeguarding innovations by deterring rivals from entering product areas closely related to the newly developed drugs, thereby securing the company against infringement cases (Upadhyaya, 2023).

2.5 Patient Treatment and Compliance

Patient compliance with treatment is a pervasive and costly problem in the pharmaceutical industry. Significant financial and intellectual resources are invested to the creation and marketing of drugs

intended to limit suffering and improve quality of life. Patients' willingness to follow the recommended treatment plans is an essential factor in the success of these therapeutic interventions. Yet, patient non-compliance with treatment plans can lead to adverse health outcomes but it's not just a personal concern; it also has a considerable impact on the economy and healthcare system. The repercussions include higher healthcare costs, more frequent hospitalizations, and wastage of valuable medicines. For the pharmaceutical industry, the problem is not just limited to financial losses, but also calls into question the effectiveness of medicines.

Study of factors influencing patient compliance

The cultural and social contexts, gender, personality, the nature of the disease and access to medication are all influential factors regarding the decision of whether to follow a prescribed treatment plan.

According to data from the "National Institutes of Health", in developed countries **only half of patients follow the treatment plans** they have been prescribed. This represents a major obstacle for pharmaceutical companies, as there is a risk that their drugs will not achieving the desired therapeutic results.

Adherence rates **vary also based on the nature of the illness**. For chronic diseases such as hypertension, where symptoms may not be immediately noticeable, non-compliance is more common, with patients taking only about half of the prescribed medications for these long-term conditions. On the other hand, adherence tends to be higher for acute conditions, where the treatment is short-term, and the effects are more evident.

Moreover, studies have shown that the rate of following treatment plans depends also on the **treatment's objective**. For therapies aimed at curing a disease, there's a higher compliance rate of 77%, compared to 63% for preventive measures. However, when medications are intended for long-term use, adherence rates decline to approximately 50%.

Another common problem in healthcare is the **lack of clear communication** between patients and their healthcare providers. Indeed, factors such as poor communication between healthcare providers

and patients, insufficient knowledge about the medication and how to use it, doubts about the necessity of treatment, concerns about potential adverse effects, the demands of long-term and complex drug regimens, costs constraints, and issues related to medication accessibility, can lead to lower treatment compliance.

Surprisingly, between 40% and 60% of patients cannot accurately recall their doctors' instructions, and more than 60% of patients misunderstand their prescribed medication directions during or following their doctor's appointments. This emphasizes the need for better patient education and more efficient communication between doctors and patients.

In addition, complicated treatment plans, issues with timing medications correctly, or the need for frequent doses can also lead to non-adherence. But when it comes to reasons for non-compliance 49.6% of patients mentioned forgetfulness as a significant unintentional factor.

2.6 Pricing and Reimbursement

Pricing

The pricing strategy allocated to each country "do not depend only on the government regulation (…) but also on several other factors, such as income per capita, exchange rates, the size of the market, the characteristics of the import (…) the patent status, the characteristics of the firm and the presence of competitors" (Florio, 2021, 30). All around Europe, there are diverse ways to address price control, depending on the country's regulations. This price control has the purpose of ensuring that medicines remain affordable and accessible for patients, have control over healthcare costs, and promote cost-effective use of healthcare resources. Pharmaceutical companies need to understand the country's regulations and adapt their strategy to comply with the specific requirements of each market.

According to the article "European Pharmaceutical Research and Development", the most frequently used policy in Europe is External Price Referencing (ERP), although it is not adopted in all member states and even the methodology of adoption varies from state to state (Florio, 2021). After External Reference Pricing, the most used ones are internal reference pricing and value-based pricing. Only a few countries have adopted the Managed Entry Agreement. This price variety can be challenging for

this industry since it carries some issues. The number one issue is profitability. It requires a lot of effort from companies to forecast and manage their revenue. Since prices vary significantly between all member states, it becomes difficult for companies to set pricing strategies, and propose prices for their products, that maximize profits throughout the entire region. To minimize this issue, companies try to address the ERP to benchmark the price. Yet, the difference in prices across countries has an impact on the company's potential to enter new markets. This leads to problems for patients in countries where the requirements are not met and access to the medicines is denied.

The price swing can encourage parallel trade, where pharmaceutical products are exported from lower-priced countries to higher-priced countries, within Europe, and create a disrupt pricing strategy that will affect profit margins for pharmaceutical companies. All the above points merge this industry into a competitive dynamic, making competing effectively between companies a hard task.

High-priced medicines

Pharmaceutical industries make use of three policies to build their decision, regarding decision-making.

The first one is **Horizon scanning**. Although it is not a pharmaceutical pricing and reimbursement policy, this approach helps "countries to be prepared for the launch of new medicines with high price tags which will likely strongly impact the pharmaceutical budget" (Vogler et al. 2018, 77).

The second is the **Health Technology Assessment (HTA)**. The use of this policy differs from country to country. Several countries exert HTA to notify decision-makers regarding the reimbursement and funding of new medicines. Now, in Europe, there's a joint work on HTA within the European Network for Health and Technology Assessment (EUnetHTA), that further develops HTA tools and directly builds up their practical application to cross-border HTA collaboration (Vogler et al. 2018).

Finally, the last is **Managed-Entry Agreement** is divided into two categories:

I. **Financially based** (or non-health outcomes-based) schemes: used in price or dose conditional discounts and price-volume accordance.

II. **Performance-based** (or health outcome-based) schemes: ensure outcomes (for instance, if the product fails the manufacturer provides a price adjustment or a refund) and coverage with evidence development.

Reimbursement

In many PPRI Network member countries, the assigned authority for pricing and/or reimbursement needs the marketing authorization holder to apply a dossier, if the latter plans their medicine to be considered for reimbursement. Following the submission of the application dossiers, scientific evidence on the medicine's benefit is frequently appraised by an independent committee tasked to advise decision-makers on reimbursement (Vogler et al., 2018). Although these decisions are applied most of the time, the type of healthcare system used in each country contributes to the reimbursement decision. There are two types of healthcare systems: **Social Health Insurance (SHI)** and **National Health Service (NHS).** On several countries where the NHS is the predominant healthcare system, the decisions for reimbursement can be taken at a national level. In the other hand, a portion of countries have the individual region acquire medicines and may reach out terms in specific arrangements, for instance, Managed Entry Agreements (PPRI Report, 2018).

To guide the decision-makers on pharmaceutical reimbursement, the PPRI network member countries decided to evaluate: the added therapeutical benefit, budget impact, cost-effectiveness, medical need/priority, safety, and others. The contrary, they are also criteria based on other metrics, such as therapeutic value (including efficacy, effectiveness, safety and adverse effects), cost-effectiveness, appraisal, decision and outputs and implementation (Franken et al. 2012)

With the creation of reimbursement lists, countries will allocate the medicines that they think are eligible to be reimbursed. These reimbursement lists can be divided into the outpatient sector and the inpatient sector.

Reimbursement lists in the outpatient sector

Outpatient medicines are the ones prescribed by a healthcare provider for a patient's use outside of a hospital or healthcare facility. To these drugs, several numbers of countries have one, or more,

reimbursement lists. These lists can be split into: Positive lists, Negative lists, a few portions of countries use both and others even use a third list. The spending on reimbursable medicines may be fully or partially covered by third-party payers. Different percentages (reimbursement rates) are allocated depending on the type of medicine that we are considering. For example, in Italy, in 2018, all reimbursable medicines had a 100% reimbursement rate. Yet, other co-payments such as prescription fees, deductibles and /or co-payments may still apply, as a consequence of the reference price system. The co-payments (a portion of the cost of a healthcare service/medication that a patient is required to pay) for outpatient medicines are divided into three types: prescription fee, percentage co-payment, and deductible.

Reimbursement lists in the inpatient sector

These lists are commonly called **Hospital Pharmaceutical Formularies (HPF)** since hospitals have their list and are eligible to decide the medicine to be administered and funded in the hospital sector. As an example, Portugal has HPF at the national level.

The reimbursement can always be considered for outpatient and inpatient medicines, leading to a joint reimbursement list.

Within the reimbursement policies, the most used is the Reference Price. In this system, the decision-makers are using the efficiency gains of lower-priced medicines. For example, using generics as a comparison.

Regarding the co-payment, most countries do not charge any co-payment. Yet, countries like Belgium, in 2018, charged a fee per patient and hospital day for reimbursed medicines.

The reimbursement policies in Europe can create challenges for pharmaceutical companies. While reimbursement is crucial to ensure patient access to medications, the healthcare systems, regulatory frameworks, and questions related to costs, originate issues in this industry.

2.7 Sustainability

The World Health Organization (WHO) identifies climate change as one of the most significant health risks of the 21st century, attributing one in four premature deaths to factors related to the environment.

