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COIMBRA

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Optimizing Perishable pharmaceutical supply chains

Dissertação no âmbito do Mestrado em Engenharia Biomédica, orientada pelo Professor Doutor Samuel Moniz e apresentada à Faculdade de Ciências e Tecnologias da Universidade de Coimbra.

Julho de 2023

FACULDADE DE
CIÊNCIAS E TECNOLOGIA
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Coimbra, 2023

Agradecimentos

Gostava de começar por agradecer ao meu orientador, Professor Samuel Moniz, pela oportunidade de desenvolver esta dissertação na área de investigação operacional, obrigada pelo voto de confiança. Aos meus colegas de projeto de investigação, obrigada por me terem recebido tão bem no DEM, em especial à Catarina Bessa, obrigada por toda a ajuda.

Aos meus colegas de laboratório que rapidamente se tornaram amigos, Camila e André, obrigada por terem sido a melhor companhia nestes últimos meses, todas as pausas ao sol e gargalhadas tornaram esta fase mais leve.

Às melhores amigas que a universidade me trouxe, obrigada por todas as memórias que criámos até hoje e pelas que ainda estão por vir. Piri, um obrigada nunca vai ser suficiente para agradecer toda a tua paciência para me ouvires e ajuda que me dás. Bia, obrigada pela tua energia contagiante e por veres sempre o melhor de cada situação, fizeste, sem dúvida, estes últimos anos mais bonitos. À Mari e à Filipa, à minha Beirão e Montenegro, um grande obrigada por terem feito parte destes últimos 5 anos, não teria sido o mesmo sem a vossa amizade.

À Nês, Nemo, e Tança, obrigada por esta amizade que já dura 12 anos. Crescemos juntas e partilhámos momentos inesquecíveis, a vida vai ser sempre mais bonita com vocês.

O obrigada mais especial ao Artur, obrigada por todo o amor, por partilharmos a vida e sonhos.

Por fim, um obrigada de coração cheio à minha irmã, à minha mãe, e ao meu pai. Rita, és a prova que nunca é tarde para seguirmos os nossos sonhos, obrigada por me inspirares todos os dias, pela motivação e apoio. Mãe e Pai, obrigada por me darem e apoiarem em tudo.

Para o Engenheiro que inspirou todo o meu percurso, o meu pai.

Resumo

A indústria farmacêutica desempenha um papel vital na sociedade, fornecendo medicamentos essenciais e melhorando a qualidade de vida das pessoas. Além disso, é responsável por garantir que os medicamentos são fornecidos no momento e local correto e na quantidade ideal. No entanto, esta indústria tem vindo a enfrentar pressões decorrentes da mudança de paradigmas e da evolução das tendências e preocupações da sociedade. As cadeias de abastecimento farmacêuticas distinguem-se das outras cadeias de abastecimento pelas suas características únicas, uma vez que os medicamentos são produtos críticos. Mesmo a mais pequena perturbação numa cadeia de abastecimento farmacêutica pode conduzir a crises graves, como evidenciado pela recente pandemia COVID-19.

Tendo em conta estes desafios, a otimização das cadeia de abastecimento farmacêuticas surgiu como um promissor campo de investigação. Este trabalho apresenta um modelo matemático que otimiza uma rede de uma cadeia de abastecimento farmacêutica de quatro níveis. Partindo da literatura existente, o modelo proposto considera o período de vida útil dos produtos, múltiplos produtos, múltiplas condições de armazenamento, e diferentes padrões de procura entre as faixas etárias da população. O modelo incorpora duas funções objetivo: a minimização do custo total e a minimização do número de encomendas em atraso.

O modelo proposto baseia-se na programação MILP e integra decisões relacionadas com a integração de instalações na rede, inventário, produção e distribuição, considerando a perecibilidade dos produtos. Para testar e analisar a eficácia do modelo, é efetuado um caso de estudo sobre a distribuição de vacinas contra a COVID-19, o que permite uma avaliação exaustiva e uma visão valiosa das implicações práticas do modelo.

Palavras-chave: Cadeia de Abastecimento Farmacêutica, Planeamento e Desenho da Rede, Otimização, Programação Linear Inteira Mista (MILP), Perecibilidade de Produtos

Abstract

The pharmaceutical industry plays a vital social role by providing essential medicines and improving the quality of life for individuals. It is responsible for ensuring that medicines are supplied at the right time, place, and quantity. However, the industry faces pressures from shifting paradigms and evolving social trends and concerns. Pharmaceutical supply chains are distinguished from other supply chains by its unique characteristics, since medicines are critical products. Even the slightest disruption in a pharmaceutical supply chain can lead to severe crises, as highlighted by the recent COVID-19 pandemic.

In light of these challenges, pharmaceutical supply chain optimization has emerged as a promising field of research. This work presents a mathematical model that optimizes the network design of a four-level pharmaceutical supply chain. Departing from existing literature, the proposed model considers the shelf life of products, multiple products and storage conditions, and different demand patterns among age groups in the population. The model incorporates two objective functions: minimizing the total cost and minimizing the number of backorders.

The proposed model is based on mixed-integer linear programming and integrates decisions related to facility integration in the network, inventories, productions, and distributions, considering the perishability of products. A case study on the distribution of COVID-19 vaccines is conducted to test and analyze the effectiveness of the proposed model, allowing a comprehensive evaluation and valuable insights into the model's practical implications.

Keywords: Pharmaceutical Supply Chain, Network Design, Optimization, Mixed-integer Linear Programming (MILP), Product Perishability

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List of Abbreviations

API Active Pharmaceutical Ingredient. 7, 11, 30, 44, 45, 46, 47, 48, 49, 50, 52, 53, 56, 60, 61, 62, 63, 64, 67, 68, 69, 70, 73, 76, 77, 79, 80, 81, 83
AtMI Access to Medicine Index. 36

CMOs Contract Manufacturing Organizations. 20
CO_2 carbon dioxide. 33, 36
COVID-19 Coronavirus disease. 1, 4, 10, 13, 35, 59, 60, 61, 65, 67, 85, 86, 87
CSCMP Council of Supply Chain Management Professionals. 13
CSR corporate social responsibility. 36

DALY Disability-Adjusted Life Year. 36
DC Distribution Centre. 12, 13, 31, 34, 37, 44, 45, 46, 47, 48, 49, 50, 51, 53, 54, 55, 56, 57, 61, 62, 64, 68, 70, 71, 73, 76

EMA European Medicines Agency. 7, 17, 60
EU European Union. 5, 10, 12, 34, 60

FDA Food and Drug Administration. 7, 17
FIFO first-in-first-out. 38, 39

GDP Gross Domestic Product. 34, 63, 64

LCA Life-Cycle Assessment. 32, 34, 36, 41

MILP Mixed Integer Linear Programming. 24, 28, 30, 31, 32, 33, 34, 35, 36, 37, 39, 46
MINLP Mixed Integer Nonlinear Programming. 24, 34, 36, 37
MIP Mixed Integer Programming. 24
MOMP Multi-Objective Mathematical Programming. 66, 68, 82

NDA New Drug Application. 7
NLP Nonlinear Programming. 24
NPD New Product Development. 7
NPV Net Present Value. 28, 30, 31, 33, 34, 36, 41

PSC Pharmaceutical Supply Chain. 1, 2, 3, 4, 5, 9, 11, 13, 15, 16, 17, 22, 24, 26, 28, 31, 33, 35, 37, 39, 40, 43, 44, 45, 60, 67, 70, 83, 85, 86, 87

R&D Research and Development. 5, 6, 7, 9, 16, 17

SC Supply Chain. 1, 2, 3, 4, 7, 9, 10, 11, 12, 13, 14, 15, 17, 18, 19, 20, 21, 23, 24, 28, 33, 34, 36, 37, 38, 39, 41, 43, 44, 49, 52, 59, 60, 63, 68, 69, 70, 76, 77, 79, 80, 81, 82, 83, 85, 86, 87
SCM Supply Chain Management. 3, 13, 14, 27, 37, 87
SSCM Sustainable Supply Chain Management. 19

TBL Tripple Bottom Line. 18, 19

WHO World Health Organization. 6, 59, 65

1

Introduction

This chapter consists of a introduction to this master dissertation. A contextualization for the problem under study is presented in section 1.1. In section 1.2 the motivation that supported this dissertation is highlighted, and in section 1.3 the dissertation's proposed objectives are defined. Finally, the structure of this document is found in the last section of this chapter, section 1.4, where the methodology employed to accomplish the proposed objectives is described.

1.1 Contextualization

The pharmaceutical industry contributes significantly to the healthcare structure of each country through the development of new medicines that directly affect population's quality of life [10]. Furthermore, the pharmaceutical industry plays a crucial part in the European economy due to the employment of thousands of people [11]. This way, the socioeconomic growth path of each country must be sustained by a strong healthcare system and therefore, by a robust pharmaceutical sector [10].

The Pharmaceutical Supply Chain (PSC) is one of the most vital networks in healthcare [12]. The PSC is a large network from product development until the customers, including the suppliers, manufacturers, distributors, and retailers. It also covers the location, number, and capacity of network facilities, as well as the flow of materials among them. The final product is created and delivered through the collaboration of all parties involved [13]. In today's global economy, the more competitive the industrial environment becomes, the more important the structure and coordination of a company's Supply Chain (SC) also becomes [14]. As highlighted by the recent Coronavirus disease (COVID-19) pandemic, the smallest disruptions in PSCs might lead to severe crises.

Moreover, the pharmaceutical sector faces significant difficulties, such as, the growth in SC complexity, the emergence of legal regulations; the increase of individualized treatments; the entry of new competitors; and the strengthened regulations

concerning economic, environmental, and social issues, all of which increase investment costs and lower profit margins [2, 15].

Since in healthcare the two most significant aspects are time and accuracy, the PSC should have the ability to adapt to changes, maintaining demand satisfaction and, therefore, coordination between all PSC parties involved is critical for effective production and delivery times [13]. By providing products on time and at the lowest possible cost, a solid SC network can increase customer satisfaction and, consequently, contribute to a company's survival in the competitive market [16].

Adding to this, the complexity and criticality of network design increases when dealing with perishable products [17]. Perishable products, such as medicines, have a limited shelf life and, if they are not consumed or used before their expiration date, they are discarded and result in waste. This leads to economic losses for companies, wastage of resources, environmental issues, and potential shortages of critical medicines [18]. Therefore, optimizing SCs for perishable pharmaceutical products is a key strategy to enhance the efficiency and resilience of these networks.

In light of these concerns, it is expected that pharmaceutical companies incorporate new strategic approaches [2]. Researchers and several companies believe that decision support systems and modeling tools should be implemented to achieve agility and improved responsiveness in the operations at every stage of the SC [19, 20].

1.2 Motivation

The creation of the *FuturePharma* project aims to improve the integration of complex decisions that take place at many levels of the PSC. This project presents the concepts of sustainability, cost-effectiveness and adaptability in light of the complexity and uncertainty of this highly regulated industry, by implementing optimization models that incorporate these objectives.

FuturePharma research project focuses on the development of mathematical optimization models for designing responsive and sustainable PSCs. Even in scenarios of considerable product and process diversification, the *supply chain of the future* must maintain short response times.

1.3 Objectives

The present dissertation intends to contribute to the *FuturePharma* project and address some of the challenges faced by the pharmaceutical industry through the conceptualization and implementation of an optimization model for the planning

and design of a perishable PSC, that aims to act as a tool for supporting decisions.

In order to achieve this, the present dissertation aims to accomplish the following additional objectives:

- Provide background information on the pharmaceutical industry;
- Comprehend the paradigm shift occurring within the pharmaceutical industry;
- Conduct a literature review on research focused on PSCs and the most commonly used optimization models;
- Develop and implement a thorough decision-support tool for the planning and design of a PSC under perishability;
- Apply the developed model to a case study and analyze its results.

1.4 Methodological Approach

The methodology employed in the present dissertation is structured as follows:

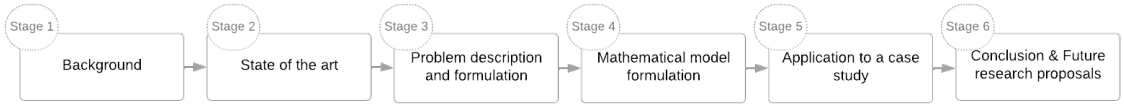

Figure 1.1: Dissertation's methodological approach.

Stage 1 - *Background: Context on the pharmaceutical industry*

The initial stage of the dissertation focuses on providing comprehensive insights into the problem being addressed. At this stage, the dissertation provides an extended analysis of the pharmaceutical industry sector and its SCs, with the aim of identifying the current challenges that it faces. A strong theoretical foundation is established to contextualize the problem under study, while also addressing concerns regarding the future of this field, emphasizing the ongoing paradigm shift and the growing significance of concepts in Supply Chain Management (SCM). By recognizing the prevailing problems and obstacles within the current pharmaceutical sector, the dissertation further explores their connection to the optimization of SC processes.

Stage 2 - *State of the art: Literature review on optimization models*

During the second stage of the research, a comprehensive literature review is conducted, specifically focusing on PSC network design models. The review encompasses an examination of the current literature on PSCs network optimization, analyzing the existing models documented in literature. By critically evaluating the

existing literature, this stage identifies a gap in the current SC network optimization models.

Stage 3 - *Problem description and formulation*

The third stage of this research is devoted to the presentation and description of the design and planning problem that the study aims to address. A comprehensive overview of a generic multi-product and multi-period four-level SC is provided, highlighting its significant components and characteristics. Additionally, the chosen optimization method to model perishability is identified.

Stage 4 - *Mathematical model formulation*

In this stage, a mathematical model is proposed to provide a decision-support tool for the design and planning of a perishable PSC. Beyond the chosen optimization method for modeling perishability, the model will undergo relevant adaptations to provide solutions that address some unique requirements of the pharmaceutical industry. The decisions supported by the model will primarily focus on strategic and tactical levels, considering factors such as patient-centered goals by the minimization of delivery delays. Simultaneously, cost control remains a key perspective, as the pharmaceutical industry must maintain profitability while ensuring efficient operations.

Stage 5 - *Application to a case study: Model validation and results analysis*

In the fifth stage of the research, the model developed to address the problem outlined in stage 3 is applied to a case study focused on the network design of a COVID-19 vaccine SC. This case study, besides validating the model developed, serves as a motivating example to demonstrate its practical applicability. The analysis is centered on a trade-off between the costs of the SC and the population that suffers a delay in vaccination.

Stage 6 - *Conclusion & Future research proposals*

The final stage of this dissertation encompasses a concise and comprehensive discussion of the main conclusions derived from the research conducted. It highlights the main conclusions and results obtained throughout the work. Additionally, this stage addresses the limitations and challenges faced during the research process, highlighting areas where further improvements can be made.

2

Background Concepts

This chapter provides a comprehensive introduction to the pharmaceutical industry, encompassing various key aspects. Section 2.1 starts with the contextualization of the pharmaceutical industry environment, emphasizing its significant impact on the healthcare sector. Additionally, subsection 2.2.3 explores the pressing issue of the limited shelf life of pharmaceutical products. Moving forward, section 2.2 introduces the concept of PSCs, revealing their dynamics and operations. Finally, section 2.3 provides a comprehensive overview of the current challenges faced by the pharmaceutical industry, considering the ongoing paradigm shift within the sector.

2.1 The Pharmaceutical Industry

2.1.1 Pharmaceutical Sector

The pharmaceutical industry encompasses a range of operations and organizations dedicated to the exploration, advancement, and manufacturing of drugs and medical products [15].

According to the European Federation of Pharmaceutical Industries and Associations [1], the pharmaceutical industry contributes to medical advancement not only via Research and Development (R&D) but also by bringing new medicines to citizens worldwide that improve their health and quality of life. In Europe, the average life expectancy of citizens in the current year of 2023 is up to 30 years longer than it was last century [1].

Furthermore, according to EUROSTAT data, the pharmaceutical industry has the highest added value per person employed when compared with other sectors. For instance, in 2020, 830,000 individuals were employed directly in the European Union (EU) by the pharmaceutical industry and three times more individuals were employed indirectly, turning it into a crucial part of the European economy [1, 11].

In 2020, the global pharmaceutical market was estimated to be worth €943,667 million at ex-factory sales, being ex-factory sales the price that a manufacturer

charges for a direct purchase, i.e., without shipping, handling or taxes [1, 21]. Furthermore, the European market counted for 23.9% of global pharmaceutical sales in 2020, while the North American market remained the largest with a 49.0% share [1].

2.1.2 Importance and Impact in Healthcare

Numerous new research directions for better treatment and disease prevention have been made possible by technological advancements in R&D. The development of new medicines increases both quality of life and average life expectancy of the population, making research-based biopharmaceutical firms play a particularly important role in enhancing global health [10].

The pharmaceutical industry plays a crucial role in supporting the healthcare systems of each country. Through the development of medicines and vaccines, it not only enhances people's health and well-being but also contributes to the financial sustainability of healthcare. By reducing the need for costly surgeries and prolonged hospital stays, medicines and vaccines generate significant cost savings, thereby supporting the long-term viability of healthcare systems [2, 10].

In Europe, medical goods, including medicines, account for the smallest proportion of healthcare spending, with an average of 19.1%. This highlights that medicines are the most cost-effective element within the healthcare sector [1].

Moreover, every country's path of socioeconomic growth must be supported by a strong healthcare system and, therefore, by a robust pharmaceutical sector [10]. However, not all populations around the world have yet completely profited from these medical advancements. A continuing objective of The World Health Organization (WHO) is to ensure that everyone has access to medicines with a reliable supply [10, 22]. In order to successfully address these concerns, governments, public society, and the private sector must make sustained commitments [10].

2.1.3 From Product Development to the Market

Nevertheless, the pharmaceutical sector confronts significant difficulties. An average time of 12 to 13 years will have passed after the first phase of developing a new pharmaceutical product by the time it is available on the market. Moreover, only 1 or 2 compounds out of every 10,000 created in laboratories successfully complete the necessary phases of development to become a commercial medicine, i.e., the chances of a new pharmaceutical achieving a successful outcome are extremely low [1].

There are five main activities in the phase of developing a new product: discovery, pre-clinical trials, clinical trials, the regulatory approval process and subsequent product launch, which also encompasses post-market pharmacovigilance [2].

The first activity, discovery, consists of identifying the therapeutic targets related to a pathology by testing thousands of chemical compounds until a promising new molecule known as an Active Pharmaceutical Ingredient (API) is discovered [2, 23].

Then follows the pre-clinical trials, where chemical and biological tests are conducted in animals to demonstrate the selectivity, safety, and efficiency of the candidate molecule [23].

The third stage is the most expensive and time consuming activity during New Product Development (NPD) due to all the procedures necessary to demonstrate the molecular entity's safety and effectiveness [24]. In 2019, pharmaceutical companies invested more than €37,700 million in R&D in Europe, with almost 50% representing clinical trial costs, as illustrated in Figure 2.1 [1]. The API is initially studied in healthy volunteers during phase I of clinical trials, primarily to determine its safety and dosage. With the results of dosage determination, the drug in then administered to diseased and unhealthy patients during phase II [23]. Finally, during phase III, extensive tests are carried out to compare the effectiveness of the new medicinal compound with other presently available therapies, as well as to assess its long-term impacts [2, 23].

The filing of a New Drug Application (NDA) occurs once all stages of clinical trials have been successfully concluded. In Europe, drugs are approved by the European Medicines Agency (EMA), and in the United States by the Food and Drug Administration (FDA) [23]. The probability of clinical success, i.e., the estimated probability of a newly developed drug successfully obtaining approval after undergoing clinical trials is 11.83% [25]. Moreover, despite continuous attempts to standardize regulatory requirements and procedures across all countries, there are still substantial discrepancies that make the product's SC more difficult. This issue will be addressed in more detail in Section 2.2 [24].

Unfortunately, the product development process in the pharmaceutical industry is generally inefficient and productively low. Hence, the main challenges faced by this industry include the need to reduce development time, accelerate time-to-market, and minimize development costs [2].

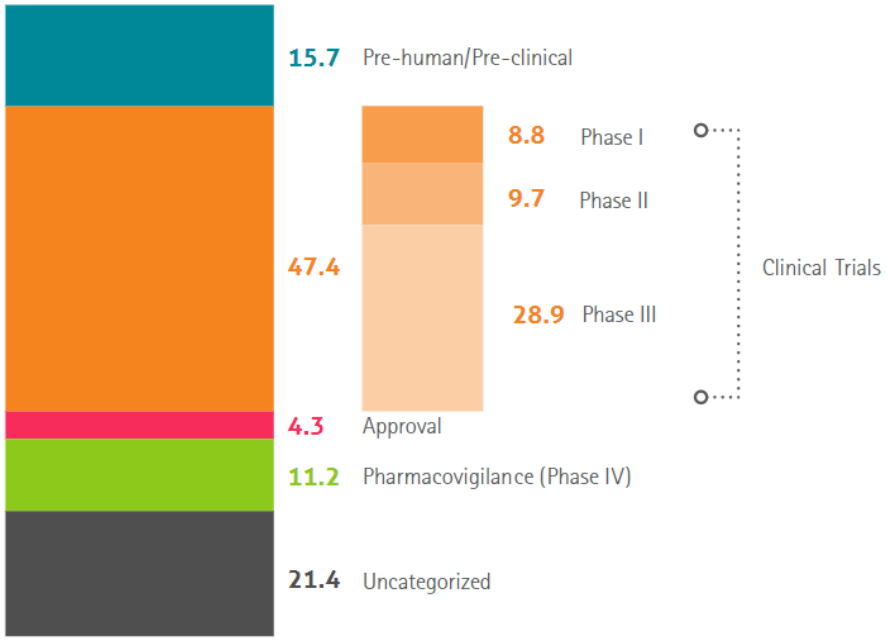

Figure 2.1: Allocation of R&D investment by main activity. From [1].

2.1.3.1 Pharmaceutical Product Life Cycle

The discovery and product development described above are part of the pharmaceutical product Life Cycle. After passing all these stages, successful products are launched into the market [24]. Once in the market, the new product goes through a growing phase in sales, reaches market maturity, and then enters a decline phase (see Figure 2.2) [26].

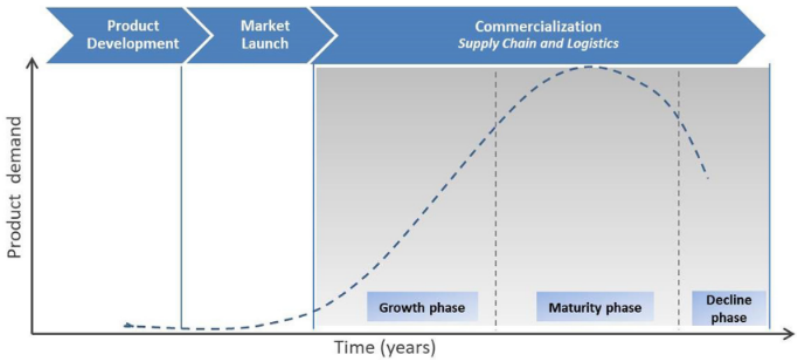

Figure 2.2: Pharmaceutical Product Life Cycle. From [2].

The growth rate depends on a variety of factors, such as the comparative effectiveness of the product versus other therapies, potential adverse effects that may appear after the medication is used, and economic factors [2]. Depending on these

factors, the level of demand that the product reaches at the maturity phase is established [2].

Furthermore, as with any other product, in the maturity phase more competitors will penetrate the market and unit sales will decline relatively quickly as customers prefer newer and usually cheaper alternatives [27]. For the pharmaceutical industry this means that after the product reaches its life patent, generics manufacturers introduce their alternatives drugs with a lower price (generally about 25% lower) to capitalize on the market that the original brand has established [24, 28].

Generic drugs are bioequivalent alternatives, with the same active components, dosage form, quality, safety, strength, and method of administration as the original brand product. However, the regulatory approval is usually much faster and does not require as many rounds of clinical trials and all the associated costs since the drug formula has already been proven safe and effective [28]. Hereupon, to respond and maintain the necessary service levels, companies must take action to guarantee adequate management of production, capacity, and supply distribution [2].

Several functional areas inside the organization, including R&D, production, and SCs, handle multiple aspects of the product life cycle. All these involved parties are guided by strategic choices made regarding capital expenditure allocation, growth and marketing plans, product and technology portfolio management and SC design choices [24].

2.2 Pharmaceutical Supply Chain

The SC and logistical organization play a crucial part in the commercialization phase of the pharmaceutical product life cycle. By providing products on time and at the lowest possible cost, a solid SC network may increase customer satisfaction and, as a result, contribute to the company's survival in the competitive market [16].

One of the most crucial SCs in healthcare is the PSC [12]. The PSC is a complex network of suppliers, manufacturers, distributors, and retailers, such as hospitals and pharmacies. It also includes the selection of network facilities' locations, numbers, and capacities and the materials' flow between them. The coordination between all involved generates and delivers the final product [13].

