TÉCNICO LISBOA

Pharmaceutical Industry Supply Chains

Planning Vaccines' Distribution

Inês Ralheta Duarte

Thesis to obtain the Master of Science Degree in

Biomedical Engineering

Supervisor(s): Prof. Bruna Alexandra Elias Mota

Prof. Ana Paula Ferreira Dias Barbosa-Póvoa

Examination Committee

Chairperson: Prof. Mónica Duarte Correia de Oliveira

Supervisor: Prof. Bruna Alexandra Elias Mota

Member of the committee: Prof. Catarina Moreira Marques

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 the Universidade de Lisboa.

Preface

The work presented in this thesis was performed at Instituto Superior Técnico (Lisbon, Portugal), during the period March-October 2021, under the supervision of Prof. Ana Póvoa and Prof. Bruna Mota.

Acknowledgments

To my siblings, thank you for always believing in me, for helping me reaching my goals. To my brother, thank you for being so kind to me, for always asking if you can help with anything, and for making jokes about everything. To my twin sister, a special thanks for always being there for me, for being so funny, even hilarious, and, of course, for giving me the best feeling of being an aunt. To my parents, thank you for allowing me to pursue my dreams despite any difficulty in reaching them.

I would like to express my deepest appreciation to Professor Ana Póvoa and Professor Bruna Mota. Thank you for all your guidance and advice, for challenging me, for allowing me to learn from your knowledge and always help me when needed.

To my university friends, thank you for the paddle sessions and dinners after long days of work. I cannot begin to express my thanks to my friends Catarina, Bia, Mariana and Rita, thank you for being the best friends I could ever ask, we made this journey together and I am so thankful for all the good memories we have. I have no doubt that a lot more good moments are yet to come. To all my “thesis buddies”, thank you for being such a good company during the last few months at Técnico. Coffee breaks and lunch times under the sun were an essential part of our days, which, together with a lot of laughing, allowed this journey to feel lighter and more enthusiastic.

To my friend Laura, the one who lives in my new favourite place on hearth, Açores, thank you for your friendship during these years. Thank you for making me laugh, no matter how distant you always seemed close. You truly deserve the best in life.

Finally, to my friends from childhood, thank you for always showing that you are proud of me, for the love and care. Thank you for making me feel capable of facing any struggles and difficulties of the past five years. Joana, my best friend, thank you for everything.

The authors acknowledge the support provided by FCT and PORTUGAL2020 under the project PTDC/EGE-OGE/28071/2017 and project PTDC/EME-SIS/6019/2020.

Abstract

Pharmaceutical supply chains (PSCs) tend to be complex, and its management faces several challenges. Together with high levels of uncertainty and the need to consider sustainability principles, have greatly increased the complexity of network's management in this sector. Addressing equity in access has proven to be a critical concern in PSCs, particularly when dealing with vaccines' distribution, thus being important to consider availability and affordability when designing and planning a vaccine' supply chain (SC).

A decision-support tool is presented following the work developed by (Mota et al., 2018), where a MOMILP model is proposed, aiming to integrate strategical-tactical decisions while considering the three pillars of sustainability. Economic assessment is performed through the Net Present Value. Environmental impact assessment follows the Life Cycle Analysis methodology. Accessibility of pharmaceutical products is the major focus for social assessment, aiming to provide an equal distribution by making products available and affordable among countries. Thus, social evaluation is made through a DALY-based metric. Beyond maximization of equity in access, a social constraint is suggested so as to respect a satisficing level of equity (Cardoso et al., 2015).

The model is applied to a case-study aiming to discuss different optimization scenarios and study trade-offs among the three pillars of sustainability. It also enables to comprehend connections among SC activities, providing an opportunity to understand the performance of combined indicators across the SC. Therefore, results can be used to better craft and perform strategic-tactical decisions, envisioning the achievement of economic, environmental, and social objectives.

Keywords: Pharmaceutical Industry, Sustainable supply chains, Equity, Mixed-integer linear programming

Resumo

O planeamento e gestão das cadeias de abastecimento farmacêuticas é um processo complexo e enfrenta inúmeros desafios dadas as características únicas e exigentes deste setor da indústria (Lemmens et al., 2016). Tornar estas cadeias de abastecimento mais sustentáveis, não só considerando objetivos económicos e ambientais, como também preocupações sociais é crucial. Em particular, incluir aspetos de equidade é de extrema relevância, no sentido de tornar estes produtos disponíveis e acessíveis a nível global.

A ferramenta de apoio à decisão apresentada segue o trabalho desenvolvido por (Mota et al., 2018), no qual um modelo multi-objetivo é proposto de forma a integrar decisões a nível estratégico e tático, considerando os três pilares de sustentabilidade. Estes pilares de sustentabilidade são incluídos no modelo através de funções objetivo.

Relativamente ao pilar de sustentabilidade social, sendo o maior foco da presente tese, é abordado através da maximização de equidade no acesso a medicamentos com base na métrica DALY, ao mesmo tempo que uma restrição é sugerida com o objetivo de garantir níveis mínimos de equidade (Cardoso et al., 2015).

Este modelo foi aplicado a um caso de estudo real cujos resultados permitem avaliar diferentes cenários de otimização, bem como estudar a influência dos objetivos económicos, ambientais e sociais nas diferentes atividades presentes na cadeia de abastecimento.

Desta forma, este trabalho propõe uma ferramenta que permite o planeamento das cadeias de abastecimento farmacêuticas, onde a integração de aspetos sociais constitui o grande foco e contributo.

Palavras-chave: Cadeias de abastecimento farmacêuticas, Sustentabilidade, Equidade, Modelo multi-objetivo

Table of contents

Figures List

Tables List

Acronyms

AtMI- Access to Medicine Index

BOM- Bill Of Materials

CLSC- Closed-Loop Supply Chain

DJSI- Dow Jones Sustainability Index

LCA- Life-Cycle Analysis

MILP- Mixed-Integer Linear Programming

NPV- Net Present Value

PSC- Pharmaceutical Supply Chain

SC – Supply Chain

SCM- Supply Chain Management

SCND- Supply Chain Network Decision

SSCM- Sustainable Supply Chain Management

TBL- Tripple Bottom Line

ToBLoOM- Tripple Bottom Line Optimization Modelling

1. Introduction

The purpose of the current chapter is to provide a context regarding the master dissertation on the decision-support tool development for pharmaceutical sustainable supply chains under uncertainty, also highlighting both its objectives and structure. In section 1.1 a brief contextualization on supply chain, sustainability, pharmaceutical industry, and uncertainty is given. In section 1.2 the dissertation's proposed objectives are described. Last of all, in section 1.3, the structure and outline of the remaining document are presented.

1.1 Problem Contextualization

In the year 2015, 17 goals were established by the United Nations Member States regarding the sustainable development of our societies. The 2030 Agenda for Sustainable Development will drive global and national policies and comprises two goals considered to be highly relevant to start this work with. Goal 3 seeks to "ensure healthy lives and promote well-being for all at all ages", more specifically regarding this work, it pretends to support research and development of vaccines and medicines and to improve access to them. Additionally, Goal 8 aims to "promote inclusive and sustainable economic growth, full and productive employment and decent work for all" (Johnston 2016).

Supply chains are vital for every organization and all the network entities are included in this system, from suppliers, manufacturers, transporters, warehouses and retailers (Barbosa-Póvoa, da Silva, and Carvalho 2018). The World Commission on Environment and Development has defined sustainable development as the "development that meets the needs of the present without compromising the ability of future generations to meet their own needs". The concept of sustainability in development was associated with the three pillars of sustainability – economic, environmental, and social-, generally known as the triple bottom line. Hence, a sustainable supply chain (SSC) refers to complex network systems involving numerous entities that manage products from suppliers to customers and their associated returns, always accounting for potential impacts on the three pillars of sustainability.

Pharmaceutical companies represent a group of healthcare companies that have been facing strengthened regulations concerning economic, environmental, and social issues, driving them towards more sustainable supply chains. Moreover, the pharmaceutical sector is challenged with planning and designing their supply chain to minimize costs, environmental impact and accomplish effective supply networks. Hence, optimization of pharmaceutical supply chains remains a major research focus on process operations and management and a great deal of research has been undertaken on facility location and design, inventory and distribution planning, capacity, and production planning (Shah, 2004; Papageorgiou, 2009; Barbosa-Póvoa, 2014). Furthermore, pharmaceutical companies dealing with vaccines need to cope with particularities regarding the product itself, such as storage temperature and shelf-life time, influencing the necessary resources that should be allocated to each facility (Lemmens et al. 2016). Vaccines are crucial to protect populations against infectious diseases and, assuring universal and equal access for all at risk has been gaining importance over the year, especially in developing countries (Pfizer 2019). Addressing equity in access when designing and planning

pharmaceutical supply chains has proven to be essential and helps driving this sector in the direction of a more socially sustainable industry. Thereby, pharmaceutical supply chains (PSCs) tend to be complex, and its management encounters multiple challenges. Decision-makers often struggle with high levels of uncertainty which, together with the need to consider sustainability principles (economic, environmental and social) in supply chain management, have greatly increased the complexity of the network's management in this sector.

There is a significant range of factors which may lead to disturbances in PSCs and an unexpected event may happen at any point of the chain, affecting the performance of one or many supply chain partners and their material flow (Blos, Da Silva, and Miyagi 2015). The current COVID-19 pandemic created uncertainty through the whole economy and new challenges were brought to the supply chain management. It strengthened the importance of this study since new challenges have been introduced in the pharmaceutical industry.

Bearing in mind the described scenario for pharmaceutical supply chains, especially when dealing with vaccines, the present thesis seeks to study how to make strategic and tactical decisions in order to help attaining sustainability objectives, where the integration of social concerns is the main focus.

1.2 Dissertation's objectives

The present thesis' goal is to contribute to the literature with the development and implementation of an optimization model for the design and planning of pharmaceutical supply chains, which aim is to serve as a decision-supporting tool, integrating several strategical-tactical decisions while considering the three pillars of sustainability. The study is being developed under the scope of the m-SSChain and FuturePharma projects.

To achieve these main goals, the present dissertation targets the following intermediate objectives:

- Perform a literature review on previous works focused on the pharmaceutical industry sector and their supply chains, as well as the most commonly used optimization models;
- Define and formulate a comprehensive decision-support tool for the design and planning of a pharmaceutical supply chain model based on the worked developed by (Mota et al. 2018);
- Apply the developed model to a real based case-study;
- Analyse and critically discuss the obtained results.

1.3 Dissertation methodology

As mentioned, this dissertation aims to explore how sustainable decisions, measured through adequate indicators, can be modeled into pharmaceutical supply chain decision making tools, such as optimization models, so as to allow the understanding of their impact and weight in the design and planning of vaccines' supply chains.

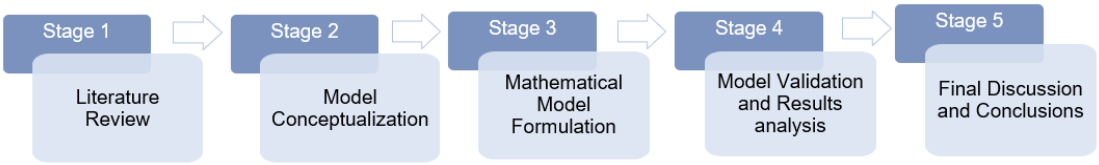


Fig.1- Dissertation's methodology steps

The methodology followed in this dissertation is presented below:

- **Stage 1 - *Literature review***

The first stage of the dissertation aims at providing sufficient information about the problem being tackled, i.e., the problem contextualization. Thus, pharmaceutical industry sector and their supply chains, along with its current challenges are identified. The problem of modelling a pharmaceutical supply chain accounting for, not only economic and environmental objectives, but social concerns, is described and key considerations highlighted in the literature regarding how to address it are presented. In a second step of this first stage, the main supply concepts are identified and described. A thorough literature review regarding the modelling of uncertainties in supply chain network design is done, as well as the most common sustainability concerns being addressed in the literature. Moreover, research gaps concerning pharmaceutical sustainable supply chains under uncertainty are identified.

- **Stage 2 – *Model conceptualization on Social Concerns***

In the second stage of the work, it is described the suggested approach to account for social concerns in the designing and planning of a sustainable supply chain, with the aim of filling a research gap present in the literature. At this stage, the selected optimization method to model uncertainty is presented and discussed considering key literature studies.

- **Stage 3 – *Mathematical model formulation***

The third stage of the work methodology is dedicated to the formulation and development of the proposed mathematical model, pproviding a decision-support tool for the design and planning of pharmaceutical sustainable supply chains.

- **Stage 4 – *Model validation and results analysis***

The formulated mathematical model is applied to a real based case-study of Sanofi Pasteur as to be validated. The obtained results are analysed and discussed, in order to understand the impact of each objective and decision considered in the overall network.

- **Stage 5 – *Final discussion and conclusions***

The final stage of the methodology considers the analysis of the work previously presented, where a critical discussion is given concerning the work developed in the dissertation. From there, future research topics are identified as interesting to be explored

2. The pharmaceutical industry sector and their supply chains

The present chapter performs a comprehensive literature review of the pharmaceutical sector, analysing its current state and emphasizing its importance and impact on the healthcare structure of a country. Moreover, a brief context on vaccine's development and distribution sector of the pharmaceutical industry is also given in this chapter, as well as a clarification of the key type of players on this industry. Afterwards, this chapter will focus on pharmaceutical industry supply chains where a review of important phases is done, as well as a brief characterization of its supply chain and logistics. Furthermore, the most relevant decision-making challenges and driving forces are identified and briefly explained, aiming to capture the major problems, trends, and challenges in the pharmaceutical industry.

2.1. Pharmaceutical sector characterization and context

The pharmaceutical industry is one of the most research-intensive industries, with special characteristics regarding its structure and nature of the business operations. This sector includes research, development, and production activities among other areas of work associated with drugs used to produce medicines and vaccines. Despite being strongly based on the chemical industry, pharmaceutical products are categorized as specialty chemicals, being highly differentiated, produced in smaller quantities with larger margins and usually purchased based on their function rather than chemical composition, hence being different from fine or bulk chemicals (Federsel 2009), (Marques et al. 2020).

A wide variety of concerns must be effectively applied, in particular regarding the chemistry process involved in the drug production, namely organic synthesis, as well as engineering procedures, safety controls, environmental concerns, specific regulations, among other aspects (Federsel 2009). Regarding the chemical process, specific analysis and measures need to be considered, including kinetic effects which may have the potential to significantly improve the efficiency of development activities, by-product formation and necessary conditions for further processes. The engineering procedures which need to be carefully studied may comprise fluid flow, heat and mass transfer, air conditioning and humidification, crystallization or sterilization (Hickey and Ganderton 2001). Ensuring safety measures and all the necessary precautions is crucial, particularly when operating in larger scale, in order to avoid unacceptable risks for both staff and the environment, as well as for patients (for instance, whether the candidate drug causes side-effects). Additionally, it is important to mention that pharmaceutical firms must follow rigid frameworks imposed by regulatory agencies such as the FDA (Food and Drug Administration) in USA, and the EMA (European Medicines Agency) in Europe.

Within the pharmaceutical industry, a continuing steam of new products is created and may offer the possibility of saving lives as well as raising the quality of life of each society. On the other hand, the development of a new pharmaceutical is extremely expensive, time-consuming and implies a considerable level of risk with an extremely low chance of achieving a successful outcome (less than 1% of candidate drugs reach the pharmacy) (Taylor, 2016). The industry sector, in particular the pharmaceutical one, has been facing considerable changes caused by scientific and technological breakthroughs, fast-changing market and competitive environment, rigorous regulations and increased

pressures, socially and economically, thereby hugely affecting the sustainability of the industry (Marques et al. 2020). Furthermore, the diversity and complexity of new drugs, the weakening patent protection, and the globalization of pharmaceutical business are also included in the several range of factors that are driving the changes in this industry sector. Therefore, each phase of the pharmaceutical business value chain is affected by these changes, from the research and development of new drugs to the management of the manufacturing networks (Papageorgiou, Rotstein, and Shah 2001).

2.1.1 Importance and Impact

The pharmaceutical industry is one of the main high-technology industrial employers in developed countries and creates nearly three or four times more employment indirectly (Marques et al. 2020). The European Federation of Pharmaceutical Industries and Associations (EFPIA) declared that more than 795,000 citizens are employed by the Pharmaceutical industry in Europe, 15% are working in Pharmaceutical Research and Development (R&D) sector and it creates about three times more employment indirectly than it does directly (EFPIA 2020).The pharmaceutical sector plays a critical role in the healthcare structure of each country by providing medicines and vaccines with direct impact on population's quality of life. Undoubtedly, medicines are responsible for preventing and treating diseases, improving or preserving health, and for avoiding the exacerbation of current conditions. This may lead to fewer visits to the emergency room, fewer surgeries, or it may even delay the necessity for long-term care services. Accordingly, along with the direct benefits for the population, medicines and vaccines also make a contribution towards significant cost reductions in the total healthcare cost of each country by decreasing the need for long-term care services and/or costly surgeries (Pfizer 2015). Hence, this is very significant and highlights the economic importance of this industry for a country, as it is a key actor in guaranteeing the economical sustainability of any healthcare system.