Furthermore, the Pharmaceutical Strategy for Europe, which was established on 25 November 2020, aims to create a robust regulatory framework for the future and a patient-centered pharmaceutical environment in which the European industry can innovate, thrive and continue to be a global leader. However, pollution of air, water, and soil, combined with inadequate waste management and declining ecosystems, pose a serious threat to human health. Moreover, healthcare facilities generate a significant amount of hazardous waste, including pharmaceuticals and medical equipment. Therefore, proper disposal and management of these waste materials are crucial to minimize their impact on the environment and protect human health. The pharmaceutical companies are under pressures to minimize their environmental impact across their product lifecycle. This involves improving research and development methods and production processes to optimizing supply chains, logistics, and engaging more proactively with patients and healthcare professionals about product usage and disposal.

Furthermore, pharmaceutical companies have a unique ability to contribute to social sustainability through the creation of life-saving medications, thereby improving public health. To reduce its environmental impacts, such as greenhouse gas emissions, and align their objectives with established scientific benchmarks, pharmaceutical companies integrate science-based targets (SBTs) by setting specific goals based on scientific evidence. This approach enables pharmaceutical firms to effectively measure and track their progress towards reducing greenhouse gas emissions and other environmental impacts.

However, there are differences in how pharmaceutical companies select targets, measure their accomplishments, and the speed at which they make progress. To achieve the objectives fostering a net-zero emissions by 2050, pharmaceutical companies need to adapt their products, supply chains and manufacturing processes to reduce their impact on global warming.

While traditionally emissions discussions have focused on industries such as mining and automotive, the pharmaceutical sector's environmental impact has received less attention. “The Embedding environmental sustainability into pharma's DNA” report (Deloitte, 2022) focuses on the

environmental aspects of ESG. It emphasizes effective management of the planet's finite resources and the industry's strategies to reduce Scope 1, 2, and 3 greenhouse gas (GHG) emissions. The majority of emissions in the healthcare sector come from Scope 3 emissions, which are not produced by the company itself but result from its activities throughout the entire value chain. Nevertheless, decarbonization is a complex process that goes beyond simply reducing emissions from pharmaceutical industry operations. It involves addressing the emissions generated throughout their entire supply chain and considering the upstream consumption that contributes to their carbon footprint. Additionally, decarbonization requires collaboration and coordination with various stakeholders to implement sustainable practices across the entire value chain.

3. Methodology

The methodology employed for writing our work project relies on a qualitative approach, involving a selective analysis of the literature and relevant documents. This analysis was complemented by structured interviews conducted with experts from the pharmaceutical industry, giving us a comparative perspective.

During the exploratory phase, we read some of the existing literature related to our topic. Then, we conducted a comprehensive search for potential pain points within the pharmaceutical industry. The goal of this phase was to identify the aspects we would focus on, rather than gathering analytical content. We selected the pain points of pharmaceutical industry based on their relevance, identified through literature analysis and during our interviews. Therefore, we focused on recurring pain points that we found pertinent for our thesis, including **Approval of Medicines, Innovation, Outcome and Value Measurement, Patent System, Patient Treatment Compliance, Pricing and Reimbursement and Sustainability.**

Our approach was first to conduct a general literature and document review to provide a broader perspective regarding the existing pain points in the European pharmaceutical industry. Then, we conducted a more specific analysis, focusing on countries such as Belgium, Italy and Portugal.

In addition to the selective analysis, we conducted 18 structured interviews with professionals working in pharmaceutical companies from Belgium, Italy, and Portugal. These discussions with experts in the pharmaceutical field enabled us to enrich our knowledge of the specific pain points we are analysing, contributing to a comprehensive approach to our analysis.

These interviews were carried between October and December 2023. The data collected during interviews were transcribed verbatim, meticulously analysed, and compared with the findings from the literature review. This triangulation approach enhanced the robustness and credibility of our research.

Throughout the data collection process, we maintained data validity and reliability with periodic reviews of the transcripts and cross-verification by multiple researchers to identify potential biases and enhance the reliability of the data.

4. Findings

4.1 Italy

To gain valuable insights into the market operations and challenges of Italian pharmaceutical companies, conducting five structured interviews has been a fundamental tool. The questions posed during the interviews were tailored to gain a profound understanding of emerging challenges and to conduct an in-depth exploration of the industry's trends. In addition, cross-referencing information obtained through interviews with data from other sources has enhanced the credibility and reliability of results. The five pharmaceutical companies interviewed are among the largest in Italy, and their insights were shared by representatives from within each company. This helped to provide substantial information about the industry, and it facilitated the learning of the most recurring topics.

To start off, an important topic discussed in the interviews was that pharmaceutical companies aim to strike a balance between ensuring their drugs are accessible to patients and generating revenue to sustain R&D. For instance, Italy spends a significant amount on R&D with the goal of bringing new innovative drugs to the market to suit patient needs. However, innovation comes at a cost, and

companies must keep drug prices relatively high to make a profit. This highlights the trade-off between supplying more medicines, thereby investing huge amounts in R&D while ensuring that they are affordable to all patients. Compared with data obtained from other sources, it is true that not all R&D investments are successful. In fact, this discrepancy has been discussed in the interviews as one of the pain points for pharmaceutical companies, especially in Italy, where R&D investments are significant. According to the literature, patents play a crucial role in incentivising innovation in pharmaceutical companies. Even though no specific strategy has been discussed during the interviews about how companies react when their patents expire, it is a form of uncertainty and threat concerning all pharmaceutical companies. Thus, it is considered a pain point of the industry.

Furthermore, environmental sustainability is another important concern for pharmaceutical companies. During the interviews, specific questions were asked on how the company strives to achieve sustainable practices and their efforts towards the environment. Recent data aligns with what has been discussed during the interviews regarding environmental targets, such as emissions and policies, confirming the consistency of the information.

Furthermore, communication with patients seems to be very important for pharmaceutical companies. In the interviews, it emerged that each company has unique communication channels to ensure patient treatment compliance. However, this can be monitored only to a certain extent, implying that there are still some limitations and challenges to be addressed to guarantee full compliance of medicines after they have been prescribed.

Another topic that emerged in the interview is the pricing and reimbursement of medicines. Italy holds a prominent position among all European countries for its highest rate of availability, which indicates when the product gains access to the reimbursement list. This implies a correct functioning of the reimbursement system in Italy.

Lastly, one of the issues shared by those interviewed was the outcomes and value measurement in Italy. In fact, Italian pharmaceutical companies lack a predefined system to measure value and assess outcomes. They rely on assessments conducted by the *Azienda Italiana del Farmaco* (AIFA, the

Italian national regulatory authority), meaning that if drugs are deemed eligible for reimbursement, they yield favourable outcomes and value for patients. This highlights that although companies have technologies to process patient information and data, they lack a specific framework for value and outcomes measurement. This would allow them to be more patient-focused.

5. Analysis

5.1 Italy

5.1.1 Approval of Medicines

In Italy, the authorization of medicines can follow two pathways. First, drugs may obtain approval through a **national route,** outlined in the Pharma Code, which encompasses three distinct authorization methods: the **national** procedure, the **mutual recognition** procedure, and the **decentralized** procedure (Pharma Boardroom, 2022). The *Agenzia Italiana del Farmaco* (AIFA) is responsible for granting marketing authorization for medicinal products through either national or European procedures, based on criteria of quality, safety, and efficacy. Otherwise, drugs may obtain approval through a **centralized route**, whereby pharmaceutical firms present a single marketing authorization application to the European Medicines Agency (EMA). The primary benefit of this approach is that it grants the marketing-authorization holder the ability to introduce the medicine to the entire EU market, serving both patients and healthcare professionals, based on a singular marketing authorization (Pharma Boardroom, 2022).

Before being introduced in the Italian market, drugs undergo classification for pricing and reimbursement considerations. For national, mutual recognition, or decentralized approaches, the classification and pricing of the drug are integrated directly into the marketing authorization granted by the Medicines Agency. In contrast, when the EMA provides marketing authorization through a centralized process, the Medicines Agency subsequently issues a decree that allocates a national classification number to the drug, defines its distribution guidelines, and determines its pricing and reimbursement categorization (Blei et al, 2019). Marketing authorizations for medicinal products,

whether granted nationally or through centralized procedures, hold a **validity period** of **five years.** Renewal is possible upon the conclusion of this initial five-year span, contingent on a reassessment of the drug's risk-benefit balance, undertaken by either AIFA or EMA. Prior to the authorization's lapse, the responsible party is required to present a renewal request, accompanied by an updated drug dossier detailing the latest insights on its quality, safety, and efficacy. **Post-renewal,** the authorization remains in force indefinitely, unless the relevant regulatory body opts for an additional five-year extension (Pharma Boardroom, 2022). Hence, for drugs to be marketed in Italy, they must have been granted Authorization for Trade Entry (AIC) by AIFA or EMA. The AIC is granted after a scientific evaluation of the medicine's quality, safety, and efficacy criteria. The applicants must submit a dossier that encompasses details on chemical-pharmaceutical, preclinical, and clinical aspects, formatted according to the standardized common technical document format. The data and studies provided in support of the AIC application must adhere to guidelines established at the European level (Pharmexcil, 2020).