Therefore, a SC is an integrated process where several different entities collaborate in the sense of acquire raw materials, transform the raw materials into the final product, and deliver the final product to retailers [3].

Hence, it is naturally characterized by the direct flow of materials and the

reverse flow of information [3].

In another way, two fundamental, interconnected processes make up a SC: the Production Planning and Inventory Control Process, and the Distribution and Logistics Process, illustrated in Figure 2.3 [3].

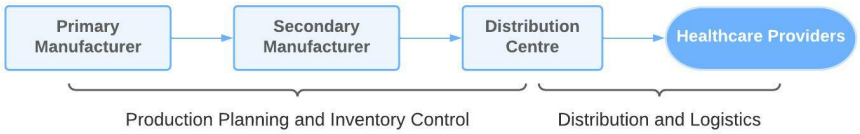

Figure 2.3: The PSC process. Adapted from [3].

Furthermore, as a result of globalization, these channel partners can be located in various locations worldwide, as represented in Figure 2.4, which forces pharmaceutical companies to cope with different policies, cultures, and tax systems from other regions [2]. When each of the parties involved operates independently and follows its own operational goals, the lack of coordination between structures is higher and enhances the probability of disruptions and inefficiencies to occur, which may spread along the whole SC network [2, 29].

Figure 2.4: Supply chains globalization. From [4].

For instance, drug shortages are a common occurrence. In 2020, the European Commission expressed concerns regarding the growing number of reports indicating shortages that have been impacting all Europe, usually caused by SC disruptions [30, 31].

Moreover, the global SC's already-existing problems have been exacerbated by the shortages of medicines needed to treat patients of hospitals both in the United States and EU during COVID-19 pandemic [31].

The availability of medicines in healthcare providers, such as, pharmacies and hospitals, is directly impacted by the lead time of the SC, i.e., the amount of time between when a supplier receives an order for a medicine and when the order is delivered to the entity submitting the request [32].

2.2.1 Pharmaceutical Supply Chain Network

For a better understanding of the PSC, a description of all the parties involved in the network is presented.

Primary Manufacturer (Supplier)

The first level of the PSC consists of the production of the API and might experience severe demand variations [33]. However, demand is generally low so, to spread the capital costs, the resources (plants) are usually shared between products. To prevent cross contamination, when a manufactured product is changed, a thorough cleaning is required, which typically takes a lot of time. This way, planning complexity (number of different products using the same resource) should be kept to a minimum [33].

As a result of the low production volumes, transportation costs are negligible at this point in the SC and the primary locations might be anywhere in the world, generally in developed countries due to the costs of establishment, such as, tax rates, availability of skilled workers, and political and economic stability [5, 33].

To summarize, this level is characterized by lengthy cycle periods, which make ensuring responsiveness challenging [33].

Secondary Manufacturer

Transportation to the secondary manufacturer facility often takes between one or two weeks by ship, the standard form of transportation, and one or two days by aircraft [15].

At the secondary manufacturers the final product is produced in a suitable form for final consumers by adding inert materials, called excipient, to the active ingredient produced at the primary manufacturer. For instance, a product available in pill form would undergo a series of steps. These include granulation, where excipient materials are added, followed by compression to form the pills. Subsequently, coating is applied, quality control measures are conducted, and finally, packaging is carried out [15].

When inert materials are added to the API and the drugs are processed and packed, the product's volume and mass increase, leading to a significant increase in transportation costs. Therefore, unlike the previous case, at this point of the

SC they can no longer be neglected. As a result, there is often a greater number of secondary manufacturing facilities compared to primary ones. These secondary facilities supply regional or local markets and are strategically located closer to these markets than the primary manufacturers [33].

Distribution Centre

The next step consists of final products' transportation to Distribution Centres (DCs) [5]. Healthcare distributors play a central role in the distribution of products and the European healthcare industry cannot function without them [34]. Wholesalers are the link between the manufacturers and the healthcare providers such as hospitals and pharmacies through firstly purchasing and warehousing. Hence, these facilities are responsible for ensuring the constant availability of a full range of products as determined by the market and the authorities [34]. Moreover, they are also responsible for order preparation and delivery of products [34].

According to the European Healthcare Distribution Association annual report of 2021/22 [34], distributors ensure the fast, continuous, and cost-effective supply of medicines to more than 200,000 healthcare retailers throughout the EU, reaching over 500 million patients.

As illustrated in Figure 2.5 below, manufacturers provide 35% of products directly to hospitals, 7% to pharmacies and 58% to wholesalers, who then handle distribution to healthcare retailers [34].

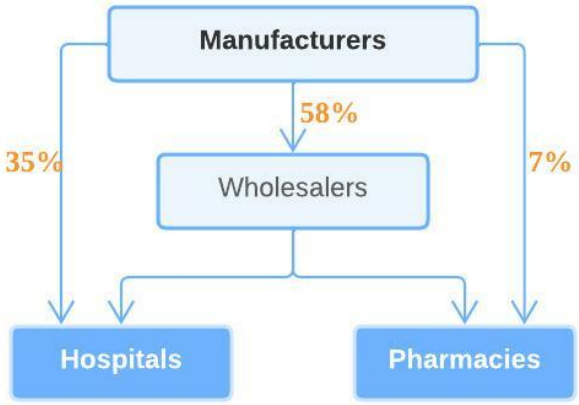

Figure 2.5: Distribution channel model for 2021. Adapted from [5].

Furthermore, DCs also have a financial function between manufacturers and retailers, insuring the cash flow.

Healthcare Providers (Retailers)

Finally, retailers correspond to the final level of the PSC. As already mentioned, healthcare providers receive most of the pharmaceutical products thought DCs and, then, deliver them to the patients.

It is based on the needs of the patients that the flow of information begins and, when the response to demand is not efficient, there may be a shortage of stock.

PSCs should be capable of satisfying demand at any and all times, adapting to changes, and withstanding disruptive events like pandemics, crises, natural catastrophes, among others. However, the accuracy of this characterization has been challenged in reality, as evidenced by the impact of the COVID-19 pandemic [31].

Nevertheless, even before COVID-19 pandemic, drug shortages were already a concern. A 2019 survey of hospital pharmacists in Europe [35] found that drug shortages are a current issue in providing patients with the best care, according to 95% of respondents, whilst 63% considered that their hospital's patient care was impacted by these shortages.

Drug shortages can result from one or multiple SC issues, such as unavailability of raw materials, or manufacturing capacity problems, but they can also result from demand issues [36, 37].

It is the retailer's responsibility to maintain an inventory of products and decide at what point and in which quantity to reorder a new batch of products [38]. While events as natural disasters and pandemics are unpredictable, average demand growth, and seasonal demand are predictable [36].

To reduce the estimated cost of acquiring and storing products, the retailer must establish an ideal inventory policy since a well-established system can avoid the shortages from predictable reasons [36, 38].

With always bearing in mind that in healthcare the two most significant aspects are time and accuracy [13], coordination between all network agents is critical for effective production and delivery times.

2.2.2 Supply Chain Management

In the current global economy, as the industrial environment becomes increasingly competitive, the organization and coordination of a company's SC becomes more crucial. This can be effectively achieved through SCM [14].

SCM is defined by the Council of Supply Chain Management Professionals (CSCMP) [39] as "the planning and management of all activities involved in sourcing and procurement, conversion, and all logistics management activities. Importantly,

it also includes coordination and collaboration with channel partners, which can be suppliers, intermediaries, third party service providers, and customers".

This definition leads to a number of conclusions. Firstly, any facility that affects system effectiveness and contributes to bringing the final product to the costumer is considered by SCM. Secondly, the objective in SCM is to achieve efficiency and cost-effectiveness throughout the entire system. This involves minimizing expenses at all levels, including raw material inventory, manufacturing processes, final product inventory, transportation, and distribution. Finally, since SCM involves planning, implementing, and controlling the logistics, it encompasses all aspects of the company's operations [38].

2.2.2.1 Decision Making Levels

Decision making is the process of selecting certain options to achieve a desired outcome [40]. It comprehends three levels, as illustrated in Figure 2.6.

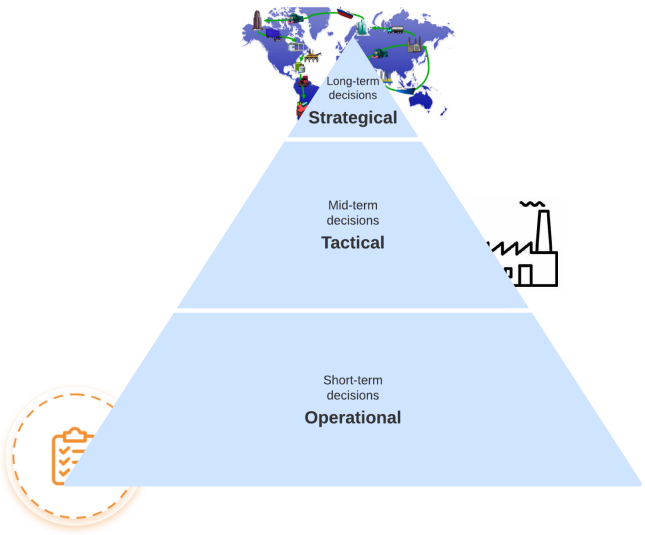

Figure 2.6: Decision making levels. Adapted from [6].

The strategic level consists of long-term decisions that generally involve large investments and have a high impact on the company [2, 38]. Strategic decisions are mainly regarding the design and structure of the SC network, such as, number, location, and capacities of facilities [14, 38].

The tactical level deals with the medium-term planning cycle decisions about production planning, distribution, and inventory management [38, 41].

The operational level refers short-term decisions. These can involve, for instance, decisions about production scheduling and control, vehicle routing, and

equipment maintenance policies that require a constant control on the SC, being taken on a daily or weekly basis [41, 42].

Tactical and operational decisions are strongly influenced by strategic decisions. For example, the location of facilities will affect vehicle routing and inventory control and, therefore, is critical to evaluate all three strategic, tactical, and operational decisions at the same time when designing a SC network [18].

2.2.3 Perishable Pharmaceutical Supply Chains

A challenging issue in a PSC is the product perishability. The shelf life of a drug refers to the period during which its pharmaceutical stability is maintained at a level greater than 90% [5]. Once a drug reaches its expiration date, it is no longer guaranteed to be safe and effective for use. Hence, when products have a limited shelf life, are denominated perishable.

Ignoring the perishability of medicines or lack of attention to its shelf life can have serious consequences. Firstly, it compromises the effectiveness of the drug, which can directly endanger the patient's life [18, 43]. Moreover, from an economic perspective, the waste of perishable goods translates into financial losses [43]. For pharmaceutical companies, the inability to sell expired products leads to lost revenue. In addition, the resources invested in producing, packaging, and transporting these items are wasted when they are not consumed. This not only affects the profitability of companies but also harms overall resource efficiency.

Furthermore, the waste of perishable goods has environmental and social consequences. Discarded perishable products, particularly medicines, contribute to environmental waste, which contains dangerous compounds that represent a threat to the environment and human health if not disposed of correctly [44].

Moreover, the expiricy of medicines can lead to shortages, impacting the availability of essential medications and affecting the well-being of patients who rely on them [18].

Hence, when products are perishable, efficient distribution network designs becomes even more sophisticated, demanding, and crucial [17, 18]. In perishable PSCs, incorrect facility location, inefficient routing, and general chain inefficiency leads to product perishing and, ultimately, an increase in lost demands [18]. A shortage of certain medicines can lead to adverse consequences for patients. In general, to avoid shortages, a potential solution could involve acquiring or manufacturing a substantial quantity of the products in advance. However, when dealing with perishable goods, this approach could potentially result in product perishing, thereby leading

to the consequences mentioned above [18, 45].

2.3 The New Pharmaceutical Paradigm

For many years, the pharmaceutical industry has relied on a business strategy centered around the discovery and development of profitable drugs. However, this strategy has not seen significant updates, leading to a general lack of effectiveness in the industry. Nevertheless, recent trends imply that the market environment for pharmaceutical firms has suffered a lot of change, such as with more individualized treatments, tougher quality control, among others [2].

2.3.1 Pharmaceutical Industry Driving Forces

It has been pointed out by several authors new driving forces that have been changing and challenging the operational panorama of health. Marques et al. [2] reviewed several market reports and identified nine driving forces that have the major impacts on PSC operations.

2.3.1.1 Internal Drivers

The driving forces influenced by companies' behavior are classified as internal drivers and are listed below [2]:

Decline in R&D productivity The discontinues flow of new drugs to replace a close expiring patent drug is, according to Garnier [46], the greatest pharmaceutical sustainability and competitiveness issue.

Decrease in effective patent life Effective patent life is the time between a product regulatory approval and patent expiration, i.e., the period of time that a company has market exclusivity for that product and, consequently, has the chance to recover the investment made in discovery and development [2].

However, the long development cycles already mentioned are delaying the time-to-market, i.e., the speed and rate at which companies can release new products into the market, and thus limiting the possibility for companies to recover the investment [2, 47].

As pointed by Marques et al. [2], currently, research on the product development process in the pharmaceutical industry primarily emphasizes cost reduction and portfolio management. However, there is a growing need for greater attention to be directed towards shortening development times.

Growth in supply chain complexity As seen in section 2.2, PSC network facilities can be located anywhere in the world, creating large and very complex SCs and distribution networks.

2.3.1.2 External Drivers

On the other hand, there are external drivers, i.e., factors that are not in companies' control [2]:

Increasingly regulatory burden The pharmaceutical sector has been facing an increasing regulatory burden since governments all across Europe have imposed fiscal austerity measures, which have had a detrimental effect on the industry [1]. Nevertheless, despite these strict requirements, regulatory agencies like the FDA or EMA are dedicated to creating improved conditions for companies in terms of both clinical trials and manufacturing procedures [2]. However, FDA has already recognized the need for improvements in the pharmaceutical industry and it has taken steps to address these challenges. The Pharmaceutical Quality for the 21st Century Initiative is an example of the FDA's vision to foster a more efficient and adaptable pharmaceutical sector, ensuring the reliable production of high-quality products while minimizing the need for severe regulatory oversight [48].

Pricing pressures As a result of generic products competition, government pressures, public health policies, and competition with other innovative products for the same medical need, the sector has been under pressure to lower prices, which is a difficulty due to the costs involved in R&D [2].

Growth of personalized medicines In contrast to the "one-size-fits-all" approach, a shift to more proactive approach focused on prevention and early treatment is growing [2, 49]. Direct patient benefits from personalization include better therapeutic results, fewer adverse effects, and higher patient adherence to treatments, but also the possibility of lower overall healthcare expenses [2]. Increasingly gaining prominence, in 2020 personalized medicines already accounted for 39% of all new drugs approved by the FDA [50].

The structure and operation of SCs will undoubtedly be significantly impacted by this paradigm change. Instead of mass production, the system needs to mass customization and give individualized treatments to patients at scale [2].

Growth of emerging markets Most of the total pharmaceutical sales are made in developed countries however, nowadays developing countries are in a rapid economic growth, which translates in growth opportunities for the pharmaceutical industry. However, as their SCs become even more global, pharmaceutical firms have to rethink their manufacturing practices and business models [51].

Increased uncertainty Every phase in the SC is subject to uncertainty [4]. There are different methods used for classifying uncertainties, for example, Garcia and You [4] classifies them as strategic if they involve socio-political context changes, unpredictable events, etc., and operational when associated to SC operations changes or execution strategies, such as costs volatility, supply delays, etc. On the other hand, Laínez et al. [24] classifies these two categories of uncertainty as external or internal, respectively. Regardless the classification system employed, it is still extremely difficult for experts to effectively identify and handle all sources of uncertainty and, hence, there is a definite need for innovative approaches [2].

Sustainability concerns Sustainable development was defined in 1987 by the World Commission on Environment and Development as the "development that meets the needs of the present without compromising the ability of future generations to meet their own needs" [52].

While in the past this concept was more focused on the environment, modern literature views sustainability as supported by three key pillars: economic, environmental, and social sustainability, generally known as the Tripple Bottom Line (TBL) (figure 2.7) [53, 54]. From the strategic to the operational level, it is the balance between these three pillars that offers a challenge. Moreover, this balance has been considered to be crucial for organizations to be agile and resilient, leading them to be prepared to react to internal and external risks [55, 56].

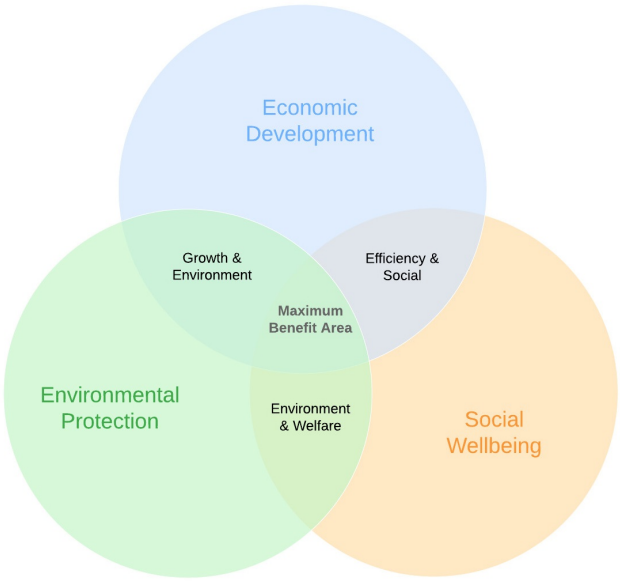

Figure 2.7: Three pillars of sustainability. Based on [7].

Sustainability management during the product development cycle is inducing a shift from cost-oriented development to sustainability-oriented development [6]. Hence, in the modern economic context, a company's long-term success is based not just on its capacity to turn a profit and stay profitable, but also on how it contributes to the future of humanity and the environment [4, 57]. Accordingly, Sustainable Supply Chain Management (SSCM) refers to the management of materials, information, and investment flow within a SC, while emphasizing collaboration among SC partners. Furthermore, it also involves incorporating sustainable development goals from the TBL [58].

2.3.2 Old vs New Paradigm

In light of these concerns, it is expected that the new pharmaceutical paradigm will incorporate the following strategic approaches: a patient-centric model, cost-oriented operations, personalized medicines, outsourcing strategies, a focus on new emerging markets, and a sustainable mindset [2].

Figure 2.8 illustrates the six key outbreaks identified by Marques et al. [2] that contribute to the transition from an old paradigm to a new paradigm: outcome, efficiency, increased value, flexibility, market expansion, and overall welfare.

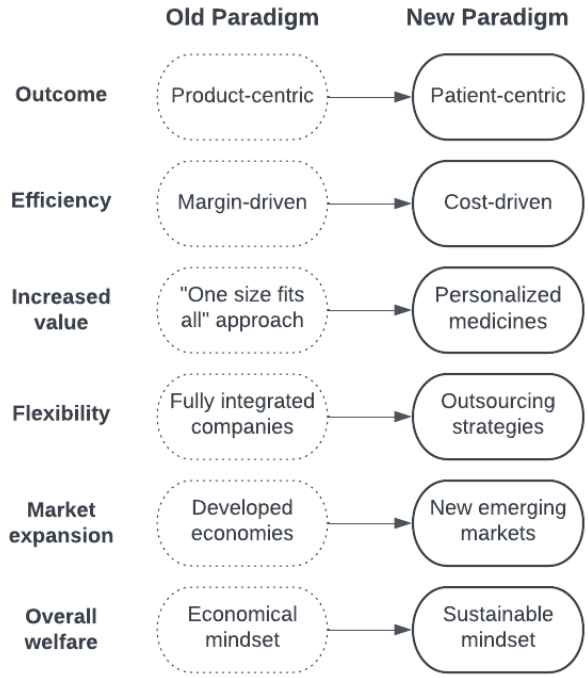

Figure 2.8: Paradigm shift in the pharmaceutical industry. Adapted from [2].

2.3.2.1 Impact of the Paradigm Shift on the PSC

Patient-centricity paradigm puts the focus on the customers instead of the product. To maintain a continuous analysis and evolution of the value proposition of their products, companies will need to strategically engage with patients, focusing on understanding their requirements, expectations, and concerns by innovative product-service solutions and the creation of new distribution and information channels [2].

Cost-driven paradigm means that companies must create advanced decision support tools in addition to cost-effective methods to achieve the aim of cost-effectiveness [2].

Personalized medicines, i.e., patient-specific autologous gene and cell therapies are achieved through a two-step process: diagnostic with tests detecting specific biomarkers and ideal drug prescription [19, 59]. This means a transformation in manufacturing to small-scale, customized agile production that can be cost-effectively made-to-order, with an extensive coordination of the stakeholders in the SC [19, 20].

Outsourcing strategies will be essential to improve the flexibility, i.e., the capability to adjust tactics and operations, of companies [2, 60]. In order to enhance manufacturing capacities and make new technological capabilities accessible, Contract Manufacturing Organizations (CMOs) will be essential [2]. These organizations consist of manufacturing facilities that produce products under contract for multinational pharmaceutical companies, while offering flexible, quicker, and less expensive access [61].

New emerging markets also benefit from outsourcing strategies due to their ability to granting locals access to new markets. With the growth of market expansion, to ensure the availability of medicines in remote areas, companies must adopt critical strategies such as utilizing multiple distribution channels and maintaining high levels of transparency [2].

Sustainable mindset paradigm means that companies must now account for the three pillars of sustainability: economic, environmental and social. In contrast to the previous paradigm only focused on the economy, environmental considerations and eco-friendly approaches must be taken in the design and management of a SC in order to reduce waste, use resources more efficiently and minimize water and energy consumption. In addition, social responsibilities such as accessibility, availability, safety issues, and general access to medicines also need to be taken into account [2, 42].

2.3.3 Pharma 4.0

Enhancing proximity to patients and meeting their needs more effectively can be achieved through the creation and implementation of digital tools. Hence, incorporating decision support systems and modern modeling tools into operations at every stage of the SC can offer agility and enhanced responsiveness, leveraging the power of current technology [19, 20, 62].

The term Pharma 4.0 has been presented to describe the adoption of digital tactics and tools from Industry 4.0 concepts and their application to practices in pharmaceutical manufacturing and SCs [20]. The concept of Industry 4.0 was established in 2011 as a new industrial stage where several developing technologies are combining to produce digital solutions [62, 63]. Industry 4.0 enables considerably better SC coordination as a result of a more integrated approach to communication, and end-to-end information exchange [19, 20]. These concepts are already put into practice by some companies. Take the example of Siemens, which has already developed digital platforms for use by manufacturers [20].

2.3.3.1 Simulation Models & Mathematical Optimization Models

Both simulation models and mathematical optimization models play a role in Pharma 4.0.

Simulation plays a crucial role in the context of the SC as it enables the representation of supply and capacity constraints [64]. Moreover, it provides a visual representation of their effects on the system's behavior over time [64]. Consequently, simulation enables the assessment of operational performance before a system is implemented, providing the following benefits according to Chang and Makatsoris [65]:

- understand of the overall SC processes and characteristics,
- modeling and understanding the impact of unexpected events on the SC,
- minimizing the risk of changes through testing many operation alternatives before effectively changing the SC.

Thus, simulation can be used as a tool to lead companies to do better planning decisions and its use has been increasing in the past years [66].

A valid simulation model is only valid for a certain set of objectives, i.e., a model that succeeds for one objective might not work for another [8].

Moreover, it is important to note that even with significant investment in model development, there is no concept of absolute model validity in simulation. Simulation models can only approximate the behavior of the actual system to a certain extent [8]. A well-known quote by Professor George Box refers to this: "All models

are wrong, but some models are useful" [8].

Figure 2.9 illustrates the approach to successfully develop a simulation study and create a reliable model, formulated by Averill M. Law [8].

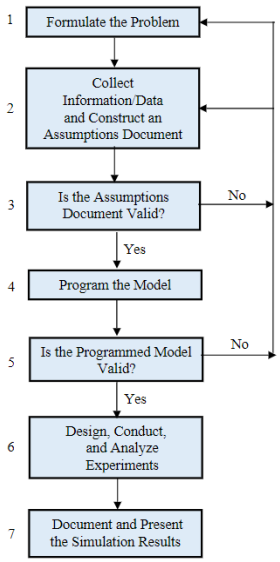

Figure 2.9: Seven step approach to build a valid simulation model. From [8].

On the other hand, mathematical optimization models aim to find the best possible solution, typically by maximizing or minimizing an objective function while satisfying a set of constraints. Thus, these models are used to make optimal decisions, allocate resources efficiently, optimize schedules, minimize costs, and maximize benefits within a given set of constraints [67].

In the context of this research, the goal is to develop a mathematical model to optimize PSCs and assist in the decision making process, therefore a more detailed focus is given to the various optimization models existing in the literature in the following chapter.