2.1.2 Key players in the pharmaceutical sector

In compliance with (Shah 2004), the pharmaceutical sector can be divided into 5 main key players, adopting the point of view of manufacturing:

- **Large Research and development-based multinationals (R&D):** focused on studying and testing new products with exclusive rights and usually have manufacturing sites in several locations. R&D based multinationals represent the sub-sector with higher importance economically for innovation and sales (Association for Accessible Medications 2017);
- **Generic manufacturers:** produce out-of-patent and over-the-counter products, thus being low-risk and low-cost businesses (Taylor 2016). On the other hand, generic manufacturers are responsible for supplying most of the medicines distributed around the world (Association for Accessible Medications 2017);
- **Local companies:** operate in their respective countries and produce generic products and branded products with a license or a contract.
- **Contract manufacturers:** can produce key intermediates, active ingredients (AI) and final products without their own product portfolio.

- **Biotechnological drug discovery companies:** concerned with drug discovery, mostly start-ups with less significant manufacturing capacity.

Different indexes can be used to recognize the leader companies in the pharmaceutical sector. The ***Dow Jones Sustainability World Index*** (DJSI) benchmarks the sustainability performance of the world's leading companies considering their economic, environmental, and social performance, as well as forward-looking indicators (RobecoSAM AG 2021). Another important index is the **Access to Medicine Index,** which aims to provide useful insights that may be translated into strategies for improved access to medicine in low and middle-income countries. Hence, this index ranks pharmaceutical companies based on their role and responsibility on enhancing both availability and affordability of medicines and health goods (Menou et al., 2021). The **Gartner's Healthcare Supply Chain** ranks the leading healthcare providers, manufacturers, distributors and retail pharmacies by performing a quantitative and qualitative analyses and highlights activities in the healthcare value chain that help improving human life, driven by a set of capabilities (Gartner et al., 2020).

The following Figure 2 lists the leader companies ranked by each of the mentioned indexes.

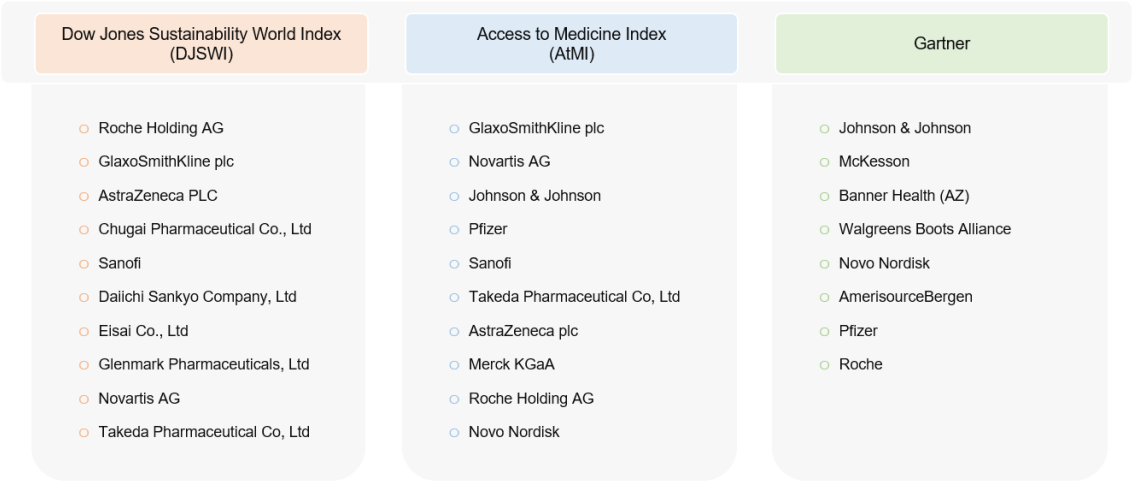


Fig.2- Leader pharmaceutical companies according to DJSWI, AtMI and Gartner indexes.

According to the ***Dow Jones Sustainability World Index*** (DJSI) , pharmaceutical companies such as Roche, GlaxoSmithKline, AstraZeneca PLC, Chugai Pharmaceutical and Sanofi were distinguished as leader companies in the pharmaceutical industry sector in sustainability in 2021 (RobecoSAM AG 2021). Roche was the company which got the highest score, hence named as Industry Leader, and considered the company in the pharmaceutical sector with the greatest capacity of benefiting from opportunities and managing risks resulting from economic, environmental, and social factors. For a company to be included in the Sustainability Yearbook Member, it must fall within a range of 15% to 30% of leading company's score. Companies whose score is within 1% of the leading company score get the Gold Class distinction, which in the present year only Roche have accomplished that distinction. The Silver Class distinction is given to the companies who got a score within a range of 1% to 5% of the leader company, being GlaxoSmithKline (GSK) the one getting this distinction. Finally, companies that score within a range of 5% to 10% of the leading company score receive the Bronze Class distinction. In this class, the year under review includes AstraZeneca PLC, Chugai Pharmaceutical and Sanofi (RobecoSAM AG 2021).

In order to compare companies' performance, the ***Access to Medicine Index*** assesses how far the world's leading pharmaceutical companies go by ranking them on their performance score, from 0 to 5. Each technical area (Governance of access, research and development, and product delivery) has a set of indicators with scoring guidelines and the respective weight. This index encourages companies to compete and cooperate on topics related with medicines and therapeutics' accessibility, while distinguishing best practices, fields of progress and gaps where further action is required. The methodology used is updated every two years in order to be consistent with the most recent developments on these topics. According to this index developed by the Access to Medicine Foundation, GlaxoSmithKline plc (GSK) holds the first position in 2021 ranking analysis, but only slightly ahead of Novartis. These leaders are followed by Johnson & Johnson, Pfizer and Sanofi. An analysis of leader companies per technical area is also made: In governance of Access, the leaders are GSK and Takeda Pharmaceutical Co, followed by Novartis, and all these three leaders reveal responsible business practices by implementing strict compliance procedures across their operations or by setting feasible incentives for worker; Regarding research and development, GSK shows to be the leader, followed by Novartis and Johnson & Johnson. Finally, in product delivery, Novartis leads while GSK goes in second.

The **Gartner** methodology for ranking the leader healthcare supply chains uses specific quantitative measures. Return on Physical Assets (ROPA) is used to measure operating effectiveness and is calculated through the division of the operating income by the sum of the net property and year end inventory. Inventory turns is used to measure supply chain effectiveness and is obtained by the cost of goods sold and the inventory. This methodology also uses qualitative measures, called Opinion Component where a polling procedure is performed. Then, the quantitative measures and the opinion votes are normalized to a 10-point scale and aggregated into a total score. Johnson & Johnson earned the first spot in Gartner's ranking, being distinguished by its approach to supply chain innovation and the further improve of its foundational capabilities. Pfizer and Roche, identified as leaders by the other indexes, are also present in the top 25 companies by Gartner. Pfizer shows to be a leader in the use of technology to enhance its network of suppliers, manufacturing locations and customers, as well as to implement new delivery solutions for challenging markets. Roche has been improving its operating model by reorganizing its products selection and shuttering manufacturing sites (Gartner et al. 2020).

A brief overview will follow to summarize information on the work behind the five companies that accomplished the highest scores as the most sustainable in the pharmaceutical industry sector according to DJSI. Johnson & Johnson and Pfizer were identified as leaders by both the AtMI and Gartner; Hence their work is also summarized below.

- **Roche Holding AG** is a leader in sustainability and a leader in personalized healthcare, being an innovator in pharmaceuticals and diagnostics committed to work on advancing science to improve people's lives. Roche is a company that makes a difference in areas such as oncology, immunology, infectious diseases, ophthalmology and diseases of the central nervous system. Moreover, Roche has a great diversity of actions to improve access to healthcare and its affordability around the world. Its global scores were the highest ones achieved in the analysed dimensions: environmental dimension, social and governance & economics. Particularly in the

environmental dimension, areas such as operational eco-friendly, health outcome contribution and climate change are the criteria where this company achieved the maximum score.

- **GlaxoSmithKline** is a company whose priority is to increase the availability and affordability of the products, through reducing prices, expanding product reach and increasing healthcare access, particularly in developing countries. To accomplish these requirements, they suggest using technology and science to create global health (focusing on science related to the immune system, human genetics and advanced technology), new medical innovations, such as vaccines, and to improve health security (helping the world to prepare for future disease outbreaks with pandemic potential and tackle antimicrobial resistance).
- **AstraZeneca PLC** has the ambition to build transparency within all the involved stakeholders, including employees, patients, partners, healthcare professionals, investors, governments and society. The company also aims to make information accessible to everyone, as well as providing equal access to healthcare, both prevention and treatment, especially respiratory diseases, cancer, cardiovascular, metabolic, and renal diseases. Internally, the company demonstrates social improvement measures with a significant focus on ethical concerns. AstraZeneca best scores was on health outcome contributions with a score of 98 and climate strategy with a score of 99.
- **Chugai Pharmaceutical** is a healthcare company whose goal is to add value through the creation of innovative medical products and services for the benefit of medical community and human health around the world. In 2019 this company has set “strengthen Sustainable Platforms” as one of its strategies that support challenge toward innovation, with a strong focus on social responsibilities (Kosaka 2021). Chugai Pharmaceutical achieved the maximum score of 100 in health outcome contribution and climate strategy criterion, which belong to the environmental dimension.
- **Sanofi** is a company working on research, production and distribution of pharmaceutical products, operating in business sectors such as pharmaceuticals, consumer healthcare and vaccines. In its work the concern of healthcare accessibility represents a significant weight, not only for community development and health improvement but also for disadvantageous communities. Moreover, employee’s health and safety, and gender equilibrium at work are also some of the social aspects valued by the company. Health outcome contribution and innovation management were the criteria with the maximum scores of 100 for Sanofi.
- **Johnson&Johnson** is a company whose business segments include consumer health, pharmaceuticals, and medical devices. It works in therapeutic areas such as neuroscience, oncology, pharmaceutical, immunology, infectious diseases, among others. It takes the third place on the AMI ranking, having a strong performance in R&D(Menou et al. 2021)(Gartner et al. 2020)**.**
- **Pfizer** is a biopharma company working on various therapeutic areas, such as oncology, inflammation, immunology, rare diseases, and vaccines. This company performs greatly in access strategies, capacity building and access planning during R&D. Hence, Pfizer is in the top 5 according to AMI, and leads when it comes to tackling access to self-administered products through distinct regions and socio-economic groups, also showing a rise in the patient reach(Menou et al. 2021)(Menou et al. 2021).

The presented overview on each company's work and the information detailed in Appendix A, where companies are evaluated on various criteria, reveals that the leader pharmaceutical companies in sustainability are not far from each other regarding their goals and challenges. They all aim to improve healthcare access, and they also attempt to end the existence of asymmetries in human rights and to stimulate inclusion and diversity within the company's employees.

2.2 Vaccines: Context, importance, and key aspects

According to (WHO 2020), immunization is the most effective way to fight infectious diseases and saves millions of lives every year. Currently, more than twenty life-threatening diseases can be prevented by vaccines, helping, and saving people of every age group to live healthier and longer. "Immunization currently prevents 2-3 million deaths every year from diseases like diphtheria, tetanus, pertussis, influenza and measles" (WHO 2020). Nevertheless, there are too many people, including almost twenty million infants every year, who do not have sufficient access to vaccines (Pfizer 2019). Furthermore, vaccines contribute for the reduction of health care cost and additional related ones, by lowering the rate of vaccine-preventable disease, as well as associated hospitalizations and mortality. Compliance with WHO's recommendations, such as the recommended vaccination schedules help preventing morbidity, mortality, as well as saving millions of dollars in direct medical costs to the health care system and prevent indirect costs associated with the diseases. Further investigation, development and proper implementation of new and innovative vaccines is essential to build more effective ways to deal with unmet medical needs and may help continuing to cut costs (Pfizer 2019).

The first step to develop a vaccine occurs at the laboratory and aims to study potential agents that will be able to influence the target disease. During this initial stage, companies produce small batches and undergo small scale studies to characterize and optimize the production process, as well as studies to obtain an appropriate formulation able to keep vaccine components stable until the end of its shelf life. When this initial stage is completed, companies can decide if they continue the development process and scale up production. Moreover, an effective quality control strategy needs to be developed in order to guarantee that the vaccine meets all the quality profile and complies with regulatory standards (EMA 2020). Afterwards, non-clinical trials, both in vitro and in vivo (animals), can be conducted to evaluate the immune response of these agents and assess whether it prevents infection. Then, the clinical trials in humans begin, through the three following phases (EMA 2020):

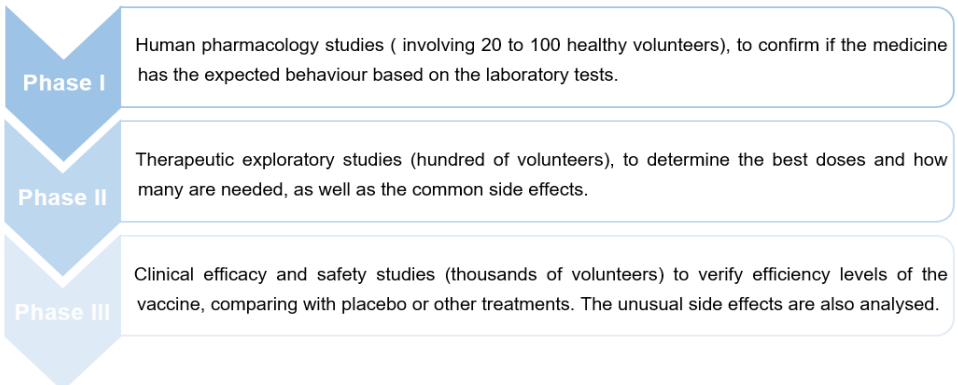


Fig.3- The three phases of vaccines' clinical trials (EMA 2020)

When these stages have been completed, regulatory organizations can decide whether they approve the vaccine, which then goes for manufacturing (to which a production scaled-up process must be developed). Overall, the manufacturing lead time can fluctuate between 9 and 22 months and the quality control and quality assurance procedures may take up to 70% of this. Thus, this makes it extremely challenging to design a responsive, cost-effective and humanitarian global vaccine supply chain (Lemmens et al. 2016).

During the current pandemic, research, development and testing of viable vaccines for COVID-19 were the centre of attention and they were being developed, evaluated, and approved according to current regulatory guidelines and legal requirements. However, due to the gravity of the present public health emergency, COVID-19 vaccines are being fast-tracked globally meaning that development is being compressed in time with a consequent need to mobilize more resources simultaneously. According to (EMA 2020), COVID-19 vaccine development is supported by an early and continuous communication between vaccine developers and regulatory specialists. Moreover, companies are expanding manufacturing capacity, as well as increasing production capacity, in order to ensure efficient vaccine deployment. The main differences between the indicative timelines for standard vaccines and for COVID-19 vaccines are illustrated in the following figure 4 (EMA 2020).

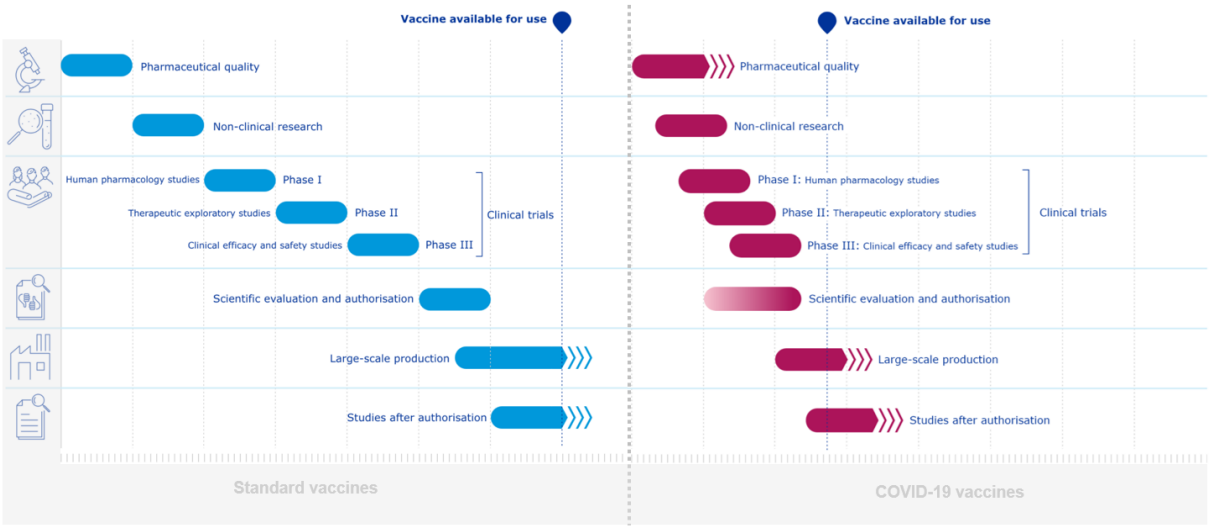


Fig.4-Indicative timelines for standard vaccines and for COVID-19 vaccines are illustrated (EMA 2020)

Concerning vaccines distribution network, the biggest challenges are associated with the rigorous storage conditions often required. During the current pandemic, logistics requirements turned the vaccine supply chain even more challenging due to the need for cooling equipment in intercontinental distribution, warehouses, downstream distribution and use points (DHL Research and Innovation 2020). Furthermore, distribution network design, not only depends on temperature requirements, but is also extremely reliant on transport volumes, distances, warehouses capacity, lead time, costs and availability of packaging equipment. Given that each of these parameters can be different depending on the vaccine, they are all needed to be considered when selecting the distribution method.

