TÉCNICO LISBOA

How can we design a supply-chain of the future?

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Thesis to obtain the Master of Science Degree in

Industrial Engineering and Management

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November 2021

Declaration

I declare that this document is an original work of my own authorship and that it fulfils all the requirements of the Code of Conduct and Good Practices of Universidade de Lisboa.

Declaração

Declaro que o presente documento é um trabalho original da minha autoria e que cumpre todos os requisitos do Código de Conduta e Boas Práticas da Universidade de Lisboa.

Acknowledgements

First of all, I would like to give special thanks to my supervisor, Professor Tânia Rute Xavier de Matos Pinto-Varela for giving me the opportunity to write this thesis on supply chain management and for always keeping me guided and on a good path during its development, since the start of the project until the last days.

A big thank you also to my family and to my girlfriend for the unconditional support they gave me, for encouraging me, and for never doubting that I would get here.

I also leave thanks to all my friends and colleagues who were present and who always encouraged me to accomplish this goal.

Abstract

The pharmaceutical supply chain is responsible for ensuring the supply of medicines in the right place, at the right time and in the right quantity and the industry is being pressured by a shifting paradigm and by changes on the trends and concerns of the society. The optimising of pharmaceutical supply chain networks a promising research field.

Recently, various optimisation models have been built to optimise the design of the pharmaceutical supply chain network. Firstly, a literature review on these models is performed to provide a theoretical basis. A second literature review identify the key elements to obtain an agile supply chain.

In this work, a mixed integer linear programming model is proposed as an optimisation tool to design a supply chain network for the pharmaceutical industry. This model addresses a multi-product, multi-active ingredient, and multi-period network. The existence of multiple storage conditions is also proposed. The decisions supported concern the facilities' integration into a pharmaceutical supply chain, along with inventories, productions and distributions. The objective is minimising the total costs of the supply chain, guaranteeing the demand satisfaction. This model is tested through an example adapted from the literature, and then applied to a case study about the COVID-19 vaccines distribution.

Keywords: Agile, Pharmaceutical Supply Chain, Optimisation, Network Design, MILP

Resumo

A cadeia de abastecimento farmacêutica desempenha um papel fundamental na sociedade por garantir o fornecimento de medicamentos no lugar certo, à hora certa e na quantidade certa. A indústria está a ser pressionada por uma mudança de paradigma e por mudanças nas tendências e preocupações da sociedade. A otimização das redes da cadeia de abastecimento farmacêutica é uma área de investigação promissora.

Recentemente, vários modelos de otimização têm sido desenvolvidos para otimizar a rede da cadeia de abastecimento farmacêutica. Primeiramente, é realizada uma revisão bibliográfica dos modelos desenvolvidos para obter fundamentação teórica. Uma segunda revisão da literatura identifica os elementos-chave para alcançar uma cadeia de abastecimento ágil.

Neste trabalho, um modelo baseado em programação linear inteira mista é proposto como uma ferramenta de otimização para projetar uma rede de cadeia de abastecimento farmacêutica de cinco níveis. Este modelo aborda uma rede multi-produto, multi-ingrediente ativo e multi-período. A existência de múltiplas condições de armazenamento também é proposta. As decisões apoiadas dizem respeito à integração das instalações em uma cadeia de abastecimento farmacêutica, juntamente com inventários, produções e distribuições. O objetivo é minimizar os custos totais da cadeia de abastecimento, garantindo a satisfação da procura. O modelo é aplicado a um exemplo adaptado da literatura e, em seguida, é abordado um caso de estudo que envolve uma cabeia de abastecimento de vacinas contra a COVID-19.

Palavras-chave: Agilidade, Cadeia de Abastecimento Farmacêutica, Otimização, Planeamento e Desenho da Rede, MILP

Contents

List of Tables

List of Figures

Acronyms

ANOVA Analysis of Variance.

ANP Analytical Network Process.

API Active Pharmaceutical Ingredient.

CEO Chief Executive Officer.

CPLEX IBM ILOG CPLEX Optimization Studio.

DC Distribution Centre.

EU European Union.

FDA Food and Drugs Administration.

GDP Gross Domestic Product.

IoT Internet of Things.

MILP mixed-integer linear programming.

MINLP mixed-integer non-linear programming.

NPV Net Present Value.

OR Operations Research.

PSC Pharmaceutical Supply Chain.

R&D Research & Development.

SC Supply Chain.

SCM Supply Chain Management.

TOPSIS Technique for Order of Preference by Similarity to Ideal Solution.

USA United States of America.

Chapter 1

Introduction

This current masters thesis is within the scope of the research project ”Pharmaceutical supply chain of the future” (PTDC/EME-SIS/6019/2020). This chapter provides an introduction to the present thesis. Section 1.1 gives a short context for the problem under study. Section 1.2 lists the objectives that this work aims to achieve. In section 1.3 the structure of the present document is presented. In section 1.4 the investigation methodology to follow in the present thesis is addressed.

1.1 Overview

The pharmaceutical industry is a key asset of the economies of the developed countries as major high-technology industrial employers, moving trillions of dollars annually and employing thousands of people. Its social importance must be also mentioned due to its direct impact on the quality of life and healthiness of the population, which guarantees economic sustainability of the healthcare systems (Marques et al., 2020).

To guarantee a smooth and robust connection between the pharmaceutical industry and the final customer, it is crucial to ensure that the PSC management is up to the task. The PSC is being constantly challenged to improve the efficiency of the drug supply. Continuous innovation and development of new products and technologies, the emergence of legal barriers and licenses, patents and regulations, entry of new competitors with new products, and the pressure prosecuted by the government and health care providers to widen the therapeutic indications of the drugs to other areas and diseases, raising the investment costs and reducing the profit margins constitute some challenges to the industry (Shah, 2004).

The pharmaceutical industry plays a crucial role in the health system. With an increasing market of the more and elder population, quickly growing economies and increasing prevalence of chronic diseases, the pharmaceutical industry has been quickly growing Mehralian et al. (2015). Therefore, the PSC has a great responsibility on delivering an adequate quantity of drugs to the right market, at the right time.

At the same time, the world we live in is facing extreme changes. The population living in urban

areas is rising at an extreme pace, originating huge population clusters commonly named mega-cities (Christopher, 2007). Society behaviour is also changing its patterns, looking with greater and greater importance to the product customisation and becoming extremely rigorous about having the product in the quantity needed, at the place needed in an adequate timing. A shortage of drugs is not tolerated because if a critical drug is in lack in pharmacies or hospitals, people's health and even their life are at risk. PSC have extreme importance in the world and must in a constant effort to efficiently and quickly adapt to the changing circumstances.

1.2 Objectives

This thesis has two main objectives.

1. Present the key concepts and define the problem under study:
    - Contextualise the pharmaceutical industry environment and the life-cycle of a drug;
    - Characterise the PSC, explaining its particularities;
    - Define the decision-making structure of a typical pharmaceutical company;
    - Understand the paradigm shift that the pharmaceutical sector is facing and define the relevant concepts of the new paradigm;
    - Analyse the concepts to consider when designing the SC of the future.
    - Elaborate a literature review of the existing models for PSC network optimisation;
    - Identify existing methodologies guarantee agility in a SC.
2. Proposed and validate an optimisation model for the PSC network design:
    - Formulate the problem as a mixed-integer linear programming (MILP) model;
    - Test and validate the model with an example from the literature;
    - Apply the model to a case study and analyse its results.

1.3 Structure

This document is divided into seven chapters that follow the structure below:

Chapter 1 - Introduction

This introductory chapter provides a brief context for the problem under study. The objectives of the thesis are enumerated and an overall structure for the document is proposed.

Chapter 2 - Pharmaceutical supply chain characterisation

In this chapter, the key concepts are defined and the problem under study is characterised. Firstly, the pharmaceutical industrial environment is explained, as well as the product life-cycle. Secondly, the SC

of a common large multinational pharmaceutical company is presented, interrelating with examples from real-world players. At the end, the new paradigm that the pharmaceutical sector faced is analysed by detailing its main characteristics.

Chapter 3 - Literature review

In this chapter, the literature review of the problem under study is performed. Firstly, a systematic review of publications contemplating SC network optimisation models is described. Then, the existing methodologies to provide agility to a SC are explored.

Chapter 4 - Problem Formulation

In this chapter, the mathematical formulation of the proposed network optimisation model is presented and described. All parameters, constraints, decision variables and objective functions are detailed.

Chapter 5 - Computational Experiments

In this chapter, a computational experiment is performed to validate the model proposed in chapter 4. Firstly, the example is presented, all the parameters associated with it are listed and a set of scenarios to analyse is proposed. Then, the results of the computational experiment are detailed, interpreted and a comparative analysis of the multiple scenarios is performed.

Chapter 6 - COVID-19 Vaccines Case Study

In this chapter, a case study regarding the network design of the COVID-19 Vaccine SC network for Portugal is formulated and a solution proposal is provided.

Chapter 7 - Conclusion

In this chapter, the main conclusions of this thesis are drawn, and topics for future research are proposed.

1.4 Research methodology

Figure 1.1 outlines the research methodology of the present thesis, which is composed of five stages: Context regarding PSCs, literature review, a proposal of a model, an implementation of the model and analysis of the results, and an application to a case study. Stages 1 and 2 are intended to provide a strong theoretical basis for this topic. The subsequent stages have the objective of developing this important matter which is the PSC optimisation. After all the stages of the methodology are finished, it is expected that a proposal to design a PSC of the future have been constructed.

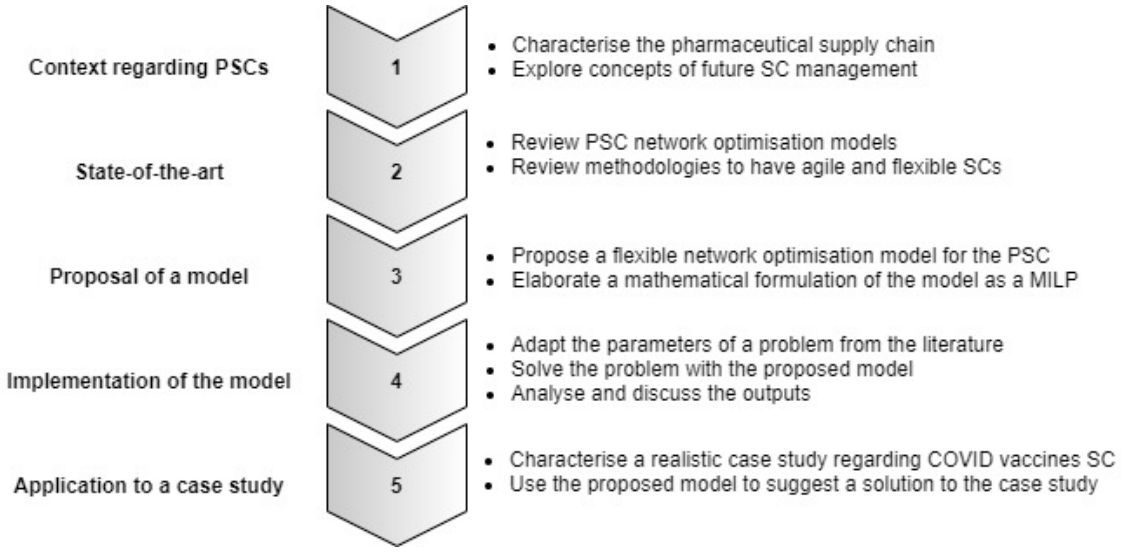

Figure 1.1: Methodology

Stage 1: Context regarding PSCs

Stage 1 consists of having a solid theoretical basis and giving a context for the problem studied. The typical PSC is characterised to understand the environment that enterprises in this industry are facing. Some concerns regarding the future of this field are also presented, relating the paradigm shift that is happening with the concepts that are gaining importance is Supply Chain Management (SCM). The issues and challenges of the modern pharmaceutical industry are identified and their relationship with SC optimisation is analysed.

Stage 2: State-of-the-art

Stage 2 consists of a literature review concerning PSC network design models and methodologies to obtain agile SCs. The review of the state-of-art about PSC network optimisation is performed, analysing the models that already exist in the literature. A literature review about the concept of agility is also developed to understand how to improve the agility of a SC and the trends on this subject. The review of the existing literature allows to properly identify a gap in the existing SC network optimisation models trying to have a focus on agility issues. The relevant publications concerning PSC network design are reviewed, by analysing and summarising the mathematical models proposed in each publication. As the literature about agile PSC is almost nonexistent, publications about methodologies to obtain agile SCs are investigated. This stage allows building a solid theoretical base to develop the next stages.

Stage 3: Proposal of a model

Stage 3 consists of the mathematical formulation of the identified problem. A mathematical model that enables the redesign of a PSC network according to different circumstances will be proposed.

The mathematical model will consider the capabilities of an agile SC, as reducing the complexity of the SC and decreasing the lead time and the cycle time. The model that will be developed will take into

account some of the agility factors found in the literature and should improve the performance of the current PSC. The decisions that the model support will focus on the strategic level decisions.

To design the optimisation model, appropriate characteristics will be selected from the literature, and pertinent adaptations will be performed to present solutions to the challenges of the pharmaceutical industry. Characteristics of SC that have not been considered yet will also make part of the model. All should be addressed in the perspective of having control over the costs, to ensure that pharmaceutical industries are also interested in the maintenance of reliable and flexible SCs.

Stage 4: Implementation and validation of the model

Stage 4 consists of performing computational experiments by using the model formulated to solve realistic problems. The mathematical model will be solved with data collected from an example from the literature review, reviewed in Chapter 3. The model will be solved with an exact algorithm, implemented in optimisation software, namely IBM ILOG CPLEX Optimization Studio (CPLEX). Variation analysis to some input parameters will be performed to test the sensitivity of the model and the validation of the proposed new features.

The outputs provided by the model as the solution to the example problem defined will be detailed. An analysis of that data will be performed to extract the most important information that the model can output about SC network design. A focus will be pointed at the type and number of facilities integrating the SC in a set of circumstances and time periods.

Stage 6: Application to a case study

In stage 6, the versatility of the model is confirmed by applying the proposed formulation to a problem regarding the network design of a COVID-19 vaccine SC that will serve as a motivation example for the applicability of the present model. In this model, the cost minimisation purpose of the network is compared with a scenario in which there is no sufficient capacity to guarantee the supply to all the demand in time. The analysis of a trade-off between SC costs and population with delayed vaccination is proposed. The possible locations for the different facilities are discussed considering the trade-off between a fast vaccination campaign with the minimum delays possible and cost minimisation.

Chapter 2

The pharmaceutical supply chain

In this chapter the pharmaceutical SC is characterised. In section 2.1 the pharmaceutical industry environment is contextualised. In section 2.2 the players involved in getting the drug from the manufacturer to the patient are analysed. In section 2.3 the decision-making structure of a SC is explained. In section 2.4 relevant concepts to build the SC of the future are defined. In section 2.5 the paradigm shift that the pharmaceutical industry is facing is presented. In section 2.6 some conclusions about this chapter are drawn.

2.1 The pharmaceutical industry

The pharmaceutical industry can be defined as a complex set of processes operations and organisations involved in the discovery, development and manufacture of drugs and medications (Shah, 2004). It is mainly composed of large Research & Development (R&D) multinationals, local companies, generic manufacturers, manufacturing organisations without their own product portfolio, and biotechnology companies highly focused on research and drug discovery (Shah, 2004; Sousa et al., 2011).

Large pharmaceutical manufacturers can be divided into two different business models: brand pharmaceutical manufacturers and generic manufacturers. The pharmaceutical multinationals who produce brand products dedicate part of their expenses to the scientific R&D of new drugs. Generic drug manufacturers normally do not develop new drugs but manufacture generic compounds that compete with the original brand drug after the brand product's patent has expired (KFF, 2005). The SCs of generic drug manufacturers are mainly characterised by large portfolios of finished products and distribution chains, avoiding the highly risky R&D and product development activities (Marques et al., 2020).

The PSC represents the path through which essential pharmaceutical products are distributed to the end-users with the right quality, at the right place and at the right time. Therefore, PSC is complicated to manage and greatly responsible for ensuring that the appropriate drug is delivered to the right people at the right time and in the right situation to fight against sickness and sufferings (Mehralian et al., 2015).

Similarly to other consumer products, the general life-cycle of a pharmaceutical product starts with product discovery, followed by the market launch and finally the commercialisation phase (Marques

et al., 2020). Figure 2.1 illustrates this cycle, according to the global demand of the drug over time.

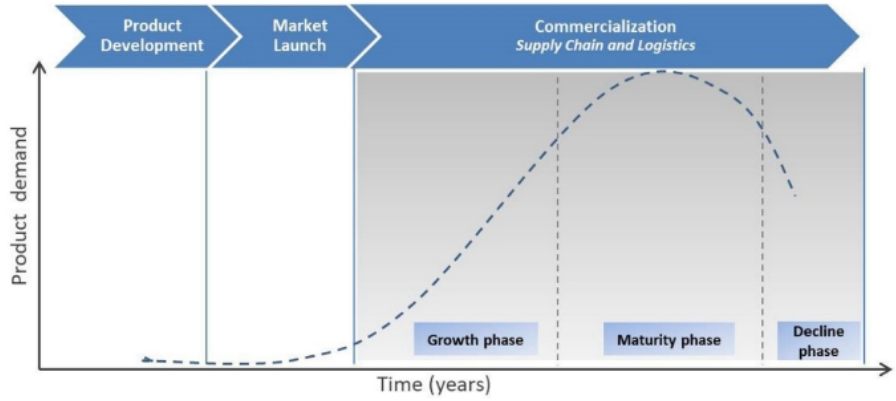

Figure 2.1: Drug life-cycle. From Laínez et al. (2012).

According to Azzaro-Pantel (2018) the pharmaceutical industry encompasses two very different types of SCs: one to support the product development and market launch phases, and the other to support the commercialisation of the drugs.

2.1.1 Product development and market launch

A new product development phase involves four main activities: discovery, pre-clinical tests, clinical trials on humans, and approval and product launch, including the pharmaco-vigilance after launch (Laínez et al., 2012). This translates into high expenditures, low success rates and long cycles.

The development of a drug means a large investment on R&D. The research phase consists in testing thousands of more or less random compounds against the aimed therapeutic targets. On average it takes ten years from the beginning of the research until the new drug is registered and patented. The new drug is tested for safety and efficacy, involving trials for toxicity and for the ability to relieve the symptoms or remove the disease. Only after that, an industrial process to produce the drug on a large scale is developed. This set of activities typically takes plus six to eight years and is usually known as the development phase.

Alongside the development of a new drug, the pharmaceutical company have to face a big number of regulatory challenges such as bio-equivalence, patent expiry, and the complexity involved in the regulated market. Strict regulations and legislation vary between different countries and regions (Shah, 2004).

Drugs usually have a limited product shelf life due to chemical instabilities. Pharmaceutical products shelf life correspond typically to the period of time in which the chemical stability of the compound is higher than 90%. After that period the drug is no longer stable enough to guarantee its safe consumption. The product perishability is, therefore, one of the most important challenges when designing a PSC. Appropriate lead times that guarantee a fast delivery from the manufacturing site to the final customer must be taken into account.

The product development process in the pharmaceutical industry is highly inefficient, with very low levels of productivity. The total cost to approve a new compound is, on average, 2.6 billion dollars. At

the development stage, the main challenges that a pharmaceutical company faces are the minimisation of the development time, the time-to-market and minimisation of the development costs (Marques et al., 2020).

2.1.2 Commercialisation

After the market launch, the process enters a growth phase in which companies try to capture and establish the higher possible market share. The growth rate depends on the relative effectiveness of the drug compared to alternative treatments and determines the demand that the product will achieve at the maturity phase (Shah, 2004).

As a successful drug product gets closer to the end of its patent life, generic manufacturers will introduce bio-equivalent products into the market. A PSC must have the ability to adapt to new realities. A typical situation is when, at the end of the product patent life, the competition starts to produce the generic drugs, lowering the final price of the drug and forcing the competitiveness (Laínez et al., 2012).

Pharmaceutical products can even be substituted with products with similar therapeutic indications or by the same product in a different configuration. For example, higher doses can be replaced with multiples of lower doses of the same principle (Zahiri et al., 2018).

2.2 Supply chain and logistics

In the commercialisation phase of the pharmaceutical product life cycle, the SC and logistical structure play an essential role. In this section, the typical PSC and logistical structure will be analysed.

PSC comprises a network of manufacturers (primary and secondary, in-house and external contractors), packaging facilities, wholesalers, and final healthcare providers such as hospitals and pharmacies. According to Shah (2004), PSC involves four indispensable echelons, as schematised in Figure 2.2: primary manufacturers, secondary manufacturers, DCs and retailers.

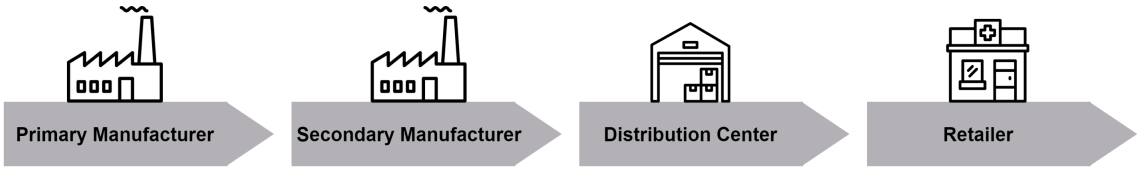

Figure 2.2: Levels of the PSC

Susarla and Karimi (2012) emphasises the particularity of each echelon having specific suppliers, which complicates the distribution network of products and materials, as illustrated in Figure 2.3.

Due to globalisation, all these agents can be located in different places around the world, forcing companies to deal with different regional policies, cultures and tax structures. Adding to this already complex network, the raw material suppliers, the contractors, and the third-party logistics providers, further extend the SC network, requiring a high level of coordination between all the agents, governments, and regulators (Marques et al., 2020).

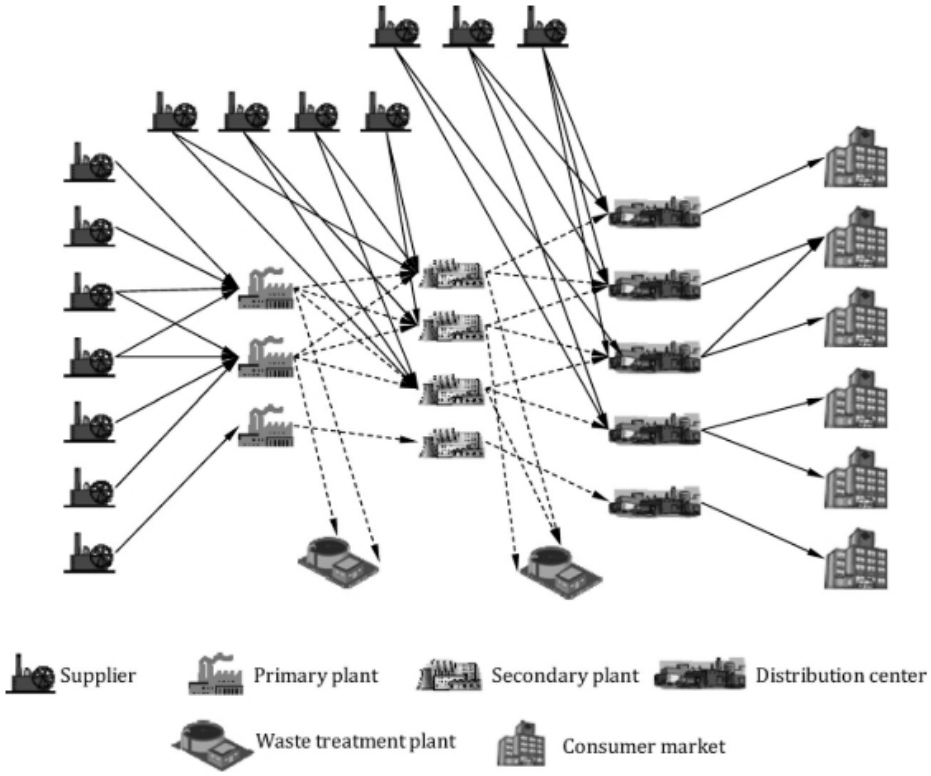

Figure 2.3: Schematic of a large multinational pharmaceutical network. From Susarla and Karimi (2012).

Primary Manufacturers

Primary manufacturers produce the active ingredient of the pharmaceutical. The active ingredient is the substance that will cause the intended pharmacological effect on the living being (Zahiri et al., 2018).

Plants require high investments, forcing large ranges of products to be produced in the same facility to dilute the investment. This suggests the production of low quantities per batch. Since the productions in those sites are characterised by long setup times for activities like cleaning and decontamination, the use of long cycle times is preferred. A trade-off is encountered. To keep a low planning complexity, the strategy of long production campaigns is often chosen, causing low equipment usage. Also, having to manage several references of products, flexibility in the SC is mandatory.

Reports from the FDA (2019) and EFCG (2021) highlight the concern about the Active Pharmaceutical Ingredient (API) producers (or primary manufacturers) being now concentrated in emerging economies. Figure 2.4 illustrates the geographic distribution of API manufacturers in United States of America (USA) and European Union (EU) markets. On another side, America, Europe and Japan are where 80% of the sales are concentrated. In 2018 North America only accounted for 48.9% of the world drugs sales and in Europe this number was 23.2%. Global spending on medicines accounted for 1.2 trillion dollars in 2018 and it is expected to exceed 1.5 trillion dollars in 2023 (Marques et al., 2020). This large distance between products and consumers puts increased pressure in the SCs, raising also the risk of shortages or quality issues (FDA, 2019).

A small quantity (when compared to other industries) of API is enough to produce a very large quantity of doses. This dilutes the transportation costs into many final products, lowering the transportation

costs of the API to negligible values and allows the primary manufacturer to be anywhere in the world, even far away from the Secondary Manufacturer. When deciding a place to locate the primary manufacturer can, though, be directed to taxes, labour supply, raw material provider, politics and economics (Sousa et al., 2011).

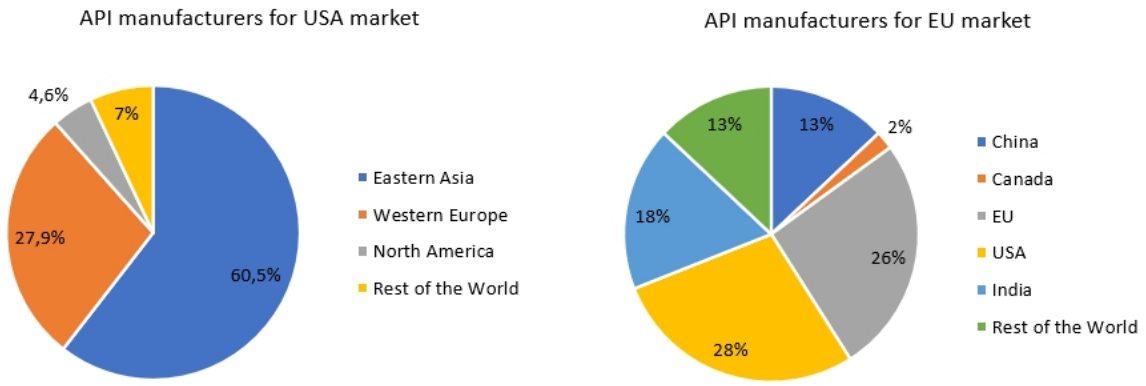

Figure 2.4: Distribution of API manufacturers: USA market on the left; EU market on the right. Adapted from FDA (2019); EFCG (2021).

Secondary Manufacturers

A drug is composed by its API and also by inert materials called excipients, which allow having a product that can be sold as a tablet, capsule, liquid, cream, ointment or aerosol. Secondary manufacturers are the plants that perform the laboratory process of mixing the API with the excipient (Zahiri et al., 2018).

There are often more secondary manufacturing plants than primary, serving local or regional markets. Transportation from the primary manufacturer to the secondary manufacturer is in the order of weeks if by ship, the most used transportation mean, and in the order of days if by aircraft Shah (2004).

The transportation cost between primary manufacturers and secondary manufactures can be neglected as stated above, but the transportation cost downwards from the secondary manufacturer can no longer be neglected. As the inert products are added, and the drugs are processed and packed, the product gains volume and mass and the transportation costs get very significant. secondary manufacturers should, therefore, be located closer to the markets than the primary manufacturer (Sousa et al., 2011).

Distribution Centre

The DC is the unit that will purchase the pharmaceutical products from the manufacturer and sell them to the retailers. Very often, the DC accumulates the task of receiving the drugs in gross and packaging the product into individual doses.

Some wholesalers sell to a broad range of potential clients while others specialise in sales of particular products (e.g. biologic products) or to particular types of customers. Wholesalers used to limit their operations to the traditional distribution functions: link manufacturers to retailers by managing inventories. Nowadays, wholesale distributors also provide some specialised services as special drug dis-

tribution, repackaging, provide electronic order services, customer support and reverse logistics (KFF, 2005).

According to EHDA (2020), in all EU countries except Cyprus, as well as China, Russia, Serbia and Turkey, more than 750 full-service healthcare distributors are accounted, with 1260 warehouses. The same source indicates 2.5 hours as the average delivery time to the retailers, with an average of 35 different pharmaceutical products per delivery from around 19 different manufacturers.

Retailers

Retailers are the final level of the PSC. Those are the channels through which the product is delivered to the final customer. In the pharmaceutical industry, most products are only delivered in hospitals and pharmacies since these drugs are subjected to regulatory laws that force the customer to have a medical prescription proofing the necessity of the drug. On another side, some drugs are not subjected to medical prescription thus, in some countries, are sold in other places like convenience stores and para-pharmacies.

Pharmacies' operations include maintaining an adequate stock of drug products, providing information to consumers about the safe and effective use of prescription drugs, and facilitating billing and payment for consumers participating in group health benefit plans.

Pharmacies also serve as a vital information link between drug manufacturers and wholesale distributors. Nowadays, PSC is highly automated and almost all transactions are handled electronically. Since pharmacies are where the pharmaceutical products are delivered to the final consumer, pharmacies serve as an interface to validate drug prescriptions and must exchange information with health service providers KFF (2005).

According to PGEU (2018), 58% of EU citizens can reach the nearest pharmacy in 5 minutes and 98% can reach the nearest pharmacy in 30 minutes. This gives a sight of how many pharmacies exist and how much they are geographically scattered. Fein (2016) counted 97000 pharmacies in EU and 64000 pharmacies in the USA.