3

State of the Art

In this chapter, a review of the state of the art on the usage of optimization methods to model SC challenges is elaborated. By assessing how the various challenges mentioned in the previous chapter have been addressed and considered in optimization models, the ultimate goal of reviewing how the use of optimization models can be implemented to support decision making is achieved, thereby improving companies' SCs and ultimately market success. Therefore, this chapter is organized as follows: in subsection 3.1.1 some important concepts for understanding optimization models are found. Subsection 3.1.2 presents a review of the mathematical optimization models most commonly used in the context SCs. Lastly, subsection 3.1.3 summarizes the findings of the literature review and identifies a gap in the reviewed SC network optimization models.

3.1 Pharmaceutical Supply Chain Network Optimization

As already mentioned, a well-designed and efficient SC is crucial for the success of a company. Thus, over the past decades, SC network design optimization models have attracted significant interest from both industry and academia [4].

In the present literature review, each model will be evaluated based on its objective functions, the decisions it aims to facilitate (its output), and the approach it employs to provide support and solutions. However, first of all, it is necessary to address the different categories of models present in the literature. Thus, in the following subsection 3.1.1, some important terms are introduced to understand the optimization models that will be analyzed.

3.1.1 Important Terms

Thereby, before beginning the review of the collected literature, it is important to contextualize some general terms addressed by the authors within: model types, approaches to handle uncertainty, solution methods, planning horizons, and time periods. Table 3.1 summarizes the concepts addressed in the literature and their notation.

3.1.1.1 Model Type

Optimization models offer a method for optimizing decisions made in complex systems such as PSCs. They can be of different types but all of them are a subset of the larger field of mathematical programming.

Mathematical programming formulations involve a objective function, i.e., a function that evaluates the quality of the solution found, and a set of variables, and constraints [67]. Variables indicate actions that can be taken in the system being simulated while constraints are the limitations of the system. An optimization model will either minimize or maximize the objective function's value, according to the purpose of the problem [67]. A brief explanation between different optimization models is listed bellow:

Mixed Integer Programming

Mixed Integer Programming (MIP) is a type of mathematical programming that uses continuous, discrete and integer variables [67]. For instance, in this context, an integer variable could be a facility be part, or not be part of a SC.

Mixed Integer Linear Programming

On the other hand, when a problem contains integer variables and all constraint functions and objective functions are linear, the program becomes a Mixed Integer Linear Programming (MILP) [67, 68].

Mixed Integer Nonlinear Programming

Mixed Integer Nonlinear Programming (MINLP) incorporates a combination of continuous and discrete variables, as well as nonlinearities, in both the objective function and problem constraints by combining the modeling capabilities of MILP and Nonlinear Programming (NLP) [69, 70]. MINLP is often considered a more difficult type of optimization model, however it is extremely useful as it makes it possible to accurately model a variety of diverse events, such as the flow of materials through a manufacturing facility, using linear and nonlinear functions [70].

3.1.1.2 Uncertainty Approaches

Real-world problems involve uncertainties and difficulties when estimating key parameters, which affect production processes [71]. According to Galbraith [72], uncertainty refers to the disparity between the information needed to complete an activity and the available information at a given moment. Modeling uncertainty has been explored using different approaches:

Stochastic Programming

In stochastic mathematical programming, information is provided via discrete or continuous probability distributions, and it can be given or estimated based on previous data [73]. In the most commonly used and researched stochastic programming models, there are two stages of decision variables and therefore, it is called two-stage stochastic programming [73, 74]. The first-stage variables are determined prior to the realization of the uncertain parameters. Once the random events have occurred, additional enhancements can be achieved by adjusting the values of the second-stage variables [74].

However, as there is rarely enough historical data for the uncertain parameters in many real-world scenarios, it is rarely possible to obtain the true probability distributions of the uncertain parameters [75]. Furthermore, when uncertainty is modeled using a large number of scenarios, it can result in large and computationally difficult challenges [75].

Fuzzy Programming

Fuzzy programming takes into account random parameters by treating them as uncertain or fuzzy numbers. Constraints are then represented as sets in this approach, whose elements have levels of membership (fuzzy sets) [74]. As a result, any event can be assigned a value between two extremes, increasing the variety of choices for real-world scenarios.

Fuzzy programming comprehends two major classes: possibilistic programming and flexible programming. Possibilistic programming combines available objective data as well as the decision maker's own knowledge to deal with model parameters uncertainties, recognizing uncertainty in both the objective function coefficients and the coefficients of the constraints [74, 76]. On the other hand, flexible programming only deals with flexible target value of objective functions and constraints [74, 76]. In both approaches, a membership function is used to describe the degree of satisfaction with constraints, the decision maker's anticipated performance level for the objective function, and the uncertainty range of coefficients [74].

Robust Possibilistic Programming

This model type aims at finding the feasible and optimal solution that, despite parametric uncertainty, can satisfy the constraints. A solution is considered feasible if it stays feasible for nearly all potential values of uncertainty parameters. Similarly, it is also considered optimal if, for almost all potential values of the uncertainty parameters, the value of the objective function remains close to or has minimal variation from the optimal value [76].

3.1.1.3 Solution Method

The models in the papers under review discuss two categories of solution methods for addressing optimization problems in the context of PSCs: exact methods and non-exact methods. While exact methods solve a problem guaranteeing the optimally of the solution, non-exact methods only obtain a near-optimal solution given the complexity of real-life data [77, 78].

Non-exact methods include heuristic and metaheuristic approaches. In problems that are too complex to be solved exactly in a reasonable computational cost (computational power or time), heuristics methods are employed and, although they do not find the optimal solution, they produce a feasible one based on previous experiences with similar problems [78, 79]. On the other hand, metaheuristic approaches integrate diverse methods for widely explore the search space and are therefore more flexible and address a broader variety of viable solutions [78, 79].

3.1.1.4 Planning Horizon

The planning horizon is the amount of time over which the production-planning problem extends [80]. As described in subsection 2.2.2.1, decisions can be of long-term, medium-term, and short-term, corresponding to a strategic, tactical, and operational planning horizon, respectively [38, 41].

3.1.1.5 Time Period

In discrete-time models, the planning horizon is segmented into periods [80]. Each period represents a specific time unit, which could be an hour, a day, a month, or any other relevant time increment depending on the application. The choice of the period length depends on the nature of the problem and the level of detail required in the analysis.

The planning horizon can be segmented into single or multiple periods [80]. In a single-period model, decisions are made only for the current period, without con-

sidering future periods. This type of model is suitable for short-term or immediate decision-making scenarios.

On the other hand, in a multiple-period model, decisions are made for each period while considering the impact on future periods. This allows for longer-term planning and optimization, as decisions in one period can affect subsequent periods. Multiple-period models are commonly used in problems where long-term implications need to be considered.

Table 3.1: Summary of terms addressed in the literature and their notation.

Model Type	
Mixed Integer Programming	MIP
Mixed Integer Linear Programming	MILP
Mixed Integer Nonlinear Programming	MINLP
Uncertainty Programming	
Stochastic	S
Fuzzy	F
Robust	R
Solution Method	
Exact	EXC
Heuristic	HEU
Metaheuristic	MHEU
Planning Horizon	
Strategic	STR
Tactical	TCT
Operational	OPR
Time Period	
Single-period	SP
Multi-period	MP

3.1.2 Optimization Models in Literature

Each reviewed model is evaluated based on its performance measures, the decision that the formulation intends to support (its output), and its solution approach. The type of model used and how uncertainty was addressed (when applicable) are also taken into account.

Knowing that in SCM, the objective function is related with performance measures [3], Table 3.2 summarizes the objective functions commonly utilized to assess

the performance of a PSC.

Table 3.2: Objective functions and respective notation.

Objective Function	
Minimization of total costs	TC
Minimization of the environmental impact	EI
Minimization of the delivery time	DT
Minimization of the non-resilience	NR
Maximization of profit	P
Maximization of the customer satisfaction	CS
Maximization of the social welfare	SW
Maximization of the net present value	NPV
Maximization of the value created	VC
Maximization of reliability	R

Furthermore, a model can have one or more outputs, i.e., its formulation may support more that one decision. Possible outputs and respective meaning are presented in Table 3.3.

Finally, a summary of the reviewed papers with PSC network optimization problems is detailed in Table 3.4.

Table 3.3: Outputs, respective notation, and meaning.

Output		Meaning
Location	L	Decide on the capacity and location of the SC facilities
Allocation	A	Decide about the assignment between facilities
Distribution	D	Decide on the flow of products between facilities
Production	P	Decisions regarding the product's manufacturing quantities
Routing	R	Decide about the product transfer vehicles' route
Inventory	I	Select the amount of product to store at each location
Transportation	T	Decide on the transportation mode between facilities
Technology	TCH	Selection of the technology used for production

In 1999, Rotstein et al. [81] presented one of the first papers addressing capacity planning, from the drug development until the final manufacture stage. The authors formulated a single-period MILP model to minimize the Net Present Value (NPV) while considering uncertain demand forecasts due to the uncertainty in the outcomes of clinical trials through a two-stage stochastic programming problem. The planning horizon of the model is both strategical and tactical. Furthermore, an industrial case study from a portfolio comprising eight products verified the applicability of the proposed model.

Table 3.4: Reviewed papers with PSC network optimization problems. Table inspired and extended from Zahiri et al. [5].

Publication	Objective Funtion	Output	Solution Method	Model Type	Uncertainty Programming	Time Period	Planning Horizon
Rotstein et al. [81]	NPV	A, P	EXT	MILP	S	SP	STR, TCT
Papageorgiou et al. [82]	NPV	A, P	EXT	MILP	-	MP	STR, TCT
Levis and Papageorgiou [83]	NPV	A, P	EXT	MILP	S	MP	STR, TCT
Moniz et al. [84]	P	P, I	HEU	MILP	-	MP	OPR
Grunow et al. [85]	TC	A, P	EXT, HEU	MILP	-	MP	OPR
Vieira et al. [86]	P	P, I	EXT	MILP	-	MP	OPR
Marques et al. [87]	NPV	P, I	MHEU	MILP	S	MP	STR, TCT
Sousa et al. [88]	NPV	A, D	HEU	MILP	-	MP	TCT
Mousazadeh et al. [89]	TC, CS	L, A, D, TCH	EXT	MILP	R	MP	STR, TCT
Marques et al. [90]	NPV, VC	P, I	MHEU	MILP	S	MP	STR, TCT
Zahiri et al. [91]	TC, EI, SW, NR	L, A	MHEU	MILP	F	MP	STR, TCT
Nasrollahi and Razmi[92]	TC, SL	L, A, D, I	MHEU	MILP	F	MP	STR, TCT
Cardoso et al. [93]	NPV, CS	D, P, I	EXT	MILP	S	MP	STR, TCT
Hansen and Grunow [94]	TC	A, D	HEU	MILP	S	MP	OPR
Goodarzian et al. [77]	TC, DT, R	A, P, D, R, I, T	MHEU	MINLP	F, R	MP	TCT, OPR
Janatyan et al. [95]	TC, EI, SW	L, D	MHEU	MILP	F	SP	STR, TCT
Mota et al. [96]	NPV, EI, SW	L, A, D, P, I, T, TCH	EXT	MILP	S	MP	STR, TCT
Cardoso et al. [97]	TC, SW	L, A	EXT	MILP	S	MP	STR, TCT
Bessa et al. [98]	NPV, SW	A, P, I	EXT	MILP	-	MP	TCT
Duarte et al. [54]	NPV, EI, SW	L, P, I, T, TCH	EXT	MILP	S	MP	STR, TCT
Sazvar et al. [99]	TC, EI, SW	L, P, I, T, TCH	EXT	MILP	R	MP	STR, TCT
Savadkoohi et al. [17]	TC	L, A, D, I	EXT	MINLP	F	MP	STR, TCT
Roshan et al. [43]	TC, CS, SW	L, A, D, I	EXT	MINLP	F	MP	STR, TCT
Susarla and Karimi [100]	TC	D, P	EXT	MILP	-	MP	TCT
Le et al. [101]	TC	R, I	HEU	MILP	-	MP	OPR
Jia et al. [102]	TC	R, I	HEU	MIP	-	MP	OPR
Zandkarimkhani et al. [18]	TC, CS	L, R, I	EXT	MILP	F	MP	STR, OPR
Xu et al. [103]	TC	L, A, I, D	EXT	MILP	S	MP	TCT, OPR
Zahiri et al. [5]	TC, CS	L, P, A, D, I	EXT	MILP	F, R	MP	STR, TCT
Sun et al. [104]	TC, EI	P, R, I	HEU	MINLP	-	MP	TCT

Papageorgiou et al. [82] proposed a MILP model to address the selection of a product development and introduction strategy, as well as a long-term capacity planning and investment strategy across several sites (thus having a strategical and tactical planning horizon) with the objective of maximizing the NPV. One illustrative example was used to demonstrate the applicability of the suggested multi-period model however, the authors state that in real case data, the approach formulated may be too large. Furthermore, the model does not account for the uncertainty associated to this industry.

This way, Levis and Papageorgiou [83] proposed an extension of the approach introduced by Papageorgiou et al. [82] to effectively handle uncertainty through the addition of a stochastic optimization dimension to the problem. In addition, the authors propose a hierarchical algorithm to lower the computational effort required for addressing the large-scale MILP. The validity and effectiveness of the approach are demonstrated through the use of illustrative examples.

In contrast to most of the papers in the literature, Moniz et al. [84] addressed short-term planning decisions by presenting a case study on the production scheduling of multipurpose batch plants in the chemical-pharmaceutical industry. Multipurpose batch plants are facilities that can produce a variety of products in different batches, allowing for flexibility in production. However, scheduling the production of multiple products in such plants can be challenging due to the complexity of managing various constraints and objectives. The primary aim of this study was to create a scheduling model and methodology capable of effectively managing both regular and non-regular production scheduling in multipurpose batch plants. Regular production can be defined as the repetitive manufacturing of established products (follow a cyclic schedule), whereas non-regular production pertains to the creation of new or infrequently produced products (have a non-cyclic schedule). A MILP model was used to formulate the scheduling problem and it incorporates various constraints such as sequence-dependent changeovers. The objective is to maximize the profit, while introducing a penalty cost for missing deliveries. The method involves the determination the cycle time for scheduling products in a campaign mode, assigning and sequencing task units for all products, determining batch sizes and storage levels for tasks, and deciding on the number of campaign cycles.

Grunow et al. [85] also addressed operation decisions by the development of a multi-period MILP model to coordinate the schedules of multiple batches of the same API type produced by the same resource before switching to producing another API. The goal of the model was the minimizing the total costs and the solution obtained is exact. Nevertheless, the authors additionally propose an approach that is near-

optimal and can be effectively implemented in more complex real-world scenario. The effectiveness of the approach was demonstrated through a case study conducted in the industry.

Focused on optimal planning and campaign scheduling in biopharmaceutical processes, Vieira et al. [86] propose a continuous-time formulation to address the complexities of these processes and optimize productivity, cost, and resource utilization. The authors developed aMILP model that incorporates discrete decisions and continuous variables related to production rates and resource allocation. The objective was to find the optimal campaign schedule that maximizes profit, while considering constraints such as equipment capacity and resource availability. A case study comparing the continuous-time formulation with a traditional batch-based approach demonstrates the superiority of the proposed method in the duration of scheduled campaign tasks in order to meet production demand.

Marques et al. [87] presented a study from the chemical-pharmaceutical industry, an industry in which decisions regarding process design and planning can significantly impact the overall performance and profitability of a company. However, these decisions often need to be made under uncertain conditions, such as product demand and clinical trial outcomes. To address this challenge, the authors propose a simulation-optimization framework that combines the use of a simulation algorithm and MILP model to maximize the NPV. The framework enables decision-makers to evaluate different medium and long-term design and planning alternatives while considering the uncertainties present in the system. By integrating simulation and optimization, the approach provides a more comprehensive understanding of the product-launch planning problem.

Also Sousa et al. [88] proposed a non-exact approach to maximize the NPV of a multi-period demand profile company's PSC while considering product allocation and distribution structure. Due to the computational complexity of the MILP model, the authors designed a heuristic method that ensured a high-quality final solution. The proposed model is evaluated by conducting tests on two illustrative examples.

An exact approach was used by Mousazadeh et al. [89] to model a PSC network design. The authors propose a multi-period MILP model to minimize the total costs and the unmet demand (maximization of the customer satisfaction) and use a robust possibilistic programming approach to handle uncertain parameters like demand, unit manufacturing costs, unit transportation, transport costs, and safety stock levels. Long-term planning decisions, such as establishing and planning the capacity of pharmaceutical manufacturing and DCs and production technologies

used, as well as mid-term planning decisions like material flows are supported by the model. The model was solved with real-world case data. First, the ϵ-constraint method was applied to optimize each objective function separately and identify the trade-off between the objectives, while reaching the respective Pareto frontier. Then, to achieve the final solution, a fuzzy approach was implemented.

In the context of multi-objective function optimization, in general, there is no one optimal solution that optimizes all objective functions at the same time [105]. This way, to select the most suitable solution, methods like the ϵ-constraint method can be implemented to generate a satisfactory set of Pareto optimal solutions along and allow the trade-off analysis between the concerned objectives. Thereby, with the set of all Pareto optimal solutions, the Pareto Front is generated and the decision maker can greatly identify the most suitable solution [89, 105, 106].

In their study, Marques et al. [90] developed MILP model as an extension of their prior research [87] to tackle the stochastic product-launch planning problem. Their novel contribution involved the development of a multi-objective model that aimed to maximize productivity. Productivity, in this context, is generally defined as the relationship between the outputs and inputs of a process. Hence, the authors propose two objective functions: minimization of the total costs and maximization of the value created. Furthermore, to quantify the value created, the authors consider two aspects: the potential value for products under development and the real value for products in commercialization. By integrating these objectives, the model seeks to strike a balance between minimizing costs and maximizing the overall value generated by the product launch planning process. This comprehensive approach allows decision-makers to make informed choices that optimize both financial considerations and the potential impact of their products in the market. Importantly, the authors recognized the presence of uncertainty in both product demand and clinical trials outcomes in the same way as their previous work.

Regarding environmental modeling, there are two approaches that can be emphasized, as outlined by Eskandarpour et al. [107]: the Life-Cycle Assessment (LCA) and a partial assessment of environmental factors. In the first case, there is, for example, the ReCiPe indicator used by Mota et al. [55] and Mota et al. [96].

The LCA quantifies emissions, resources, environmental and health consequences, and resource depletion connected with any product or service. It includes extraction, manufacture, usage, recycling, and disposal of the product, i.e., it includes the entire life cycle of the product [108]. This way, according to the European Commission, the LCA is the best method for assessing product environmental implications [109].

On the other hand, a partial evaluation of environmental issues focuses on one or

more environmental concerns, such as greenhouse gas emissions, waste, and energy consumption, based on what is most pertinent to a particular case study [107]. Take for example the study conducted by Chaabane et al. [110] that has the minimization of carbon dioxide (CO_2) emissions as objective function. Also Zahiri et al. [91] formulated the objective function of minimization of the total environmental impact given that distinct production and shipping modes have different CO_2 emissions.

Carrying on from the previous paper, Zahiri et al. [91] developed a multi-objective MILP model for designing a multi-period PSC network under uncertainty. The authors include the combination of sustainability and resilience in the SC by proposing four objective functions that aim to: (1) minimize the total costs, (2) maximize the economic development and job opportunity (maximization of the social welfare), (3) minimize the environmental impact, and (4) minimize the non-resilience. Non-resilience is a concept that was only found in the work developed by Zahiri et al. [91] and its minimization is achieved by combining 5 metrics: node criticality, flow complexity, node complexity, demand dissatisfaction level, and production with old technologies. Furthermore, to address uncertain parameters the authors propose a novel fuzzy possibilistic-stochastic approach. Moreover, to solve the large-sized instances, a metaheuristic algorithm was implemented. The model was validated through numerical examples and a case study.

Nasrollahi and Razmi [92] proposed a multi-period model that supports decisions on facility location, network allocation, inventory management, and flow of products in the same echelon of the PSC. The bi-objective model aims to increase the coverage of demand requests (maximize customer satisfaction) while minimizing the total costs, and uses a fuzzy programming approach to handle uncertainty about the amount of demand. To solve the model, the authors developed a metaheuristic algorithm and validated it using a real-case study.

Cardoso et al. [93] explored in their study five SC structures, first with no disruptions, and then submitted to different types of disruptions under demand uncertainty modeled through stochastic programming. The authors created a bi-objective and multi-period MILP model to maximize the customer satisfaction and the NPV, with the goal of understanding the key factors that managers should take into account when designing and planning resilient supply networks. Location, production, distribution and inventory are the outputs of the model. The formulated model was applied to an European SC.

Hansen and Grunow [94] propose a two-stage stochastic model to aid in the preparation of market launch risks. The model balances off the costs of embracing these risks, such as the risk of packing prior to permission, against the revenue

lost due to risk-averse operating. Furthermore, the model has the minimization of the total costs as the objective function and allocation and distribution as its output being, consequently, a decision support tool for product launch operations, even when complicated regulatory issues must be taken into account. The authors provided a detailed case study of a pharmaceutical company that used this framework to successfully launch a new product, demonstrating the effectiveness of their approach.

Goodarzian et al. [77] developed a multi-objective MINLP model to not only minimize total costs, but also to minimize delivery time and maximize the reliability of the transportation system and routes. The model comprises tactical and operational decisions since it provides information on allocation, production, distribution, inventory, transportation, and routing. Furthermore, to solve the optimization problem, the authors compared the performance of several metaheuristics and evaluated the performance of these algorithms based on different metrics.

Using a MILP model, Janatyan et al. [95] propose a new approach for a sustainable pharmaceutical distribution network under uncertainty with three main objectives: (1) minimization of the total costs, (2) minimization of the environmental impact, and (3) maximization of the social welfare. The outcome of the model assists managers in determining the main and local DCs as strategic decisions and the flow of products as tactical decisions. The model is evaluated in one of Iran's leading pharmaceutical distribution companies.

Considering the three pillars of sustainability, the work of Mota et al. [96] can be highlighted. The three pillars of sustainability are incorporated by developing a multi-objective model. Hence, the model has the following objective functions: (1) maximization of the NPV, (2) minimization of the environmental impact, through the LCA methodology ReCiPe, and (3) maximization of the social welfare, through a developed Gross Domestic Product (GDP) metric, a social and economic measure used by the EU in its strategy for Sustainable Development. The model combines strategic decisions, such as facility location and capacity determination, with tactical decisions, like setting purchase levels, planning supplies, and recovering and remanufacturing products.

The previous authors, Mota et al. [96], conducted a review in which they conclude that literature mostly addresses economic and environmental aspects of sustainability. Nevertheless, it is possible to highlight that the most frequently employed indicators for the social pillar of sustainability are: job creation, workers' safety, health impacts, amount of working hours, and indicators that benefit SC activities' location in less developed regions. Take for instance Mota et al.'s [55]

Social Benefit indicator to encourage the creation of jobs in areas that are less developed, so contributing to the development of regional areas. This indicator contains a regional factor that can take on different values based on the objective of the study, for example, the unemployment rate or population density.

Social responsibility is a global metric to evaluate the social performance of a company. It evaluates the company's social impacts on all its stakeholders, particularly its employees, through the assessment of working conditions, level of remuneration, and discrimination [111].

Still taking into account the social impact, designing and planning PSCs with equity in mind has shown to be vital and a key factor in pushing the pharmaceutical industry in the direction of a more socially sustainable one however, it has not yet been handled sufficiently in the literature [54]. As an example of the lack of equity, the recent COVID-19 pandemic can be mentioned. According to *The New York Times* [112], low-income countries had their first COVID-19 vaccine purchase agreements eight months after the United States and the United Kingdom, resulting in a significant divergence in vaccination delivery rates.

In addressing equity, the work of Cardoso et al. [97] can be highlighted. The authors propose a two-stage stochastic MILP model to support the planning of both strategical and tactical decisions in the long-term healthcare sector. While the objective function consists of minimizing the expected costs, with the assurance of a minimum level of demand satisfaction, the various levels of equity are represented as constraints, with the goal of achieving access, usage, socioeconomic, and geographical equity.

Moreover, Bessa et al. [98] developed a capacity allocation model that incorporates an unfairness indicator that accounts for drug shortages to reach an equilibrium between market demands and economic goals. To highlight the difference between equality and fairness, take the example given by the authors that follows the idea of the divergence in COVID-19 vaccination delivery rates stated above: knowing that around 85% of all vaccinations were administered in high-income and upper-middle-income countries, and 75% of those vaccines were distributed to only ten countries [113], if every country received the same quantity of vaccines, equality would be achieved, but the result would be unfair, considering that countries have distinct population numbers. This way, a fair outcome would be to give each country the same relative number of vaccines. Thus, fairness refers to the application of equity to the desired outcome, i.e., granting each region an equal share of resources in proportion to its need. The study came to the conclusion that a significant amount of unfairness may be addressed with comparatively little influence on economic goals.