In order to address COVID-19 vaccine distribution challenges, DHL identified three possible methods of end-to-end logistics solutions (DHL Research and Innovation 2020):

- **Direct shipment**: most direct and fastest distribution option, through which vaccines go from the fill-finish point to its destination, via truck or air.
- **Local cross-docking**: cooling boxes on pallets are flown to the destination country by truck, where they are cross-docked, labelled, and then transported to various endpoints, reducing cross-border costs.
- **Local warehousing**: for this type of distribution, warehouses are used for storing pallets of vaccines which, afterwards, are broken into smaller parcels and distributed for last-mile delivery, in accordance with the needs of each region.

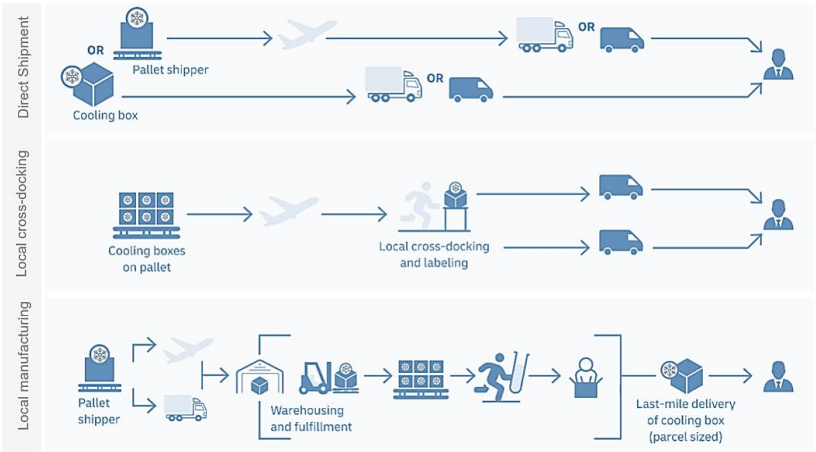


Fig.5 –Logistics solutions to address vaccine distribution challenges (DHL Research and Innovation 2020).

2.3 Pharmaceutical Industry Supply Chain

As it was mentioned, one important system within the Pharmaceutical Sector are their supply chains. Pharmaceutical products have a similar life cycle as other consumer products, beginning with **product discover and development, market launch of the successful products**, followed by a **growth phase in sales**, **maturity phase** and lastly, the **decline phase**, when the product has reached the end of life. However, in the pharmaceutical industry, in each of these stages we can find specific features, thereby establishing unique management **challenges** distinct from other industries. This sector will focus on a clearer understanding of these challenges, as well as on their strategic and tactical planning problems and decision-making processes. (Settanni, Harrington, and Srai 2017) proposed in a recent work a reconfiguration of opportunities in pharmaceutical SC through planning and classifying the existing models and these authors also reveal that the existing definitions of pharmaceutical SC rely on a "product-centric perspective and linear sequence of stages across the manufacture and physical distribution of medicines".

In such an environment, supply chain debottlenecking and decoupling plans in collaboration with coordinated inventory control are critical for rapid answers to the changing market developments. Thus, a better understanding of the challenges this industry has to face and what actually drives supply chain is helpful and will be assessed in this section (Shah 2004).

2.3.1 Pharmaceutical Industry supply chain and logistics

Challenges can be found in the pharmaceutical supply chain and logistics due to complex drug distribution systems, usually hard to manage.

After market launch, the growth phase begins, and companies strive to capture and establish the major market share possible. Pharmaceutical supply chains are normally complex and large since it involves a network of manufacturers, packaging resources, wholesalers, and final healthcare providers (hospitals, pharmacies, among others), as well as the raw material suppliers, third-party logistic providers and contractors. Hence, pharmaceutical supply chains require huge level of coordination among all the involved operatives, regulators, and other government bodies. On the other hand, each of these agents involved tend to operate independently, following its own operational goals, usually with not enough transparency (Marques et al. 2020). As a consequence, one can find disconnected structures, with more probability of disruptions and inefficiencies to occur, which may spread along the whole supply chain network(Privett and Gonsalvez 2014). Thus, pharmaceutical supply chains need to guarantee sufficient production and management capacity, together with a responsive supply distribution (more flexible to sudden changes), being capable of sustaining the service levels needed during this phase (Danese, Romano, and Formentini 2013) (Marques et al. 2020).

In order to secure an adequate level of **responsiveness, inventories tend to be high.** On the other hand, there is a limitation regarding product hold times since **chemical and physical stability need to be considered**, limiting product shelf life (Federsel 2009). As an example of such rigorous conditions, (Hoek et al. 2012) mentions that the shelf life of rotavirus vaccines is quite short (up to 24 months) and that they are temperature sensitive, hence requiring to be kept at refrigerator temperature, between 2◦C and 8◦C. More recently and serving also as an example of such rigorous conditions, one can note that COVID-19 vaccine developed by AstraZeneca can remain in a refrigerator for up to 6 months, while Moderna's vaccine can be stored up to 6 months at -20ºC and 30 days in a refrigerator. The more demanding conditions are the ones required by Pfizer's vaccine, which can remain in -70ºC for 6 months, and 5 days after the vaccine is transferred to a refrigerator, typically at 2ºC to 8ºC (Agrawal et al. 2021). Therefore, maintaining the cold chain from production until the final administration is a costly and challenging task, especially when in hot and/or large developing countries. The work developed by (Assi et al. 2014) report transport capacity utilization and storage capacity utilization as supply chain performance measures for a designed model which simulates all processes, storage locations, administering locations, and storage equipment in the vaccine supply chain.

Continuous manufacturing raises new opportunities, and it has been successfully adopted by many manufacturing sectors such as oil and gas, polymers and also food and beverage sector, where the so called "cold supply chains" are applied (Wang and Zhao 2021) (Reinhardt, Oliveira, and Ring 2020). However, despite the improvements and progress in continuous manufacturing, the support by regulators and the rising consciousness of its benefits, the traditional **batch** operating mode still prevails in the primary manufacturing phase, when API production occurs. Since batch processes are commonly used for low volumes and high product variability, it provides an easier quality control and easier decontamination procedures in case of a batch is contaminated, higher flexibility as well as a good capital efficiency (due to the use of manufacturing resources on various products) and well-defined

steps, thereby providing a better knowledge of the supply chain intermediaries. Finally, lot traceability is also a positive aspect facilitated by batch processes.

According with (Marques et al. 2020), one can find a poor performance in **production** due to:

(i) Extended production times;
(ii) Weak responsiveness;
(iii) Certain tasks are not productive, for instance, changeovers, Cleaning-in-Place (CIP) and Sterilization-in-Place (SIP), leading to extensive setup times and use of resources;
(iv) Higher inventory as a compensation for low responsiveness;
(v) Higher levels of expired end products caused by the excess of inventory mostly at the end of the distribution chain;
(vi) inefficient materials utilization as a result of low production performance;
(vii) minimal use of equipment.

Moreover, adjustments should be implemented by pharmaceutical companies for healthcare practitioner (HCP) teams to become more customer centric, as well as delivering remote digital communication tools for HCP and real-time data access (Klutz et al. 2015).

Depending on specific characteristic of the product and the final dosage form, **different costs** and **challenges** may arise associated to the manufacturing process and its related distribution network. In addition, the **decontamination process** is very long and complex, being decisive concerning the changeovers and global production efficiency (Yabuta et al. 2018). Furthermore, there are considerable challenges regarding **control and sensitivity to temperature**, thus requiring the need for complex and costly **cold chain distribution systems** (Marques et al. 2020).

At the supply chain level, **the range of challenges include** (Marques et al. 2020):

(i) reduction of supply chain's complexity;
(ii) More agility and responsiveness on the supply chain;
(iii) minimization of production and distribution costs;
(iv) improvement in visibility across the entire SC;
(v) strategies for consistent integration and coordination across the SC network;
(vi) inventory reduction;
(vii) integration of sustainability principles.

2.3.2 Pharmaceutical Decision-making challenges

Addressing decision-making challenges is crucial to understand which planning problems have been tackled in the pharmaceutical industry and how they have been managed.

As already mentioned, supply chains tend to be complex and difficult to manage, especially for R&D based multinationals, and thus, they are more vulnerable to **uncertainty.** Because of such uncertainty, they are also more susceptible to higher **risk** levels. This is due to various reasons: firstly, the considerable impact of technical uncertainty related with the outcomes of clinical trials throughout the development process; secondly, it is important to identify the uncertainty at the commercial production

and distribution levels, which may lead to a higher growth in complexity. For innovators, both the product development process and market demand at the commercial stage have considerable levels of uncertainty, and therefore, they face higher levels of risk associated when compared with generic manufacturers whose regulatory approval have far fewer risks associated and the market is more advanced and well-established. Furthermore, some authors stressed in their work that sometimes vaccine demands may act significantly different from the historical pattern, such as during and epidemic. Sadjadi, Ziaei, and Pishvaee (2019) referred that demand for influenza vaccine was a good example of this type of uncertainty since there were years that influenza was epidemic in some regions and the demand for influenza vaccine increased, while in some other years, it only infected a few people in those areas.

Garcia and You (2015) classified uncertainties as operational if they are related to alterations in supply chain operations or execution tactics and strategic uncertainties when they refer to changes in unpredictable occurrences, socio-political situation, climate impacts, etc.

Another important aspect to consider as a great challenge is the lot-sizing. In conventional batch manufacturing systems, the size of the lot can be hard and costly to change due to regulatory control processes and time-consuming approval processes. Thus, these decisions have a considerable effect on the global operations' performance.

With respect to **sustainability**, concerns such as an efficient water and energy consumption, optimization of carbon emissions, waste management, reverse flows on supply chains and social issues are being considered in some works regarding sustainable supply chain decision frameworks. Moreover, the rise in unused and expired medicines is pushing the pharmaceutical companies to restructure their supply chains so as to adopt new sustainable technologies.

An extremely complex social challenge also faced is regarding **equity**, geographical and socioeconomic, since there are many actors with influence on the accessibility of pharmaceuticals and it is an essential aspect to which governmental influence can be the main contributor. Kochhar et al. (2013) highlighted in their study that geographical locations are one of the main causes for low vaccination rate and challenging introduction of a new vaccine in developing countries due to the difficulty of getting proper infrastructure, transportation, human-resource, and health-care facilities in some geographical regions. Hence, the chance to provide access, in an equitable manner, to each person who needs healthcare services, treatments or vaccines, regardless of their socioeconomic situation or geographical location is an extremely important aspect to consider.

Moreover, **population density** may vary across distinct regions within a country. While the density in some areas is very high, in other regions people may be harder to reach. Thus, vaccine manufacturers have been trying to expand the accessibility of their products, particularly in developing countries. Creating local distribution centres is a decision which implies the allocation of people to these centres and various models based on travel distances have been applied within quantitative analysis with the aim to enhance demand coverage based on travel distances (Lemmens et al. 2016).

2.3.3 Driving forces

Several authors such as (Settanni et al. 2017) have been referring that healthcare operating environment is changing and is being chapped by market and political factors or scientific and technological breakthroughs. These factors have been helping to identify driving forces and enablers that may challenge the traditional business model for the pharmaceutical industry.

Marques et al. (2020) classified the driving forces as external, meaning that firms are not capable of controlling, and internal drivers, those that might be able to manipulate. As external drivers the following can be considered: Increasing regulatory burden, growth of personalized medicines, pricing and cost pressures, increased uncertainty and risk and sustainability matters. As internal drivers, one can point out the decrease in effective patent life, growth in the supply chain complexity and the decline in R&D productivity.

The following drivers were considered the most relevant ones in the context of this work.

The **increasing regulatory** burden in an external factor which has been gaining more focus by FDA and EMA, particularly on the evaluation of safety and effectiveness, requiring more arduous protocols and quality criteria before market approval. As mentioned by (Khanna 2012), currently, additional trials to confirm both efficacy and long-term safety are needed. Moreover, there are stricter regulations regarding logistics with a stricter control of temperature and relative humidity. This regulatory context and the resultant challenging quality needs are pushing companies to adapt and create strategies to better meet these requirements, while strengthening both productivity and operational efficiency.

Studies have been done regarding cold chain monitoring and temperature control in various developing countries, showing that it remains a major challenge to control the temperature of the cold chain, being important to monitor, maintain and record the temperature of vaccines throughout the cold chain for successful immunization programs(Chandra and Kumar 2020).

The **growth of personalized medicines** has been encouraging a shift from the conventional focus on reactive treatments to a more proactive approach focused on prevention and early treatment (Taylor 2016). Benefits include an improvement of therapeutic outcomes, decrease on adverse effects and consequent increasing of patient's adherence to treatments, as well as a reduction on the overall healthcare system's costs. Hence, the business model of innovators and the design and operation of their supply chains will experience significant changes, not only at scientific and technological levels, but also on the design of an efficient and effective delivering system. A distribution network which starts and ends with the patient will replace the traditional one (where wholesalers play central role) and a considerable growth in product quality metrics to review, validate and manage, will be essential to assure a personalized dosage quality.

As mentioned in the previous chapter, the increased levels of **uncertainty** and consequent **risk** as well as **sustainability** concerns are great decision-making challenges that companies have been facing, and thus important drivers for change in the pharmaceutical industry.

2.4 Chapter Final Remarks

Within this chapter, one can find an overview on the pharmaceutical industry sector and their supply chains. Starting with a characterization of the pharmaceutical industry and its context in subchapter 2.1, highlighting key aspects of vaccines as a pharmaceutical product of this industry in chapter 2.2, and finally ending with chapter 2.3 where a review on pharmaceutical industry supply chains and logistics, the main decision-making challenges and driving forces are given.

Pharmaceutical products have distinctive characteristics, long and complex production processes, and it is also characterized as a product with high value and impact on society. Moreover, the development of a new product needs to undergo on a long research process, which is 15 years on average until market launch, and faces strict regulatory policies.

Designing a vaccine supply chain is particularly challenging, not only due to the complexity of pharmaceutical products' supply chains, long clinical trials, regulatory practices, manufacturing, quality control and quality assurance procedures, but also its distribution network design, which depends on rigorous temperature requirements, transport volumes, distances between entities of the supply chain, warehouses capacity, costs, and availability of packaging equipment. Furthermore, these requirements may differ depending on each vaccine, thus being important to consider all these specific characteristics when designing and planning a vaccine supply chain network.

The need to consider sustainability objectives, including economic, environmental, and social principles, in supply chain management, have greatly increased the complexity of the network's management in this sector. Specially regarding the products being addressed, social concerns have been gaining importance over the years and societal pressure triggers pharmaceutical companies to work towards a better sustainable performance, focusing their contribution on the enhancement of healthcare access and affordability.

The increasing regulatory burden and quality of products were identified as a major driving force for the pharmaceutical industry by pushing companies to adapt and create strategies to better meet the requirements, while strengthening both productivity and operational efficiency. Another important driver identified is the growth of personalized medicines which encourages a shift from the conventional focus on reactive treatments to a more proactive approach focused on prevention and early treatment.

As a final remark, it is important to highlight that pharmaceutical industry supply chains have a complex structure, its management faces several challenges and decision-makers often struggle with the high levels of uncertainty. On the other hand, identifying and managing all the relevant sources of uncertainty remains a major challenge for researchers. Hence, there is a necessity to build techniques that can help and support the decision-making process at the three levels of decision-making: strategical, tactical, and operational. One way possible to tackle this is the optimization models, considering the challenges mentioned such as uncertainty, risk, equity, among others. Therefore, the next chapter will focus on some concepts and considerations regarding supply chains and the more relevant optimization models to deal with multiple objectives and tackle uncertainty.

