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THESIS

PHARMACEUTICAL SUPPLY CHAIN– NEW OBSTACLES AND CHALLENGES

BY

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It is submitted in partial fulfillment of the requirements for the Master of Science in healthcare management.

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DEDICATIONS

Dedicated

to

my family and friends for their support and encouragement.

ACKNOWLEDGMENT

I would like to express my sincere gratitude to all those who have contributed to the completion of this master's thesis. Their support and guidance have been invaluable throughout this journey.

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ABSTRACT:

***Background**:* In any health system, the provision of medicine is one of the highest priorities, and any medication shortage could significantly impact the patient's health and cost. Thus, healthcare organizations must take all necessary steps to prevent and manage medication shortages. This includes having a plan in place to identify and address potential challenges and obstacles within the pharmaceutical supply chain. Downstream domains of PSC (suppliers, wholesalers, community pharmacies, hospital pharmacies, and patients), are major players in the drug supply chain and are subject to many challenges and obstacles. These challenges disrupt the supply of medicine in many ways such as their quantity and quality and their delivery to the right place and customers and at the right time. Therefore, challenges and obstacles identified in pharmaceutical companies' supply processes and mitigated are highly recommended.

***Purpose**:* This thesis aims to investigate and analyze the challenges and obstacles faced in the pharmaceutical supply chain from the perspective of suppliers, wholesalers, pharmacies, and patients. By examining these issues, the study aims to contribute to a better understanding of the complexities associated with the pharmaceutical industry and provide insights into potential strategies for overcoming these challenges and developing more robust and resilient supply chain strategies.

***Materials and Methods**:* As part of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol, this scoping review gathered research manuscripts that described challenges and obstacles related to pharmaceutical supply chain management. To conduct this study, a systematic and structured literature review was carried out using several online databases, including PubMed and Google Scholar. A review of more than 200 online articles was conducted after assessing for relevance in a four-step process of comparing the title, abstract, and full text against stipulated criteria for inclusion and exclusion to identify the most significant obstacles and challenges facing the pharmaceutical supply chain currently. In addition, the search was limited to the English language and within the last 10 years.

***Results**:* A comprehensive study of 55 articles has carefully examined the recent challenges in the pharmaceutical supply chain (PSC). The findings highlight various areas that require attention to optimize the PSC's efficiency and effectiveness. The first significant challenge identified is inventory management, which constitutes 34.54% of the overall articles. Ensuring accurate demand prediction and forecasting is the second-

most pressing challenge, accounting for 25.45% of the articles. Waste management and environmental issues are also critical concerns, which account for the same percentage of 25.45% of the identified articles. Another key area of focus is the lack of coordination and communication issues, which represent, 20.00% of selected articles. Lack of risk management is present in 16.36% of the studied articles. Lastly, complexity issues are also prevalent, making up 14.54% of the identified articles. These findings shed light on the crucial areas that demand immediate attention and effective strategies to overcome the obstacles and challenges faced in the pharmaceutical supply chain.

Keywords: Pharmaceutical supply chain; Challenges and obstacles; Downstream supply chain; Drug shortage; Healthcare.

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LIST OF ABBREVIATIONS

AI, API Active Pharmaceutical Ingredient

ASHP American Society of Health-System/ Hospital Pharmacists

CLM Council of Logistics Management

CMO Contract manufacturing organizations

CP Community Pharmacist

CSCMP Council of Supply Chain Management Professionals

EOF Greek National Organization for Medicines

EOPYY The National Organization for Healthcare Provision

ESP Environmentally sensitive product

EU European Union

FDA Food and Drug Administration

FEFO First-Expired-First-Out

FY Fiscal year

GP General practitioner

GPS Global Positioning System

GSCM Green Supply Chain Management

HR Human Recourses

IoT Internet-of-Things

IQVIA International Quality and Value Institute Advisors

IT Informational Technology

JIT Just in Time

LMP Locally Manufactured Products

MAD Mean Absolute Deviation

MAPE Mean Absolute Percentage Error

MIIR Mellon Institute of Industrial Research

MSE Mean Square Error

NGO Non-Governmental Organization

NP Nurse practitioner

OM Operational Management

PBM Pharmacy Benefit Manager

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PSC Pharmaceutical supply chain

R&D Research and Development

RFID Radio Frequency Identification

RL Reverse Logistics

SC Supply Chain

SCIS Supply Chain Information System

SCM Supply Chain Management

SS Safety Stock

TPS Toyota Production System

US United States

UUDIS University of Utah Drug Information Services

WD Wholesalers/Distributors

WHO World Health Organization

CHAPTER 1: INTRODUCTION

1.1. Purpose and Objectives

In the pharmaceutical industry, the supply chain plays a crucial role in ensuring the availability, affordability, and quality of medicines to patients worldwide. However, this complex network of activities faces numerous challenges and obstacles that need to be addressed for the efficient functioning of the pharmaceutical supply chain.

This means, any disruptions in the supply chain can hinder the timely delivery of medications to patients. Thus, the issue of medication shortages has become a growing concern for patients as well as healthcare providers. As the demand for certain medications continues to rise, the supply often falls short, resulting in significant disruptions to patient care.

The purpose of this master thesis is to investigate and analyze the challenges and obstacles faced in the pharmaceutical supply chain. As the pharmaceutical industry operates within a complex and highly regulated environment, making the supply chain susceptible to various challenges. This research aims to identify and analyze these challenges, with the ultimate objective of proposing strategies to overcome them.

By understanding the obstacles that hinder the efficiency and effectiveness of the pharmaceutical supply chain, this thesis seeks to contribute to the improvement of supply chain management practices in the industry. The findings of this thesis will help pharmaceutical companies and supply chain stakeholders better understand the complexities and unique challenges of the pharmaceutical supply chain and develop more robust and resilient supply chain strategies.

The objectives of the research study are identified as the following:

- Identify the concepts of supply chain management and pharmaceutical supply chains.
- Clarify the main activities, actors, types, and characteristic of PSC.
- Explain the current Greek pharmaceutical supply chain in terms of production, revenue, research and development, sales, and number of pharmacies and wholesalers.
- Illustrate the recent obstacles and challenges of PSC, especially in the downstream domain.

1.2. Thesis Structure

To find the answer and to understand the challenges and obstacles of PSC, this work is structured into five chapters. Specifically, in Chapter 1, the objectives of the present work and the methodology are developed and followed to collect all necessary information.

In Chapter 2, the literature review is conducted, and the concept of supply chain Management and the pharmaceutical supply chain are defined. The structure and operation of the supply chain are described in particular in the area of care. Moreover, types of SCM and integration of the supply chain are illustrated. More importantly, this chapter analyses the main activities related to SCM.

Then, in Chapter 3, it is clarified what the main characteristics are that distinguish pharmaceutical products and the pharmaceutical industry from other industries and products. Secondly, the role of the key players or stakeholders in the pharmaceutical supply chain will be analyzed. Using statistics, we will explain the current Greek pharmaceutical supply chain in terms of production, revenue, research and development, sales, and the number of pharmacies and wholesalers. Finally, we will explore the phenomenon of drug shortages and the role of PSCs in this regard.

In Chapter 4, the recent obstacles and challenges of PSC are illustrated in depth after analyzing and studying many articles from different scientific websites, such as PubMed and Google Scholar. In pharmaceutical supply chains, manufacturers, distributors, central pharmacies, hospital pharmacies, and hospital care services are all involved. As this chain is complex and diverse, we mainly focus on the main challenges and obstacles within the downstream part (suppliers, retailers, central pharmacies, hospital pharmacies, and care services).

Finally, in Chapter 5, the conclusions and proposals of this research are presented.

1.3. Methodology

A systematic review is a rigorous and structured approach to gathering, analyzing, and synthesizing existing research studies related to pharmaceutical supply chain challenges and obstacles. A systematic review methodology is an invaluable tool that enables researchers to assess the available evidence comprehensively. This document aims to provide an extended description of the systematic review methodology employed to investigate the challenges and obstacles faced by pharmaceutical supply chains.

The first step in conducting a systematic review is defining a clear and focused research question. In the case of pharmaceutical supply chain challenges and obstacles, the research question was: "What are the major challenges and obstacles faced by pharmaceutical supply chains, especially downstream supply chains, in the contemporary healthcare landscape?"

After selecting the main thesis question, establishing the criteria for selecting relevant studies were defined. The inclusion criteria include studies published between 2012 and 2022, written in the English language. For the purpose of collecting data, systematic search strategies were employed across multiple databases, such as PubMed and Google Scholar, in addition to the search for grey literature, such as conference proceedings and reports from relevant organizations. The search process was involved using a combination of keywords and advanced search operators to retrieve relevant articles. Searching through databases was done with different keywords: *Pharmaceutical supply chain* AND *challenges* OR *obstacles*, *ideal pharmaceutical supply chain* AND *barriers*. The words “pharmaceuticals”, “medicines”, and “drugs” have the same meaning and were used interchangeably to refine the search results.

Once the initial search is completed, the screening process begins. This involves reviewing the titles and abstracts of the retrieved articles to identify potentially relevant studies. Based on the predefined inclusion and exclusion criteria, the full-text articles in detail for more than 200 articles were assessed. Studies meeting the criteria were selected for further analysis.

Then relevant data from the selected studies was extracted and organized and the findings were analyzed and interpreted. This involves summarizing the key challenges

and obstacles identified in the selected studies and exploring potential explanations or underlying factors.

The final step involved writing a comprehensive report of the systematic review, adhering to established reporting guidelines such as Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) as illustrated is Figure (1) and Table (1).

Figure (1): The steps of selecting the articles using the PRISMA flowchart.

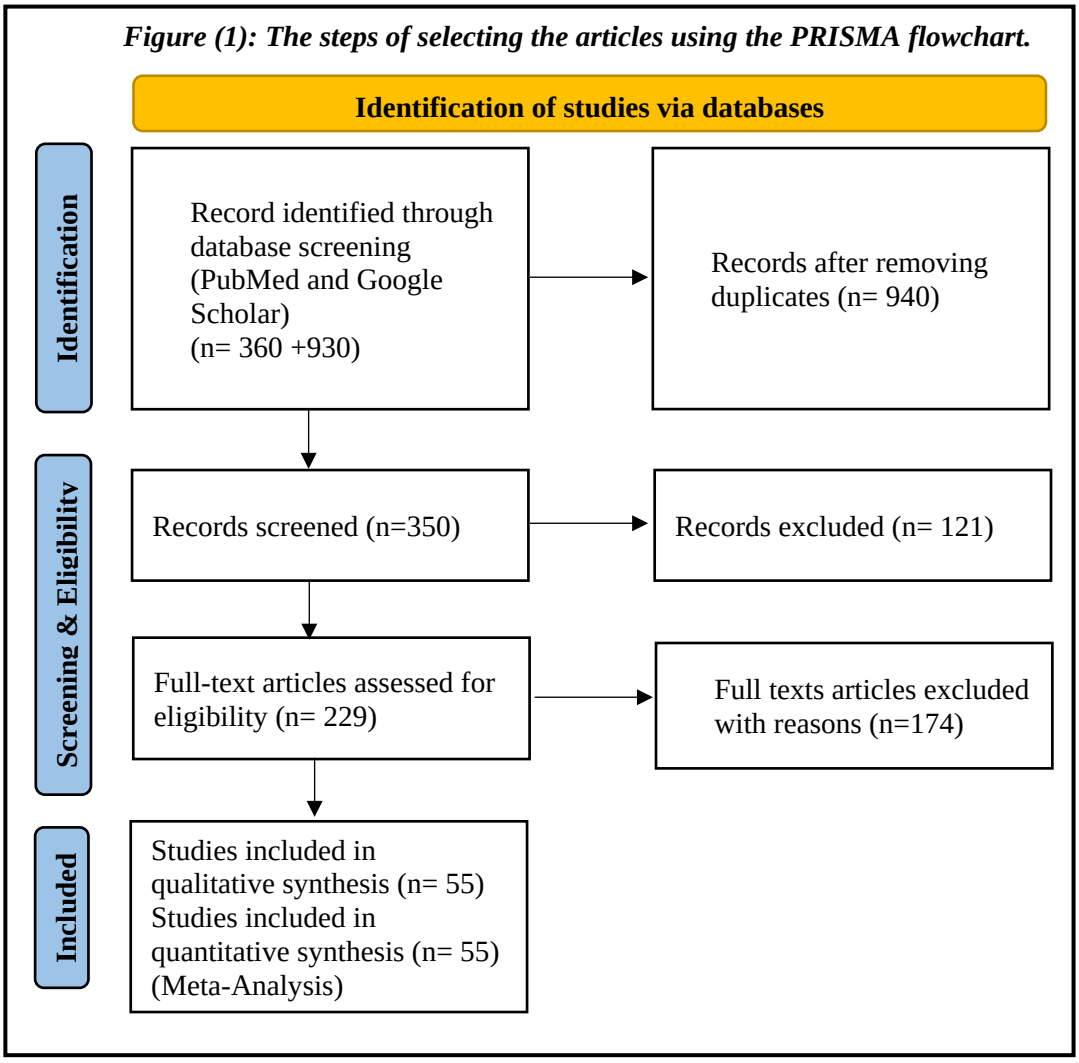
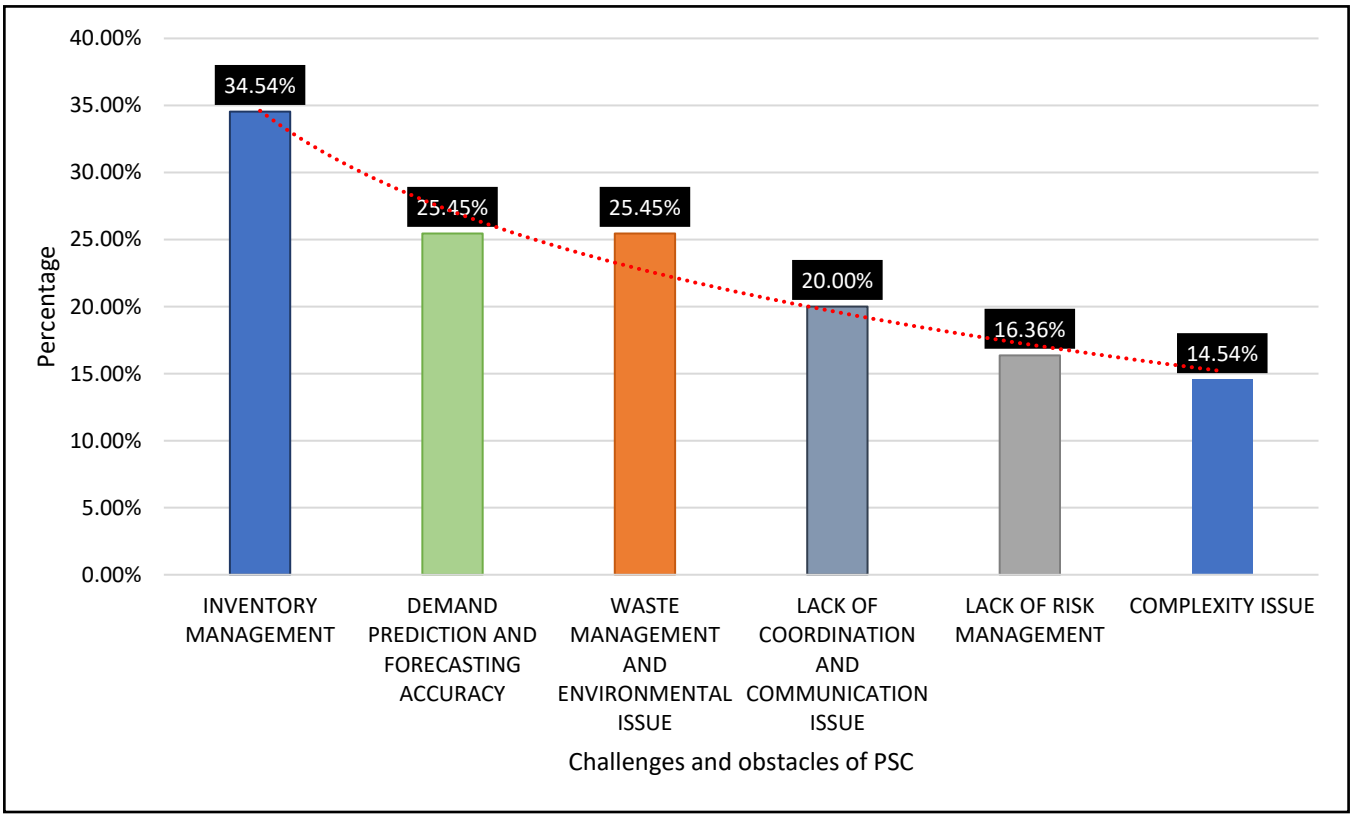