5.1.2 Innovation

Italy has emerged as a prominent pharmaceutical producer within the European Union, due to strategic investments in innovation throughout the entire supply chain. According to the *Italian Trade Agency,* pharmaceutical companies in Italy have increased their R&D investments to 1.7 billion euros in 2023 annually and have employed around 3000 specialised R&D workers to foster innovation (Italian Trade Agency, 2023). The prosperity of the Italian pharmaceutical industry thrives because of a supportive environment that encourages growth, innovation, and global trade (Italian Trade Agency, 2023).

Given the country's robust ecosystem to foster innovation, Italy has the most prominent, largest, and rapidly advancing pharmaceutical industry in Europe, generating a substantial €32 billion in gross value-added revenues. This industry makes up 11% of the nation's GDP. In addition, due to a diverse combination of well-established pharmaceutical giants and emerging, innovative small and medium-sized enterprises (SMEs) across biotechnology and medical technology, Italy has experienced a 117%

increase in growth rates for pharmaceutical exports in Europe over the last ten years (Italian Trade Agency, 2023).

Moreover, patents foster innovation in pharmaceutical companies, preventing generic competitors from entering the market. In turn, this exclusivity prevents a decline in drug prices and enables companies to generate profits from new inventions. According to recent research, Italy is one of the countries with a lower degree of generic penetration and price reduction after the loss of exclusivity (Perna et al. 2023). This encourages innovation initiatives in the country. In 2021, generic drugs represented 21% of the total expenditure and constituted 29.6% of consumption by the population. In addition to this, the analysis also reveals that there is a significant difference in spending on generic drugs among different regions in Italy. For instance, in some regions, 43% of the money is spent on generic drugs, while in other regions, the percentage was as low as 19%. This implies that the use and spending on generic medicines vary widely depending on the specific region in Italy (Perna et al. 2023).

5.1.3 Outcome and Value Measurement

To suit the needs of patients, there must be a strong relationship between patients and pharmaceutical companies. By being more patient-centered, companies can provide essential drugs, however, it is important to measure their value and outcomes effectively.

There are three main measures of value, namely the **value of drugs**, the **value of treatments**, and the **economic value** in terms of benefits to patients.

To begin with, according to the five interviews held with different Italian pharmaceutical companies, the value of their drugs and medicines is assessed by the AIFA. As mentioned in the sub-chapter "Price and Reimbursement", AIFA is responsible for authorizing medicines for production, utilization, and marketing in Italy. By obtaining reimbursement from AIFA, pharmaceutical companies feel assured that their clinical trials have demonstrated efficacy and that drugs are non-toxic. Thus, Italian pharmaceutical companies use this evaluation as a means of measuring the value of the medicine. However, it is crucial to highlight that the classification of drugs for obtaining

reimbursement mainly focuses on cost reimbursement and takes no consideration of the effectiveness of the drugs (The Economist, 2015). Thus, there is no framework to assess the value of drugs following the patient's use of the drug (Russo et al. 2021).

Following this, the Health Technology Assessment (HTA) assesses the value of new treatments by comparing the performance of a drug with its alternatives (The Economist, 2015). The criteria employed often include demographic and cost-related elements. Nevertheless, a regular examination of benefits and costs has not become standard practice, and social and economic advantages are not yet consistently considered as part of the assessment process (The Economist, 2015). In addition, innovation, such as digital health data, could help to reduce R&D costs, diminish the costs associated with clinical trials, and provide crucial post-launch monitoring insights. They could also hold value in optimizing participant recruitment for clinical trials and in making monitoring more cost-effective using various tools and devices (Mallender, 2023).

Lastly, the economic value of pharmaceuticals is assessed by considering the positive effects they have on individuals and society. Drugs play a crucial role in delivering the correct treatment so to improve people's lives, alleviate the effects of diseases, and enhance overall quality of life. The Quality-Adjusted Life Year (QALY) is a tool used by AIFA and serves as a measure that comprises both the value and benefits of health outcomes into a single numerical representation (AIFA, 2023).

In the context of the pharmaceutical industry, measuring outcomes includes assessing clinical outcomes, humanistic outcomes, economic outcomes, and service outcomes (Newham et al. 2023). First, as previously mentioned, in Italy, AIFA is responsible for ensuring the safety of drugs throughout their entire lifecycle, from clinical trials to market surveillance. Second, humanistic outcomes comprise factors such as quality of life, health status, and lifestyle, resulting from the influence of primary care on patient functioning and overall well-being (Newham et al. 2023). Besides using QALY as a unit of measurement for the quality of life, the development of Telemedicine would allow us to find new solutions to traditional issues in medicine and create new opportunities for the improvement of healthcare services. This would result in an increased

collaboration among various healthcare professionals and patients, helping pharmaceutical companies to become more patient-focused.

Third, the economic outcomes include a cost-effectiveness analysis that is performed by pharmaceutical companies and delivered to AIFA. **Cost-effectiveness analysis** evaluates the costs and health outcomes of interventions by comparing them and estimating the cost required to achieve a unit of a health outcome, such as a gained life year or a prevented death (CDCP, 2021). This implies that, in Italy, drug prices consider the value that these medicines bring to patients and society.

Moreover, due to the **integrated negotiation process** for price and reimbursement by the Italian government, the country has increased its focus on outcomes. Indeed, Italy has established **Managed Entry Agreements** (MEAs) with pharmaceutical companies, which represent a unique approach wherein risks are shared, and extensive clinical evidence is collected once new drugs are already in use (Russo et al. 2021). The primary goal is to mitigate the possibility of health systems adopting treatments that may prove not to be cost-effective in the long run. The overarching goal is to implement registries that not only furnish data about the products but also offer insights into real-world outcomes, contributing to a more comprehensive understanding of the impact of pharmaceutical interventions. Italy is among of the countries with a **substantial prevalence** of Managed Entry Agreements. These agreements include **financial-based schemes**, such as cost-sharing, budget cap, and price-volume agreements, and **outcome-based schemes**, such as payment by result and risk sharing, have the goal of following a value-based allocation of healthcare resources and effectively managing pharmaceutical expenditures (Russo et al. 2021).

Overall, Italy lacks a predefined value framework for setting drug prices. The development of a more standardized and transparent approach to value assessment in medicine pricing could enhance the effectiveness and fairness of these negotiations between AIFA and pharmaceutical companies.

In addition, according to the five interviews conducted, some companies have now started Patient Reported Outcome instead of clinical outcomes. They are trying to perform decentralised clinical trials or hybrid studies where the improvement of patient outcomes is the primary endpoint.

Secondary endpoints are adherence, health-related quality of life, sleep quality, disease-related outcomes, device usability, economic resources consumption, and safety.

5.1.4 Patent System

The rights granted by Italian pharmaceutical patents for new inventions are confined within the specific territory and confer the exclusivity to use the invention. An Italian patent confers protection across the entire Italian territory, but also in the State of San Marino, and may be recognized in the Vatican City (SIB, 2023). The process, rights, and advantages of pharmaceutical patents are consistent across all of Europe, with only small details specific to the Italian patent system to add.

The initial stage of filing a patent involves preparing and submitting a patent application, which is subsequently subject to examination. The *Italian Patent and Trademark Office* (UIBM, Ufficio Italiano Brevetti e Marchi) handles applications for Italian patents. This rigorous process ensures that inventions align with the necessary standards for patent protection (Jacobacci, 2023). After filing the patent application, the applicant receives an application number and filing date, and the examination process begins. Italian patent applications undergo a novelty search conducted directly by the EPO, and the results are subsequently forwarded to the UIBM. The office then shares the findings with the applicant. If, following this examination, the UIBM reputes the patent in line with requirements, it proceeds to grant it. Once the patent is granted the holder is eligible to receive the corresponding registration certificate (Brevetti, 2023). Finally, in Italy, there are no specific opposition procedures (SIB, 2023).

5.1.5 Patient Treatment and Compliance

Drug compliance is typically difficult to measure considering that most of the data about the number of drugs prescribed to patients is not accessible. In 2022, approximately 30 percent of Italian pharmacies participated in initiatives focused on enhancing medication adherence (Gagliardi, 2023). Within these projects, 67.8% specifically targeted individuals with chronic diseases. The data indicates that 83.2% of Italian pharmacies engaged in initiatives during 2022 aimed at enhancing medication compliance specifically among individuals with diabetes (Gagliardi, 2023).

The issue of patient treatment compliance has been always at the heart for pharmaceutical companies. For instance, by leveraging data obtained from surveys conducted in Italy many years ago, researchers observed a trend among patients who are dealing with hypertension and dyspepsia. These individuals tend to decrease drug compliance, due to low income levels and challenges in affording drugs (Atella et al. 2006).