3.Supply chain main Concepts and Optimization in the Pharmaceutical Context

This chapter begins with section 3.1 presenting relevant concepts such as supply chain, supply chain management and sustainability, stressing its importance and emphasizing the main challenges and concerns. Afterwards, section 3.2, reviews the most used optimization models, firstly focusing on modelling uncertainty and risk, and afterwards focusing on how multiple objectives have been tackled within the available literature. Afterwards, it is relevant for the present work to assess the modelling of the social pillar of sustainability, reviewing if and how previous works have been incorporating these parameters in supply chain optimization models. Hence, section 3.3 will focus on this. Lastly, in section 3.4 the chapter conclusions are presented.

3.1 Supply chain: concepts and considerations

Oliver and Webber firstly described the concept of supply chain in 1982. In its classical form, also known as **forward supply** chain, it can be defined as the combination of processes to satisfy customers' needs. Moreover, this system covers all possible network entities, namely suppliers, manufacturers, transporters, warehouses, retailers, and customers (Govindan, Soleimani, and Kannan 2015)(Marques et al. 2020). According to Munir et al. (2020), at the minimum level of complexity, a supply chain comprises a firm, a supplier, and a customer, who are directly involved in all flows of information, products, services, and finances. Furthermore, modern companies work in complex environment due to its fast changing and increasingly more reliance on complex networks of supply chain partners to provide supplies and services complying the correct quantity in due time and right place under constant pressure with respect to cost and quality (Munir et al. 2020a)

Over the years, there has been an increasing awareness regarding environmental concerns, which led to the integration of **reverse logistics** in SC's activities. In general forms, it starts from end users (first customers) where used products are collected from customers (return products) and then attempts to manage end-of-life (EOL) products through different decisions and activities such as gathering and treatment of EOL products through recycling or manufacturing, restoring, and disposing of used parts (Barbosa-Póvoa 2012) (Govindan et al. 2015).

In the **Healthcare sector**, supply chains are complex structures covering several organizational and geographical boundaries and independent entities can be found within these structures, from raw material suppliers, manufacturer, distributor, pharmacies, hospitals and patients, thereby providing crucial backbone to services for daily life. The complex nature of these systems may entail the introduction of impurities such as inaccurate information, lack of transparency and limited data provenance, possibly leading to a higher level of vulnerability and supply chain risks (Musamih et al. 2021) (Munir et al. 2020b). Particularly in the pharmaceutical industry's SCs, products often have specific features which affect and impact supply chain's operations and, consequently, decision-making process. One of those features is the non-discrete nature of the end-product since it makes harder to treat products as countable and individual units (Marques et al. 2020).

3.1.1 Supply chain management

The highly complex environment and dynamic context is pushing pharmaceutical industries to move forward to greater levels of sustainability, agility, efficiency, and customer value creation. Hence, supply chain management in this industry is becoming more and more demanding, with new possible decision-making challenges interacting in a complex network (Marques et al. 2020). To survive such a complex environment, companies need to be flexible, agile and ready to respond rapidly to all the challenges. This need of deepen SC understanding may have worked as an incentive for the development of supply chain management (SCM).

An early definition mentioned by (Mukhamedjanova 2020) and proposed by Oliver and Webber in 1982 described SCM as "the process of planning, implementing and controlling the operations of the supply chain with the purpose to satisfy customer requirements as efficiently as possible. SCM spans all movement and storage of raw materials, work-in-progress inventory and finished goods from point of origin to point of consumption." Later on, SCM has been defined as a group of approaches used to integrate suppliers, manufacturers, warehouses, and stores in an efficient way so that stock is produced and distributed at the right quantity, to the right locations, and at the right time, to minimize system wide costs while satisfying service level requirements (Simchi-Levy, D., Kaminsky, P. and Simchi-Levy 2008). Every decision concerning products or services delivered to customers are included in SCM, and the massive number of aspects needed to be considered make the **optimization of a supply chain** a very difficult task. Improving economic performance on its own, only considering cost reduction (by reducing the number of employees, innovation, environmental protection, or safety) or increasing production (demanding more raw material and industrial facilities) can lead to negative consequences to the environment such as pollution, resources exhaustion, worsen quality of life, among other implications.

3.1.2 Decision-making levels: strategic, tactical, and operational

After reviewing the supply chain main concepts, it is important to better understand the different levels of decision within the supply chain management. This comprehends three levels of decision, which are highly affected by uncertainty: strategic level, tactical level and operational level. Many authors, such as (Lemmens et al. 2016) and (Barbosa-Póvoa et al. 2018), discuss the importance of integrating these decision levels, so as to target an unified approach that can be useful for the design of competitive supply chains.

The **strategic level**, which addresses a long planning cycle, involves decision on the configuration of the supply chain, including allocation and location issues. The first one is an important strategic decision since it is crucial to consider factors such as travel distances between individuals and health care centres (and associated transportation cost), as well as the time and the difficulty to reach customers, especially in a vaccine supply chain context. Regarding location, decision-makers may have to decide production facilities' location, as well as the location of decision centres and/or suppliers. Such a location decision refers to locating production facilities, DC's and/or suppliers in the supply chain network. (Hammami et al. 2009) propose a mathematical formulation for a supply chain design problem in a delocalization context. The authors emphasize that facility location and technology selection decisions are connected: on the one hand, manufacturers would like to profit from the low labour costs in developing countries,

but on the other hand they want to use the same manufacturing technologies as in the original plant to maintain a high labour productivity level and high standards of quality.

According to (Ekambaram 2014), when designing a vaccine supply chain, it is highly recommended to integrate both the facility location and technology selection. However, this approach lacks the lead time consequences of locating a vaccine manufacturing facility: the adoption of an old or a new production technology at a facility has a large impact on the time for regulatory approval.

At the **tactical level**, decision-makers focus on shorter planning cycle decisions. These can involve, for instance, decisions related with distribution capacity, inventory planning and production capacity planning (demand and/or supply planning). Distribution capacity refers to the available storage space of the installed distribution centres and is mentioned by researchers as being a crucial aspect on vaccine's supply chain distribution. (Tancrez, Lange, and Semal 2012) suggested a supply chain network design model which accounts for shipment sizes. Inventory planning is considered by many authors to be extremely important in vaccine's supply chain due to the perishable nature of vaccines which limits stock building. Regarding production capacity planning, (Sabri and Beamon 2000)'s work considers it as a decision variable in their work.

At the third decision level, namely the **operational level**, decisions such as demand fulfilment, production and distribution, scheduling and monitoring tasks that require a constant control on the supply chain, being daily or weekly decisions (Barbosa-Póvoa et al. 2018). The batch sizing is a decision made at the operational level and very few works include it as a decision variable in their model. Nevertheless, in the case of vaccines' supply chain, it can be a determinant decision due to biochemical and regulatory consequences of changing a batch size.

3.1.3 Sustainability in SCM

Sustainable development was defined by the Brundtland Commission (World Commission on Environment and Development, 1987) as the "development that meets the needs of the present without compromising the ability of future generations to meet their own needs"(Keeble 1988).

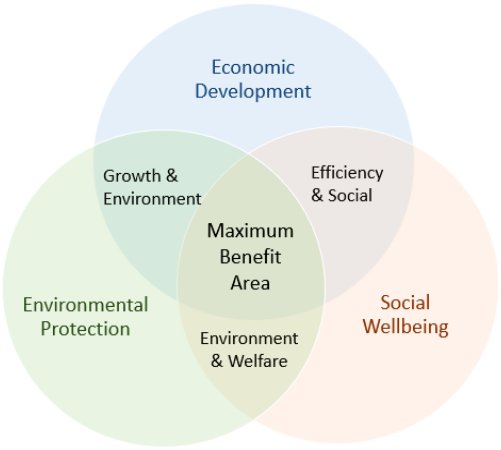


Fig.6 – Tripple Bottom Line of Sustainability (based on Kannegiesser, Günther, and Autenrieb 2015)

Over time, sustainability started to focus, not only on environmental and economic aspect, but also on social and safety concerns. Integrating them has been considered crucial for organizations to be agile and resilient, thus being well prepared to react to internal and external vulnerabilities (Ahi and Searcy 2013) (Heintz, Belaud, and Gerbaud 2014). Moreover, the commonly known as **triple bottom line (TBL)**, firstly proposed in 1997 by Elkington, associates the three pillars of sustainability: economic, environmental and social (Richardson 2013), as represented in figure 6. Thus, as the entire process industry areas have been experiencing some changes, a possible transition from a cost-driven to a more sustainable-driven development began to happen (Marques et al. 2020). Accordingly, sustainable supply chain management (SSCM) alludes to the management of materials, information and investment flow, as well as cooperation between the SC partners, while applying sustainable development goals (Bui et al. 2020).

3.2. SC Optimization models in the pharmaceutical industry

The present section analyses, and reviews available literature on the usage of optimization methods to model supply chain challenges, with the final objective to support decision-making at the strategic-tactical level. On the one hand, the goal is to improve understanding on the optimization models that can be used to deal with the uncertainty associated to pharmaceutical's supply chain. On the other hand, it is pretended to review how the different aspects/challenges identified in the previous chapter have been handled and incorporated in the optimization models.

Therefore, this section is organized as follows: In section 3.2.1 the most common models used to deal with uncertainty are presented and section 3.2.2 reviews the models that have been used to integrate multi-objectives, being them economic, environmental, and social aspects. Within these sections, the challenge is to, whenever possible, refer to previous works where these aspects have been incorporated into the supply chain design networks, especially in the pharmaceutical industry.

3.2.1. Modelling uncertainty

Quantifying and modelling uncertainty remains significantly challenging for researchers, who consider it as a key area of development for the industry sector. According to (Barbosa-Póvoa and Pinto 2018), the quantification of uncertainty is likely to "become one of the backbones of process systems engineering in the near future". Deterministic optimization problems are formulated using known parameters; Thus, they are not considered the best-suited to model uncertainty. In Fact, real-world problems include uncertainties and difficulties when estimating key parameters. Therefore, some authors have worked on methods to correctly deal with uncertainty, such as (Sahinidis 2004) , who discussed about stochastic programming where uncertainty parameters are characterized as random variables with known probabilities, fuzzy programming which assumes that some variables are fuzzy numbers, and robust optimization.

- **Stochastic Programming**

In stochastic mathematical programming, information is given by discrete or continuous probability distributions, and it can either be given, when based on historical data, or estimated. Thus, in contrast with deterministic programming, the numbers which represent the data may be unknown.

The recourse-based stochastic approach is the most used, which main objective is to minimize the expected recourse cost. This approach has two stages of decision variables: the first-stage variables, also known as “here and now” decisions, are the ones that must be determined before the realization of the uncertain parameters and the second-stage variables, “wait and see” decisions, where design and operational policy improvements may be done by choosing, at a certain cost, the values of these parameters (Sahinidis 2004). Another common method, but more difficult to solve, is the probabilistic/chance-constrained stochastic approach, which guarantees that the probability of meeting a given constraint is above a specific level, increasing the solution confidence level trough the feasible region restriction.

The main advantages and drawbacks of the stochastic programming method are presented in Figure 7 (Pishvaee, Razmi, and Torabi 2014)(Sahinidis 2004).

Advantages	Widely applicable and strong presence in the literature;	Possible computationally challenging problems from a great number of possible scenarios;	**Disadvantages**
	Based on commonly known probability concepts;	High dependency on historical data;	
	Complete overview of the effects of uncertainties:	Increased difficulty in building a probability distribution with lack of historical information and high costs for acquiring it;	
	Establishes relationships between uncertain inputs and resulting solutions.	Inherent subjectivity in decision-makers judgements.	

Fig.7 – Advantages and drawbacks of the stochastic programming model

(Tsang, et al. 2007) developed a stochastic model to address capacity planning and investment with application in a multiple vaccine production case study. This model provides an optimized solution for the decision-making process involving product selection and manufacturing, capacity expansion, while contributing with logistics aspects such as resource allocation and operations management.

- **Fuzzy Programming**

Another method commonly applied to model uncertainty is the fuzzy programming, used when the situation is not clearly specified, or an exact value is not critical to the problem. In this method, random parameters are treated as uncertain (fuzzy) numbers and constraints are considered as sets whose elements have levels of membership (fuzzy sets). Thus, each event may be allocated in a range of values between two extremes, increasing the number of possibilities on real-case scenarios.

Fuzzy programming comprehends two major types: flexible programming, which copes with right-hand side uncertainties, being usually applied when there is uncertainty concerning the exact values of the

coefficients and the possibilistic programming that identifies uncertainties in the objective function coefficients and in the constraint coefficients (Pishvaee and Razmi 2012) (Sahinidis 2004). Both approaches use the membership function to represent the constraints satisfaction level, the decision-maker's expectations about the objective function level, and the range of coefficients' uncertainty (Sahinidis 2004).

Different types of uncertainties have been modelled applying this method, for instance, supply and inventory costs uncertainty, logistics and production uncertainties, demand uncertainties (Pishvaee and Razmi 2012), environmental and social uncertainties (Archibald and Marshall 2018)(Saffar, Hamed Shakouri, and Razmi 2015)(Tsao et al. 2018) as well as issues related with closed-loop supply chains, reversed-logistics and green supply chain (Tsao et al. 2018). Additionally, (Yazdian and Shahanaghi 2011) developed a work in the field of vaccine supply chains where the customer demand and capacity of each distribution centre have a possibilistic distribution, expressed by trapezoidal fuzzy numbers.

Furthermore, (Chandra and Kumar 2020) used a fuzzy approach to identify, analyse and prioritize the key issues in vaccines' supply chain necessary to immunize children in developing countries.

Figure 8 reviews the major advantages and disadvantages of fuzzy programming (Saffar et al. 2015)(Rommelfanger 2004).

Advantages	Does not require a collection of extensive data, neither high cost for obtaining information;	The results obtained may depend on the type of fuzzy method applied;	**Disadvantages**
	Can estimate trough possibility rather than probability, which can be crucial in ambiguous information	Not capable of representing the exact nature of the uncertainty.	
	Can model in a simple and practical way qualitative data		

Fig.8- Overview on advantages and drawbacks of the fuzzy programming model

- **Robust Optimization**

Robust optimization is a method to model uncertainty by providing a framework that is able to immunize the optimal solution for any realization of the uncertainty in a given bounded uncertainty set, thus being able to deal with the uncertainty parameters (Pishvaee and Razmi 2012). This model aims to discover the feasible and optimal solution which, regardless of the parametric uncertainties, can satisfy the constraints. Many robust approaches have been considered, such as strict robustness, cardinality constrained robustness, adjustable robustness, lightweight robustness, regret robustness and recoverable robustness.

(Sadjadi et al. 2019) developed a study with the aim of designing a supply chain network for the vaccine supply chain under uncertain conditions. In their work, they applied a robust optimization programming approach considering uncertainty parameters such as vaccine demands (high-priority and low-priority demands), the opening costs of province repositories and the opening cost of districts storehouses.

The following figure 9 shows the main advantages and disadvantages of the robust optimization model.

Advantages	Reduced computational costs;	Usually leads to overconservative results;	Disadvantages
	Easy to understand, intuitive and very useful in practice;	Emphasis on the worst-case scenario;	
	Combines the structural properties of the optimal solution and computational tractability.	Feasibility frequently comes at a cost of performance.	

Fig.9- Overview on advantages and drawbacks of robust optimization model

Moreover, with the purpose of mitigating the conservatism present in this method, the Adaptive robust optimization approach was created. This model includes two decision phases by using the wait-and-see mode, aiming to reach the desirable objective, while predicting the worst-case manifestation of the uncertain parameters within an uncertainty set (Zhao, Ning, and You 2019).

- **Dynamic Optimization**

As the name suggests, dynamic optimization methods, also known as multi-stage programming, involves optimization over time, where decisions are made in stages and focus on maximizing benefits and minimizing costs of a given objective function (Hinderer, Rieder, and Stieglitz 2016). Moreover, in dynamic optimization problems, the global performance depends on all decisions made sequentially during a given time interval since each decision, not only provides an immediate reward, but also affects future rewards and future decision's context. (Iyengar 2005).

Figure 10 reviews the major advantages and disadvantages of dynamic programming.

Advantages	Decisions are made in phases	Model complexity analysis	Disadvantages
	Immediate rewards taken from decisions made at each stage	Significant computational burden	
	Efficient computation for a good overall strategy	Intrinsic subjectivity in decision-makers judgements	
	Given its changes over time, it can be considered as a more realistic form of modelling uncertainty	Possibility of inaccurate data	

Fig.10- Overview on advantages and drawbacks of the dynamic optimization model

(Thompson et.al 2016) explored in their study some opportunities to develop and maintain optimal global vaccine stockpiles, with the aim of, not only deal with disruptions and unexpected demand but also to ensure rapid access to a vaccine supply, for both universal vaccines (characterized by large global demand) and for nonuniversal vaccines. They assumed a dynamic optimization of a stockpile to maximize the difference between public health benefits and total financial costs by proposing and designing a framework for the development of a vaccine stockpile for an endemic or epidemic vaccine-preventable disease where they used a dynamic transmission model to estimate disease incidence as a function of all factors that influence incidence. Furthermore, several authors have been combining dynamic optimization with other methods, for instance, the stochastic and robust optimization.