2.3 Decision-making process

Managing manufacturing and distribution operations with the players spread across the entire world requires an effective decision-making process.

According to Méndez et al. (2006), decisions that must be taken in the companies are grouped into three enterprise levels, according to their planning horizon: the business management (long-term decisions), the production management (mid-term decisions) and production process (short-term decisions), as illustrated in Figure 2.5. Pharmaceutical enterprises generally follow the same decision hierarchy.

Strategical decisions are long-term decisions that imply high investments and have a higher impact on the company operations. Therefore they are taken by executives or directors (Heintz et al., 2014). These decisions can be the location and size of the different facilities and infrastructures, determine the

production volume of critical products, and allocate the most valuable resources (Papageorgiou et al., 2001; Zahiri et al., 2018).

Tactical decisions are mid-term decisions that have a medium impact on the company operations and less weight on the company finances. Usually, they are taken by business units managers (Heintz et al., 2014). These decisions are determinant to define the quantity of the inventories and the productions (Zahiri et al., 2018).

Operational decisions are short-term decisions and have a lower impact on the firm budget. They are taken on a regular basis by operational managers (Heintz et al., 2014). These decisions are, for example, defining the schedules of the production, and allocating the resources on a daily basis (Zahiri et al., 2018).

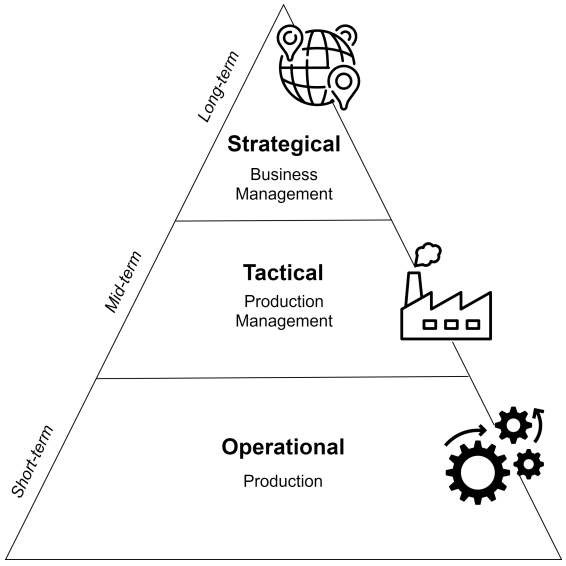

Figure 2.5: Levels of decision. Adapted from Heintz et al. (2014).

2.4 Future of supply chain management

Today's market is characterised by higher levels of turbulence and volatility. Business, economic and political environments are increasingly subjected to unexpected shocks and discontinuities. SCs are vulnerable to disruption and, as a result, the risk to business continuity is increased (Christopher, 2007).

When the COVID-19 pandemic started, almost every country raised barriers to the movement of people and products, and many companies suspended or reduced their production to avoid the spread of the virus. China reacted quickly to the dissemination of the virus, minimising the disruption created by the pandemic in the drugs supply. In India the scenario was different. As this country has the largest number of Food and Drugs Administration (FDA) approved plants outside USA and accounts for around 40% of the generic drugs in USA, the pandemic caused some turbulence in the supply of drugs to the USA. Also, the pandemic is generating an increased sense of protectionism. Some countries are stockpiling raw materials and drugs as insurance in the case of a global supply breakdown, either denying the shipment of these products to the occidental countries or taking advantage of the situation by increasing prices and taxes (Ras-Work, 2021).

Despite drugs' shortages having slightly increased in the last years, in middle 2020 the number of drug shortages already had detonated the value of 2019, as illustrated in Figure 2.6.

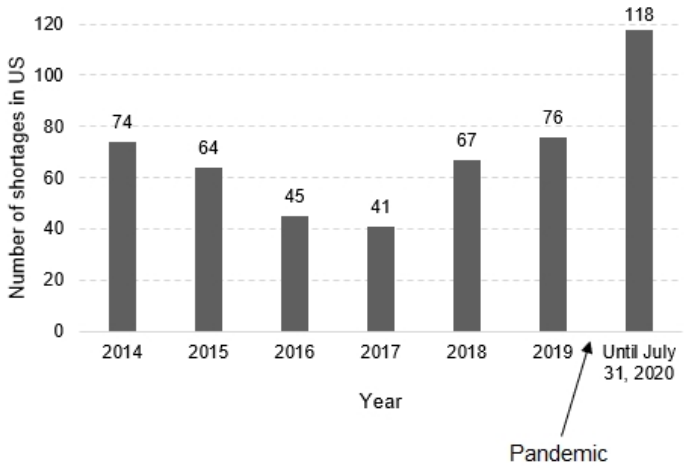

Figure 2.6: Drug shortages in the USA between 2014 and 2020. Adapted from Lesmeister et al. (2020).

Guaranteeing a smooth and robust supply of pharmaceutical products to the global markets is crucial. Agility and resilience have been identified as necessary characteristics of modern-day SCs (Gligor et al., 2019). Their roles have been well recognised in helping firms and SCs to deal with challenges such as globalisation, constant change, shorter product life cycles, diverse customer requirements and increased uncertainty of demand (Christopher, 2000; Christopher and Peck, 2004). In this vein, agile and resilient PSC can manage better the risks and the market volatility, avoiding shortages as identified. According to Gligor et al. (2019), the ability to empower the customer and customise the products to meet the customer needs is also a characteristic of an agile SCs.

The existing conceptualisations of agility and resilience are often contradictory or confusing. Because of that, Gligor et al. (2019) studied a total of 439 agility-related articles and 1013 resilience-related articles and developed a scheme to clarify the concepts, presented in Figure 2.7.

"Agile" was first time used in operations in 1992 by Nagel (1992), who proposed that agility would be a key to gaining competitiveness. Three years later, Goldman et al. (1995) defined the concept of agility in the SC as a strategy of responsiveness and readiness to change in a volatile market (Shashi et al., 2020).

According to Ghatari et al. (2013), agility means the capacity of using the knowledge about the market and about the organisation itself to explore opportunities of profiting in fast-growing markets and on markets in constant change. An agile SC is a SC that rapidly adapts to variable demands.

As illustrated in Figure 2.7, Gligor et al. (2019) considered three key themes of agility. First, the SC must have the ability to quickly change the direction of the organisation, independently of the existence of disruption events. Second, an agile SC is characterised by the capacity to empower the customer and the customisation of the products. And the last key theme is the ability to integrate processes within and across organisations. It is not sufficient for organisations to integrate their internal processes, but they must also integrate with their SC members, suppliers and customers.

The growing customer and technological requirements are pushing manufacturers to develop agile SC capabilities in order to keep competitiveness (Yusuf et al., 2004).

Whereas in the past the main objective in SC design was cost minimisation, the emphasis now must be on resilience. Resilience refers to the ability of the SC to cope with unexpected disturbances. Even the best-managed SC will hit unexpected turbulence or be affected by events that are impossible to forecast. Hence, managers should incorporate resilience in the SC (Christopher, 2007). Usually, improving the SC resilience requires taking strategic decisions, such as relocating facilities or changing sources of supply. The impact of those decisions on the SC risk profile must be fully understood (Christopher, 2007).

As illustrated in Figure 2.7, according to Gligor et al. (2019), there are three key themes that characterise resilience. First, resilience is about the ability to survive from disruptions, as the recent Covid-19 pandemic. An organisation should have adaptive qualities to overcome stressful moments. Second, a resilient SC must be able to recover to the original form after the disruption. Lastly, a key objective of a resilient SC is the capacity to avoid the shock caused by a disruption altogether, "by breaking the tsunami into small waves". This involves proactive measures, where the disruptions are anticipated and actions are taken before the disruption really takes place. Gligor et al. (2019) concludes by stating that strategic resilience is about having the capacity to change before the case for change becomes desperately obvious.

As illustrated in Figure 2.7, Gligor et al. (2019) realised that agility and resilience have some similar meanings. The author considered that it is important to determine the distinct and common characteristics of agile and resilient SCs because allocating resources to the development of the common characteristics of agility and resilience can help companies to minimise the impact of such investments. By investing in the common characteristics they will improve both, SC agility and SC resilience.

Gligor et al. (2019) identified three common themes, as illustrated in Figure 2.7. First, resilience and agility are the ability to speed operations and processes. The ability to speed operations is not about achieving the maximum speed, but rather the ability to accelerate and decelerate properly. Second, resilience and agile SCs should have the ability to anticipate. The organisations must be capable of scanning the environment and reading the real demand. Therefore, they can respond quicker and better to changes or alerts. Lastly, flexibility, as the capacity to adjust, is mandatory.

According to Christopher (2007), flexibility also reflects the ability of the SC to adapt or reconfigure its architecture in response to major changes on the demand side or the supply side. SCs with enhanced structural flexibility are able to cope with the high levels of volatility commonly found in a twenty-first-century business environment. The author claim that to obtain resilience and agility, a SC must imperatively be flexible. To a SC become more agile and more resilient, the companies should invest in the common themes since they have an impact on both agility and resilience.

Feizabadi et al. (2021) also considered agility as a source of superior firm performance. Moreover, the authors enumerated adaptability and alignment as characteristics that will constitute the SC of the future. SC agility is the ability to respond to short-term changes in supply, demand and business environment. SC adaptability is the ability to respond to long-term and structural changes to supply, demand

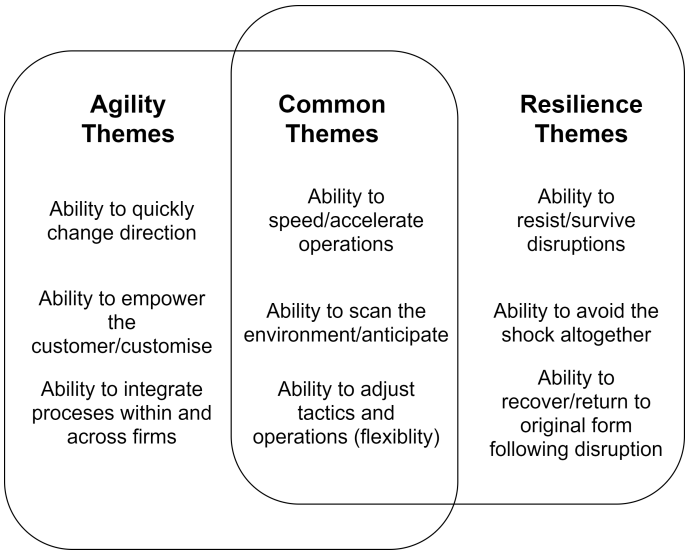

Figure 2.7: Agility themes, resilience themes, and common themes. Adapted from Gligor et al. (2019).

and business environment. Finally, SC alignment consists of aligning the incentives of SC partners by sharing the risk and the rewards. Agility, adaptability and alignment are known as the Triple As (Feizabadi et al., 2021).

According to Christopher (2007); Gligor et al. (2019); Feizabadi et al. (2021), the future of the SC design will undergo an acquisition of characteristics and capabilities that provide flexibility and responsiveness to SC: agility, resilience, adaptability and alignment. The complexity of the SC should also be minimised.

2.5 The new pharmaceutical paradigm

Disruptive alliances, innovations, and collaborations are forcing traditional “healthcare” companies to bring patient services to the forefront. The industry as a whole has expanded efforts to develop complementary support programs, customised to help ensure patients have the best possible experience. According to the Chief Executive Officer (CEO) of Ayogo, ”a patient engagement software company, to be successful today, the focus needs to be much more on patient and physician behaviour than on product benefit and features” (PharmaVOICE, 2018).

Marques et al. (2020) developed an impact matrix on the SC, considering the drivers, challenges and enablers of the pharmaceutical industry, and realised that companies are now evolving from their traditional product-centric and margin-driven organisational perspective to an enterprise-wide perspective. The shift from an old paradigm to a new paradigm carries six main components, each one with a different focus: outcome, efficiency, increased value, flexibility, market expansion, and overall welfare. Figure 2.8 illustrate the different approaches of components on the old and new paradigms.

To improve the outcome of the PSC, companies will need to engage more strategically with patients, focusing on understanding the patient needs, expectations and fears in order to continuously revise and update the value proposition of their products. Patient-centricity is a paradigm that puts the focus on

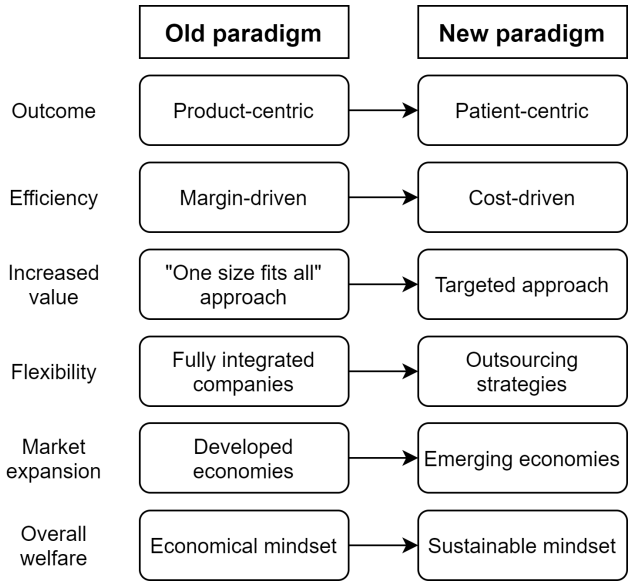

Figure 2.8: Old paradigm *versus* new paradigm. Adapted from Marques et al. (2020).

the customers. Therefore, new product-service solutions will be expected through the exploitation of innovative technological breakthroughs, and new distribution and information channels will have to be created to enhance relationships with patients and build partnerships based on trust (Marques et al., 2020).

Increased drug specificity and demand uncertainty are adding a further level of complexity when it comes to the design and operation of robust distribution networks. The pharmaceutical industry has taken significant steps towards the improvement of existing and the development of novel processes that promise agile, responsive, and reproducible manufacturing (Sarkis et al., 2021). In the future, PSCs will not be driven by products and processes but by customer needs.

The cost-driven paradigm is becoming a focus for pharmaceutical companies as they recognise the importance of having a competitive advantage. To achieve efficiency, companies must develop not only cost-efficient processes but also advanced decision support tools capable of assisting the managers to make informed decisions based on scientific evidence (Marques et al., 2020).

Pharmaceutical companies are now concerned with adding value by using targeted product strategies based on market segmentation and customisation. In the pharmaceutical industry, beyond the importance of analysing the market needs and specifications to develop a drug, it is now becoming a reality the analysis of specific patients to maximise the potential of a drug (Marques et al., 2020).

According to Gligor et al. (2019), flexibility can be defined as the capacity to adapt strategies, tactics and operations. In recent years, companies are betting on outsourcing and joint ventures strategies, moving from single to extended collaborative SCs. In this way, pharmaceutical companies increase their flexibility in matching market dynamics as well as capacity to manage risk.

With developing economies representing the most significant growth in the pharmaceutical industry, the market for pharmaceuticals is becoming global and a market expansion is happening. Market segmentation and multiple distribution channels will be critical strategies for companies to ensure drug supply in a remote place. Higher levels of end-to-end visibility will become critical to ensure quality in

the management and monitoring of the SC operations (Marques et al., 2020).

The pharmaceutical companies have to take into account the overall welfare. Strategic decision-making should embrace the sustainability component and include strategies to reduce waste, minimise resources consumption, and improve operational efficiency. Companies should also invest on innovative decision-support frameworks that address social responsibilities, in conjunction with the agility needed to tackle the other components (Marques et al., 2020).

Sarkis et al. (2021) agrees that the pharmaceutical sector is undergoing a paradigm shift where the capabilities of decentralised models must be explored. The authors suggest the improvement of communication between process units, production plants and distribution nodes. The authors also reinforce the importance of decision support systems and modelling tools based on nowadays technology, as mechanisms to obtain agility and productivity in the operations of the pharmaceutical sector.

One way to get closer to the patients and to satisfy better their needs is the development of digital tools. They are extremely useful for capturing patient symptoms, improving medication adherence, monitoring activity and other elements that when charted or tracked provide critical insights to patients, caregivers, and healthcare professionals (PharmaVOICE, 2018). A change of paradigm in the pharmaceutical industry suggests the need for a reformulation on the concerns when designing or redesigning the PSC. This leads to a change of paradigm in the SC itself, driving managers to study new concepts and approaches in an effort to understand the future of SCM.

2.6 Conclusion

According to Christopher (2007), in the relatively short time that companies have been focusing on managing SCs, the world has changed dramatically. New thinking and new technologies are revolutionising many industries.

Although, PSC is a highly conservative industry (Marques et al., 2020). It takes a long time to implement changes. Usually, it implements concepts and ideas from other industries, that are more innovative, but in a delayed way compared with another.

Now what is required to the SCs are that they become more agile and better able to cope with rapid change and higher levels of variety and even customer customisation. Flexibility is increasingly a prerequisite for doing business in a volatile and turbulent environment (Christopher, 2007). SC needs to become resilient, agile, adaptable and aligned in order to face the challenges of the future.

Patient-centricity concept or new technological developments have been revolutionising the pharmaceutical industry (Marques et al., 2020). The pharmaceutical SCs not only must incorporate the new capabilities but also needs to take into account this new concept and the evolution of the technologies.

In addition, Marques et al. (2020) propose opportunities for improvement the PSC: development of SC agility and responsiveness, minimisation of production and distribution costs, reduction of SC complexity, improvement in end-to-end visibility across the entire SC, strategies for seamless integration and coordination across the SC network, inventory reduction at every node of the SC, and the integration of sustainability aspects.

Chapter 3

Literature Review

In this chapter, a review of the state-of-the-art of the PSC is elaborated. Section 3.1 consists of a literature review of PSC network optimisation models. In section 3.2 the new capabilities concepts can be found in the SC are defined and characterised. In section 3.3 a conclusion regarding this chapter is drawn.

3.1 Pharmaceutical supply chain network optimisation

Optimal SC design is vital to the success of industries. Optimisation models and methods for SC network design have been of great interest to industry and academia over the past decades (Garcia and You, 2015). PSC optimisation is an area of the SCM that has been using Operations Research (OR) as a tool to improve its performance towards the existing challenges. SCM is a subject very studied since the fifties. However, the specific case of the pharmaceutical industry was not approached in the literature until the late nineties.

In this chapter, the PSC network optimisation models in the existing literature are addressed and its solution approach is analysed.

Searches on Google Scholar and Web of Science databases were performed to encounter publications regarding PSC optimisation. The search was performed with keywords according to the following logic: ”Pharmaceutical” AND ”Supply Chain” AND ”Network Design” AND (”Optimisation” OR ”model” OR ”MILP” OR ”MINLP” OR ”Heuristic” OR ”Algorithm”).

The publications were screened to guarantee that the paper is published in a peer-reviewed journal and that a quantitative optimisation-based approach was used to determine strategic decisions for a PSC network. The literature reviews of the encountered publications were also carefully analysed to ensure that all the relevant research made about the subject is included.

The search returned 27 relevant publications between 1999 and 2020, as plotted in Figure 3.1. Those 27 publications are published in 17 peer-reviewed journals, as plotted in Figure 3.2.

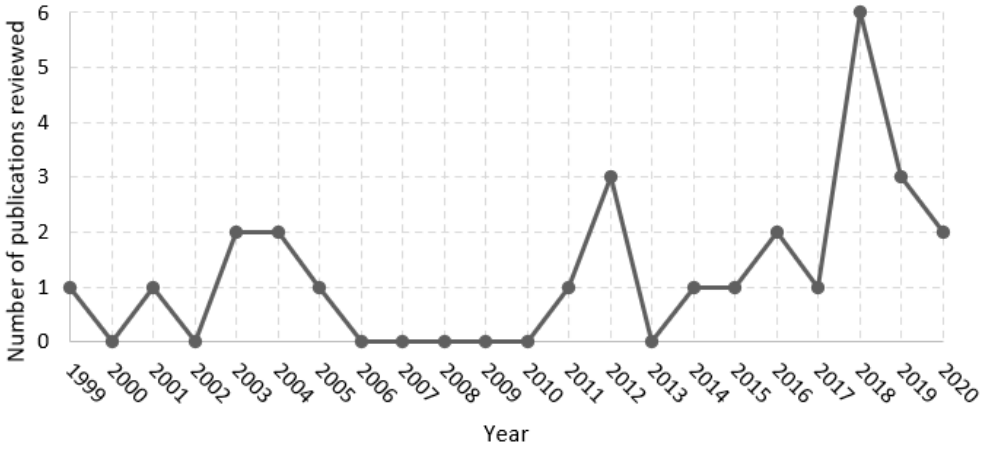

Figure 3.1: Number of publications reviewed *versus* year of publication

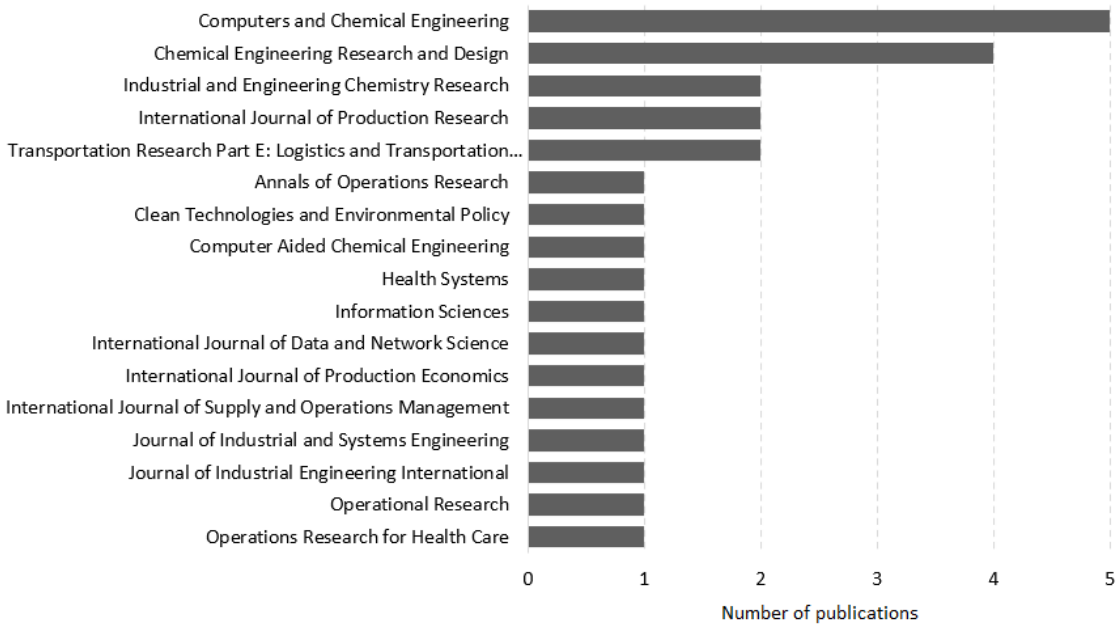

Figure 3.2: Number of publications reviewed *versus* peer-reviewed journal

Each reviewed model is characterised according to its objective functions, its output (that is, the decision that the formulation aims to support) and its solution approach. Table 3.3 summarises the reviewed models.

The reviewed models address two types of solution methods to solve the PSC optimisation problem proposed: exact and non-exact. Exact methods, denoted by the letter E, solve a problem guaranteeing the optimality of the solution. Non-exact methods, denoted by the letter N, refer to optimisation techniques that do not guarantee the optimality of the solution found. Subsection 3.1.1 includes the models solved through exact methods and subsection 3.1.2 includes models solved through non-exact methods. Some of the models reviewed were solved through both exact and non-exact methods, which are denoted by both the letters E and N. Those models are analysed in subsection 3.1.2.

to determine the efficiency and effectiveness of an existing system, the performance measures must

be defined (Beamon, 1998). Performance measures are the objective functions of the models. The most used objective functions to measure the PSC performance (Susarla and Karimi, 2012; Savadkoohi et al., 2018; Zahiri et al., 2018; Goodarzian et al., 2020) are summarised in Table 3.1.

Table 3.1: Objective functions

Objective Function	**Notation**
Maximisation of profit	P
Minimisation of total costs	TC
Minimisation of the unmet demand	UD
Maximisation of the service level	SL
Maximisation of the customer satisfaction	CS
Minimisation of the environmental impact	EI
Maximisation of the social welfare	SW
Minimisation of the social impact	SI
Maximisation of the net present value	NPV
Minimisation of the delivery time	DT
Maximisation of reliability	R
Minimisation of the non-resilience	NR

A model can support one or more decisions, then, it may have one or more outputs (Lashine et al., 2006; Savadkoohi et al., 2018; Zahiri et al., 2018). Outputs and respective notation and meaning are summarised in Table 3.2.

Table 3.2: Outputs

Output	**Notation**	**Meaning**
Location	L	decide about the location and capacity of the facilities of the SC
Allocation	A	decide about the assignment between facilities
Distribution	D	decide about the flow of products from one facility to another facility
Production	P	decide about the manufacturing quantities of the products
Routing	R	decide about the routing of the vehicles that will transfer the products
Inventory	I	decide about the quantities to store at each location

3.1.1 Exact methods

An exact approach was used by Rotstein et al. (1999) to model a SC of a pharmaceutical company considering multiple scenarios. He proposed an optimisation based approach to determine the product development, introduction strategy, capacity planning and investment strategy. Despite being focused on a portfolio selection, this model is considered in the present review because it is the elder publication concerning PSC optimisation found and it decides about investment or disinvestment on facilities basing on the portfolio chosen. The authors formulated a MILP problem to minimise the Net Present Value (NPV) and solved it with less instances. Since real case problems involve prohibitively large instances to solve in a reasonable time, the authors proposed and validated a ranking-based hierarchical procedure.

Papageorgiou et al. (2001) applied a mathematical programming technique to facilitate the strategic SC decision-making process for pharmaceutical industries. The authors proposed an optimisation-

based approach to select both the optimal product development and introduction strategy together with long-term capacity planning and investment strategy at multiple sites, considering also some particularities associated with the pharmaceutical industry, as scaling and product lifetime constraints. Similarly to Rotstein et al. (1999), the authors solved the MILP to tackle small instance problems and developed a hierarchical procedure to deal with real-world problems.

Papageorgiou et al. (2001) left the challenge of developing a similar approach but considering the uncertainty on the demand and the outcome of the clinical trial, common in this industry. Gatica et al. (2003) worked on the uncertainty on the clinical outcome, developing a multi-period stochastic optimisation problem considering four scenarios for the outcome of one clinical trial. The authors formulated the problem as a MILP.

In the same year, Grunow et al. (2003) proposed a multi-period MILP model to minimise the total costs of a distribution SC considering the production processes. To reduce the computational time needed, the authors introduced several aggregation schemes and a novel MILP model formulation which is based on a continuous representation of time. The authors also proposed an iterative near-optimal solution procedure that can be successfully applied to even exceptionally large real-world problem instances. The applicability of the approach is proven through a case study.

Levis and Papageorgiou (2004) also presented an extension of Papageorgiou et al. (2001) to cope with uncertainty on the outcome of the clinical trial. This time the uncertainty considers the typical trading structure of a typical pharmaceutical industry. Firstly, the authors propose a two-stage, multi-scenario, MILP model to minimise the NPV. After, a hierarchical algorithm is proposed to reduce the time needed for the solution of large-scale MILPs. The approach is validated by some illustrative examples.

Oh and Karimi (2004) proposes an approach in four steps to capacity-planning on the general chemistry industry. First, the authors introduce trade regulations that can significantly influence the business operations of multinational companies. Second, the authors present a new deterministic capacity expansion planning MILP model to maximise the NPV in which sizes of expansions or new facilities are variables and domestic and international regulatory factors are explicitly taken into account. Third, an extension of the deterministic model is proposed, to address distribution centres, outsourcing, and stochastic uncertainty in problem parameters with a simple scenario-planning approach. Finally, some illustrative examples are used to validate the approach. This publication is included in the present review since the authors suggested that with the modification or addition of some constraints, the formulation can accommodate and have utility in the pharmaceutical industry.

Susarla and Karimi (2012) developed a MILP model aiming for multi-period enterprise-wide planning in pharmaceutical industry. The model integrates procurement, production, distribution and inventory strategies on a long-term perspective, and includes some particularities of the sector: the international tax differentials, inventory holding costs, material shelf-lives, and waste treatment and disposal. If the model becomes prohibitively large to be solved through the exact approach in a reasonable time, the authors propose to consider one specific variable as zero. This relaxes several constraints and enables the resolution of the problem in an acceptable time, even in large instances, with a small compromise on the quality of the solution.

Mousazadeh et al. (2015) developed a multi-period bi-objective MILP model to minimise the total costs and the unmet demand. The model aims to support decisions as locating and planning the capacity of pharmaceutical manufacturing centres and main/local distribution centres over long-term planning, along with material flows over mid-term planning. The authors used a robust possibilistic programming approach to deal with the uncertainty in demand, unit manufacturing costs, unit transportation and transhipment costs and safety stock levels. The model is tested in a real case study and the authors provide a business interpretation of the results by applying the ϵ-constraint method and the TH approach, from Torabi and Hassini (2008), to obtain good approximations of the Pareto front.

Zahiri et al. (2017) built a multi-objective MILP model to design a PSC network. To combine sustainability and resilience in the SC, four objective functions are proposed: minimise the total cost of the system, maximise the job opportunity and economic development of the region, minimise the total environmental impact and minimise the non-resilience of the network. The authors considered five measures of resilience: node criticality (a node is critical if the total inflows and outflows exceed a certain threshold); new technology (reassignment policy to transfer the production to a backup technology if the less costly and less reliable technology fails); flow complexity (measures the total interaction between the nodes of the network); node complexity (measures if the total number of active nodes is higher than a pre-defined value); and unmet demand. To cope with the uncertainty on costs, environmental and social impacts, incident probability and demand, a new fuzzy possibilistic-stochastic programming approach is developed. To solve the problem, a novel Pareto-based lower bound method is proposed, as well as a new metaheuristic algorithm based on the differential evolution algorithm, variable neighbourhood search algorithm and game theory. The approach is validated through numerical examples and a case study.