This resulted in poor adherence to drug therapies and a decrease in the effectiveness of the treatment, which led to significant implications for health. Indeed, there is evidence that 80% compliance with a medication for hypertension lowers blood pressure to normal, whereas 50% compliance is ineffective (Atella et al. 2006). The challenge to enhance healthcare in Italy concerns all pharmaceutical companies. This explains why, in 2022, the Italian association of pharmaceutical companies, *Farmindustria*, decided to release a new version of its Code of Ethics, which includes provisions for Patient Support Programs (PSPs) (Curti, 2022). These are innovative digital platforms for monitoring therapy and ensuring patient adherence and offer a well-organized and structured framework of homecare and online services to assist patients throughout their medical treatments (Omnys, 2023). Tailored PSPs have been shown to enhance therapy adherence rates, reaching up to 100% in some cases (Omnys, 2023). This initiative aims to offer supplementary services, without replacing those offered by the SSN, to benefit patients undergoing treatment with a specific drug (Curti, 2022). The purpose is to develop a patient-centric platform that is capable of coordinating tasks for all involved stakeholders in a treatment plan. This serves to provide comprehensive information on the patient's journey and improve communication with patients for the appropriate use of drugs. Nowadays, pharmaceutical companies are not aware of how their products behave underground, therefore, implementing this platform can be a way to get closer to patients.

Lastly, the five interviewees have explained their focus on offering educational materials such as adherence support programs and disease awareness campaigns, as well as online resources, educational videos, printed brochures, and tools for patient engagement (mobile apps, online

communities, and wearable devices). In conclusion, Italian pharmaceutical companies have diversified communication channels, enabling them to gradually adopt a patient-focused approach.

5.1.6 Pricing and Reimbursement

The Italian public healthcare system constitutes the "*Servizio Sanitario Nazionale*" (SSN, National Health Service), which is comprised of a group of entities, bodies, and functions organized under the Ministry of Health and administered on a decentralized regional basis (Global Legal Insights, 2023). Its function is to ensure access to national healthcare services, providing significant benefits to almost 58,95 million citizens by addressing certain clinical conditions or risk factors that have been scientifically validated (Global Legal Insights, 2023).

The organizational structure of the SSN incorporates dual-levels of governance, namely the national level, represented by the State, and the regional level. The State determines the core principles for the healthcare sector and sets the Essential Levels of Assistance (LEAs), which must be consistently enforced across the nation and cannot be subject to restriction or alteration by the Regions. The Regions are entrusted with defining healthcare policy, organization, and expenditure, to reduce deficits or prevent the surpassing of budgetary limits (Global Legal Insights, 2023).

The price of drugs is reimbursed by the SSN after it has been negotiated between the AIFA and the Marketing Authorization Holder (Simmons & Simmons, 2020). AIFA conducts comprehensive clinical, scientific, and economic evaluations of pharmaceuticals, and subsequently grants authorization for the marketing of approved drugs (Prada et al. 2017). This evaluative process is supported by two expert technical-scientific committees, namely the *Commissione Tecnico Scientifica* (CTS, Technical Scientific Committee) and *Comitato Prezzi e Rimborso* (CPR, Prices and Reimbursement Committee). The role of the CTS is to evaluate national and European marketing authorization applications, offer advisory opinions, and provide reimbursement classifications, whilst the CPR negotiates with pharmaceutical companies to establish prices for medicinal products reimbursed by the SSN (Prada et al. 2017).

Drugs are categorized into prescription and non-prescription classes. Prescription drugs require a doctor's authorization. The more significant the risk associated with the drug, the more stringent the prescription requirements for dispensing (Global Legal Insights, 2023). Non-prescription drugs are sold in pharmacies and are authorized for online retail through pharmacy websites that are officially registered by the Ministry of Health. These drugs are entirely paid by the patient and the price is freely established by the producer and consistent throughout Italy. Pharmacists can determine discounts on the displayed price, provided that it is applied to all clients (Global Legal Insights, 2023). Moreover, drugs are further grouped into distinct "classes" based on pharmacological and economic factors that consider the importance and effectiveness of medications in treating various medical conditions (Labcorp, 2019). In Italy, a medicine can be classified as:

1. Class A drugs comprise essential drugs for chronic and serious diseases.
2. Class H drugs include Class A products, but exclusively for hospital use and specialist supervision, such as oncology medications. Both Class A and Class H drugs are 100% reimbursed by the SSN.
3. Class C drugs do not reach any negotiation with the Health Technology Assessment and AIFA committee and therefore are not reimbursed, implying that the cost is fully borne by the patient.

The criteria to define the price and reimbursement of medicines in Italy is established by Law. To seek reimbursement from the SSN, pharmaceutical companies must demonstrate scientific evidence that their drug provides additional therapeutic value compared to existing main therapies (Global Legal Insights, 2023). By proving added value, the medicine is categorized as "innovative" for a maximum of 36 months and may undergo reassessment after 18 months (Labcorp, 2019). This allows for a prompt prescription at a regional level. However, if a drug fails to provide additional therapeutic benefits, the company will be required to provide additional evidence regarding economic benefits, such as information on marketing, sales, and reimbursement details from other countries. This serves to offer a comprehensive understanding of the medicine's overall performance and market dynamics

beyond its scientific attributes. Additionally, companies will have to provide information about public contributions and incentives received for R&D initiatives, as well as transparent and current information regarding the patent status of the relevant medicinal product and the company's production capacity and capability to effectively address unforeseen events that may jeopardize manufacturing and supply. The price negotiated with AIFA represents the highest selling price for the SSN, but it can be open to further trade discounts. It relies on adding profit margins for wholesalers and pharmacists in retail sales and it maintains its validity for 24 months unless mutually agreed otherwise. The window for either party to suggest amendments to the agreement before renewal is 60 days before expiration (Global Legal Insights, 2023). If no changes are proposed, the agreement will be automatically renewed for an additional 24 months. The AIFA releases the Transparency List, cataloging all equivalent Class A drugs and their associated reference prices, subject to periodic reviews. Drugs designated exclusively for hospital use, orphan drugs, or those with extraordinary therapeutic, negotiations for pricing and reimbursement can start before obtaining marketing authorization and may extend for a maximum duration of 100 days (Labcorp, 2019).

Nevertheless, if no agreement is reached, the drug is classified as a Class C drug, and the payment is borne entirely by the patient. These drugs are freely priced by the manufacturer. Hence, the pharmaceutical company has the flexibility to independently set the maximum retail price, which must remain consistent throughout Italy. Also, it is allowed to increase prices only in January of an odd-numbered year. In addition, if medicines categorized under Class C drugs are to be sold to public authorities, pharmaceutical companies are forced to give a 50% discount on the retail price (Labcorp, 2019).

In addition, if the achieved benefits are lower than those expected, AIFA has the authority to reopen negotiation procedures, before the expiration of the agreement with the Marketing Authorization holder, to reconsider the terms of the existing agreement under the following circumstances (Global Legal Insights, 2023). First, if a market change occurs during the negotiation period, indicating a foreseeable increase in the medicine's usage. Second, if there is new evidence regarding the

medicine's effectiveness and safety, leading to a significant shift in its therapeutic positioning or a substantial reduction in the initially estimated clinical benefits during the negotiation, or in case of a supply shortage.

There are two main channels through which patients receive reimbursed drugs, namely retail and direct distribution. On one hand, in the retail channel, the SSN acquires the drug from a price list. This price comprises the "allocated quotas", which represent the percentages of compensation designated for the two entities in the distribution process, namely pharmacists and wholesalers (Global Legal Insights, 2023). On the other hand, using direct distribution channels, regions can ensure the provision of necessary medications for patients undergoing home or residential treatments, as well as drugs required immediately post-hospitalization. Medications intended for direct distribution are procured by local health authorities via public procurement processes, starting from a base price that does not exceed the ex-factory price negotiated with AIFA. Following this, the local health authority administers the medication directly to patients within its healthcare facilities, without involving wholesalers or pharmacies. In addition, regions can implement an additional distribution channel, namely the distribution on behalf of the local health authority (DPC). In this alternative approach, the local health authority directly procures drugs through tenders and subsequently distributes them to patients via pharmacies in the retail channel. Pharmacies receive compensation, distinct from the allocated quota, as part of this process. The objective of this distribution method is not solely centered on achieving cost savings but also on ensuring the ongoing provision of assistance and monitoring the appropriate usage of specific drugs. When determining price reimbursement, the AIFA specifies whether a drug can be distributed through this method (Global Legal Insights, 2023).

Currently, the Italian pharmaceutical system operates within an annual spending limit for drugs, with mandatory reimbursement from pharmaceutical companies for any excess spending. In 2022, the public pharmaceutical spending cap was set at 15% of the national healthcare fund (Global Legal Insights, 2023). This cap is divided into two main components: agreed spending (7% of the fund) for

drugs distributed through the retail channel and direct procurement spending (8% of the fund) for drugs purchased directly by local health authorities (Global Legal Insights, 2023).

5.1.7 Sustainability

Pharmaceuticals are pervasive contaminants that pose a significant environmental challenge. Considering the potential for pharmaceuticals to persist in the environment, there is a heightened risk of accumulation, leading to detectable and biologically active levels (Zuccato et al. 2006). Recent analytical studies conducted in Italy highlight the limited efficacy of sewage treatment plants (STPs) in removing various pharmaceuticals, suggesting that they could be important sources of environmental contamination. Manufacturing facilities are also noteworthy local sources of pharmaceutical pollution (Zuccato et al. 2006). This explains why the Italian Pharmaceutical companies are making continuous efforts to keep low the environmental impact of their drug production.