- **Hybrid Optimization**

Lastly, one can use the **hybrid optimization**, where it is possible to combine at least two approaches in order to achieve global improvements and mitigate multiple drawbacks. Several authors have been focusing on hybrid optimization approaches and it is becoming clearer that these approaches can provide many compensatory solutions for multiple conflictive objectives problems in a supply chain network (Farrokh et al. 2018), (Hao et al. 2014).

(Tsang, Samsatli, and Shah 2006) used a hybrid model to assist the batches scheduling in order to meet delivery dates. In their model, they included key decisions such as the sequence of activities, batch sizes, and timing of process operations. The main goals of their work were to comprehend how distinct parameters and decisions affect performance, to distinguish the key factors in the supply chain, to evaluate a new operational strategy and to lower time-to-market without a large investment.

The work of (Tsao et al. 2018) already mentioned in the fuzzy programming subsection is a good example of an hybrid approach which lies on the **combination of stochastic and fuzzy programming** models, so as to model various uncertain parameters, such as demand, cost, capacity, number of job opportunities, among others. The aim of their work was to address **strategic-tactical problems** considering **economic, environmental, and social concerns**. Specifically, the goals included to define the number and location of production and distribution centres, along with the product flows, while bearing in mind the following three objective functions regarding the sustainability pillars:

(i) minimize the **total costs** of the sustainable supply chain network;

(ii) minimize the **environmental impacts** by considering CO_2 emissions caused by production and transportation, as well as the investments in environmental protection at the production centres;

(iii) maximize **social benefits** received from creating the network. This was estimated, not only through the number of job opportunities generated, but also through the number of hazardous by-products related to the selection of materials and technology for production, and through the number of workdays lost due to work-related hazards.

Hence, the authors used a two-phase stochastic programming approach to separate the decision variables into two sets: recourse-related variables and output variables. The first ones are determined using random variables and include materials, technologies, and the number of facilities. The second ones are determined using the achieved value of random variables, being influenced by stochastic variables in the model, such as demand in particular regions. Lastly, fuzzy possibilist programming was used in order to transform the multi-objective mixed-integer linear programming model obtained into an equivalent crisp model and thus reducing the complexity of the problem by adjusting the objective functions and the constraints.

The work developed by (Farrokh et al. 2018) focused on closed loop supply chain network design problem under hybrid uncertainty. The authors developed and applied a model that considers the effects of uncertainty in a closed-loop supply chain, where economic and environmental concerns are included. The aim of their study was to extend a robust optimization method into fuzzy scenario based stochastic programming model resulting in an approach that can tackle both operational risks, such as uncertain demand, capacity planning and supply, production, and shipping costs, as well as disruption risks. Since two sources of uncertainty were treated for most of the parameters, a strong robustness analysis was

needed. On the one hand, one source of uncertainty is regarding the uncertain parameters that can be based on the future scenarios, which are considered according to the probability of their occurrence. On the other hand, the second source of uncertainty is that usually values of these parameters in each scenario are not precise and can be specified using possibilistic distributions. Furthermore, in order to provide model's validity, the authors used a simulation method to compare the proposed robust model in terms of mean costs and total variability with the models developed by (John M. Mulvey; Robert J. Vanderbei 1995) and (Pishvaee, Razmi, and Torabi 2012). These models can either control the scenario variability or the possibilistic variability, unlike the model proposed by (Farrokh et al. 2018) which tackles both variabilities, hence revealing to be a superior model over the two others in decreasing the total variability as a measure of the optimal robustness. (Farrokh et al. 2018) concluded that it would be more suitable for most managers to control both disruption and operational risks by considering the scenario variability and the possibilistic variability simultaneously and lead to believe that better results can be achieved when considering a hybrid approach which applies all three methods in the modelling of uncertainty in supply chain systems.

One can conclude that the inevitable uncertainty in supply chain systems can be modelled through different optimization methods, which can either focus on static or dynamic optimization problems. A few examples of such approaches are the stochastic programming method, fuzzy programming method, robust optimization method and dynamic optimization method. Moreover, and despite having the same purpose, these approaches work in distinctive ways, and thus several differences separate them.

3.2.2. Multi-objective programming methods

When working with various objectives in a supply chain, a multi-objective decision making (MODM) procedure may be necessary. This sub-section reviews the most representative and used mathematical modelling approaches that deal with multiple objectives and provides examples of some author's works who applied these models to assess different important objectives, such as economic, environmental, and social concerns. For each model, some methods are exclusively used to single-criterion or multiple-criterion, while other approaches can be adjusted to both cases.

- **Goal programming**

Goal programming is a multiple criteria mathematical programming method used to model multiple, often conflicting, performance measures and each of them has a goal or desired value to be reached, hence undesirable deviations should be minimized in an achievement function.

Some authors, such as (Badri 1999) used this methodology, combined with Analytic Hierarchy process to help in strategic global location-allocation decisions. (Azaron et al. 2008) developed a multi-objective stochastic programming approach for supply chain design under uncertainty where uncertain parameters such as demands, supplies, processing, transportation, shortage, and capacity expansion costs were considered, and the goal programming technique was used to obtain the Pareto-optimal solutions that can be used for decision-making. Moreover, (Azaron et al. 2008) included in their model the minimization of the financial risk or the probability of not meeting a certain budget.

- **Weighted sum method**

In the weighted sum method, a multiple criteria problem is converted into a scalar problem by creating a weighted sum of all the criteria. Some authors, such as (Zuo-Jun Max Shen 2005) used this approach to assess the cost/service trade-off by incorporating the customer demand satisfaction in a cost minimization objective function. Moreover, (Wang et al. 2011) considered the trade-off between the total cost of a supply chain and the effect on the environment.
Some authors referred that the determination of these weights can be subjective and difficult, largely impacting the final solution, thus in some cases weighting methods should be avoided (Lemmens et al. 2016).

- **Epsilon-constrained method**

In the epsilon constraint method, Pareto-efficient solutions are obtained from a multi-objective program and the major goal is to consider one of the objective functions as the primary objective while the other (secondary) objectives are assigned as constraints. Concerning these secondary objectives, its allowable levels change on an iterative way (Lemmens et al. 2016).
Some authors used this method to optimize profit, demand satisfaction, and financial risk cost. (Franca et al. 2010) used the multi-objective epsilon-constrained method in order to optimize the profit and quality objective function. (Lemmens et al. 2016) reveals that multi-objective optimization and the epsilon constraint method are the most frequently used mathematical programming and heuristic method respectively to deal with multiple criteria SCND models. These methods avoid weighting multiple criteria but lack the practical relevance for the satisfaction of the preferences of a stakeholder group.

3.3 Social concerns in supply chain optimization

As already mentioned in 3.1.3 when addressing the concept of sustainability in supply chains, most researchers focus on economic and environmental concerns, which are the most studied and researched pillars of sustainability. However, not including social concerns in the supply chain design and planning may have negative consequences to the companies involved. According to (Barbosa-Póvoa et al. 2018), although it still represents a research gap in sustainable SCM modelling, social concerns have been gaining importance over the years. Therefore, the present subchapter focuses on the social pillar and aims to analyse how optimization models assess and quantify social concerns.
The social dimension of sustainability is described by the Global Reporting Initiative (GRI) as the impact that an organization makes on the social system within which it operates. Due to the difficulty in measuring this impact (measures are usually subjective and qualitative), there is still lack of literature on the assessment of social impact. Moreover, most of the indicators are either based on past occurrences or meant to assess the social performance at the operational level of SCDM. Therefore, there's a need to deepen the knowledge on social sustainability at the strategical-tactical level (Mota et al. 2015).
(Kravanja 2013), suggested a sustainability index covering the three pillars of sustainability as objective function. The authors suggested a Relative Sustainability Index (RSI) which may account for economic, environmental, and social indicators, although they need to be normalized these indicators have different

units. Moreover, a Relative Direct Sustainability Index (RDSI) and a Relative Total Sustainability Index (RTSI) were suggested to account for direct effects or for direct and indirect effects on the environment and/or society, respectively. Regarding the social aspects, the ones mentioned in this work were essentially employment/job creation, human rights, poverty, education, health, and safety. However, in their paper, a two-stage multi-objective approach was performed on a case study of an integrated biogas process, and social indicators were not defined nor included since their assessment would not be a straightforward task.

In the review developed by (Barbosa-Póvoa et al. 2018), the social indicators identified as the most commonly used were **job creation, safety, health, number of working hours and discrimination**, as well as indicators related to **satisfaction** and **community development** aspects.

Job creation is considered to be a great driving force in social welfare (not only social welfare of a family, but also of a community or a country). Companies need employees, not only to install and operate in their facilities, but also to work on services such as transportation and distribution. Moreover, local development can be enhanced by a chosen factory location since it creates employment in regions that may have higher unemployment rate, as well as it may promote industrial activity in places with lower GDP, or with a lower economically active population. Thus, companies can be great contributors for job creation and play an important role in local economies, eventually alleviating poverty (Mota et al. 2015). Employment has been the most applied social indicator and has been often modelled as a single-criteria objective function. Some authors propose the maximization of new job opportunities, while other authors choose to minimize social impacts related to employment due to alterations or reconfigurations of their supply chain.

Mota et al. (2015) used the maximization of a social benefit (SB) indicator to promote job creation in less developed regions, thus contributing to regional development. This indicator has a regional factor which can assume different values depending on the purpose of the study, for instance, unemployment rate, population density or income distributions. The model was used in a real case study to help deciding on facility location, where social benefit would arise from job creation in less populated regions, thus the regional factor selected was represented by the division between the population density of continental Portugal and the population of density of the region.

Günther, Kannegiesser, and Autenrieb (2015) estimates the number of dismissals caused by production processes across all periods and locations, based on the process quantities and the respective labour requirements. The same authors (Kannegiesser et al. 2015) suggest a triple bottom line sustainability strategy which integrates multiple and often incompatible objectives within the economic, environmental and social dimension. In contrast to conventional approaches, these authors proposed the minimization of the social impacts caused by employee dismissals associated with delocalization or closing of a facility, being a negative social impact since it creates instability in employee's life.

Devika, Jafarian, and Nourbakhsh (2014) developed a work where, not only job creation but also worker's safety was applied as objective functions. In their model, they included created fixed job opportunities, variable jobs which depend on the used capacity of the facility and work's damage caused either during the establishment of facilities or in the course of the production and management of products.

Another work where social concerns were considered is (Pishvaee et al. 2014). Here the authors used a multi-objective possibilistic programming model with the main goal of designing a sustainable medical supply chain network under uncertainty. Within this model, the authors considered, economic, environmental, and social objectives, where the social dimension was accounted for by calculating the result from adding job creation to the value for local communities' development minus the consumer risk, minus the damage to health.

Some authors have been considering social objectives as constraints in their models, imposing a minimum number of, for instance, jobs created, or minimum health levels and minimum safety requirements (Chardine-Baumann and Botta-Genoulaz 2014).

(Bing shen How 2018) assessed health associated with chemical processes that are often present in chemical industry's supply chain models. These authors developed an Inherent Safety Index (ISI) which goal is to maximize this index while considering not only process safety concerns (e.g., inventory, equipment safety, temperature conditions) but also the chemical inherent safety associated with chemical contact, flammability, corrosiveness, explosiveness, and toxic exposure.

The authors (Charmondusit, Phatarachaisakul, and Prasertpong 2014) developed an Eco-efficiency tool using three key indicators of sustainability: (i) economic indicator: net sale and gross margin; (ii) environmental indicator: energy material, waste disposal and water consumption; (iii) social indicator: incidence rate of accidents, employment, and social responsibility, including issues regarding social poverty. The socio-eco-efficiency is represented as a ratio of the economic value measurement to the environmental value impact measurement, multiplied by the sum of weighted social values. This Eco-efficiency tool was applied to the wooden toy industry where the number of socially responsible projects they support was calculated, as well as the respective investment in their social performance.

Addressing **equity** has proven to be a critical concern when dealing with vaccine and medicine distribution by pharmaceutical companies. According to (Keith Collins and Josh Holder 2021), low-income countries made their first covid vaccine purchase agreements eight months after the United States and the United Kingdom which has resulted in a big difference on the percentage of vaccines' administration: in March 30, 2021, only 0,1% of doses have been administered in low-income countries.

(Cardoso, Duarte, et al. 2015) proposed an integrated approach based on a two-stage stochastic mixed integer linear programming (MILP) model aiming to support the planning of strategical-tactical decisions in the long-term healthcare sector. Their model accounts for **cost and equity aspects**, where the main goal is to minimize the expected cost, ensuring a minimum level of demand satisfaction, thus dealing with demand uncertainty, while equity concerns are modelled as constraints. The study assesses data uncertainty associated with future demand in terms of the number of individuals requiring long-term care as well as the number of services needed by those individuals in the future. The authors assumed that the probability distributions associated with the uncertain parameters are known and a two-stage MILP stochastic approach was used where first-stage decision included the opening and closure of services and second-stage decisions included allocation and reallocation of resources and individuals. The equity aspects considered were **equity of access**, where the goal was to provide healthcare services to patients as close as possible to the place of residence; **equity of utilization**, corresponding to the imposition of a minimum service level across services, avoiding that only the cheapest services are

delivered; **socioeconomic equity**, where unsatisfied demand for the population groups with lower income should not exceed a maximum level, thus avoiding financial dependency situations where individuals are not provided with medicines due to poverty; Lastly, **geographical equity**, where unsatisfied demand across geographical areas should not exceed a maximum level, in order to avoid a complete lack of service delivery in some geographical areas. Rather than maximizing equity, the authors proposed a set of equity satisficing constraints, aiming to respect acceptable levels of equity.

An alternative method to integrate the social component of sustainability is the Guidelines for Social Life Cycle Assessment of Products (**GSLCAP**). It consists in a product-oriented social impact assessment approach, based on LCA methodologies and able to help stakeholders to improve social and socio-economic conditions of production and consumption. The Life-Cycle Assessment (LCA) approach has been described as the most scientifically reliable method to use for studying and evaluating the environmental impacts of a certain product or process. This method considers the whole life cycle of a product or service, since resources' extraction, passing through production, utilization, recycling, and disposal. It quantifies the resources and emissions consumed, as well as the associated effects on health, environmental impacts and resource depletion problems associated with any goods or services. Hence, the social-LCA approach applies an environmental assessment methodology in supply chain design, such as the ReCiPe 2008, to further ease the design and development of the model. Hence, a better modelling of social concerns may result from the incorporation of an analogous integrated approach (Messmann et al. 2020).

In the work of (Ghaderi, Moini, and Pishvaee 2018), the environmental and social life-cycle assessment-based methods were applied to the proposed model for the design of a sustainable bioethanol supply chain network where environmental and social impacts were measured. Moreover, a multi-objective robust programming approach was built to deal with uncertain parameters, where maximizing the mean value of supply chain performance, maximizing feasibility robustness, and minimizing risk were assessed as objective functions.

In light of this, one can look closely at the work developed by (Mota et al. 2018), where a multi-objective mixed integer linear programming model was used, integrating several strategical-tactical decisions while considering the three pillars of sustainability. Additionally, demand uncertainty was considered in this approach using stochastic optimization. Hence, a decision support tool for the design and planning of sustainable supply chains was developed, named as Tripple Bottom Line Optimization Modelling (ToBLoOM).

The following Table 1 summarizes the articles chosen as the most representative for the aim of this thesis, where the goal is to incorporate social quantification within pharmaceutical supply chains while simultaneously accounting for uncertainty conditions.