Table 1: Reported challenges with source of studies

CHALLENGES	FREQUENCY	%	AUTHORS
INVENTORY MANAGEMENT	19	34.54%	(Papalexi, et al., 2015) (Candan & Yazgan, 2016) (Bhakoo, et al., 2012) (Niakan & Rahimi, 2015) (Nematollahi, et al., 2018) (Emmett, 2019) (Shukar, et al., 2021) (Gupta & Huang, 2013) (Sarkis, et al., 2021) (SRAI, et al., 2015) (Spieske, et al., 2022) (Campling, et al., 2022) (Azghandi, et al., 2018) (Uthayakumar & Priyan, 2013) (Papalexi, et al., 2022) (Shah, 2014) (Rajesh, et al., 2016) (Moosivand, et al., 2019) (Privett & Gonsalvez,, 2014)
DEMAND PREDICTION AND FORECASTING ACCURACY	14	25.45%	(Moktadir, et al., 2018) (Merkuryeva, et al., 2019) (Zhu, et al., 2021) (Phuong, et al., 2019) (Shukar, et al., 2021) (Yousefi & Alibabaei, 2015) (Campling, et al., 2022) (Fadaki, et al., 2019) (Papalexi, et al., 2022) (Shah, 2014) (Moosivand, et al., 2019) (Sadraoui & Mchirgui, 2014) (Privett & Gonsalvez,, 2014) (Dobrzykowski, 2019)
WASTE MANAGEMENT AND ENVIRONMENTAL ISSUE	14	25.45%	(Kongar, et al., 2015) (Xie & Breen, 2012) (Hui, et al., 2020) (Verma & Gangele, 2012) (Papalexi , et al., 2019) (Windfeld & Brooks, 2015) (Papalexi, et al., 2022) (Gebremariam, et al., 2019) (Rajesh, et al., 2016) (Bungau, et al., 2018) (Privett & Gonsalvez,, 2014) (Weraikat, et al., 2015) (Wang, et al., 2015) (Deshmukh & Vasudevan, 2014)
LACK OF COORDINATION AND COMMUNICATION ISSUE	11	20.00%	(Edwards, et al., 2021) (Regin, et al., 2022) (Privett & Gonsalvez,, 2014) (Costantino, 2021) (Torres, 2019) (Nematollahi, et al., 2018) (Abdallah, 2013) (Campling, et al., 2022) (Papalexi , et al., 2019) (Bamford, et al., 2015) (Papalexi, et al., 2022)
LACK OF RISK MANAGEMENT	9	16.36%	(Ghatari, et al., 2013) (Mehralian, et al., 2012) (Grida, et al., 2020) (Kamath, et al., 2012) (Wang & Jie, 2019) (Jaberidoost, et al., 2015) (Jaberidoost, et al., 2013) (Sreedharan & Kamala, 2019) (Socal, et al., 2021)
COMPLEXITY ISSUE	8	14.54%	(Bhakoo, et al., 2012) (Utiger & Mencer, 2017) (Sarkis, et al., 2021) (Campling, et al., 2022) (Papalexi , et al., 2019) (Tremblay, 2013) (Bamford, et al., 2015) (Papalexi, et al., 2022)
TOTAL	75		55

Figure (2): Percentage of challenges and obstacles of PSC found within selected articles.



1.4. Introduction

The pharmaceutical industry plays a critical role in ensuring the availability and accessibility of medications for individuals around the world and pharmaceutical supply chain is considered one of the major anchors to achieve this. However, numerous challenges and obstacles that hinder the smooth functioning of the pharmaceutical supply chain. These challenges include issues related to manufacturing, distribution, regulatory compliance, and the complex nature of global pharmaceutical markets. As a result, medication shortages have become a growing concern, impacting patient care and public health. This introduction aims to provide an overview of the importance of investigating challenges and obstacles faced by the pharmaceutical supply chain, as well as shed light on the alarming statistics related to medication shortages.

The pharmaceutical supply chain encompasses various stages, starting with the procurement of raw materials, through manufacturing and distribution, and ending with the delivery of medications to healthcare providers and patients. This intricate process involves numerous stakeholders, including pharmaceutical manufacturers, wholesalers, distributors, healthcare providers, and regulatory authorities. Each stage presents its own set of challenges and potential bottlenecks, creating a complex network that requires efficient coordination and management.

Given the complexity of the pharmaceutical supply chain, in this thesis, we will explore the significance of studying the challenges faced in the downstream part of the pharmaceutical supply chain. After a drug has been manufactured, the downstream part of the pharmaceutical supply chain has a particular importance for the availability of the medicine. Thus, understanding the challenges in the downstream part of the pharmaceutical supply chain is crucial for ensuring patient safety. Once medications leave the manufacturing facility, they pass through various intermediaries, such as wholesalers, distributors, and pharmacies, before reaching end consumers. Any disruption or inefficiency in this part of the supply chain can have serious consequences for the quality and availability of medications. By studying and addressing these challenges, we can minimize the risk of counterfeits, shortages, tampering, or other quality issues that may compromise patient health.

Medication shortages have emerged as a critical issue in recent years, posing a threat to patient health and well-being. According to statistics from the American

Society of Health-System Pharmacists (ASHP), the number of reported medication shortages has been steadily increasing. In 2019 alone, there were 166 new shortages reported, impacting a wide range of medications, including antibiotics, chemotherapy drugs, and sterile injectables. These shortages not only affect patients' access to essential medications but also place an additional burden on healthcare providers, who must find the main root cause of medication shortages (API, 2023).

Medication shortages are a result of various factors. Some of the main causes include manufacturing disruptions, increased demand, political and ethical issues, and, most importantly, supply chain management. Hence, the role of supply chain management is crucial in ensuring the availability of medicine. Efficient and effective management of the entire supply chain, including procurement, storage, and distribution, is vital to ensuring a steady supply of medicines.

Additionally, supply chain management plays a vital role in preventing drug shortages by proactively identifying potential bottlenecks and taking steps to mitigate them effectively. Consequently, this research aims to identify and address the challenges that the pharmaceutical supply chain is facing, focusing on the downstream part. This will streamline processes, reduce waste, and ultimately lower the overall cost of medication delivery. This can have a significant impact on healthcare systems, making medications more affordable and accessible to patients in need.

CHAPTER 2 – LITERATURE REVIEW

2.1. Definitions

2.1.1. Concept of Supply Chain Management

There are several definitions of supply chain management in the literature, and there is still a lack of a unitary and widely accepted definition. The fundamental cause of this is the SCM concept's broad breadth, which can be viewed from many different viewpoints, such as purchasing and supply, logistics and transportation, industrial organization, marketing, strategic management, and many others (Croom et al., 2000; Cigolini et al., 2004).

Handfield and Nicholas (2002) explain that the term "supply chain" refers to all businesses and activities involved in moving products from their initial condition as raw materials to their final destination, including information movement. In other words, a supply chain includes the entire process, including internal and external functions of a company, that enables the value chain to produce goods and offer services to final customers (APICS Dictionary, 2013).

The supply chain is a network of entities through which materials move. These entities may consist of suppliers, transporters, factories, warehouses, retail stores, and clients (Lummus & Alber, 1997). Moreover, Quinn (1997) defines the supply chain as "*all of those activities associated with moving goods from the raw-materials stage through to the end user. This includes sourcing and procurement, production scheduling, order processing, inventory management, transportation, warehousing, and customer service. Importantly, it also embodies the information systems so necessary to monitor all of those activities*."

The emergence of supply chain management started when issues of mass manufacturing appeared throughout the 1950s and 1960s, which manufacturing applied to reduce unit production costs with limited flexibility in terms of products or production methods (Farmer, 1997). In addition, there seems to have been little focus on cooperative and strategic buyer-supplier partnerships since sharing technology and experience with customers or suppliers was seen as too dangerous and unethical (Sadraoui & Mchirgui, 2014).

Management became aware of the effects of significant work-in-process on manufacturing cost, quality, new product development, and delivery lead time during the

introduction of manufacturing resource planning in the 1970s. The idea of supply chain management (SCM) arose in the 1980s when manufacturers started to see the potential value and significance of a strategic and cooperative buyer-supplier relationship in the fast-paced Just in Time (JIT) manufacturing environment where there was minimal inventory to cushion production or schedule difficulties to provide affordable, dependable goods with more design flexibility (Sadraoui & Mchirgui, 2014; Farmer, 1997).

Together with procurement specialists, experts in logistics and transportation expanded the idea of materials management to include the logistics of physical distribution and transportation, giving rise to the idea of integrated logistics, often known as supply chain management. During the 1990s, the evolution of supply chain management proceeded by expanding best practices in value chain management among organizations, including supplier efficiency, quality control, and customer-centered vision (Sadraoui & Mchirgui, 2014).

There are many definitions of a supply chain since supply chain management is a wide concept that has gained popularity over the past few years and whose meanings may range greatly according to the context (Lummus & Vokurka, 1999). The following is the definition of SCM created and utilized by the Global Supply Chain Forum members: "*Supply Chain Management is the integration of key business processes from the end user through original suppliers that provide products, services, and information that add value for customers and other stakeholders*" (Lambert, et al., 1998; Lambert & Cooper, 2000). Although there are many different ways to describe supply chain management, they ultimately boil down to the need for improved cooperation amongst supply chain participants to generate more value. There are many participants in the total supply chain, and each one plays a part in achieving the end result. The ultimate objective is to efficiently satisfy the demands and expectations of the consumer.

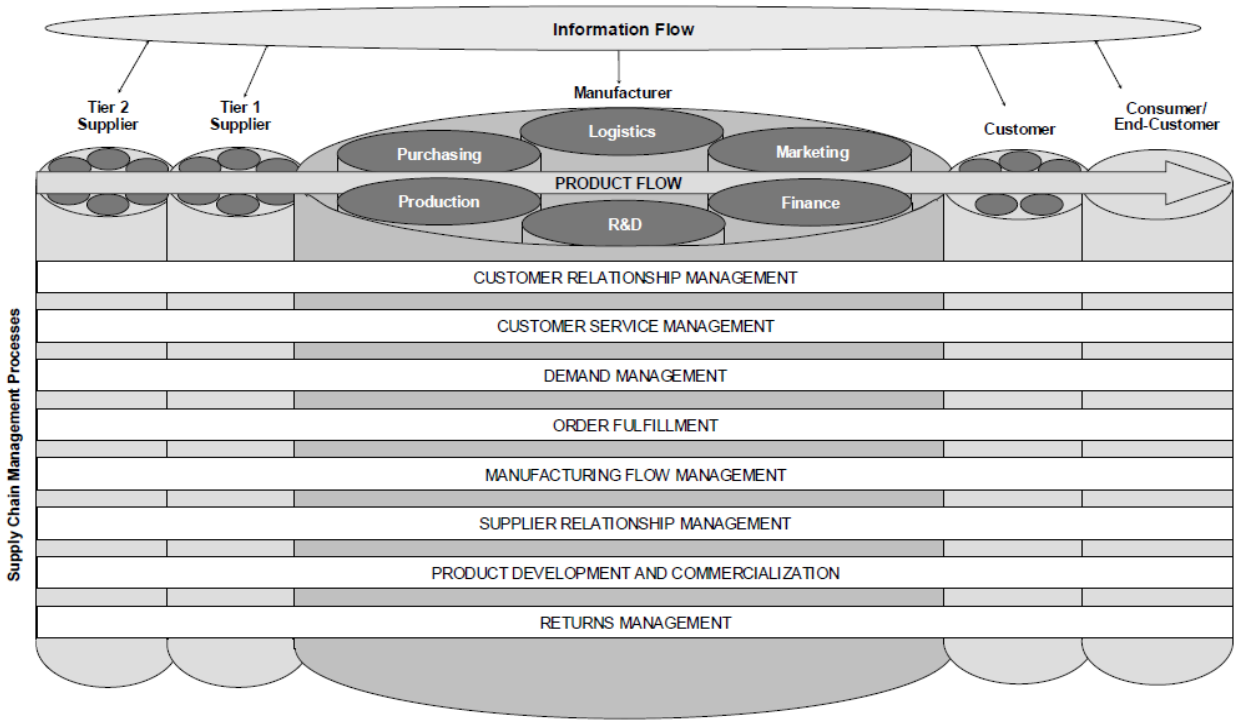
Logistics and supply chain management are frequently conflated. While supply chain management focuses on the external interactions between the actors in the whole supply chain, logistics management is centered on the need to increase the efficiency of each business's logistics system through internal and external planning and control. SCM provides a broader view of the entire supply chain than logistics since its objective is to enhance commerce generally (Lambert, et al., 1998). In October 1998, the Council of Logistics Management (CLM) announced a revised definition of logistics based on the increasing difference between SCM and logistics. "*Logistics is that part of*

the supply chain process that plans, implements, and controls the efficient, effective flow and storage of goods, services, and related information from the point-of-origin to the point-of-consumption in order to meet customers' requirements" [www.CLM1.org].

Supply chain management (SCM), according to the Council of Supply Chain Management Professionals (CSCMP), "*encompasses the planning and management of all activities involved in sourcing, procurement, conversion, and logistics management. It also includes the crucial components of coordination and collaboration with channel partners, which can be suppliers, intermediaries, third-party service providers, and customers*" [www.cscmp.org].

Figure (3) clarifies the comprehensive view of supply chain management and how business processes are integrated and managed across the supply chain, according to Lambert, et al. (1998).

Figure (3): Supply Chain Management: Integrating and Managing Business Processes Across Supply



Source: (Lambert, et al., 1998).

2.1.2. Concept of Pharmaceutical Supply Chain

Narayana et al. (2014) demonstrate that pharmaceutical supply chain, drug distribution, and medicine logistics refer to the movement of materials in the pharmaceutical industry's manufacture and distribution. These terminologies have been utilized in more studies over the past few years. This reveals the growing understanding of the supply chain as a system with traits that characterize the problems and complexity in the pharmaceutical sector.

According to academic experts and practitioners, pharmaceuticals are distinct from other commodities. As a result, producing, transporting, and consuming medications are considered part of a unique supply chain called the pharmaceutical supply chain (PSC) (Savage, et al., 2006).

In the view of Handfield & Nicholas (2002), a pharmaceutical supply chain (PSC) is defined as the "*integration of all activities associated with the flow and transformation of drugs from raw materials through to the end user, as well as associated information flows, through improved supply chain relationships to achieve a sustainable competitive advantage.*"

Based on Whewell (2009), the pharmaceutical supply chain includes a variety of healthcare services and related industries that support the efficient operation of the various phases of medication research and development, production, distribution, and application. Due to the large number of markets, goods, procedures, and intermediaries it entails, the pharmaceutical and healthcare sectors are extremely complicated.

To put it another way, the PSC is relatively distinct from other physical item supply chains due to its importance, urgency, secure storage, safe movement, regulation, etc. In addition, PSC includes medication R&D, manufacture, distribution, and use through a variety of healthcare facilities and other businesses that support the efficient operation of these many stages. The supply chain also includes manufacturers and suppliers, transporters, warehouses, retailers, and other stakeholders that are involved in the transfer of goods, information, and money to meet customer demands (Moktadir, et al., 2018).

2.2. Structure of a supply chain

In the most basic model of a supply chain, a single product is routed through several businesses, each of which gives the product more value. The configurations of supply chains can take a very wide variety. Some, like the pharmaceutical supply chain, are quite long and complex, as materials are collected from many different suppliers and products are distributed to meet the demands of various consumer types, while others are relatively short and straightforward (Waters, 2007).