In the interviews conducted, the concern about sustainability has always been at heart. Regarding drug production, pharmaceutical companies strive to have meticulous waste management. For instance, 88% of Italian pharmaceutical companies will reduce the waste they produce in the next 3-5 years, and 55% of them are dedicated to minimizing or mitigating the use of plastics at every stage of the production process (Farmindustria, 2021).

Moreover, numerous incentives are given to employees to reduce all kinds of emissions. In Italian pharmaceutical companies, mobility is highly regulated to reduce CO2 emissions as much as possible. For example, they encourage employees to use electric travel by supplying electric company cars and support travel by train rather than by other means. This also includes sustainable delivery of drugs to other places in the country. This aligns with recent data that states that the value of investments in environmental protection per employee in the pharmaceutical industry has exhibited a positive difference of 150% (Farmindustria, 2021). Moreover, it has been mentioned in the interviews that pharmaceutical companies organize events and send numerous emails to employees to remind them of the company's 360-degree focus on sustainability. This explains the results from Farmindustria in

2021, whereby it has been registered a 59% reduction in energy consumption by the pharmaceutical industry over the last 10 years and there has been a 32% reduction in greenhouse gas emissions (Farmindustria, 2021)

Moreover, the EU has granted €1.5 million to one of the biggest Italian Pharmaceutical Companies, Angelini, to achieve sustainable drug production. This allowed the company to implement a highly advanced energy-saving system in its production plant, resulting in a reduction of over 830 MWh in electricity consumption and conservation of 10,000 m3 of drinkable water per year (Angelini Pharma, 2022). In addition, the Angelini Pharma Packaging Design structure is dedicated to minimizing the environmental footprint of packaging by integrating "green" innovations while ensuring product conservation. This reduced packaging weight and volume, optimizing transport logistics and decreasing vehicle emissions and atmospheric pollution. Overall, this confirms that pharmaceutical companies in Italy are currently investing in ecological transitions.

Moreover, there is a huge commitment to transition to net zero GHG emissions by 2035 and reinforce its mitigation plan for greenhouse gas emissions mitigation plan (Chiesi Farmaceutici S.p.A., 2022)

6. Discussion

6.1 Approval of Medicines

The drug approval processes in Belgium, Italy, and Portugal present different regulatory frameworks and methodologies, which illustrate the different behaviors adopted by these countries to guarantee the safety, effectiveness, accessibility, and affordability of pharmaceutical products.

The Belgian regulatory landscape encompasses FAMHP, FPS Economy, and NIHDI. FAMHP guarantees product quality, safety, and efficacy, while FPS Economy handles price negotiations and NIHDI sets reimbursement criteria. This heterogeneous approach aims to balance rigorous standards with affordability and accessibility. Portugal entrusts INFARMED with the approval process, focusing on scientific and evidence-based assessments. A collaborative approach is used by the NHS and HTA assessments to guide funding decisions, interweaving scientific rigor with funding criteria.

Italy's AIFA leads comprehensive assessments, supported by expert committees (CTS and CPR). It is the AIFA's responsibility to evaluate the clinical, scientific, and economic aspects of the project, while the CTS provides advice on authorizations, and the CPR negotiates prices and reimbursements. Italy's framework emphasizes robust assessments and negotiations within its decentralized healthcare structure.

Regarding the approval process for medicines, Belgium uses community and national procedures, emphasizing centralized, mutual recognition, and decentralized routes for marketing authorization. Despite ensuring EU alignment, the process faces challenges with potentially long approval times. Portugal takes advantage of EMA approvals, emphasizing scientific criteria, but faces concerns about delayed market entry, impacting patient access and innovation. In the interviews, it was mentioned that, even after assessment by the EMA, Portugal conducts its assessment, which further delays the process. Meanwhile, the Italian AIFA conducts rigorous evaluations that include clinical, scientific, and economic analyses, culminating in the negotiation of prices and reimbursements. As a result of its regional autonomy, Italy emphasizes the balance between prices and accessibility to ensure a systematic evaluation process.

There are potential delays in approval deadlines in Belgium and Portugal, which could impede patient access and innovation. Several stakeholders in Portugal express concern about the stagnation of innovation as a result of delays in approval, which adversely affects both companies and patients. In contrast, the Italian AIFA emphasizes comprehensive assessments that aim for accessibility and balanced pricing within its decentralized healthcare structure. The emphasis on robust assessments and negotiations ensures a balance between fiscal sustainability and accessibility to medicines.

Although each country navigates its distinct regulatory landscape, they all aim to ensure the safety, efficacy, accessibility, and affordability of medicines, while employing different methodologies and facing unique challenges.

6.2 Innovation

Innovation plays a key role in the pharmaceutical industry as it enables companies to develop new drugs and treatments, ultimately enhancing the quality of life for both individuals and society.

On one hand, Belgium and Italy hold prominent positions in this industry. Their respective governments provide incentives to pharmaceutical companies for promoting growth and innovation, which in turn encourages huge investments in R&D. Belgium has the highest R&D investment per capita, and, according to data reported in 2022, it allocated 5,7 billion euros in R&D investments. Italy strategically invests throughout the entire supply chain, dedicating 1,7 billion euros for R&D annually. These figures explain why both countries have experienced fast growth rates for exports and highlight how both countries prioritize innovation and drug

development within the pharmaceutical sector. Belgium, in particular, is supported by government initiatives to safeguard its dominant position in Europe.

On the other hand, Portugal is far behind in terms of R&D investment to foster innovation. Despite ongoing efforts to enhance its market position, Portuguese pharmaceutical companies struggle to reach leading positions in this industry since they face numerous challenges. First, high development costs and lengthy drug approval procedures act as a deterrent to investments in R&D and drug development. Second, inadequate compensation for physicians and professionals, coupled with long hiring processes, impacts the efficiency of clinical trials. As a result, the country loses competitiveness compared to other European countries. This explains why the Portuguese pharmaceutical industry contributes only 0,4% to the global market. Overall, the main concern for Portugal's pharmaceutical sector lies within the substantial investments required to achieve competitiveness and drive innovation.

To sum up, all three countries exhibit a strong commitment to promoting innovation in this sector. Portugal could rely on internalisation to foster the growth of the pharmaceutical business. However, the country must overcome some barriers, such as restrictions related to the new drug registration, access to licenses or reimbursement from government entities, and the presence of patents, for this to

be successful. Italy benefits from a low degree of generic penetration, which allows the country to maximise the use of patent protection. For instance, recent data indicates that, in Italy, there is a higher spending on brand-name drugs rather than generic drugs, suggesting that companies can maintain brand reputation, charge higher prices, and sustain demand. Lastly, pharmaceutical companies in Belgium mainly focus on promoting growth, drug development, and innovation, as it is shown by the 8.7% share of Belgian patent applications in Europe. This implies that Belgian pharmaceutical companies are protected by rights on their inventions, which in turn ensures high profits for the industry.

6.3 Outcome and Value Measurement

Measuring outcomes and value in Belgium, Italy, and Portugal reflects different approaches to their health systems, each emphasizing patient-centered care while employing different methodologies and priorities.

The three countries highlight the importance of patient-centered care, integrating Patient-Reported Outcome Measures (PROMs) and Patient-Reported Experience Measures (PREMs) to assess the effectiveness of healthcare from the patient's perspective. The three countries make use of the Health Technology Assessment (HTA) as a fundamental tool to evaluate new medicines, ensuring relevant patient outcomes and economic viability.

Belgium focuses on quality indicators covering mortality rates, infection rates, readmission rates, and patient-reported outcomes (PRO). The emphasis on value-based healthcare is evident, guaranteeing optimal outcomes relative to the costs incurred. The country maintains comprehensive healthcare registries that track patient outcomes and integrate robust measures like PROs to assess treatment success from the patient's perspective.

Italy underlines comprehensive assessments through AIFA, integrating physiological, treatment-related, and economic values. Health Technology Assessment (HTA) and QALYs play key roles in assessing treatment effectiveness and economic impact. The country has initiated Managed Entry

Agreements (MEAs) to share risks and collect extensive real-world evidence post-drug launch, improving understanding of the impacts of pharmaceutical interventions.

Portugal takes a proactive stance towards patient-reported outcomes. The nation integrates QALYs, emphasizing patient-relevant outcomes and economic value. Portuguese pharmaceutical companies are increasingly adopting patient-centric strategies, leveraging technology and patient engagement to build brand loyalty and trust.

6.4 Patent System

Pharmaceutical patents play a crucial role in safeguarding intellectual property for new inventions. In Portugal, patents are overseen by the National Institute for Industrial Property (INPI). Similarly, in Belgium, the Federal Public Service Economy manages patent regulations through its Office for Intellectual Property (OPRI), ensuring the protection of intellectual assets. Meanwhile, Italy relies on the Italian Patent and Trademark Office (UIBM) to process applications for Italian patents.