Table 1. Summary review of representative articles in the pharmaceutical industry sector

Article	Social Indicators	How is it tackled?
(Tsao et al. 2018)	Health and safety of workers Employment	Objective function that maximizes the number of social benefits earned from establishing the network, including: • Number of jobs created, assumed to be dependent on the used capacity and production technology. • Number of hazardous by-products associated with the selection of both technology and materials. • Number of workdays lost due to workplace hazards. **Maximization of social benefits** = Number of jobs created - Number of hazardous by-products – Number of workdays lost
(Pishvaee et al. 2014)	Health and Safety of workers and consumers Employment Local development Safety of workers	**Maximization of Social Responsibility** = Created job opportunities + value for local development – Consumer risk – Damage to worker's health
(Devika et al. 2014)	Employment Safety	Maximization of an objective function integrating: • Fixed job opportunities created. • Variable job opportunities created. • Damages during the establishment of facilities, manufacturing, or handling products.
(Bing shen How 2018)	Employment	Inherent Safety Index: $$\boldsymbol{ISI} = \sum_{n} (I_n^{CI} + I_n^{PI})$$ *I_n^{CI} is the chemical inherent safety; I_n^{PI} is the process inherent safety; n refers to the different process paths*
(Charmon dusit et al. 2014)	Social responsibility Frequency rate of accidents Employment	**Socio-eco-efficiency =** $$\frac{Economic\ value}{\sum weighted\ environmental\ values} \times \sum weighted\ social\ values$$

Table 1. Continuation - Summary review of representative articles in the pharmaceutical industry sector

(Kannegiesser et al. 2015)	Employment	**Minimization of number of employee dismissals in period t:** $N_t = \sum_{l \in L} N_{lt}^{proc}$ N_{lt}^{proc} ***represent the dismissals by production processes over all locations*** $l \in L$
(Mota et al. 2015)	Employment	Social Benefit Indicator: $SB = \sum_{i \in I} w_i \mu_i Y_i$ *w_i is the number of jobs created at region i; μ_i represents a regional factor, which can assume different value; Y_i is a binary variable*
(Cardoso, Duarte, et al. 2015)	Equity of access	Equity of access sastificing constraints: expected travel time per patient accessing intitutional care should not exceed the satisficing level.
	Geographical Equity	Geographical equity satisficing constraints: expected proportion of individuals who belong to each geographical area not receiving long-term care should not exceed the satisficing level.
	Socioeconomic equity	Socioeconomic equity satisficing constraints: expected proportion of lower income individuals not getting long-term cate should not exceed the satisficing level defined.
	Equity of utilization	Equity of utilization satisficing constraints: expected proportion of individuals in need of each type of service but not receiving it should not exceed the satisficing level defined.

3.4 Chapter Final Remarks

This chapter begins with a short overview on the definitions of supply chain and supply chain management. Afterwards, the concept of sustainability was assessed and its relevance and potential impact when addressing supply chain management. By the end of the 20th century, these ideas started to gain more importance by the industry sector. The concept of supply chain has been defined with various scopes, by different stakeholders and its coverage in business context has been expanding over the years, from the supplier to the final consumer, passing through the entire transformation and production process and logistics.

Uncertainty is inevitable in supply chain systems, and it can be present through various types on the course of the supply chain, either externally or internally affecting it. Moreover, uncertainty is very much associated with great levels of risk which can affect the performance of pharmaceutical supply chains with possible negative consequences for public health within a country, especially when addressing vaccines supply chains.

Accounting for uncertainty in the steps of designing, planning, and operating of a sustainable supply chain has been a recent and challenging subject in the literature. In this third chapter, a literature review was made on how to model uncertainty parameters, giving attention towards the three pillars of sustainability and decision levels considerations. Hence, different optimization models were reviewed, which can focus on static or dynamic optimization problems, and despite having the same purpose, they work in distinctive ways, and thus several differences separate them.

Demand uncertainty has been the most studied when modelling uncertainty in supply chains (Govindan, Fattahi, and Keyvanshokooh 2017). Moreover, one can conclude that, depending on the type of uncertainty parameters to be considered, the optimization model to choose may differ. For instance, when historical data is provided or can be easily acquired (e.g., demand), optimization models dealing with exact values should be explored, being stochastic programming the preferred one. (Govindan et al. 2017)'s research shows that a vast majority of the available literature up until 2015 have been greatly considering the usage of the stochastic optimization approach to model uncertain parameters in the supply chain network design. Hence, it is understandable that stochastic programming has greatly contributed to the study of optimization methods, followed by fuzzy and robust programming. Furthermore, the application of more advanced approaches, namely, adaptive robust programming and dynamic programming, combined with either stochastic or robust programming should be explored.

Although uncertainty is an extremely strong parameter to consider, one can find other important factors with influence on the performance of pharmaceutical supply chains. Imposing multiple performance criteria requires an appropriate multi-criteria decision-making method. Thus, the choice of multi-objective programming methods, although not very encouraged when many stakeholders are involved, it can be very helpful since it can include several criteria in the optimization model. As mentioned by (Lemmens et al. 2016), the industrial sector is not specified in most of the manuscripts reviewed, and it is hard to compare the other industrial sectors with the pharmaceutical industry, especially when tackling the complexities of vaccine's supply chains.

To better fulfil the aim of the literature review of the present thesis, which includes dealing with, not only uncertainty aspects, but also economic, environmental, and social concerns, the most representative and used multi-criteria decision models to deal with multiple indicators were summarized.

Important social concerns were identified in order to provide sufficient information to further include in the proposed model. Job creation is recognized as the most discussed and used in the literature, being modelled in different ways by different authors and contributing with many benefits for community development and social welfare. Equity aspects were also identified as crucial to consider, especially when addressing pharmaceutical industry supply chains. However, in a context of a strong pressure to minimize the delivery costs, equity becomes a secondary concern. The work developed by (Cardoso, et al. 2015) was found to be very elucidative when it comes to the understanding of different levels of equity (equity of access, equity of utilization, socioeconomic equity, and geographic equity), as well as how it could be integrated in the modelling of supply chains.

Moreover, the use of LCA-based methods proves to be a potential approach for the environmental pillar assessment. In order to consider and model social concerns, an integrated approach was mentioned by (Messmann et al. 2020) as a valuable approach, where social-LCA methods may be successful.
Lastly, one can conclude that concerns related with both strategical-tactical and tactical-operational levels of decision are not fully studied nor handled in an efficient and effective way, for all the industry sectors, in particular pharmaceutical industry. Therefore, the present dissertation proposes to develop a multi-objective model, in a context of uncertainty, while considering the three pillars of sustainability, focusing on social aspects such as different levels of equity.

3.4.1 Applicability in the Pharmaceutical Industry Sector

The aim of this study includes to address strategical-tactical challenges that can be found within pharmaceutical industry's supply chain, while accounting for sustainability aspects, particularly social concerns, in a context of uncertainty. Hence, and considering the main findings of the literature review provided in both chapters 2 and 3, it is possible to summarize the most relevant papers in the pharmaceutical industry sector by considering key aspects of the developed researched. The following Table 2 presents and categorizes selected articles from this literature review, detailing the decision levels, the optimization model used, uncertainty parameters and sustainability concerns considered in the model. From it, one can observe that, when studying strategical and/or tactical decisions, demand uncertainty is more often studied, stochastic optimization models are commonly used, and sustainable economic objectives are often considered.
The work recently published by (Sazvar et al. 2021) shows to be very complete by applying a multi-objective model to design a resilient supply chain accounting for economic, environmental and social sustainability aspects, while applying uncertainty to various parameters which are considered as important when designing and planning pharmaceutical supply chains. Job creation, societal anxiety leading to a surge in demand (for instance, when disastrous events happen), and deprivation, which occurs when client zone's demand is not satisfied, are the social objectives being considered in (Sazvar et al. 2021)'s work.

Nevertheless, other concerns need to be explored when designing and planning sustainable pharmaceutical supply chains. In particular, social concerns related with equity in access to medicines is yet to be fully incorporated when assessing the social pillar of sustainability. Bearing these concerns in mind, one can find valuable the work developed by (Mota et al. 2018), where a generic multi-objective model is provided to design and plan sustainable supply chains under uncertainty. Hence, it is possible and beneficial to follow the work developed by the mentioned authors in order to integrate the major social concerns identified in the pharmaceutical industry sector, thereby, improving the design and planning of this sector's challenging supply chains.

Table 2. Summary review of representative articles in the pharmaceutical industry sector

Articles	Decision Levels	Uncertainty Parameters	Optimization Approach	Sustainability Considerations	Social concerns
(Tsang et al. 2007)	Strategical	Demand	Multi-scenario/ two-stage stochastic MILP model	Economic	None
(Pishvaee et al. 2014)	Strategical	-Epistemic uncertainty - Supply, process, and demand	Multi-objective fuzzy programming model	Economic, Environmental, Social	- Job creation - Value for local communities (development) - Health and safety
(Cardoso, Duarte, et al. 2015)	Strategical-Tactical	- Distribution capacity - Services' location	Stochastic mixed integer linear programming model	Economic, Social	- Equity of access - Equity of utilization - Socioeconomic equity - Geographical equity
(Thompson and Duintjer Tebbens 2016)	Strategical and Tactical	- Demand - Global vaccine stockpile	Dynamic programming model	Economic	None
(Zahiri, Zhuang, and Mohammadi 2017)	Strategical and tactical	- Uncertainty of the input data	Fuzzy possibilistic-stochastic programming	Economic, Environmental, Social	Job Creation
(Sadjadi et al. 2019)	Strategical and Tactical	- Demand (High or Low priority) - Opening costs of province repositories and district storehouses	Robust programming model	Economic	None
(Sazvar et al. 2021)	Strategical and Tactical	- Demand -Processing and manufacturing times -Shipment times -Travelling costs -Transportation pollution - Resilience parameters	Multi-objective Robust fuzzy programming model	Economic, Environmental, Social	- Job Creation -Societal anxiety -Deprivation

4. Model Conceptualization & Formulation

In the present chapter, a mathematical model revealing a generic sustainable supply chain under uncertainty will be presented and described through its formulation and development, highlighting some considerations on economic, environmental, and social objectives as well as uncertainty parameters' integration. In section 4.1 the problem definition is provided, and the network representation of the investigation procedure is presented. Section 4.2 provides the mathematical formulation of the model with the incorporation of crucial and previously highlighted aspects. Section 4.3 focuses on optimization model selection. Lastly, in section 4.4 the chapter final remarks are stated.

4.1 Problem definition

The conceptualization and development of the decision-support tool for the design and planning of a sustainable supply chain under uncertainty follows the work developed by (Mota et al. 2018), where the authors suggest a decision-support tool for the design and planning of closed-loop supply chains with a focus on strategic-tactical challenges. The generic supply chain representation considers a four-echelon structure, as depicted in Figure 11, where the raw materials flow from suppliers to factories to be transformed into final products. At factories, production technology selection is possible. Once the final products are obtained, they can either flow to warehouses or directly to markets to be sold. At warehouses, storage technology selection is possible. Moreover, transhipment between warehouses is allowed and transportation between different entities may be done by either unimodal or intermodal transportation. Intermodal transportation may include road, sea and air transportation modes, which are included in the model as outsourced by the company. Hub terminals are modelled as supply chain entities since they connect and enable material transport from one transportation mode to the other. The three pillars of sustainability are introduced as objective functions and the boundaries for this analysis are set to only include internal costs of the company, as well as both environmental and social impacts. Generally, uncertainty often present in a sustainable supply chain is associated with parameters such as product demand. But specifically in the pharmaceutical sector, uncertainty may be present in raw materials supply, facilities construction, production times, storage resources used, such as refrigerators and freezers, and not only at factories and warehouses, but also regarding the transportation modes used.

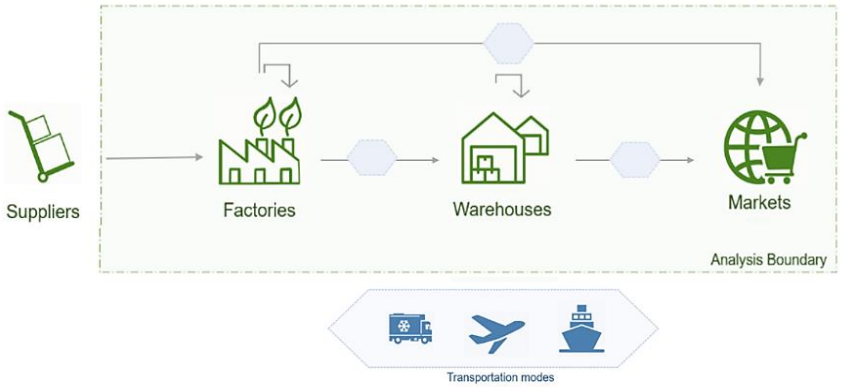


Fig 11. – Network representation, adapted from (Mota et al. 2018)

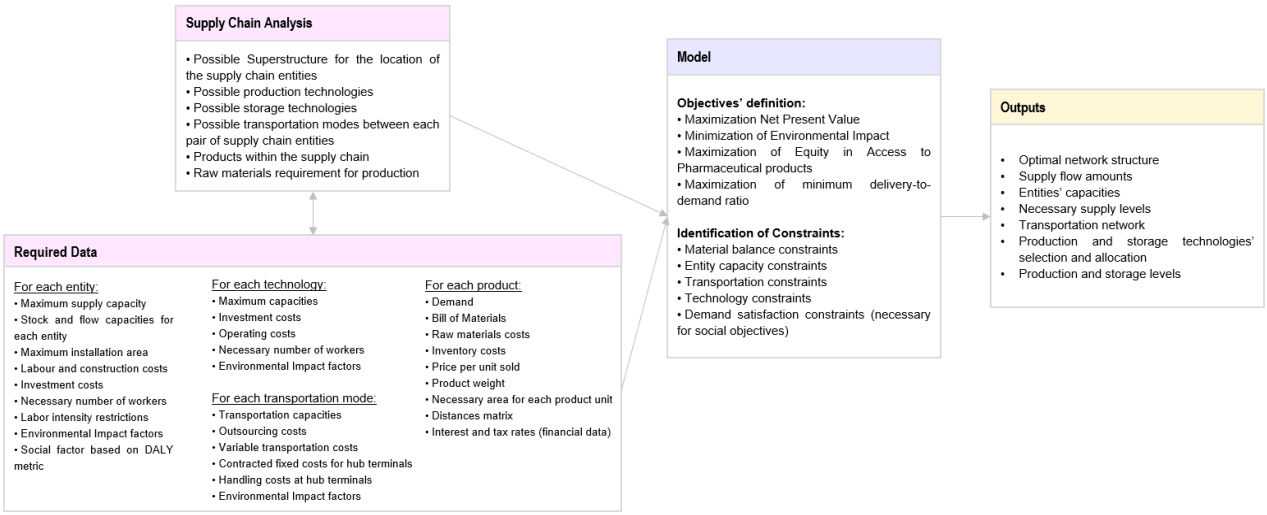


Fig 12. – Conceptual framework of the investigation procedure

Considering the above model features, which account for the pharmaceutical supply chain main characteristics, a conceptual framework is defined, describing the procedure followed in this work (see Figure 12), the input data required include the overall superstructure for the location of entities, production and storage technologies available (to produce pharmaceutical products at factories and to store these products at warehouses, respectively), transportation modes (to transport products between pairs of entities in the supply chain), and also the raw materials required for the production of each product being considered within the supply chain. Moreover, specific data regarding each entity, technology transportation mode and products are needed as input data to the model. The second procedure's step is to model the objective functions while accounting for a set of constraints. Four objective functions are included in the model, one economic, one environmental, and two that include social concerns regarding equity in access to pharmaceutical products.

Henceforth, the present study provides the following contributions:

- Economical assessment based on the calculation of the net present value (NPV) where adaptations are made to the work of (Mota et al. 2018) in order to better portray the particular situation of the pharmaceutical industry.
- Environmental assessment based on the ReCiPe -LCA methodology, considering environmental characterization factors for entities, production technology, storage technology and transport modes (trucks, plane, and boat).
- Social assessment through the incorporation of social indicators related with equity in access to pharmaceutical products and based on the referred approach detailed in subchapter 4.2.1.
- Accounting for uncertainty in supply of raw materials, thus studying the influence of uncertainty at the first critical step of a supply chain.

4.2 Mathematical Formulation

In the present subsection the mathematical formulation of the proposed model following the work developed by (Mota et al. 2018) is provided, beginning with indices and related sets, parameters, followed by decisions variables and constraints. Afterwards, the objective functions related to each pillar of sustainability are presented. For the social assessment, one can find in section 4.2.1 the described approach followed, together with social objective functions and corresponding social constraint. Lastly, in section 4.2.2, the optimization method selected to deal with uncertainty is explained.