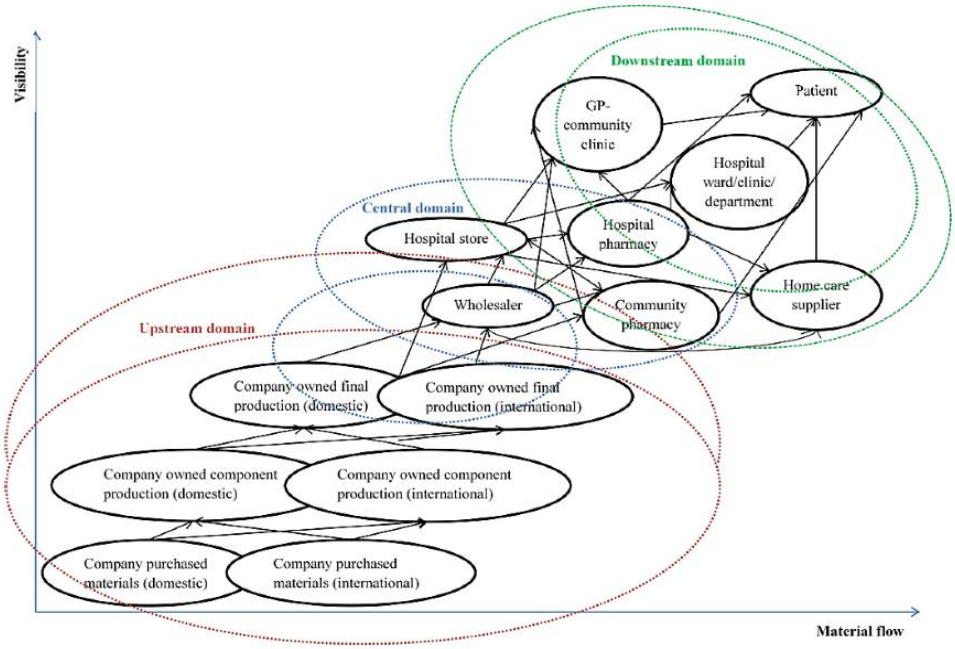
Due to the complexity of the supply chain, many companies divide their supply chain into two significant parts, which are the upstream and downstream supply chains. Christopher (2004) defines a supply chain as "the network of organizations that are involved, through upstream and downstream linkages, in the different processes and activities that produce value in the form of products and services in the hands of the ultimate consumer."

The upstream supply chain could refer to all activities in a supply chain that relate to an organization's supplier, so this would have everything to do with the manufacturing of the product. So upstream deals with the production capacity, the inventory levels, the scheduled delivery, and payment terms that have to do with purchasing and distributing a product into a warehouse. In brief, upstream is about the supply of the product and moving materials inward, and the pharmaceutical manufacturers that make the medications are usually the main stakeholders in the upstream domain of the PSC, although distributors and wholesalers may also be included (Waters, 2003).

The second part, the downstream supply chain, refers to activities that have to do with distributing and getting the product to the final consumers, involving everything from delivering the product to the warehouse to selling it to the customers. In sum, downstream is about the sales or demand of the product after manufacturing, moving materials outward (Waters, 2003).

Papalexi et al. (2019) illustrate the structure of the PSC conceptual model divided into three domains: upstream, central, and downstream (Figure 4).

Figure (4): A conceptual model of the PSC upstream, central, and downstream domains (Papalexi, et al., 2019)



2.3. Product Flow and information flow in PSC

Numerous studies have looked at the “traditional logistics” technique as a solution to smooth out material flow fluctuations and increase supply chain efficiency through the interfaces between channel players. This is mostly in the logistics and transportation sectors. Besides, they lowered inventory levels in the absence of more consideration for other interface activities, such as new product development and information flows. Nevertheless, the "modern logistics" school evolved to highlight the need for system-wide coordination of both physical and information flows; information is regarded as a critical method of providing all the players with the right feedback to drive their behavior. The emphasis of the research switched from simple cost reduction to encompassing service and quality improvement, and logistics became a widespread and unifying framework for SCM (Cigolini, et al., 2004).

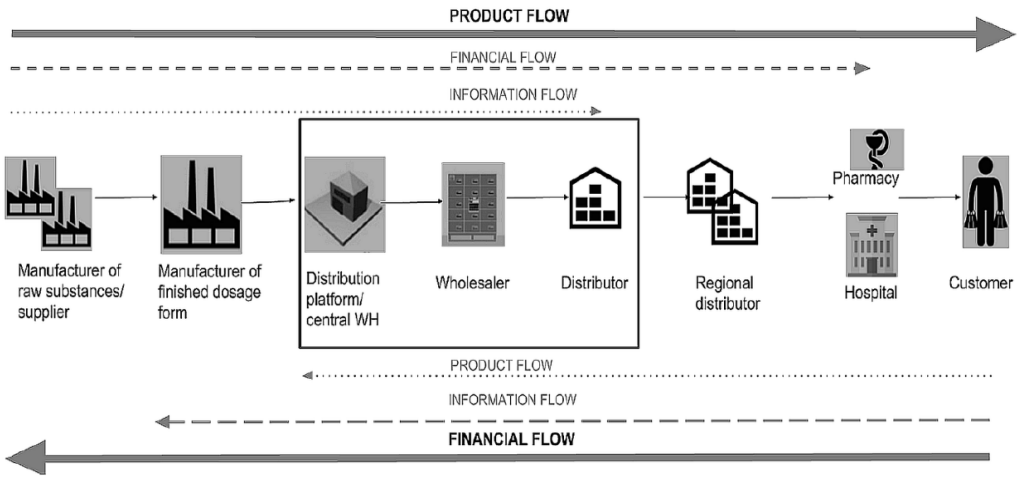
Therefore, the Council of Logistics Management highlights the combination of materials and information flow in their definition: *“Logistics is the process of planning, implementing, and controlling the efficient, cost-effective flow and storage of raw materials, in-process inventory, finished goods, and related information from point of origin to point of consumption to conform to customer requirements.*” The management

has concluded that adopting a process-based approach to the business is necessary to optimize product flows.

Members of the Global Supply Chain Forum recognized the following as the major supply chain processes: customer relationship management, customer service management, demand management, order fulfillment, manufacturing flow management, supplier relationship management, product development, and commercialization returns management (Lambert & Cooper, 2000; Cooper, et al., 1997; Lambert, et al., 1998). The network structure for sourcing, production, and distribution along the supply chain is referred to as the product flow facility structure (Cooper, et al., 1997; Lambert, et al., 1998).

In PSC, the main product is the medication or pharmaceutical preparation, which the World Health Organization (WHO) describes as "*any substance or mixture of substances manufactured, sold, offered for sale, or represented for use in the diagnosis, treatment, mitigation, or prevention of disease, an abnormal physical state, or the symptoms thereof in man or animal; [and for use in] restoring, correcting, or modifying organic functions in man or animal."* A typical pharmaceutical supply chain consists of various numbers of suppliers, consumers, and material flow throughout supply chains and several possible distribution lines make PSC not linear and complex in nature (Papalexi, et al., 2019).

Figure (5): Supply chain of pharmaceutical products. (Merkuryeva, et al., 2019)



Despite the complexity of the pharmaceutical supply chain, we will try to simplify the overall product flow process into several steps, according to Shah (2004):

1. Research and Development step: in this step, manufacturers invest in R&D to create new medication against a specific disease by testing thousands of less or more random chemicals, and the average time it takes for a possible new medicine to be registered is around 10 years. The proposed new medicine must subsequently undergo effectiveness and safety testing. This comprises a range of tests, initially for toxicity and subsequently for the capacity to treat disease and reduce symptoms. This sequence of actions, which is sometimes referred to as the development activity, normally takes 6–8 years (Shah, 2004).

Branded medication manufacturers are required to make investments in the new medicine's research and development, which can be expensive and involve significant risks. Yet, until the drug's patent expires, there are no rival products available once it is put on the market. To recover the expenditures associated with the R&D process, branded medicine makers have more control over the price of the drug during this time and profit from the absence of competitors on the market. So, the high unit price of the product is crucial for branded medicine makers to maximize profits.

2. Manufacturing (primary and secondary): The primary manufacturing site is responsible for the production of the active pharmaceutical ingredient (AI, API). It is distinguished by lengthy task processing durations, which are frequently rounded to numerous shifts. Before being permitted for use further along in the process, material from an intermediate stage frequently has to undergo some sort of quality control check. This can cause the system to delay even more. Many manufacturers are looking forward to outsourcing API production to contract manufacturers due to the complexity and lengthy manufacturing process, and as well as focusing more on developing existing medications and researching innovative ones. The supply chain becomes even longer and more complex due to the external involvement of suppliers and third parties, which also causes coordination issues. Mainly, raw materials for production are assumed to have been purchased from India or China.

Secondary manufacturers create the finished medicine by mixing and processing the API with inert components known as excipients. They are also in charge of the final product's processing and packaging. Depending on the final finished product (e.g.,

tablets, syringes, or capsules), different types of equipment and process adjustments are required, and the product will be produced in multiple locations (Shah, 2004).

3. Distribution: Upon the completion of production and packing, the product is moved to a market warehouse or distribution center, and from there, it is sent to a wholesaler. Wholesalers and retailers play a significant role in this sector.

4. Consuming: Ultimately, the medicine will be ready for commercialization and can be distributed to hospitals or retail pharmacies to reach the final consumers.

Previously, supply chain definition consisted of three steps: procurement, manufacturing, and distribution, which have since been simplified to three major flows: material, finances, and information. Information flow is seen as being the most significant since there can be no product flow without it (Yousefi & Alibabaei, 2015). Alongside the physical flow of materials is the associated flow of information. This links all parts of the supply chain, passing information about products, customer demand, materials to be moved, timing, stock levels, availability, problems, costs, service levels, and so on. The type of information shared and the frequency of information updates have a significant impact on the supply chain's effectiveness. This might be the first part to be integrated throughout all or a portion of the supply chain (Lambert, et al., 1998). Coordinating the flow of information can be very difficult, and logistics managers often describe themselves as processing information rather than moving goods (Waters, 2007). In order to ensure the accuracy of this information, it should be made freely available to those who require it, and only authorized parties should be able to modify it. Additionally, the information should be conducted in a manner that preserves all parties (King & Zhang, 2007).

As supply chain risks may be decreased via information management and exchange, it is essential for coordination and collaboration among supply chain participants. The key competitive advantage might be regarded as the supply chain information system (SCIS) (Yousefi & Alibabaei, 2015). To illustrate, a supply chain information system (SCIS) can help project future demand and facilitate effective planning, as well as coordinate all of the actions of all active components of a supply chain, including manufacturing, storage, and transportation. In addition, SCIS plays an important role in improving visibility and accuracy and facilitating the processing and availability of the supply chain, thus enhancing operational effectiveness, flexibility, and

efficiency, maximizing customer services, and lowering costs and issues (Yousefi & Alibabaei, 2015).

Information between internal and external consumers, suppliers, distributors, and other participants in a supply chain is coordinated using supply chain information systems (SCISs). In this regard, the information systems in supply chains can be separated into four levels: **1**. **Transaction level** (which initiates and records individual logistics activity data related to order management, order processing, preparations for distribution, transportation and shipping, and procurement). **2. Management control system level** (which emphasizes measuring performance, reporting, providing feedback, and identifying potential problems). **3. Decision analysis systems level** (which supports managers in identifying, assessing, and comparing various strategies and techniques). **4. Strategic planning systems** (which focus on information support systems to create and improve the supply chain strategy). So, to better organize and coordinate pharmaceutical and medical procedures, the health system uses a variety of software, information systems, and databases (Yousefi & Alibabaei, 2015).

2.4. Integration of supply chain

Systems for the supply chain vary depending on the various businesses, organizations, and industries (Wang & Jie, 2019). The level of competition has shifted from single enterprises to groups or chains of businesses due to the high complexity of goods and the consequent growth in outsourcing (Rice & Hoppe, 2001). Thus, supply chain management's strategic importance emerged as a source of competitive advantage. As a result, many organizations started to adopt taking the network as a whole and integrating all of the crucial business operations, from end users to original suppliers, to pursue global optimization as opposed to local optimization. Thus, increasing its competitive advantage (Cooper, et al., 1997; Lambert, et al., 1998).

The SCI phenomenon has mainly been highlighted as a way of integrating material coordination and smooth information flow between and among SC partners (Abdulmalek & Rajgopal, 2007). The "integrated process redesign" school investigates ways to restructure the whole supply system to achieve more effective and efficient flows of materials and information using quantitative models applied to a systemic perspective of the supply chain (Cigolini, et al., 2004). Integration is now widely regarded as the foundational element of a successful SCM and has grown to be a significant trend in SCM. According to Juanqiong et al. (2007), the word “integration” is defined as a process of redefining and connecting parts of a whole to form a new one

that is less "part" and more "whole" in its effect. The definitions of parts in traditional supply chain integration are frequently constrained by the borders of the businesses; instead, the emphasis is placed on linking each business with logistical and informational communications, as the supply chain is a dynamic, interconnected system where all businesses work together to optimize the whole chain.

SCM has several varying definitions and is frequently used to describe either a process-oriented management strategy for sourcing, manufacturing, and delivering products and services to end users or, in a broader sense, the coordination of the numerous players involved in the same supply chain. According to Harland (1996), cited in Cigolini et al. (2004), SCM is defined according to the Council of Logistics Management as the integration of material, information, and financial flows in a network of companies or organizations that make and transport products and services from the source to the consumer (Wang & Jie, 2019). As defined by Lambert & Cooper (2000), *supply chain management is the integration of key business processes from the end user through original suppliers that provide products, services, and information that add value for customers and other stakeholders.* The majority of business processes and functions, if not all of them, are engaged to accomplish the goal of integrated SCM (Cooper, et al., 1997).

From these definitions, we can realize the importance of the process integration from sourcing to manufacturing and distribution across the SC, business process integration within and across organizational environs, integration of information and knowledge sharing between SC partners, and activity integration into strategic SC processes in the successful implementation of SCM. Supply chain integration is rigorously related to collaboration mechanisms and, in particular, implies that business processes should be streamlined and connected both within and outside the company boundaries, especially for companies that depend extensively on external sources for their strategic operations, are obliged to concentrate on their core competencies, and required to engage in global competition (Romano, 2003). Thus, a supply chain that is genuinely integrated does more than just cut costs. Moreover, it generates value for the company's owners, consumers, and partners in the supply chain (Kamal & Irani, 2014).

Supply chain management, which aims to improve therapeutic results while containing costs, is frequently used to describe the information, suppliers, and finances associated with the procurement and transfer of goods and services from the supplier to the end user. A supply chain management strategy's fundamental premise is the notion

that strong coordination and integration across operational operations may result in improved supply chain performance (Vries & Huijsman, 2011). It is mentioned in the (Sadraoui & Mchirgui, 2014) article that Ragatz et al. (1997) pointed out that the "effective integration of suppliers into product value and supply chains will be a key factor for some manufacturers in achieving the improvements necessary to remain competitive".

Supply chain integration has been approached from different perspectives. For example, healthcare supply chain and pharmaceutical supply chain integration not only relates to the integration and coordination of processes that may refer to physical products (like pharmaceuticals, medical devices, and health aids) or processes associated with the flow of patients, but several kinds of integration can be used to describe integrated pharmaceutical and health supply chains, such as integration and coordination of information flows, planning processes, intra- and inter-organizational processes, and integration of market-approach. They can also be linked to joint "market development" and offering new "care-products".

It is important to mention that the coordination and integration of operational processes are directly related to information technology and the implementation of e-business. Electronic patient record systems are a well-known example of integrated information technology being used in health systems throughout the world (Vries & Huijsman, 2011).

2.5. Types of SC

2.5.1. Traditional supply chain

The traditional supply chain is defined as an integrated production process where raw materials are transformed into finished goods before being shipped to consumers (via distribution, retail, or both). Its modelling, research, and design have been largely focused on maximizing the distribution of products to consumers and the procurement of raw materials from suppliers (Beamon, 1999). Traditional supply chains aim to secure supply while achieving the lowest initial purchase prices. Informal discussions, suppliers' assessments based on purchase price, cost-based information bases, many suppliers, formal short-term contracts, and centralized purchasing are some common characteristics of a traditional supply chain. This may cause forecasts to be inaccurate and slow to adapt to changing market conditions (Deshmukh & Vasudevan, 2014; Spekman & Davis, 2004). Customer satisfaction, service, responsiveness, or cost are

considered performance measures to evaluate traditional supply chain effectiveness and efficiency (Beamon, 1999).