Based on a case study of a SC where vaccine production and distribution are considered, Duarte et al. [54] validated a sustainable MILP model that integrates economic, environmental, and social sustainability objectives through the NPV, the environmental LCA methodology, and concerns regarding equity in the distribution of vaccines, respectively. To integrate the social sustainability indicator, an index that evaluates and publicly acknowledges the top twenty pharmaceutical corporations for improving medical access- the Access to Medicine Index (AtMI), is analyzed by the authors. Then, two social objective functions are formulated: (1) maximization of the equal accessibility of pharmaceutical products by giving preference, using the metric Disability-Adjusted Life Year (DALY), to the location of entities facilities in regions with a higher disease burden, and (2) maximization of the minimum delivery-to-demand ratio of each country, ensuring pharmaceutical products availability. Strategic decisions such as facility location, as well as tactical decisions like production levels, storage levels, and transportation network establishment are supported by the model.

Sazvar et al. [99] developed a multi-objective model to design a resilient SC that takes into account economic, environmental, and social sustainability aspects, while also applying uncertainty to various parameters. This model offers an approach for considering the social anxiety that arises from a rise in demand, as can happen, for example, after a natural disaster. The model also considers deprivation caused by the inability to meet consumer demand when the company is very susceptible to operational risks and disruption. The model has the following sustainability goals: (1) minimize the total costs (economic component of a sustainable SC), (2) minimize CO_2 emissions rate (environmental impact of a sustainable SC), and (3) maximize the corporate social responsibility (CSR) by lowering lost sales and enhancing accessibility to order fulfillment locations as well as job creation (social aspect of a sustainable SC); and it aims at making strategic decisions, such as facilities location, transportation mode selection, and technology selection, as well as tactical decisions, more specifically inventory and production levels.

3.1.2.1 Models that Account for Perishability

As discussed in subsection 2.2.3, neglecting the limited shelf life of pharmaceuticals can result in significant consequences, yet this is not taken into account in the previous optimization models.

Indeed, most papers on distribution network design models disregard products' lifetime [17]. Contraryly, Savadkoohi et al. [17] proposed a MINLP model that takes into account the perishability of products by incorporating the concept of

expiration dates and spoilage rates. Specifically, the authors developed a multi-period inventory location-allocation model that considers the perishability of the pharmaceutical products over multiple periods. The spoilage rate represents the percentage of the product that spoils per unit of time, and the expiration date represents the maximum shelf life of the product. The model aims to determine the optimal location and inventory levels of warehouses and retailers, as well as the optimal allocation of products to each location, such that the total cost of the SC is minimized, while meeting the demand for the products and respecting the perishability constraints.

Also Roshan et al. [43] integrated product's perishability in their mathematical model by incorporating the concept of degradation rate. The degradation rate is considered in the model as a constraint on the maximum amount of time that the product can be stored before its quality deteriorates beyond an acceptable level. Hence, this constraint limits the amount of inventory that can be produced for a given product and time period. By considering the degradation rate in their model, the authors are able to develop an optimal production plan that balances the trade-off between meeting demand and minimizing the amount of inventory that may become unusable due to spoilage. Moreover, the MINLP model proposed is able to manage the PSC during crises. A Pareto front is performed to obtain a compromise between the three objective functions : (1) minimize the total costs, (2) maximize the customer satisfaction, by the minimization of the unmet demand, and (3) maximize the social welfare.

Susarla and Karimi [100] developed an exact MILP model to support a multi-period corporate planning. The model aims to minimize the total costs while addressing the product manufacturing and distribution, as well as some peculiarities of the pharmaceutical industry, such as international tax differences. Moreover, the authors considered expiration dates as one of the constraints in their mathematical optimization model. Specifically, the model ensures that products are allocated to customers or DCs based on the expiration date, thus avoiding waste caused by expired products. To achieve this, the authors considered the time required for transportation and storage of products, as well as the expiration dates of products. In addition, one of the key contributions of the paper is the inclusion of regulatory compliance requirements in the optimization model. The authors considered regulatory constraints related to product approval, labeling, and packaging, ensuring that the proposed SC network design meets all relevant regulations.

Le et al. [101] proposed a heuristic algorithm as a solution to an inventory routing problem, a specific issue in SCM. The inventory routing problem involves the

simultaneous optimization of inventory management and vehicle routing decisions. In the context of perishable goods, the problem becomes more challenging due to the limited shelf life of the products. Therefore, efficient management of inventory and routing is crucial to minimize waste and ensure timely delivery. The proposed model takes into account perishability constraints, which restrict the quantities of goods that can be delivered to customers at any given time based on the shelf life of the products. By considering these constraints, the algorithm aims to ensure that the delivered goods are still within their acceptable shelf life limits.

In their study, Jia et al. [102] also addressed the integrated inventory routing problem. To achieve the coordination of inventory management and routing decisions, the authors developed a model that takes into account the time-dependent deterioration of items, which significantly impacts their quality over time. By considering quality time windows and incorporating the time-dependent deterioration factor, the proposed model aims to minimize the total costs associated with inventory holding, transportation, and loading. Additionally, the model ensures that customer demand is met within the specified quality time windows, ensuring that products are delivered to customers within acceptable quality limits.

Zandkarimkhani et al. [18] modeled product perishability by considering the shelf life of the products in the SC network. To model perishability, the authors introduced a fuzzy parameter called the quality decay rate, which captures the reduction in product quality over time due to perishability. The decay rate is assumed to be a fuzzy number, as the exact rate of quality decay may vary based on various factors such as temperature, humidity, and handling conditions. Then, the quality decay rate was used to calculate the remaining shelf life of the products at each stage of the SC network. Following that, this information was used to determine the optimal routing and inventory decisions for the products to minimize the overall cost while ensuring that the products meet their quality requirements. In addition, the first-in-first-out (FIFO) method is employed for inventory management.

The FIFO method is a common practice for managing inventory and means that the products or resources that were manufactured or acquired first are sold or used first [114]. By analyzing the applicability of this method in the literature, the work of Weraikat et al. [115] can be highlighted. The authors study the optimal amount of medication that must be sent from a manufacturer to a hospital throughout each period of time during the course of a planned horizon and use the FIFO method in order to minimize the quantity of the expired medicines at the hospitals. However, although issuing a FIFO policy may frequently contribute in reducing waste and total costs since products approaching expiration may be used

sooner, Xu et al. [103] observes that enforcing a FIFO policy is not required for achieving optimal performances.

Xu et al. [103] studied a platelets SC and the impact of transshipment between hospitals in it. Platelets and other blood components are extremely perishable, causing them to be susceptible to expiration and waste. This way, the authors present an optimization model to minimize the total costs considering the possibility of transshipment. Also demand uncertainties, and stock age data are taken into account. The model uses a perishability index to represent the remaining lifetime of the platelets, which was determined by the time elapsed since the platelets were collected and the temperature at which they were stored. Furthermore, it provides both tactical and operational decisions on production (amount of whole blood collected), allocation, inventory, and flow.

Zahiri et al. [5] developed a MILP model that aims to minimize the total cost and the unmet demand (maximization of the customer satisfaction) on a PSC network design problem. The exact model supports decisions on facility location, network allocation, production, inventory management and flow of products from facilities in distinct or in the same level of the PSC, i.e., it includes both strategical and tactical decisions. The authors also address uncertainties in costs and demand by implementing a novel robust possibilistic optimization approach. Moreover, this model was the pioneer in addressing simultaneously product substitutability, perishability and quantity discounts, which are highly prevalent challenges in the real-world industry. To address perishability, the authors defined the shelf life period of each product and used an index of production periods and an index of delivery periods to establish inventory and flow restrictions. Moreover, the concept of product substitution allows the use of alternative products when the primary product is unavailable or expired.

More recently, Sun et al. [104] addressed the challenges and trade-offs involved in managing the production, inventory, and routing decisions for multiple perishable products while considering both economic and environmental goals. In its objective function for minimizing total costs, the model takes into account the deterioration of products over their lifetime. Through constraints, the authors impose that perishable goods cannot be held, delivered, or utilized after their expiration dates.

Hence, it can be observed that there exist various methods to integrate the concept of product perishability. While some methods provide waste prevention, by not allowing products to exceed their shelf life, others only considered waste reduction, as highlighted by Malladi and Sowlati [116].

When optimization models are designed to prevent products from expiring,

it eliminates the need to consider the lost value of perished products. This is in contrast to situations where product expiration is allowed and the potential loss of value must be taken into account [116].

Table 3.5 summarizes the different ways of modeling perishability found in literature.

Table 3.5: Literature's different approaches of modeling perishability.

Paper	Perishability Modeling	Waste Prevention	Waste Reduction
Savadkoohi et al. [17]	Expiration Date and Degradation Rate		x
Roshan et al. [43]	Degradation Rate		x
Susarla and Karimi [100]	Expiration Date		x
Le et al. [101]	Shelf Life Limit	x	
Jia et al. [102]	Degradation Rate	x	
Zandkarimkhani et al. [18]	Degradation Rate		x
Xu et al. [103]	Remaining Lifetime Index		x
Zahiri et al. [5]	Production and Delivery Periods Indexes	x	
Sun et al. [104]	Degradation Rate		x

3.1.3 Chapter Final Remarks

In the decision-making process, optimization models are applied to provide valuable insights. Each model is specifically designed to tackle one or more particular decisions, addressing various aspects of the decision-making process. The predominant focus in the existing literature is on models pertaining to location decisions, often in conjunction with allocation and distribution decisions. Moreover, integration of lower-level decisions such as production, routing, and inventory management with network design considerations is commonly observed. This emphasizes the importance of these lower-level decisions in the designing of a PSC network.

Based on the number of instances and the level of complexity of the model, researchers may select between exact and non-exact methods to address a problem. While some authors rely solely on exact methods, others combine an exact method with a non-exact method if they find that the former is insufficient to obtain a single optimal solution within a computationally feasible timeframe. In contrast, some authors exclusively use non-exact methods.

When it comes to modeling uncertainty in PSC, demand uncertainty has been the most studied. It is possible to conclude that the type of uncertainty programming may depend on the type of uncertainty parameters that need to be taken into account.

Moreover, according to the literature review conducted, it is possible to confirm the effects of the paradigm shift (discussed in section 2.3.2) on PSCs, mostly regarding the Outcome, Flexibility, and Overall Welfare.

The shift to the patient-centric paradigm is present in models that have the objective of increasing the customer satisfaction by minimizing the unmet demand, or that impose constraints on demand satisfaction.

Flexibility is incorporated into the optimization models through outsourcing strategies. Most of the models output location decisions, which provides decision support regarding which manufacturers (i.e., outsourcing facilities) should be incorporated into the network.

Although all analyzed models have an objective function focused on the economic aspect (minimization of total costs, or maximization of profit, or maximization of the NPV), some also have environmental and social concerns. Since companies must remain profitable to survive on the market, economic concerns will always exist and, therefore, the important thing to do is try to combine them with environmental and social aspects to contribute to a more sustainable SCs. Environmental concerns are present in the literature when the objective of minimizing the environmental impact is formulated, which can be done through LCA or through a partial assessment of environmental factors, based on what is most pertinent to a particular case study [107]. On the other hand, the most frequently employed indicators for the social pillar of sustainability are job creation, workers' safety, health impacts, amount of working hours, and indicators that benefit SC activities' location in less developed regions [96], all of which attempt to maximize the social welfare. Besides that, equity aspects were also considered as relevant, particularly when addressing pharmaceutical industry SCs. Yet, when there is a lot of pressure to reduce costs, equity is not the first concern.

Furthermore, it is important to point out that many papers do not take into account the shelf life of products. This oversight is particularly problematic for perishable pharmaceutical products, as neglecting their perishability not only reduces their effectiveness and jeopardizes patient safety, but also leads to financial losses for the company. In addition, expired medicines become useless and constitute environmental waste, making it important to address this issue.

In addition, the reviewed papers did not specifically discuss the integration of multiple perishable products to meet demand based on the specifications of different age groups. Considering a general demand for the entire population can sometimes be inaccurate or inadequate, particularly when it comes to medicines, as each age group may have distinct and specific needs. For example, factors such as dosage, formulation, and potential contraindications can vary depending on age. Therefore, it is essential to take into account the unique requirements of different age groups when optimizing inventory and meeting demand for pharmaceutical products. As a

result, the focus of the subsequent research will be to address this challenge.

4

Model Conceptualization & Formulation

This chapter focuses on the mathematical formulation development of a perishable PSC network. The chapter begins by defining the generic problem under study in section 4.1. Subsequently, section 4.2 introduces the proposed mathematical formulation, which is further divided into subsections. In subsection 4.2.1, detailed information is provided on the indices, sets, and parameters involved in the formulation. Subsection 4.2.2 discusses the decision variables, while subsection 4.2.3 explores the objective functions. Finally, in subsection 4.2.4, the constraints of the model are presented and explained, providing a comprehensive understanding of the various limitations and considerations within the formulated model.

4.1 Problem Formulation

The approach adopted to model the perishable nature of products is the one that ensures the prevention of product expiration, as it offers significant advantages over allowing products to expire. By implementing this strategy, the risks associated with product expiration can be effectively avoided.

Based on this objective, the model developed by Zahiri et al. [5] stands out as preferable due to its efficient management of perishable products within a SC network. By defining the shelf life period for each product and establishing inventory and flow restrictions based on production and delivery periods, their model offers a systematic and practical approach to handle perishability. The model also considers strategic and tactical decisions related to facility location, network allocation, production, inventory management, and distribution, which are very important decisions when designing an efficient SC and ultimately lead to customer satisfaction.

This way, the model developed by Zahiri et al. [5] inspired the conceptualization and development of the present decision-support tool for the design and planning of

a reliable, and flexible perishable PSC. Yet, significant adjustments were made to address some significant challenges facing the pharmaceutical industry, such as the need for different storage conditions, demand according to different age groups, and the possibility of backorders creation.

The proposed model includes API manufacturers, product manufacturers, DCs, and demand zones, as depicted in Figure 4.1. This way, in a four-level SC, the model developed encompasses strategic and tactical decisions on facilities' location, production and inventory levels, and product flows.

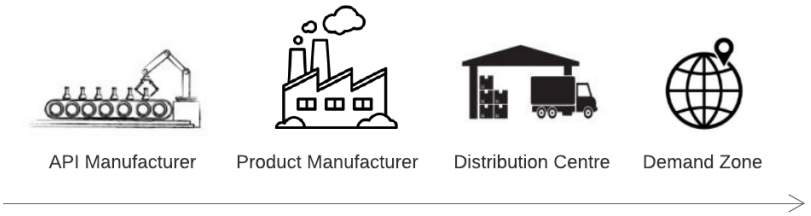

Figure 4.1: Pharmaceutical supply chain of the proposed problem.

Thus, at API manufacturers, the raw materials needed for each product are produced and carried to the product manufactures to be transformed into final products. The maximum quantity of goods that can be stored from one period to the next is determined by the storage capacity of each API manufacturer and product manufacturer for each type of good manufactured and per time period. Afterwards, products flow to the DCs, which in turn are in charge of directly satisfying demand zones. Also the DCs have their own storage capacity, as well as handling capacity, defined by the maximum quantity of items that can pass through each DC in a specified time period. In addition, all facilities integrated in the first three levels of the SC have inventories: at the API manufacturers, it is possible to keep a stock of finished APIs, and at the product manufacturers, and DCs, there are product inventories.

The proposed model supports the flow of multiple APIs and multiple products, as well as different storage conditions in the inventory of each facility. Pharmaceutical products are regulated by strict storage requirements to prevent product degradation [117]. Thus, when planning and designing a PSC, it may be insufficient to consider a general inventory for all the products. This way, the model considers the fact that each product must be kept along the SC in accordance with a particular set of storage conditions. Also, the shelf life of each product is considered in the model, as proposed by Zahiri et al. [5]. Hence, the problem under research aims to optimally locate API and product manufactures and DCs, establish the op-

timal levels of production and inventory, as well as establish the interaction between facilities in each period during products' shelf life.

Furthermore, the model proposed by Zahiri et al. [5] aims to minimize the total costs and the unfulfilled demands, however, the current model allows demand to be delayed and accumulated until the next time period. This way, a backorder is defined as the delaying of the supply of one product for one period of time. Therefore, the current model's goal is to minimize the backorders and minimize the network total costs. The costs to be minimized are the costs that are incurred by the facilities in order to integrate the network (integration costs), the costs incurred in order to distribute the goods between facilities (transportation costs), and the costs of storing the goods (inventory costs).

Table 4.1 presents the characteristics of each entity of the concerned PSC.

Table 4.1: Characteristics of each entity of the concerned supply chain.

Entities	Features
API manufacturers	Have a maximum production capacity Have a maximum inventory capacity to hold API stock Is able to respond to orders from product manufacturers Sends APIs to product manufacturers
Product manufacturers	Have a maximum production capacity Have a maximum inventory capacity to hold products Is able to respond to orders from DCs Sends products to DCs
DCs	Have a maximum handling capacity Have a maximum inventory capacity to hold products Is able to respond to orders from demand zones Sends products to demand zones
Demand zones	Have a known location Have their demand segmented by age groups

4.2 Mathematical Formulation

The mathematical formulation of the proposed MILP model is described in this section, beginning with the indices and related sets, parameters, and decision variables. Following that, the objective functions and model constraints are presented.

4.2.1 Indices, Sets, and Parameters

Let A represent the set of APIs that are produced in the set of API manufacturers F. Each API manufacturer f has a maximum production capacity for each API a, denoted as M_{af}^{prod}. Then, APIs may be transferred to product manufacturers within the set S, or may be stored under diverse storage conditions, denoted by C within each API manufacturer f. With regards to the storage of APIs within a specific storage condition c, a predetermined maximum capacity is assigned to each API manufacturer f, which is represented as M_{fc}^{stor}. Furthermore, the retention of an API storage unit in the API manufacturer f incurs a cost, denoted as C_{fc}^{inv}. The notation U_{ac} is used to represent the storage space requirement, measured in units, to store a single unit of API a under condition c.

A cost of C_{afs}^{tran} occurs for each API unit transported from a API manufacturer f to a product manufacturer s. In product manufacturers, a set of pharmaceutical products, denoted by P are produced in a given production period i. Let T be the set of time periods under consideration, the set of production periods for each product p is denoted by I and has the same domain as T. Furthermore, for producing one unit of product p, an amount of API a in required, defined as ρ_{ap}. For each product manufacturer s, a maximum production capacity of product type p to be administrated to age group g is represented by M_{pgs}^{prod}. Each age group g is part of the set of considered age groups denoted by G. After manufactured, the products can be sent immediately to the DCs (from set L) or can remain in inventory. Each product manufacturer s has a maximum storage capacity of M_{sc}^{stor} units under condition c and a cost of C_{sc}^{inv} per units of storage space for each time period in inventory, being that a unit of product p requires U_{pc} units of storage space under condition c. The problem under consideration deals with perishable products, therefore, to each product p is associated its shelf life S_p.

A product of type p is transported from a product manufacturer s to a DC l with a C_{psl}^{tran} cost per unit. When a product p arrives at a DC, it is assigned an delivery period e. Let E be the set of delivery periods within the set of time periods T under consideration. Also within each DC, it is possible to stock each product p under specific storage conditions c. As such, a maximum storage capacity for the

DCs is established and denoted as M_{lc}^{stor}. Additionally, a cost is associated with storing a storage unit of a product p in the DC l, indicated as C_{lc}^{inv}. The occupancy of storage space by a unit of product p under condition c is represented by U_{pc}. The maximum capacity of products that each DC l can handle per time period is defined as M_l^{hand}.

Lastly, based on the demand per age group g in each demand zone r at time period t, defined as D_{rgt}, the products are transported from the DCs to the respective demand zones at a cost of C_{plr}^{tran}. The location of the demand zones is known and, with the exception of these, all other facilities have network integration costs. Integration costs of the API manufacturer f, product manufacturer s, and DC l are denoted by C_f^{open}, C_s^{open}, C_l^{open}, respectively.

Table 4.2 summarizes the indices and related sets of the present mathematical model model, while Table 4.3 summarizes its parameters.

Table 4.2: Indices and related sets of the mathematical model.

Indices		**Sets**	
f	API manufacturer	F	API manufacturers
s	Product manufacturer	S	Product manufacturers
l	DC	L	DCs
r	Demand zone	R	Demand zones
a	API	A	APIs
p	Product	P	Products
g	Age group	G	Age groups
c	Storage condition	C	Storage conditions
t	Time period	T	Time periods
i	Production period	$I \in T$	Production periods
e	Delivery period	$E \in T$	Delivery periods

Table 4.3: Parameters of the mathematical model.

	Integration Costs
C_f^{open}	Cost of open API manufacturer f
C_s^{open}	Cost of open product manufacturer s
C_l^{open}	Cost of open DC l

	Transportation Costs
C_{afs}^{tran}	Cost of transporting API a from the API manufacturer f to the product manufacturer s
C_{psl}^{tran}	Cost of transporting product p from the product manufacturer s to the DC l
C_{plr}^{tran}	Cost of transporting product p from the DC l to the demand zone r
	Inventory Holding Costs
C_{fc}^{inv}	Cost of storing one storage unit in the API manufacturer f for one time period under conditions c
C_{sc}^{inv}	Cost of storing one storage unit in the product manufacturer s for one time period under conditions c
C_{lc}^{inv}	Cost of storing one storage unit in the DC l for one time period under conditions c
	Production Capacities
M_{af}^{prod}	Maximum production capacity of API a at the API manufacturer f
M_{pgs}^{prod}	Maximum production capacity of product p for age group g at the product manufacturer s
	Handling Capacities
M_{l}^{hand}	Maximum handling capacity of DC l
	Storage Capacities
M_{fc}^{stor}	Maximum storage capacity of APIs by the API manufacturer f, under conditions c
M_{sc}^{stor}	Maximum storage capacity of products by the product manufacturer s, under conditions c
M_{lc}^{stor}	Maximum storage capacity of products by DC l, under conditions c

	Bill of Materials
ρ_{ap}	Required amount of API a for producing one unit of product p
	Shelf Life
S_p	Shelf life period of product p
	Storage Units Required
U_{ac}	Number of units of storage space required to store a unit of API a, under conditions c
U_{pc}	Number of units of storage space required to store a unit of product p, under conditions c
	Demand
D_{rgt}	Demand of products in demand zone r, for age group g, during period t

4.2.2 Decision Variables

The decision variables to which the model intends to provide a response are divided into two groups: binary variables and continuous variables. The first group is concerned with the decision-making process regarding whether the facilities should be included in the network or, in other words, whether they should be opened or not. The decision whether a API manufacturer f, product manufacturer s, or DC l should open is represented by X_f, X_s, and X_l, respectively.

On the other hand, the continuous variables are divided into four subgroups of non-negative variables. Firstly, the production variables P_{aft} and P_{pst} indicate the quantity of goods produced in each manufacturer and time period. The product flow variables ψ_{afst}, ψ_{pslt}, ψ'^{i}_{pslt}, ψ_{plrgt}, and ψ'^{ie}_{plrgt} indicate the amount of each good that flows from one facility to another facility in the subsequent level of the SC, within each time period. The quantity of APIs/products that must be kept in inventory at each facility and time period is determined by the inventory variables I_{aft}, I^{i}_{pst},

and I^{ie}_{plt}. Finally, the decision variable backorders B_{rtg} is used to determine the quantity of products that will not be satisfied in the time period in which they were demanded. The description of each variable can be found in more detail in the Table 4.4.

Table 4.4: Decision variables of the mathematical model.

Binary Variables	
	Network Integration
X_f	1 if API manufacturer f is opened, 0 otherwise
X_s	1 if product manufacturer s is opened, 0 otherwise
X_l	1 if DC l is opened, 0 otherwise
Continuous Variables	
	Production
P_{aft}	Quantity of API a produced in API manufacturer f at period t
P_{pst}	Quantity of product p produced in product manufacturer s at period t
	Product Flow
ψ_{afst}	Quantity of API a shipped from the API manufacturer f to the product manufacturer s at period t
ψ_{pslt}	Quantity of product p shipped from the product manufacturer s to DC l at period t
ψ'^{i}_{pslt}	Quantity of product p shipped from the product manufacturer s to the DC l at period t that is produced in period i
ψ_{plrgt}	Quantity of product p shipped from DC l to the demand zone r, to attend demand age group g at period t
ψ'^{ie}_{plrgt}	Quantity of product p shipped from DC l to the demand zone r, to attend demand age group g at period t, that is produced in period i and received in period e
	Inventory
I_{aft}	Quantity of API a in inventory at the API manufacturer f at the end of the period t

I^{i}_{pst}	Quantity of product p in inventory at the product manufacturer s at the end of period t produced in period i
I^{ie}_{plt}	Quantity of product p in inventory at DC l at the end of period t produced in period i and received in period e
	Backorders
B_{rtg}	Number of units demanded to attend demand age group g by demand zone r but undelivered in the time period t

4.2.3 Objective Functions

When dealing with models that have multiple objective functions, there are two approaches that can be employed: treating the objective functions individually or integrating them into a single objective function [105].