Zahiri et al. (2018) presented a model to minimise the total cost and the unmet demand on a pharmaceutical supply network design problem that supports decision about facility location, and flow of products from facilities in different or in the same echelon of the SC. Certain particularities of the pharmaceutical sector were considered as the product perishability, substitutability and quantity discounts and uncertainty in the transportation cost, fixed establishment cost, capacity and demand. The authors developed a new fuzzy model and converted it into a conventional mathematical model, while managing the uncertainties basing on various interpretations of the problem. In the second phase, the converted mathematical model is solved by an optimisation technique. The derived solution is optimal to the converted mathematical model but is not always optimal to the original fuzzy model. If the solution is not optimal, the fuzzy model is rebuilt to a new mathematical model based on the improved interpretation until the optimal solution is achieved. A modified game theory is used to convert the two objective functions into a new objective function to find the Pareto optimal solution.

Savadkoohi et al. (2018) developed a model to solve a location-inventory problem on a three-echelon PSC network that support both strategic and tactical decisions as opening manufacturing and distribution centres, material flows in the network, and the optimal inventory policy taking into account products' perishability. The model is formulated as a MILP that aims to minimise the total cost with uncertainty in demand, costs and capacities. The model is tested on a real case study and some business interpreta-

tions are provided by conducting sensitivity analyses.

Halim et al. (2019) proposed a framework to support strategic decisions as supplier selection and network design in a PSC. Initially, an analytic hierarchy process is used as a multi-criteria tool to rank the suppliers. Then, a bi-objective MILP model is proposed to find an acceptable trade-off between the total cost minimisation and the greenhouse gases emission minimisation. A network design tool (SC Guru) is used to solve the optimisation problem and find the Pareto front.

Roshan et al. (2019) addresses crisis management in PSCs by creating a multi-objective non-linear model to minimise the network total cost, minimise the unmet demand and maximise the satisfaction of social responsibility. Product perishability, substitutability and uncertainties associated with the demand and the transportation costs are considered. The possibilistic uncertainty is converted into a non-possibilistic model so that the problem could be solved as a mixed-integer non-linear programming (MINLP). To obtain the Pareto front of the three objective functions, the already mentioned TH approach is used.

Singh and Goh (2019) proposed an approach to maximise supplier efficiency and minimise the total logistics cost. The supplier efficiency is quantified by a reliability parameter given for a set of suppliers that were pre-selected through a multi-criteria approach. The total logistic cost considers decisions about production and inventory strategies. The model is formulated as a fuzzy multi-objective MILP, with uncertainty associated with the demand parameter, supplier capacity and costs parameters and the TH approach is used to obtain an efficient solution from the multi-objective problem.

Zandkarimkhani et al. (2020) developed a bi-objective mixed-integer linear programming model for designing a perishable PSC network under demand uncertainty. The objectives of the MILP formulation are to simultaneously minimise the total cost of the network and the lost demand. The proposed model is multi-product and multi-period and includes facilities location, vehicle routing, and inventory management decisions. A hybrid approach, based on fuzzy theory, chance-constrained programming, and goal programming approach is developed to solve the bi-objective problem. The model is validated through a real case study.

3.1.2 Non-exact methods

When the use of an exact method is impossible or impracticable to find the solution, non-exact methods can be applied. Non-exact methods encompass heuristic and metaheuristic approaches. Heuristics are strategies based on previous experiences with similar problems. Metaheuristics are a type of heuristics that make use of random choices to obtain non-optimal solutions, demonstrating greater efficiency in most cases. Both heuristics and metaheuristics are usually used to solve optimisation problems for which exact algorithms are not efficient due to their high resource consumption (computational power or time).

Sousa et al. (2005) proposed a global SC network optimisation procedure for pharmaceuticals. The authors developed a model that aims to maximise NPV to solve the problem of allocating and determining product flows from primary manufacturers to secondary manufacturers and from secondary man-

ufacturers to demand zones. The authors solved the problem using two decomposition algorithms: a Lagrangian decomposition method and the Product Frames Algorithm heuristic.

Sousa et al. (2011) expanded the investigation of Sousa et al. (2005). The authors explored two decomposition algorithms to reduce the solution time when solving: the spatial decomposition algorithm and the temporal decomposition algorithm. In the first method, the SC is decomposed into two sub-problems, one for each echelon and solve the problem as a MILP for each sub-problem. In the second method, the main problem is separated into multiple independent problems, one per time period. The multiple problems are solved in two stages: firstly, the constraints with continuous variables are modified and the binary variables are calculated through a MILP; then, the binary variables are fixed and an LP solves the continuous variables.

Considering a drug shortage scenario, Vila-Parrish et al. (2012) proposed a multi-period LP model to minimise the total costs. The authors developed a multi-echelon perishable production and inventory model. In the model, the production decision, which converts the raw material to the finished good, increases the perishable nature of the product. The developed model involves two stages: the first consists of the development of a Markov decision process to represent medicines demand as a function of the patient condition; the second phase consists of the use of simulation to evaluate the inventory policies characterised in the first phase (Franco and Alfonso-Lizarazo, 2020).

Kelle et al. (2012) discussed the PSC and the common practices in a case hospital, examining the conflicting objectives that arise between various stakeholders and exploring the trade-offs present at operational, tactical, and strategic levels of decision making. Despite focusing on the inventory management of a local storage centre, this publication is included in the present due to its high concern on providing an exceptional service level, by avoiding shortages. The authors created a non-linear model to minimise the total costs, simplified and linearised it and created a procedure to solve the model iteratively, by using an exact approach to solve each variable at a time.

Izadi and Kimiagari (2014) designed a single-period distribution network under demand uncertainty. To consider the uncertainty, a set of possible scenarios is created basing on the Monte Carlo simulation method and for each scenario, the distribution network was optimised using a genetic algorithm. The proposed model was validated with a pharmaceutical company case study.

Chung and Kwon (2016) proposed an approach to optimise product flows between facilities in different levels of a PSC. The authors consider the oligopolistic competition across wholesalers that drives price and demand fluctuations. The authors developed a model to maximise the profit of the company and propose the solution by determining the Nash Equilibrium, and, then, using the interior-point barrier algorithm which involves Gaussian elimination and the resolution of sub-problems formulated as MILPs.

Abbas and Hosseininezhad (2016) proposed a location-allocation model for pharmaceutical centres trying to locate a set of new facilities to minimise the transportation cost from these facilities to the customer. The authors considered two objectives: minimisation of costs and maximisation of customer satisfaction by defining social justice. The authors solve the problem through exact methods and, after, apply the ϵ-constraint method to find the Pareto solution.

Bijaghini and Seyedhosseini (2018) presented a bi-level bi-objective model for a PSC that assigns

distribution centres to retailers, respective product flows and appropriate a appropriate vehicle to perform the transport, aiming to minimise total costs along with the unmet demand. Uncertainty is considered in demand, inventory levels and shipping costs. Then the robust approach was used to handle the associated uncertainty of related parameters and the resulted problem is solved by the Benders decomposition algorithm. The solutions found for a numerical example for both objective functions are submitted to an Analysis of Variance (ANOVA).

Janatyan et al. (2018) develop a multi-period multi-objective model to design a pharmaceutical distribution network while minimising the costs and the adverse environmental effects and maximising the welfare of society. Location, allocation and distribution decisions are supported by the model. The authors chose to use one multi-objective evolutionary algorithm that allows finding multiple Pareto-optimal solutions in one single run, the non-dominated sorting genetic algorithm (NSGA-II). The approach is applied to a case study of an Iranian pharmaceutical distribution company.

Zhu and Ursavas (2018) studied a facility location and vehicle routing problem on a distribution pharmaceutical network. The authors considered two types of distribution centres: depots (main) and satellites (secondary). The customer can be fulfilled directly from a depot, or a satellite if the vehicle route starts in a depot. The authors model the problem as a linear function that aims to minimise the total cost. To solve the problem, a technique is developed which iterates between an upper bound and a lower bound, based on Lagrangian relaxation combined with a branch-and-cut approach.

Nasrollahi and Razmi (2019) developed a four-echelon multi-period approach to design a pharmaceutical distribution network allowing the flow of products inside one level of the SC considering fuzzy uncertainty on the demand. The bi-objective model aims to maximise the service level while minimising the system's cost. The authors developed a modified non-dominated sorting genetic algorithm by including a combination of elitism strategy and fitness proportional selection in the chromosome selection to improve the quality of the solutions in the Pareto front and used the centroid method to perform the "defuzzification".

Goodarzian et al. (2020) proposed a model to design a multi-echelon multi-product multi-period PSC network. The authors create a multi-objective approach to minimise the total costs, minimise the delivery time and maximise the reliability of the transportation system to determine both strategic, tactical and operational decisions. To cope with the uncertainty on the transportation costs, purchase costs, capacity of the warehouses, the distribution centres, and vehicles, the authors use a trapezoidal fuzzy programming technique. To obtain the Pareto front of the multi-objective problem and using numerical examples, the authors compare five metaheuristics: multi-objective social engineering optimisation algorithm, multi-objective simulated annealing algorithm, multi-objective Keshtel algorithm, multi-objective particle swarm optimisation algorithm, multi-objective firefly algorithm. The authors conclude that the multi-objective firefly algorithm can detect better solutions in relatively less time, confirming its better efficiency.

Table 3.3: Reviewed publications with PSC network optimisation problems

Publication	Objective Function												Output						Solution	
	P	TC	UD	SL	CS	EI	SW	SI	NPV	DT	R	NR	L	A	D	P	R	I	E	N
Rotstein et al. (1999)									x					x					x	x
Papageorgiou et al. (2001)									x					x		x			x	x
Gatica et al. (2003)									x					x		x			x	
Grunow et al. (2003)									x					x		x			x	x
Levis and Papageorgiou (2004)									x					x		x			x	x
Oh and Karimi (2004)									x				x	x	x				x	
Sousa et al. (2005)									x					x	x			x		x
Sousa et al. (2011)									x					x	x	x		x		x
Susarla and Karimi (2012)	x														x	x		x	x	x
Kelle et al. (2012)		x																x		x
Vila-Parrish et al. (2012)		x														x		x		x
Izadi and Kimiagari (2014)		x											x	x	x					x
Mousazadeh et al. (2015)		x	x										x	x	x				x	
Chung and Kwon (2016)	x													x		x				x
Abbas and Hosseininezhad (2016)		x			x								x	x					x	
Zahiri et al. (2017)		x				x		x				x	x	x						x
Bijaghini and Seyedhosseini (2018)		x	x											x		x	x	x		x
Zhu and Ursavas (2018)		x											x		x		x			x
Zahiri et al. (2018)		x	x										x	x	x	x		x	x	
Savadkoohi et al. (2018)		x											x	x	x			x	x	
Janatyan et al. (2018)		x				x	x						x	x	x					x
Halim et al. (2019)		x				x							x		x				x	
Nasrollahi and Razmi (2019)		x		x									x	x	x			x		x
Roshan et al. (2019)		x	x				x						x	x	x			x	x	
Singh and Goh (2019)		x													x	x		x	x	
Goodarzian et al. (2020)		x								x	x		x	x	x	x	x	x		x
Zandkarimkhani et al. (2020)		x	x										x	x			x	x	x	

3.1.3 Discussion

All reviewed models aim to minimise costs, maximise profit, or maximise the NPV. Also, the models that aim to maximise the NPV include portfolio selection decisions. Multi-objective problems are also presented in PSC models. Many authors developed multi-objective approaches by combining more than an objective function, as social concerns, environmental concerns, or improvement of SC characteristics.

Models are used in the decision-making process and, therefore, each model addresses one or more decisions. In the existing literature, the majority of the models involve location decisions, which are usually addressed together with allocation and distribution decisions. Lower-level decisions as production, routing and inventory are also modelled together with network design decisions, demonstrating that those lower-level decisions can also have relevance when designing the PSC network design.

The size of the instances and the complexity of the model take the authors to use exact or non-exact methods to solve the problem. Some authors consider only an exact method to solve the problem, others apply an exact method and a non-exact method after having realised that the exact method is not enough to get the optimal solution in a reasonable computational time. Others only use non-exact methods.

A ”future” SC, as defined in section 2.4, must be flexible and responsive, being characterised by the ability to be agile, resilient, adaptable and aligned. According to the reviewed literature, none of the authors considered these characteristics in the models proposed, thus, the development of models capable of carrying the tradition PSC to a future PSC is a fruitful research field.

Regarding the shift to the patient-centricity paradigm, the authors also do not consider it in detail. Minimising the unmet demand could be one of the objective functions to take into account in future models, aiming to achieve a SC focused on the patient.

In conclusion, mathematical models to optimise the PSC network design, considering the characteristics identified as being the attributes of the future and the patient-centric paradigm, are not yet developed.

3.2 The supply chain of the future

During the recent decades, SCM has become a popular agenda for both the pharmaceutical industry and the non-pharmaceutical industry. Events such as globalisation, outsourcing, single sourcing, just-in-time SC management, lean and agile SC have made PSC more sensitive to the environment. Therefore, to survive and progress in the 21^{th} century, pharmaceutical companies should learn how to manage the ongoing challenges in their environment (Mehralian et al., 2015). Pharmaceutical companies must manage their SC to become agile and take advantage of the recent changes in the world economy.

3.2.1 Agile supply chains

Despite the existence of literature on PSC optimisation, there are very few authors studying the agility concept in PSC. Mehralian et al. (2015) introduces agility in a PSC through a Technique for Order of

Preference by Similarity to Ideal Solution (TOPSIS) approach. Although no network design optimisation model considering agility was found in the reviewed PSC literature.

The SC of the future must have the capabilities to adapt in different conditions: resiliency, agility, adaptability and alignment. This literature review will address agility since this has been identified as one of the most salient issues of contemporary SCM (Gligor and Holcomb, 2012).

Speed, quality, flexibility and responsiveness are the key elements of agility necessary to meet the unique needs of customers and markets. Companies enjoy such agile characteristics by forecasting uncertainties and allowing quick changes to respond to the requirements greatly in their business (Baramichai et al., 2006).

As lean management suits best in markets of predictable demands and high volumes, agile management suits best for markets with unpredictable demands and lower quantities (Christopher, 2007). As proposed by Naylor et al. (1999) and Christopher (2000), Figure 3.3 summarises the different applications of agility and leanness, in which two variables are compared: the variety of products and variability in production. Low variety of products means that few types of products cross the SC and, high variety of products means that the SC deals with a wide range of different products. Low variability in production happens when the production rarely changes, usually in cases with predictable demand, and high variability in production exists when the production suffers several changes, usually in cases with unpredictable demand. Darker areas on Figure 3.3 tend towards leanness and the lighter areas tend to agility (Naylor et al., 1999).

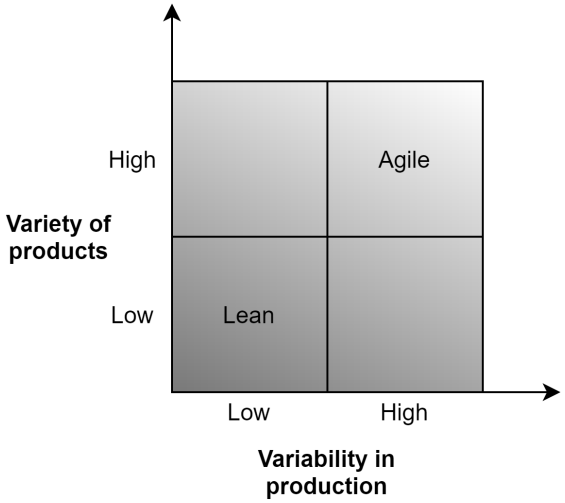

Figure 3.3: Lean *versus* Agile. Adapted from Naylor et al. (1999).

Agility means using market knowledge and a virtual corporation to exploit profitable opportunities in a volatile market-place, while leanness means developing a value stream to eliminate all waste, including time, and to ensure a level schedule (Naylor et al., 1999). The authors consider Agility and lean management as opposite strategies. Nevertheless, by considering the differences between the two paradigms, the authors show that the authors should not be considered in isolation.

Christopher and Towill (2001) developed a framework to obtain an agile SC by integrating both manufacturing and logistic strategies. The model is a three-layer qualitative model. The first level represents

the key principles that underpin the agile SC as rapid replenishment and postponed fulfilment. The second level identifies the individual programmes as lean production, organisational agility, and quick response which must be implemented. The third level specifies individual actions to be taken to support the second level.

Christopher and Peck (2004) defended that the route to agility necessarily involves the occurrence of a digitisation process in the SC. The author proposed four ”ingredients” to achieve agility in a fashion industry SC, but the model can be extended to other manufacturing sectors. Those ingredients are schematised in Figure 3.4. Are the authors market sensitivity, virtualisation, process integration and network-basing.

An Agile SC is market sensitive if it is capable of reading and responding to real demand. Most organisations are forecast-driven rather than demand-driven. Since the flow of information about the order requirements is too slow, companies are forced to make forecasts based on past sales. Recent technology allows sharing the demand data from the point-of-sale to all elements of the SC in real-time, giving to the company the ability to track the market. A virtual SC is the creation of an information-based SC that shares data in real-time between all its players. Shared information between all SC players can only be achieved with process integration. It consists of collaborative working between buyers and suppliers, joint product development, common systems and shared information. This allows companies to focus on managing their core competencies and outsource other activities. The success of the SC relies on the effort of every player, becoming like a confederation of partners linked together as a network. Nowadays companies are recognising that individual businesses no longer compete as stand-alone entities. Organisations should establish closer relationships with their partners, improving the agility of their SC.

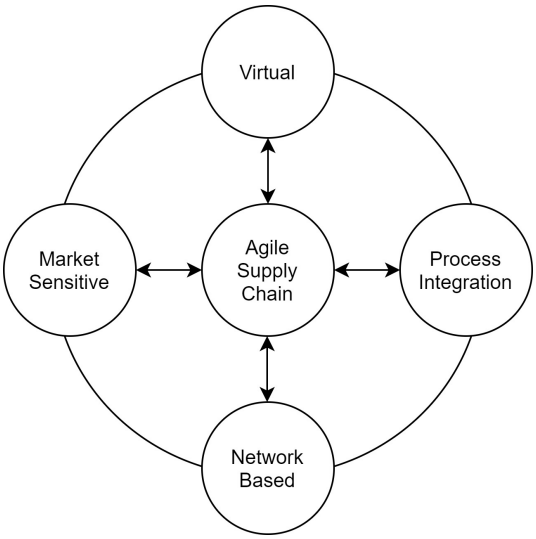

Figure 3.4: The four ”ingredients” to obtain an agile SC. Adapted from Christopher and Peck (2004).

Ismail and Sharifi (2006) proposed a conceptualisation of a holistic approach to an agile SC by identifying the market influencing factors as the customer preference, product type, competition degree, technology advancement, and external business environment.

Lin et al. (2006) developed a fuzzy agility index to measure the agility in a SC. The model is developed from the concept of multi-criteria decision making with fuzzy logic and qualitative and quantitative indicators, named agile SC attributes. The model is based on four pillars: dealing with change and uncertainty; innovative management structures and virtual organisations; cooperative relationships; and flexible and intelligent technologies.

Agarwal et al. (2006) stated that an SC can adapt to changes if it is flexible and agile. Flexibility is important to counter the uncertainty associated with the decision parameters. The authors developed an Analytical Network Process (ANP) encapsulating market sensitiveness, process integration, information driver and flexibility measures of SC performance. The authors concluded that the desired service level, lead-time, cost and product quality are the most important criteria that define an agile SC.

Wadhwa et al. (2007) state that since flexibility is considered a property that provides change capabilities of different enterprise-wide resources and processes in time and cost dimensions, SC flexibility can be considered a tool to meet agility needs. The authors propose a framework based on an ANP that consists of a three-level network to attain agility from the perspective of market, product and customer. The goal depends on sub-strategies taken by each actor constituted by manufacturing, logistic, sourcing, and information technology flexibility decisions.

Abbasi et al. (2014) proposed an agile design for a three-echelon SC network design considering interval data uncertainty. The authors formulated the problem as a MILP to minimise total costs, and inserted the key characteristics of agile SC management, as direct shipments, outsourcing, different transportation modes, discount and strategic alliances. Location, allocation, distribution and production decisions are outputted by the model. Uncertainty is considered in fixed opening costs, outsourcing costs, transportation costs, production costs, inventory costs, shortage costs, alliance costs and amount of discounts. The uncertainty is accounted for in the MILP through a robust optimisation model. The model is validated with numerical examples.

Sangari et al. (2015) developed a practical evaluation framework to identify critical factors for achieving SC agility. To start, the authors built a reference framework of the factors that contribute to achieving agility in SC based on a systematic analysis of the literature. Then, a hybrid evaluation method integrated fuzzy logic, the decision making trial and evaluation laboratory and ANP is created. The final ranking of agility critical factors is calculated to an automotive industry case study.

Feizabadi et al. (2021) performed a survey of subjective measures to analyse the interaction between the three As, agility, adaptability and alignment. The authors found that there is no empirical evidence of three-way complementary between the three As. However, evidence of complementary in bi-variate interactions for alignment and adaptability and a substitution relationship between all pairs of As were observed.

Zhu et al. (2021) developed an agile SC framework that incorporates recent technological developments. Two sub-domains of Industry 4.0, Internet of Things (IoT) and block-chain technology, can improve the visibility that facilitates ease of tracking and tracing, characteristics required in agile SCs.

3.2.2 Discussion

According to the reviewed literature, quantitative measures of agile capabilities in a SC are not yet defined. However, it is possible to identify some steps to improve the agility of a SC. According to the different inputs obtained from the reviewed publications, Figure 3.5 was designed to summarise the building blocks and factors identified that enable the achievement of an agile SC.

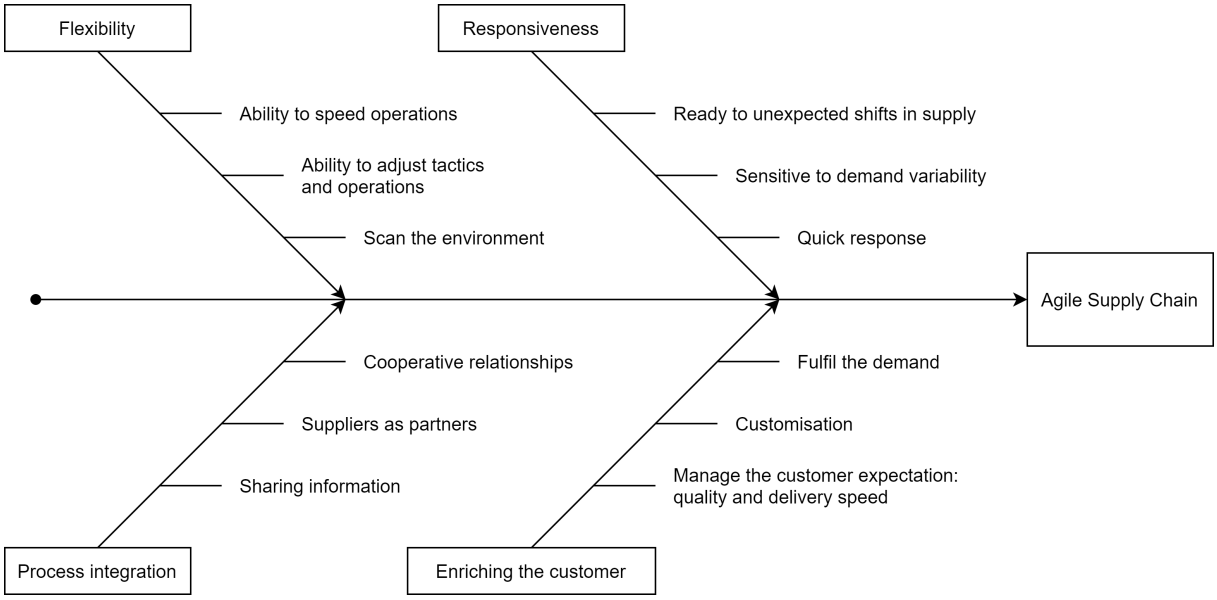

Figure 3.5: Fishbone diagram of concepts leading to agility

To improve the agility of a SC, it is crucial to quickly detect changes in the environment, identifying the opportunities and perceiving the threats. Whereby, the SC becomes flexible, being capable to accelerate and decelerate their operations and adjusting their tactics.

Flexibility is one of the building blocks identified. The SC must be flexible in its activities, meaning that it can upscale and downscale the operations and tactics quickly. A fast reconfiguration of the SC network is also required to respond to the changes in markets and the increasing customisation demanded by the customer.

Unexpected shifts in supply and high demand variability are events that can occur and the SC should be able to quickly respond. The quick response to these events is defined by responsiveness and is one of the building blocks identified.

Process integration is also a building block, achieved by sharing the information: the SC always should send the information about the needs to the suppliers and receive information from customers demand. Cooperative relationships between the different players of the SC can be established.

The last building block is the enrichment of the customer. SCs should be not only able to fulfil the demand but also to properly manage the customer expectations, delivering the orders on time and with promised quality. This way, companies will retain and develop relationships with customers. Customisation is a concept that must be implemented to meet the increasing customer expectations.

Patient-centricity, or the focus of the organisation on the patient rather than on the product, is one of the characteristics of the new paradigm of PSC management that is coming up.

In the future, a SC should integrate these concepts in its network design to achieve better performance, better serve customers and keep up with the competition.

3.3 Conclusion

More and more companies are realising that to increase the performance of the company, the SC should be optimised as a whole (Pan and Nagi, 2013). SC network design models have been studied in recent years.

PSCs require efficient optimisation techniques to improve their performances (Shah, 2004; Masoumi et al., 2012; Zahiri et al., 2018). In this chapter, publications regarding PSC optimisation were reviewed. Despite existing several proposals of mathematical models to the network design of PSCs in the literature, none of the reviewed models considered ”future” characteristics as agility.

Then, a review of methodologies to achieve agility in a SC was performed. No methodology to achieve agility specifically in the PSC was found, reinforcing the need to develop an optimisation model to the network design of an agile PSC. The building blocks of agility were identified, which will reveal themselves useful when building that model.

This state-of-the-art is a necessary step to perform since it provided a theoretical basis that enables the advance to the formulation and of a novel optimisation model for the PSC network design.

Chapter 4

Model Formulation

In this chapter, the problem of designing a Pharmaceutical Supply Chain Network will be mathematically formulated. In Section 5.1 the problem is defined. Afterwards, in Section 5.2, the proposed mathematical formulation is introduced, detailing the sets, parameters and variables. In Section 5.3, the constraints of the model are presented and explained. In Section 5.4, the cost-minimisation objective function of the mathematical formulation is proposed. In Section 5.5, some conclusions regarding the proposed model are outlined.

4.1 Problem definition

The present model features the common SC of the pharmaceutical industry. It was inspired by the model from Mousazadeh et al. (2015), however, major changes were performed to address multiple problems and challenges faced by the pharmaceutical industry and not included in any of the models reviewed. The model proposed by Mousazadeh et al. (2015) encompassed location and capacity decisions and product flows on a four-level SC. Meanwhile, the present model approaches location, allocation, inventory and production decisions on a five-level SC.

As explained in Chapter 2, the manufacturing of the pharmaceutical products is typically performed in two different facilities: the Primary Manufacturer, which produces the API, and the Secondary Manufacturer, which produces the final product. Those two manufacturing agents will be appended to the model of Mousazadeh et al. (2015). Therefore, the proposed model should encompass a PSC with five levels: the primary manufacturers, the secondary manufacturers, the main DCs, the local DCs and the retailers (or demand zones).

The current model considers two sets of goods: the set of API, which are carried from the Primary Manufacturer to the Secondary Manufacturer; and the products, which are the actual drugs, that are carried from the Secondary Manufacturer downwards on the SC. The model allows the design of a PSC considering the flow of multiple APIs and multiple products. Figure 4.1 illustrates the macro-structure of the SC that will be addressed.

Pharmaceutical products have strict storage rules to prevent damage to the product itself. For that

reason, considering a general inventory for all the products can become insufficient when planning and designing a PSC. The current model supports the existence of various storage conditions in the inventory of each facility. It is considered that each product must be stored under a specific storage condition along the SC.

Figure 4.1: Levels of PSC considered for the model formulated

A concept of network is established in the present SC. This is a group of entities that will work together to accomplish the objective, which is to meet the demand with the least cost possible. Entities that integrate the network will incur integration costs, henceforth designated *fixed costs*. Those costs can be considered as the investments that each facility will need to perform to integrate the distribution network. Those investments may involve the agility drivers identified in Chapter 3, namely, process integration technologies that enable cooperative relationships, partnerships and information exchange between facilities. The share of data as demand, capacities and costs between the levels of the SC is important to guarantee the accuracy of the parameters used and reduce the uncertainty associated with those parameters. Other costs as adaptation of processes or acquisition of new technologies necessary to enter the SC of determined product can also be included in this cost category.

Inventories exist in four-levels of the SC. In the Primary Manufacturer, an inventory of finished APIs can be kept. In the Secondary Manufacturer, Main DC and Local DC, there are inventories of finished products. Each primary manufacturers and secondary manufacturers have their own production capacity for each type of product produced and per time period, and their storage capacity (maximum number of products that can be stored from one period to another). Each main and local DC have their own handling capacity (maximum number of products that can flow through each facility in each time period), and storage capacity.

Minimising the total costs is the objective of the present model. The costs to be minimised are the fixed costs, that is, the costs incurred by the entities to integrate the network, the distribution costs, that is, the costs to transport the products between the entities and, the inventory costs, that is, the costs incurred to store the APIs and the products.

4.2 Problem formulation

In this section, all the inputs to the problem, modelled as a MILP, will be presented. Sets, parameters and decision variables will be addressed.

Let A be the set of APIs that must be carried from the set of Primary Manufacturers, denoted by F to the set of Secondary Manufacturers, denoted by S. In those Secondary Manufacturers, the APIs is converted into a set of pharmaceutical products P. Those pharmaceutical products are then shipped to

the main DCs M and therefore to the local DCs L. Finally, the products are transported from the local DCs to the retailers R, according to their demand. Let T be the set of time periods.

On this problem, all entities have a cost to integrate the consortia, except the Primary Manufacturers. Integration costs of the Secondary Manufacturer s, the Main DCs m and Local DCs are denoted by fc_s^S, fc_m^M and fc_l^L, respectively.