2.5.2. Lean Supply Chain

The Toyota Production System (TPS) is where the lean concept first emerged, and it focuses on eliminating all waste, including time, to ensure a level schedule. Lean refers to a set of procedures or ideas designed to remove non-value-added activities, eliminate waste, and enhance processes that generate value. Businesses have used strategies including total quality management, JIT, business process reengineering, and SCM to improve performance and gain an advantage in a highly competitive global market (Zaman & Ahsan, 2014; Soni & Kodali, 2011). The lean supply chain is defined as the supply chain that identifies all forms of waste in the supply chain's value stream and takes action to eradicate it and reduce lead times (Abdulmalek & Rajgopal, 2007; Zaman & Ahsan, 2014).

2.5.3. Agile Supply Chain

Agility is described as a business-wide competence that encompasses organizational structures, information systems, logistical procedures, and, in particular, attitudes to focus on sustaining strong productivity under pressure from unpredictability (Walter, 2021). By creating a seamless supply chain where all "players" think and act as one, an agile supply chain has been acknowledged as a competitive approach for businesses to survive and grow, especially in a volatile business environment where customer demands are becoming more dynamic and the frequency of environmental changes is increasing significantly. Thus, there is growing complexity and uncertainty in the market (Vinodh, 2010).

2.5.4. Leagile Supply chain

Leagile believes that for optimal SCM, a combination of lean and agile methodologies should be used at a decoupling point where the activities of order-driven and forecast-driven meet (Naylor, et al., 1999). Rachel et al. (2000) suggested that agility was employed downstream and leanness was used upstream of the supply chain's decoupling point. Leagile, therefore, enables the upstream chain's cost-effectiveness and the downstream chain's excellent service standards in a competitive market.

2.5.5. Green supply chain

The term "Green SC Management" (GSCM) first appeared in the late 1990s. It includes proactive operations like recycling, reclamation, remanufacturing, and reverse

logistics (RL), as well as the reactive monitoring of general environmental management initiatives (Zhu & Sarkis, 2004). Throughout the past 20 years, companies have used GSCM to reduce environmental hazards, improve ecological efficiency, and ultimately boost profit and market share (Van Hock & Erasmus, 2000).

Zhu and Sarkis (2004) defined four categories of GSCM approaches, including **eco-design** (or design for the environment, e.g., design of products for reduced consumption of material or energy, for reuse, recycling, recovery of material, and to avoid or reduce the use of hazardous products and/or their manufacturing process), **investment recovery** (sale of excess inventories or materials, scrap and used materials, and sale of excess capital equipment), **external GSCM** (e.g., supplier ISO 14000 certification, cooperation with suppliers for environmental objectives and with customers for eco-design, cleaner production, and for green packaging), and **internal environmental management** (e.g., managers Commitment and support for GSCM, total quality environmental management, and ISO 14001 certification are key to improving enterprises' performance.

These four GSCM practices are becoming the foundations of a strategic decision framework that aids managerial decision-making in selecting GSCM alternatives in the product life cycle, operational life cycle (including procurement, production, distribution, and RL), organizational performance measurements, and ecologically friendly business techniques (Zhu & Sarkis, 2004).

2.5.6. Reverse supply chain (Reverse Logistics, RL)

According to Rogers and Tibben-Lembke (1998), RL is defined as "*the process of planning, implementing, and controlling the efficient, cost-effective flow of raw materials, in-process inventory, finished goods, and related information from the point of consumption to the point of origin to recapture or create value or for proper disposal.*"

Reverse logistics includes processing damaged returns, seasonal inventory, restocks, salvage recalls, and surplus inventory. Also, it includes programs for recycling, remanufacturing, and refurbishment operations, handling hazardous materials, disposing of old equipment, and asset recovery (Rogers & Tibben-Lembke, 1998).

The RL network is considered one of the most significant operational functions that serve as a foundation for GSCM practices and one of the main resources required to facilitate product recycling (Zhu & Sarkis, 2004; Xie & Breen, 2012). In PSC, the RL

network encourages returning expired or unwanted medications to the manufacturer to remove the medication from circulation and the domestic environment for proper disposal or recycling. Thus, it lowers the risk of unintentional damage or deliberate product misuse and increases environmental protection. Additionally, RL provides valuable information about the efficiency of the medication prescription process and the quantity of dispensed medications, which can be used to manage future prescribing more efficiently. Hence, financial savings (Xie & Breen, 2012).

2.5.7. Cold supply chain

A cold supply chain is a type of supply chain with a controlled temperature from the stage of manufacture through the transportation stages, storage, distribution processes, and delivery to the end-user, especially for environmentally sensitive products (ESPs) such as food, medications, and others. Based on the type and characteristics of the product, their transportation is accomplished by refrigerated railcars, trucks, cargo ships, and air cargo (Rodrigue, 2020; Hosseini Bamakan, et al., 2021). Based on its direct impacts on public health and people's lives, the pharmaceutical cold chain in particular is a complex and sensitive chain that has to be controlled correctly, and pharmaceuticals' products are usually transported in cold packages that are arranged in pallets onboard aircraft (Hosseini Bamakan, et al., 2021).

2.5.8. Blockchain-based supply chain

Blockchain is an open, distributed online database ledger that is built sequentially and chronologically, and the network of computer servers records and validates it. These blocks are not centrally saved; rather, they are dispersed across several infrastructure nodes. Each block provides details on all system transactions throughout a specific period. For instance, the data contains the transaction details, the hash of the preceding block, and the timestamp of its creation (Esposito, et al., 2018). Supply chain management methods and business models are thought to benefit greatly from the use of blockchain (Helo & Hao, 2019).

A blockchain-based supply chain means applying blockchain technologies to track and contribute to all actions and operations in the supply chain, such as who is performing the actions, at what time, and where the location of each action is. (Kshetri, 2018). It is noteworthy that blockchain technology is well suited to address the challenges that supply chains face due to their complex structures, difficult tasks, and diversity of stakeholders, making it difficult to have an integrated view of the entire

supply chain. As a result, it is crucial to adopt blockchain technology to increase supply chain visibility and security (Helo & Hao, 2019; Chen, et al., 2018).

The supply chain, among the numerous activities that are expected to be revolutionized by blockchain, merits particular attention. The usage of Internet-of-Things (IoT) apps will be more frequent, which is one of the developments that will impact supply chain management (SCM). IoT, Radio Frequency Identification (RFID) tags, sensors, barcodes, Global Positioning System (GPS) tags, and chips allow for the tracking of items, shipments, and shipping containers at every stage of their journey. Therefore, a blockchain-based supply chain reduces the workload and enables better traceability of goods starting at their point of origin, while boosting efficiency, lowering costs, and boosting consumer trust that the goods are genuine and of exceptional quality (Kshetri, 2018).

2.6. SC-related activities

There are fundamentally two different sorts of supply chain decisions. The first is mostly strategic and creates the ideal chain structure. The second step focuses on implementation and identifies the most effective means to transfer materials throughout the chain (Waters, 2007). According to Waters's book (2007), this double role was summarized as "*logistics is both the glue that holds the materials/product pipeline together and the grease that speeds product flow along it*" (Harrington, 1996).

A SCM system integrates several tasks that are responsible for different parts of the material flow. Waters (2007) describes the main activities included:

Supply chain design is the strategic process that determines the ideal supply chain structure, including the number of participants, length, breadth, locations, systems employed, relationships, and more.

Location: Several locations can be used to complete some logistical tasks. Inventories of finished items, for instance, may be kept after manufacturing is complete, transferred to adjacent warehouses, placed in stores closer to clients, given to other businesses by third-parties to handle, or any number of other options. The optimum places for these activities should be found, or logistics could at least significantly influence the selections. It also takes into account relevant queries regarding the size and quantity of amenities. These are significant choices that have an impact on the supply chain's overall design.

***Procurement or purchasing*:** An organization's material flow typically begins when procurement delivers a purchase order to a supplier. In other words, procurement accomplishes everything required to bring items into the organization, including finding qualified suppliers, negotiating terms and conditions, organizing delivery, setting up insurance and payment, and more. This step considered the establishment of primary ties and an essential linkage with upstream processes.

Inward transport or traffic: This includes selecting the appropriate mode of transportation (road, rail, air, etc.) to move materials from suppliers to the organization's receiving area. Moreover, locating the best transport provider, planning the route, ensuring compliance with all safety and legal standards, obtaining delivery on schedule and at a fair price, and other factors are taken into consideration.

Receiving: performs the appropriate inspections and receives deliveries into the company by verifying that the items supplied match the order, acknowledging receipt, unloading delivery trucks, checking the materials for damage, and sorting them.

***Warehousing or stores*:** this includes moving goods into storage and looking after them until they are required. Pharmaceuticals and fume-emitting chemicals are considered commodities that require specific handling. Warehouse management ensures that products have the proper surroundings, care, and packaging to preserve their quality as well as their ability to be made immediately available when needed.

Stock control determines inventory policies. It takes into account the items to be stored, the total investment, customer service, stock levels, order quantities, timing, and processes, as well as purchasing patterns.

Material handling: this is a general concept for transferring items inside a company and between operations, and it also transports materials taken from shops to the location where they are required. The goal of material handling is to provide quick, efficient movements with minimum damage while employing the right tools, customized packaging, and handling when necessary.

Order picking is to remove materials from stores. The usual procedure is to find, identify, inspect, remove from racks, combine into a single load, assemble, and convey the materials for a client order to a departure location for loading onto delivery trucks.

Outward transport distributes materials to clients after taking them from the departure area (with concerns that are similar to inward transport).

Physical distribution management is the general term for all processes, including outward transportation, that bring finished goods to clients. It frequently

coordinates with marketing and serves as a crucial connection for actions that take place downstream.

Recycling, returns, and waste disposal: This process, also known as reverse logistics or reverse distribution, involves returning different kinds of goods to clients. For instance, there can be issues with items that were provided, whether they were defective, too many were delivered, or they were the incorrect type; therefore, they need to be retrieved and brought back. Pallets, delivery boxes, cable reels, and containers—the typical metal 20-foot-long boxes used to convey goods—and other related items are occasionally utilized again by suppliers. Metals, glass, paper, plastics, and oils are just a few examples of things that are sent back for recycling rather than being used again. Then there are items, like hazardous chemicals, that cannot be used again but are brought back for proper disposal.

***Communication*.** The linked flows of money and information go simultaneously with the flow of materials. Communication connects the supply chain by transmitting data about the goods, client demand, moving materials, timeliness, stock levels, availability, issues, costs, service levels, and so forth. Logistics managers frequently define themselves as processing information rather than moving things, since it may be exceedingly challenging to coordinate the flow of information. According to M. Christopher, "supply chain competitiveness is based upon the value-added flow of information" (Christopher, 2004).

Depending on the circumstances, several more actions may fall under the category of logistics. Organizations sometimes include sales forecasting, manufacturing planning, customer service administration, international relations, third-party activities, etc. Waters (2007) emphasizes the importance of understanding that every function must work in harmony with each other to ensure an efficient flow of materials.

In addition, Myerson (2012) explains that broadly, the supply chain is divided into five management processes with functional responsibilities by the Supply Chain Council [www.supply-chain.org, 2011]:

1. **Plan** (This includes all of the information involved in producing and exchanging data about customers, forecasts, and production required to ensure that supply matches demand throughout the supply chain.)

2. **Source** (relates to all processes for procurement of goods, including identifying, selecting, and measuring the performance of sources of supply, as well as delivering and receiving materials to meet demand).

3. **Make** (which refers to the transformation of raw materials into finished products).

4. **Deliver** (which consists of shipping, order management, and warehousing to accurately and efficiently move materials and goods along the supply chain, from suppliers to manufacturing and then to customers).

5. **Return** (which refers to the procedure used in reverse logistics for returning goods or materials, including maintenance, overhaul, and repairs).

These five management processes include a variety of functions, including risk management, asset management, inventory management, measurement management, performance measurement, business rules, and regulatory requirements.

CHAPTER 3-PHARMACEUTICAL SECTOR

3.1. Characteristics of the Pharmaceutical Sector

In the medical and health systems, the pharmaceutical industry is crucial in supplying life-saving medication to people (Yu, et al., 2010). The system of procedures, operations, and companies that are engaged in the discovery, development, and manufacture of pharmaceuticals is referred to as the pharmaceutical industry (Ghatari, et al., 2013). In addition, access to medications is considered an essential component of health care and a fundamental human right (Hogerzeil, 2006).

There are several characteristics that distinguish the pharmaceutical industry from other industries (Mcguire, et al., 2012). First, the pharmaceutical sector is becoming increasingly significant on a worldwide scale, generating a massive amount of revenue annually. In 2022, the total global pharmaceutical market was valued at 1.48 trillion U.S. dollars and is expected to reach USD 1.6 trillion by 2025 (IQVIA Institute, 2021; Mikulic, 2023). The pharmaceutical industry is led by the US, Europe, and Japan in terms of size contribution. These markets have driven a significant increase in the global demand for pharmaceutical products, which is likely to continue growing as these markets gain more and more prominence (Abdallah, 2013). A more vigorous pharmaceutical industry can contribute to national resilience, and improved health outcomes, particularly COVID-19 recovery, and economic growth.

Second, the research, development, and production of pharmaceuticals and treatments are all part of the pharmaceutical sector, which may be characterized as a complex of processes, operations, and organizations (Shah, 2004). The pharmaceutical industry can certainly be considered a dynamic and research-intensive industry for its role in the discovery of new drugs. There is no other industry investing as much in R&D projects (Schuhmacher, et al., 2016). Therefore, pharmaceuticals are special; they cannot be handled like other products. Reasons for this included the expensive and prolonged R&D process, as well as the direct impact on people's quality of life, which, in certain situations, can put their lives in danger when the medicine is not available on time (Savage, et al., 2006; Mehralian, et al., 2017).

Drug treatment is the most prevalent type of healthcare intervention (Savage, et al., 2006). The World Health Organization (WHO) defines a medication or drug as "*any substance or mixture of substances manufactured, sold, offered for sale, or represented for use in the diagnosis, treatment, mitigation, or prevention of disease, abnormal*

physical state, or the symptoms thereof in man or animal; [and for use in] restoring, correcting, or modifying organic functions in man or animal." (Shah, 2004; Abdallah, 2013). Pharmaceuticals and other health-related items are crucial for society, the government, companies, and healthcare system executives (Mehralian, et al., 2017).

Two market categories, ethical (prescription) and "over-the-counter" medicines, can be widely distinguished in the pharmaceutical sector. In the ethical segment, two separate supply chain components can be characterized, i.e., the pre-production (discovery) chain and the post-development (production) chain. These two parts combine to create a long and complicated supply chain that is challenging to analyze from a holistic standpoint. Nonetheless, the total procedure may present a considerable opportunity for increased productivity and increased product profitability (Savage, et al., 2006).

The third characteristic in the pharmaceutical industry is the asymmetric information between patients and doctors, which leads to the end user (patient) not choosing the medication, especially the ethical (prescribed) medicines, besides the potential for the patient to contribute to prescription charges. Therefore, in many countries, there is a complex interaction between the medical profession, governments, and insurance groups that pay many of the costs of this industry's products and are the main financial consumers of the country's government (Savage, et al., 2006; Mcguire, et al., 2012).

Additionally, the pharmaceutical sector is heavily regulated at all stages of manufacture and distribution. The scope of regulations extends to a wide range of operational aspects, including testing, quality control, auditing, production, final product requirements, raw material standards, packaging, etc. (Savage, et al., 2006). In addition to requiring price approvals, price regulation is important due to its impact on profits and the ability to reinvest in new research in the pharmaceutical industry, as well as its impact on healthcare costs (Mcguire, et al., 2012). Successful pharmaceutical companies follow these rules and sometimes add additional ones. The US, European, and Japanese pharmacopeias are the primary sources of rules. The majority of pharmaceutical companies that supply goods to international markets rely on these sources, which are often updated (Abdallah, 2013). Due to the particular nature of supply and demand, the pharmaceutical industry is highly controlled in many nations (Yu, et al., 2010).

Lastly, according to Shah (2004), the pharmaceutical industry is very complex as it involves challenges to coordination among multiple actors.

The main categories of players in the pharmaceutical industry are presented as follows:

1. the companies with several production facilities and Research and Development (R&D) centers for branded medication, both ethical/prescription and over-the-counter;
2. the generic manufacturers who produce over-the-counter and non-patent products;
3. local manufacturers working under a license or contract to produce both branded and generic goods in their own country;
4. Contract manufacturing organizations (CMO) that provide outsourcing services for the production of primary intermediates, active ingredients (AI), or final products but do not have their own product portfolio;
5. Biotechnology and drug discovery companies' start-ups with no significant manufacturing capacity;
6. the companies that provide components required for product manufacture but not included in pharmaceutical product composition (e.g., disposables, devices, equipment calibration standards);
7. the companies that offer outsourcing services for quality control;
8. companies that provide transportation when that service is outsourced.