If the single objective function approach is chosen, it requires the use of weighting factors. However, this method can lead to unfavorable effects, particularly in terms of subjectivity and uncertainty. These factors can diminish the model's clarity and make it more challenging to comprehend the trade-offs between the objectives [105].

Therefore, in the proposed model, the objective functions are treated separately. Consequently, there are two distinct objectives: (1) minimization of the total costs, and (2) minimization of the backorders.

Minimization of the Total Costs

$$
\begin{aligned}
\min \quad & \sum_{f} X_f C^{open}_{f} + \sum_{s} X_s C^{open}_{s} + \sum_{l} X_l C^{open}_{l} \quad + \\
& \sum_{a}\sum_{f}\sum_{s}\sum_{t} \Psi_{afst} C^{tran}_{afs} + \sum_{p}\sum_{s}\sum_{l}\sum_{t} \Psi_{pslt} C^{tran}_{psl} + \\
& \sum_{p}\sum_{l}\sum_{r}\sum_{g}\sum_{t} \Psi_{plrgt} C^{tran}_{plr} \quad + \\
& \sum_{t}\sum_{f}\sum_{c}\left(\sum_{a} I_{aft} U_{ac}\, C^{inv}_{fc}\right) + \sum_{t}\sum_{s}\sum_{c}\left(\sum_{p} I^{i}_{pst} U_{pc}\, C^{inv}_{sc}\right) + \\
& \sum_{t}\sum_{l}\sum_{c}\left(\sum_{p} I^{ie}_{plt} U_{pc}\, C^{inv}_{lc}\right)
\end{aligned}
\tag{4.1}
$$

The first objective function defined in equation 4.1 aims to minimize the costs of the entire SC by adding all the costs. The equation terms correspond to the costs of facility integration, transportation, and inventory, respectively. Integration costs are calculated as the sum of the integration costs of all facilities to establish a network, taking into account the binary variable that is 1 if the facility integrates the network and 0 otherwise. Furthermore, transportation costs are given as the sum of the amount of goods that flow from each origin facility to each destination facility multiplied by the cost of transporting that good in that path for all goods, time periods, origin facilities, and destination facilities. Lastly, inventory costs are the sum of the final inventory of each good in each facility and in each time period, multiplied by the storage space that that good requires for the storage condition considered, and multiplied by the cost of one storage space under the storage condition considered, in each facility.

Minimization of the Backorders

$$\min \quad \sum_{t} \sum_{r} \sum_{g} B_{rtg} \tag{4.2}$$

Equation 4.2 defines the second objective function, which minimizes the network's total number of backorders as the sum of backorders for all demand zones, age groups, and time periods.

4.2.4 Constraints

The imposed constraints are categorized as follows: material balances, entity capacity, demand satisfaction, and variables' constraints. From equation 4.3 to equation 4.35, these constraints are defined and characterized.

1. Material Balances

1.1 API Consumption

$$\sum_{p \in P} (P_{pst}\, \rho_{ap}) = \sum_{f \in F} \Psi_{afst}, \quad \forall\, a \in A, s \in S, t \in T \tag{4.3}$$

The parameter ρ_{ap} of the proposed model allows the definition of the amount of API a units needed to produce one unit of product p, therefore, in the product manufacturers, APIs are used sole or combined to produce pharmaceutical products. Since in the context of the proposed model, the product manufacturers receive APIs just-in-time and the consumption is immediate, equation 4.3 assures that the

consumption of API a needed to produce pharmaceutical products in each product manufacturer s is equal to the inflow of that API a in that facility.

1.2 Flow Balance on each Facility

$$I_{aft} = P_{aft} - \sum_{s \in S} \Psi_{afst}, \quad \forall\, a \in A, f \in F, t \in T,\ t = 1 \tag{4.4}$$

$$I_{aft} = I_{aft\text{-}1} + P_{aft} - \sum_{s \in S} \Psi_{afst}, \quad \forall\, a \in A, f \in F, t \in T,\ t > 1 \tag{4.5}$$

Constraints 4.4 and 4.5 are concerned to the inventory of API manufacturing facilities and are differentiated by the time period to which they refer. For the first time period (i.e., $t = 1$), there are not any APIs in inventory thus, the inventory level corresponds to the APIs manufactured minus the outflow to product manufacturers, as assured by equation 4.4. On the other hand, for the remaining time periods it is necessary to take into account the accumulated stock from the previous period.

$$\sum_{i=1}^{t} I^i_{pst} = \sum_{p \in P} P_{pst} - \sum_{l \in L} \Psi_{pslt}, \quad \forall\, p \in P, s \in S, t = 1 \ \wedge\ t < S_p \tag{4.6}$$

$$\sum_{i=1}^{t} I^i_{pst} = \sum_{i=1}^{t-1} I^i_{pst\text{-}1} + \sum_{p \in P} P_{pst} - \sum_{l \in L} \Psi_{pslt}, \quad \forall\, p \in P, s \in S, 1 < t < S_p \tag{4.7}$$

$$\sum_{i=t+1-S_p}^{t} I^i_{pst} = \sum_{i=t+1-S_p}^{t-1} I^i_{pst\text{-}1} + \sum_{p \in P} P_{pst} - \sum_{l \in L} \Psi_{pslt}, \quad \forall\, p \in P, s \in S, t \geq S_p \tag{4.8}$$

Constraint sets 4.6 to 4.8 calculate the inventory of products p within their perish time for a product manufacturer s in different periods t. Equation 4.6 calculates the stock level for the first time period (i.e., $t = 1$), when there are not any stocked products added from its previous period. On the other hand, constraints 4.7 and 4.8 guarantee that the products that are kept in inventory in product manufacturers are equal to the inventory from the last time period plus the products produced minus the products that are sent to DCs. Furthermore, the constraints are treated separately for different values of time period t since, when the time period exceeds the perish time (i.e., $t \geq S_p$), constraint 4.8 guarantees that the production of the products in stock occurred within the product's perish time (i.e., $i \in [t+1-S_p, \mathrm{t}]$).

$$I^i_{pst} = \sum_{p \in P} P_{pst} - \sum_{l \in L} \Psi'^{i}_{pslt}, \quad \forall\, p \in P, s \in S,\ t \in T, i = t \tag{4.9}$$

$$I^{i}_{pst} = I^{i}_{pst\text{-}1} - \sum_{l \in L} \Psi'^{i}_{pslt}, \quad \forall\, p \in P, s \in S,\ t - i < S_p\ \wedge\ t > i \tag{4.10}$$

Furthermore, constraints 4.9 and 4.10 determine the inventory level for product manufacturers based on the products' production period. That is, when the time period equals the production period (i.e., $i = t$), as in equation 4.9, the inventory level is calculated by the addition of the products manufactured in that time period to the previous inventory level minus the outflows to DCs. On the other hand, when t-$i < S_p$ (equation 4.10), the production and the current periods are still within the product's shelf time and the inventory level should be determined as the previous stock level minus the outflows in that period.

$$\Psi_{pslt} = \sum_{i=1}^{t} \Psi'^{i}_{pslt}, \quad \forall\, p \in P, s \in S, l \in L, t < S_p \tag{4.11}$$

$$\Psi_{pslt} = \sum_{i=t+1-S_p}^{t} \Psi'^{i}_{pslt}, \quad \forall\, p \in P, s \in S, l \in L, t \geq S_p \tag{4.12}$$

Equations 4.11 and 4.12 determine the total flow of product type p between a product manufacturer s and a DC l with regard to its production period. The same way as in equations 4.7 and 4.8, total product flows between concerned facilities are treated differently depending on the value of $t < S_p$ and $t \geq S_p$.

$$\sum_{e=i}^{t} \sum_{i=1}^{t} I^{ie}_{plt} = \sum_{s \in S} \Psi_{pslt} - \sum_{r \in R} \sum_{g \in G} \Psi_{plrgt}, \quad \forall\, p \in P,\ l \in L,\ t = 1\ \wedge\ t < S_p \tag{4.13}$$

$$\sum_{e=i}^{t} \sum_{i=1}^{t} I^{ie}_{plt} = \sum_{e=i}^{t-1} \sum_{i=1}^{t-1} I^{ie}_{plt\text{-}1} + \sum_{s \in S} \Psi_{pslt} - \sum_{r \in R} \sum_{g \in G} \Psi_{plrgt}, \quad \forall\, p \in P,\ l \in L,\ 1 < t < S_p \tag{4.14}$$

$$\sum_{e=i}^{i+S_p-1} \sum_{i=t+1-S_p}^{t} I^{ie}_{plt} = \sum_{e=i}^{t-1} \sum_{i=t+1-S_p}^{t-1} I^{ie}_{plt\text{-}1} + \sum_{s \in S} \Psi_{pslt} - \sum_{r \in R} \sum_{g \in G} \Psi_{plrgt}, \quad \forall p \in P, l \in L, t \geq S_p \tag{4.15}$$

Constraint sets 4.13 to 4.15 calculate the stock level for each DC over different time periods. When $t < S_p$ as in equations 4.13 and 4.14, the authorized interval for the production period is $i \in [1,\ t]$ and $e \in [i,\ t]$ for the delivery periods. There is a distinction between these two equations since for the first time period (i.e., $t = 1$), the

DCs have no products in inventory. On the other hand, if the time period is greater than the product's shelf life, as in equation 4.15, production and distribution must occur within the product's shelf life. This way, the production period transforms to $i \in [t{+}1\text{-}S_p,\ t]$ and, by changing the minimum allowable production time to $i = t{+}1\text{-}S_p$, the time period changes to $t{=}i\text{-}1{+}S_p$ and, consequently, the acceptable interval of delivery period is given as $e \in [i,\ i\text{-}1{+}S_p]$.

$$I^{ie}_{plt} = \sum_{s \in S} \Psi'^{i}_{pslt} - \sum_{r \in R} \sum_{g \in G} \Psi'^{ie}_{plrgt}, \quad \forall\, p \in P,\ l \in L, i \in I,\ e = t \tag{4.16}$$

$$I^{ie}_{plt} = I^{ie}_{plt\text{-}1} - \sum_{r \in R} \sum_{g \in G} \Psi'^{ie}_{plrgt}, \quad \forall\, p \in P,\ l \in L, i \in I,\ t - e < S_p \ \wedge\ i \leq e < t \tag{4.17}$$

Based on the delivery period of products, equations 4.16 and 4.17 calculate the inventory levels of DCs. If the time period is equal to the delivery period of products in the DC (i.e., $e{=}t$), as in equation 4.16, the inventory level is calculated as the products that arrive from the product manufacturers minus the flows to demand zones. However, when $t\text{-}e < S_p$ (equation 4.17), there are no inflows from the product manufacturers thus, the inventory level is given as the subtraction of the products that flow to demand zones from the inventory level of the previous period.

$$\Psi_{plrgt} = \sum_{e=i}^{t} \sum_{i=1}^{t} \Psi'^{ie}_{plrgt}, \quad \forall\, p \in P, l \in L, r \in R, g \in G, t < S_p \tag{4.18}$$

$$\Psi_{plrgt} = \sum_{e=i}^{i+S_p-1} \sum_{i=t+1-S_p}^{t} \Psi'^{ie}_{plrgt}, \quad \forall\, p \in P, l \in L, r \in R, g \in G, t \geq S_p \tag{4.19}$$

Constraints 4.18 and 4.19 calculate the flow of products from DCs to demand zones based on the products' delivery periods. So that the products do not expire in inventory, when the time period exceeds the product's shelf life, constraint 4.19 assures that the flow of products occurred within the product's shelf life. Thus, the production period's interval transforms to $i \in [t{+}1\text{-}S_p,\ t]$ and, consequently, the acceptable interval of delivery period is given as $e \in [i,\ i\text{-}1{+}S_p]$.

2. Entity Capacity

2.1 Production Capacity

$$P_{aft} \leq X_f M_{af}^{prod}, \quad \forall\, a \in A, f \in F, t \in T \tag{4.20}$$

$$P_{pst} \leq X_s\, M_{pgs}^{prod}, \quad \forall\, p \in P, s \in S, t \in T \tag{4.21}$$

The production capacity constraints limit the production of each manufacturing facility based on its installed capacity. If a facility has a limited capacity for producing a certain number of units, it cannot manufacture more than that amount. Equation 4.20 ensures that the amount of API a produced by the API manufacturer f does not exceed the facility's production capacity for each API and time period, while equation 4.21 ensures that the amount of product p produced by the product manufacturer s does not exceed the facility's production capacity for product type p and age group g, per time period. In addition, both equations (4.20 and 4.21) need to account for whether the manufacturers are part of the network or not.

2.2 Handling Capacity

$$\sum_{g \in G} \sum_{r \in R} \sum_{p \in P} \Psi_{plrgt} \leq X_l\, M_l^{hand}, \quad \forall\, l \in L, t \in T \tag{4.22}$$

DCs have limited resources thus, the handling capacity is the maximum amount of products that the DCs can handle in each time period. Constraint 4.22 guarantee that the flow exiting each DC does not exceed their handling capacity for all products, in each time period.

2.3 Storage Capacity

$$\sum_{a \in A} (I_{aft}\, U_{ac}) \leq X_f\, M_{fc}^{stor}, \quad \forall\, f \in F, c \in C, t \in T \tag{4.23}$$

$$\sum_{p \in P} (I_{pst}^{i}\, U_{pc}) \leq X_s\, M_{sc}^{stor}, \quad \forall\, s \in S, c \in C, t \in T \tag{4.24}$$

$$\sum_{p \in P} (I_{plt}^{ie}\, U_{pc}) \leq X_l\, M_{lc}^{stor}, \quad \forall\, l \in L, c \in C, t \in T \tag{4.25}$$

Storage capacity constraints found in 4.23 to 4.25 ensure that the maximum storage capacity of any given facility at any time period and for any given storage

condition is never exceeded, regardless of the facility, the time period, or the storage condition.

3. Demand Satisfaction

$$\sum_{l \in L} \sum_{p \in P_g} \Psi_{plrgt} \geq D_{rgt} - B_{rtg}, \quad \forall\, r \in R,\ g \in G, t = 1 \tag{4.26}$$

$$\sum_{l \in L} \sum_{p \in P_g} \Psi_{plrgt} \geq D_{rgt} + B_{rtg\text{-}1} - B_{rtg}, \quad \forall\, r \in R, g \in G, t \in T,\ t > 1 \tag{4.27}$$

$$B_{rtg} = 0, \quad \forall\, r \in R, g \in G,\ t = T \tag{4.28}$$

Not all the products are safe to be administrated to all age groups, so by creating a new set P_g, the model focuses on considering only the relevant products to satisfy the demand. To this end, the selection criteria requires that for each combination of a demand zone and age group, only products that can be used in that age group, as determined by the M^{prod}_{pgs} parameter, are included in the new set P_g.

Thus, to ensure that demand is satisfied, constraint 4.26 guarantees that, in the first time period, the flow of all products from all DCs to each demand zone is higher than the demand of that demand zone minus the backorders that will be fulfilled in the subsequent time period. For the remaining time periods, constraint 4.27 additionally takes into account the backorders accumulated from the previous time period. Both constraints 4.26 and 4.27 allow for flexibility in the products used to meet demand. As long as the products are safe for the age group corresponding to the demand to be satisfied, and the total flow of products is sufficient to meet the demand of each demand zone in each time period, any product can be used.

Finally, at the end of the time horizon (i.e., $t = T$), equation 4.28 ensures that all demand zones have their demand satisfied, since no backorders are allowed.

4. Variables' Constraints

4.1 Binary Variables

$$X_f, \quad X_s, \quad X_m, \quad X_l \quad \in \{0,1\} \tag{4.29}$$

The integration or not of a given facility in the network is defined by the binary decision variables, which can only take the value 0 or 1, as guaranteed by equation 4.29.

4.2 Null Variables

$$I^{i}_{pst} = 0 \quad \forall\, p \in P,\ s \in S,\ i \in I,\ t \in T,\ t < i \tag{4.30}$$

$$I^{ie}_{plt} = 0 \quad \forall\, p \in P,\ l \in L, i \in I,\ e \in E,\ t \in T,\ t < i \tag{4.31}$$

$$I^{ie}_{plt} = 0 \quad \forall\, p \in P,\ l \in L, i \in I,\ e \in E,\ t \in T,\ e < i \tag{4.32}$$

Equations 4.30 to 4.32 display the decision variables that must take on a value of zero. When the time period is shorter than the production period (i.e., $t < i$) or the delivery period is shorter than the production period (i.e., $e < i$), the inventory must be null.

4.3 Non-negative Variables

$$\begin{aligned} \psi_{afst},\quad \psi_{pslt},\quad \psi'^{i}_{pslt},\ \psi_{plrgt},\quad \psi'^{ie}_{plrgt} \quad &\geq 0, \\ &\forall\, a \in A, p \in P, f \in F,\ s \in S, \\ &l \in L,\ r \in R, i \in I,\ e \in E,\ t \in T \end{aligned} \tag{4.33}$$

$$\begin{aligned} I_{aft},\quad I^{i}_{pst},\quad I^{ie}_{plt} \quad \geq 0, \quad &\forall\, a \in A, p \in P, f \in F,\ s \in S, \\ &l \in L,\ r \in R, i \in I,\ e \in E,\ t \in T \end{aligned} \tag{4.34}$$

$$P_{aft},\quad P_{pst} \quad \geq 0, \quad \forall\, a \in A,\ p \in P,\ f \in F,\ s \in S,\ t \in T \tag{4.35}$$

Finally, negative values cannot exist for flows, inventories, or productions, which is assured by equations 4.33, 4.34, and 4.35, respectively.

5

Model Validation & Results Analysis

This chapter focuses on the practical application of the formulated model to the Portuguese COVID-19 vaccine SC network and it is organized as follows: section 5.1 defines and characterizes the case study chosen for analysis. In section 5.2, the approach employed to solve the multi-objective problem is defined and justified. Finally, the results obtained from the application of the model to the case study are analyzed in section 5.3, followed by a discussion of the findings in section 5.4.

5.1 Case Study: Portugal's COVID-19 Vaccines

The COVID-19 is an infectious disease caused by the SARS-CoV-2 virus that can affect individuals of all ages and may result in severe illness or even death when contracted [118]. In 2020 and 2021, the WHO estimated that the pandemic caused approximately 15 million deaths. Nonetheless, the launch of vaccinations has saved millions of lives. Notably, researchers have determined that the initial year of COVID-19 vaccination played a significant role in reducing global deaths by more than half, averting an estimated 14 to 20 million fatalities [119].

Even though the WHO officially announced the conclusion of the emergency phase of the pandemic in May 2023, it emphasized that COVID-19 still poses a health risk. This is due to the potential of new virus variants to evade the body's immune system, leading to infections, severe illness, and even death. Therefore, it is crucial for countries to continue monitoring infection rates and ensuring the availability of COVID-19 vaccination [119].

Vaccines against COVID-19 have a limited shelf life and must be stored in freezing temperatures, making its management a significant logistical challenge. To ensure the success of vaccination programs, it is imperative to implement efficient and effective planning and management of the SC. Failing to do so can result in the

waste of valuable vaccine doses, leading to significant financial losses and increased environmental waste.

This way, a study on the SC of COVID-19 vaccines in Portugal is carried out based on publicly available information in order to apply and validate the model developed. However, it should be noted that due to the lack of substantial data, the case study serves only as a representative study of a perishable PSC network.

5.1.1 Data Gathering

Based on the data provided by EMA, as of April 2023, there are eight vaccines authorized for use in the EU for protecting people against COVID-19: Comirnaty (commercialized by BioNTech and Pfizer), Spikevax (commercialized by Moderna), Vaxzevria (commercialized by AstraZeneca), Jcovden (commercialised by Janssen), Nuvaxovid (commercialized by Novavax), COVID-19 Vaccine Valneva (commercialized by Valneva), VidPrevtyn Beta (commercialized by Sanofi Pasteur), and Bimervax (commercialized by HIPRA) [119]. By analyzing the product information documents, it is possible to identify the API and final product manufacturers for each vaccine. For this case study, only manufacturers located in Europe are considered.

Products Information

Comirnaty and Spikevax are the only vaccines currently available that can be administered to any age group, however, they are the ones that need more expensive storage conditions. Comirnaty vaccine requires ultra-freezing conditions (store in a freezer at -90°C to -60°C), which will be referred to as C1 hereafter, and is manufactured by two secondary manufacturers in Mainz (Germany) and Puurs (Belgium). As for its API, it can be manufactured in four different locations, Dublin (Ireland), Mainz, Marburg, and Laupheim (Germany) [120]. On the other hand, Spikevax vaccine can be manufactured in six different manufactures, whereas three of them are located in Madrid (Spain), one in Monts (France) and two in Monza and Ferentino (Italy), while its API can only be manufactured in Visp (Switzerland) [121]. This vaccine requires freezing storage conditions (-50°C to -15°C), henceforth designated C2.

The remaining available vaccines cannot be administered to children, which further restricts their use. Nevertheless, apart from Jcovden vaccine, which needs to be kept in ultra-cold temperatures of -25°C to -15°C (referred to as C3 hereafter), the storage requirements for the remaining vaccines are no longer as stringent, as they solely mandate cold conditions within the range of 2°C to 8°C, henceforth designated C4. As to their manufacturers, Jcovden vaccine has one API manufacturer in Leiden

(The Netherlands), which also works as a final product manufacturer and, therefore, there will be no associated costs for transportation between these two facilities, and another possible product manufacturer in Beerse (Belgium) [122].

Vaxzevria vaccine is manufactured in Nijmegen (The Netherlands) and its API can be manufactured in multiple locations, such as Seneffe (Belgium), Oxford (United Kingdom), and Leiden (The Netherlands) [123].

Moreover, both the Nuvaxovid vaccine and its API are manufactured in Jevany (Czechia) therefore, there are no transportation costs between both manufacturers [124].

Furthermore, COVID-19 Vaccine Valneva has its API manufactured in Livingston (Scotland) or Dessau-Rosslau (Germany), while the vaccine itself can be manufactured in Solna (Sweden) or Vienna (Austria) [125]. This particular vaccine is contraindicated for individuals above the age of 65.

VidPrevtyn vaccine is manufactured, as well as its API, in France yet, in the different cities of Marcy l'Etoile and Vitry sur Seine Cedex, respectively [126].

Finally, both Bimervax API and vaccine are manufactured in Girona (Spain) thus, there are no associated transportation costs between the manufactures of this vaccine [127].

It is essential to recognize the criticality of batch testing and transportation time in the distribution of various COVID-19 vaccines. Extensive testing is an indispensable process for ensuring the safety and efficacy of vaccine batches. Consequently, the duration required for this testing can span several days, thereby influencing the overall lead time before vaccines can be made available to the public. To address this, an approximation of the lead time, encompassing both batch testing and transportation time, is made by considering the remaining shelf life since manufacture for the COVID-19 vaccines, including Comirnaty, Spikevax, Vaxzevria, Jcovden, Nuvaxovid, COVID-19 Vaccine Valneva, VidPrevtyn Beta, and Bimervax, as 12, 5, 5, 7, 5, 12, 8, and 8 months, respectively.

Table 5.3 at the end of this section summarizes the information of each vaccine and respective assigned code in the case study, while Table 5.2 presents each vaccine specification considered in the case study and its assigned code.

Portugal's Distribution Network

In the context of this study, it is assumed that each district of Portugal represents a demand zone and it is proposed that each district has the capacity to accommodate a DC. Since Portugal comprises 18 districts along with 2 Autonomous Regions, the distribution network will include a total of 20 possible DCs and 20

demand zones. This assumption enables a comprehensive coverage of the entire geographical area of Portugal, ensuring efficient distribution and accessibility to each district and Autonomous Region. Table 5.1 presents each DC considered in the case study and its assigned code.

Table 5.1: Distribution centres codification in the case study.

Distribution Centres							
Lisboa	d0	Faro	d5	Funchal	d10	Évora	d15
Porto	d1	Leiria	d6	Ponta Delgada	d11	Beja	d16
Setúbal	d2	Santarém	d7	Viana do Castelo	d12	Guarda	d17
Braga	d3	Coimbra	d8	Vila Real	d13	Bragança	d18
Aveiro	d4	Viseu	d9	Castelo Branco	d14	Portalegre	d19

Transportation Costs

Given the criterion of exclusively considering manufacturers situated in Europe, only truck transportation is accounted for among the manufacturers and between product (vaccine) manufacturers and DCs, with the exception of the autonomous regions of Açores and Madeira (islands). In Portugal, after the vaccines arrive to the DCs, except for Açores and Madeira, the transportation mode considered is also the truck. For routes to Funchal and Ponta Delgada, air transportation by plane is considered. As suggested by Mousahadeh et al. [89], the transportation costs between manufacturers, DCs, and demand zones are calculated based on the weight of each good and kilometers traveled, whose distances were calculated for each route using Google Maps [1].