In each primary manufacturer, the APIs can be stocked, under different conditions (room temperature, frozen, refrigerated, etc.). The set of storage conditions are denoted by C. Regarding the storage of APIs under condition c, a maximum capacity of the primary manufacturer f is defined as s_{fc}^F and a cost of storing a storage unit of API in primary manufacturer f is defined as ic_{fc}^F. A unit of API a occupied σ_{ac} number of units of storage space. Each primary manufacturer f has an initial inventory of API a, ii_{fa}^F, and a maximum production capacity of API a, pc_{fa}^F.

Then, the APIs are transported to the secondary manufacturers with a tc_{afs} cost per unit. In each second manufacturer, there is an inventory of APIs, but products p can be stocked, under different conditions also. Regarding the storage of products under condition c, a maximum storage capacity of the secondary manufacturer s is defined as s_{sc}^S and a cost of storing a storage unit of a product p is defined as ic_{sc}^S. A unit of product p occupied σ_{pc} number of units of storage space. Each secondary manufacturer s has an initial inventory of product p, ii_{sp}^S, and a maximum production capacity of product p, pc_{sp}^S. To produce a unit of product p, ρ_{ap} needs to be consumed.

The product p are transported to the main DCs with a tc_{psm} cost per unit. In each main DC, each product p can be stocked under a certain storage conditions c, so, a maximum storage capacity of the main DCs m is defined as s_{mc}^M and a cost of storing a storage unit of a product p is defined as ic_{mc}^M. A unit of product p occupied σ_{pc} number of units of storage space. Each main DCs has an initial inventory of product p, ii_{mp}^M, and a maximum handling capacity, h_{mp}^M.

Then, the product p are transported to the local DCs with a tc_{pml} cost per unit. In each local DC, each product p can be stocked under a certain storage conditions c, so, a maximum storage capacity of the local DCs l is defined as s_{lc}^L and a cost of storing a storage unit of a product p is defined as ic_{lc}^L. Each local DCs has an initial inventory of product p, ii_{lp}^L, and a maximum handling capacity, h_{lp}^L.

Finally, the product p are transported to the retailers with a tc_{plr} cost per unit. There are no storage of products. The products are received according the demand of product p in the retailer m at time period t, d_{prt}.

Table 4.1 summarises the sets of the present model.

Tables 4.2 and 4.3 summarises the ten groups of parameters used in the current model.

Table 4.1: Sets

Notation	Description
$a \in A$	Set of APIs
$c \in C$	Set of storage conditions
$p \in P$	Set of product
$t \in T$	Set of time periods
$f \in F$	Set of Primary Manufacturers
$s \in S$	Set of Secondary Manufacturers
$m \in M$	Set of Main DCs
$l \in L$	Set of Local DCs
$r \in R$	Set of Retailers

1. **Fixed costs** - These costs are associated to the entrance of a facility in the network;
2. **Transportation costs** - These costs are associated to the shipment of a product or API from a given facility to another facility. It is given as the cost per unit transported;
3. **Storage costs** - Those are the costs for storing one item in each facility, under each storage condition for one time period. They are defined for each facility and for each storage condition. Storage costs are given as the cost per storage space unit and per time period;
4. **Storage capacity** - The maximum number of units of storage space of each storage condition that exists in each facility. These parameters are defined for each facility and for each storage condition;
5. **Production capacity** - Each manufacturing facility can output a maximum quantity of each API or product on each time period. That quantity is denoted as production capacity and can be defined for each facility and for each API or product;
6. **Handling capabilities** - At each distribution centre, a maximum number of units of all products can be handled in each time period. That quantity is denoted as handling capacity and can be defined for each distribution centre;
7. **Demand** - It represents the number of units of each product that each retailer demands in each time period;
8. **Initial Inventory** - A facility can start the planning horizon with a defined initial inventory. That initial inventory can be defined for each facility and for each API (in the case of primary manufacturers) or product (in the case of other entities, downwards on the SC);
9. **Bill of Materials** - APIs are produced by the Primary Manufacturer and sent to the Secondary Manufacturer. The Secondary Manufacturer receives the APIs and converts them into finished products. The bill of materials is used by the Secondary Manufacturer as a recipe to process its products. In the current model, the parameter ρ represents that proportion between API and product, or, by other words, the amount of each API necessary to produce one product;

10. **Storage Requirement** - It is the number of units of storage space for each storage condition consumed by a unit of API or product. When setting this parameter, it must be had into account that this parameter also controls the storage condition in which an API or product must be stored. Therefore, if the storage requirement for a given product and for a given storage condition is positive, the storage requirement for that product must be zero for all the other storage conditions.

Table 4.4 summarises the variables used in the model. The variables are divided into four categories. The decisions of integrate the consortium is defined by the binary variable $X \in \{ 0 , 1 \}$. The product flows are non-negative integer variables that indicates the quantity of each product, flowing from each facility to each facility in the next level of the SC, in each time period: $Y \in \mathbb{N}^0$. The final inventories decisions are non-negative integer variables that indicates the final inventory of each product, in each facility, in each time period: $I \in \mathbb{N}^0$. The decisions of production are given by non-negative integer variables which the production of each product, in each manufacturing facility, in each time period: $P \in \mathbb{N}^0$.

Table 4.2: Parameters

Fixed Costs	
fc_s^S	Integration cost of the Secondary Manufacturer s
fc_m^M	Integration cost of the Main DCs m
fc_l^L	Integration cost of the Local DCs l
Transportation Costs	
tc_{afs}^{α}	Cost of transporting API a from the primary manufacturer f to the secondary manufacturer s
tc_{psm}^{β}	Cost of transporting product p from the secondary manufacturer s to the main DC m
tc_{pml}^{γ}	Cost of transporting product p from the main DC m to the local DC l
tc_{plr}^{δ}	Cost of transporting product p from the local DC l to the retailer r
Storage Costs	
ic_{fc}^F	Cost of storing one storage unit, under conditions c, in the primary manufacturer f during one time period
ic_{sc}^S	Cost of storing one storage unit, under conditions c, in the secondary manufacturer s during one time period
ic_{mc}^M	Cost of storing one storage unit, under conditions c, in the main DC m during one time period
ic_{lc}^L	Cost of storing one storage unit, under conditions c, in the local DC l during one time period

Table 4.3: Parameters (continuation)

Storage Capacities	
s^F_{fc}	Storage capacity of primary manufacturer f to stock APIs, under conditions c
s^S_{sc}	Storage capacity of secondary manufacturer s to stock products, under conditions c
s^M_{mc}	Storage capacity of main DC m to stock products under conditions c
s^L_{lc}	Storage capacity of local DC l to stock products, under conditions c
Production Capacities	
pc^F_{fa}	Production capacity of API a in the primary manufacturer
pc^S_{sp}	Production capacity of product p in the secondary manufacturer s
Handling Capacities	
h^M_m	Handling capacity of the main DC m
h^L_l	Handling capacity of the local DC l
Demand	
d_{prt}	Demand of product p in retailer r at time period t
Initial Inventories	
ii^F_{fa}	Initial inventory of API a in the primary manufacturer f
ii^M_{mp}	Initial inventory of product p in the main DC m
ii^L_{lp}	Initial inventory of product p in the local DC l
Bill of Materials	
ρ_{ap}	Number of units of API a required to produce one unit of product p at the Secondary Manufacturer
Storage Requirement	
σ_{ac}	Number of units of storage space under condition c, required to store a unit of API a
τ_{pc}	Number of units of storage space under condition c, required to store a unit of product p

Table 4.4: Variables

Network integration	
X_s^S	1 if the secondary manufacturer s integrates the consortia, 0 otherwise
X_m^M	1 if the main DC m integrates the consortia, 0 otherwise
X_l^L	1 if the local DC l integrates the consortia, 0 otherwise
Product flow	
ψ_{afst}^{α}	Quantity of API a shipped from the manufacturer f to the secondary manufacturer s at period t
ψ_{psmt}^{β}	Quantity of product p shipped from the secondary manufacturer s to the main DC m at period t
ψ_{pmlt}^{γ}	Quantity of product p shipped from the main DC m to the local DC l at period t
ψ_{plrt}^{δ}	Quantity of product p shipped from the local DC l to the retailer r at period t
Inventory	
I_{fat}^F	Inventory of API a in the primary manufacturer f at the end of the period t
I_{spt}^S	Inventory of product p in the secondary manufacturer s at the end of the period t
I_{mpt}^M	Inventory of product p in the main DC m at the end of the period t
I_{lpt}^L	inventory of product p in the local DC l at the end of the period t
Production	
P_{fat}^F	Quantity of API a produced in the primary manufacturer f, in the period t
P_{spt}^S	Quantity of product p produced in the secondary manufacturer s, in the period t

4.3 Constraints

Demand Satisfaction

The demand satisfaction constraints set the minimum value for the outgoing flows at Local DCs. The demand satisfaction group of constraints guarantee that the total flow of products from all the Local DCs to each Retailer is greater or equal than the demand existing on that retailer. The inequality must be verified for all retailers, products and time periods. The group of constraints is expressed in Equation 4.1.

$$\sum_{l} \Psi_{plrt}^{\delta} \geq d_{prt} \quad \forall\, p,\ r,\ t > 0 \tag{4.1}$$

Production Capacity

The production capacity constraints are the constraints that limit the production of each manufacturing facility according to its installed capacity. The rationale behind these constraints is that if a facility has the capacity to produce a limited number of units, the production at that facility cannot be higher than that value. This group of constraint apply to all facilities, products and time periods.

Equation 4.2 guarantees that the quantity of API a produced in the primary manufacturer f, does not exceed the capacity of that facility for each API and time period.

$$P^F_{fat} \leq pc^F_{fa} \quad \forall\ f\ , a\ , t > 0 \tag{4.2}$$

Equation 4.3 guarantees that the quantity of product p produced in the secondary manufacturer s, does not exceed the capacity of that facility if it integrates the consortia, for each product and time period.

$$P^S_{spt} \leq X^S_s * pc^S_{sp} \quad \forall\ s,\ p,\ t > 0 \tag{4.3}$$

API Consumption

In the secondary facility, APIs are used sole or combined to produce pharmaceutical products. This conversion respects the proportionality parameter ρ. Since, in the context of the model used, the secondary manufacturer receives APIs just-in-time and the consumption is immediate, the inflow of each API at each Secondary Manufacturer and time period will be equal to the consumption of that API. Also, all the APIs consumed are considered to be converted to pharmaceutical products (there is no waste). The consumption of an API will, therefore, be the total production of products in that facility and time period multiplied by the parameter that stores the ratio between products and APIs.

Rephrasing, the quantity of API a necessary to produce all products which require that API in each Secondary Manufacturer is equal to the inflow of that API in that facility. This logic applies to all facilities, APIs and time periods. The group of constraints regarding this API to Product Conversion is expressed in Equation 4.4.

$$\sum_p (P^S_{spt} * \rho_{ap}) = \sum_f \Psi^{\alpha}_{afst} \qquad \forall\ s,\ a,\ t > 0 \tag{4.4}$$

Storage Capacity

Storage capacity constraints guarantee that the storage capacity for each storage condition of each facility is never exceeded in any facility, time period and storage condition.

The inventory of API a, stored under condition c in the primary manufacturer f, at the end of the period, cannot exceed the storage capacity of that facility under that condition on each time period t, as expressed in Equation 4.5.

$$\sum_a (I^F_{fat} * \sigma_{a,c}) \leq s^F_{fc} \qquad \forall\ f,\ c,\ t > 0 \tag{4.5}$$

Equation 4.6 guarantees that the inventory of product p, stored under condition c in the secondary manufacturer s, at the end of the period t, does not exceed the storage capacity of that facility under that condition (if it integrates the consortia) on each time period.

$$\sum_{p}(I^{S}_{spt} * \tau_{p,c}) \leq X^{S}_{s} * s^{S}_{sc} \qquad \forall\ s,\ c,\ t > 0 \tag{4.6}$$

Equation 4.7 guarantees that the inventory of product p, stored under condition c in the main DC m, at the end of the period, does not exceed the storage capacity of that facility under that condition on each time period.

$$\sum_{p}(I^{M}_{mpt} * \tau_{p,c}) \leq X^{M}_{m} * s^{M}_{mc} \qquad \forall\ m,\ c,\ t > 0 \tag{4.7}$$

Equation 4.8 guarantees that the inventory of product p, stored under condition c in the local DC l, at the end of the period, does not exceed the storage capacity of that facility under that condition (if it integrates the consortia) on each time period.

$$\sum_{p}(I^{L}_{lpt} * \tau_{p,c}) \leq X^{L}_{l} * s^{L}_{lc} \qquad \forall\ l,\ c,\ t > 0 \tag{4.8}$$

Handling capacity

Handling capacity constraints are intended to limit the flow exiting the distribution centres. The handling capacity is the maximum quantity of products that the distribution centres can handle in each time period, since distribution centres have limited resources.

Equations 4.9 and 4.10 guarantee that the outflow from each main DC and local DC, respectively, cannot exceed their handling capacity for all products, in each time period.

$$\sum_{p}\sum_{l} \Psi^{\gamma}_{pmlt} \leq X^{M}_{m} * h^{M}_{m} \qquad \forall\ m,\ t > 0 \tag{4.9}$$

$$\sum_{p}\sum_{r} \Psi^{\delta}_{plrt} \leq X^{L}_{l} * h^{L}_{l} \qquad \forall\ l,\ t > 0 \tag{4.10}$$

Mass-balance

Mass-balance constraints guarantee that the inputs and outputs of each facility are equal in all facilities and time periods, and for all products. In primary manufacturers, the inputs are the API productions and the inventory that comes from the last period. The outputs are the final inventory and the outflow to secondary manufacturers. In secondary manufacturers, the inputs are the product productions (restricted by Equation 4.4) and the inventory that comes from the last period. The outputs are the final inventory and the outflow to main DCs. In main DCs, the inputs are the inflow from secondary manufacturers and the inventory that comes from the last period. The outputs are the final inventory and the outflow to local

DCs. In local DCs, the inputs are the inflow from main DCs and the inventory that comes from the last period. The outputs are the final inventory and the outflow to retailers.

Equation 4.12 guarantees that the initial inventory of API a, plus the quantity of API produced, in the primary manufacturer f, in the period t, is equal to the final inventory plus the outflow of that API in that facility.

$$I^F_{fat-1} + P^F_{fat} = I^F_{fat} + \sum_s \Psi^\alpha_{afst} \qquad \forall\ f,\ a,\ t > 0 \tag{4.11}$$

Equation 4.12 guarantees that the initial inventory of product p, plus the quantity of product produced, in the secondary manufacturer s, in the period t, is equal to the final inventory plus the outflow of that product in that facility.

$$I^S_{spt-1} + P^S_{spt} = I^S_{spt} + \sum_m \Psi^\beta_{psmt} \qquad \forall\ s,\ p,\ t > 0 \tag{4.12}$$

Equation 4.13 guarantees that the inputs of product p in the main DC m (sum of the initial inventory and the inflows) at the end of the period t corresponds to the outputs (sum of the final inventory and the outflows) of that product in that facility and period.

$$I^M_{mpt-1} + \sum_j \Psi^\beta_{psmt} = I^M_{mpt} + \sum_l \Psi^\gamma_{pmlt} \quad \forall\ m,\ p,\ t > 0 \tag{4.13}$$

Equation 4.14 guarantees that the inputs of product p in the local DC l (sum of the initial inventory and the inflows) at the end of the period t corresponds to the outputs (sum of the final inventory and the outflows) of that product in that facility and period.

$$I^L_{lpt-1} + \sum_k \Psi^\gamma_{pmlt} = I^L_{lpt} + \sum_r \Psi^\delta_{plrt} \quad \forall\ l,\ p,\ t > 0 \tag{4.14}$$

Initial inventory

Initial inventory constraints guarantee that the initial inventory of the first period matches the initial inventory stipulated in the model input parameters.

Equations 4.15, 4.16, 4.17 and 4.18 guarantee that the inventory at the end of the time period zero are equal to the initial inventory defined.

$$I^F_{f,a,0} = ii^F_{fa} \tag{4.15}$$

$$I^S_{s,p,0} = ii^L_{sp} \tag{4.16}$$

$$I^M_{m,p,0} = ii^M_{mp} \tag{4.17}$$

$$I^L_{l,p,0} = ii^L_{lp} \tag{4.18}$$

Binary variables

Equations 4.19 defines the binary decision variables of the present model: the integration or not of a given facility in the network.

$$X_s^S \; X_m^M \; , \; X_l^L \; \in \; \{ \, 0 \, , \, 1 \, \} \tag{4.19}$$

Non-negative variables

Equations 4.20, 4.21 and 4.22 defines the non-negatives variables: flows, inventories and productions cannot take negative values.

$$\Psi_{pfst}^{\alpha} \; , \; \Psi_{psmt}^{\beta} \; , \; \Psi_{pmlt}^{\gamma} \; , \; \Psi_{plrt}^{\delta} \quad \in \quad \mathbb{N}^0 \tag{4.20}$$

$$I_{fat}^F \; , \; I_{spt}^S, \; I_{mpt}^M, \; I_{lpt}^L \quad \in \quad \mathbb{N}^0 \tag{4.21}$$

$$P_{fat}^F \; , \; P_{spt}^S, \quad \in \quad \mathbb{N}^0 \tag{4.22}$$

4.4 Objective

For the case in hand, the objective of the model will be the minimisation of the SC costs. The objective function, which is the minimisation of the sum of the fixed costs, distribution costs and inventory costs is expressed in Equation 4.23.

$$\text{minimise} \quad z = \text{Fixed costs + Transportation costs + Inventory costs} \tag{4.23}$$

Fixed costs are given as the sum to all facilities of the product of the fixed costs associated with the entry of a facility in the network and the binary variable that takes the value 1 if that facility integrates the network, and 0 otherwise.

$$\text{Fixed costs} = \sum_s X_s^S f c_s^S + \sum_m X_m^M f c_m^M + \sum_l X_l^L f c_l^L \tag{4.24}$$

Transportation costs are calculated as the sum for all products, time periods, origin facilities and destination facilities of the number of products transported from each origin facility to each destination facility multiplied by the cost of transporting that product in that path. The transportation costs are expressed in Equation 4.25.

$$\begin{aligned} \text{Transportation costs} = & \sum_a \sum_f \sum_s \sum_t \Psi_{afst}^{\alpha} * dc_{afs}^{\alpha} + \sum_p \sum_s \sum_m \sum_t \Psi_{psmt}^{\beta} * dc_{psm}^{\beta} + \\ & + \sum_p \sum_m \sum_l \sum_t \Psi_{pmlt}^{\gamma} * dc_{pml}^{\gamma} + \sum_p \sum_l \sum_r \sum_t \Psi_{plrt}^{\delta} * dc_{plr}^{\delta} \end{aligned} \tag{4.25}$$

Inventory costs are the costs of storing an API in the primary manufacturer or a product in other facilities for one period of time.

The inventory costs are calculated as the sum for all storage conditions, facilities and time periods of the final inventory of each product in each facility and time period, multiplied by the storage space that that product requires for the storage condition considered, and multiplied by the cost of one storage space under the storage condition considered, in each facility. The inventory costs are calculated as expressed in Equation 4.26

$$\begin{aligned}\text{Inventory costs} = &\sum_{t}\sum_{f}\sum_{c}(\sum_{a} I^{F}_{fat} * \sigma_{ac}) * ic^{F}_{fc}) + \sum_{t}\sum_{s}\sum_{c}(\sum_{p} I^{S}_{spt} * \tau_{pc}) * ic^{S}_{sc}) + \\ &+ \sum_{t}\sum_{m}\sum_{c}(\sum_{p} I^{M}_{mpt} * \tau_{pc}) * ic^{M}_{mc}) + \sum_{t}\sum_{l}\sum_{c}(\sum_{p} I^{L}_{lpt} * \tau_{pc}) * ic^{L}_{lc})\end{aligned} \tag{4.26}$$

4.5 Conclusion

The mathematical model proposed considers the existence of a five-level SC for the pharmaceutical industry. The model allows the existence of inventory in all manufacturing facilities and distribution centres, with multiple storage conditions. Having multiple storage conditions is an important feature in a PSC since pharmaceutical products require specific and strict conservation characteristics to guarantee the quality and the integrity of the compounds from the manufacturing until their consumption by the final customer. The existence of limited resources in all facilities is assumed, namely production and inventory capacities in manufacturing facilities and handling and inventory capacities in distribution centres. Regarding product considerations, the proposed model considers a multi-API and multi-product network, in which, the conversion of API to product is performed in the secondary manufacturers as common in the pharmaceutical industry.

The objective of the proposed model is to minimise the total costs. Those costs can be divided into three categories, fixed costs, transportation costs and storage costs. Fixed costs are about expenses that the facilities are required to have to integrate a flexible pharmaceutical network which can encompass process integration investments, partnership costs, technological investment to allow the sharing of information, and strategic adjustments to the facility *modus operandi*. Transportation costs are the unit costs of transportation a product between two facilities. Finally, storage costs are the costs that a facility will incur to store a unit of product for a time period.

It is expected that the proposed model allows the design of a flexible PSC network, providing a competitive advantage to its agents and a secure and fast manner of redesigning the SC structure according to market variations, cost variations and other sources of variability that exist in the real-world pharmaceutical industry.

Chapter 5

Computational Experiments

To test and validate the proposed model, two experiments will be performed. Firstly, a problem with the parameters adapted from the publication of Mousazadeh et al. (2015); and, secondly, a multi-API, multi-product and multi-storage condition problem, with data also inspired in the same authors.

In Section 5.1, a context about the data used to recreate this problem is provided. The main characteristics of the problem in hands are highlighted and the locations of the different facilities available to integrate the network are exposed. In Section 5.2, the parameters relative to Experiment 1 (single-API, single product and single-storage condition) are proposed and detailed. The same exposition is performed about Experiment 2 (multi-API, multi-product and multi-storage condition). In Section 5.3, the results outputted by the model to address the problems identified for both experiments are detailed and analysed. In Section 5.4, some conclusions regarding the computational experiments and respective results analysis are drawn.

5.1 Context

The problem addressed in these computational experiments is inspired by the problem addressed by Mousazadeh et al. (2015). The authors' model is tested via an empirical case study, based on the data collected from Iran's National Organisation of Food & Drug. According to the total national sales report, Amoxicillin 500 mg pill was the drug with most prescriptions and purchases, among more than five thousand different drugs, from the ones on sale between 2004 and 2013 in Iran. According to the data, around 900 million capsules are sold per year. This happens because amoxicillin can treat a broad range of bacterial infections.

Despite their model approaches a multi-product problem, the authors used a single product problem for simplification. According to the authors, designing the SC for a single product does not limit the application of the model, since in the proposed model, different products are just interconnected by sharing the same facilities.

The conversion of API to a product in these experiments will be considered as one to one ratio. The storage requirement will be one unit of storage space for one tonne of amoxicillin, and it will be

considered only one storage condition. Amoxicillin must be stored at room temperature.

Regarding the possible locations for facilities and infrastructures, Mousazadeh et al. (2015) considered the existence of 8 secondary manufacturers. As Mousazadeh et al. (2015) did not consider the existence of the level of primary manufacturers in its pharmaceutical network design optimisation model, it will be assumed the existence of 4 primary manufacturers, each one located near one of the biggest cities of Iran. Ten locations for main DCs are considered in the same publication.

According to the experts' opinion acquired by Mousazadeh et al. (2015), from the Iranian Ministry of Health, each province can be considered a demand zone. Each one of the 31 Iranian provinces also has a local DC candidate to enter the network. Table 5.1 summarises all this information.

Figures A.1, A.2, A.3 and A.4, which are available for consultation in the Appendix of the present document, illustrate maps with the facilities considered and above mentioned.

Table 5.1: Number of facilities per level of the SC

Type of facility	Number of facilities
Primary Manufacturer	4
Secondary Manufacturer	8
Main DC	10
Local DC	31
Retailer	31

5.2 Data gathering and adaptation

5.2.1 Experiment 1

The main purpose of Experiment 1 is to test and validate the model by analysing the outputs for the empirical example developed by Mousazadeh et al. (2015). In this subsection, an explanation regarding the sample data that will be solved afterwards is provided.

Retailers

Based on Mousazadeh et al. (2015), a temporal horizon of 4 years is considered. Mousazadeh et al. (2015) had access to the forecast of the overall Iranian consumption of Amoxicillin from 2014 to 2017. According to the expert's indications, the consumption rate of amoxicillin varies among seasons following the distribution expressed in Table 5.2, with an evident increase in demand in cold seasons, which is the winter in the northern hemisphere. For this reason, a total of 16 time periods is considered, being one time period equivalent to one yearly season, given a temporal horizon of 4 years.

Table 5.2: Distribution of the annual demand per season

Season	Percentage
Spring	11 %
Summer	9 %
Autumn	30 %
Winter	50 %

The seasonal demand for Amoxicillin is divided into retailers by considering the population of each demand zone. Table A.1 details the demand of Amoxicillin expressed in metric tonnes, at each retailer and in each time period.

Facilities' parameters

The storage capacities, production capacities, fixed integration costs and inventory costs of the primary manufacturers are available in Table 5.3. The same parameters, but associated with the secondary manufacturers, is detailed in Table 5.4.

The storage capacities, handling capacities, fixed integration costs and inventory costs of each main DC were adapted from the data provided by Mousazadeh et al. (2015) and are detailed in Table 5.5. The same parameters of each local DC are detailed in Table A.2.

Table 5.3: Parameters: primary manufacturers

Primary Manufacturer ID	Storage Cap. (ton)	Prod. Capacity (ton)	Inventory cost (€/ton)
1	36	360	37.5
2	36	360	42.5
3	36	360	40
4	36	360	40

Table 5.4: Parameters: secondary manufacturers

Sec. Man. ID	Storage Cap. (ton)	Prod. Cap. (ton)	Fixed cost (€)	Inv. cost (€/ton)
1	18	180	24000	75
2	18	180	24576	42.5
3	18	180	23400	40
4	18	180	24576	42.5
5	18	180	24576	37.5
6	18	180	24000	40
7	18	180	24000	40
8	18	180	24576	42.5

Table 5.5: Parameters: main DCs

Main DC ID	Storage Cap. (ton)	Handling Cap. (ton)	Fixed cost (€)	Inventory cost (€/ton)
1	120	120	11520	75
2	120	120	6528	42.5
3	120	120	6144	40
4	120	120	6528	42.5
5	120	120	5760	37.5
6	120	120	6144	40
7	120	120	6144	40
8	120	120	6528	42.5
9	120	120	5760	37.5
10	120	120	6144	40

It is important to notice that the capacities are stated in metric tonnes and the currencies were converted from Iranian Rials to Euro at an exchange rate of 1 Euro equivalent to 0.00002 Rials.

The transportation costs between secondary manufacturers, main DCs, local DCs and retailers were estimated by Mousazadeh et al. (2015) based on the weight and volume of each Amoxicillin dose, the average cost of transportation for 100 kilometres, provided by shipping agencies, and distances calculated through Google Maps.

5.2.2 Experiment 2

Experiment 2 proposes the validation of the model with a multi-API and multi-product problem, with also multiple storage conditions.

Two APIs are distributed throughout the network: the Amoxicillin and the Clavulanic Acid, which is an enzyme inhibitor used to enhance the effectiveness of beta-lactam antibiotics as Amoxicillin. According to Saudagar et al. (2008), Clavulanic Acid is often combined with antibiotics to prevent the development of drug-resistant strains of bacteria, promoting also their therapeutic antibacterial effects.

Two products are also distributed by the network: Amoxicillin 500mg and the combination between Amoxicillin 500mg/g and Clavulanic Acid 200 mg/g which will be hereinafter referred to as product A and product B, respectively. Product B is also a very prescribed antibiotic, which has demonstrated more effectiveness against some types of infections (Johnson, 2019) and is available on the market as a pill and injectable solution.

This second product is composed of two APIs. For this instance, it will be considered that to produce 1 unit of the combination product Amoxicillin + Clavulanic Acid, it will be required 1 unit of the API Amoxicillin (henceforth designated API1) and 1 unit of API Clavulanic Acid (henceforth designated API2).

Table 5.6 shows the bill of materials (APIs) of the two products which are now considered.

Table 5.6: Bill of Materials

Product	API1	API2
A	1	0
B	1	1

Multiple storage conditions are considered in this scenario. It considered that Clavulanic Acid requires a special storage condition, as it must be conserved in a freezer, between 2 ºC and 5 ºC (henceforth designated storage condition C2). Therefore, product B also requires storage under that condition. Each product requires 1 unit of refrigerated storage space. Product A can be stored at room temperature (henceforth designated C1). Table 5.7 details the number of units of storage space required to store one unit of each product.

Table 5.7: Storage requirement of the Products

Product	Room Temperature (C1)	Freezer (C2)
A	1	0
B	0	1

The demand of the product A will be considered the same as used for Experiment 1, which is available in Table Table A.1. For simplification reasons, the product B will be considered to have the same demand profile proposed by Mousazadeh et al. (2015). Therefore, the demand parameters of the product B can also be consulted in Table A.1. The production capacities of both primary and secondary manufacturers were also considered to be the same as in Experiment 1. This means that the overall production capacity has duplicated, but also the overall demand.

5.2.3 Analysis of different scenarios

To study the flexibility of the proposed SC network, a set of variations will be performed to those parameters and the results will be analysed and compared. The different scenarios studied in this subsection have the purpose of understanding the network behaviour and sensibility to variations in the input parameters. To perform this approach, a set of scenarios is proposed in Table 5.8 and, after it, explained.

Table 5.8: Summary of the experiments and scenarios computed

	Experiment 1 (single product and single-API)	**Experiment 2 (multi-product and multi-API)**
Baseline	Solve the problem with data from Mousazadeh et al. (2015)	Solve the problem with the data from Mousazadeh et al. (2015) adapted to the characteristics of the proposed model
Exploring the demand	a) Resolve the baseline problem, but with half the demand initially considered b) Resolve the baseline problem, but with twice the demand initially considered	a) Resolve the baseline problem, but half the demand initially considered b) Resolve the baseline problem, but with twice the demand initially considered
Studying the fixed integration costs	Resolve the problem considering different value for the fixed integration costs	Resolve the problem considering different value for the fixed integration costs

The first stage contemplates the computation and critical analysis of the results for the baseline scenario.

In a second stage, the intention directs to test the model in a scenario with demand much above the typical one. In this stage, two different demand scenarios will be considered. Firstly, the model will be processed with half the demand initially considered. Secondly, the model will be processed with double the demand initially considered.