Candan and Yazgan (2016) clarify that there is a great deal of complexity involved in the pharmaceutical supply chain when compared to other types of supply chains. In contrast to other sectors, the pharmaceutical supply chain is characterized by long setup times, resource-intensive operations, short shelf lives, and a high production of waste.

An important part of the health system is the pharmaceutical supply chain, which entails all processes, data, assets, and participants, including suppliers, manufacturers, intermediaries, third-party service providers, logistics activities, merchandising and sales activities, finance, and information technology (Shah, 2005; Jaberidoost, et al., 2013). Pharmaceutical supply chain structure is becoming more and more intricate, and pharmaceutical businesses are showing an increased interest in optimizing their supply

chains to reduce costs and, perhaps more importantly, obtain a competitive advantage (Savage, et al., 2006). One of the top issues in developing countries is the supply of medicines. Thus, effective pharmaceutical supply chain management is crucial. To achieve the objectives of the healthcare system, the pharmaceutical supply chain must offer medications in the right quantities, of acceptable quality, to the appropriate patients at the proper times, and at the lowest possible cost. It must also satisfy its stakeholders (Kaufmann, et al., 2005; Jaberidoost, et al., 2013). Breen (2008) illustrates that product discontinuity, product shortages, inferior performance, patient safety/dispensing mistakes, and technology errors all represent hazards of disruption in the pharmaceutical supply chain (Breen, 2008).

3.2. Players in PSC

The supply chain network is currently complex and fragmented in large part. This is because of the large number of actors (stakeholders) involved and the interconnected action steps or phases necessary to make medicines available and accessible. There are many resulting risks for those involved, such as high and multifaceted stakes, including firm profit, patient and public health, product satisfaction, firm reputation, and liability. The actors, actions, and aversions of pharmaceutical supply chains can also be studied in terms of the cost structure of R&D and the rapid technological changes characteristic of the pharmaceutical industry itself, which support product innovation, pricing, and distribution in the supply chain (Mendoza, 2021).

The main stakeholders in the drug supply chain are pharmaceutical companies (pharmaceutical manufacturers), wholesale distributors, pharmacy benefit managers (PBMs), pharmacies, whether retail pharmacies (usually dealing with short-term diseases), specialized pharmacies (focusing on complex and chronic diseases that require more hands-on care), or healthcare providers. mail and online pharmacy, etc., and of course consumers (The Health Strategies Consultancy LLC, 2005).

According to The Health Strategies Consultancy LLC (2005), the pharmaceutical supply chain has five fundamental main actors or stakeholders, as shown below, despite some minor variances from country to country and occasionally from product to product:

3.2.1. Pharmaceutical Manufacturers:

Two main business models constitute the pharmaceutical manufacturing sector: those of brand-name medication manufacturers (such as Pfizer, Merck, and Novartis) and those of generic drug manufacturers (e.g., Mylan, Roxane, and Barr). The manufacture and packaging of pharmaceutical products is the main emphasis of both the branded and generic sectors of the company.

The majority of branded product manufacturers allocate a percentage of their budget for scientific R&D to create new pharmacological treatments, which are the source of prescription drugs. In most cases, once the patent protection on the original branded medicine has expired, generic drug manufacturers produce a generic product that directly competes with the brand product rather than creating new treatments. Manufacturers are responsible for overseeing the actual distribution of medicines from manufacturing facilities to drug wholesalers and, in some situations, to hospital chains, mail-order and specialty pharmacies, government purchasers, and some health plans.

At the most fundamental level of economics, a pharmaceutical manufacturer often supplies a number of their goods equal to the demand for those products from consumers or patients (consumer demand in this market is, of course, expressed through the use of a prescribing doctor or other qualified health care provider). A pharmaceutical company determines the price and marketing of a drug in response to expected demand, market competitiveness, and marketing expenditures. This is done to set wholesale acquisition costs.

3.2.2. wholesalers

Pharmaceutical products are acquired by wholesale distributors from manufacturers, who then distribute them to a wide variety of customers, such as hospitals, long-term care institutions, retail and mail-order pharmacies, and other medical services (e.g., community clinics, physician offices, and diagnostic labs).

Wholesalers used to limit their business to the standard distribution role. By warehousing products and controlling inventory, they acted as a channel between manufacturers and pharmacies (as well as other organizations, such as government sites and doctors). Nowadays, wholesale distributors offer a variety of specialized services, such as specialty medicine distribution, drug repackaging, computerized order services, reimbursement support, and drug buy-back programs.

Throughout the past 30 years, there has been a large amount of change and consolidation in the wholesale distribution sector, partly as a result of rising pressure to reduce costs. This has obligated the sector to modify its revenue model, transforming its core distribution business into a low-margin enterprise that generates profits by maximizing economies of scale, realizing physical efficiencies in the distribution system (like "just-in-time" deliveries to customers), and achieving financial efficiencies (such as retaining discounts for prompt payment). The sector has expanded and strengthened its business model by adopting specialized pharmacy and disease management services.

3.2.3. Pharmacy Benefit Managers (PBMs)

PBM is the intermediary between pharmaceutical manufacturers and payers by determining which medicines are paid, the quantity of pharmaceuticals provided to other receivers, and the amount of consumer compensation for filling prescriptions based on rebates and other discounts negotiated by PBM with pharmaceutical manufacturers and health insurers.

PBMs manage consumer drug purchases by working with third-party payers (private insurers, self-funded employers, and public health programs) to specify which drugs will be covered, how much the pharmacy will receive, and how much the patient will have to pay out-of-pocket when the prescription is filled.

3.2.4. Pharmacies

Before medications reach the patient or customer, pharmacies are the last stage in the pharmaceutical supply chain. Pharmacies purchase medications from wholesalers and occasionally straight from manufacturers due to their existing operational infrastructure, which includes warehouse facilities, distribution channels, and inventory control systems, before being physically taken into their possession. Pharmacies are responsible for buying pharmaceuticals and safely storing them before giving them to customers. Pharmacy operations include keeping a sufficient supply of pharmaceutical items on hand, educating customers on the safe and efficient use of prescription medications, and enabling invoicing and payment for customers enrolled in group health benefit programs.

Community retail pharmacies, specialty pharmacies (hospital pharmacies, long-term pharmacies), and mail-order pharmacies (online pharmacies) are considered the majority types of pharmacies. The most typical kind of pharmacy that gives the general public access to their prescriptions and health advice is the community pharmacy,

commonly referred to as a retail pharmacy. The majority of community pharmacies offer a commercial store with a mix of medications that may be bought over-the-counter and those that require a prescription (Tiwari, 2022).

Specialty pharmacies provide expensive biotechnology medications to people with chronic conditions. These types of medications are frequently given by a clinical professional at a doctor's office and are generally given by injection or infusion (intravenously). An additional form of specialty pharmacy is long-term care pharmacy, often known as institutional pharmacy.

Long-term care pharmacies cater to the unique requirements of nursing homes by offering packaging for controlled administration (often referred to as bubble packs or unit-dose supplies) and specialized services that go beyond what is offered by retail pharmacies. A central site is where mail-order pharmacies (online) collect prescriptions by mail, fax, phone, or Internet. These pharmacies then process the prescription in sizable, largely automated centers and deliver the patient's medications back, in particular for pharmacological therapies for major chronic illnesses like diabetes and depression.

3.2.5. Consumers

Based on a prescription written by a doctor, when the medicine has undergone the aforementioned procedures or stages and is ready to be distributed, patients and other consumers buy it from a pharmacy, and occasionally from a doctor's office, hospital chain, health plan, etc.

Additionally, physicians, employers, and health plans have a role in the pharmaceutical supply chain. Physicians are the first people in the supply chain to communicate with the consumer (i.e., patient), the end-user. Doctors typically make medical diagnoses and write prescriptions for patients. The right dosage and amount of the prescribed medication must be used, which is the doctor's responsibility as well. Physicians and patients/consumers are more important than ever in influencing market demand for medications. To provide employees with pharmaceutical coverage, large employers who self-insure their health benefits typically negotiate contracts with PBMs (and occasionally with specialty pharmacy companies as well). The agreements that employers make with PBMs allow them to exert control over the supply chain.

Health plans use a variety of tactics to manage prescription drug benefits, the majority of which involve PBMs or tactics that are similar to PBMs. There are still a few

plans that pay pharmacies on a fee-for-service basis, but they are being used less frequently because they do not allow for the use of cost-containment techniques to reduce the price of prescription drugs.

3.3. Greek Pharmaceutical Supply Chain

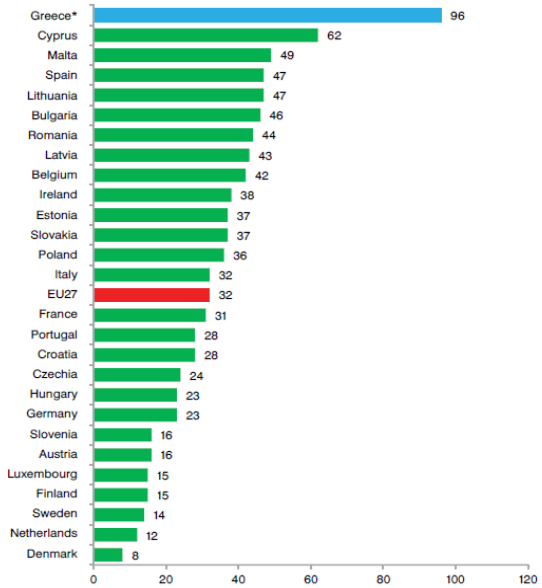
It has been estimated that the Greek pharmaceutical industry is growing at a rapid rate over the last five years (up by 80% vs. 43% in the EU and 7% for other Greek manufacturing). Exports have been the main driver of this growth, with extroversion reaching 50% of sales by 2021, compared with 30% in 2016 (Voumvaki, et al., 2022).

Pharmaceutical production and distribution are one of the most dynamic sectors of the Greek industry. The supply chain for pharmaceutical products consists of pharmaceutical companies (the manufacturer and importer), wholesalers (the storage and distribution), and pharmacies. Specifically, pharmaceutical products, except for products for hospital use provided through hospital sales, follow the following path: pharmaceutical company -wholesaler- pharmacy (Voumvaki, et al., 2022).

In Greece, there are nearly 106 multinational and national Pharmaceutical companies (SFEE & PEF members), and 136 wholesalers and pharmacists' cooperation. Also, 10,427 pharmacies and pharmacies of 128 hospitals and 32 EOPYY pharmacies, according to ELSTAT, EOPYY, and Pan-Hellenic Association of Pharmaceutical Wholesalers (SfEE & IOBE, 2021). Nowadays, 32 EOPYY pharmacies are operating and providing expensive medications for the treatment of serious diseases without a charge or the prescription being approved by the appropriate social security fund.

As shown in Figure 6, with the EU-27 average of 32 pharmacies per 100.000 inhabitants, Greece ranks top in 2020 with 96 pharmacies per 100.000 inhabitants.

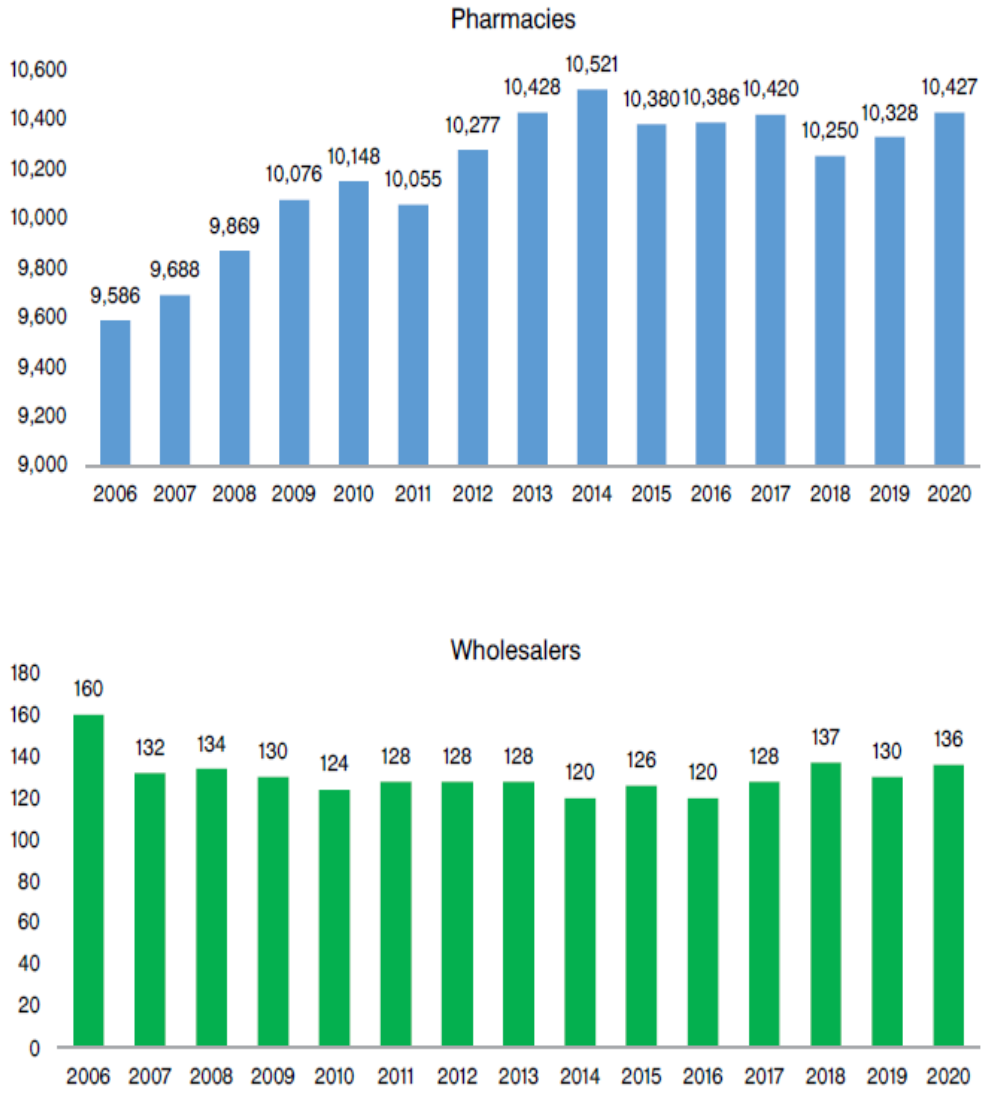
Figure (6): Number of pharmacies per 100,000 inhabitants, EU27 (2020)



Source: ABDA. German Pharmacies, Figures Data Facts 2021, ELSTAT., 2021

Figure 7 shows that there were 3,674 pharmacies (35.2%) in the Region of Attika out of the 10,427 pharmacies that were in operation across Greece in 2020. In 2019 and 2020, there were 136 more wholesalers than there were in 2019.

Figure (7): Pharmacies and wholesalers- Greece

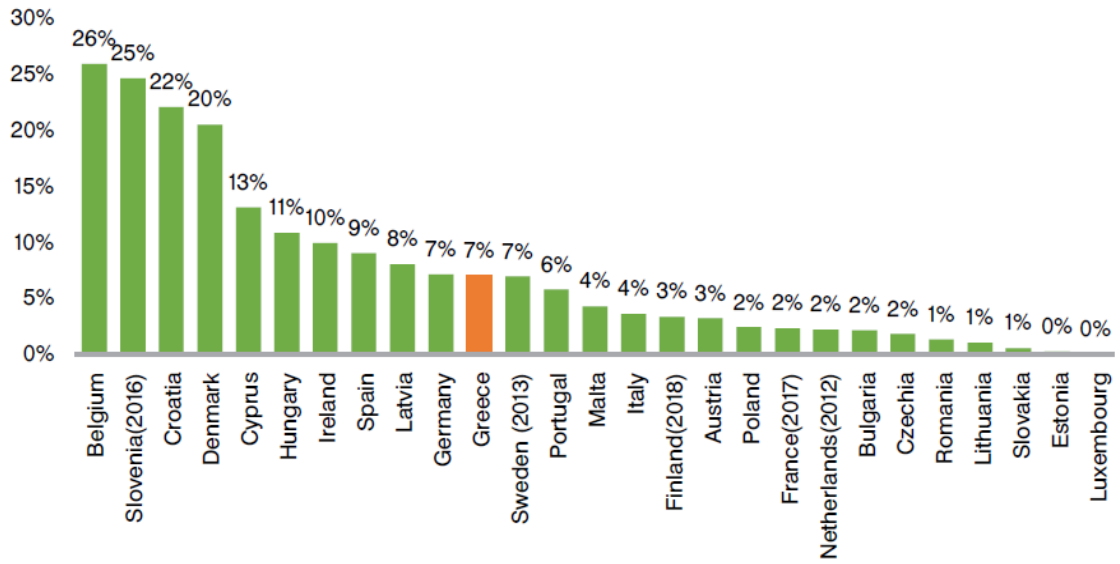


Source: ELSTAT, 2021

3.3.1. Research and Development (R&D) in Greece

Research and development spending in the pharmaceutical sector, which totaled €76 million in 2019 (€51 million in 2017), represents 7% of all R&D spending in Greece, an increase from 5% in 2017, which is evident in Figure 8.