Across all three countries, there is a strictly regulated process to verify that inventions meet the required standards for patent protection. This becomes particularly evident in the pharmaceutical industry, where companies seeking patents for new drugs must face a series of formalities. This process ensures that the resulting drugs adhere to the patent laws of Portugal, Belgium, and Italy, respectively. In addition to this, the standard duration of patent protection is uniform across these nations, lasting for 20 years from the date of the application.

The concept of the "patent cliff" becomes a focal point, especially in Belgium. This term refers to a significant drop in revenue or profitability experienced by pharmaceutical firms when their patents expire, opening the market to competition. In Belgium, the patent cliff leads to a notable 44.75% reduction in the ex-factory price of a drug when a more affordable alternative emerges. In cases where molecules are fully reimbursed, the price reduction is even more substantial, reaching 51.52%. However, it is important to note that the information about the patent cliff applies specifically to Belgium, with no similar details provided for Portugal or Italy.

6.5 Patient Treatment and Compliance

Patient treatment compliance is a critical concern for pharmaceutical companies across Belgium, Italy, and Portugal. In fact, only half of patients globally adhere correctly to their treatment plans, which can lead to serious health consequences and increased healthcare costs. In Belgium, the accessible and high-quality healthcare system provides affordable care for all citizens, encouraging them to adhere more closely to their treatment plans. Interestingly, in both Belgium and Portugal, there is a significant relationship between patient adherence and the reimbursement systems. Greater adherence can lead to better health outcomes, favoring specific medicines, which can benefit pharmaceutical companies in terms of sales and market share.

However, in Italy, the situation is different. Historical data indicates that patients with conditions such as hypertension and dyspepsia tend to have lower drug compliance, mainly due to economic challenges and the affordability of drugs. This economic factor led to poor adherence and reduced effectiveness of treatments. In response, Italy has implemented Patient Support Programs (PSPs) through Farmindustria, offering digital platforms for monitoring therapy and ensuring patient adherence.

Across all three countries, pharmaceutical companies recognize the need to be closer to patients. They understand that adherence rates are generally higher for short-term conditions than chronic diseases, where longer treatments and less noticeable symptoms complicate compliance. Therefore, these companies focus on enhancing healthcare accessibility, implementing support programs, and strengthening patient education and engagement. Despite these efforts, measuring drug compliance remains a significant challenge in Belgium, Italy, and Portugal due to limited access to data on prescribed medications, which restricts the ability to fully assess adherence levels and the efficacy of interventions.

6.6 Pricing and reimbursement

The pricing and reimbursement systems in Belgium, Italy and Portugal follow different approaches. The Portuguese healthcare system applies a differentiated pricing system for medications in the out-

patient and in-patient sectors. The out-patient pricing is based on an external price reference, referencing neighboring countries such as Spain, France and Italy for prescription medicines, while over-the-counter medicines allow companies to set their own prices. Reimbursement within the SNS involves a comprehensive evaluation by the Ministry of Health and Infarmed, considering therapeutic value, safety and clinical effectiveness, leading to four levels of reimbursement aimed at reducing patient cost burdens. However, this system has created barriers to market entry and delayed access to medicines due to the complexity of the assessment processes.

Belgium's healthcare system applies a pricing system where the government determines maximum ex-factory prices for medications. The Commission on Pharmaceutical Specialties Prices evaluates requests for price fixing or increases, affecting the overall "maximum public price." Reimbursement is structured around a positive list approach, deciding which drugs are eligible for partial or full reimbursement. However, the drug reimbursement negotiation process in Belgium is not transparent and slower, leading to delayed access to innovative medicines, as pharmaceutical companies often prioritize countries with higher prices and quicker reimbursement processes.

In Italy, the Servizio Sanitario Nazionale (SSN) manages the reimbursement system where AIFA negotiates with Marketing Authorization Holders to establish drug prices, categorized based on clinical conditions, which has an impact on reimbursement levels. Italy emphasizes demonstrating added therapeutic value, which influences the categorization and subsequent reimbursement of medications. The negotiation terms are flexible and can be modified according to market dynamics or shifts in a medicine's effectiveness.

Each country's healthcare system has different approaches to pricing and reimbursement. In fact, Portugal's dependence on external price referencing poses problems related to market fluctuations, while Belgium seeks a balance between government-regulated prices and industry profitability. However, Italy focuses on demonstrating added therapeutic value, which determines its negotiation and reimbursement criteria.

6.7 Sustainability

In Belgium, Italy, and Portugal, the pharmaceutical industry faces significant environmental challenges due to pervasive contaminants. Each country has adopted various measures to address these issues, reflecting their commitment to sustainability.

Belgium is a substantial contributor to carbon emissions within the European Union. Moreover, the European Commission critiqued Belgium's National Energy and Climate Plan in 2020 for lacking coherence, emphasizing the need for improved collaboration between the federal government and regional entities. Nevertheless, the Belgian government has taken proactive steps in the pharmaceutical sector towards sustainable development.

In Italy, manufacturing facilities have also been identified as significant local sources of pharmaceutical pollution. Italian pharmaceutical companies are making concerted efforts to improve waste management. These companies are also working to reduce CO2 emissions through sustainable mobility initiatives and drug delivery methods. Additionally, the EU granted €1.5 million to Angelini, one of Italy's biggest pharmaceutical companies, for sustainable drug production, leading to significant decreases in electricity and water usage and a focus on eco-friendly packaging.

The Portuguese pharmaceutical industry is similarly focusing on sustainability, aiming to reduce environmental impact through waste minimization, process optimization, and eco-efficient medicine development. This includes the use of green technologies and improved chemical waste management.

All three countries share the target of achieving net zero emissions by 2050. However, they each face environmental challenges related to pharmaceuticals and their impact on the ecosystem, underscoring the need for ongoing efforts in sustainable practices within the pharmaceutical industry.

7. Conclusion

This paper explores the main pain points that the pharmaceutical industry in Europe is facing, with a particular focus on Belgium, Italy, and Portugal. Despite being a crucial player in providing essential drugs for both chronic and acute diseases, the pharmaceutical industry encounters numerous challenges to ensure a smooth transition from product-centric to patient-centric.

After a thorough analysis, it is evident that each country employs unique regulatory frameworks to ensure the safety, efficacy, accessibility, and affordability of pharmaceutical products. For instance, Belgium adopts a heterogeneous approach to balance rigorous standards with accessibility and affordability. Portugal relies on INFARMED for scientific assessments and collaborates with the NHS and HTA for funding decisions. Lastly, in Italy, AIFA leads comprehensive assessments with support from expert committees, and its regulatory framework emphasizes robust evaluations and negotiations within its decentralized healthcare structure.

Despite shared commitments to patient-centered care, the three countries differ in their drug approval timelines. Belgium faces challenges with potentially long approval times, while Portugal, conducts its evaluations, leading to delays in market entry. Differently, Italy, due to its decentralized structure, prioritizes robust assessments and negotiations. Concerns about approval delays in Belgium and Portugal raise issues regarding patient access and innovation. Portugal expresses fear about innovation stagnation due to delayed approvals. Conversely, Italy's emphasis on comprehensive assessments and negotiations aims for balanced pricing and accessibility. Moreover, to enhance the goal of the pharmaceutical industry of becoming more patient-centered, there is a need for effective measurement of both value and outcomes. Belgium focuses on quality indicators and Patient Reported Outcomes, Italy on Managed Entry Agreements for real-world evidence, and Portugal on technology-driven and patient engagement. All three countries share a commitment to patient-centered healthcare and recognize the importance of Quality Adjusted Life Years (QALYs) and HTA in their assessment of cost-effectiveness and therapeutic value.

Furthermore, innovation plays a significant role in fostering growth and drug development in the pharmaceutical industry. Belgium and Italy demonstrate similar results, that is, robust government support and significant R&D investments, resulting in fast export growth and dominant positions in Europe. In contrast, Portugal faces challenges with limited R&D investment, high development costs, and inefficient clinical trial processes, hindering its global market contribution.

Lastly, the commitment to sustainability within the pharmaceutical industry is central to every company's operation. An increasing number of efforts to mitigate environmental impact and promote sustainable practices are pervasive across all European countries in the industry. The industry recognizes its vital role in fostering a responsible and eco-friendly approach to the production and distribution of drugs and reflects the industry's acknowledgment of its role in contributing to a sustainable future.

In conclusion, the pharmaceutical sector, while playing a crucial role in delivering essential treatments, encounters multifaceted challenges that vary across these countries. By recognizing and addressing the pain points within the pharmaceutical sector, each country would have to focus more on different areas for fostering innovation, improving patient-centered care, and ensuring the sustained development of essential pharmaceutical products. This emphasizes the need for tailored strategies to address industry challenges.