In a third stage, the focus will turn to the variation of the fixed integration costs. To integrate the network, entities will support integration costs, which can be considered as investments. As explained above, secondary manufacturers, main DCs, local DCs and retailers must manage those fixed integration costs that impact the design of the SC network. To study the size of that impact, an analysis of different scenarios is proposed to be performed. Firstly, the network where the fixed integration costs are equal to zero in all the facilities will be computed. Secondly, the network will be studied when the fixed integration costs take lower values than the in the baseline scenario. Specifically, the problem with be solve for 1%, 5% 10%, 25%, 50%, 60%, 65% and 75% of the baseline fixed integration costs.

To study the flexibility of the proposed SC network, the problem will also be computed for fixed integration costs higher than the original values, namely, 125%, 150%, 175%, 200%, 300%, 400%, 500%, 1000% and 2000% of the baseline costs. Due to lack of space in the present dissertation, only the most relevant scenarios, in which the network suffers visible changes will be shown and analysed.

The computation and analysis of the set of scenarios will be performed for both Experiment 1 and Experiment 2.

5.3 Results analysis

In this section, the problem presented in chapter 6 and the model proposed in chapter 4 were implemented in DOcplex Python Modeling API, which uses the ILOG CPLEX Optimization Studio 12.9.0 (CPLEX). The optimisation model was executed for all sets using a personal laptop with a processor Intel I5-5200U CPU @ 2.70 GHz and 12 GB of RAM.

In sub-section 5.3.1, Experiment 1 is performed. Firstly, the most important figures of the solution of the baseline scenario are provided and interpreted. Then, the same approach is performed to the scenarios in which the demand is increased and to the scenarios in which the fixed integration costs are varied. In sub-section 5.3.2, the focus changes to Experiment 2 and the solutions of the different scenarios tested are provided and analysed.

5.3.1 Experiment 1

Baseline

The CPLEX solver engine took 244 seconds to solve the MILPs with 2912 rows and 23089 columns and returned a total cost as an objective function of €147982.40. The number of facilities that will integrate

the network for each level of the SC and the total number of facilities available in each level is shown in Table 5.9.

Table 5.9: Network structure: Baseline

Entity	# Facilities integrating network	# Total facilities
Primary Manufacturers	2	4
Secondary Manufacturers	2	4
Main DCs	3	10
Local DCs	11	31
Retailers	31	31

It can be depicted that despite the existence of 4 primary manufacturers which are possible to integrate the network, only 2 indeed integrated the network in the optimal solution. The same happens with the other levels of the SC. From 8 secondary manufacturers, only 2 integrate the network; from 10 main DC, only 3 integrate the network; and from 31 local DCs, only 11 integrate the network.

In Table 5.10, productions in primary manufacturers (Prod. F) and second manufacturers (Prod. S), inventories in local DCs (Inv. L) and demand in the retailers are detailed for all each time period. The values of the demand were rounded up to the next integer, as the proposed model is a MILP. All other facilities except the local DCs do not store inventories.

Table 5.10: Outputs: Experiment 1 (baseline)

Time period	Prod. F	Prod. S	Inv. L	Demand
1	103	103	0	103
2	84	84	0	84
3	302	302	50	252
4	**360**	**360**	**0**	**410**
5	104	104	0	104
6	84	84	0	84
7	308	308	54	254
8	**360**	**360**	**0**	**414**
9	105	105	0	105
10	87	87	0	87
11	318	318	59	259
12	**360**	**360**	**0**	**419**
13	107	107	0	107
14	89	89	0	89
15	323	323	62	261
16	**360**	**360**	**0**	**422**

The demand is higher than the capacity of opened manufacturing facilities in winter seasons, which correspond to periods 4, 8, 12, and 16 (highlighted in bold in the table). Thus, to satisfy the demand for all the seasons, 2 secondary manufacturers are required to open.

Despite the production capacity of a secondary manufacturer being half of the production capacity of

a primary manufacturer, as depicted in section 5.2, 2 primary manufacturers are still open to minimise the transportation costs between primary and secondary manufacturers. This event happens because there is no fixed cost to open a new primary manufacturer, and, therefore the model tends to connect the primary and secondary manufacturers with the lowest transportation costs possible. Those transportation costs vary according to the distances between facilities and the far the cities where the facilities a located, the higher the transporting costs between them. Therefore, to supply APIs to a specific secondary manufacturer, the closest primary manufacturer possible is chosen.

In the winter season, the demand exceeds the production capacity of those periods. To balance this excess of demand, inventories are built in local DCs is the period previous to winter. The local DCs which are integrating the network are the facilities with lower inventory costs of the entire network and, therefore those are chosen to store products that will be supplied in winter.

The time period 16 is the one with highest demand, and in that period the demand only exceeds the production capacity of the primary and secondary manufacturers by 12.5%. The decision to stock products in local DCs to guarantee the demand satisfaction in winter is preferred rather than opening new secondary manufacturing facilities which would carry significant fixed integration costs to supply only a total of 225 tonnes of product in the entire temporal horizon. Storing 225 tonnes of product represents, in the worst case, a cost of € 9562.50, but choosing another secondary manufacturer to reinforce the capacity of the network would carry a minimum fixed integration cost of € 23400.

In figure A.5, a graph representing the network design diagram for this scenario in the time period 16 is provided since it is the time period with higher demand, and therefore, where the network complexity is higher. The nodes represent facilities and edges represent the flow of products between facilities. A node with the label F_f refers to the primary manufacturer f; with the label S_s refers to the secondary manufacturer s; with the label M_m refers to the main DC m; with the label L_l refers to the local DC l; and, with the label R_r refers to the retailer r.

Half demand

Considering the scenario in which the demand is half of the original scenario, the network is composed of 1 primary manufacturer, 1 secondary manufacturer, 2 main DCs, 6 local DCs and 31 retailers. Comparing it with the baseline scenario, the network is composed of half the number of the manufacturers. The number of main DCs reduces from 3 to 2 and the number of local DCs reduces from 11 to 6. As expected, fewer facilities integrate the network to satisfy the minor demand. Table 5.11 presents the number of facilities integrating the network. The computational time to solve this problem was 393.77 seconds, and the MILPs contains 2912 rows and 23089 columns. The objective function cost value achieved is € 85724.16. An objective function with a cost 42% lower than the baseline objective function was achieved to supply the demand 50% lower. This represents an increase of 15.7% in the total cost per tonne of product supplied.

Table 5.11: Network structure: Experiment 1 (half demand)

Entity	# Facilities integrating network	# Total facilities
Primary Manufacturers	1	4
Secondary Manufacturers	1	8
Main DCs	2	10
Local DCs	6	31
Retailers	31	31

Table 5.12 summarises the outputs of the model for this scenario: production quantities in primary manufacturers (Prod. F) and secondary manufacturers (Prod. S), inventories in local DCs (Inv. L) and the total demand per period.

Similarly to the baseline scenario, in the winter periods (4, 8, 12 and 16) the demand is higher than the total production capacity. Therefore, the network planning model proposed the built-up of inventory on local DCs in periods that precede winter (3, 7, 11 and 15).

Table 5.12: Outputs: Experiment 1 (half demand)

Time period	Prod. F	Prod. S	Inv. L	Demand
1	58	58	0	58
2	50	50	0	50
3	164	164	32	132
4	180	180	0	212
5	58	58	0	58
6	50	50	0	50
7	168	168	35	133
8	180	180	0	215
9	58	58	0	58
10	50	50	0	50
11	174	174	37	137
12	180	180	0	217
13	59	59	0	59
14	51	51	0	51
15	177	177	38	139
16	180	180	0	218

In figure A.6, a graph representing the network design diagram for this scenario in the time period 16 is provided for being the time period with higher demand, and therefore, where the network complexity is higher. The elements of the graph follow the same structure explained in the baseline scenario. When comparing this network to the network obtained in the baseline scenario, it can be found that with half the demand, a concentration of the flows happens in the primary manufacturer 1, the secondary manufacturer 1, the main DCs 7 and 8 and the local DCs 7, 17, 18, 26, 27 and 29. According to the Iran Map (provided in figure A.4), those facilities, which tend to integrate the network when the demand is lower, are the facilities located near big cities, where the demand is higher, in an effort to minimise the transportation costs.

Double demand

Considering the scenario in which the demand is duplicated, the network is composed of 4 primary manufacturers, 4 secondary manufacturers, 7 main DCs, 22 local DCs and 31 retailers. Comparing it with the baseline scenario, the network is composed of twice the manufacturers and more than twice the DC. Therefore, as expected, more facilities integrate the network to satisfy the demand. Table 5.13 presents the number of facilities integrating the network. The computational time to solve the MILPs with 2912 rows and 23089 columns was 126.91 seconds, which was faster than the baseline scenario.

Table 5.13: Network structure: Experiment 1 (double demand)

Entity	# Facilities integrating network	# Total facilities
Primary Manufacturers	4	4
Secondary Manufacturers	4	8
Main DCs	7	10
Local DCs	26	31
Retailers	31	31

The total cost of the network is 282887.54 euros and comparing it with the baseline scenario, represents an increase of 91%. However, the total costs per tonne of product provided to the retailer are around 5% lower. Therefore, the network can respond to an increase of 100% of the demand, and its efficiency increases since the cost per tonne supplied decreases.

Table 5.14: Outputs: Experiment 1 (double demand)

Time period	Prod. F	Prod. S	Inv. L	Demand
1	206	206	0	206
2	168	168	0	168
3	604	604	100	504
4	720	720	0	820
5	208	208	0	208
6	168	168	0	168
7	616	616	108	508
8	720	720	0	828
9	210	210	0	210
10	174	174	0	174
11	636	636	118	518
12	720	720	0	838
13	214	214	0	214
14	178	178	0	178
15	646	646	124	522
16	720	720	0	844

Table 5.14 summarises the outputs of the model for this scenario: production quantities in primary manufacturers (Prod. F) and secondary manufacturers (Prod. S), inventories in local DCs (Inv. L) and the total demand per period. Similarly to the baseline scenario, in the winter periods (4, 8, 12 and 16) the demand is higher than the total production capacity. Therefore, the network planning model proposes the built-up of inventory on local DCs in periods that precede winter (3, 7, 11 and 15).

In figure A.7, a graph representing the network design diagram for this scenario in the time period 16 is provided for being the time period with higher demand, and therefore, where the network complexity is higher. The elements of the graph follow the same structure explained in the baseline scenario. When comparing this network to the network obtained in the baseline scenario, it can be found that with the double of the demand, the maximum capacity is achieved in main DCs 1 to 4, but not in main DCs 6, 7, 8 and 10. While main DC 1 is located near Tehran, where the demand is higher, main DCs 2, 3 and 4 are spread across the country, providing good intermediate points to connect the manufacturing facilities to remote retailers.

Varying fixed integration costs

In this section, the analysis of the behaviour of the network when the fixed integration costs are varied is proposed, to understand the sensibility of the network to the variation of this model parameter.

Figure 5.1 illustrates the participating actors when the integration costs changes. As expected, when the fixed integration costs are lower, more actors participate in the network and vice-versa.

In the scenario in which the facilities do not have to spend on fixed integration costs, 53 facilities integrate the network. This is the maximum number of facilities available on this problem. As the fixed integration costs grow, the number of facilities decreases to 33. Only 1% of the fixed integration costs is enough to reduce the number of facilities by almost 40%. Variations between 65% and 2000% of the base fixed integration costs return more similar networks, with the number of facilities varying in only 2 units. With higher fixed integration costs, the network becomes more compact. The more compact a network is, the more difficult is to subtract even more facilities without jeopardising the demand satisfaction.

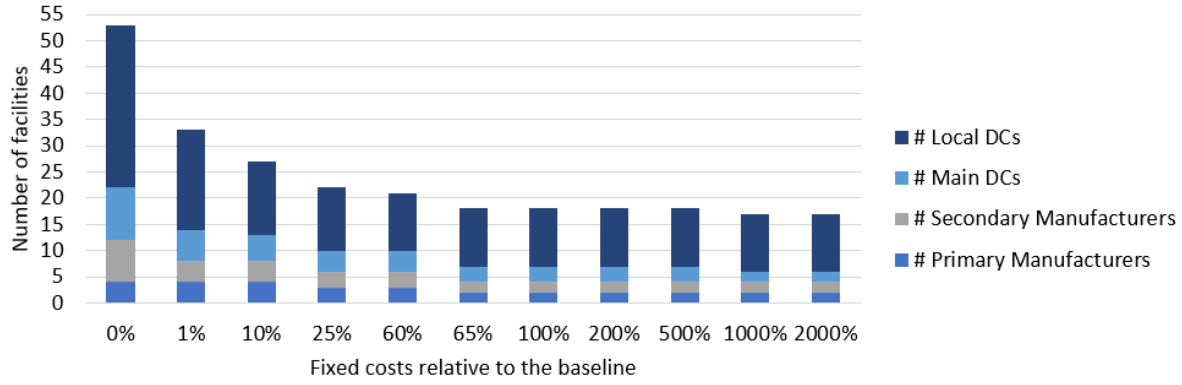

Figure 5.1: Number of facilities *versus* Fixed integration costs: Experiment 1

Table 5.15 presents the total production and the total inventory according to the variation of the fixed integration costs. From Table 5.15, it is possible to depict that when the fixed integration costs are lower, it carries fewer costs to add facilities into the network than storing products to guarantee the supply in peak demand periods. However, when the fixed integration costs are higher, incurring inventory costs reveals less expensive than adding more facilities into the network, which leads to an increase in the usage of inventory and to a reduction in the usage of capacity.

Table 5.15: Fixed costs, productions and inventories: Experiment 1

Coefficient	Total Production	Total Inventory L
0	3454	0
1%	3454	0
10%	3454	0
25%	3454	0
60%	3454	0
65%	3454	225
100%	3454	225
200%	3454	225
500%	3454	225
1000%	3454	1631
2000%	3454	1631

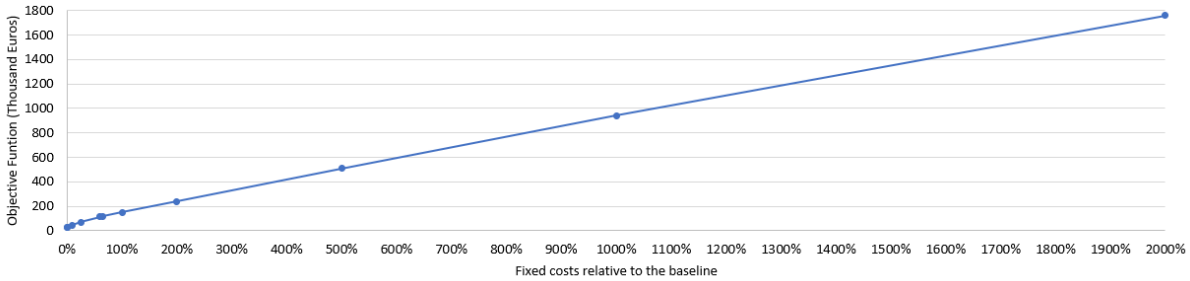

Figure 5.2: Optimal objective function *versus* Different multiples of the fixed integration costs

Figure 5.2 shows a plot that compares the objective function of the problem with the proportion of the fixed costs when compared to the baseline scenario. This plot reinforces that in the present example, the fixed costs have a great influence on the objective function, and, therefore, in the design of the present SC network.

5.3.2 Experiment 2

Baseline

Experienced 2 was executed in the same machine as experiment 1. In the baseline instance, the computational time to solve the MILP with 5416 rows and 46377 columns was 978.84 seconds, reaching an objective function of 153206.04 euros. In Table 5.16, the number of facilities that will integrate the network is indicated for each level of the SC.

Table 5.16: Network structure: Experiment 2 (baseline)

Entity	# Facilities integrating network	# Total facilities
Primary Manufacturers	3	4
Secondary Manufacturers	3	8
Main DCs	7	10
Local DCs	22	31
Retailers	31	31

In Table 5.17, productions of both products in primary manufacturers and second manufacturers and inventories in both storage conditions in local DCs are detailed for each time period and each product. Only values for these facilities are provided, since inventories in primary manufacturers, secondary manufacturers and main DCs are equal to zero.

Table 5.17: Outputs: Experiment 2 (baseline)

Time period	Production F		Production S		Inventory L		Demand	
	API1	API2	A	B	C1	C2	A	B
1	206	103	103	103	0	0	103	103
2	168	84	84	84	0	0	84	84
3	504	252	252	252	0	0	252	252
4	820	410	410	410	0	0	410	410
5	208	104	104	104	0	0	104	104
6	168	84	84	84	0	0	84	84
7	508	254	254	254	0	0	254	254
8	828	414	414	414	0	0	414	414
9	210	105	105	105	0	0	105	105
10	174	87	87	87	0	0	87	87
11	518	259	259	259	0	0	259	259
12	838	419	419	419	0	0	419	419
13	214	107	107	107	0	0	107	107
14	178	89	89	89	0	0	89	89
15	526	261	265	261	4	0	261	261
16	840	422	418	422	0	0	422	422

In the present scenario, the inventory is only required on period 15, to store 4 tonnes of product A. This happens since the total demand on period 16 is 844 tonnes of products and the total capacity of the 7 main DCs in the network is only 840 tonnes. Therefore, the solution that carries fewer costs to the SC is to store 4 units of product 1 in one of the local DCs. The fixed integration costs of opening one more main DCs would be higher than keeping 4 units of product in inventory storage.

In figure A.8, a graph representing the network design diagram for this scenario in the time period 16 is provided for being the time period with higher demand, and therefore, where the network is under more pressure. Solid black edges represent the flow of API1 and product A. Solid red edges represent the flow of API2 and product B. Dashed black and red edges represent the flow of both products.

Half demand

Considering the scenario in which the demand was reduced to one half, or 50% less, of the original baseline demand, the network is composed of 2 primary manufacturers, 4 secondary manufacturers, 7 main DCs and 11 local DCs. The computational time required to solve this problem was 394.58 seconds, to reach an objective function cost of € 146300.88. The total computational time required to solve this problem was 394.58 seconds, and the reduced MILP problem contains 5416 rows and 46377 columns.

In table 5.18, the optimal number of facilities to integrate each level of the SC for this scenario is compared to the total number of facilities available.

Table 5.18: Network structure: Experiment 2 (half demand)

Entity	# Facilities integrating network	# Total facilities
Primary Manufacturers	2	4
Secondary Manufacturers	2	8
Main DCs	4	10
Local DCs	11	31
Retailers	31	31

In table 5.19, the productions in primary manufacturers, secondary manufacturers, inventories in local DCs are compared with the demand for each time period.

Table 5.19: Outputs: Experiment 2 (half demand)

Time period	Production F		Production S		Demand	
	API1	API2	A	B	A	B
1	116	58	58	58	58	58
2	100	50	50	50	50	50
3	264	132	132	132	132	132
4	424	212	212	212	212	212
5	116	58	58	58	58	58
6	100	50	50	50	50	50
7	266	133	133	133	133	133
8	430	215	215	215	215	215
9	116	58	58	58	58	58
10	100	50	50	50	50	50
11	274	137	137	137	137	137
12	434	217	217	217	217	217
13	118	59	59	59	59	59
14	102	51	51	51	51	51
15	278	139	139	139	139	139
16	436	218	218	218	218	218

In this scenario the optimal solution considers inventories equal to zero in all the facilities and in all the time periods. This means that in this scenario, inserting more facilities into the network is preferable rather than storing products in inventory.

In figure A.9, a graph representing the network design diagram for this scenario in the time period 16 is provided since it is the time period with higher demand, and therefore, where the network is more complex. The elements of the graph follow the same structure explained in the baseline scenario.

Double demand

A problem with twice the demand of the baseline scenario was loaded into the optimisation model developed. However, an infeasible situation was achieved due to the excess of demand or lack of capacity in the SC facilities. To be able to analyse a scenario in which the demand is over the baseline demand, the demand was iterative from the original demand on steps of 10% until a feasible problem is achieved. With a demand 40% above the demand of the baseline scenario, the CPLEX solver engine

found a feasible solution to the problem. However, with a demand 50% above the baseline scenario, the model becomes infeasible.

Table 5.20, outlines the number of facilities integrating the PSC network when the demand in 40% above the baseline scenario. On this scenario, the total cost of the optimal network is 353177.84 euros. The total computational time required to solve this MILP with 5416 rows and 46377 columns was 5.08 seconds.

Table 5.20: Outputs: Experiment 2 (40% more demand)

Entity	**# Facilities integrating network**	**# Total facilities**
Primary Manufacturers	4	4
Secondary Manufacturers	4	8
Main DCs	10	10
Local DCs	31	31
Retailers	31	31

With the demand 40% above the demand of the baseline scenario, all the facilities must integrate the network to guarantee the satisfaction of the demand.

Table 5.21 summarises the outputs of the model when the demand is increased by 40%. The production of both products in primary manufacturers, secondary manufacturers, inventories in both storage conditions in local DCs are detailed and compared to the demand in each time period.

In winter periods, the demand for both products is higher than in the other periods. On this occasion, all the facilities are integrating the network, but only 2 units are stored in local DCs, in time period 14.

To investigate the cause for the demand 40% above the baseline scenario be fulfilled without the use of inventories, but a demand of 50% above the baseline scenario cannot be fulfilled by the network, the capacities of the main and local DCs must be recalled. In this scenario, the total number of facilities available are integrating the network, which corresponds to a handling capacity of 1200 tonnes per time period in main DCs, and 1240 tonnes per time period in local DCs. The difference in demand between a scenario with the demand 40% above the baseline and a scenario with the demand 50% above the baseline corresponds to 120 tonnes of product. This means that in a scenario with the demand 40% above the baseline, a bottleneck (or point of congestion of the network) is situated in the main DCs, and, therefore, products can be accumulated in the local DCs to fulfil the demand of peak periods (winter).

Table 5.21: Outputs: Experiment 2 (50% more demand)

Time period	Production F		Production S		Inventory L		Demand	
	API1	API2	API1	API2	C1	C2	A	B
0	314	157	157	157	0	0	157	157
1	260	130	130	130	0	0	130	130
2	730	365	365	365	0	0	365	365
3	1168	584	584	584	0	0	584	584
4	318	159	159	159	0	0	159	159
5	260	130	130	130	0	0	130	130
6	734	367	367	367	0	0	367	367
7	1180	590	590	590	0	0	590	590
8	320	160	160	160	0	0	160	160
9	266	133	133	133	0	0	133	133
10	752	376	376	376	0	0	376	376
11	1194	597	597	597	0	0	597	597
12	326	163	163	163	0	0	163	163
13	272	136	136	136	0	0	136	136
14	760	379	381	379	2	0	377	377
15	1200	601	599	601	0	0	601	601

With the demand 50% above the baseline, the bottlenecks would be both main and local DCs, preventing the satisfaction of the demand and turning the problem infeasible. In figure A.10, a graph representing the network design diagram for this scenario in the time period 16 is provided since it is the time period with higher demand, and therefore, where the network is under more pressure. The elements of the graph follow the same structure explained in the baseline scenario.

Varying fixed integration costs

To understand the sensibility of the model when fixed integration costs are varied, the problem was repeatedly solved for different proportions of the fixed integration costs initially considered. In figure 5.3 a plot is available which compares the number of facilities with fixed integration costs. For this, a set of scenarios similar to Experiment 1 was computed, which include no fixed integration costs at all, 1% of the fixed integration costs, 5%, 25%, 50%, 100%, 150%,500%, 1000% and 2000%.

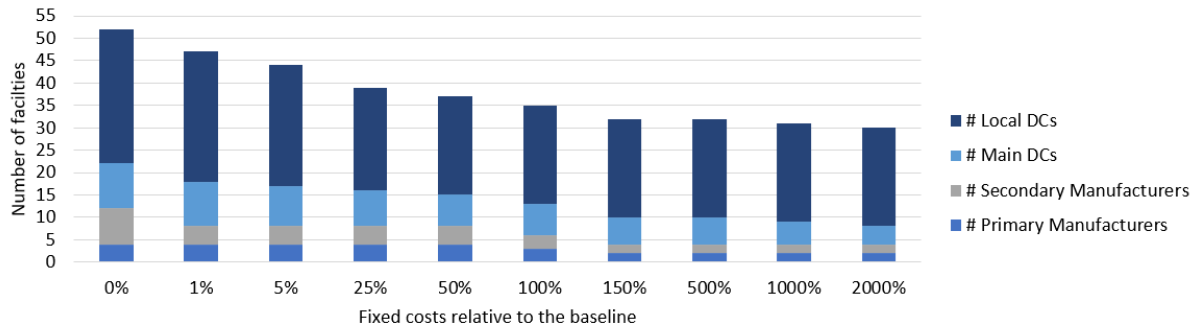

Figure 5.3: Number of facilities when fixed integration costs are varied.

As in Experiment 1, when the fixed integration costs increase, the optimal number of facilities also

gets lower. In the present experiment, 2 products are being supplied through this multi-product network. Given this, the variation of the number of facilities according to the fixed integration costs becomes less relevant. One reason to justify this occurrence is that while the facilities must pay the same fixed cost to integrate the network, more products are being transported, stored and delivered, diluting those costs. For example, when the costs are zero, 52 facilities integrate the network and when the costs are 1% of the original, 47 facilities are still integrating. In the single product studied, instead of 47 facilities, 34 facilities were integrating the network.

Table 5.22: Production and inventory according to the fixed integration costs

	Production F		**Production S**		**Inventory L**	
Coefficient	**API1**	**API2**	**A**	**B**	**C1**	**C2**
0	6908	3454	3454	3454	0	0
1%	6908	3454	3454	3454	0	0
5%	6908	3454	3454	3454	0	0
25%	6908	3454	3454	3454	0	0
50%	6908	3454	3454	3454	4	0
100%	6908	3454	3454	3454	4	0
150%	6908	3454	3454	3454	225	225
500 %	6908	3454	3454	3454	225	225
1000%	6965	3470	3495	3470	1287	225
2000%	6908	3454	3454	3454	2901	361

Table 5.22 details the productions of both products and the inventories under both conditions according to the fixed integration costs. When the fixed costs are lower than 50% of the original fixed costs, there is no need to store products in inventory in any of the facilities. When the fixed costs are lower than 150% of the baseline fixed integration costs, the total inventory of products in all the 16 time periods is only 4 tonnes. This means that when the fixed costs are lower than 50% of the baseline's one, opening more facilities to store products is preferred rather than storing products in inventory. However, when the fixed integration costs are over 150% of the originals, incurring in inventory costs could compensate instead of adding more facilities to the network.

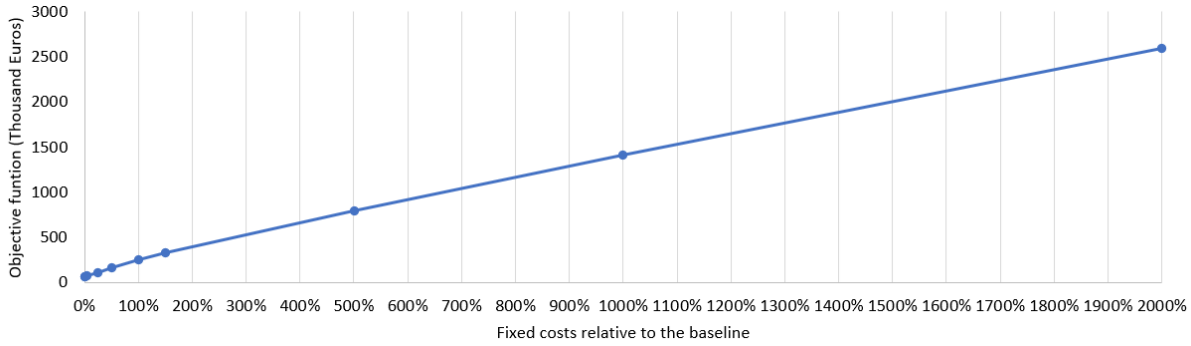

Figure 5.4: Optimal objective function *versus* Different multiples of the fixed integration costs

Figure 5.4 plots the total cost of the network according to the incurred fixed integration costs, and as expected, the fixed integration costs have a big impact on the SC total costs, making the relationship almost linear.

5.4 Conclusion

In this chapter, two experiments were formulated with data-inspired in the publication of Mousazadeh et al. (2015). Experiment 1 was designed to validate the model with existing data from the literature, as well as test the model capabilities under different scenarios by varying the model parameters. Experiment 2 enabled the validation of the proposed features of the model, by adapting the input parameters to match the model specifications. An analysis of the parameters demand and fixed integration costs is proposed to investigate the model sensibility associated with those parameters.

Then, the results of the problem enunciated were obtained by solving the PSC optimisation model proposed in Chapter 4.

To explore the sensitivity of the model, changes in the input parameters demand and fixed integration costs were performed in both experiments to create a set of scenarios that can be analysed.

Regarding the demand parameter, the demand was first reduced to half for all retailers, products and time periods and the optimisation model was applied. Then, the demand parameter was also increased by a factor of 2, in the first experiment, and by 40% in the second experiment. It was found that the proposed optimisation model accomplish its goal since efficient solutions were found in both scenarios. Increases in the demand are normally associated with a smaller increase in costs, which can be possible by optimising the number of facilities integrating the network or recurring to inventory in strategic points of the network. The allocation of facilities in different levels of the supply chain also allows the minimisation of the costs by the facilities supplying and being supplied by other facilities with closer locations.

The model is sensitive to the variations in the demand of the problem since the network design adapts to the different demand scenarios. However, the variations of the demand inside specific temporal horizons do not affect the composition of the network. Since the fixed integration costs are already spent to satisfy the demand in periods of high demand, the facilities are used along the other periods to guarantee resource optimisation. Regarding fixed costs, the model reveals more flexibility to the variations in fixed costs when those are lower. Comparing scenarios with low fixed costs, big variations in the number of facilities composing the network is perceived. Comparing scenarios with higher fixed costs, it can be realised that the variations in the fixed costs have a smaller impact on the design of the network. High fixed costs are related to more compact networks, and the more compact a network is, the more difficult is to reduce even more the number of facilities.

The discussed characteristics are fundamental on a network optimisation tool to an application in an industry like the pharmaceutical. Challenges as cost minimisation, reliability on different scenarios and sensitivity to variations on the demand and the costs are important characteristics to guarantee that pharmaceutical products arrive at the final customer with the maximum quality, in the right quantity and with the necessary flexibility. A network that can provide multiple products flowing through multiple locations and with reduced inventory is very important to guarantee the demand satisfaction in an industry in which the service level must be 100% and the quality of the delivery system must be ensured to guarantee the healthiness of the society.