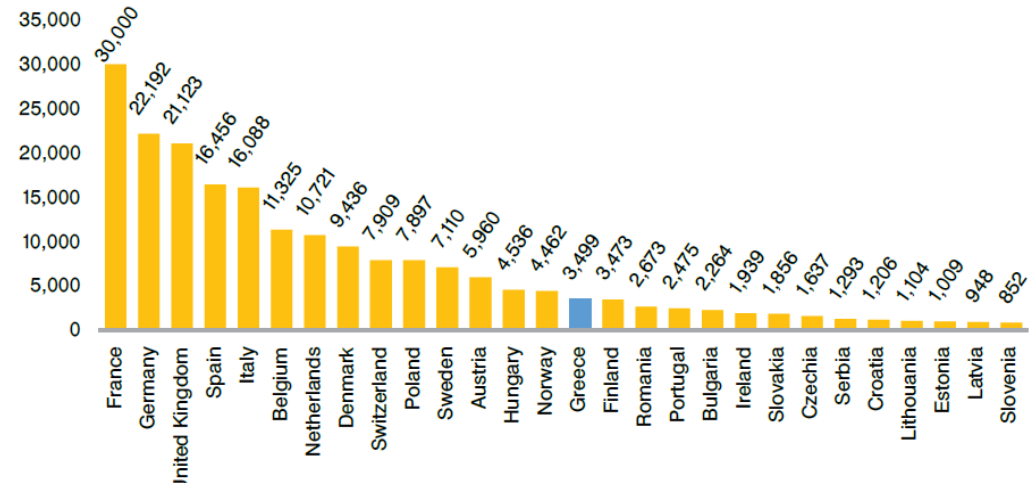
Figure (8): Pharmaceutical R&D expenditure (% of total R&D expenditure) (2019)



Source: Eurostat, 2022, data processing IOBE

From 2002 to 2021, 3,499 clinical investigations of various types and phases were carried out in Greece, of which 2,000 were completed (Figure 9).

Figure (9): Total number of clinical trials, all phases and stages (2002-2021)

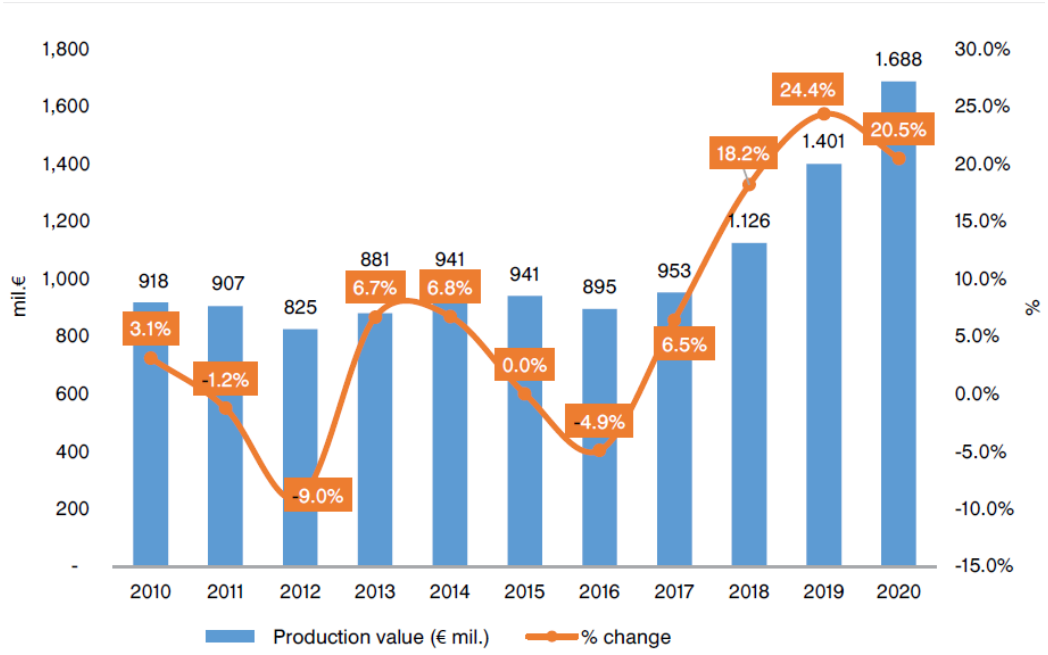


Source: Clinical trials.gov, 2021

3.3.2. Production

Pharmaceutical manufacturing or production in Greece was worth €1.7 million. in 2020, up €287 million from 2019, and up 82% from the average for the years 2010–2017 (€907 million). This information comes from Eurostat, which measures the value (ex-factory prices) of production, as seen in Figure 10.

Figure (10): Production of pharmaceutical products (mil. €)



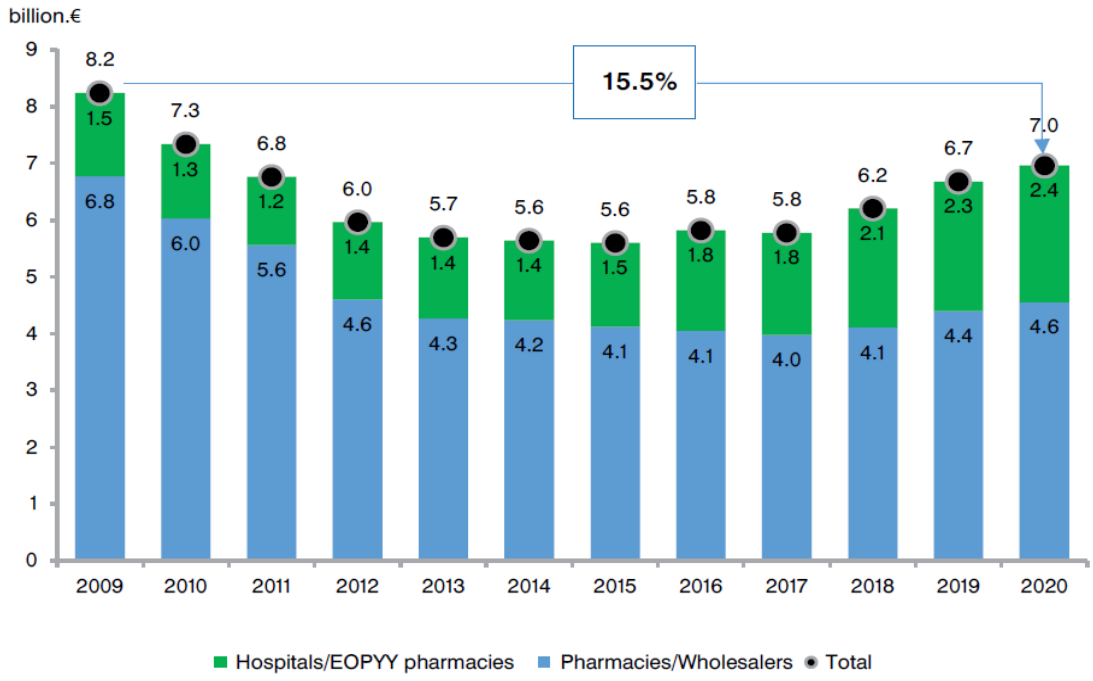
Source: Eurostat 2022, PRODCOM Database, data processing IOBE

One of the key pillars of the pharmaceutical sector's activity in the country is enhancing cooperation between domestic and foreign factories. According to the IQVIA FY2021, 34% of pharmaceuticals are made in domestic factories and certified production facilities with highly educated workers; however, with the right incentives, domestic production of foreign pharmaceutical products could increase. 53% of pharmaceutical products in Greece are imported, and 14% of production products are from international companies that are manufactured or packaged in Greece (locally manufactured products (LMP) abroad).

3.3.3. Sales

Figure 11 shows that in 2020, the sales of pharmaceutical products to pharmacies and wholesalers in value accounted for €4.6 billion, which increased by 3.7% compared to 2019. Corresponding to this, sales to hospitals and EOPYY pharmacies totaled €2.4 billion in 2020, representing an increase of 5.0% over the previous year and a decline of 15.5% over 2009.

Figure (11): Sales of pharmaceutical products in values (billion. €)-Greece



SOURCE: EOF, 2022 (Pharmacies/Wholesalers at retail prices and Hospitals at hospital prices) Total pharmaceutical sales recorded monthly by the National Organization of Medicines (EOF) and include pharmaceutical sales by pharmaceutical companies to hospitals (at hospital prices) and Wholesalers / Pharmacies (at retail prices). Sales also recorded in terms of number of packages. Parallel exports in 2020 were €427 mil. and are included here.

3.4. Drug shortage

Drug shortages are widespread across the world due to many factors, such as demand issues or regulatory issues, but more commonly due to disruptions in the supply chain. These shortages usually affect countries with low and middle-income levels, in addition to countries with high-income levels (Tucker & Daskin, 2022; Shukar, et al., 2021). Manufacturing problems, financial pressures, shortages of raw materials, logistics issues, and just-in-time inventory have been identified as the primary causes of medicine shortages in developed countries and developing countries (Shukar, et al., 2021). A review of the FDA's approach to medical product shortages was published by the FDA in 2011. The study identified the leading reasons for drug shortages as manufacturing problems (43%), delays in manufacturing or shipping (15%), and lack of supply of active pharmaceutical ingredients (10%) (Fox, et al., 2014).

Medicine shortages, according to a note from the Commission to the Pharmaceutical Committee in March 2020, are part of a wider problem of access, affordability, and availability of medicines in the EU. As explained in the note, a shortage occurs when the supply of an already-marketed medicine is not sufficient to meet the demand from healthcare professionals or patients (Scholz, 2020).

The American Society of Hospital Pharmacists (ASHP) and the University of Utah Drug Information Services (UUDIS) describe a drug shortage as "*a supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternate agent.*" (Fox, et al., 2014; Phuong, et al., 2019). In the event of a disruption in the drug supply, there may be a shortage of drugs (for example, when the supply of drugs does not meet the demands of pharmacies and wholesalers and so does not meet the demands of the consumer or patient level) (De Weerdt, et al., 2017).

All parties are impacted by the drug shortage, but patients and consumers are particularly affected. Whether from an economic, clinical, or humanistic perspective, all parties are aware that there is a drug shortage, and suppliers are forced to manage the shortage of raw materials through additional operations. Retailers are forced to start compounding, make logistical changes, or buy several medications in low supply at higher prices. To address the scarcity, the hospitals must incur additional fees, including those for expensive brands, surplus supplies, and training programs for staff (Shukar, et al., 2021).

Clinical effects of medication shortages have been documented, and these include treatment changes, inadequate care, inaccurate prescriptions, incorrect dispensing, incorrect administration, delayed or denied treatment, extended hospitalization, unfavorable drug interactions, and even death. Drug shortages have a variety of humanistic consequences for patients and healthcare personnel, including an increase in complaints from patients and a decline in adherence to treatment, as well as psychological repercussions. In addition, the medicine shortage issue makes doctors angry, agitated, frustrated, lose patients' trust, and even threaten them (Shukar, et al., 2021).

Despite the positive production and distribution indicators in the Greek pharmaceutical industry based on (SfEE & IOBE, 2021), there are 148 medicine shortages reported in the latest announcement from the Greek National Organization for Medicines (EOF). In mid-March 2023, there were approximately 400 medications in limited supply. The number of shortages is much greater, but they report less. In September 2022, the National Organization for Medicines (EOF) released a press stating that shortages have increased since 2019, and they have already reported that for over a year they have been experiencing much more shortages", according to Ilias Giannoglou, a member of the Athens Pharmaceutical Association's Board. Moreover, it appears that manufacturing or product quality problems (55.3%), supply chain delays (33.7%), and increased demand (14%) are the main causes of drug shortages in Greece for 2022, according to MIIR's analysis (Zafeiropoulos, et al., 2022). There are no certainties regarding the future of drug shortages, but there are encouraging signs that quality improvements and increased capacity may contribute to fewer shortages (Fox, et al., 2014).

CHAPTER 4- CHALLENGES AND OBSTACLES

1.1. Pharmaceutical Supply Chain Challenges and Obstacles

1.1.1. Inventory Management

As reported by Niakan & Rahimi (2015), drug shortages increased by up to 40% in the United States between 2007 and 2011. Of the shortages, 13% were attributed to inventory and distribution strategies (Niakan & Rahimi, 2015).

A major challenge facing pharmaceutical supply chains is managing the variety of products within short time frames. Additionally, raw materials and products have a limited shelf life. The pharmaceutical supply chain is more complex than that of other products. Compared with other industries, the pharmaceutical supply chain is characterized by long set-up times, resource-intensive operations, short shelf lives, and high waste production. Also, demand is one of the main drivers of the pharmaceutical industry (Candan & Yazgan, 2016).

It is also important to consider the perishability of the drugs in the PSC. The majority of drugs have a fixed shelf life and can therefore not be stored indefinitely. It is the responsibility of pharmacies and hospitals to manage surplus stock to ensure large amounts of medicine are available for certain medical situations. The management of a safety stock level for drugs is a challenge that is not as straightforward as it would be for fast-moving consumer goods. Pharmaceutical products are, therefore, more difficult to manage in terms of inventory and distribution (Nematollahi, et al., 2018; Weraikat, et al., 2016).

In contrast to medical devices, pharmaceutical products have long development cycles. As a result of these long lead times, capacity planning and supply chain strategies, in particular inventory management, will be significantly affected. This is especially true for emergency interventions since it is difficult to predict what type of patient will present to the hospital. The implications are significant, especially for hospitals with pharmacy departments that carry high levels of safety stock to mitigate daily fluctuations in demand and supply. Consequently, hospital pharmacies must maintain excess inventory to protect themselves from emergencies and unpredictable demand. Pharmacy departments in hospitals experience perennial problems such as stock-outs and drug expirations as a result of these factors (Bhakoo, et al., 2012).

Pharmaceutical production is a batch process that involves the production of chemicals, and the manufacturing of chemicals takes place in multiproduct plants. In most cases, the manufacturer does not deliver the product to the pharmacy or patient. Instead, they deliver the product to the consumer through wholesalers (pharmaceutical warehouses) (Candan & Yazgan, 2016).

Managing inventory risks can be achieved through good warehousing practices and logistics planning (Kamath, et al., 2012). Pharmaceutical supply chain inventory management is a complex task, especially since there is a lack of information and a unique context. Part of controlling inventory levels is managing capacity, quantification, and replenishment decisions. These decisions are made with accurate information, but even then, uncertainty can prove detrimental. Despite this, these supply chains are far from optimal at present. (Privett & Gonsalvez, 2014).

Inventory management plays an important role in planning. A pharmaceutical company must develop effective inventory control policies to compete in the global market. To avoid falling below a safety stock level and to meet customer demands at the highest level, product storage is preferred. This results in the accumulation of high inventory costs. Despite reducing inventory levels to minimize costs, firms cannot meet demands, delivery dates are delayed, and service levels are reduced (Privett & Gonsalvez, 2014). In supply chains, firms usually determine inventory levels by analyzing direct customer orders, which has many deficiencies. One of these deficiencies is the bullwhip effect, which occurs when demand variability is amplified along the supply chain (Rouibi & Burlat, 2010).