This way, almost all transportation costs are calculated based on the average cost of road transportation in Europe, which can range from 0.08 to 0.20 euros per kilogram per kilometer (€/(km.kg)), according to a freight quote agency. Since vaccines require specific transportation conditions and careful handling, an average value of 0.15 €/ (km.kg) is considered for the present problem. Transportation costs are converted from cost per weight to cost per vaccine dose, assuming an average weight of 4.2 grams per dose [2], resulting in an average of 0.00063 €/ (km.dose). On the other hand, APIs do not require such strict transportation conditions, so an average of 0.08 €/ (km.kg) is considered between API manufacturers and final product manufacturers. An average weight of 2 grams per API is considered, resulting in an average of 0.00016 €/ (km.API). In the case of the routes by air (to Funchal and Ponta Delgada), the transportation costs were calculated based on the average cost of air transportation of 0.40 €/ (km.kg) and therefore, 0.00168

[1] https://www.google.nl/maps

[2] https://expresso.pt/sociedade/2020-12-26-Covid-19-Primeiro-lote-de-vacinas-ja-chegou-a-Portugal

€/ (km.dose). Routes to the islands were only considered for demand zones with airports or aerodromes.

Transportation costs based on the distances between each facility can be found in appendix, from Table A.11 to Table A.14.

Inventory Holding Costs

The storage costs were estimated using data provided by Mousazadeh et al. [89]. In the mentioned case study, an average of €40 per ton and per time period is considered, which in the present study would result in an average of €0.18 per thousand doses and per time period. Nevertheless, the product under consideration is the amoxicillin 500 mg capsules. Capsules, by their nature, do not require stringent storage conditions and, as such, in order to obtain a more accurate representation of the storage requirements for vaccines, an estimation is made. This estimation entails considering the cost of €0.36, €0.72, €1.44, and €2.88 per thousand doses and per time period for vaccines stored in C4, C3, C2, and C1 conditions, respectively.

Integration Costs

Since realistic information about the costs of opening a facility in Europe is difficult to obtain, the average cost of Mousazadeh et al. [89] is adapted to the European market in proportion to the GDPs of both regions, according to the World Bank [3].

It is considered that the average cost of opening a product manufacturer is approximately 121 million Iranian Rials based on Mousazadeh et al. [89], which is equivalent to €2,597,199.50 at the current market exchange rates. Based on this value, the cost of opening each product manufacturer can be calculated in proportion to the GDP of the country in which the manufacturer is located. Table 5.3 shows the cost of integration of each product manufacturer in the SC under study, calculated using the ratio of Iran's GDP to the GDP of each facility's country (see Table A.1 in appendix).

In this study it is considered that the costs associated with opening API manufacturers are encompassed by the overall opening costs of product manufacturers. Considering this interdependence, open API manufacturers is considered to only incur a cost of €100. This minimal cost is applied to avoid a scenario where the model would automatically open every API manufacturer without any cost consideration since the aim is to identify the API manufacturers that should be established within the network.

[3] https://data.worldbank.org/indicator/NY.GDP.MKTP.CD

As for the costs of opening a DC, an average of 4,096 million Iranian Rials is considered based on Mousazadeh et al. [89]. At the current exchange rate this value corresponds to €87,918.42, which is adapted to the Portuguese market in proportion to the GDPs of both countries according to the World Bank (see Table A.1 in appendix). This way, is considered the cost of €109,019 for opening each DC.

Production, Storage, and Handling Capacities

Due to the limited publicly available information, in the present case study, it is estimated that API manufacturers possess a production capacity of 600 thousand units per time period. In this study, each time period is considered to correspond to a duration of one month. This estimation is based on the consideration that API manufacturers are equipped with the necessary resources and infrastructure to produce a significant quantity of units. On the other hand, product manufacturers are estimated to have a production capacity of 135 thousand doses per time period. This estimation can be attributed to various logical reasons. Firstly, vaccine production involves a complex and intricate process that requires meticulous attention to detail, stringent quality control measures, and adherence to regulatory guidelines. These factors can potentially limit the production capacity of vaccine manufacturers compared to API manufacturers.

Regarding storage capacities, it is assumed that both API and vaccine manufacturers have varying capacities based on different conditions. For conditions C1, C2, C3, and C4, the storage capacities are considered to be 600, 700, 800, and 900 thousand doses per time period, respectively. These values reflect the facilities' capabilities to accommodate the storage needs for the produced units while ensuring proper conditions for preservation and stability.

Moreover, it is assumed that each DC has the capacity to handle 12 million doses per time period to ensure that a single DC is capable of managing the entire volume of vaccines within a given time period.

Demand

To accommodate the fact that certain vaccines are not appropriate for all age groups, the demand of the present problem has been categorized into three groups: individuals aged 65 and above, those under 18, and the rest of the population, which falls between 18 and 65 years old. As a result, the demand for each group is calculated based on the population in each district belonging to the relevant age group.

Therefore, the determination of total demand in the present problem was made

from official statistics provided by the National Institute of Statistics, which involved an evaluation of the population of Portugal according to age groups in the year 2021. Subsequently, the estimation of the demand for each district, i.e., the demand in each demand zone, was made taking into account the proportion of inhabitants residing in each respective district and can be found in Table A.2 of the appendix.

Furthermore, it is considered that the demand is not constant, but occurs in peaks, in order to simulate a scenario closer to reality. In Figure 5.1, the data from the WHO illustrates a clear pattern where COVID-19 outbreaks predominantly occur during January, coinciding with the coldest month of the year. To effectively curb the spread of an outbreak, it is crucial to ensure that the population is already immunized in the months when the risk of infection is highest. Consequently, in this particular study, a precautionary measure is implemented by providing a booster dose to the population. As part of this approach, individuals over 65 years of age (henceforth designated G1) are vaccinated in September, those between 18 and 65 years of age (henceforth designated G2) in October, and individuals under 18 years of age (henceforth designated G3) in November. Figure 5.2 illustrates the total demand per time period. It is important to note that although the figure represents the overall demand, it does not explicitly present the distribution of demand by each age group and demand zone.

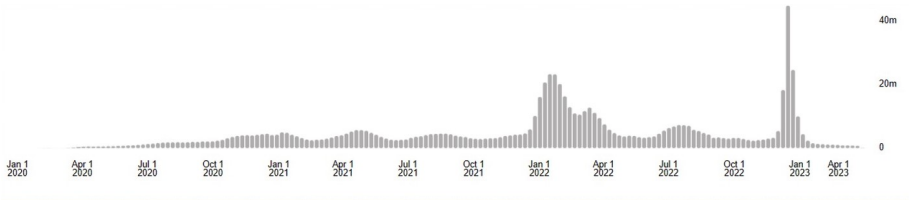

Figure 5.1: Global COVID-19 confirmed cases. From [9].

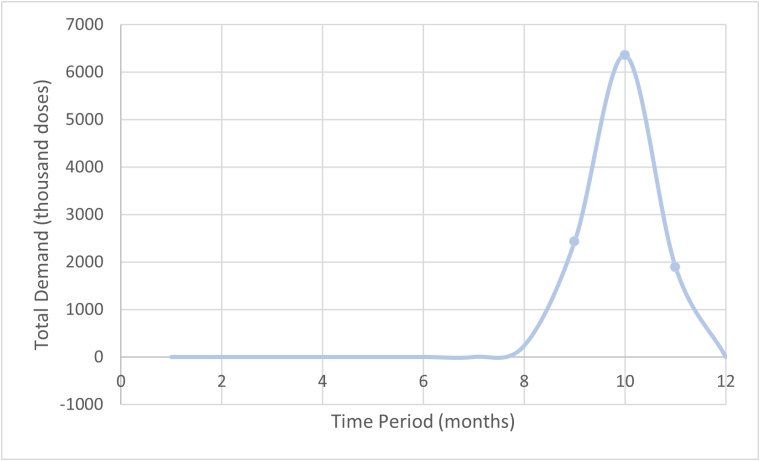

Figure 5.2: Total demand per time period.

Table 5.2: Vaccine specifications' codification.

Population eligible for administration	
65 years old	G1
18 – 65 years old	G2
18 years old	G3
Storage Conditions	
-90ºC to -60ºC	C1
-50ºC to -15ºC	C2
-25ºC to -15ºC	C3
2ºC to 8ºC	C4

Table 5.3: Vaccines' information and respective codification in the case study.

Vaccines		**API Manufacturers**		**Product Manufacturers (ant their opening costs (€))**			**Shelf Life (months)**	**Age Groups**	**Storage Cond.**
Comirnaty	v0	Mainz (Germany) Marburg (Germany) Laupheim (Germany) Dublin (Ireland)	a0 a1 a2 a3	Mainz (Germany) Puurs (Belgium)	p0 p1	207,776 1,558,320	12	G1, G2, G3	C1
Spikevax	v1	Visp (Switzerland)	a4	Monts (France) Monza (Italy) Ferentino (Italy) Madrid (Spain) I Madrid (Spain) II Madrid (Spain) III	p2 p3 p4 p5 p6 p7	311,664 441,524 441,524 649,300 649,300 649,300	5	G1, G2, G3	C2
Vaxzevria	v2	Seneffe (Belgium) Oxford (UK) Leiden (NL) I	a5 a6 a7	Nijmegen (NL)	p8	934,992	5	G1, G2	C4
Jcovden	v3	Leiden (NL) II	a8	Leiden (NL) Beerse (Belgium)	p9 p10	934,992 1,558,320	7	G1, G2	C3
Nuvaxovid	v4	Jevany (Czechia)	a9	Jevany (Czechia)	p11	3,324,415	5	G1, G2	C4
COVID-19 Vaccine Valneva	v5	Livingston (Scotland) Dessau-Rosslau (Germany)	a10 a11	Solna (Sweden) Vienna (Austria)	p12 p13	1,480,404 1,947,900	12	G2	C4
VidPrevtyn Beta	v6	Vitry sur Seine Cedex (France)	a12	Marcy l'Etoile (France)	p14	311,664	8	G1, G2	C4
Bimervax	v7	Girona (Spain)	a13	Girona (Spain)	p15	649,300	8	G1, G2	C4

5.2 Multi-objective Approach

The decisions involved in this problem must consider multiple trade-offs resulting from minimizing both the total costs of the network and the backlog of orders, which are the two objective functions. In Multi-Objective Mathematical Programming (MOMP), there are multiple objective functions, and generally, there is no optimal solution that simultaneously optimizes all objective functions. Therefore, in these situations, the search for an single optimal solution is replaced by the achievement of a compromise solution that takes into account the decision-maker's preference between the two objectives [105].

The current classification of MOMP methods defines three categories: a priori, interactive, and a posteriori. These classifications differ based on the moment in

the decision-making process at which the decision maker makes their preferences [105]. A priori methods involve the establishment of predetermined goals or weights for objectives by the decision-maker prior to the resolution process. On the other hand, interactive methods involve iterative cycles of computation and communication with the decision-maker until a state of convergence is achieved [105].

The method chosen in the present problem is a posteriori method, which involves the identification of a set of efficient solutions, commonly referred to as a Pareto optimal set, rather than relying on a single solution. Subsequently, in posteriori methods, the decision-maker selects the most desirable solution from this set. Pareto optimal solutions are defined by the property that any attempt to enhance one objective function would result in a decline in at least one of the other objective functions [105].

The approach used to generate the Pareto Set is the ϵ-constraint method, which consists of optimizing one of the objective functions while the other is constrained [89]. Hence, the problem was first solved for the cost minimization objective function, and then for the backorders minimization objective function (determination of the two extreme points of the Pareto front). Subsequently, an approximation of the Pareto efficient frontier was determined by dividing the linear space between the two extreme points into equal distance vertical lines, and then determining the ordinate of the point by adding the ϵ-constraint [89]. In other words, by knowing the two extreme points of the decision variable representing the number of backorders, and dividing its linear space with an distance ϵ, is possible to solve the problem for the cost minimization objective, with the number of backorders as a constraint. Then, by gradually changing the value of the constraint, a diverse set of solutions representing different trade-offs between the cost and backorders objectives are gererated.

5.3 Results Analysis

In this section, the results obtained from the application of the model proposed in chapter 4 to the case study described in the previous subchapter 5.1 are presented. The model has been implemented in DOcplex Python Modeling API, which uses the ILOG CPLEX Optimization Studio 22.1.1, in an Intel Core i7-1065G7, 1.30-1.50 GHz processor with 12GB RAM.

The problem under study consists of a four-level PSC with 8 distinct products (COVID-19 vaccines), which can be manufactured in 16 possible product manufacturers, while the production of the 8 types APIs can be distributed among 14 API manufacturers. Following the manufacturing stage, the vaccines are subsequently

transported to 20 possible DCs and subsequently distributed across 20 demand zones. The study evaluated the model's performance over a duration of one year, comprising 12 time periods, with each time period representing one month.

5.3.1 Pareto Front

To solve the MOMP, the ϵ-constraint method was implemented with an ϵ value of 212,000 in accordance with the prescribed procedure detailed in section 5.2, allowing the exploration of 12 diverse optimal solutions. For the backorders minimization objective function, the model successfully achieved the goal of zero backorders, resulting in a total cost of €18,315,981. However, since no constraint is set for the maximum cost, the model opens all facilities, leading to an extremely high cost. Yet, with this objective function it is found that it is possible to achieve a backorder value as low as 0, therefore, to obtain the Pareto extreme points, the problem was first solved for the cost minimization objective function, and then for the cost minimization objective function with the additional constraint of zero backorders, disallowing any backlog of orders.

Table 5.4 provides an overview of the trade-off values between backorders and total costs for each optimal solution. Additionally, Figure 5.3 illustrates the Pareto front curve, which represents the optimal solutions resulting from the multi-objective problem.

In Table 5.5, the comparison between solution 1 and solution 12 reveals significant differences in their SC designs and cost minimization strategies. Solution 1 focuses on minimizing total costs while maintaining the additional constraint of zero backorders. In contrast, solution 12 solely aims to minimize total costs, allowing for backlogged orders in subsequent time periods. This discrepancy in objectives leads to distinct SC configurations.

Solution 12 represents an extreme Pareto optimal solution, demonstrating that the minimum cost achievable by this SC is €4,744,963. However, to achieve this cost efficiency, a substantial number of 2,333,000 orders are backlogged. This approach results in a SC design where specific vaccine types, namely v0, v1, v3, v6, and v7, are manufactured. To understand this choice further, an analysis of the selected product manufacturers and their opening costs is necessary. Analyzing Table 5.3, it becomes evident that p0, p2, p14, p3, p4, p5, p6, p7, p15, p8, and p9 product manufacturers are the most cost-effective options. Notably, the model chooses to open the p0 product manufacturer, responsible for manufacturing the v0 vaccine, along with the corresponding API manufacturer, a0. It is particularly interesting to observe that the model selects a0 as the API manufacturer because it is located

in the same city as the product manufacturer (Mainz, Germany). This decision is driven by the model's consideration of transportation costs, as having the API manufacturer in close proximity to the product manufacturer results in the lowest transportation expenses.

Moreover, despite v1 vaccine having only one API manufacturer, its high production capacity enables it to supply APIs for multiple product manufacturers, including p2, p3, p4, p5, and p6. This flexibility allows v1 vaccine to be produced in a larger number of facilities compared to other vaccines. Consequently, v1 vaccine emerges as the most widely produced vaccine due to the availability of multiple product manufacturing facilities, as depicted in Figure 5.4.

Due to the comparatively lower opening costs associated with p14 product manufacturer, the model chooses to manufacture the v6 vaccine using this facility. Consequently, the corresponding API manufacturer, a12, is opened.

Furthermore, although p15 and p7 product manufacturers have the same opening costs, the model prioritizes p15 as the preferred choice. This preference can be attributed to the fact that p15 is responsible for producing the v7 vaccine, which has a longer shelf life compared to the v1 vaccine produced by p7. This consideration aligns with the model's objective to maximize SC efficiency by minimizing the risk of vaccine expiration. Additionally, the fact that a13 API manufacturer, which supports the production of v7 vaccine, is located in the same city as the p15 facility (Girona, Spain) also justifies the preference for p15 product manufacturer since it reduces transportation costs associated with the movement of APIs between the API manufacturer and the product manufacturer.

On the other hand, solution 1 successfully satisfies the constraint of zero backorders, aligning with the expected outcome. However, achieving this constraint necessitates the opening of two additional product manufacturers: p1 and p7. This product manufacturers are responsible for the production of v0 and v1 vaccines, which were already being manufactured in solution 12. Therefore, the number of vaccine types manufactured and the number of API manufacturers opened remains consistent across both solutions.

The selection of p7 as a product manufacturer aligns with the same reasoning as solution 12, as it offers lower opening costs compared to other possible options. On the other hand, the decision to open p1 as a product manufacturer is no longer based on its opening costs, as it actually has one of the highest costs. However, the objective of solution 1 is to prevent backorders, necessitating an increased production volume and inventory to meet demand promptly. In this context, the v0 vaccine stands out due to its longer shelf life, ensuring it does not expire within the

studied time horizon. Therefore, the opening of the p1 facility, which specializes in manufacturing the v0 vaccine, is justified to ensure an adequate supply and reduce the risk of potential stock shortages. The implementation of these additional product manufacturers, as well as the increase of products in inventory, results in an increased total cost of €6,975,767.

However, one might question why the model did not choose to produce the v5 vaccine instead of v0 since it also has the maximum shelf life in the time horizon studied. Several factors likely influenced this decision. Firstly, v5 vaccine has a smaller population coverage, limited to age group G2. Furthermore, since the API manufacturer for v0 vaccine was already opened to supply p0 facility, utilizing it for p1 manufacturer avoids the additional costs associated with opening another API manufacturer specifically for v5 vaccine.

A more detailed analysis of these extreme Pareto optimal solutions is presented in the following subsection 5.3.1.1.

By also analyzing the non-extreme points of the Pareto front (solutions 2 to 11) in Table 5.4, it becomes clear that the PSC total cost increases as less backorders are allowed to exist. Although there is not a large variation in the number of open facilities, this increase of costs can be justified by the amount of products in stock. As evident in Table 5.5, the substantial reduction in backorders makes the model suggest the use of more inventory. Given the inherent production capacity limitations of the product manufacturers, relying solely on production in each time period would lead to delays in meeting demand. Therefore, this outcome aligns with expectations, as the prevention of backorders and timely demand fulfillment require the increase of inventory.

Finally, for all the suggested solutions, exclusively the d1 DC, which corresponds to Porto, is established. The establishment of a single DC was anticipated since the handling capacity of all possible distribution center is sufficient to accommodate the storage and distribution requirements for all vaccines. Hence, by consolidating distribution in a single location, the model promotes efficiency and cost-effectiveness in the SC.

Table 5.4: Pareto optimal solutions.

Solution	Backorders	Total Cost (€)
1	0	6 975 767
2	212 000	6 316 225
3	424 000	5 695 242
4	636 000	5 692 990
5	848 000	5 515 771
6	1 060 000	5 407 342
7	1 272 000	5 407 009
8	1 484 000	5 406 406
9	1 696 000	5 032 899
10	1 908 000	4 757 009
11	2 120 000	4 755 862
12	2 333 000	4 744 963

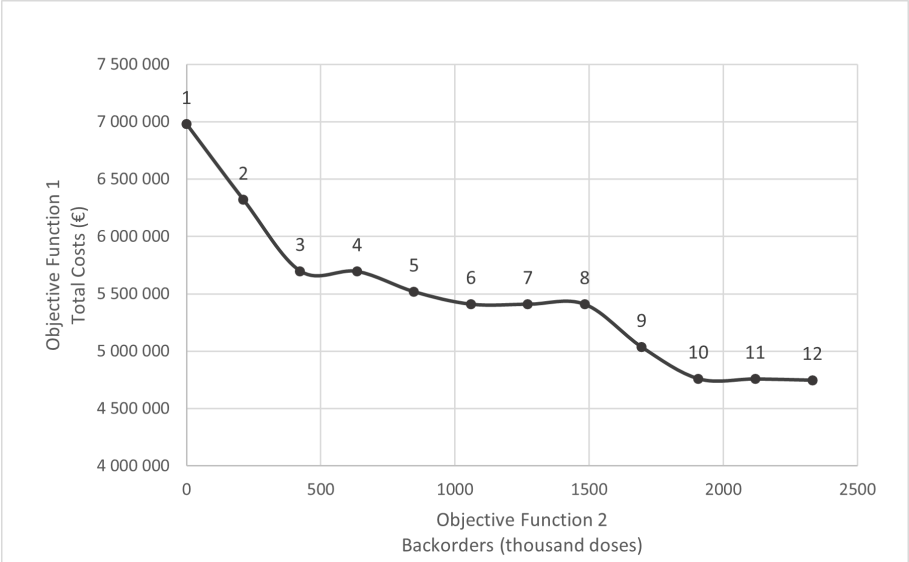

Figure 5.3: Pareto front: The trade-off between total costs and number of backorders.

5.3.1.1 Extreme Solutions Analysis

In order to analyze the model's output in more detail, Tables 5.6 and 5.7 exhibit the results of the model per time period for the solutions in which the minimum cost is reached (solution 12), and in which the minimum cost is reached with the constraint of no backorders (solution 1), respectively.

In Table 5.6, it is possible to observe that a higher number of products are kept in inventory at the DC starting from time period 5. This can be seen as a precautionary measure to mitigate the risk of expiration that exists in the previous time periods. Nevertheless, although maintaining a high level of inventory incurs

Table 5.5: Outputs for each optimal solution.

Solution	Vaccines IDs	Nº of API Man.	API Man. IDs	Nº of Prod. Man.	Prod. Man. IDs	DCs IDs	Total Inv.
1	0, 1, 3, 6, 7	5	0, 4, 8, 12, 13	11	0, 1, 2, 3, 4, 5, 6, 7, 9, 14, 15	1	31 830
2	0, 1, 3, 6, 7	5	0, 4, 8, 12, 13	10	0, 1, 2, 3, 4, 5, 7, 9, 14, 15	1	28 183
3	0, 1, 3, 6, 7	5	0, 4, 8, 12, 13	10	0, 1, 2, 3, 4, 5, 7, 9, 14, 15	1	29 492
4	0, 1, 3, 6, 7	5	0, 4, 8, 12, 13	10	0, 2, 3, 4, 5, 7, 8, 9, 14, 15	1	28 803
5	0, 1, 3, 6, 7	5	0, 4, 8, 12, 13	10	0, 2, 3, 4, 5, 6, 7, 9, 14, 15	1	27 468
6	0, 1, 3, 6, 7	5	0, 4, 8, 12, 13	10	0, 2, 3, 4, 5, 6, 7, 9, 14, 15	1	27 464
7	0, 1, 3, 6, 7	5	0, 4, 8, 12, 13	10	0, 2, 3, 4, 5, 7, 9, 14, 15	1	27 259
8	0, 1, 3, 6, 7	5	0, 4, 8, 12, 13	10	0, 2, 3, 4, 5, 6, 7, 9, 14, 15	1	26 788
9	0, 1, 3, 6, 7	5	0, 4, 8, 12, 13	10	0, 2, 3, 4, 5, 6, 7, 9, 14, 15	1	26 513
10	0, 1, 3, 6, 7	5	0, 4, 8, 12, 13	9	0, 2, 3, 4, 5, 6, 9, 14, 15	1	26 164
11	0, 1, 3, 6, 7	5	0, 4, 8, 12, 13	9	0, 2, 3, 4, 5, 6, 9, 14, 15	1	26 077
12	0, 1, 3, 6, 7	5	0, 4, 8, 12, 13	9	0, 2, 3, 4, 5, 6, 9, 14, 15	1	23 749

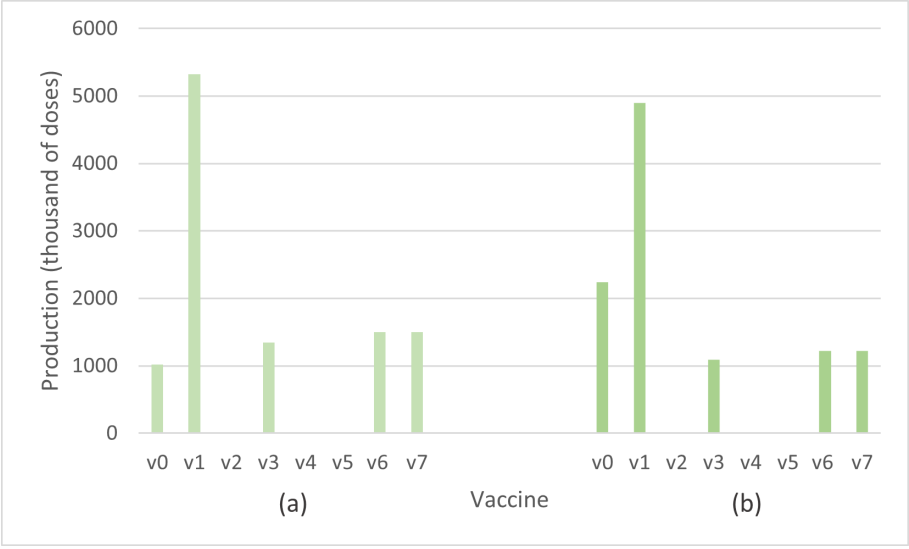

Figure 5.4: Production level per vaccine type for: (a) solution 12, and (b) solution 1.

costs, it is observed that a cummulative total of 23,749 thousand vaccines are kept in stock. This decision is possibly made because the alternative of opening more

manufacturers to increase production capacity would result in even higher costs. Another significant finding is that, except for the first time period, production takes place in all time periods. This indicates a well-implemented production strategy where vaccine manufacturing is consistently maintained throughout the analyzed period.