Chapter 6

Case Study: COVID-19 vaccines

In this chapter, a specific problem regarding the COVID-19 vaccine SC network is addressed. In section 6.1, the case is presented by providing a brief context and detailing the parameters and assumptions performed. In section 6.2, the particular characteristics of the case are defined and a solution approach is proposed to address them. In section 6.3, the case study results are presented and analysed, basing on the model formulated in chapter 4. Is section 6.4, the maximum demand supported by the network is computed. In section 6.5, the main conclusions of the chapter are discussed.

6.1 Case characterisation

Coronavirus Disease-2019 (COVID-19) pandemic has affected millions of people since December 2019. This global crisis carried devastating health, social and economic impacts. COVID-19 is a disease that can cause light to severe symptoms or even death. It has unknown long-term consequences in people of all ages, including in healthy people. (EMA, 2021)

Since the first moments of the pandemic, big pharmaceutical companies raced to devise a product that could cure or prevent the disease. COVID-19 vaccines are medicines that are intended to prevent the disease caused by the novel coronavirus SARS-CoV-2 by triggering an immune response by the human body. The European Commission has authorised several vaccines to prevent COVID-19 in the European Union (EMA, 2021).

In October 2021, four vaccines are available in the European Union to prevent COVID-19: Comirnaty (commercialised by Pfizer/BioNTech), Spikevac (commercialised by Moderna), Vaxzevria (commercialised by AstraZeneca/Oxford), and Janssen (commercialised by Janssen Pharmaceuticals).

Gathering data for a problem of network design for an ongoing situation as the COVID-19 vaccine SC is a complex process. Despite demand data, location of the secondary manufacturers, distribution centres and product characteristics being publicly available, other parameters such as costs and capacities can be very challenging to collect.

Pfizer produces the API for its vaccine in Puurs-Sint-Amands (Belgium). There are 6 secondary manufacturers of the mentioned vaccine, which are located in Puurs-Sint-Amands (Belgium), Saint-Rémy-

Sur-Avre (France), Marburg (Germany), Frankfurt (Germany), Stein (Switzerland) and Kundl (Austria). Since the facility in Belgium acts both as a Primary and Secondary Manufacturer, there will be considered no costs for the transportation between this pair of facilities. Pfizer vaccine storage requires ultra-cold conditions (henceforth designated C1).

Moderna produces the API for its vaccine in Monts (France). Two secondary manufacturers are producing that vaccine, located in Monts (France) and Visp (Switzerland). Since the facility in France acts both as a Primary and Secondary Manufacturer, there will be considered no costs for the transportation between this pair of facilities. Moderna vaccine storage requires ultra-cold conditions (henceforth designated C1).

AstraZeneca produces the API for its vaccine in Leiden (Netherlands). Two secondary manufacturers are producing that vaccine, located in Leiden (Netherlands) and Seneffe (Belgium). Since the facility in the Netherlands acts both as a primary and secondary Manufacturer, there will be considered no costs for the transportation between this pair of facilities. AstraZeneca vaccine storage requires cold conditions (henceforth designated C2).

Janssen produces the API for its vaccine also in Leiden (Netherlands). Two secondary manufacturers are producing that vaccine, located in Leiden (Netherlands) and Dessau-Roßlau (Germany). Janssen vaccine storage requires cold conditions (henceforth designated C2).

The primary manufacturers have sufficient capacity to supply the entire network. The production capacities are defined according to the parcel of vaccines allocated by the European Union and the inventory capacities will be maintained sufficiently high.

Since all the primary and secondary manufacturers are located in Central Europe, and the distances between them are relatively short, the transportation mode considered for the transportation costs is the truck, and the transportation costs will be calculated based on the average freight rate per mile and tonne. The transportation costs for the present case considered an average freight rate per kilometre and tonne of 0.078 €/ (km * tonne), in Europe and 2021, as provided by a freight quote agency. The transportation costs were converted from cost per weight to cost per dose of vaccine at an average of 5 grams per dose. It was also considered that the transportation costs of the APIs are 10 times lower than the transportation costs of the vaccines. Transportation costs between Primary and Secondary Manufacturers and between Secondary Manufacturers and the Main DCs are available in Table B.1. A matrix is available Transportation costs between Main DC and Local DCs and between Local DCs and Retailers are available in Table B.3.

For the present case, an average of € 40 per tonne and per time period was considered as proposed by Mousazadeh et al. (2015). For vaccines stored in cold conditions, € 0.20 per thousand doses and per time period was considered. For vaccines stored in ultra-cold conditions, € 2 per thousand doses and per time period was considered.

To estimate the production capacities, the total doses allocated for Portugal by the European Union was considered. According to the Portuguese Health Ministry, 38 million doses are being distributed to Portugal. It was considered that from those 38 million doses, 40% are of Pfizer vaccine, 20% from Moderna, 20% from AstraZeneca and 20% from Jansen, as initially stated by the Portuguese Health

Ministry. To allocate dose vaccines per time period, 8 time periods were considered during a 2-year time horizon. This means that per time period can be produced 1.9 million doses by Pfizer, 950 thousand doses by Moderna, 950 thousand doses by AstraZeneca and 950 thousand doses by Janssen. For the producing capacity on secondary manufacturers was considered that 600 thousand doses are allocated per time period and per facility for the Portuguese market. It will be considered that each manufacturing facility (either primary or secondary) can store 400 thousand doses per time period in cold conditions and 100 thousand doses per time period in ultra-cold conditions. Due to the difficulty in achieving realistic information about the fixed costs of adapting a secondary manufacturer in Europe to participate in a vaccine SC, the average cost of Mousazadeh et al. (2015) will be adapted to the European market in proportion to the Gross Domestic Products (GDPs) of both regions, according to the World Bank. Therefore, the fixed costs for each secondary manufacturer will be considered 150 thousand Euros.

Due to the urgency of the situation, the Portuguese government streamlined a warehouse in Montemor-o-Velho, near Coimbra, where all conditions required to store pharmaceutical products are satisfied, to serve as Main DC. However, for this case study, other possible locations for the Main DCs will be proposed. The proposed locations are one for each NUTS-2 of the continental territory. Locations in Oporto, Coimbra, Lisbon, Évora and Faro will be considered. To adapt a main DC in Portugal to participate in a vaccine SC, the average cost of Mousazadeh et al. (2015) is adapted to the Portuguese market in proportion to the GDPs of both countries according to the World Bank. Therefore, the fixed costs for each main DC will be considered 28 thousand Euros. It will be assumed that each Main DC has the capacity to handle 8 million doses per time period to guarantee that a single main DC is able to handle all the vaccines in a time period. It will be assumed that the Main DC has the capacity to store four hundred thousand doses per time period in cold conditions and 10 thousand doses ultra-cold per time period in ultra-cold conditions.

For the local DCs let us suppose that one facility as local DC could integrate the network in each Portuguese district to facilitate the delivery of vaccines from the main DC to the retailers. For the present work, it will be assumed that the handling capacity of each one of these facilities is 400 thousand doses per time period and that each one can store up to 10 thousand doses per time period in cold conditions and 1 thousand doses per time period in ultra-cold conditions. Due to the difficulty in achieving realistic information about the fixed costs of adapting a local DC in Portugal to participate in a vaccine SC, the average cost of Mousazadeh et al. (2015) will be adapted to the Portuguese market in proportion to the GDPs of both countries according to the World Bank. Therefore, the fixed costs for each local DC will be considered 10 thousand Euros.

For the present work, it will be considered that each district will be a demand zone, and therefore a retailer. It will also be considered that each district has a Local DC. In Portugal, there are 18 districts plus 2 Autonomous Regions, and therefore, it will be assumed that the distribution network in hands has 20 Local DCs and 20 retailers. The demand was calculated by considering the population in each district and that 85% of the population will be vaccinated. It will be considered that 40% of the population receive Pfizer vaccine, 20% receive Moderna vaccine, 20% receive AstraZeneca and finally, 20% receive Janssen. To allocate the demand per time period, the vaccination phases proposed by the Portuguese

Health Ministry will be considered: 10.8% of the population will receive their vaccine in the first time period, 10.2% in the second time period and 79% in the third time period. It will also be considered that 10.8% of the population will receive a third boost dose on the fourth period. Table B.2, available for consultation in the Appendix of the present document details the demand for each retailer, time period and product. Pfizer vaccine is denoted by Pf, Moderna vaccine by Mo, AstraZeneca vaccine by AZ and Janssen vaccine by Ja.

6.2 Solution approach

In order to perform a network design of the vaccine SC network for the Portuguese market, some particular characteristics will be considered, due to the specificity of the situation.

The huge demand for vaccines at the beginning of the vaccination programme makes it impossible to cover all demand with the installed capacity of the manufacturers. Moreover, despite the vaccination of one individual have a contribute to the immunisation of the population in general, does not have a direct impact on the individual's health, as the vaccine is intended to prevent the disease and not for its cure. For those reasons, it makes sense to allow the demand to delay and accumulate that demand to the next time period. Within the context of this problem, delaying the delivery of one dose of the vaccine for one period is a backorder. The concept of backorder will be considered as a decision variable, and corresponds to the number of units of product p that will not be distributed to the retailer r in the time period t, and, therefore, will be satisfied in the next time period.

B_{prt} := number of units of product p demanded, but undelivered in retailer r, in the time period t

The constraint in equation 6.1 will substitute the equation 4.1 to consider the existence of backorders in the model formulated in chapter 4. This constraint guarantees that the flow from all local DCs to each retailer is higher than the demand of that retailer, plus the backorders accumulated from the previous time period, and minus the backorders that will be satisfied in the following time period.

$$\sum_{l} \Psi^{\delta}_{plrt} \geq d_{prt} + B_{prt-1} - B_{prt} \quad \forall \ p, r, t \tag{6.1}$$

To guarantee that at the end of the time horizon, all retailers will end with their demand satisfied, the equation 6.2 must also be added to the model constraints. Notice that NTP is the number of time periods (and therefore, this constraint applies only for the last period of time).

$$B_{prt} = 0 \quad , \quad t = \#\text{NTP} \quad , \quad \forall \ p, r \tag{6.2}$$

On one hand, the demand for vaccines will happen entirely at the beginning of the vaccination campaign, and therefore, the concept of having backorders will become relevant. On the other hand, the desire of the decision-makers might be the satisfaction of a greater portion of the demand as soon as possible, even if it comes with a more expensive distribution network. For that reason, it is important

to explore a multi-objective approach, using both minimisation of costs and minimisation of backorders. The second objective function, which aims to minimise the total number of backorders in the network as the sum of the backorders for all the retailers, all the products, and all the time periods is defined in Equation 6.3.

$$\text{minimise} \quad w = \sum_{t} \sum_{r} \sum_{p} B_{prt} \tag{6.3}$$

To propose a solution for this multi-objective model, the ϵ-constraint method was chosen to find an approximation of the Pareto Front. The ϵ-constraint characterise the Pareto front which shows the set of solutions beyond which it is impossible to improve one of the objective functions without jeopardising the other one. Solutions in the Pareto front are non-dominated solutions since they cannot be improved in both objective functions simultaneously. Outside the Pareto front, solutions are said to be dominated, since it is possible to improve them in both objective functions simultaneously. Figure 6.1 shows an illustrative example of those concepts. The blue line represents the Pareto front, being E1, E3 and E3 efficient solutions. The green point A represents a solution that does not exist and is impossible to achieve. The orange point B represents an inefficient solution, whose both objective functions can be improved.

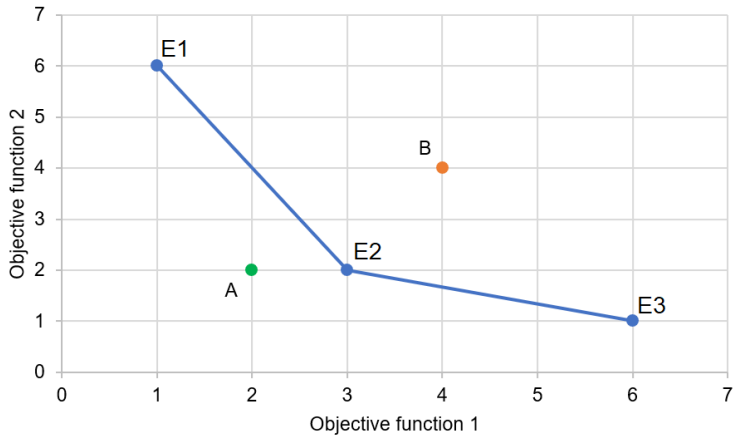

Figure 6.1: Illustrative example of a Pareto front

To apply a ϵ-constraint method to this problem, the following approach will be performed.

Part A

This part is intended to define the research boundaries, by finding the two extreme points (E1 and E3 in figure 6.1) of the Pareto front, and then, to perform its optimisation.

1. Solve the problem for the cost minimisation objective function (Equation 4.23).
2. Solve the problem for the backorders minimisation objective function (Equation 6.3).

3. Solve the cost minimisation problem subjected to a constraint that guarantees that the maximum number of backorders is the one found in 2., as formulated in Equation 6.4.

4. Solve the backorder minimisation problem subjected to a constraint that guarantees that the maximum cost is the one found in 1., as formulated in Equation 6.5.

$$\begin{aligned} & minimise \quad \text{Equation 4.23} \\ \text{s.t.} \quad & \text{Equation 6.3} \quad \leq \quad w^* \\ & \text{Equations 4.1 to 4.22} \end{aligned} \tag{6.4}$$

$$\begin{aligned} & minimise \quad \text{Equation 6.3} \\ \text{s.t.} \quad & \text{Equation 4.23} \quad \leq \quad z^* \\ & \text{Equations 4.1 to 4.22} \end{aligned} \tag{6.5}$$

Part B

In part B, the main purpose is to obtain a better resolution of the objective function, by determining non-extreme points of the Pareto front (as E2 in Figure 6.1). This is possible by dividing the linear space between the two extreme points in equidistantly vertical lines (with distance ϵ), and then determining the ordinate of the point by adding the ϵ-constraint. ϵ-constraint, in equation 6.6, is a constraint that should be added to the model and allows the optimisation of one objective function by defining the other objective function as a constraint and limiting its value accordingly.

$$\text{Equation 4.23} < z^* + \epsilon \tag{6.6}$$

With,

$z^* :=$ SC cost of the optimal solution found for the first objective function

$\epsilon :=$ step, or vertical distance between the equidistantly horizontal lines mentioned above

6.3 Results analysis

In this section, the COVID-19 vaccine SC case study will be computed using the model formulated in Chapter 4 with the adaption proposed in section 6.2. The case under study consists of a five-level PSC, with 4 products and 8 time periods. Those 4 products are produced in 12 possible dedicated secondary manufacturers, with 4 types of API which are produced in 4 dedicated primary manufacturers. Then, the product is carried to 5 possible main DCs. From the main DC the product is carried to 20 possible local DCs and therefore transported to the 20 retailers. The problem was solved through the ϵ-constraint method, following the procedure described in section 6.2. An ϵ equal to multiples of 2966 was considered in the ϵ-constraint to allow the exploration of 10 different optimal solutions.

The backorders and the total costs of each optimal solution are detailed for each optimal solution in table 6.2. The number of secondary manufacturers (Sec. Man.), main DCs and local DCs, and what

facilities will integrate the SC network are detailed in Table 6.2 and mapped in . Figure 6.2 plots the curve of the Pareto front defined by the set of optimal solutions which result from the multi-objective problem.

Table 6.1: Backorders and total cost for each optimal solution.

Solution	Backorders	Total cost
1	5493	1855707
2	8249	1393670
3	11005	1232674
4	13761	1062468
5	16517	1041569
6	19273	1031113
7	22029	871235
8	24785	870684
9	27541	860916
10	30297	859014

Table 6.2: Number of facilities and facilities for each optimal solution.

Solution	# Sec. Man.	Sec. Man. IDs	# Main DC IDs	Main DC	# Local DC	Local DC IDs
1	10	1,2,4,5, 7 to 12	20	All	20	All
2	8	1,2,5, 7 to 11	1	2	15	1 to 10, 13 to 16, 20
3	7	1,2,5, 7, 9, 10 11	1	2	14	1 to 10, 13 to 16
4	6	1,2,5,7,9,11	1	2	12	1 to 5, 7 to 10,13,15,20
5	6	1,2,5,7,9,11	1	2	10	1 to 5, 7 to 10,13
6	6	1,2,5,7,9,11	1	2	9	1 to 5,7,8,9,10
7	5	1,2,7,9,11	1	2	8	1,2,4,5,7,8,9,10
8	5	1,2,7,9,11	1	2	8	1,2,4,5,7,8,9,10
9	5	1,2,7,9,11	1	2	7	1,2,4,5,8,9,10
10	5	1,2,7,9,11	1	2	6	1,2,5,7,8,9

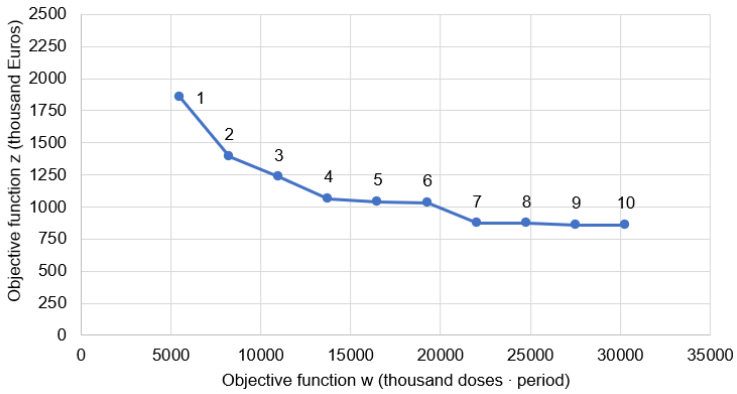

Figure 6.2: Pareto front of the COVID-19 vaccines case study

In figures B.4, B.5 and B.6, graphs representing the different solutions of network design for this problem are provided. The diagrams chosen encompass the third time period, for being the time period

with higher demand, and therefore, where the network is more complex. Due to the complexity of representing four products in the same network, in this graph, only the network design is shown, and the flows corresponding to each edge are hidden.

Solution 1 corresponds to the case in which the minimal number of backorders is achieved. Due to the excess of demand in the first periods, it is not possible to fulfil all the demand without delays even if all facilities integrate the network, and therefore, 5493 thousand backorders still exist. For this case, a total SC cost of approximately 1.86 million Euros is achieved. To achieve this scenario, 4 of the secondary manufacturers that can produce Pfizer vaccines must integrate the network (1, 2, 4 and 5), one secondary manufacturer that produces Moderna does not integrate the network and all facilities that can produce the other vaccines must open (7 to 12). All main DCs and all local DCs must also integrate the network.

Solutions 2 to 9 corresponds solutions in which a trade-off between backorders and costs must be considered.

From solution 1 to solution 2, the backorders increase 50%, and the costs decrease 25% with the closure of 2 secondary manufacturers (one of Pfizer and one of Johnson do not integrate the network), four main DCs (only Coimbra main DC remains in the network) and 5 local DCs are also out of the network (Funchal, Ponta Delgada, Beja, Guarda and Bragança do not integrate the network). It is interesting to notice that Funchal and Ponta Delgada have low connectivity to the remaining districts since those are located in islands, serving only their own markets; supply products from there to the other districts would carry high transportation costs. The other local DCs that close serve markets with few demand and have other local DCs fairly close (Évora and Faro for Beja, Castelo-Branco and Viseu for Guarda, and Vila Real for Bragança).

From solution 2 to solution 3, the number of backorders increases 33%, while the costs reduce 12% with the closure of one secondary manufacturer producing the AstraZeneca vaccine. The unique main DCs continues Coimbra. The local DC in Portalegre also do not integrate the network.

From solution 3 to solution 4, the number of backorders increases 25% and the costs reduced 14%. To achieve this, the local DCs located in Faro, Vila Real and Castelo Branco also do not integrate the network, but the local DC located in Portalegre reintegrate the network.

From solution 4 to solution 5, the levels of secondary manufacturers and the main DCs do not suffer any changes. Nevertheless, the local DCs located in Castelo Branco and Portalegre join the group of local DCs that will not integrate the network. This event start to cause a lack of supply in the interior regions, which can be confirmed by an increase of 20% in the number of doses in backorder, but only a decrease of 2% in the costs.

From solution 5 to solution 6, the local DC located in Viana do Castelo joins the group of local DCs that will not integrate the network, causing an increase of 17% in the number of backorders and a decrease of 1% in the costs.

From solution 6 to solution 7, the secondary manufacturer number 5, which produced the Pfizer vaccine join the group of secondary manufacturers which will not integrate the network. Notice that in this solution, the minimum number of secondary manufacturers is achieved. The local DC located

in Setúbal joins the group of facilities that will not participate in the network. These events cause an increase of 14% in the number of backorders, but a decrease of 16% in the costs. Indeed, increasing the number of backorders from 19273 to 22029 is the only time that the relative decrease in costs is higher than the relative increase in backorders. In solution 8, the model found the same network as in solution 7; the 5% difference in the costs leads to 12.5% in the number of backorders because only inventory optimisations are performed between these two solutions.

From solution 8 to solution 9, the local DC located in Leiria also does not integrate the network, leading to an increase of 11% in the number of backorders and to a decrease of 1.2% in the costs. From solution 9 to solution 10, the number of backorders decreases 10%, but the variation in the costs is almost imperceptible, 0.22%.

Analysing those observations along with the Pareto front that resulted from the present problem, it can be realised that the gradient of the curve is higher when the number of backorders is lower. Actually, between solution 4 and solution 6, the difference in costs is almost unnoticeable, but the number of delayed doses of vaccines administrated is 33% lower. If the decision was between these two options, choosing the option of having 16517 thousand backorders would be recommended. The same occurrence happens after solution 8. Between solution 7 and solution 10 the difference in costs is negligible, but a difference of 38% in the number of backorders is accounted for.

Figure 6.3 plots the inventory usage per storage conditions for the 10 optimal solutions computed (S1 to S10).

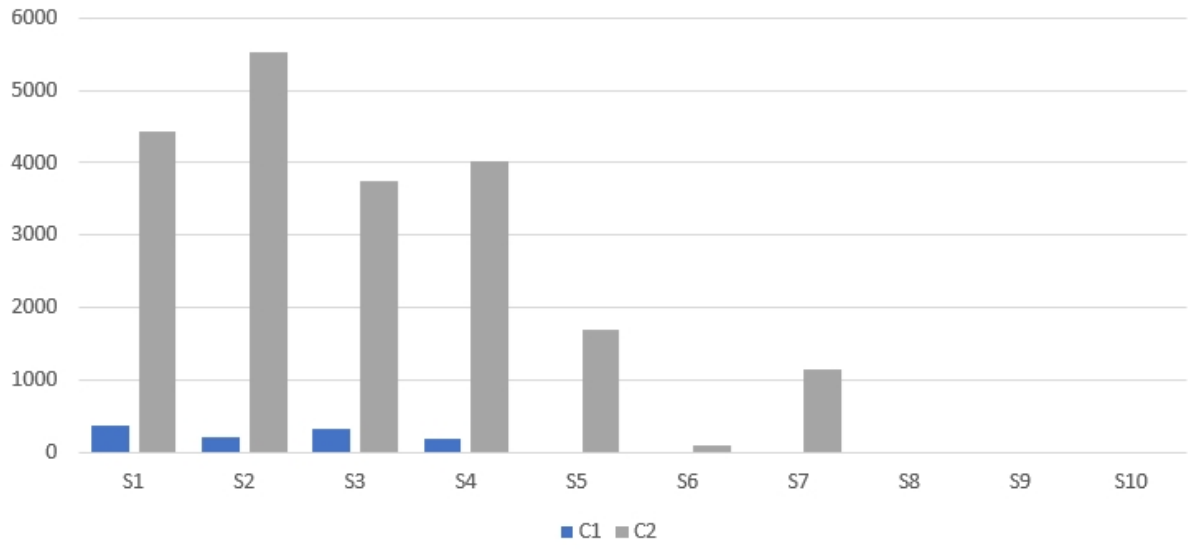

Figure 6.3: Inventory usage per storage condition

By analysing the plot, it can be realised that when required, the products which are preferably stored are the products that are stored under condition C2, due to the storage cost, which is 10 times minor in this storage condition. Also, it can be depicted that in the solutions with a more limited number of backorders, the inventory is more often used than in solutions in which the main concern becomes cost minimisation. The inventory utilisation is higher in solutions 1 to 4. Also, after solution 4, inventory under condition C1 is no more used, and after solution 7, inventory under condition C2 also ceases to be used.

Tables 6.3 to 6.9 exhibit the results of the model per time period for the different solutions of the resolution method adopted. Due to space limitations and the existence of similar solutions, solutions 5, 8 and 9 are not included. In those tables the results of the model regarding production in primary and secondary manufacturers, inventory in primary manufacturers, secondary manufacturers, main DCs and local DCs, the demand and the number of backorders (in thousand of doses) are presented per time period.

Table 6.3: Outputs: Solution 1

Time period	Prod. F	Prod. S	Inv. F	Inv. S	Inv. M	Inv. L	Demand	Backorders
1	3233	3233	0	924	400	0	1909	0
2	3756	3406	350	1712	1186	220	1612	0
3	4532	4882	0	0	0	0	12501	4501
4	4457	4457	0	0	0	0	948 (+4501)	992
5	992	992	0	0	0	0	0 (+992)	0
6	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0

In solution 1, a concentration of the productions in the first four periods, following the demand profile, is perceived. This is justified because the facilities open have sufficient capacity to fulfil the demand, leaving a reduced number of backorders in comparison to the other solutions. In the first 2 periods, the demand is below the production capacity, justifying the inventory built up to anticipate the peak demand in the third period.

Table 6.4: Outputs: Solution 2

Time period	Prod. F	Prod. S	Inv. F	Inv. S	Inv. M	Inv. L	Demand	Backorders
1	3133	2783	350	844	0	30	1909	0
2	3489	3459	380	2146	410	165	1612	0
3	4300	4582	98	1283	0	20	12501	6501
4	4300	4398	0	0	0	0	948 (+6501)	1748
5	1748	1748	0	0	0	0	0 (+1748)	0
6	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0

In solution 2, the large reduction in the number of facilities when compared to solution 1, makes the model suggest the use of more inventory in the first periods. Also, the number of products being stored increased from 4792 thousand vaccines to 5726 thousand vaccines.

Table 6.5: Outputs: Solution 3

Time period	Prod. F	Prod. S	Inv. F	Inv. S	Inv. M	Inv. L	Demand	Backorders
1	2725	2725	0	762	0	54	1909	0
2	3247	3193	54	1833	410	154	1612	0
3	3950	4004	0	746	0	55	12501	6901
4	3950	3950	0	0	0	0	948 (+6901)	3098
5	2295	2295	0	0	0	0	0 (+3098)	803
6	600	600	0	0	0	0	0 (+803)	203
7	203	203	0	0	0	0	0 (+203)	0
8	0	0	0	0	0	0	0	0

In solution 3, the higher number of backorders allowed the SC to save costs on inventories. With one less secondary manufacturers and one less local DC, the manufacturing facilities will need to produce also in periods 5 and 6 to guarantee that all the doses accumulated in backorders will arrive at the retailers.

Table 6.6: Outputs: Solution 4

Time period	Prod. F	Prod. S	Inv. F	Inv. S	Inv. M	Inv. L	Demand	Backorders
1	2705	2705	0	786	0	10	1909	0
2	3123	3123	0	1765	410	132	1612	0
3	3600	3600	0	1047	0	60	12501	7701
4	3600	3600	0	0	0	0	948 (+7701)	3942
5	2283	2283	0	0	0	0	0 (+3942)	1659
6	1200	1200	0	0	0	0	0 (+1659)	459
7	459	459	0	0	0	0	0 (+459)	0
8	0	0	0	0	0	0	0	0

According to solution 4, the primary manufacturers no more needs to store APIs in inventory. The higher number of backorders allowed the number of facilities and inventories to decrease even more. In constraint, the production in manufacturing facilities goes on until time period 6 to satisfy the pending demand that did not receive its vaccine yet.

Table 6.7: Outputs: Solution 6

Time period	Prod. F	Prod. S	Inv. F	Inv. S	Inv. M	Inv. L	Demand	Backorders
1	1909	1909	0	0	0	0	1909	0
2	1710	1710	0	0	98	0	1612	0
3	3502	3502	0	0	0	0	12501	8901
4	3600	3600	0	0	0	0	948 (+8901)	6249
5	3287	3287	0	0	0	0	0 (+6249)	2962
6	1801	1801	0	0	0	0	0 (+2962)	1161
7	1161	1161	0	0	0	0	0 (+1161)	0
8	0	0	0	0	0	0	0	0

In solution 6, 19273 backorders are allowed, which is even higher than the demand. This means that it is allowed to delay more than one unit of demand for one period. In this situation, the inventory is only

98 thousand doses in the main DC. Since having backorders carries any cost, the model is now trying to save costs by reducing inventories the much as possible.

Table 6.8: Outputs: Solution 7

Time period	Prod. F	Prod. S	Inv. F	Inv. S	Inv. M	Inv. L	Demand	Backorders
1	2006	2006	0	87	0	10	1909	0
2	2336	2336	0	518	273	30	1612	0
3	2588	2588	0	209	0	0	12501	9301
4	3000	3000	0	9	0	0	948 (+9301)	7049
5	3000	3000	0	0	0	0	0 (+7049)	4040
6	2401	2401	0	0	0	0	0 (+4040)	1639
7	1639	1639	0	0	0	0	0 (+1639)	0
8	0	0	0	0	0	0	0	0

In solution 7 the inventory is used to allow the reduction of one more secondary manufacturer and one local DC without delaying the demand in the first 2 time periods. In this scenario, the network is becoming too compact and backorders until the time period 6 are necessary. It can be noticed that in the time period where the network is only supplying backorders, the inventory is equal to zero. This happens since there is no cost to have a backorder in the cost minimisation function, but an inventory cost exists.