Issues such as inventory inaccuracies, quantification, uninformed push systems, inventory allocation, product availability management, and appropriate IT systems can contribute to such issues (Privett & Gonsalvez, 2014). Developing long-term coordination and cooperation can also significantly mitigate the bullwhip effect and significantly enhance supply chain efficiency (Rouibi & Burlat, 2010).

In the context of a pharmaceutical supply chain, the Baboli et al. (2011) case presented a problem of replenishment in the downstream part of the system. Traditional methods of inventory control and replenishment are unable to optimize the overall costs of the system due to not taking transportation costs, the expiration date, the regulations, and the price of the products (some of which are free) into consideration (Baboli, et al.,

2011). As a practical matter, the transportation costs are determined by the size of the shipment. Consequently, the order quantity should be determined to minimize the overall logistic costs.

Further, different types of decision-making can be classified according to whether re-ordering is carried out in a centralized or decentralized manner. Decentralized supply chains involve each company in the chain attempting to reduce its own costs independently from the other members of the chain (local optimization). The centralized system seeks to achieve the global optimum through collaboration among the partner companies (Baboli, et al., 2011). In addition, it is important to note that the centralized model can be applied to both warehouses and retailers if they are part of the same organization. For cases where external suppliers are involved, other models (such as contract-based coordination) are more appropriate (Baboli, et al., 2011).

In today's competitive market, companies have to reduce their replenishment costs as much as possible and reduce response times to increase customer satisfaction. As a result of holding inventories, they can serve their final customers as quickly as possible. For situations in which demand or lead time are probabilistic, safety stocks are used. Having a high level of safety stock (SS) and a low level of safety stock (SS) increases the holding and shortage costs, respectively. In addition, due to the perishable nature of pharmaceutical supplies, an excessive level of SS may result in a loss of goods (Baboli, et al., 2011).

Suppliers that supply retailers can reduce these costs by obtaining information about retailer demand and centralizing replenishment decisions across all supply chain members in multi-echelon inventory systems. A supply chain can reduce inventory costs (i.e., holding, ordering, and shortage costs) with this kind of decision. It is also possible to optimize inventory and transportation costs together. Policies that fully exploit the capacity of vehicles are the most advantageous, as they lower not only transportation costs but also CO2 emissions and noise (Baboli, et al., 2011).

Two components of holding costs could be separated for clarity: one relates to the volume of storage needed (e.g., heating and rent of the building), and the other to the investment (e.g., interest rate). The preferred approach is to separate these two terms in a way that allows us to explicitly examine specific cases in the pharmaceutical supply

chain (e.g., products at a low price but requiring large storage volumes or very small items with high prices) (Baboli, et al., 2011).

Raw materials and drugs are aligned with current requirements in JIT inventory management. When the pharmacy or institution has a low financial budget, stakeholders often purchase a fixed quantity of stock for a fixed duration without a backup plan. Due to the lack of buffer stock, the strategy is widely used to run the system at a low cost but presents a greater risk of drug shortages in high-income countries (Emmett, 2019). It has been demonstrated that high market concentration of manufacturers, limited spare production capacity, and "just-in-time" inventory practices often result in reductions in supply, which are not easily remedied by simply extending the period of delivery (Gupta & Huang, 2013).

Poor storage, organization, capacity, and shared space management are the main problems relating to warehouse management that can result in inventory management obstacles. In national warehouses, the conditions are often the best, while in other warehouses, the management is poor. There are many reasons for poor storage and organization, including an inadequate facility, a lack of proper warehouse equipment and electricity, as well as a lack of training. A warehouse often lacks designated areas for storing damaged and expired products, as well as for receiving, shipping, and storing products. As a result of poor organization, issues can arise regarding capacity, inventory policies, discrepancies, and control (Privett & Gonsalvez, 2014).

It is imperative to manage warehouses effectively to maximize their capacities, both in terms of storage space and human resources. Logistics and inventory data are also improved through warehouse management. However, warehouse management requires a combination of human resources, financial resources, and physical resources (Privett & Gonsalvez, 2014).

1.1.2. Demand Prediction and Forecasting Accuracy

In the modern corporate environment, companies operate in a context characterized by increased complexity, increasing outsourcing, global dispersal of partners, and continual reductions in production costs. Due to all of these factors, supply chains are increasingly exposed to risks and disruptions, resulting in greater uncertainty (Messina, et al., 2018).

Logistics and supply chain management depend heavily on demand forecasting (Merkuryeva, et al., 2019). As part of the business process management process,

demand forecasting is an essential component. Forecasting processes vary in complexity and execution, but the purpose remains the same: to plan and organize businesses based on historical data and current environmental conditions (e.g., political, social, and economic). In the pharmaceutical industry, forecasting accuracy remains a challenging task (Durbha, 2016).

In logistics and supply chain management, demand forecasts are the basis for all managerial decisions. A supply chain system starts with demand forecasting, regardless of whether it is push or pull. It is important to consider push processes that anticipate customer needs - sourcing, production, transportation, operating activities, and actions- all of which require input from demand forecasts. Pull processes are similarly influenced by customer demand data; this is the starting point for planning the necessary levels of activity and inventory (Merkuryeva, et al., 2019).

The combination of uncertain demand forecasts with a high error rate and long delivery lead times results in oversupplies and overstocks. The forecasting error can be reduced by using more efficient and advanced methods of demand forecasting if the distance between the market and the point of sale is fixed. Top-level management has acknowledged and valued the importance of forecasting (Jain & Malehorn, 2006). An error could hurt the health of the population and nations. This is why pharmaceutical stockouts cannot be expressed as purely financial losses. Consumer-centric best practices involve avoiding out-of-stocks and forecasting accurate customer demand, which leads to higher inventory levels (Walker, et al., 2017).

A common problem in procurement and management is that the availability of demand information is often lacking and/or aggregated, resulting in serious consequences for both parties. It is difficult to gather sufficient information to inform procurement and supply decisions (Privett & Gonsalvez, 2014).

A supplier may only see one order over an entire year if it is an intermediary order for multiple countries. Orders may even be aggregated from multiple countries as a result of the procurement process. As a result of this aggregation, large inaccuracies can be found, as well as poor decision-making. It is common for healthcare facilities to be unaware of the actual demand for their services (Privett & Gonsalvez, 2014).

To measure the accuracy of demand forecasts, the following metrics are commonly used: Forecast Bias, Mean Absolute Deviation (MAD), Mean Square Error (MSE), and Mean Absolute Percentage Error (MAPE) (Merkuryeva, et al., 2019). In

addition to determining how forecast errors or accuracy should be measured at each level of a supply chain, there are a few other considerations to be considered. It is especially important to consider the interrelationships between accuracy-based measures and forecast aggregation levels over time and to match these with the chosen accuracy metrics. Furthermore, it is well known that forecast errors are influenced by the location of forecasters within the chain. In other words, forecasts created closer to the demand point will be more accurate, while forecasts created further up the supply chain will be more inaccurate. It should be noted that collaborative forecasts based on sales to the end customer will lower forecast errors for upstream organizations (Chopra & Meindl, 2007).

Just-in-time inventories, average demand growth, and seasonal demand can be predicted with an established system; however, outbreaks, epidemics, and disasters cannot be predicted (Phuong, et al., 2019). Designing, operating, and maintaining robust manufacturing processes and distribution networks is becoming more complex due to drug specificity and demand uncertainty (Sarkis, et al., 2021).

1.1.3. Waste Management and Environmental Issue

Pharmaceutical waste is defined by the World Health Organization (WHO) as unwanted pharmaceutical products, including expired, unused, spilled, infected products, medications, vaccines, and sera, which are no longer needed and should be disposed of appropriately (WHO, 1999).

According to Grayling (1999), one of the significant causes of pharmaceutical product waste is temperature failure caused by exposure to hot or freezing temperatures. Waste of such products results in a large monetary loss and a high risk to patients since exposure to high temperatures can adversely affect medication effectiveness (Grayling, 1999). Refrigerated containers or cold storage rooms constantly maintain temperatures in storage under the manufacturer's ownership. Generally, refrigerated storage or cold rooms are also used. They are often measured and monitored, but not always, and frequently lack temperature history charts (Privett & Gonsalvez, 2014).

Additionally, temperatures cannot be continuously monitored while in transit. In most cases, sensors used to monitor the temperature only report when they arrive at intermediate points, which does not ensure that the temperature will not be exceeded. The most common method of transporting cold chain products is by ice or dry ice. By using ice and dry ice, products could freeze if not packed appropriately (for example, by

touching ice directly) and overheat when delays are poorly managed. Temperature deviations throughout the supply chain are typically caused by delays in transit and inadequate oversight at the lowest levels (Privett & Gonsalvez, 2014).

Besides temperature, increasing patient and prescription numbers, as well as overuse and overproduction of medicines, have contributed to the increase in pharmaceutical waste. Unused, expired, and misplaced medicines may result in shortages of medicines, high pharmaceutical waste levels, and higher costs of medicine disposal, and a systemic approach is required to address this issue on a global scale (Hui, et al., 2020). Medications account for the majority of medical waste. As a result of an increasing number of diseases to be treated, improved access to medical services, and self-medication, its consumption has steadily increased. Medical waste is rapidly increasing as a result of increased consumption, particularly in developing countries (Windfeld & Brooks, 2015).

How clinicians prescribe and the attitude of patients are considered factors in medication wastage. Patients often request more medication by visiting a variety of physicians until they find one that they believe is effective. On the other hand, each doctor tends to prescribe a different medication—the one they believe will treat their patients most effectively (Papalexi, et al., 2019). Additionally, it is common for people to purchase their prescriptions, use them until they feel better, and then store them in their cupboards for future use; however, several expired medicines are stored in these cupboards. Even though the spare medication usually makes a patient feel safer, they are unwilling to return it to the pharmacy (Papalexi, et al., 2019). To illustrate, many cases of pharmaceutical waste may result from patients not using all of their medication because of unfavorable impacts (side effects), daily dosage changes, health improvements, medicine expiration dates, doctor prescribing practices, or dispenser practices. In addition, medication stockpiling may be caused by non-adherence to prescriptions. It has been reported by the WHO that half of the patients fail to take their medications as directed (Holloway & Van Dijk, 2011).

The level of waste that exists within the PSC hinders the effective and efficient delivery of medicines (Papalexi, et al., 2019). Expired products are a major source of product waste, resulting in monetary losses, disposal efforts, and a lack of available inventory. Expiration usually results from medicine selection, forecasting, demand measurement, purchasing, warehouse management, and inventory management. There is inadequate management in these areas, resulting in excess product that cannot be

consumed before it expires. In addition to poor warehouse management and employee training, expiration occurs because First-Expired-First-Out (FEFO) inventory pull policies are not followed (Privett & Gonsalvez, 2014). Several factors contribute to the generation of pharmaceutical waste, including supply chain management and related variables. Furthermore, poor storage conditions, the storage of medications on the floor, the absence of a specific stocking plan, poor temperature control, and overstocking of expired medicines can result in significant medication spoilage (Gebremariam, et al., 2019).

For example, palliative medicines have a low turnover because they are high-value and are not commonly prescribed, as well as a limited number of prescriptions issued per month, high prices, and short shelf lives for some medicines, along with added issues regarding controlled drugs (e.g., the need to store them in locked cabinets. It is also possible that community pharmacists (CPs) may be concerned about the possibility of medicines not being collected by patients or their families, which would serve as a strong disincentive for stocking such medicines. As a result, there could be a supply barrier (Campling, et al., 2022). As well as these wastes, there are also some types of medications (boxes of emergency medicines) that must be stored in the pharmacy under the guidance of the General Pharmaceutical Council, including antidotes for poisoning, in case they are needed. Due to their infrequent use, they often become out of date (Papalexi, et al., 2019).

According to hospital pharmacists, the main cause of waste is poor communication and the lack of synchronization between the pharmacy and the wards. The pharmacy receives medications daily due to changes in treatment or because patients leave the hospital without taking their medication. As soon as this medication is used or ordered for a particular patient, it must be destroyed, resulting in waste (Papalexi, et al., 2019). To illustrate, medication prescribed in the name of a deceased patient may not be used in any other way. Additionally, many examples are considered causes of waste issues in hospital wards, clinics, and estates, such as ineffective rotation or use of medicine (manual intervention based on expiration dates) or inadequate use of inventory management systems to reduce stock obsolescence, loss of a patient's own medicine on admission, waste segregation and disposal are insufficiently supported, prescription of incorrect medication and inadequate or unclear information provided to the patient, and holding and requesting excess stock by wards (Alshemari, et al., 2020).

In the pharmaceutical delivery system, there is a high level of waste, which results in inefficiency. Since pharmaceuticals play a crucial role in human health, pharmacies must keep a large stock, increasing the risk of generating waste (Bhakoo, et al., 2012). There is an overordering of stock as well as inadequate storage conditions within the pharmacy (Alshemari, et al., 2020). Due to the relatively centralized environment of healthcare organizations, pharmacies are unable to operate independently and fully control their storage, as shown by functional rules drawn from the legal context. When these practices are followed, medicines can expire or a critical shortage can result (Papalexi, et al., 2019; Bamford, et al., 2015).

Reverse SC is another challenge for the PSC. As a result of the potential for abuse, it is extremely important to collect contaminated, unused, and expired drugs from pharma-retail stores. In contrast to other profitable reverse chains, the reverse PSC is completely different. In this regard, it is necessary to develop new policies to assist in the recovery of medications. As the pharmaceutical industry is highly regulated, legislation plays a significant role (Nematollahi, et al., 2018; Yu, et al., 2010).

In light of the tendency to not return spare medicines to the system, there have been significant concerns raised regarding possible impacts on the ecological environment and human health associated with the conversion of spare medicines into dangerous or useless products (Kongar, et al., 2015). The presence of pharmaceuticals in various environmental compartments, such as surface water and groundwater, has been documented. Therefore, in 2011, the EU launched a campaign to raise public awareness about the need to safely dispose of hazardous waste, including expired or unwanted medicines (Wang, et al., 2015; Kongar, et al., 2015).

Upon disposal of pharmaceutical waste, a burning technique or a non-burning technique may be used. Pharmaceutical waste is divided into two categories: hazardous waste (15%) and general waste (85%) (WHO, 2018). Several studies have shown that a percentage of prescribed pharmaceutical waste is contaminating waterways, streams, and groundwater and also affecting the climate and the environment. The effects of their interactions with non-target organisms are unclear, such as the effects of their metabolite excretion by animals or humans or inappropriate disposal of unused medicinal products. Their presence in the environment and pollution of the soil and waters not only harm organisms but also destabilize the hormonal system and contribute to antibiotic

resistance. Concentrations of active substances increase negative effects (Bungau, et al., 2018).

Therefore, as ageing populations and the development of new drugs lead to an increase in pharmaceutical usage, it is extremely important to properly manage unused medication. Open dumping of medical waste causes medical residues to enter the soil and water. Also, drugs and their degradation derivatives can harm the environment and human health once they reach the groundwater (Bungau, et al., 2018). An estimated 35 percent of all prescription drugs dispensed in the US are unused. Undisposed medications can adversely affect the environment and human health. Thus, an effective reverse logistics system is necessary to address these issues and reduce financial losses associated with medication waste. The reverse logistics system begins with the efficient collection of expired medications and ends with their redistribution, recycling, and/or proper disposal (Kongar, et al., 2015).

1.1.4. Lack of Coordination and Communication Issue

Human resources play an essential role in the pharmaceutical supply chain. In developing countries, human resource constraints are increasingly recognized as a major bottleneck. A lack of qualified personnel will likely result in a high workload and low performance while leaving key responsibilities unattended. Many warehouses and health facilities lack adequate supply chain staff to perform even basic functions (Dowling, 2011). It is common for medical personnel to be responsible for making supply chain calculations and decisions. Despite their best intentions, the few qualified staff have to handle a heavy workload as a result of a lack of qualified personnel and unqualified staff; they often make poor decisions to serve the organization. Additionally, most in-country healthcare providers (NGOs, public health systems, international wholesalers, and procurement agents) lack training in logistics and supply chain functions. Supply chain visibility may reduce the need for HR expertise and training; however, it is still crucial to combine responsible, trained people with easy-to-use IT systems (Privett & Gonsalvez, 2014).