8. Appendix

Participants

Company	*Country*	*Function*
ASTRAZENECA	Italy	Project Manager
BIAL	Portugal	Director, Medical Affairs – Portugal and Spain
BAYER	Italy	Head of Marketing Consumer Health
	Italy	Marketing Director
CHIESI GROUP	Italy	CEO and Managing Director
	Italy	General Director
GSK	Belgium	European Commercial Director
	Belgium	Continuous Improvement deployment leader
LABIALFARMA	Portugal	General Director
LYFEGEN	Switzerland	Founder and Chief Financial Officer
TAKEDA	Belgium	Vice President of Manufacturing
	Germany	Lead Patient Affairs Manager Oncology
ROCHE	Portugal	Senior Negotiator
	Portugal	Project Manager
THE JANSSEN PHARMACEUTICAL COMPANIES OF JOHNSON & JOHNSON	Portugal	Country Medical Affairs and Regulatory Director
YELLOW PILL	Belgium	Founder

Table 1. Participants

9. References

AFMPS. 2022. “ Procédure centralisée : Généralités”. https://www.afmps.be/fr/humain/medicaments/medicaments/procedures_damm/Procedures_enregistrement/procedure_centralisee/generalites

AFMPS. 2020. “ Cadre réglementaire”. https://www.afmps.be/fr/humain/medicaments/medicaments/procedures_damm/Procedures_enregistrement/procedure_mrp_dcp/cadre_reglementaire

AFMPS. 2020. “ Procédure Nationale : Généralités”. https://www.afmps.be/fr/humain/medicaments/medicaments/procedures_damm/Procedures_enregistrement/procedure_nationale/generalites

AIFA. 2023. “Economic evaluations”. https://www.aifa.gov.it/en/valutazioni-economiche

Alves, M. 2014. “Poderá Portugal sustentar a inovação?” https://estudogeral.uc.pt/handle/10316/88426

Angelini Pharma. 2022. “Sustainability”. https://www.angelinipharma.com/our-responsibility/sustainability/

Atella, Peracchi, Depalo, Rossetti. 2006. “Drug compliance, co-payment and health outcomes: evidence from a panel of Italian patients” https://onlinelibrary.wiley.com/doi/10.1002/hec.1135

Blei, M. Gambini, L. Stefanini, E. 2019. “Distribution and Marketing of Drugs in Italy: Overview”. https://portolano.it/news/distribution-and-marketing-of-drugs-in-italy-overview

Centers for Disease Control and Prevention. 2021. “Cost-Effectiveness Analysis”. https://www.cdc.gov/policy/polaris/economics/cost-effectiveness/index.html

Christophe Goethals, Marcus Wunderle. 2018. “Le secteur pharmaceutique en Belgique”. https://www.cairn.info/revue-courrier-hebdomadaire-du-crisp-2018-1-page-5.htm

Cockburn, I. 2015. “The importance of patents to innovation: updated cross-industry comparisons with biopharmaceuticals”. https://www.tandfonline.com/doi/full/10.1517/13543776.2015.1040762

Coelho, Anabela, Katherine de Bienassis, Niek Klazinga, Susan Santo, Patrícia Frade, Andreia Costa, and Tânia Gaspar. 2022. “Mental Health Patient-Reported Outcomes and Experiences Assessment in Portugal.” *International Journal of Environmental Research and Public Health* 19 (18). https://doi.org/10.3390/ijerph191811153.

Constantino Portela M, Campos Fernandes A. 2015. “Medicines Compliance and Reimbursement Level in Portugal” https://journals.sagepub.com/doi/10.1177/2333392815601972

Curti, I. 2022. “The new version of the code of ethics of the italian association of pharmaceutical companies: key developments” https://portolano.it/en/blog/life-sciences/the-new-version-of-the-code-of-ethics-of-the-italian-association-of-pharmaceutical-companies-key-developments

De Almeida J, Gonçalo S, Augusto F, Fronteira I, Hernández-Quevedo C. 2017. “Health Systems in Transition- Portugal”. http://ihmtweb.ihmt.unl.pt/PublicacoesFB/HiT-Portugal

Dean S, Al Sayah F, Johnson J. 2021. “Measuring value in healthcare from a patient’s perspective” https://jpro.springeropen.com/articles/10.1186/s41687-021-00364-4

Delgado R. 2022. “Pharmaceutical Patents and the right to health- Portugal and Brazil” https://repositorio.ual.pt/handle/11144/5432

Deloitte, Pharma.be. 2020. “Belgium as clinical trial location in Europe”. https://pharma.be/sites/default/files/2022-01/pharma.be_deloitte_study_belgium-as-a-clinical-trial-location-_key_results_2020_0_0.pdf

EFPIA. 2023. “Intellectual Property”. https://www.efpia.eu/about-medicines/development-of-medicines/intellectual-property/

European Commission. 2021. “Autumn 2021 Economic Forecast: From recovery to expansion, amid headwinds” https://economy-finance.ec.europa.eu/economic-forecast-and-surveys/economic-forecasts/autumn-2021-economic-forecast-recovery-expansion-amid-headwinds_en

European Commission. 2021. “State of Health in the EU, Belgium Country Health Profile”. https://health.ec.europa.eu/system/files/2021-12/2021_chp_be_english.pdf

European Federation of Pharmaceutical Industries and Associations. 2023. “Assessment of main provisions and key EFPIA recommendations on the revision of the pharmaceutical package”. www.efpia.eu

European Parliament. 2021. “Climate action in Belgium”. https://www.europarl.europa.eu/RegData/etudes/BRIE/2021/690578/EPRS_BRI(2021)690578_EN.pdf

European Patent Office. 2022. “The EPO at a glance”. https://www.epo.org/en/about-us/at-a-glance

Farmindustria. 2021. “Farmindustria 2021 Report” https://www.farmindustria.it/app/uploads/2017/12/Farmindustria2021_ENG_2021-07-28.pdf

Chiesi Farmaceutici S.p.A. 2022. “Sustainability Report”. https://www.chiesi.com/en/sustainability-report-2022/

Fox B, Hofmann C, Paley A. 2016. “How pharma companies can better understand patients” https://www.mckinsey.com/industries/life-sciences/our-insights/how-pharma-companies-can-better-understand-patients

Franken, Margreet, Maïté Le Polain, Irina Cleemput, and Marc Koopmanschap. 2012. “Similarities and Differences between Five European Drug Reimbursement Systems.” *International Journal of Technology Assessment in Health Care* 28 (4): 349–57. https://doi.org/10.1017/S0266462312000530.

Gagliardi, J. 2023. “Share of pharmacies in Italy involved in projects aimed at promoting medication adherence that promoted adherence for selected chronic diseases in 2022”. https://www.statista.com/statistics/954483/pharmacies-involvement-in-medication-adherence-by-disease-in-italy/

Garattini L, Cornago D, De Compadri P. 2007. “Pricing and reimbursement of in-patent drugs in seven European countries: A comparative analysis” https://www.sciencedirect.com/science/article/abs/pii/S0168851006002600

Global Legal Insights. 2023. “Italy: Pricing and Reimbursement Laws and Regulations”. https://www.globallegalinsights.com/practice-areas/pricing-and-reimbursement-laws-and-regulations/italy

Heshmati A, Tsionas M. 2023. “Green innovations and patents in OECD countries” https://www.sciencedirect.com/science/article/pii/S0959652623022503

Hogan Lovells. 2014. “EU Pricing & Reimbursement”. https://www.hoganlovells.com/~/media/hogan-lovells/pdf/publication/eu-pricing--reimbursement-newsletter--november-2014_pdf.pdf

INAMI. n.d. “La Commission de remboursement des medicaments”. https://www.inami.fgov.be/fr/l-inami/nos-organes/la-commission-de-remboursement-des-medicaments#.VrB1XSlitFQ

Italian Trade Agency. 2023. “Innovation DNA: Italian Life Science Sector', ICE - Italian Trade Agency”. https://www.ice.it/en/invest/innovation-dna-italian-life-science-sector

Jacobacci & Partners S.p.A. 2023. “Filing of Italian, European, and International Patents”. https://www.jacobacci.com/en/patents/filing-of-italian-european-and-international-patents

Jommi C, Bertolani A, Armeni P et la. 2023. “Pharmaceutical pricing and managed entry agreements: An exploratory study on future perspectives in Europe” https://www.sciencedirect.com/science/article/pii/S2211883723000473

José Vinhas; Sofia Dias; Antonio Melo Gouveia; Catarina Viegas Dias; Diana Sousa; João Oliveira; Julian Perelman; Luís Azevedo; Nuno Marques; Pedro Saramago; Rita Faria; Sofia Torres; Alex Correia; Sara Couto. 2022. “Metodologiade avaliação farmacoterapêutica de tecnologias de saúde metodologia.” www.infarmed.pt

Kulkov, I. 2021. “The role of artificial intelligence in business transformation: A case of pharmaceutical companies” https://www.sciencedirect.com/science/article/pii/S0160791X21001044

Labcorp. 2019. “Pricing and Reimbursement in Italy. Covance Biopharma”. https://biopharma.labcorp.com/content/dam/covance/assetLibrary/salessheets/Pricing-Reimbursement-Italy-SSCMA055.pdf

Mandal, A. 2023. “Drug Patents and Generic Pharmaceutical Drugs” https://www.news-medical.net/health/Drug-Patents-and-Generics.aspx#:~:text=The%20lifetime%20of%20the%20patent,around%20seven%20to%20twelve%20years.