Table 6.9: Outputs: Solution 10

Time period	Prod. F	Prod. S	Inv. F	Inv. S	Inv. M	Inv. L	Demand	Backorders
1	1909	1909	0	0	0	0	1909	0
2	1612	1612	0	0	0	0	1612	0
3	2400	2400	0	0	0	0	12501	10101
4	2400	2400	0	0	0	0	948 (+10101)	8649
5	2400	2400	0	0	0	0	0 (+8649)	6249
6	2400	2400	0	0	0	0	0 (+6249)	3849
7	2400	2400	0	0	0	0	0 (+3849)	1449
8	1449	1449	0	0	0	0	0 (+1449)	0

In solution 10, the minimal costs of the network are achieved. In this situation, the production happens in all time periods leading to an accumulated value of backorders of 32097. The inventory is also totally avoided since it carries extra costs and the network is the most compact as possible, with only 5 secondary manufacturers open, 1 main DC and 6 local DC. This causes the maximum production in a time period to be 2400 thousand doses, limited by the handling capacity of the local DCs. In this scenario, the administration of each dose of the vaccine will suffer a delay of 0.79 time periods.

6.4 Maximum demand

To calculate the maximum demand, instead of considering the element d_{prt} in equation 4.1 a model parameter, it will be considered as a decision variable. To obtain the maximum demand that the entire

network can support, a sub-problem with the objective function expressed in Equation 6.7 will be solved as an intermediate step.

$$\text{maximise Demand} = \sum_{p} \sum_{r} \sum_{t} d_{prt} \tag{6.7}$$

The main objective of this analysis is to enable the search for the bottlenecks of the proposed network. A bottleneck is an agent or a set of agents that limit the flow of products along the network considered.

Solving the problem for this objective function, a total demand of 38 million doses that can be supplied to retailers is obtained. This result confirms that the bottleneck of this network locates in the primary manufacturer since the entire capacity of all these facilities is achieved. It also guarantees the integrity of all the constraints of the used model, since the flows and mass balances through all the levels of the SC are correctly defined, and, therefore, all the products produces at the primary manufacturers arrive at the retailers.

6.5 Conclusion

In this chapter, an application of the proposed model to a case study regarding the current worldwide issue of optimising the COVID-19 vaccine SC network was performed.

The problem, in particular, addressed the distribution of vaccines from the big pharmaceutical manufacturers located in Central Europe to the Portuguese districts. The four vaccines approved in Europe were considered as the four products, which are produced by dedicated primary and secondary manufacturers located in France, Belgium, Netherlands, Germany, Switzerland and Austria. Before reaching the retailer (or demand zone), the vaccines must pass on one of the main DCs (located in Porto, Coimbra, Lisbon, Évora and Faro) and on one of the local DCs (located in each Portuguese district). To produce each one of those products, one API is required, and its storage must be under two different storage conditions. The demand is the population electable for vaccination in Portugal and it is distributed by the 18 districts and 2 autonomous regions accordingly. The demand is also distributed along the 8 time periods of one quarter each following the 3-phases vaccination campaign approved by the Portuguese government.

The objective of the case study is to determine how much and what facilities (secondary manufacturers, main DCs and local DCs) should pay integration and modification costs to be able to integrate the COVID-19 vaccine SC network. Due to the lack of information publicly available regarding production capacities of the primary and secondary manufacturers, handling capacities of the main and local DCs, inventory capacities of the facilities and respective costs, some assumptions and adaptations from the existing literature had to be performed. Nevertheless, is expected that this limitation does not affect the overall results of the model.

The issue contemplates the allowance of backorders which is the possibility of delaying the delivery of doses of vaccines to the retailer. To solve the problem, a reformulation of the model proposed in

chapter 4 is proposed to enable the analysis of the trade-off between backorder minimisation and cost minimisation. The problem is formulated as multi-objective MILP, and the ϵ-constraint method is used to obtain an approximation of the Pareto front which contain the set of efficient solutions.

It is found that while minimising backorders allow the population to be vaccinated earlier, more facilities must integrate the network to satisfy all the demand in time. This carries extra costs which the decision-maker may not consider investing. Also, the reduction in the number of facilities is many times balanced by the increase in inventory in the remaining facilities. In solutions that are biased for cost minimisation, the vaccination campaign tends to get delayed to the last periods, and, therefore, the manufacturing facilities must be allocated more time to the production of COVID-19 vaccines. In any solution it is possible to satisfy all the demand in the pretended time period, meaning that backorders are always necessary. This occurs since all the demand is placed at the beginning of the temporal horizon. With any decision taken based on the results proposed, it is guaranteed that an efficient solution is used. Nevertheless, solutions 5, 6, 8, 9 and 10 do not represent a great advantage regarding cost minimisation but represent a great disadvantage regarding the number of backorders, when compared to solutions 1, 2, 3, 4 and 7.

Chapter 7

Conclusion

The pharmaceutical industry generates a big impact on society, enabling the treatment of diseases and increasing people's life expectancy and quality of life. The increase in average life expectancy caused an aged population with more needs for pharmaceutical products. At the same time, society has become health-conscious and customer expectation has enlarged. Pharmaceutical companies are being constantly challenged by risks that can have consequences in the quantity and quality of supply of medicines and their delivery to the customers at the right time. The pharmaceutical industry is facing turbulent and volatile markets and disruptions. Another challenge of the sector is the undergoing shift of paradigm from a cost-centred vision to a patient-centred vision.

A state-of-art review was performed concerning PSC network optimisation models. It returned that some algorithms to support network design in this industry are already developed, but a limited number of publications considers agility as a critical characteristic that the SC should have. A second literature review, about methodologies to obtain agile SCs, was performed, in which any model considering agile PSC was encountered. Several approaches to include agility in SCs were reviewed, where flexibility, responsiveness, process integration and customer enrichment were identified as building blocks. Changing environments force manufacturers to develop agile SC capabilities to remain competitive. Flexibility and agility are required to respond in real-time to market needs.

The study of models to enable the optimisation of the PSC network design become a pertinent academic interest. Those models should be capable of taking advantage of the environmental changes and should adapt to varying demands, costs and expectations. In this thesis, a model to optimise the PSC network is formulated and proposed. The proposed mathematical model considers a five-level PSC with storage under multiple storage conditions in all manufacturing facilities and distribution centres. A multiple storage condition inventory is an important characteristic of the PSC due to the strict conservation policies that pharmaceutical products are subjected, to guarantee that they arrive with quality to the final customer. Also, all facilities are assumed to have specific capacities. In manufacturing facilities (primary and secondary manufacturers), production capacities limit the number of products produced. In manufacturing facilities, handling capacities limit the number of products flowing through that facilities. Inventory capacities are considered in both manufacturing facilities and distribution centres

and limit the number of products stored. The proposed model considers a multi-API and multi-product network, in which, the conversion of API to product is performed in the secondary manufacturers as common in the pharmaceutical industry.

The objective of the proposed model is to minimise the total costs. Those costs are divided into three categories, fixed costs, transportation costs and storage costs. Fixed costs include the expenses that the facilities must have to order to integrate a flexible pharmaceutical network, encompassing process integration investments, partnership costs, technological investment, information technologies, and adjustments to the infrastructure itself; transportation costs are the unit costs of transportation a product between two facilities; finally, storage costs are the costs that a facility will incur to store a unit of product for one time-period. The decisions considered encompass decisions at the strategic level, specifically the number and location of facilities, distribution, inventory positioning and production.

To test and validate the model, two experiments based on the empirical examples proposed by Mousazadeh et al. (2015): a single-API and single-product experiment, and a multi-API and multi-product experiment. To explore the sensitivity of the model, changes in the parameters of the model were performed, namely on the demand and on fixed integration costs to create a set of scenarios that are analysed.

The computational experiments performed revealed that the model is sensitive to the variations in the demand of the problem since the network adjusts to the different demand scenarios. The model is also sensitive to the fluctuation of fixed costs. More flexibility is encountered when fixed costs are lower than when they are higher: with lower fixed costs, the number of facilities participating in the network is higher. A higher variation in the number of facilities when comparing scenarios with lower fixed costs is also observed. The proposed model addressed challenges as cost minimisation, reliability on different scenarios and sensitivity to variations on the demand and on the costs, which are important characteristics to guarantee that pharmaceutical products arrive at the final customer with the maximum quality, in the right quantity and with the necessary flexibility.

Finally, an application of the model to a COVID-19 vaccine distribution SC is performed. The case study consists in determining the optimal secondary manufacturers, main DCs and local DCs to integrate the network of vaccine distribution. The manufacturing facilities considered are located in Central Europe and the markets considered are the districts and autonomous regions of Portugal for a temporal horizon of two years. In this problem, backorders are allowed and the minimisation of backorders becomes a second objective. To solve it, the problem was reformulated as a multi-objective MILPs, to study the trade-off between backorder minimisation and cost minimisation. It is found that while minimising backorders allow the population to be vaccinated sooner, more facilities must integrate the network to satisfy all the demand in time, carrying extra costs to the SC. In the solutions that tend for cost minimisation, the vaccination campaign gets delayed.

Using an optimisation model as the proposed one to perform the PSC network design allows the determination of an optimum number and location of facilities, having into account inventories, productions and distribution flows. Connecting the analysis performed to the results with the agility research performed, it is possible to understand that exists a trade-off between costs as agility. In the compu-

tational experiment performed, lower costs enabled higher variations in the network design. For this reason, when designing an agile PSC, attention must be paid to the fixed costs considered. Trying to model an agile PSC considering facility construction costs or expensive technological investments as fixed costs can limit the agility of the network. To model an agile PSC, working over a pool of facilities already existing and considering only integration or adaptation costs might reveal a good path. Another recommendation is to consider the use of multi-objective approaches to compare cost-minimisation with other indicators that consider customer satisfaction. The objective of minimising the delays of delivering vaccine doses is a benefit to the patient, revealing itself also a good driver for agility: regarding the set of solutions of the multi-objective problem analysed, solutions more restrictive about the delay of delivering vaccine doses also seems to allow more flexible networks. This reinforces that a cost-oriented vision pushes a SC away from the agility.

As a future research proposal, including demand uncertainty in the optimisation model parameters should be considered. The PSC is very susceptible to market volatility, even more under an ongoing paradigm shift. Other sources of uncertainty should also be listed and analysed so that the network optimisation models for the PSCs can become more reliable and the closest possible to reality.

Other topic for future work is the development of heuristic methods to address SC network design problems, since when large scale problems are considered, the computational time required to solve them may become unreasonable. Some authors in the literature had already studied the implementation of heuristic methods in SC network design problem. However, it is a fruitful research area because of its complexity.

Finally, including additional particularities of the PSC that are gaining importance in the modern world, as product perishability and customisation can be integrated in the SC optimisation models. Considering other characteristics of SC networks as direct shipment and different transportation means could reveal fruitful, specially if other objectives as environmental impacts or lead-times are analysed.

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Appendix A

Computational Experiments

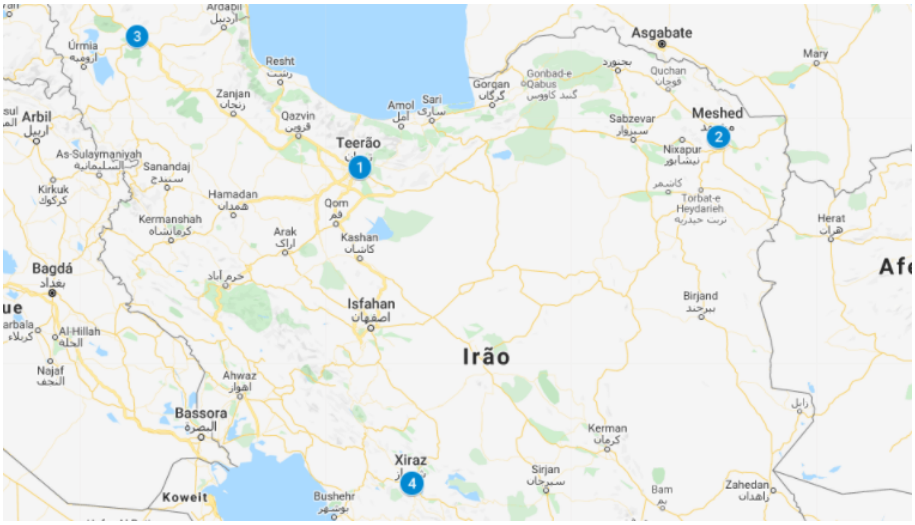

Figure A.1: Map of primary manufacturers in Iran

Figure A.2: Map of secondary manufacturers in Iran

Figure A.3: Map of main DCs in Iran

Table A.1: Demand in each retailer

Retailer ID	Year 1	Year 2	Year 3	Year 4
1	40	40	41	42
2	33	34	34	34
3	14	14	14	14
4	52	53	54	54
5	6	6	7	7
6	11	12	12	12
7	130	131	133	135
8	10	10	10	10
9	8	8	8	8
10	64	65	66	67
11	10	10	10	10
12	49	49	50	50
13	11	11	12	12
14	7	7	7	7
15	27	28	28	28
16	49	50	51	51
17	13	13	14	14
18	13	13	13	13
19	16	17	17	17
20	32	32	32	33
21	21	21	22	22
22	7	8	8	8
23	19	20	20	20
24	27	27	27	28
25	19	19	20	20
26	33	34	34	34
27	15	16	16	16
28	17	17	18	18
29	19	19	20	20
30	12	12	12	12
31	18	18	19	19

Figure A.4: Map of retailers and local DCs in Iran

Table A.2: Parameters associated to Local DCs

Local DC ID	Storage Cap. (ton)	Handling Cap. (ton)	Fixed cost (€)	Inv. Cost (€/ton)
1	40	40	3840	42.5
2	40	40	2176	40
3	40	40	2048	40
4	40	40	2176	42.5
5	40	40	1920	40
6	40	40	2048	40
7	40	40	2048	75
8	40	40	2176	37.5
9	40	40	1920	37.5
10	40	40	2048	40
11	40	40	3840	37.5
12	40	40	2176	37.5
13	40	40	2048	37.5
14	40	40	2176	40
15	40	40	1920	37.5
16	40	40	2048	42.5
17	40	40	2048	40
18	40	40	2176	40
19	40	40	1920	37.5
20	40	40	2048	37.5
21	40	40	3840	37.5
22	40	40	2176	37.5
23	40	40	2048	40
24	40	40	2176	40
25	40	40	1920	37.5
26	40	40	2048	37.5
27	40	40	2048	37.5
28	40	40	2176	37.5
29	40	40	1920	37.5
30	40	40	2048	37.5
31	40	40	3840	40

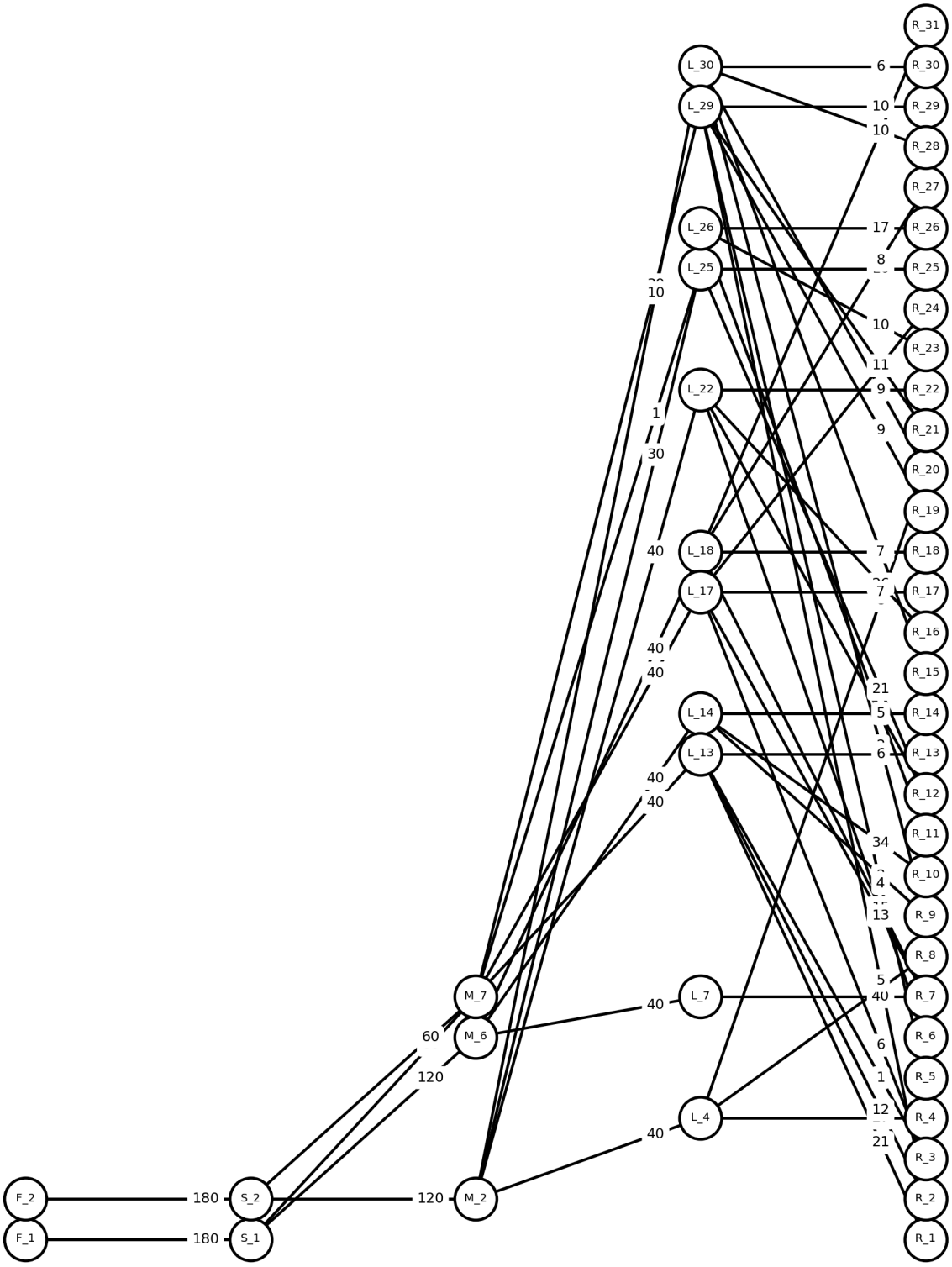

Figure A.5: Network diagram: Experiment 1 (baseline)

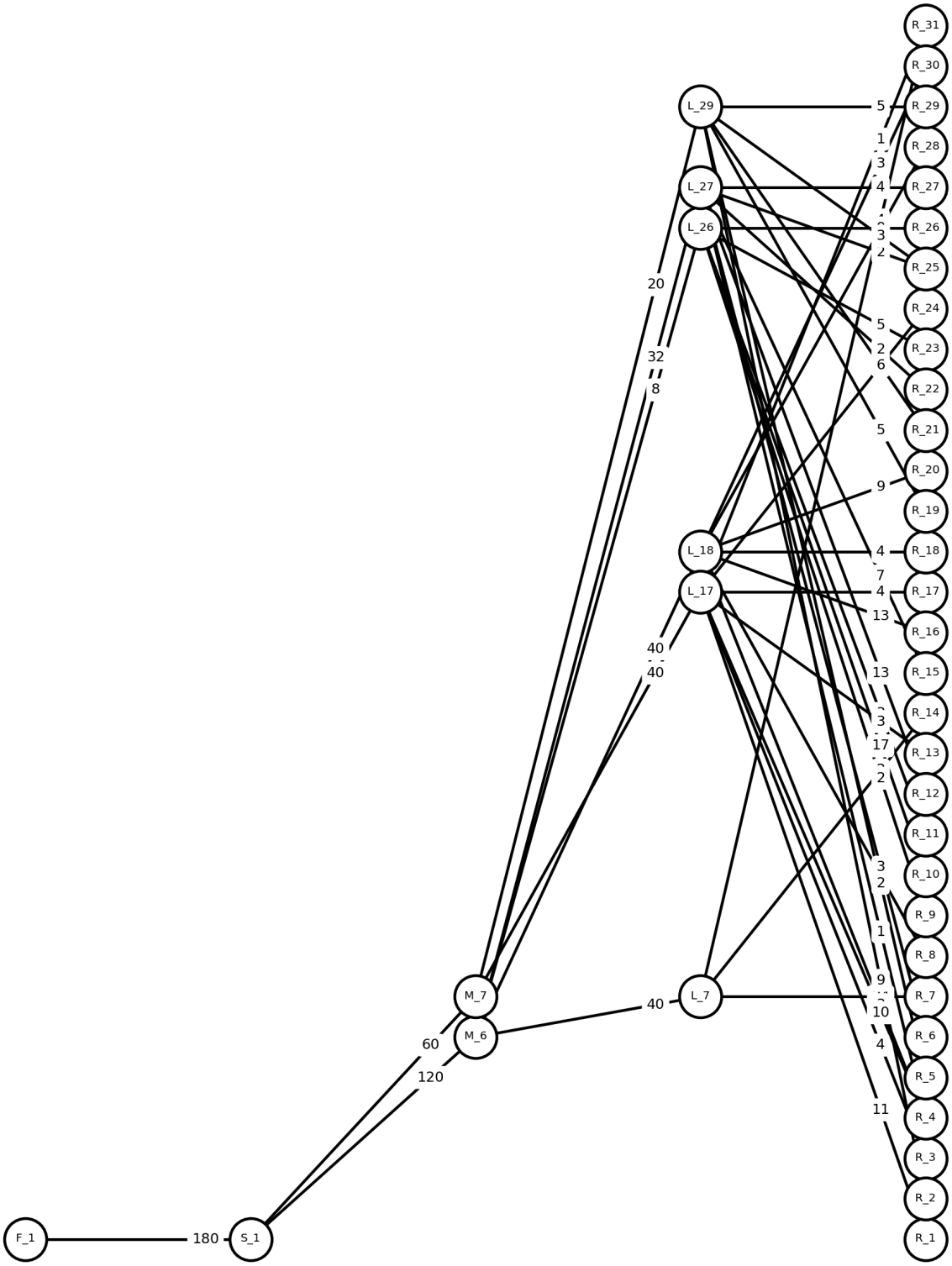

Figure A.6: Network diagram: Experiment 1 (half demand)

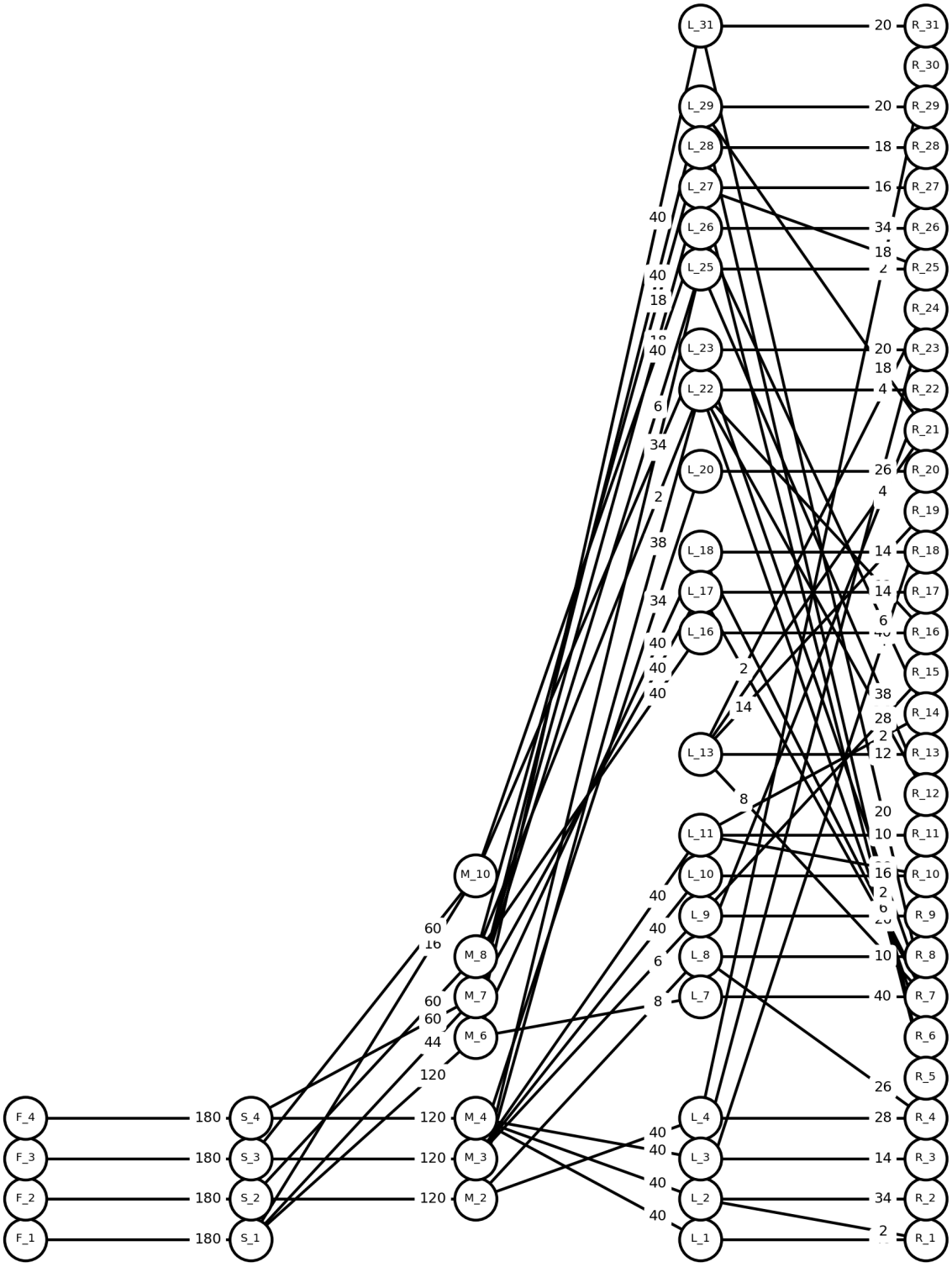

Figure A.7: Network diagram: Experiment 1 (double demand)

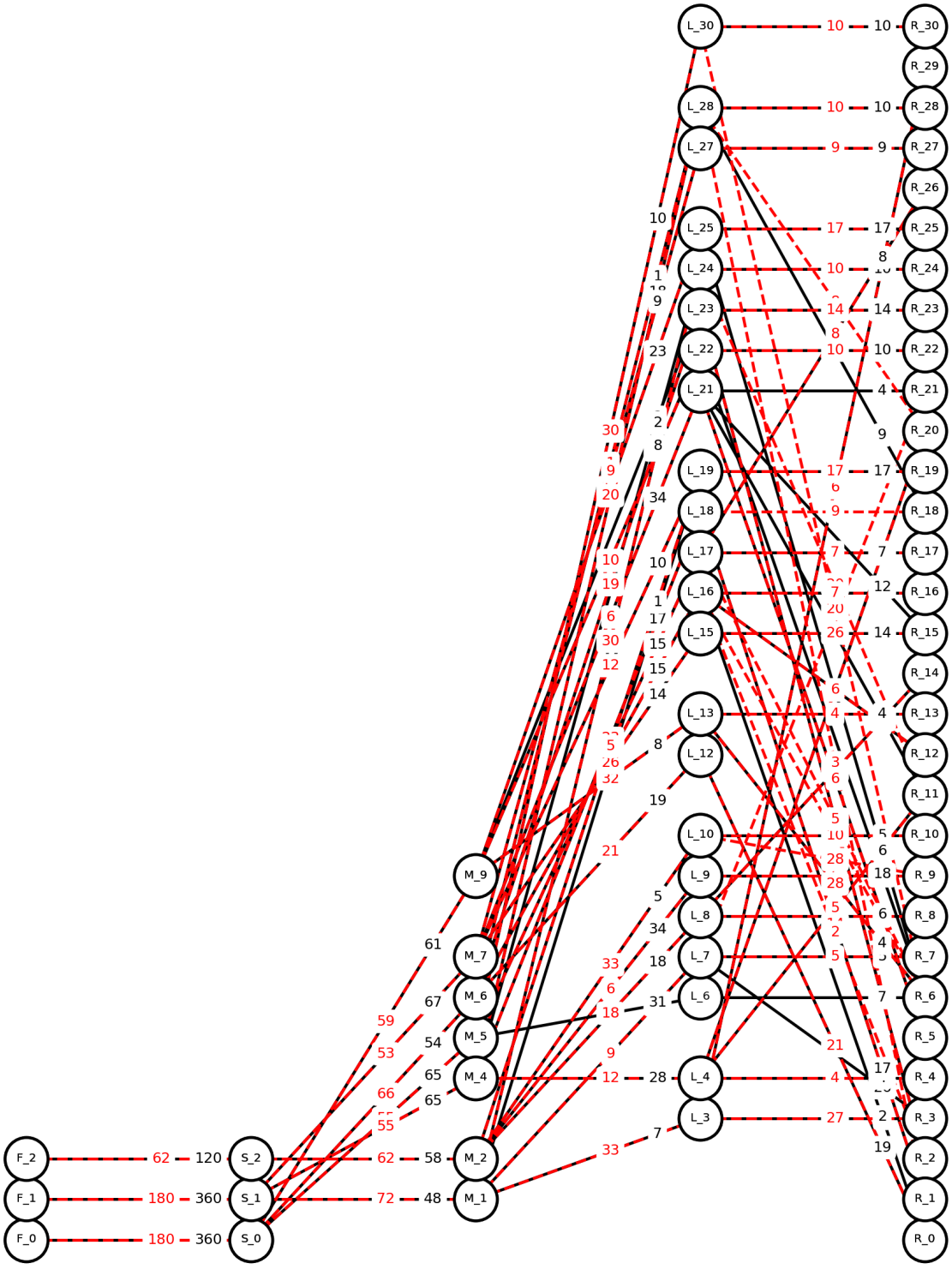

Figure A.8: Network diagram: Experiment 2

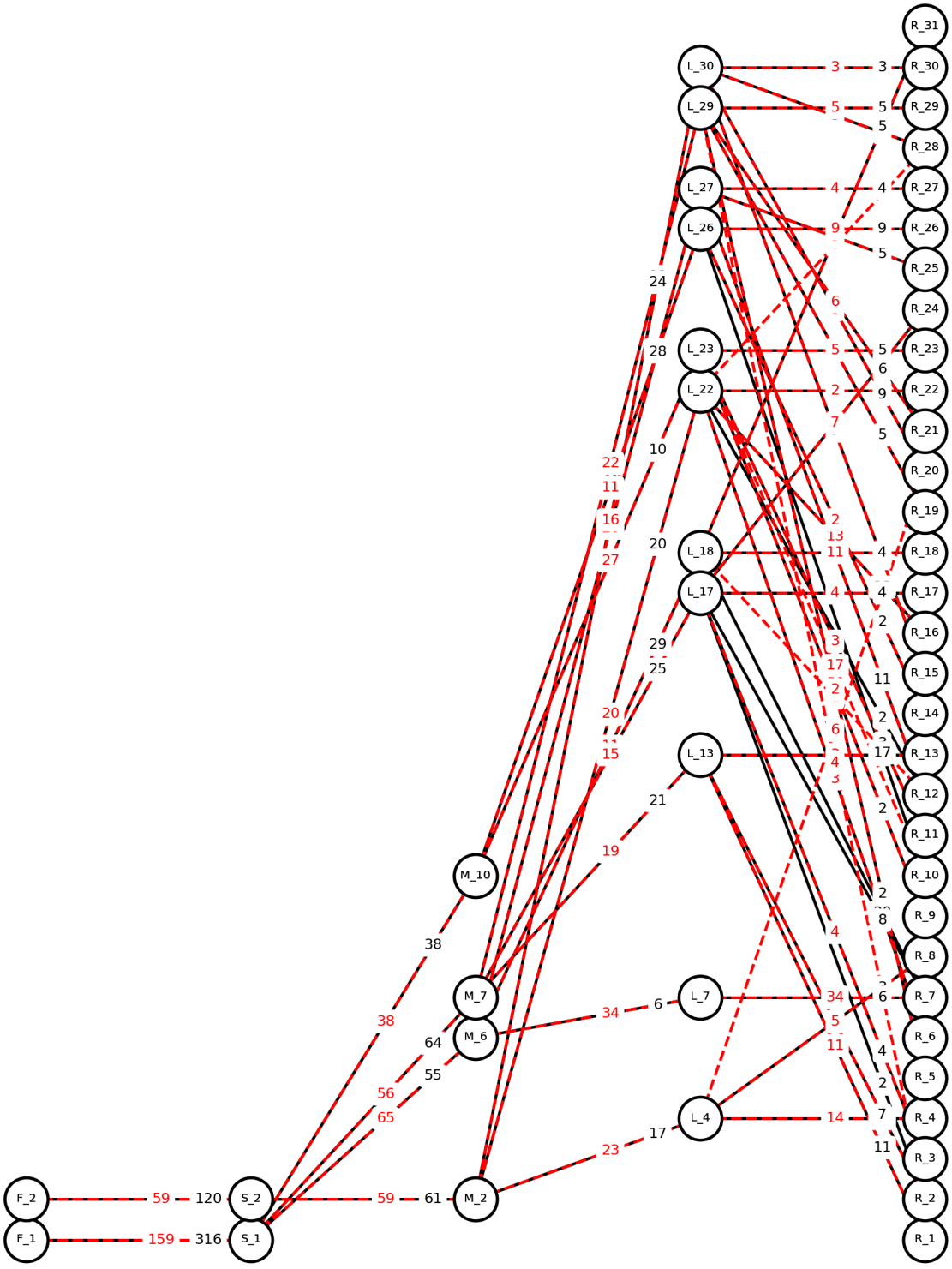

Figure A.9: Network diagram: Experiment 2 (half demand)