In addition, physicians are unfamiliar with operations management (OM) and SCM practices, which further complicates the delivery system. Although clinicians are primarily responsible for providing quality healthcare, good management skills are crucial to delivering effective healthcare. In turn, these skills would facilitate the management of inventory and would be able to improve patient care operations

(Schneller, et al., 2006; Breen & Xie, 2015; Uthayakumar & Priyan, 2013). There is therefore a need for expert knowledge to maximize healthcare organization resources, reduce duplication of services, and improve customer satisfaction among the stakeholders in the PSC (Radnor, et al., 2012).

In the PSC, there are various members, including, initially, manufacturers, secondary producers, market warehouses, distributors, wholesalers, and retailers/hospitals, as well as patients (Ballou, et al., 2000). The lack of coordination among the actors in the pharmaceutical industry was identified as one of the major challenges (Privett & Gonsalvez, 2014). Ideally, stakeholders work together to achieve a common goal, and as such, they are inherently dependent on one another, but the level of influence and power varies depending on the stakeholder relationship and context (Campling, et al., 2022). In the eyes of community pharmacists (CPs), they are at the end of the supply chain and are unable to acquire products at the beginning. As a result, CPs were placed in a vulnerable position. As an intermediary between manufacturers and distributors, WDs was able to source stocks and ensure their availability in numerous regional storage and distribution centers.

Therefore, having a coordinating body to set targets, meet deadlines, and implement strategies would be beneficial to PSC (Breen, 2008). To achieve responsiveness and share risks and benefits, information sharing is critical in the pharmaceutical supply chain. For example, since CPs did not have a consistent source for providing information on medicine shortages, they were forced to gather information from a variety of sources, including pharmaceutical wholesalers, manufacturers, pharmacy press, other pharmacies, colleagues, and social media, to respond to shortages (Campling, et al., 2022). Information sharing regarding supply issues and shortages would benefit CPs and reduce unnecessary work.

According to Breen (2008), the fragmentation of the supply chain is the highest-ranked PSC risk, which causes a lack of uniformity in decision-making within the PSC, thus causing many problems and adversely affecting the effectiveness of the entire supply chain. Considering this, the risk had to be addressed urgently since it affected all parties and could result in financial losses. This view is in agreement with the concerns within the industry concerning the growing involvement of suppliers, manufacturers, parallel importers, generics, and wholesalers.

Insufficient information is shared between the various stakeholder groups, and communication and synchronization issues are the main obstacles for the pharmaceutical supply chain (Papalexi, et al., 2019). It is beneficial for pharmaceutical companies to coordinate their efforts to improve performance and to ensure the safety of their products, as well as to maximize the profitability of their collaboration with other SC partners (Mehralian & Moosivand, 2017).

In other words, a lack of meaningful communication (two-way information transfer supported by trust) between pharmacists and wholesalers/distributors and the subsequent lack of relationships hinder pharmaceutical supply. When community pharmacists (CPs) need to communicate with wholesalers/distributors (WDs), they call the customer service department of the telephone company. The process is considered time-consuming by them, resulting in a lack of meaningful communication and relationships between CPs and WDs (Papalexi, et al., 2019; Campling, et al., 2022). In addition, conflicting cultures and priorities exacerbate this, as CPs argue that they are focused on patient's needs and their responsibility to the patient. In contrast, WDs and manufacturers focus on commercial objectives (Campling, et al., 2022).

Fragmentation and duplication of services have been reported as a result of weaknesses in communication and synchronization between the different stakeholders within the PSC (Bamford, et al., 2015). It has been demonstrated that in UK hospitals, medication does not follow the patient due to miscommunication that results in reordering of the medication, especially when the patient is moved from one ward to another without coordination or communication with the previous ward (Papalexi et al., 2019).

Other examples are from Greek hospital pharmacies, as nurses often approach the pharmacy asking for products without first checking the cupboards in the ward. As well as the medicines prescribed for a particular patient, some medicines are kept in the ward cupboard for general use. In this regard, miscommunication between the staff increases the level of waste as well as the amount of time it takes to distribute the appropriate medicines or verify their availability (Papalexi, et al., 2019).

According to Maddox et al. (2016), a Low level of transparency during delivery is the main cause of perceived miscommunication. It could be explained by doctors, nurses, and pharmacists' differing perceptions of their role and attitude towards

teamwork in producing healthcare services (Maddox, et al., 2016). It is possible, for example, for doctors to make changes to prescriptions without notifying pharmacists. These actions cause delays and waste during the production of the service, which results in greater inefficiency and increased costs (Papalexi, et al., 2019). Hence, by establishing relationships among SC actors, potential opportunities can be explored and exploited through knowledge transfer, information sharing, and common strategies (Hwang & Rho, 2014).

1.1.5. Lack of Risk Management

As pharmaceuticals are a key input to healthcare treatment and a critical product, it is imperative to assess risks within the entire PSC. In supply chain management, risk management has only recently been recognized as an issue that must be addressed immediately. Risks are growing within the PSC, but there is no coordination in assessing and managing them. Providing end-users with treatment is the purpose of the PSC, so any risks within the PSC would be worrying. The risks would negatively impact supply chain performance (from sourcing raw materials to dispensing medication) (Breen, 2008).

Several risks are involved in the pharmaceutical supply chain, including organizational and strategy risks (planning and operation issues, skill of workers, R&D, company strategies, information flow, waste management, cost and visibility of stock); Financial risks (Currency and fluctuation rate, Tax payable change, costs related to supply, interest rate, and cash flow); Logistic risks (Transportation risk and Counterfeit) and according to Jaberidoost et al. (2013), supply and supplier risks were the most important risks discussed in the articles reviewed including partnership with suppliers, ordering cycle time, quality of raw materials and flexibility of supplier, contract and agreement issues, delivery reliability, environmental assessment, in addition to technology level, information systems, goodwill, technology development, flexibility in delivering, flexible quantities, quality management system of supplier and timely delivery.

Additionally, several challenges are faced by actors (stakeholders) in the pharmaceutical supply chain in the United States as well as in many other countries. For example, risk aversions and risk management strategies, especially concerning product, rebate, and payment flows, can impact on their responses (Mendoza, 2021).

Generally, supply chain risks can be divided into two categories: technological risks and strategic risks. In both types, there is an over-reliance on products, processes, technology, and suppliers, which is associated with an increased potential risk. The PSC is prone to many risks, including product discontinuity, product shortages, poor performance, patient safety/dispensing errors and technological errors that lead to stock shortages in pharmacies, internet pharmacies, and counterfeit drugs. All of these cause delays in the system and anguish for patients (Knight, 2005; Cousins, et al., 2004). According to Breen (2008), many factors were considered to be the most significant risk, including fragmentation of the supply chain as multiple channels lead to poor communication, a lack of visibility regarding stock availability and placement, inaccurate forecasting by the customer, and the inability to meet demand in general.

To manage PSC risks and maintain a high level of quality, frequent ordering, frequent replenishment, large buffer stocks, and emergency orders are necessary. As a result, such order and replenishment cycles are often far from optimal, causing inefficiencies in inventory management and planning. In regards to large buffer stocks, warehouses do not have sufficient space to hold the large inventory that is required to be kept. As a result of large inventories, both the cost and the risk of product expiration are increased (Privett & Gonsalvez, 2014). There is considerable effort put forth by each participant in the supply chain to ensure the product is delivered promptly to compensate for human error, technical faults, shipment delays, and other unforeseen circumstances.

There are a variety of risks associated with the pharmaceutical industry in the present environment of high competition and increasing business targets, such as regulatory failures, counterfeiting, inventory mismanagement, and financial losses. To mitigate these risks, pharmaceutical companies should incorporate appropriate risk management strategies. In this manner, proper risk management strategies have proven to be effective in gaining shareholder trust and improving performance and profit margins (Kamath, et al., 2012).

The pharmaceutical supply chain is not only subject to internal risks but also to many external risks. To illustrate, global economic disruption and high uncertainty are characteristic of the COVID-19 pandemic that rocked supply and business greatly in the last period. It is estimated that a pandemic similar to the COVID-19 pandemic will disrupt the supply chain for a long period of time, resulting in a long-term disruption that cannot be determined. When the epidemic spreads, supply, demand, and logistics are

disrupted simultaneously (Grida, et al., 2020). Consequently, organizations are beginning to recognize the importance of risk management. Despite this, managing and mitigating risks is one of the most challenging tasks for managers. A decision-maker must be able to rank and prioritize a portfolio of supply chain risk factors to effectively manage risks (Mehralian, et al., 2012).

1.1.6. Complexity Issue

Complexity is considered one of the most significant barriers to improving pharmaceutical supply chain performance and efficiency. The pharmaceutical supply chain is highly complex, and the delivery channels to customers are highly regulated. For instance, in the United States, the Food and Drug Administration (FDA) regulates how drugs are marketed, shipped, and stored in order to ensure they are safe and effective (Utiger & Mencer, 2017).

One of the main causes of PSC complexity is the characteristics of medicine: As PSCs deal with sensitive products as well as very expensive ones, they are more complex than SCs in other sectors. Within the PSC, there are different distribution lines; they cannot treat all that they manage in the same manner. It is generally accepted that medicines can be transformed into dangerous or useless products for consumers. In other words, store products differently based on how frequently they are used (Papalexi, et al., 2019).

Medicine availability and quality are determined by the frequency with which products are delivered. To ensure successful SCM, organizations need to manage their supplier relationships because the performance of the companies is influenced by these relationships (Alhussan, et al., 2017). In the pharmaceutical supply chain, it is common to have many stockholders and suppliers involved. To illustrate, medicine shortages prompted the use of multiple WDs. CPs needed to increase the number of WDs to meet the shortage. The necessity of utilizing multiple wholesalers, distributors, and third parties created a barrier to supply. As a result, there were difficulties in establishing a straightforward supply chain, which increased the complexity of routes into pharmacies and increased their workload (Campling, et al., 2022). Additionally, due to the involvement of multiple intermediaries, it becomes difficult to track and trace products accurately. This lack of transparency can result in counterfeit or substandard drugs entering the market, posing serious risks to patient safety.

To provide the best possible service to patients, PSC requires excellent relationships with suppliers and a high level of trust. Many hospitals have established contracts with a few big wholesalers, which enables them to negotiate prices and obtain better deals. In contrast, community pharmacies are not in a privileged position to negotiate contracts with their suppliers; instead, they develop collaborations with their suppliers or establish their own wholesaler company and supply their stores (Papalexi, et al., 2019).

Various types of contracts serve as evidence of promises regarding the performance of various types of transactions in a given timeframe. They outline the methods, means, and procedures for conducting certain events between two parties. In general, contracts are enforceable, which means that neither party can deny fulfillment of the agreed promises, whether they are manufacturers, suppliers, or distributors. An enforcing body must be able to verify the validity of a contract for it to be enforceable. It will become a legally binding contract if there is a verifiable body, such as a court. Choosing the right contract design can assist in solving problems such as zigzag material flow, uncertain demand and supply, constrained production capacity, and technological effort (Sharma & Modgil, 2013).

It is not only the suppliers that create complexity in the system but also the presence of multiple stakeholders. For instance, there are several stakeholders involved in the delivery of medicines in the PSC, including general practitioners (GPs), nurse practitioners (NPs), secondary care physicians, and pharmacists. These diverse stakeholders have different roles and responsibilities, and they are all required to work closely together to ensure that the medicines are prescribed correctly and delivered on time. As a result of this complexity, the system becomes more difficult to manage (Papalexi, et al., 2019).

PSC's complexity is also derived from forecasting demand in push-based SC, which guides the quantity and type of products to be kept. Push-based SC requires forecasting demand in order to properly plan inventory levels. However, a high level of demand uncertainty exists within the pharmaceutical supply chain due to both the nature of pharmaceutical products and regulatory constraints (Jamali, et al., 2010; Bhakoo, et al., 2012).

CHAPTER 5- CONCLUSION

5.1. Conclusion

During the last decade, many obstacles and challenges have been experienced across the pharmaceutical supply chain that have adversely affected the quality and availability of medications to patients and have had a detrimental impact on the price and quality of medications on the market. This paper summarizes those challenges and obstacles.

Several factors contribute to drug shortages, including manufacturing issues, supply chain disruptions, regulatory challenges, and unforeseen events such as natural disasters or pandemics. So, it is important to note that drug shortages are caused by inadequate supplies of pharmaceutical products that cannot meet the increasing demand, which can have serious consequences for patients, healthcare providers, and the entire healthcare system. The Greek pharmaceutical industry has shown positive production and distribution indicators (SfEE & IOBE, 2021), however, the Greek National Organization for Medicines (EOF) reported 148 medicine shortages in its latest announcement, and approximately 400 medications were in short supply as of mid-March 2023. Shortages are much more common than reported, but they are reported less often.

In light of the complexity and extensive nature of the pharmaceutical supply chain, this paper highlights the challenges and obstacles that face the downstream portion of the supply chain. In other words, these are challenges and obstacles that affect the activities that involve products after they are produced, from distribution to delivery to the final consumers or customers. All participants in the downstream pharmaceutical supply chain are involved in some way. These include suppliers, retailers, central pharmacies, hospital pharmacies, and care services.

To address the thesis problem, it was necessary to define supply chain management and pharmaceutical supply chain, as well as discuss and analyze the types of supply chains and their activities (Chapter 2). Additionally, it was important to highlight the main characteristics of pharmaceutical products and the pharmaceutical industry compared to other products and industries. It was also explained in Chapter 3 the role of the key players or stakeholders is in the pharmaceutical supply chain, as well as the current Greek pharmaceutical supply chain.

According to an analysis of many articles, six main obstacles and challenges facing the downstream pharmaceutical supply chain during the past decade have been identified. First, inventory management: Pharmaceutical products are unique in that they have a limited shelf life and long development cycles, which makes it extremely challenging to find a point where safety stock can be maintained with minimum wastage and the lowest overall cost while also ensuring sufficient quantities are available in case of emergency or unpredictable demand.

The second challenge facing PSC is inaccurate forecasting and forecasting of demand with a high error rate and long delivery lead times. This can pose a significant obstacle to inventory management and can lead to excess inventory, stockouts, and ultimately financial losses.

Inadequate inventory management and inaccurate demand forecasting could lead to the third obstacle, waste management. Patients' and physicians' behavior, temperature control, and poor communication among the actors in the PSC are also considered to be major factors contributing to medicine waste. There are, however, several challenges associated with managing pharmaceutical waste due to the complex nature of the supply chain. One key challenge is the diverse range of waste types, each requiring specific handling and disposal methods. Additionally, the strict regulations governing pharmaceutical waste disposal add complexity to waste management practices. Therefore, environmental issues have arisen.

Lack of coordination and communication among pharmaceutical supply chain stockholders is another barrier to an ideal PSC. When there is a lack of coordination and communication, ensuring that the right medicines are available in the right quantities and at the right time becomes challenging. This can result in increased wastage of pharmaceuticals as expired or unused medications are not properly identified and removed from the supply chain.

There are many risks associated with the pharmaceutical supply chain. Counterfeit drugs, product recalls, supply chain disruptions, and data security concerns pose significant challenges requiring proactive risk management strategies. Therefore, inadequate risk management is the fifth challenge facing PSC.

Finally, the complexity of the pharmaceutical supply chain poses significant challenges and obstacles to achieving an ideal supply chain. The intricate and multifaceted nature of the pharmaceutical supply chain, involving various stakeholders

such as manufacturers, distributors, wholesalers, and retailers, contributes to its complexity. This complexity often leads to inefficiencies, delays, and increased costs, which can impede the smooth flow of pharmaceutical products from manufacturers to end-users.

5.2. Limitation and further research

This study, like any others, is not without limitations. There were only 55 articles selected for the study. It has been shown that the selection of keywords and the screening procedure can be arbitrary and biased. However, text mining has been used to confirm the selection of keywords in an attempt to overcome this limitation.

Additionally, because the research primarily focuses on the challenges and obstacles in PSC from the downstream part, studies that do not have a clear connection to this part may be overlooked.

Future attention should be paid to the technological and blockchain obstacles that the downstream part of PSC may face, as well as the legal and regulatory problems of PSC, which are not fully considered. In this study, the focus is on the downstream practices of the PSC. In addition, it would be beneficial to examine the PSC as a whole to better understand the influences generated by other stakeholders' actions, such as those of pharmaceutical companies.

Furthermore, the theoretical perspective of this study generates another avenue for future research in which innovative approaches can be identified and implemented to enhance PSC performance and the role of artificial intelligence in finding a solution for PSC obstacles and challenges.

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