Moreover, the production, inventory, and flow levels match for all time periods, which suggests that the material balances constraints (found in subsection 4.2.4) were successfully implemented. In the specific case of time period 9, the analysis shows that the vaccines in inventory are sufficient to meet the demand. Consequently, no orders are backlogged during this time period. However, in the subsequent time period, no inventory remains left, resulting in backorders being created. This is best illustrated in Figure 5.5, in which it is possible to see the relation between backorders and age groups. The G1 age group, being the first to be vaccinated, benefits from having all the necessary products in inventory to meet their demand. This successful allocation ensures that no backorders are accumulated for the G1 age group, indicating an efficient planning. For the G2 age group, a high accumulation of backorders is observed due to the absence of inventory and a demand for 6,353 thousand doses. On the other hand, vaccination for the G3 age group occur in the penultimate time period. This approach to scheduling reduces the possibility of high backorders creation for this age group since all demand must be met in the subsequent time period.

On the other hand, the solution in which backorders are not allowed is analyzed in Table 5.7. As expected, during the periods of vaccination (time periods 9, 10, and 11), it is observed that the total flow of vaccines from the DC to the demand zones meets the total demand, leading to the absence of backorders. This result verifies the constraint's effectiveness. Moreover, to achieve this, the model adjusts the production levels in each time period, increasing them.

A comparison between solution 1 and solution 12 reveals noticeable differences in inventory management. Notably, solution 1 exhibits a larger number of vaccines in stock, aligning with expectations. This increase in inventory demonstrates the model's sensible decision-making in achieving a sufficient supply of vaccines during vaccination periods to satisfy the zero backorders constraint. Additionally, solution 1 demonstrates a higher quantity of APIs stored by API manufacturers. This strategic approach highlights the model's proactive measures to ensure a consistent and reliable supply of vaccines throughout the distribution process to avoid backorders. Once again, the synchronization of production, inventory, and flow levels across all time instants demonstrates the successful implementation of material balances

constraints (found in subsection 4.2.4).

In Figure 5.6 the inventory usage per storage condition is evaluated. In (b) solution 1 is depicted and the inventory analysis reveals that condition C2 is the most frequently verified storage condition. It is worth to notice that condition C2 incurs the second-highest storage costs. However, this high presence of C2-conditioned vaccines can be justified by the fact that the v1 vaccine, which requires C2 storage conditions, is the most produced vaccine in this solution. This production prioritization justifies the increased inventory of C2-conditioned vaccines, despite the associated storage costs.

On the other hand, condition C1, which requires the highest storage costs, is still found in large quantities in solution 1. This is attributed to the v0 vaccine, which necessitates C1 storage and has the longest shelf life. The longer shelf life of the v0 vaccine allows it to be manufactured earlier and remain in stock for a longer duration, explaining the substantial presence of C1-conditioned vaccines in inventory.

In contrast, solution 12 (in (a)) exhibits a different inventory pattern due to the allowance of backorders. The model strategically avoids the expensive storage condition C1. Instead it opts for the storage of products under condition C4, which is the cheapest to maintain in inventory. This decision highlights the model's goal of minimizing the total costs through the reduction of storage costs. However, the high presence of condition C2 is still observed. This can be attributed to the fact that the v1 vaccine, requiring C2 storage, remains the most produced vaccine in this solution.

Overall, the analysis in Figure 5.6 highlights the trade-off between storage conditions (which have different associated costs in inventory) and inventory levels. While solution 1 emphasizes the presence of C2 and C1 conditions, reflecting the production and longer shelf life considerations respectively, solution 12 prioritizes cost-effectiveness by favoring C4 storage. The presence of C2 in both solutions can be justified by the prominence of the v1 vaccine in production.

Table 5.6: Outputs: Solution 12.

Time Period	API's Production	Flow API Man. to Prod. Man.	Inv. API Man.	Product's Production	Flow Prod. Man. to DC	Inv. Prod. Man.	Flow DC to Demand Zones	Inv. DCs	Demand (in thousand of doses)	Backorders (in thousand of doses)
1	0	0	0	0	0	0	0	0	0	0
2	272	272	0	272	272	0	0	272	0	0
3	408	408	0	408	276	132	0	548	0	0
4	933	408	525	408	268	272	0	816	0	0
5	1082	1157	450	1157	1158	271	0	1974	0	0
6	1143	1218	375	1218	885	604	0	2859	0	0
7	1143	1218	300	1218	1218	604	0	4077	0	0
8	1143	1218	225	1218	938	884	0	5015	0	0
9	1143	1218	150	1218	608	1494	2434	3189	2434	0
10	1143	1218	75	1218	2365	347	5554	0	6353	799
11	1126	1201	0	1201	1412	136	1157	255	1892 (+799)	1534
12	1143	1143	0	1143	1279	0	1534	0	0 (+1534)	0

Table 5.7: Outputs: Solution 1.

Time Period	API's Production	Flow API Man. to Prod. Man.	Inv. API Man.	Product's Production	Flow Prod. Man. to DC	Inv. Prod. Man.	Flow DC to Demand Zones	Inv. DCs	Demand (in thousand of doses)	Backorders (in thousand of doses)
1	204	204	0	204	0	204	0	0	0	0
2	476	476	0	476	21	659	0	21	0	0
3	712	612	100	612	320	951	0	341	0	0
4	1212	612	700	612	205	1358	0	546	0	0
5	1212	1312	600	1312	544	2126	0	1090	0	0
6	1211	1311	500	1311	1408	2029	0	2498	0	0
7	1212	1312	400	1312	802	2539	0	3300	0	0
8	1212	1312	300	1312	1498	2353	0	4798	0	0
9	1212	1312	300	1312	1721	1944	2434	4085	2434	0
10	1212	1312	100	1312	2311	945	6353	43	6353	0
11	804	904	0	904	1849	0	1892	0	1892	0
12	0	0	0	0	0	0	0	0	0	0

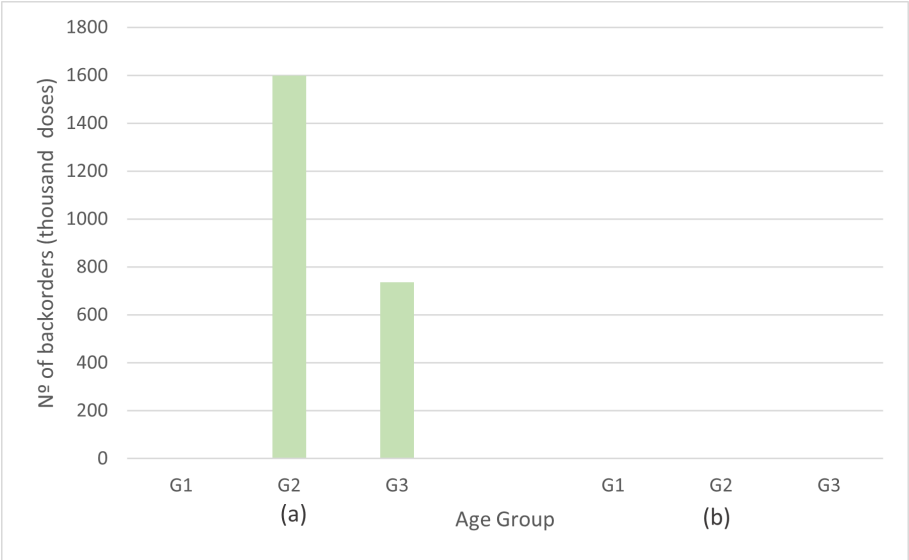

Figure 5.5: Number of backorders per age group for: (a) solution 12, and (b) solution 1.

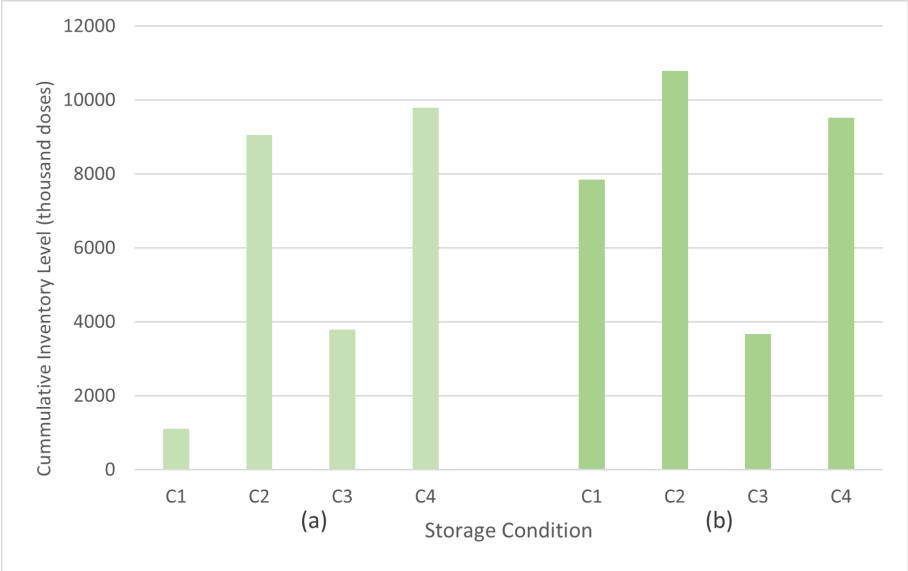

Figure 5.6: Inventory level per storage condition for: (a) solution 12, and (b) solution 1.

Subsequently, the model response is evaluated through various simulated scenarios, namely changing the open DC, increasing and decreasing vaccines' shelf life, and maintaining a constant level of demand. For all scenarios, when possible, results are presented in comparison with the baseline scenario studied so far for two distinct solutions: solution A, in which the minimum cost is reached (solution 12 in the baseline scenario, as seen in Table 5.4), and solution B, in which the minimum possible cost is reached, given the constraint that no backorders are allowed (solution 1 in the baseline scenario, as shown in Table 5.4).

5.3.2 Opening of Coimbra's Distribution Centre

The model proposes the opening of d1 DC (in Porto), however, in the urgent situation of 2020, the Portuguese government decided to allocate the vaccines in Coimbra. Based on this, the simulation of only considering the Coimbra DC (herein referred to as d8) is conducted to see what impacts this has on the SC. Tables 5.8 and 5.9 show the comparison of the impact that the opening of this two different DCs has on the SC, without and with the maximum number of backorders restriction, respectively. Based on the results presented in the Tables 5.8 and 5.9, it is possible to conclude that, despite the fact that the same vaccines are manufactured using the same API and product manufacturers, the d1 DC enables a lower minimum total cost in both situations, certainly due to transportation costs, demonstrating the model's efficiency by choosing this DC in the present case study.

Table 5.8: Comparison of the impact of d1 and d8 DCs on the SC for solution A.

Scenario	Nº of Vaccines	Vaccines IDs	Nº of API Man.	API Man. IDs	Nº of Prod Man.	Prod. Man. IDs	Total Cost (€)	Backorders (doses)
Porto (d1)	5	0, 1, 6, 7	5	0, 4, 8, 12, 13	9	0, 2, 3, 4 5, 6, 9, 14, 15	4 744 963	2 333 000
Coimbra (d8)	5	0, 1, 6, 7	5	0, 4, 8, 12, 13	9	0, 2, 3, 4 5, 6, 9, 14, 15	4 753 942	2 442 000

Table 5.9: Comparison of the impact of d1 and d8 DCs on the SC for solution B.

Scenario	Nº of Vaccines	Vaccines IDs	Nº of API Man.	API Man. IDs	Nº of Prod Man.	Prod. Man. IDs	Total Cost (€)	Backorders (doses)
Porto (d1)	5	0, 1, 3, 6, 7	5	0, 4, 8, 12, 13	11	0, 1, 2, 3, 4 5, 6, 7, 9, 14, 15	6 975 767	0
Coimbra (d8)	5	0, 1, 3, 6, 7	5	0, 4, 8, 12, 13	11	0, 1, 2, 3, 4 5, 6, 7, 9, 14, 15	6 975 877	0

5.3.3 Vaccines with unlimited shelf life

To assess the impact of vaccines with an unlimited shelf life, the shelf life parameter was set to the maximum (12 months) for all vaccine types. Tables 5.10 and 5.11 present the results of the SC structure for solutions A and B, respectively.

For both solutions, when comparing the two scenarios, it can be observed that having an unlimited shelf life reduced the number of vaccine types manufactured. V3 vaccine is not produced, therefore, the model does not open a8 API manufacturer and p9 product manufacturer, in which v3 vaccine is produced, which results in a reduction of total costs.

Moreover, for solution B, also p7 product manufacturer is not established, which suggests that v1 vaccine is able to be produced in one less product manufacturer. This can be explain since the prolonged shelf life of vaccines reduces the urgency for rapid distribution and administration. Vaccines with shorter shelf lives require faster production, delivery, and utilization to prevent wastage. However, with unlimited shelf life, there is more flexibility in the distribution and administration of vaccines, allowing more vaccines to be kept in inventory since there is no risk or expiry. This can better be seen in Figure 5.7 in which the total inventory usage is depicted. According to it, in the scenario where shelf life is unlimited (scenario (b)), the inventory level is higher, which results in a reduction of backorders since more vaccines are available to meet the demand, as seen in Figure 5.8. This can also explain the fact that although the same facilities are open for the scenario of unlimited shelf life of both solutions, for solution B the total costs are slightly higher

since there are additional storage costs.

Table 5.10: Impact of unlimited shelf life on the SC for solution A

Scenario	Nº of Vaccines	Vaccines IDs	Nº of API Man.	API Man. IDs	Nº of Prod Man.	Prod. Man. IDs	Nº of DCs	Total Cost (€)	Backorders (doses)
Limited shelf life (a)	5	0, 1, 3, 6, 7	5	0, 4, 8, 12, 13	9	0, 2, 3, 4 5, 6, 9, 14, 15	1	4 744 963	2 333 000
Unlimited shelf life (b)	4	0, 1, 3, 6, 7	4	0, 4, 12, 13	8	0, 2, 3, 4 5, 6, 14, 15	1	3 184 504	1 706 000

Table 5.11: Impact of unlimited shelf life on the SC for solution B.

Scenario	Nº of Vaccines	Vaccines IDs	Nº of API Man.	API Man. IDs	Nº of Prod Man.	Prod. Man. IDs	Nº of DCs	Total Cost (€)	Backorders (doses)
Limited shelf life (a)	5	0, 1, 3, 6, 7	5	0, 4, 8, 12, 13	11	0, 1, 2, 3, 4 5, 6, 7, 9, 14, 15	1	6 975 767	0
Unlimited shelf life (b)	4	0, 1, 6, 7	4	0, 4, 12, 13	8	0, 2, 3, 4 5, 6, 14, 15	1	3 842 674	0

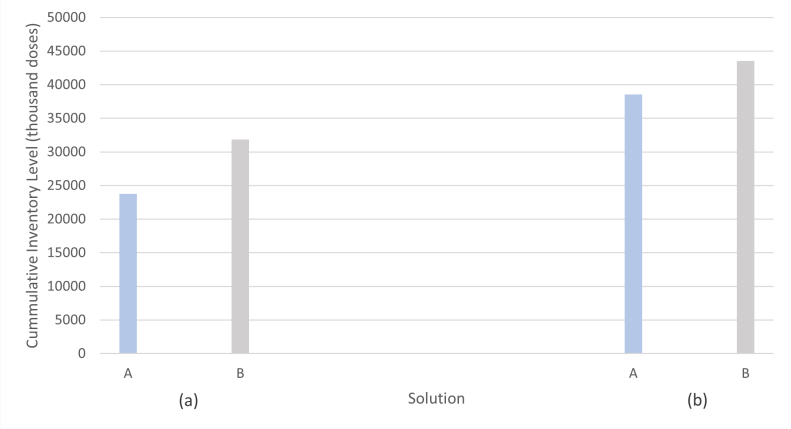

Figure 5.7: Total inventory usage for scenario with: (a) limited shelf life, and (b) unlimited shelf life.

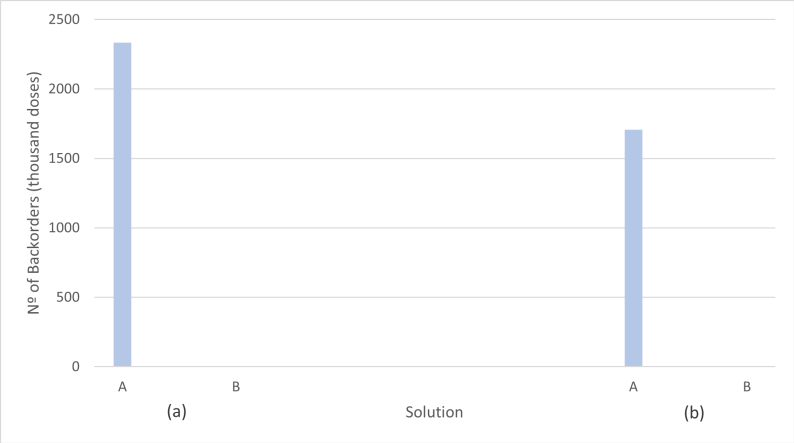

Figure 5.8: Total number of backorders for scenario with: (a) limited shelf life, and (b) unlimited shelf life.

5.3.4 Vaccines with a shorter shelf life

In order to evaluate the effects of vaccines with a reduced shelf life, a shelf life parameter of 3 months was established across all vaccine types. Tables 5.12 and 5.13 present the results of the SC structure for solution A and solution B, respectively. Comparing the two scenarios within each solution, it is evident that a shorter shelf life has a notable impact on the SC dynamics since it leads to an expansion in the number of vaccine types manufactured and therefore the model is forced to establish new facilities (both API and product manufacturers) compared to the baseline scenario (scenario (a)). This expansion results in higher total costs and a larger number of backorders.

For solution A, a shorter shelf life causes the SC to add v2 and v4 vaccines to the vaccine types manufactured and, consequently, the API and product manufactures in which these vaccines are produced are also established. It is interesting to note that v2 vaccine is manufactured in p8 (Nijmegen, the Netherlands) however, its API can be produced in a5 (Seneffe, Belgium), a6 (Oxford, United Kingdom), or in a7 (Leiden, the Netherlands). The model opted for the opening of the API manufacturer that led to the lowest transport costs, i.e. manufacturer a7, since it is located in the same country as the product manufacturer. Furthermore, the choice for the v2 vaccine is easily understood because it is the one, among those that were not manufactured (v2, v4, and v5 vaccines), that has the lowest costs for opening a product manufacturer, as Table 5.3 suggests.

In addition, the model also suggests manufacturing the v4 vaccine. This vaccine is manufactured in p11, which is a product manufacturer with higher opening costs when compared to the product manufacturer for v5 vaccine. This may be attributed

to the fact that v5 vaccine has a smaller population coverage, i.e., it can only be used in age group G2, while v4 vaccine can be administrated to age groups G1 and G2.

Moreover, the model also increased the production levels of v0, v1, and v3 vaccines, as suggested by the opening of the additional product manufacturers p1, p7, and p10. This can be attributed to the reduced shelf life, which imposes restrictions on the timing of vaccine production. Due to the risk of product expiration, the model is unable to produce vaccines in advance and store them in inventory. Instead, it suggests that the manufacture of vaccines should occur within a specific time window to ensure they are still within their shelf life. Since product manufacturers have limited production capacities for each time period, it was already expected that the production of a high amount of vaccines in a short window of time was not possible. As a result, the model optimizes the solution by opening additional product manufacturers closer to the time of demand.

On the other hand, when no backorders are allowed the model did not solve successfully, being possible to infer that for a shorter shelf life, backorders are always necessary. Therefore, the model was then applied for the backorders minimization objective function, resulting in a objective value of 3,044,000. Hence, in this case, solution B for scenario (b) represents the solution in which the minimum cost is reached with the constraint of 3,044,000 backorders and is depicted in Table 5.13. According to it, to minimize backorders as much as possible, the model is forced to manufacture all vacine types, and open all API and product manufacturers, which translates into a SC with very high costs.

Again, the behavior of the inventory levels and number of backorders in studied for this new scenario. The total inventory is illustrated in Figure 5.9 in which is possible to see that, for a shorter shelf life (scenario b) the inventory level decreases since there is a higher risk or expiration. This decrease in inventory level makes it difficult to meet demand effectively, increasing the number of backorders, as Figure 5.10 suggests.

Table 5.12: Impact of a shorter shelf life on the SC for solution A

Scenario	Nº of Vaccines	Vaccines IDs	Nº of API Man.	API Man. IDs	Nº of Prod Man.	Prod. Man. IDs	Nº of DCs	Total Cost (€)	Backorders (doses)
Peak demand	5	0, 1, 3, 6, 7	5	0, 4, 8, 12, 13	9	0, 2, 3, 4 5, 6, 9, 14, 15	1	4 744 963	2 333 000
Shorter shelf life (b)	7	0, 1, 2 3, 4, 6, 7	7	0, 4, 7 8, 9, 12, 13	14	0, 1, 2, 3, 4, 5, 6 7, 8, 9, 10, 11, 14, 15	1	14 240 587	4 270 000

Table 5.13: Impact of a shorter shelf life on the SC for solution B.

Scenario	Nº of Vaccines	Vaccines IDs	Nº of API Man.	API Man. IDs	Nº of Prod Man.	Prod. Man. IDs	Nº of DCs	Total Cost (€)	Backorders (doses)
Limited shelf life (a)	5	0, 1, 3, 6, 7	5	0, 4, 8, 12, 13	11	0, 1, 2, 3, 4 5, 6, 7, 9, 14, 15	1	6 975 767	0
Shorter shelf life (b)	8	all	14	all	16	all	1	16 239 050	3 044 000

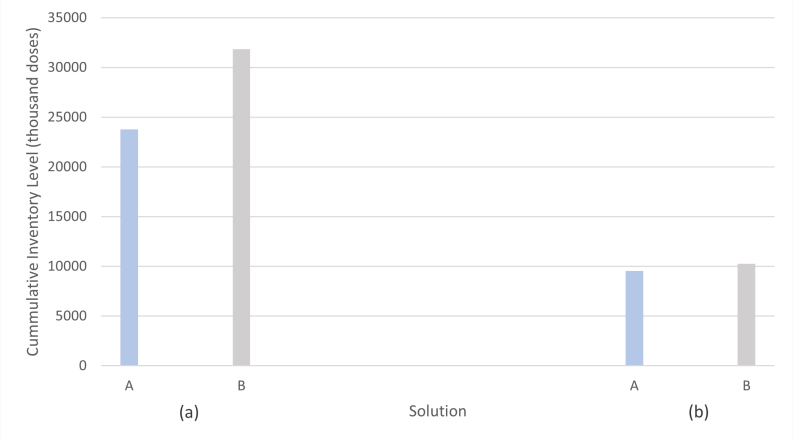

Figure 5.9: Total inventory usage for scenario with: (a) limited shelf life, and (b) shorter shelf life.

5.3.5 Constant Level of Demand

The demand in the present problem occurs in peaks since it is considered that vaccination phases happen in September, October, and November. In this subsection, the effects of a constant level of demand are investigated. To simulate this scenario, the demand for each age group and demand zone was divided for the 12 time periods.

Surprisingly, for this scenario, the solution that gives the lowest costs is simultaneously the solution that minimizes backorders to 0, i.e., both objectives are met without the need to treat one of them as a constraint. This is justified because manufactures have a maximum production capacity greater than the demand in each time period and therefore the model is capable of satisfying demand without the need to create inventory. Moreover, beyond the costs saved by reducing inventories, is is also feasible to manufacture one less vaccine type, as seen in Table 5.14. As expected, the vaccine eliminated from the SC is the v3 vaccine since it is the one that is manufactured at the product manufacturer with the highest opening costs. Naturally, as a consequence, the model closes a8 API manufacturer, and p9 product manufacturer. In addition, also p5 product manufacturer is closed, which suggests that the SC can meet demand even with fewer v1 vaccine production.