Indices and related sets

i,j	Entities or locations	$I = I_{sup} \cup I_f \cup I_w \cup I_c \cup I_{air} \cup I_{port} = I_{loc1} \cup I_{loc2} \cup \dots$	
		I_{sup}	Suppliers
		I_f	Factories
		I_w	Warehouses
		I_c	Markets/Clients
		I_{air}	Airports
		I_{port}	Seaports
		I_{loc1}, I_{loc2}	Location 1, Location 2
a	Transportation Modes	$A = A_{truck} \cup A_{plane} \cup A_{ship}$	
		A_{truck}	Truck
		A_{plane}	Airplane
		A_{ship}	Ship
g	Technologies (i.e., processes)	$G = G_{prod} \cup G_{stor}$	
		G_{prod}	Production Technologies
		G_{stor}	Storage Technologies
m, n	Products	$M = M_{rm} \cup M_{fp}$	
		M_{rm}	Raw Materials
		M_{fp}	Manufactured Products
t	Stages		
s	Scenarios		
γ	Investments		
c	Environmental midpoint categories		
U	Allowed entity-entity connections	$U = \{(i,j) : i,j \in I\}$	
V	Allowed product-entity relations	$V = \{(m,i) : m \in M \wedge i \in I\}$	
H	Product-technology pairs	$H = \{(m,g) : m \in M \wedge g \in G\}$	
		H_{prod}	Product-technology pairs for production technologies
		H_{stor}	Product-technology pairs for storage technologies

F	Allowed flow of materials between entities	$\mathrm{F} = \{ (m, \mathrm{i}, \mathrm{j}) : (\mathrm{m}, \mathrm{i}) \in \mathrm{V} \ \wedge (\mathrm{i}, \mathrm{j}) \in \mathrm{U} \}$
	The description of each subset considers the given examples:	
	F_{INFFP} – final product (FP) that enters (IN) factories (F) and comes from entity i	
	F_{OUTFFP} – final product (FP) that leaves (OUT) factories (F) and goes to entity i	
	F_{OUTW} – allowed flows of products leaving (OUT) warehouses (W)	
Net	Allowed transport modes between entities	$\mathrm{Net} = \{ (\mathrm{a}, \mathrm{i}, \mathrm{j}) : \mathrm{a} \in \mathrm{A} \ \wedge (\mathrm{i}, \mathrm{j}) \in \mathrm{U} \}$
NetP	All allowed network	$\mathrm{Net} = \{ (\mathrm{a}, \mathrm{m}, \mathrm{i}, \mathrm{j}) : (\mathrm{a}, \mathrm{i}, \mathrm{j}) \in \mathrm{Net} \ \wedge (\mathrm{m}, \mathrm{i}, \mathrm{j}) \in \mathrm{F} \}$

Parameters

The considered parameters are grouped by type (entity, product, technology, transportation mode, environment, stochastic, and others), as follows.

Entity related parameters

sc_{mi}^{max}	Maximum supply quantity of product m by supplier i
sc_{mi}^{min}	Minimum supply quantity of product m at supplier i
ec_{i}^{max}	Maximum flow capacity in entity i
ic_{mi}^{max}	Maximum inventory capacity for product m in entity i
ic_{mi}^{min}	Minimum inventory level for product m in entity i
ins_{mi}	Stock of product m in entity I in time period 1
ea_{i}^{max}	Maximum installation area of entity i
ea_{i}^{min}	Minimum installation area of entity i
hhc_i	Handling costs at the hub terminals
w_i	Workers needed when opening entity i
lc_i	Labour cost at location i
$wpsq_i$	Necessary number of workers per square meter for entity i
$sqmc_i$	Construction cost of entity i per square meter

Product related parameters

dmd_{mit}	Demand of product m by client i in time period t
BOM_{mn}^{prod}	Production bill of materials
BOM_{mn}	Bill of materials at warehouses, airports, and seaports
apu_m	Necessary area per unit of product m
$apur_m$	Necessary area per unit of product m assuming product rotation
vpu_m	Necessary volume per unit of product m
psu_{mi}	Price per unit sold of product m for each cliente i
rmc_{mi}	Cost of raw material m supplied by supplier i
pw_m	Weight of product m
sc_m	Inventory cost of product m

Technology related parameters

pc_g^{max}	Maximum production capacity of technology g
pc_g^{min}	Minimum production level of technology g
sc_g^{max}	Maximum storage quantity of technology g
sc_g^{min}	Minimum storage quantity of technology g
opc_g	Operational costs of technology g
w_g	Fixed workers per technology g
tec_g	Installation cost of technology g

Transportation related parameters

ct_a^{max}	Maximum capacity of transportation mode a
ct_a^{min}	Minimum cargo to be transported by transportation mode a
cca_a^{max}	Contracted capacity with airline/freighter
tc_a	Variable transportation cost of transportation mode a per kg km
cfp_i	Contracted payment to the airline or freighter for allocated capacity per stage and/or for hub terminal use

Environmental related parameters

ei_{mgc}	Environmental impact characterization factor of producing/storing product m with technology g at midpoint category c (per product unit)
ei_{ac}	Environmental impact characterization factor of producing product m with transportation mode a at midpoint category c (per kg km)
ei_{ic}	Environmental impact characterization factor of installing entity i at midpoint category c (Per square meter)
η_c	Normalization factor for midpoint category c

Social related parameters

e_i^{DALY}	Social factor of location i based on DALY
δ_{it}	Satisficing level of access of each location i in time period t
θ_{it}	Minimum coverage rate foreach location i in time period t

Other parameters

d_{ij}	Distance between entities i and j (km)
$BigM$	Large number
yth	Number of periods in time horizon (e.g., years)
wpt	Number of weeks per time period
ir	Interest rate

sv_γ	Percentage salvage value of investment γ
tr	Tax rate
wwh	Weekly working hours

Decision variables

Continuous variables

S_{mgit}	Amount of inventory of product m stored with technology g at entity i in time period t
P_{mgit}	Amount of product m produced with technology g at entity i in time period t
X_{maijt}	Amount of product m transported by transport mode a between entities i and j in time period t
YC_i	Necessary capacity of entity i
YCT_{it}	Used capacity in entity i in time period t

Integer variables

Q_{aijt}	Number of trips with transportation mode a between entities i and j in time period t
pr_{mit}	Number of products m allocated to entity i in time period t

Binary variables

Y_i	=1 if entity i is installed
Z_{gmi}	= 1 if technology g that produces/stores product m is installed in entity i

Auxiliary variables at objective functions

NPV	Net Present Value
CF_t	Cash flow in time period t
NE_t	Net earnings in time period t
FDC_t	Fraction of the total depreciation capital in time period t
FCI_γ	Fixed capital investment of investment γ
FCI	Fixed capital investment (total)
DP_t	Depreciation of the capital at time period t
$EnvImp$	Environmental impact indicator
$PharmAccess$	Social indicator based on DALY metric
$PharmDistr$ibution	Social Indicator based on minimum delivery-to-demand ratio

Constraints

The applied constraints are grouped into five categories, namely: material balances; entity capacity; transportation; technology; and, non-anticipatively. These constraints are defined and characterized below from equation (1) to (31).

Material Balances

Material balance at the factories:

$$\sum_{g:(m,g)\in H_{stor}} S_{mgi\,(t-1)} + \sum_{g:(m,g)\in H_{prod}} P_{mgit} = \sum_{g:(m,g)\in H_{stor}} S_{mgit} + \sum_{\substack{n,j:(n,i,j)\in F_{OUTFFP} \\ a:(a,n,i,j)\in NetP}} BOM^{f}_{mn} X_{naijt} \quad , \qquad (1)$$

$$t \in T \wedge m \in M_{fp} \wedge i \in I_f$$

$$\sum_{\substack{j\in I_{sup} \\ a:(a,m,j,i)\in NetP}} X_{maijt} = \sum_{(n,g)\in H_{prod}} BOM^{prod}_{mng} P_{ngit} \quad , m \in M_{rm} \wedge i \in I_f \wedge t \in T \qquad (2)$$

Material balance at the warehouses:

$$\sum_{g:(m,g)\in H_{stor}} S_{mgi\,(t-1)} + \sum_{\substack{n,j:(n,j,i)\in F_{INW} \\ a:(a,n,j,i)\in NetP}} BOM_{mn} X_{najit} = \sum_{g:(m,g)\in H_{stor}} S_{mgit} + \sum_{\substack{n,j:(n,i,j)\in F_{OUTW} \\ a:(a,n,i,j)\in NetP}} BOM_{mn} X_{naijt} \,,$$

$$t \in T \wedge m \in M_{fp} \wedge i \in I_w \qquad (3)$$

Cross-docking at the airports:

$$\sum_{\substack{n,j:(n,j,i)\in F_{INAIR} \\ a:(a,n,j,i)\in NetP}} BOM_{mn} X_{najit} = \sum_{\substack{n,j:(n,i,j)\in F_{OUTAIR} \\ a:(a,n,i,j)\in NetP}} BOM_{mn} X_{naijt} \,, \quad t \in T \wedge m \in M_{fp} \wedge i \in I_{air} \qquad (4)$$

Cross-docking at the seaports:

$$\sum_{\substack{n,j:(n,j,i)\in F_{INPORT} \\ a:(a,n,j,i)\in NetP}} BOM_{mn} X_{najit} = \sum_{\substack{n,j:(n,i,j)\in F_{OUTPORT} \\ a:(a,n,i,j)\in NetP}} BOM_{mn} X_{naijt} \,, \quad t \in T \wedge m \in M_{fp} \wedge i \in I_{port} \qquad (5)$$

Considering the constraints above and according to (Mota et al. 2018), constraint (1) models material balance constraints at factories, during each time unit, thus ensuring that the existing stock of final products (first term of the equation) plus the new products (second equation term) must equal the amount kept in stock plus the outgoing product flow. To simplify, the constraint for the first time period was not included, and thus, when t=1, the variable $S_{mgi\,(t-1)}$ should be replaced by parameter ins_{mi} which corresponds to the initial stock of product *m* in entity *i*.

Additionally, production operation is algo considered by constraint (2) which sets the necessary amount of raw materials to be sent by suppliers.

The warehouse balance is assured by constraint (3), where products in stock at the previous time unit plus the inbound flows must equal the current stock volume plus the outbound flows. At t=1 the variable $S_{mgi\,(t-1)}$ should be replaced by parameter ins_{mi} .

Regarding airports and seaports, they operate in a cross-docking, meaning that stocks amounts are not made available at these sites. Constraints (4) and (5) ensure that for each product and time unit, the inbound flow at each location equals the outbound flow.

Entity Capacity constraints

Supply capacity:

$$\sum_{\substack{a,j:(a,m,i,j)\in NetP \\ (m,i,j)\in F_{OUTSUP}}} X_{maijt} \leq sc_{mis}^{max} Y_i \,, \qquad i \in I_{sup} \wedge m \in M_{fp} \wedge t \in T \wedge s \in S \tag{6}$$

$$\sum_{\substack{a,j:(a,m,i,j)\in NetP \\ (m,i,j)\in F_{OUTSUP}}} X_{maijt} \geq sc_{mis}^{min} Y_i \,, \qquad i \in I_{sup} \wedge m \in M_{fp} \wedge t \in T \wedge s \in S \tag{7}$$

Flow capacity:

$$\sum_{a,m,j:(a,m,i,j)\in NetP} X_{maijt} \leq ec_i^{max} Y_i, \qquad i \in I \wedge t \in T \tag{8}$$

$$\sum_{a,m,i:(a,m,i,j)\in NetP} X_{maijt} \leq ec_j^{max} Y_j, \qquad j \in I \wedge t \in T \tag{9}$$

Stock capacity:

$$\sum_{g:(m,g)\in H_{stor}} S_{mgit} \leq ic_{mi}^{max} Y_i, \qquad m \in M_{fp} \wedge i \in \left(I_f \cup I_w\right) \wedge t \in T \tag{10}$$

$$\sum_{g:(m,g)\in H_{stor}} S_{mgit} \geq ic_{mi}^{min} Y_i, \qquad m \in M_{fp} \wedge i \in \left(I_f \cup I_w\right) \wedge t \in T \tag{11}$$

Entity capacity:

$$YCT_{it} = \sum_{maj:(m,a,j)\in NetP} apur_m X_{majit} + \sum_{\substack{m:(m,i)\in V \\ g:(m,g)\in Hstor}} apu_m S_{mgit} \,, \quad i \in I_f \cup I_w \wedge t \in T \tag{12}$$

$$YC_i \geq YCT_{it} \,, \qquad i \in I_f \cup I_w \tag{13}$$

$$YC_i \leq ea_i^{max} Y_i \,, \quad i \in I_f \cup I_w \tag{14}$$

$$YC_i \geq ea_i^{min} Y_i \,, \quad i \in I_f \cup I_w \tag{15}$$

Entity existence constraints:

$$\sum_{a,m,i,t:(a,m,i,j)\in NetP} X_{maijt} \geq Y_j\,, \qquad j \in I \ \wedge t \in T \tag{16}$$

$$\sum_{a,m,i,t:(a,m,i,j)\in NetP} X_{maijt} \geq Y_i\,, \qquad i \in I \ \wedge t \in T \tag{17}$$

Constraints (6) to (17) are intended to set capacity limits: maximum and minimum supply of raw-materials – constraints (6) and (7), flow amounts between each pair of entities in the network – constraints (8) and (9), minimum and maximum stock capacity at factories and warehouses – constraints (10) and (11). These constraints ensure that the related variables can only differ from zero if the facilities integrate the supply chain, that is, when Y_i =1.

While the above entities capacities are pre-established, the installation area of warehouses and factories is modelled differently, being a matter of decisions. Hence, with equation (12), the capacity needed at each time unit at each facility is defined by guaranteeing that it is sufficient to accommodate the incoming flow and the current stock levels. On the other hand, constraint (13) establishes the maximum capacity required over the time horizon. Considering this, it should be noted that, and according to (Mota et al. 2018), the authors have followed a minmax approach, since variable YC_i is minimized at the economic objective function (addressed below). Moreover, constraints (14) and (15) are used to limit the installation area at each location, with a maximum and minimum, respectively.

Finally, constraints (16) and (17) have been included in the model in order to ensure that entities are only installed if there is material flow going through them, which can also be viewed as minimum flow constraints. Finally, for such an extension, one should define the minimum flow parameter, which should be multiplied to variable Y_i (similarly to constraint (9)).

Transportation constraints

Physical constraints:

$$\sum_{\substack{a,j:(a,m,j,i)\in NetP \\ j\in I(I_{air}\cup I_{\sup})}} X_{majit} = \sum_{\substack{a,j:(a,m,i,j)\in NetP \\ j\in I_{air}}} X_{maijt}\,, \qquad m \in M_{fp} \ \wedge i \in I_{air} \ \wedge t \in T \tag{18}$$

$$\sum_{\substack{a,j:(a,m,j,i)\in NetP \\ j\in I(I_{port}\cup I_{\sup})}} X_{majit} = \sum_{\substack{a,j:(a,m,i,j)\in NetP \\ j\in I_{port}}} X_{maijt}\,, \qquad m \in M_{fp} \ \wedge i \in I_{port} \ \wedge t \in T \tag{19}$$

Necessary number of trips:

$$\sum_{m:(a,m,i,j)\in NetP} X_{maijt} \leq ct_a^{max} Q_{aijt}\,, \qquad (a,i,j) \in Net \ \wedge t \in T \tag{20}$$

$$\sum_{m:(a,m,i,j)\in NetP} X_{maijt} \geq ct_a^{min} Q_{aijt}\,, \qquad (a,i,j) \in Net \ \wedge t \in T \tag{21}$$

$$Q_{aijt} \leq BigM.Y_i\,, \qquad (a,i,j) \in Net \ \wedge t \in T \tag{22}$$

$$Q_{aijt} \leq BigM.Y_j\,, \qquad (a,i,j) \in Net \ \wedge t \in T \tag{23}$$

Contracted capacity with road, air and sea carrier:

$$\sum_{m:(a,m,i,j)\in NetP} X_{maijt} \ \leq cca_a^{max}\,, \qquad (a,i,j) \in Net \ \wedge a \in A_{plane} \cup A_{ship} \cup A_{trucks} \ \wedge \ t \in T \tag{24}$$

Constraint (18) and (19) state that material flow entering an airport/seaport must be transported by plane/boat to another airport/seaport, respectively. Moreover, the network superstructure established when defining the provided sets ensures that intercontinental trips can only make use of air or sea transportation.

Through constraint (20) it is ensured that the number of trips between entities times the capacity of the corresponding transportation mode is larger than the flow between entities. Additionally, equation (21) imposes minimum cargo in each transportation mode. Constraints (22) and (23) assure that variable Q_{aijt} is only activated if both the entities of origin and destination are installed, respectively.

On another note, equation (24) establishes that the transportation performed by either air, sea or road in each stage is limited by a contracted capacity, respectively.

Technology constraints

Technology capacity:

$$P_{mgit} \leq pc_g^{max} Z_{gmi}\,, \qquad i \in I_f \wedge (m,g) \in H_{prod} \wedge t \in T \tag{25}$$

$$S_{mgit} \leq sc_g^{max} Z_{gmi}\,, \qquad i \in I_w \ \wedge (m,g) \in H_{refr} \wedge t \in T \tag{26}$$

$$P_{mgit} \geq pc_g^{min} Z_{gmi}\,, \qquad i \in I_f \wedge (m,g) \in H_{prod} \wedge t \in T \tag{27}$$

$$S_{mgit} \geq sc_g^{min} Z_{gmi}\,, \qquad i \in I_w \ \wedge (m,g) \in H_{refr} \wedge t \in T \tag{28}$$

Technology installation:

$$\sum_{g:(m,g)\in H_{prod}} Z_{gmi} \ \leq Y_i\,, \qquad m \in M_{fp} \ \wedge \ i \in I_f \tag{29}$$

$$P_{mgit}, X_{maijt}, S_{mgit}, YC_i, YCT_i \geq 0 \tag{30}$$

$$K_{ai}, Q_{aijt} \ \geq 0 \ \ and\ integer$$

$$Y_i, Z_{gmi} \ \in \{0,1\}$$

Equations (25) – (30) represent the technology constraints. Constraints (25) and (26) model production and storage maximum capacity, respectively, while constraints (27) and (28) impose minimum production and storage levels in each stage. Additionally, they also ensure that, if the technology is not established ($Z_{mgi} = 0$), the corresponding manufacturing and refrigerating storage volumes are set to zero. Moreover, as stated in equation (29), at most one production technology can be allocated to open

facilities (when $Y_i = 1$). Different production and storage technologies can differ in the number of necessary workers to operate them, production/storage capacities, environmental impact and involved costs. Lastly, constraints (30) entail the domains of the decision variables.