Massimo Florio; Chiara Pancotti; David Prochazka. 2021. “European Pharmaceutical Research and Development Could Public Infrastructure Overcome Market Failures?” https://www.europarl.europa.eu/thinktank/en/document/EPRS_STU(2021)697197

Max Newton; Kelsey Stoddart; Marco Travaglio; Per Troein. 2023. “EFPIA Patients W.A.I.T Indicator 2022 Survey” https://www.efpia.eu/media/s4qf1eqo/efpia_patient_wait_indicator_final_report.pdf

Medicines Agency, E. 2019. “From laboratory to patient- the journey of a medicine assessed by EMA” https://www.ema.europa.eu/en/documents/other/laboratory-patient-journey-centrally-authorised-medicine_en.pdf

Michael E. Porter; Thomas H. Lee. 2013. “The Strategy that will fix healthcare” https://hbr.org/2013/10/the-strategy-that-will-fix-health-care

Muriel Levy, Lieven Annemans. 2023. “Sustainability and Resilience in the Belgian Health System”. https://www3.weforum.org/docs/WEF_PHSSR_Belgium_2023.pdf

Nawrat, A. 2019. “From evergreening to thicketing: exploring the manipulation of pharma patents”. https://www.pharmaceutical-technology.com/features/pharma-patents-manpulation/?cf-view

Newham, Weir, Ferguson, Bennie. 2023. “Identifying the important outcomes to measure for pharmacy-led, clinical services within primary care: A nominal group technique approach”. https://www.sciencedirect.com/science/article/pii/S1551741122003928

Newton M, Stoddart K, Travaglio M, Troein P. 2023. “EFPIA- Patient W.A.I.T Indicator” https://www.efpia.eu/media/s4qf1eqo/efpia_patient_wait_indicator_final_report.pdf

Norman, Gail A Van. 2016. “Drugs and Devices Comparison of European and U.S. Approval Processes.” https://www.sciencedirect.com/science/article/pii/S2452302X16300638

Omnys. 2023. “A PSP (Patient Support Program) digital platform for the pharma industry” https://www.omnys.com/en/news/a-psp-patient-support-program-digital-platform-for-the-pharma-industry

Patel, S. 2019. “Regulatory Exclusivity in the United States and European Union and its Impact on Generic Entry”. https://www.nujps.com/regulatory-exclusivity-in-the-united-states-and-european-union-and-its-impact-on-generic-entry/

Pereira L, Queirós A, Rocha N. 2021. “Is the Portuguese software industry ready for eHealth? Na exploratory study” https://www.sciencedirect.com/science/article/pii/S1877050921002258

Perelman J, Soares M; Mateus C, Duarte A, Faria R, Ferreira L, Saramago P, Veiga P. 2022. “Orientações metodológicas para estudos de avaliação económica de tecnologias de saúde” https://www.infarmed.pt/documents/15786/4001413/Orientações+metodológicas+para+estudos+de+avaliação+económica+de+tecnologias+de+saúde/736f57a0-fa36-5e3e-65ae-00730de4dac9

Perna, Cangini, Marini, Guerrizio, Da Cas, Traversa & Trotta. 2023. “Dynamics of price competition in Italian pharmaceutical off-patent market” https://www.frontiersin.org/articles/10.3389/fmed.2022.1045374/full

Pharma.be. 2021. “Communiqué de presse - Une étude récente démontre l'impact positif des médicaments sur les patients et la société”. https://pharma.be/fr/medias/actualites/communique-de-presse-une-etude-recente-demontre-limpact-positif-des-medicaments-sur-les-patients-et-la-societe

Pharma.be. 2021. “Le secteur bio-pharmaceutique Belge: Acteur phare de l’écosystème innovant. ” https://pharma.be/sites/default/files/2022-06/pharma-figures2021-fr.pdf

Pharma.be. 2021. “Report to Society 2021”. https://pharma.be/sites/default/files/2021-12/pharma_ReportTS2021ENG_FINAL.pdf

Pharma.be. 2022. “Les médicaments innovants nécessitent une réglementation innovante”. https://pharma.be/fr/medias/actualites/les-medicaments-innovants-necessitent-une-reglementation-innovante

Pharma.be. 2022. “ Les produits originaux, les génériques et les biosimilaires sont tout aussi bon marché”. https://pharma.be/fr/medias/actualites/les-produits-originaux-les-generiques-et-les-biosimilaires-sont-tout-aussi-bon-marche

Pharma.be. 2023. “Belgium: the (bio)pharmaceutical innovation hub in the heart of Europe”. https://pharma.be/sites/default/files/2021-11/20190201_brochure_europa_en.pdf

Pharma.be. 2023. “Sans brevets, pas d’innovation”. https://pharma.be/fr/medias/actualites/sans-brevets-pas-dinnovation

Pharma.be. 2023. “Prix et remboursement des médicaments remboursables”. https://pharma.be/sites/default/files/2023-06/prix-et-remboursement_fr_def.pdf

Pharma Boardroom. 2022. “Regulatory, Pricing and Reimbursement Overview/Italy”. https://pharmaboardroom.com/legal-articles/regulatory-pricing-and-reimbursement-overview-italy/

Pharmexcil.2020. “Italy pharma market & regulatory report” https://pharmexcil.com/uploads/countryreports/Italy_Market_Regulatory_report2020.pdf

Portela C. 2009. “Reference pricing system and competition: Case study from Portugal” https://pubmed.ncbi.nlm.nih.gov/19839066/

Prada, Ruggeri, Sansone, De Fazio, Tettamanti, Mantonvani. 2017. “Timeline of authorisation nd reimbursement for oncology drugs in Italy in the last 3 years”. https://www.intexo.it/wp-content/uploads/2017/04/MAAPOC-D-16-00013-3.pdf

Projections of health expenditure. 2019. “In *Health at a glance”*. https://doi.org/10.1787/3d1e710c-en

PWC. 2013. “Managing Innovation in pharma” www.pwc.com/innovationsurvey

Russo, Marcellusi, Zanuzzi, Favato, Staniscia, Romano. 2021. “Drug Prices and Value of Oncology Drugs in Italy”. https://www.valueinhealthjournal.com/article/S1098-3015(21)01527-8/fulltext

SIB Società Italiana Brevetti. 2023. “Italian Patents”. https://www.sib.it/en/patents/inventions-insights/patents/italian-patents/

Simmons & Simmons. 2020. “Italy sets new criteria for drug pricing and reimbursement”. https://www.simmons-simmons.com/en/publications/ckf6tbn0fht4r0a25zveyo6oh/italy-sets-new-criteria-for-drug-pricing-and-reimbursement

Statista. 2023. "*Belgium: carbon dioxide emissions 1970-2022"*.

https://www.statista.com/statistics/449509/co2-emissions-belgium/

Statista. 2023. "Share of patent applications from Belgium to the EPO in 2022, by field of technology". https://www.statista.com/statistics/413010/share-of-european-patent-applications-by-technology-field-belgium/

Statista. 2023. *"Top European pharma and biotech companies by market cap 2023"*

https://www.statista.com/statistics/443621/market-value-leading- pharmaceutical-biotechnology-companies-europe/

Studio Brevetti Turini. 2023. "The Italian Patent: Preliminary Choices".

https://ufficiobrevetti.it/en/patents/the-italian-patent/#preliminary-choices

The Economist. 2015. "Value-based Health Assessment in Italy: A decentralised model".

https://www.gimbe.org/report_attivita/pubblicazioni/interviste/20150706-the_economist.pdf

Upadhyaya, P. 2023. "How Patents Help Protect Pharmaceutical Innovation".

https://sagaciousresearch.com/blog/patents-protect-pharmaceutical-innovation/

Van Wilder, P. 2021. The Off-Patent Biological market in Belgium: Is the health system creating a hurdle to fair market competition?". *Pharmaceuticals*, *14*(4), 352.

https://doi.org/10.3390/ph14040352

Vieira J, Frade R, Ascenso R et la. 2021. “Determinants of internationalization as levers of sustainability: A study of the Portuguese pharmaceutical study” https://www.mdpi.com/2071-1050/13/17/9792

Vogler S, Dedet G, Pedersen H. 2019. “Financial Burden of prescribed medicines included in outpatient benefits package schemes: Comparative analysis of co-payments for reimbursable medicines in European countries” https://link.springer.com/article/10.1007/s40258-019-00509-z

Vogler, Sabine, Nina Zimmermann, Manuel Alexander Haasis, Margit Gombocz, Valentin Kandler, and Romana Landauer. 2018. “Pharmaceutical Pricing and Reimbursement Policies in 47 PPRI Network Member Countries Authors.” https://ppri.goeg.at.

Walker, A. 2023. “Pharmaceutical Patents: an overview”. https://www.alacrita.com/blog/pharmaceutical-patents-an-overview

Zuccato, Fanelli, Castiglioni, Bagnati. 2006. “Pharmaceuticals in the Environment in Italy: Causes, Occurrence, Effects and Control”. https://www.researchgate.net/publication/7355579_Pharmaceuticals_in_the_Environment_in_Italy_Causes_Occurrence_Effects_and_Control