This scenario represents the most cost-effective SC between all the tested sce-

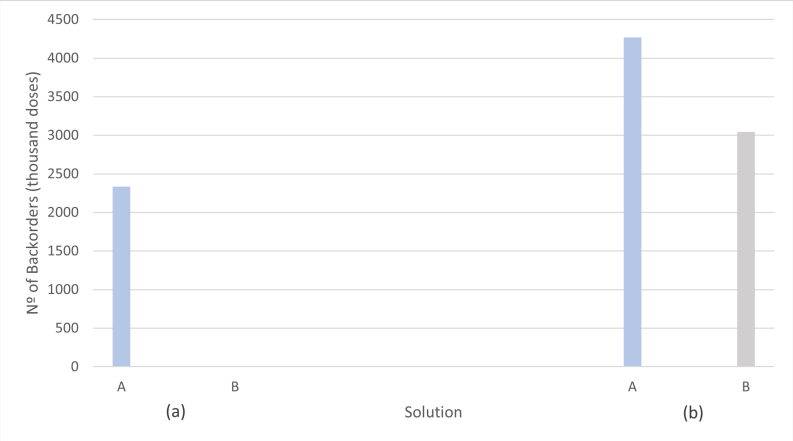

Figure 5.10: Total number of backorders for scenario with: (a) limited shelf life, and (b) shorter shelf life.

narios, and it accomplishes this without any delivery delays, being therefore the ideal scenario.

Table 5.14: Impact of a constant level of demand on the SC.

Scenario	Nº of Vaccines	Vaccines IDs	Nº of API Man.	API Man. IDs	Nº of Prod Man.	Prod. Man. IDs	Nº of DCs	Total Cost (€)	Backorders (doses)
Peak demand	5	0, 1, 3, 6, 7	5	0, 4, 8, 12, 13	9	0, 2, 3, 4 5, 6, 9, 14, 15	1	4 744 963	2 333 000
Constant demand	4	0, 1, 6, 7	4	0, 4, 12, 13	7	0, 2, 3 4, 6, 14, 15	1	3 135 564	0

5.4 Discussion

The study employed the ϵ-constraint method to address the MOMP, leading to the identification of the Pareto front. The Pareto front represents a set of optimal solutions, where each solution reflects a compromise between conflicting objectives (i.e., total costs minimization and backorders minimization). From this set, the decision maker can select the most desirable solution based on their preferences and priorities.

The analysis of the Pareto front reveals a clear trade-off between backorders and total costs since, as backorders decrease, total costs tend to increase. This is due to the fact that minimizing backorders necessitates higher production and increased inventory levels to meet demand promptly.

Solution 1 and solution 12 represent the extreme Pareto solutions and exhibit significant differences in their SC designs. Solution 1 focuses on minimizing total costs while maintaining the additional constraint of zero backorders. On the other

hand, solution 12 solely aims to minimize total costs, allowing for backlogged orders in subsequent time periods. Hence, network total costs are higher for solution 1 as more product manufacturers are established and the total inventory level increases. This way, inventory management strategies play a crucial role in the different solutions. Solution 1 maintains a larger inventory to prevent backorders and meet demand promptly, resulting in increased total costs. In contrast, solution 12 allows for backorders, leading to a lower total cost but a significant number of orders being backlogged. These approaches reflect the trade-off between inventory costs and the risk of stock shortages or delays in meeting demand.

Furthermore, the selection of product and API manufacturers is driven by various factors, including cost-efficiency, vaccine shelf life, and transportation considerations. The results showed that by carefully selecting manufacturers, the SC can optimize production capacities and reduce operational costs.

Moreover, the characteristics of vaccines, such as their shelf life and population coverage, also influence their prioritization in production and inventory management. Vaccines with longer shelf life, such as the v0 vaccine, are prioritized to minimize the risk of expiration and stock shortages. These considerations demonstrate the need to take into account the unique characteristics of each vaccine when designing a SC for efficient distribution of perishable goods.

Subsequently, the model's responsiveness was evaluated by conducting distinct simulated scenarios to determine its performance under different situations.

Among the scenarios, the one with a constant level of demand stood out as the most favorable in terms of SC costs and patient-centered outcomes since it resulted in the lowest SC costs while still meeting the demands of population effectively.

Furthermore, the scenario assuming unlimited shelf life for vaccines revealed a beneficial trade-off between the objective functions. With vaccines having an unlimited shelf life, it becomes feasible to meet demand on time without incurring high SC costs. This scenario allowed for the possibility of opening fewer manufacturers since vaccines could stay longer in inventory, reducing the need for excessive production and logistics.

On the contrary, the scenario with a shorter shelf life represented the worst-case scenario. In this scenario, a significant number of manufacturers needed to be established due to the limited shelf life of vaccines. The short shelf life imposed constraints on inventory management, leading to a higher frequency of backorders. This scenario highlighted the challenges associated with managing perishable products and the importance of carefully considering shelf life when designing a PSC.

Overall, the results of the various scenarios demonstrated that the model ex-

hibits sensitivity towards alterations in demand patterns and the products' shelf life. Hence, the model's adaptability in making decisions based on specific situations is demonstrated by its sensitivity. Furthermore, the model successfully determined the optimal number of facilities, the quantity of vaccines to be produced, and the optimal inventory levels in each scenario.

6

Conclusion & Future Work

In conclusion, this work presents a new optimization model aimed at supporting decision-making in the design of a perishable PSC. The main objectives of this model are to enhance SC flexibility, improve management of perishable products, reduce costs, meet the needs of society and minimize consequences due to products' expiration.

To validate the effectiveness of the proposed model, a case study was conducted focusing on optimizing the distribution of COVID-19 vaccines to Portugal. The study considered the distribution of eight approved vaccines from various European manufacturers to the different districts of Portugal. The model considered different storage conditions, demand patterns across age groups and districts, and vaccination phases over a one-year time horizon.

The objective of the case study was to determine the optimal number and location of facilities, production quantities, and distribution schedules while minimizing costs and backorders. To address the multi-objective problem, the ϵ-constraint method was employed to obtain an approximation of the Pareto front, which represents the set of optimal solutions. This allows the decision-maker to choose the most preferable solution based on the available information.

The findings of the study indicate that minimizing backorders is crucial for timely vaccination, but it requires the creation of additional inventory, leading to increased costs. The decision-maker must carefully evaluate the trade-off between minimizing costs and ensuring sufficient vaccine availability.

Furthermore, various scenarios were simulated to explore the sensitivity of the model. In return, the computational studies revealed that the model is sensitive to changes in demand patterns and product shelf life. The different scenarios demonstrated the model's flexibility in terms of determining the appropriate number of facilities, the quantity of vaccines to be produced, and the optimal inventory levels, demonstrating the model's ability to adapt. Moreover, the change in the demand pattern revealed that a constant level of demand would result in the lowest SC

costs and the best patient-centered outcomes. However, maintaining population immunity for an entire year poses a significant challenge, especially for the most at-risk groups. Therefore, advancements in medicine and vaccine development are necessary to achieve this ideal scenario.

It is important to note that given the limited availability of publicly accessible information on production, handling, and inventory capacities of facilities, and their associated costs, certain assumptions and adaptations from existing literature were necessary in this study. Despite this limitation, it is expected that the overall results of the model remain valid and provide valuable insights for decision-makers.

Furthermore, while the model was developed specifically for the pharmaceutical industry and tested on the COVID-19 vaccine distribution, it can be easily generalized for other scenarios, such as the annual influenza virus outbreak.

As part of future research proposals, several approaches can be explored to further enhance the optimization model and address additional aspects of the PSC design. Firstly, extending the time horizon of the study beyond the current 12 months would be highly recommended. This is particularly important as some vaccines have a shelf life longer than a year. Studying the model's outputs over a three-year horizon could provide valuable insights into long-term planning and decision-making. However, it should be noted that the extension of the time horizon may present challenges in terms of computational resources. In the present case study, attempting to include a longer time period resulted in memory errors with the CPLEX solver.

In addition, expanding the scope of the study to include producers outside of Europe would contribute to a more comprehensive analysis. This global perspective would require considering different modes of transportation and allowing the model to choose the preferred mode based on various factors. This expansion would lead to a larger-scale problem and therefore, developing heuristic methods could be a promising approach for future research.

Addressing demand uncertainty is another crucial aspect that can be incorporated into the optimization model. The COVID-19 pandemic has highlighted the significance of uncertainty in SC management. Including demand uncertainty in the model's parameters would provide more robust and adaptable solutions to dynamic market conditions. The PSC is particularly susceptible to market volatility, making this an important consideration for future research.

Furthermore, considering the real lead time of the COVID-19 SC and reformulating the model accordingly would enhance its accuracy and practical relevance. Incorporating lead time variability and considering the time required for various

stages of the SC, including production, batch testing, transportation, and distribution, would enable a more realistic representation of the system.

In summary, this work presents a novel optimization model that contributes to the design of efficient and effective PSCs. The case study on COVID-19 vaccine distribution demonstrates the model's applicability and provides insights into decision-making for vaccine SCM. Further research and improvements in data availability would contribute to the ongoing improvement and applicability of the optimization model in addressing complex challenges within the PSC.

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A

Supplementary Data

Table A.1: Ratio of Iran's GDP to the GDP of each facility's country.

Country	**GDP (billion $)**	**Ratio**
Iran	***359,71***	-
Portugal	253,66	1,42
Germany	4259,90	0,08
Ireland	504,18	0,71
Belgium	594,10	0,60
Italy	2107,70	0,17
France	2957,90	0,12
Spain	1427,38	0,25
United Kingdom	3131,40	0,11
The Netherlands	1012,85	0,36
Czechia	281,78	1,28
Sweden	635,66	0,57
Austria	480,37	0,75

Table A.2: Demand considered in the present problem (by demand zone and age group).

District	**Age Group**	**Demand (thousand doses)**
Lisboa	<18 years	410
	19 - 64 years	1377
	>65 years	526
Porto	<18 years	328
	19 - 64 years	1101
	>65 years	422
Setúbal	<18 years	161
	19 - 64 years	542

Table A.2 continued from previous page

	>65 years	207
Braga	<18 years	155
	19 - 64 years	523
	>65 years	200
Aveiro	<18 years	129
	19 - 64 years	434
	>65 years	166
Faro	<18 years	85
	19 - 64 years	287
	>65 years	110
Leiria	<18 years	84
	19 - 64 years	280
	>65 years	107
Santarém	<18 years	78
	19 - 64 years	261
	>65 years	100
Coimbra	<18 years	76
	19 - 64 years	255
	>65 years	98
Viseu	<18 years	64
	19 - 64 years	217
	>65 years	83
Madeira	<18 years	46
	19 - 64 years	153
	>65 years	58
Açores	<18 years	44
	19 - 64 years	146
	>65 years	56
Viana do Castelo	<18 years	42
	19 - 64 years	140
	>65 years	53
Vila Real	<18 years	34
	19 - 64 years	115
	>65 years	44
Castelo Branco	<18 years	32
	19 - 64 years	108

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	>65 years	41
Évora	<18 years	28
	19 - 64 years	96
	>65 years	37
Beja	<18 years	27
	19 - 64 years	89
	>65 years	34
Guarda	<18 years	27
	19 - 64 years	89
	>65 years	34
Bragança	<18 years	23
	19 - 64 years	76
	>65 years	29
Portalegre	<18 years	19
	19 - 64 years	64
	>65 years	29

Table A.3: Distances and transportations costs between manufacturers of v0 vaccine (km/ €).

	Mainz	**Marburg**	**Laupheim**	**Dublin**
Mainz	0	120/ 0,192	325/ 0,052	1327/ 0,21232
Puurs	390/ 0,0624	429/ 0,06864	652/ 0,10432	959/ 0,15344

Table A.4: Distances and transportations costs between manufacturers of v1 vaccine (km/ €).

	Visp
Monts	784/ 0,12544
Monza	186/ 0,02976
Ferentino	803/ 0,12848
Madrid 1	1590/ 0,2544
Madrid 2	1590/ 0,2544
Madrid 3	1590/ 0,2544

Table A.5: Distances and transportations costs between manufacturers of v2 vaccine (km/ €).

	Seneffe	**Oxford**	**Leiden**
Nijmegen (NL)	239/ 0,03824	636/ 0,10174	124/ 0,01984

Table A.6: Distances and transportations costs between manufacturers of v3 vaccine (km/ €).

	Leiden
Leiden	0/ 0
Beerse	120/ 0,0192

Table A.7: Distances and transportations costs between manufacturers of v4 vaccine (km/ €)

	Jevany
Jevany	0/ 0

Table A.8: Distances and transportations costs between manufacturers of v5 vaccine (km/ €)

	Livingston	**Dessau**
Solna	2557/ 0,40912	1187/ 0,18992
Vienna	2132/ 0,34112	644/ 0,10304

Table A.9: Distances and transportations costs between manufacturers of v6 vaccine (km/ €)

	Vitry sur Seine
Marcy l'Etoile	455/ 0,0728

Table A.10: Distances and transportations costs between manufacturers of v7 vaccine (km/ €)

	Girona
Girona	0/ 0

Table A.11: Distances between product manufacturers and distribution centres of the case study (km).

	Lisboa	Porto	Setúbal	Braga	Aveiro	Faro	Leiria	Santarém	Coimbra	Viseu	Funchal	Ponta Delgada	Viana do Castelo	Vila Real	Castelo Branco	Évora	Beja	Guarda	Bragança	Portalegre
Mainz	2300	1800	2270	1700	1890	2750	1900	2030	1915	1835	3300	3600	1700	1750	1790	2020	2240	1660	1370	2100
Puurs	2150	1950	2110	1880	1780	2410	1880	2010	1810	1710	2800	3000	1930	1790	1790	2060	2220	1570	1530	2170
Monts	1489	1160	1490	1210	1230	1810	1330	1350	1280	1160	3400	3300	1240	1100	1220	1540	1600	1140	1180	1470
Monza	2400	1990	380	2090	2110	2780	2170	2230	2040	2040	3300	3600	2110	2090	2150	2510	2620	2020	2350	2390
Ferentino	2730	2320	2729	2440	2370	3040	2520	2580	2460	2390	3200	3600	2470	2410	2630	2970	3080	2330	2660	2400
Madrid 1	630	560	640	800	610	470	640	590	530	470	1200	2100	800	720	380	320	410	390	820	450
Madrid 2	630	560	640	800	610	470	640	590	530	470	1200	2100	800	720	380	320	410	390	820	450
Madrid 3	630	560	640	800	610	470	640	590	530	470	1200	2100	800	720	380	320	410	390	820	450
Nijmegen	2050	1960	2030	2220	2080	2770	2070	2000	2000	1900	3400	3600	2280	2090	2040	2200	2260	1920	2230	2100
Leiden	2320	2070	2300	2290	2050	2890	2190	2230	2090	2030	3300	3500	2370	2270	2110	2300	2350	2010	2360	2160
Beerse	2100	1900	2050	2150	1950	2500	2000	2030	1930	1930	2800	3000	2200	2150	1940	2250	2320	1930	2380	1950
Jevany	2950	2740	2930	2990	2790	3530	2880	2890	2830	2700	4200	4200	3070	2920	2830	3100	3190	2660	3230	2840
Solna	3500	3180	3500	3360	3190	3870	3260	3300	3240	3110	4100	4300	3380	3310	3260	3540	3620	3010	3470	3280
Vienna	3070	2790	3070	2930	2750	3480	2870	2910	2840	2710	3600	3800	3090	2940	2850	3140	3220	2650	3150	2800
Marcy l'Etoile	1550	1330	1540	1590	360	1950	1450	1490	1390	1280	3300	3700	1640	1470	1340	1630	1700	1280	1690	1370
Girona	1150	1050	1120	1300	1070	1620	1090	1140	1150	1220	1900	2400	1420	1310	1210	1200	1310	1280	1440	950

Table A.12: Transportation costs between product manufacturers and distribution centres of the case study (€).

	Lisboa	Porto	Setúbal	Braga	Aveiro	Faro	Leiria	Santarém	Coimbra	Viseu	Funchal	Ponta Delgada	Viana do Castelo	Vila Real	Castelo Branco	Évora	Beja	Guarda	Bragança	Portalegre
Mainz	1.449	1.134	1.4301	1.071	1.1907	1.7325	1.197	1.2789	1.20645	1.15605	5.544	6.048	1.071	1.1025	1.1277	1.2726	1.4112	1.0458	0.8631	1.323
Puurs	1.3545	1.2285	1.3293	1.1844	1.1214	1.5183	1.1844	1.2663	1.1403	1.0773	4.704	5.04	1.2159	1.1277	1.1277	1.2978	1.3986	0.9891	0.9639	1.3671
Monts	0.93807	0.7308	0.9387	0.7623	0.7749	1.1403	0.8379	0.8505	0.8064	0.7308	5.712	5.544	0.7812	0.693	0.7686	0.9702	1.008	0.7182	0.7434	0.9261
Monza	1.512	1.2537	0.2394	1.3167	1.3293	1.7514	1.3671	1.4049	1.2852	1.2852	5.544	6.048	1.3293	1.3167	1.3545	1.5813	1.6506	1.2726	1.4805	1.5057
Ferentino	1.7199	1.4616	1.71927	1.5372	1.4931	1.9152	1.5876	1.6254	1.5498	1.5057	5.376	6.048	1.5561	1.5183	1.6569	1.8711	1.9404	1.4679	1.6758	1.512
Madrid 1	0.3969	0.3528	0.4032	0.504	0.3843	0.2961	0.4032	0.3717	0.3339	0.2961	2.016	3.528	0.504	0.4536	0.2394	0.2016	0.2583	0.2457	0.5166	0.2835
Madrid 2	0.3969	0.3528	0.4032	0.504	0.3843	0.2961	0.4032	0.3717	0.3339	0.2961	2.016	3.528	0.504	0.4536	0.2394	0.2016	0.2583	0.2457	0.5166	0.2835
Madrid 3	0.3969	0.3528	0.4032	0.504	0.3843	0.2961	0.4032	0.3717	0.3339	0.2961	2.016	3.528	0.504	0.4536	0.2394	0.2016	0.2583	0.2457	0.5166	0.2835
Nijmegen	1.2915	1.2348	1.2789	1.3986	1.3104	1.7451	1.3041	1.26	1.26	1.197	5.712	6.048	1.4364	1.3167	1.2852	1.386	1.4238	1.2096	1.4049	1.323
Leiden	1.4616	1.3041	1.449	1.4427	1.2915	1.8207	1.3797	1.4049	1.3167	1.2789	5.544	5.88	1.4931	1.4301	1.3293	1.449	1.4805	1.2663	1.4868	1.3608
Beerse	1.323	1.197	1.2915	1.3545	1.2285	1.575	1.26	1.2789	1.2159	1.2159	4.704	5.04	1.386	1.3545	1.2222	1.4175	1.4616	1.2159	1.4994	1.2285
Jevany	1.8585	1.7262	1.8459	1.8837	1.7577	2.2239	1.8144	1.8207	1.7829	1.701	7.056	7.056	1.9341	1.8396	1.7829	1.953	2.0097	1.6758	2.0349	1.7892
Solna	2.205	2.0034	2.205	2.1168	2.0097	2.4381	2.0538	2.079	2.0412	1.9593	6.888	7.224	2.1294	2.0853	2.0538	2.2302	2.2806	1.8963	2.1861	2.0664
Vienna	1.9341	1.7577	1.9341	1.8459	1.7325	2.1924	1.8081	1.8333	1.7892	1.7073	6.048	6.384	1.9467	1.8522	1.7955	1.9782	2.0286	1.6695	1.9845	1.764
Marcy l'Etoile	0.9765	0.8379	0.9702	1.0017	0.2268	1.2285	0.9135	0.9387	0.8757	0.8064	5.544	6.216	1.0332	0.9261	0.8442	1.0269	1.071	0.8064	1.0647	0.8631
Girona	0.7245	0.6615	0.7056	0.819	0.6741	1.0206	0.6867	0.7182	0.7245	0.7686	3.192	4.032	0.8946	0.8253	0.7623	0.756	0.8253	0.8064	0.9072	0.5985

Table A.13: Distances between distribution centres and demand zones of the case study (km).

	Lisboa	Porto	Setúbal	Braga	Aveiro	Faro	Leiria	Santarém	Coimbra	Viseu	Funchal	Ponta Delgada	Viana do Castelo	Vila Real	Castelo Branco	Évora	Beja	Guarda	Bragança
Porto	314																		
Setúbal	49.5	349																	
Braga	363	54.5	398																
Aveiro	253	76	291	126															
Faro	278	554	244	604	494														
Leiria	143	187	182	236	117	389													
Santarém	80.1	248	118	298	188	307	82.3												
Coimbra	204	122	239	171	61.4	444	76.4	136											
Viseu	290	128	325	178	84.9	531	163	222	91.1										
Funchal	972	1197	-	1242	-	951	1072	1041	1132	1198									
Ponta Delgada	1445	1508	-	1534	-	1566	1478	1486	1514	1562	975								
Viana do Castelo	385	74.5	421	61.5	147	625	259	318	193	200	-	-							
Vila Real	397	95	432	105	158	638	269	328	184	93	1259	1585	161						
Castelo Branco	224	259	260	309	199	465	168	156	137	171	1161	1591	331	266					
Évora	132	411	100	461	350	226	245	163	293	387	1046	1554	482	494	195				
Beja	176	454	143	503	393	147	288	206	338	430	-	-	525	537	275	80.3			
Guarda	318	201	352	251	158	559	238	248	166	75.8	-	-	273	171	97.1	289	366		
Bragança	485	207	520	217	270	726	358	417	287	198	1332	1669	274	118	272	462	541	177	
Portalegre	227	294	194	344	234	382	174	162	173	260	-	-	365	355	95.3	103	182	189	362

Table A.14: Transportation costs between distribution centres and demand zones of the case study (€).

	Lisboa	Porto	Setúbal	Braga	Aveiro	Faro	Leiria	Santarém	Coimbra	Viseu	Funchal	Ponta Delgada	Viana do Castelo	Vila Real	Castelo Branco	Évora	Beja	Guarda	Bragança
Porto	0.19782																		
Setúbal	0.031185	0.21987																	
Braga	0.22869	0.034335	0.25074																
Aveiro	0.15939	0.04788	0.18333	0.07938															
Faro	0.17514	0.34902	0.15372	0.38052	0.31122														
Leiria	0.09009	0.11781	0.11466	0.14868	0.07371	0.24507													
Santarém	0.050463	0.15624	0.07434	0.18774	0.11844	0.19341	0.051849												
Coimbra	0.12852	0.07686	0.15057	0.10773	0.038682	0.27972	0.048132	0.08568											
Viseu	0.1827	0.08064	0.20475	0.11214	0.053487	0.33453	0.10269	0.13986	0.057393										
Funchal	1.63296	2.01096	-	2.08656	-	1.59768	1.80096	1.74888	1.90176	2.01264									
Ponta Delgada	2.4276	2.53344	-	2.57712	-	2.63088	2.48304	2.49648	2.54352	2.62416	1.638								
Viana do Castelo	0.24255	0.046935	0.26523	0.038745	0.09261	0.39375	0.16317	0.20034	0.12159	0.126	-	-							
Vila Real	0.25011	0.05985	0.27216	0.06615	0.09954	0.40194	0.16947	0.20664	0.11592	0.05859	2.11512	0.99855	0.10143						
Castelo Branco	0.14112	0.16317	0.1638	0.19467	0.12537	0.29295	0.10584	0.09828	0.08631	0.10773	1.95048	1.00233	0.20853	0.16758					
Évora	0.08316	0.25893	0.063	0.29043	0.2205	0.14238	0.15435	0.10269	0.18459	0.24381	1.75728	0.97902	0.30366	0.31122	0.12285				
Beja	0.11088	0.28602	0.09009	0.31689	0.24759	0.09261	0.18144	0.12978	0.21294	0.2709	-	-	0.33075	0.33831	0.17325	0.050589			
Guarda	0.20034	0.12663	0.22176	0.15813	0.09954	0.35217	0.14994	0.15624	0.10458	0.047754	-	-	0.17199	0.10773	0.061173	0.18207	0.23058		
Bragança	0.30555	0.13041	0.3276	0.13671	0.1701	0.45738	0.22554	0.26271	0.18081	0.12474	2.23776	1.05147	0.17262	0.07434	0.17136	0.29106	0.34083	0.11151	
Portalegre	0.14301	0.18522	0.12222	0.21672	0.14742	0.24066	0.10962	0.10206	0.10899	0.1638	-	-	0.22995	0.22365	0.060039	0.06489	0.11466	0.11907	0.22806