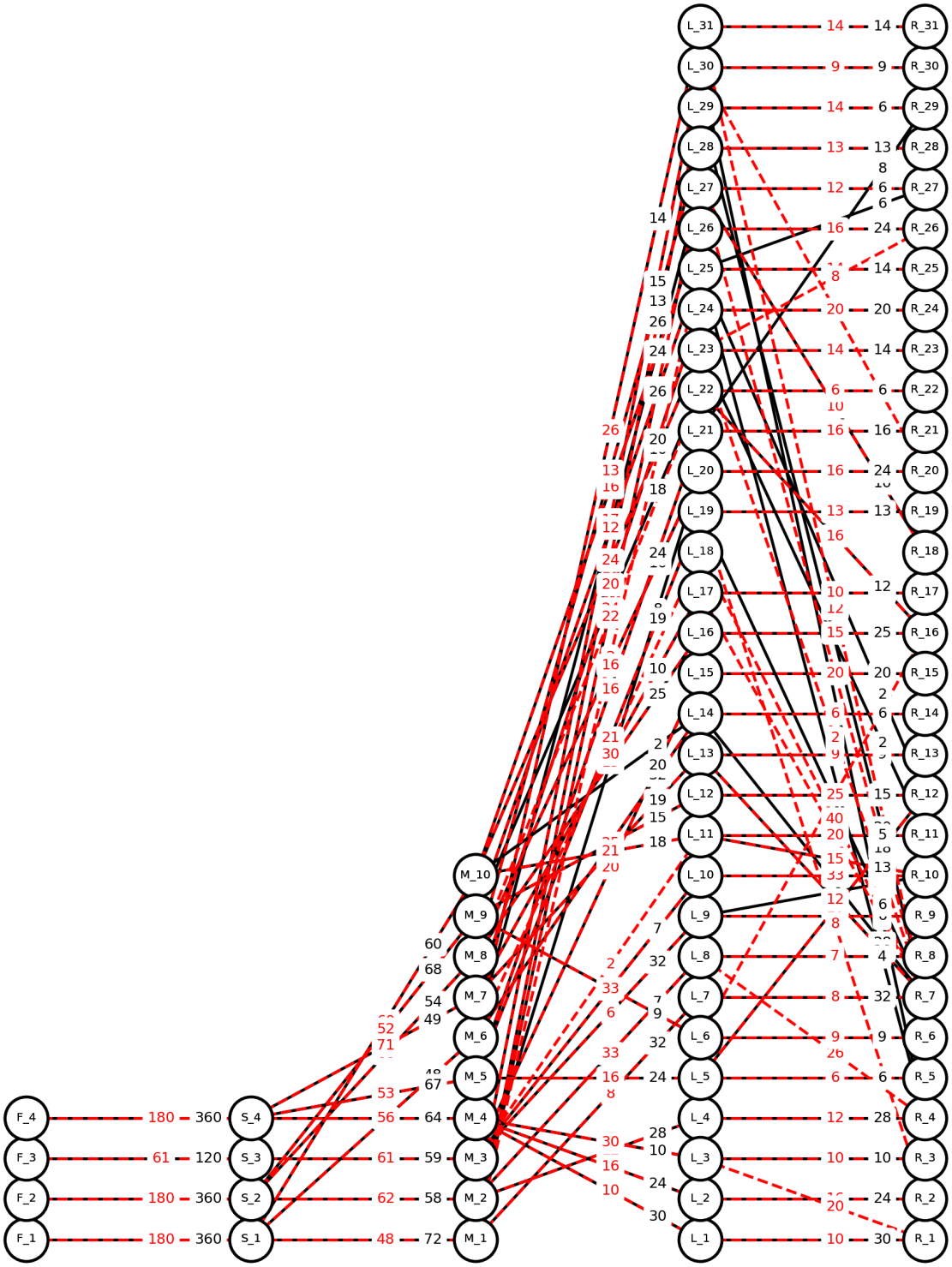

Figure A.10: Network diagram: Experiment 2 (double demand)

Appendix B

Case Study: COVID-19 vaccines

Figure B.1: Map of primary manufacturers: vaccine case study

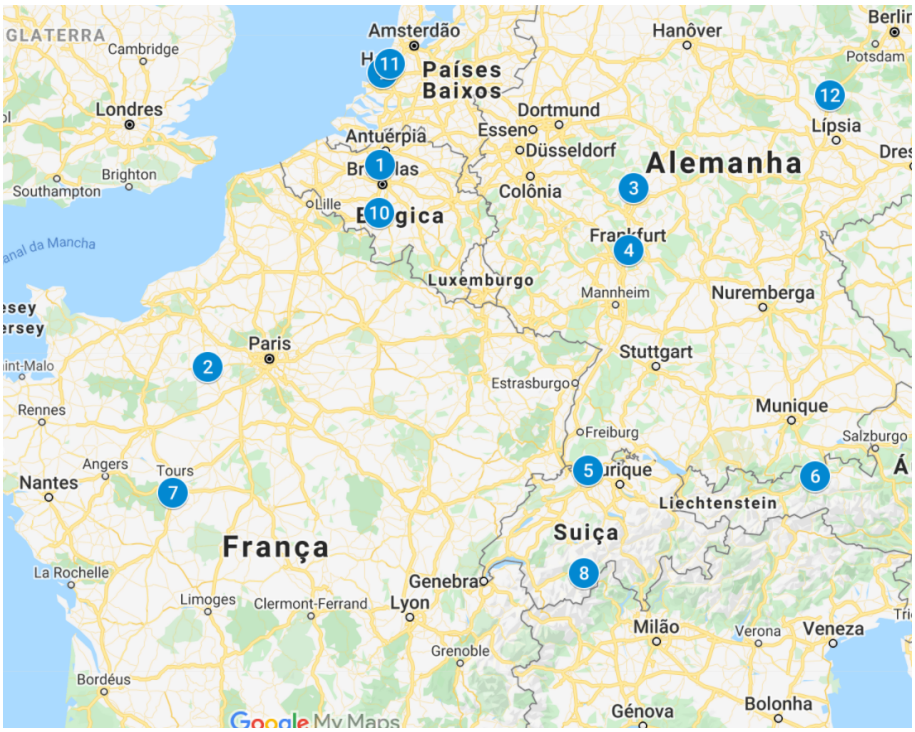

Figure B.2: Map of secondary manufacturers: vaccine case study

Table B.1: Transportation costs between primary manufacturers and secondary manufacturers and secondary manufacturers and main DCs

	Primary Manufacturers				Main DC				
	Puurs	**Monts**	**Leiden (AZ)**	**Leiden (J)**	**Porto**	**Coimbra**	**Lisboa**	**Évora**	**Faro**
Puurs	0.000	0.232	0.058	0.064	0.753	0.752	0.812	0.783	0.886
Saint-Remy	0.194	0.105	0.219	0.226	0.625	0.567	0.685	0.656	0.758
Marburg	0.170	0.099	0.177	0.217	0.883	0.883	0.943	0.914	1.016
Frankfurt	0.166	0.329	0.180	0.178	0.850	0.850	0.910	0.880	0.983
Stein	0.250	0.287	0.303	0.310	0.745	0.744	0.804	0.775	0.877
Kundl	0.349	0.438	0.375	0.373	0.909	0.896	0.969	0.939	1.042
Monts	0.232	0.000	0.286	0.288	0.525	0.524	0.585	0.555	0.658
Visp	0.311	0.304	0.364	0.371	0.749	0.747	0.809	0.779	0.882
Leiden (AZ)	0.058	0.283	0.000	0.006	0.809	0.804	0.869	0.839	0.942
Seneffe	0.028	0.204	0.085	0.093	0.727	0.725	0.786	0.757	0.859
Leiden (Jo)	0.064	0.288	0.006	0.000	0.810	0.809	0.869	0.840	0.942
Dessau	0.262	0.493	0.244	0.243	1.014	1.015	1.074	1.044	1.147

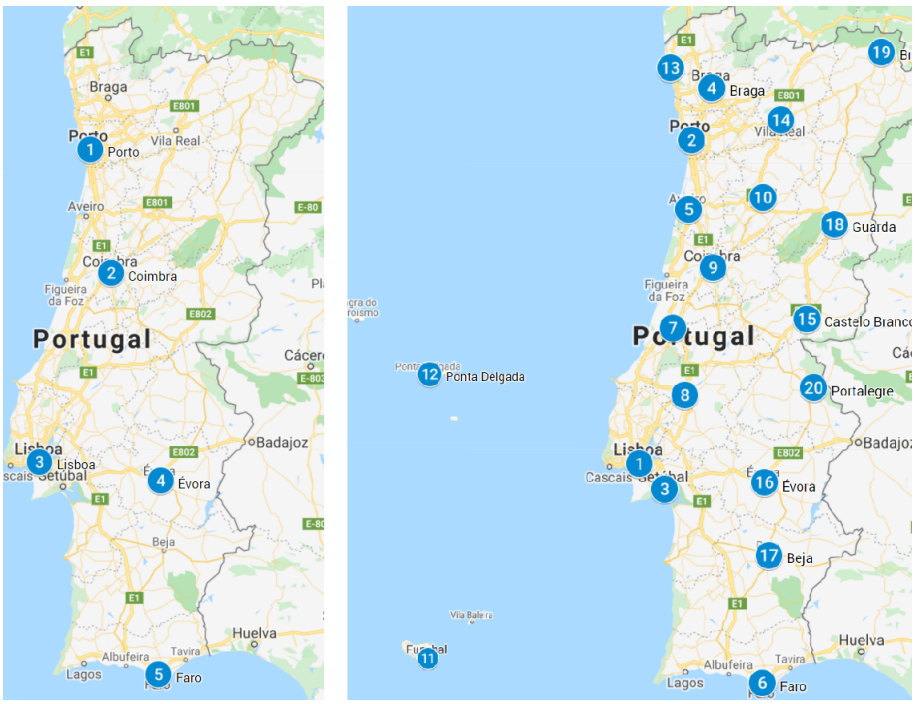

Figure B.3: Map of main DCs: vaccine case study

Table B.2: Demand of vaccines in doses, per product, retailer and time-period.

	1st time-period				2nd time-period				3rd time-period				4th time-period			
Retailer (ID)	**Pf**	**Mo**	**AZ**	**Ja**	**Pf**	**Mo**	**AZ**	**Ja**	**Pf**	**Mo**	**AZ**	**Ja**	**Pf**	**Mo**	**AZ**	**Ja**
Lisbon (1)	250696	83565	83565	0	158334	79167	79167	39584	1221937	610968	610968	305484	146239	62674	0	0
Oporto (2)	196831	65610	65610	0	124314	62157	62157	31079	959391	479696	479696	239848	114818	49208	0	0
Setúbal (3)	96469	32156	32156	0	60928	30464	30464	15232	470206	235103	235103	117551	56274	24117	0	0
Braga (4)	93258	31086	31086	0	58900	29450	29450	14725	454558	227279	227279	113639	54401	23315	0	0
Aveiro (5)	77224	25741	25741	0	48773	24386	24386	12193	376401	188200	188200	94100	45047	19306	0	0
Faro (6)	51503	17168	17168	0	32528	16264	16264	8132	251034	125517	125517	62758	30043	12876	0	0
Leiria (7)	50532	16844	16844	0	31914	15957	15957	7979	246299	123150	123150	61575	29477	12633	0	0
Santarém (8)	46868	15623	15623	0	29602	14801	14801	7400	228446	114223	114223	57112	27340	11717	0	0
Coimbra (9)	45018	15006	15006	0	28432	14216	14216	7108	219425	109712	109712	54856	26261	11255	0	0
Viseu (10)	38734	12911	12911	0	24463	12232	12232	6116	188796	94398	94398	47199	22595	9683	0	0
Madeira (11)	27659	9220	9220	0	17469	8734	8734	4367	134813	67406	67406	33703	16134	6915	0	0
Azores (12)	26072	8691	8691	0	16466	8233	8233	4117	127079	63540	63540	31770	15209	6518	0	0
Viana do C. (13)	25502	8501	8501	0	16106	8053	8053	4027	124303	62152	62152	31076	14876	6376	0	0
Vila Real (14)	20478	6826	6826	0	12934	6467	6467	3233	99812	49906	49906	24953	11946	5120	0	0
Castelo B. (15)	19600	6533	6533	0	12379	6190	6190	3095	95534	47767	47767	23884	11433	4900	0	0
Évora (16)	16794	5598	5598	0	10606	5303	5303	2652	81854	40927	40927	20464	9797	4199	0	0
Beja (17)	15910	5303	5303	0	10048	5024	5024	2512	77545	38772	38772	19386	9281	3977	0	0
Guarda (18)	15756	5252	5252	0	9951	4976	4976	2488	76798	38399	38399	19199	9191	3939	0	0
Bragança (19)	13532	4511	4511	0	8546	4273	4273	2137	65958	32979	32979	16490	7894	3383	0	0
Portalegre (20)	11567	3856	3856	0	7305	3652	3652	1826	56377	28188	28188	14094	6747	2892	0	0

Table B.3: Transportation costs between main DCs and local DCs, and local DCs and retailers

	Lisboa (1)	Porto (2)	Setúbal (3)	Braga (4)	Aveiro (5)	Faro (6)	Leiria (7)	Santarém (8)	Coimbra (9)	Viseu (10)	Funchal (11)	Ponta Delgada (12)	Viana do Castelo (13)	Vila Real (14)	Castelo Branco (15)	Évora (16)	Beja (17)	Guarda (18)	Bragança (19)
Porto	0.124																		
Setúbal	0.020	0.136																	
Braga	0.144	0.022	0.157																
Aveiro	0.100	0.029	0.114	0.049															
Faro	0.109	0.215	0.096	0.235	0.192														
Leiria	0.058	0.071	0.071	0.091	0.049	0.150													
Santarém	0.032	0.097	0.046	0.116	0.073	0.120	0.031												
Coimbra	0.081	0.046	0.094	0.066	0.024	0.173	0.029	0.054											
Viseu	0.114	0.050	0.128	0.070	0.033	0.206	0.063	0.092	0.036										
Funchal	0.382	0.469	0.401	0.491	0.482	0.490	0.438	0.413	0.462	0.496									
Ponta D.	0.567	0.592	0.586	0.613	0.621	0.676	0.624	0.599	0.638	0.642	0.949								
Viana do C.	0.152	0.029	0.165	0.024	0.057	0.244	0.099	0.126	0.075	0.079	0.499	0.622							
Vila Real	0.156	0.037	0.169	0.041	0.062	0.242	0.104	0.122	0.071	0.036	0.507	0.629	0.063						
Castelo B.	0.089	0.100	0.102	0.120	0.078	0.181	0.064	0.062	0.055	0.067	0.469	0.655	0.129	0.103					
Évora	0.052	0.158	0.039	0.178	0.135	0.089	0.092	0.063	0.115	0.149	0.434	0.619	0.186	0.191	0.077				
Beja	0.069	0.175	0.056	0.195	0.153	0.058	0.110	0.080	0.133	0.167	0.451	0.636	0.204	0.202	0.107	0.031			
Guarda	0.126	0.078	0.139	0.099	0.063	0.218	0.102	0.097	0.060	0.030	0.507	0.670	0.107	0.066	0.039	0.113	0.145		
Bragança	0.201	0.081	0.214	0.085	0.106	0.292	0.148	0.165	0.111	0.078	0.550	0.672	0.107	0.648	0.107	0.181	0.212	0.069	
Portalegre	0.089	0.115	0.076	0.135	0.092	0.145	0.067	0.064	0.068	0.105	0.471	0.656	0.148	0.139	0.038	0.040	0.071	0.072	0.142

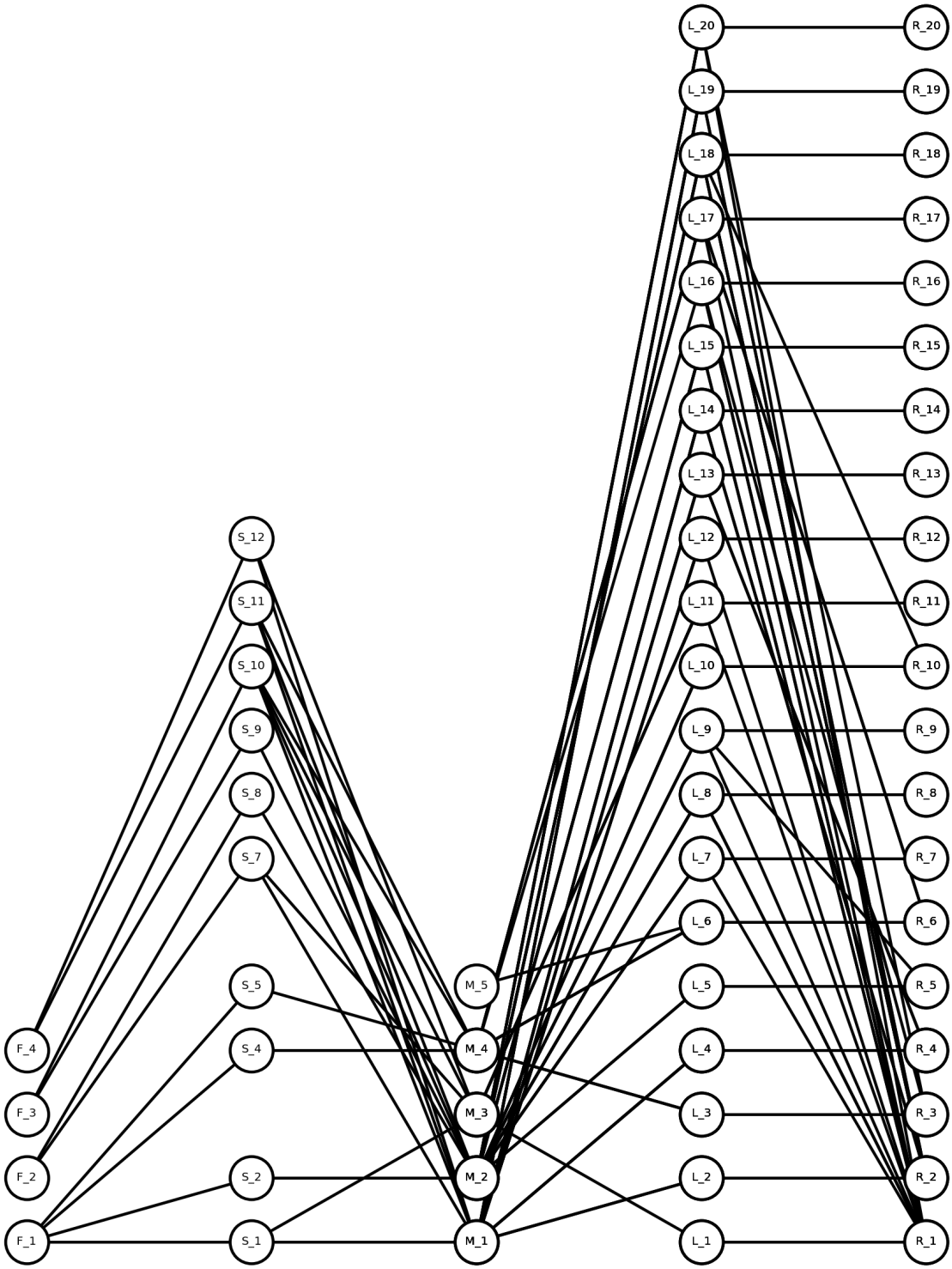

Figure B.4: Network diagram: Solution 1

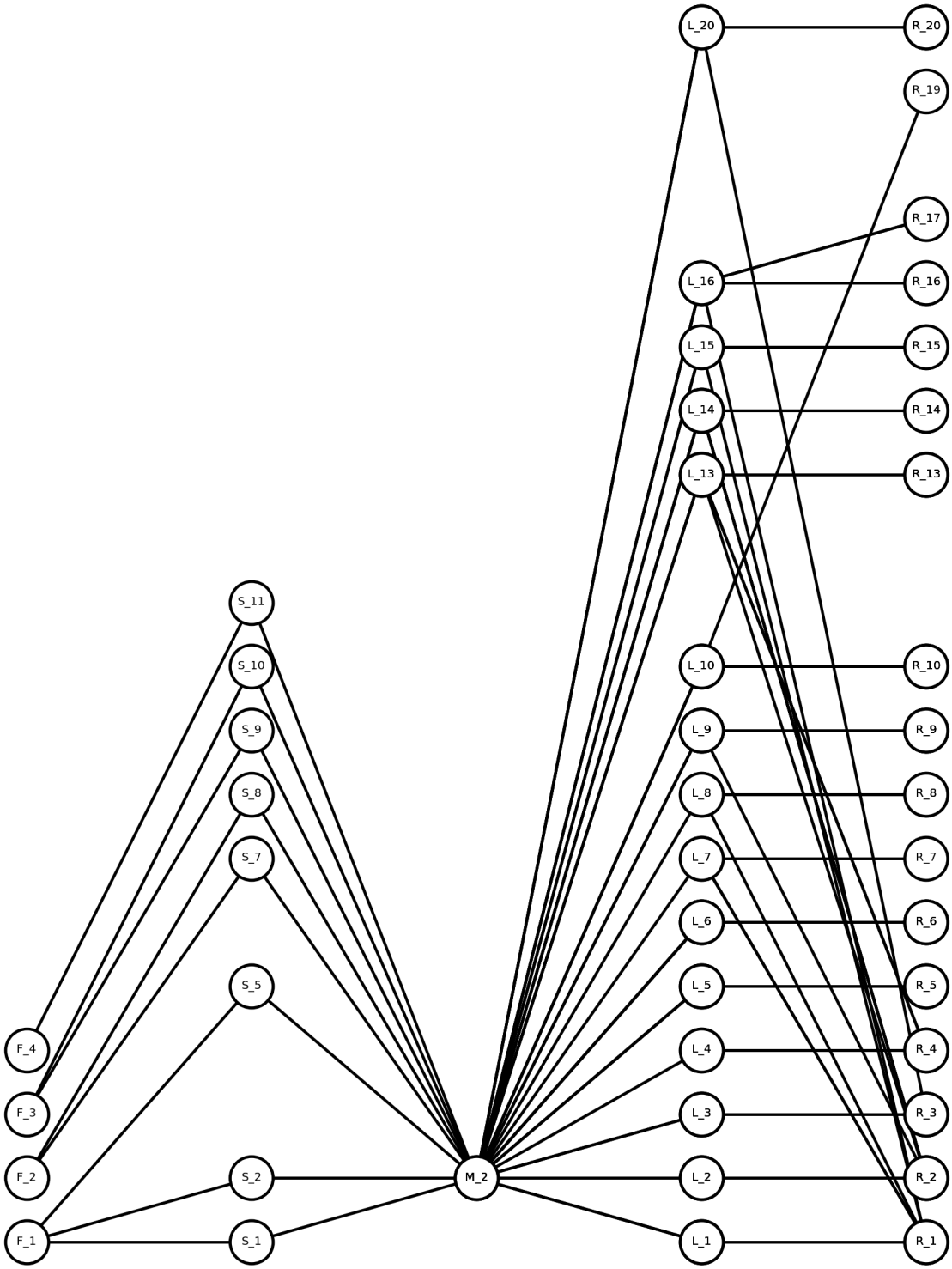

Figure B.5: Network diagram: Solution 2

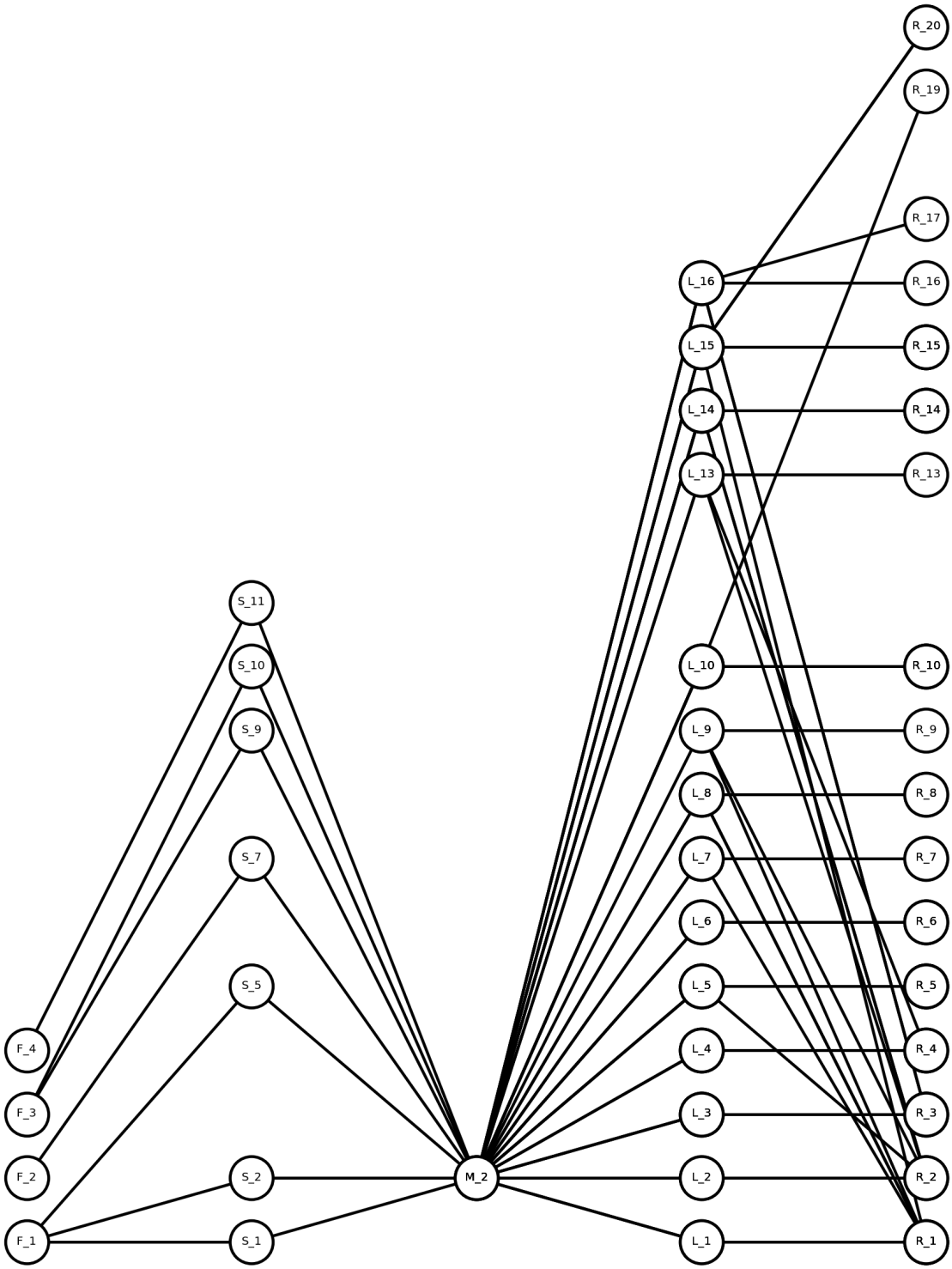

Figure B.6: Network diagram: Solution 3