Objective Functions

When modelling a multi-objective problem, there are two options, which are either by condensing multiple objectives in the same objective function or by modelling the objective functions separately according to each specific objective. If it is the case of modelling all the pretended objectives together in a single objective function, the method has an additional step of using weighting factors. Nevertheless, some negative consequences may emerge, specifically regarding subjectivity and the uncertainty, which affect the clarity of the model and making it more difficult to comprehend the trade-offs between the objectives. Hence, each objective of the triple bottom line –economic, environmental, and social – were modelled as individual objective functions.

Economic Objective Function

Equation (31) represents the economic objective function, which maximizes the NPV for the time horizon modelled.

$$\max NPV = \sum_{t \in T} \frac{CF_t}{(1+ir)^t} - \sum_{\gamma} FCI_\gamma \tag{31}$$

$$CF_t = \begin{cases} NE_t & t = 1, \dots \dots NT-1 \\ NE_t + \sum_{\gamma} (sv_\gamma + FCI_\gamma) & t = NT \end{cases} \tag{32}$$

$$\begin{aligned} NE_t = (1-tr) \Bigg[& \sum_{\substack{(m,i,j) \in F_{INCFP} \\ (a,m,i,j) \in NetP}} psu_{mi} X_{maijt} - \Bigg(\sum_{\substack{(m,i,j) \in F_{OUTSUPRM} \\ (a,m,i,j) \in NetP}} rmc_{mi} X_{maijt} + \sum_{\substack{(m,g) \in H_{prod} \\ i \in I_f}} opc_g P_{mgit} \\ & + \sum_{\substack{(m,g) \in H_{stor} \\ i \in (I_f \cup I_w)}} opc_g S_{mgit} + \sum_{\substack{(a,m,i,j) \in NetP \\ a \in (A_{plane} \cup A_{boat} \cup A_{trucks})}} tc_a . pw_m . d_{ij} . X_{maijt} \\ & + \sum_{\substack{(a,m,i,j) \in NetP \\ (j \in I_{plane} \wedge i \notin I_{plane}) \cup (j \in I_{boat} \wedge i \notin I_{boat})}} hhc_j . X_{maijt} + \sum_{i \in (I_{plane} \cup I_{boat})} cfp_i . Y_i \\ & + \sum_{\substack{(m,g) \in H_{stor} \\ (m,i) \in V}} sc_m S_{mgit} + \sum_{i \in (I_f \cup I_w)} w_i . lc_i . wwh . wpt . Y_i \\ & + \sum_{i \in (I_f \cup I_w)} wpsq . lc_i . wwh . wpt . YC_i + \sum_{\substack{(m,g) \in H \\ i \in I_f}} w_g . lc_i . wwh . wpt . Z_{gmi} \Bigg) + tr . DP_t \Bigg] \end{aligned} \tag{33}$$

$$DP_t = \sum_\gamma DP_{\gamma t} FCI_\gamma \tag{34}$$

$$FCI_\gamma = \begin{cases} \sum_{I \in I_f \cup I_w} sqmc_i . YC_i & \gamma = 1 \\ \sum_{(m,g) \in H} tec_g . Z_{gmi} & \gamma = 2 \end{cases} \quad (35)$$

Equation (31) represents the sum of the discounted cash flows of each stage, at interest rate ir. In order to obtain the necessary data, auxiliary equations have been considered, such as equation (32), which represents the cash flow calculation for each time period, obtained through the net earnings NE_t for every stage excluding the final one, where the recovery of the salvage value, sv_γ, of each type of investment, FCI_γ, is also considered. Moreover, the net earnings of each time period are considered in equation (33), and thus obtained through the difference between incomes and overall costs, where the former is represented by the amount of products sold times the price per unit, psu_m, and the latter by the following costs:

- raw material costs (first term)- number of products purchased from suppliers times the unit raw material cost (rmc_{mi});
- production operating costs (second term) - amount of final products produced (P_{mgit}) times the unitary operating costs of each production technology (opc_g);
- storage costs (third term)- amount of final products stored with technology g (S_{migt}) times the unitary operating cost of storage technology (opc_g);
- transportation costs for road, air and sea transportation (fourth term)- flow of products transported through transportation mode a (X_{maijt}) times the transportation cost per kg.km (tc_a) times the weight of each unit of product transported (pw_m) times the distance traveled (d_{ij});
- hub handling costs (fifth term)- flow of products through the hub terminals at the airports or seaports times the unit handling costs at these terminals (hhc_j);
- airline/freighter contracted costs - contracted costs with the airliner/freighter (cfp_i) for the allocated transportation capacity and/or for hub terminal use per time period (sixth term), where it is assumed that a contract is established with companies operating at hub terminals;
- inventory costs (seventh term)- amount of product in stock (S_{mit}) times the unitary stock cost, (sc_m);
- labour costs at entities (eighth and ninth terms) and labour costs for the use of technologies (tenth term) – these costs vary with the fixed (w_i), the variable ($wpsq$) number of workers at each entity and the number of workers needed for each technology (w_g), respectively. Moreover, the labour costs at each location (lc_i), the weekly working hours (wwh) and the number of weeks per time period (wpt) are also considered in labor costs' calculations.

The last term of equation (33) describes the depreciation of the invested capital, DP_t, with the tax rate represented by tr. Hence, the depreciation is calculated for each type of investment considered, γ , as represented in equation (34).

Finally, the fixed capital investment, FCI, is described in equation (35) considering the following terms:

- facilities investment (first term)- necessary installation area (YC_i) times the construction costs which vary according to the location of the facilities ($sqmc_i$);
- technologies investment (second term)- number of installed technologies Z_{gmi}, times the installation cost of each technology (tec_g);

Environmental Objective Function

The environmental objective function is obtained through the minimization of the environmental impact represented in equation (36), and modelled by the ReCiPe methodology, thus following the work developed by Mota et al. (2018). Therefore, and as the functional unit is the supply chain, the aggregated obtained results should only be used to compare distinctive supply chain designs and decisions and not as a tool to accurately determine the environmental impact of the supply chain.

$$\min EnvImpact = \sum_{c} \eta_c \left(\sum_{\substack{t \in T \\ (m,g) \in H}} ei_{mgc} pw_m P_{mgit} + \sum_{\substack{t \in T \\ (m,g) \in H}} ei_{mgc} vpu_m S_{mgit} + \sum_{\substack{t \in T \\ (a,m,i,j) \in H}} ei_{ac} pw_m d_{ij} X_{maijt} + \sum_{\substack{t \in T \\ (a,m,i,j) \in H}} ei_{ic} YC_i \right) \quad (36)$$

Thus, and according to equation (36), the environmental impact of four supply chain activities is calculated for each midpoint category c, namely:

- environmental impact of production (first term)- environmental impact per kg produced with technology g (ei_{mgc}) times the weight of product m times the amount of final products produced (P_{mgit});
- environmental impact of storage technology (second term)- environmental impact per volume stored, with technology g (ei_{mgc}) times the volume of product m per unit times the amount of final products stored (S_{mgit});
- environmental impact of transportation (third term)- environmental impact per kg km transported with transportation mode a (ei_{ac}) times the weight of each unit of product transported (pw_m) times the distance travelled (d_{ij}) times the product flow (X_{maijt});
- environmental impact of entity installation (fourth term)- environmental impact per square meter of entity i installed (ei_{ic}) times the installed area (YC_i);

The final calculation of the environmental impact is given by the normalised sum of the impact of each individual activity described just now with the normalization factor η_c . The use of this normalisation factor is justifiable since the results of each impact category need to be in the same units.

4.2.1 Social assessment approach

As concluded in chapter 3, the overall literature's contribution on the assessment of the social pillar of sustainability relies on aspects such as job creation, health, and safety of workers. However, it is crucial to account for social equity concerns when planning and designing a pharmaceutical sustainable supply chain.

In the present dissertation, the Access to Medicines Index (AtMI), mentioned in subchapter 2.1, was chosen as the starting point for the development of the quantitative social indicators. This index considers three main technical areas, with its indicators each: governance of access, research & development, and product delivery. The third technical, which accounts for 55% of the total index, represents the main concerns of the supply chain that are important to be tackled, being measured in a qualitative way by the index. The most relevant indicators within the product delivery technical area were grouped into three main qualitative indicators: Registration and coverage (1), donation programmes (2) and equitable pricing strategies (3). The following table organizes the main ideas behind these three groups of qualitative indicators.

Table 3. Description and grouping of indicators within the technical area of product delivery

Indicator description (AtMI)	Group of indicators	Why is the indicator important when addressing equity in access for medicines?
Registration	Registration and Coverage (1)	A product can only be marketed in a country once it is registered for sale. This registration allows for distribution, marketing, and patient access to life-saving products across the country. In lower-income countries, registration of newly launched products typically occurs less frequently and usually later than in higher-income ones with larger markets.
Coverage strategies		
Ad hoc donations	Donation programmes (2)	Products donations were identified by this index as crucial programmes that play an important role in the management of many diseases closely related to poverty (inadequate sanitation systems), close contact with infectious vectors, among others. Thus, it's important to identify populations with no capacity to acquire products and thus helping them with donations.
Long-term donation programmes		
Supranationally procured products: access strategies	Equitable pricing strategies (3)	Equitable pricing strategies are at the heart of patient-oriented business operations. Top-performing companies consider affordability and continuous supply to increase patient reach at all levels of the income pyramid. They enter into supranational procurement agreements and develop patient assistance programmes (PAP) to provide personalized, income-tailored support based on intra-country pricing solutions and economic conditions.
Health practitioner-administered products: access strategies		
Self- administered products: access strategies		

Two important questions arise at this point: firstly, it is important to understand how the index addresses the qualitative indicators mentioned in Table 3. Afterwards, it is needed to construct a quantitative way to account for these aspects that AtMF finds as the most important when tackling equity in access.

- **Registration and coverage**: the index look for companies to file new products for registration widely and rapidly across low- and middle-income countries, starting where the need is the highest. Hence, there is an opportunity for companies to prioritize countries with high burden of disease when planning for registration, especially for products on the WHO Essential Medicines List (EML). This requires tactical planning throughout the research and development phase. Such access planning can help facilitate registration and rapid access to new products in a higher number of countries.
- **Donation programmes**: the index evaluates if companies are able to identify populations with less or no capacity to acquire medicines and help these countries with donations. The index includes geographical scope, timeline scale and patient reach of the company's donation programmes. Additionally, the index refers that companies should have the responsibility to ensure that their programmes lead to sustainable improvements in access to medicine, therefore ensuring that populations can continue to access donated products for as long as they are needed, both during an endemic period and after.
- **Equitable Pricing strategies**: The index looks for companies that assess Equitable Pricing strategies for relevant products in low- and middle-income countries (subsets of products: Supranationally procured products, Healthcare practitioner administered products and Self-administered products), for instance, by setting prices within the ability of specific populations to pay, with reference to a range of socioeconomic factors. Thus, the index focuses on whether equitable pricing strategies are being applied in the countries with the highest burden and lowest ability to pay (i.e., in priority countries).

These three groups of indicators help improving **availability** and **affordability** of medicines, helping countries where the need is the highest and with lower ability to pay for the products, thus improving equity in access.

Social Objective Function

As the goal of the present social study is to provide a sustainable supply chain model formulation with a mechanism to evaluate the social pillar in terms of equity, while applying an adequate methodology that can bring great importance to the model, this is here explored. Hence, and considering the main findings described in subchapter 4.1, through the study of the indicators defined by the AtMI, will be used to construct a quantitative way to measure equity in access to medicines.

As mentioned, availability and affordability are considered by the index as the two indicators that mostly allow for an equal access to medicines, and within these indicators, AtMI considers that countries with highest disease burden and less ability to pay need to be prioritized. The burden of disease of a country can be measured through a metric called DALYs (Disability Adjusted Life Years), which reflects the sum of mortality and morbidity, providing a more encompassing view on health status of a population (Max

Roser and Hannah Ritchie, 2016). DALYs are a standardized metric which allows for a direct comparison of disease burdens across countries over time, or between populations within a country. Conceptually, one DALY represents one lost year of healthy life, i.e., corresponds to one lost year in good health due to premature death, disease, or disability.

Moreover, according to *Our World in Data* (Max Roser and Hannah Ritchie, 2016), countries with the highest disease burden correspond to the countries with the lower levels of health expenditure. In this way, by using the metric DALY, we are not only accessing countries with higher burden of disease but also countries with lower ability to pay for products, thus addressing both availability and affordability indicators using a quantitative approach (Abbafati et al. 2020).

Henceforth, the above-mentioned metric is incorporated into an objective function, obtained through the maximization of pharmaceutical accessibility, as represented in equation (38):

$$\max PharmaAccess = \left(\sum_{i \epsilon (I_f \cup I_w)} e_i^{DALY} \, . \, Y_i \right) \tag{38}$$

According to equation (38), pharmaceutical accessibility is calculated taking into account the entity related parameter e_i^{DALY}, which represents the social factor of location i based on DALYs metric, and the decision variable Y_i. By analysing this same equation, one can note that, the higher the disease burden, the higher will be the value of the social factor, thus prioritizing the location of entity i in countries with higher disease burden, as well as countries with lower levels of health expenditure.

In order to study a possible approach to distribute pharmaceuticals in an equitable way among countries, one can follow the work developed by (Rastegar et al. 2021) and build the following equation (39):

$$\max PharmaDistribution = min \left(\frac{pr_{mit}}{dmd_{mit}} \right) = \min(r) \tag{39}$$

This second objective function distributes pharmaceuticals equitably by maximizing the minimum-delivery-to-demand ratio (r) in each country, thus enforcing access equity among countries. The factor $\frac{pr_{mit}}{dmd_{mit}}$ corresponds to the delivery-to-demand ratio, calculated by the ration between the variable pr_{mit} and the parameter dmd_{mit}. In other words, the factor represents the ratio between the amount of product m allocated to a country where entity i is located and the total demand of the same product that country i needs, in time-period t.

On another note, and in times of economic and financial crisis, the aim is often to minimize costs while respecting acceptable (non-optimal) levels of equity, rather than maximizing equity. To attain this possibility, which is of great importance when addressing the pharmaceutical industry supply chain, the following equation was used as a social constraint, based on both works of (Cardoso et al. 2015) and (Rastegar et al. 2021):

$$\left(1 - \frac{pr_{mit}}{dmd_{mit}}\right) \leq \delta_{it} \quad \leftrightarrow \quad pr_{mit} \geq \theta_{it} \times dmd_{mit} \tag{40}$$

By analysing this social constraint, one can note that the two equations represent two different ideas and choosing one over another will depend on what is more suitable for the case being study. The idea behind the equation on the left follows the work developed by Cardoso et.al where the percentage of demand that is not satisfied should not exceed the satisficing level defined δ_{it} . The constraint on the right is used to guarantee that pharmaceuticals are assigned to each location at least at the coverage rate (θ_{it}). Hence, the social constraint could be used to guarantee minimum levels of pharmaceuticals distribution across regions and avoiding a total lack of medication provision in some geographical areas, as well as ensuring a minimum level of access for those with lower ability to pay for pharmaceuticals, thus avoiding situations of lack of provision due to poverty.

4.2.2. Optimization method selection

Based on the previous highlighted challenges, the present subchapter aims to present the model conceptualization by discussing and reviewing relevant research which will guide the future model formulation, namely on a possible assessment of social considerations and on the uncertainty incorporation. Therefore, this subchapter is dedicated to describing the selected optimization method to model uncertainty highlighting key considerations.

Considering the review given in subchapter 3.2 on optimization methods frequently used to model uncertainty in supply chains, stochastic optimization was the selected approach given its characteristics. In stochastic optimization, probability distributions of the uncertain parameters are assumed as known a *priori* and the uncertainties are often characterized by discrete realizations of the uncertain parameters, as an approximation to the original probability distribution. Thus, the main goal of stochastic programming is to optimize the expected value of an objective function over all the scenarios.

Two-stage stochastic programming is a special case of stochastic programming where, in the first stage, 'here and now' decisions are made, at the beginning of the planning horizon, being regarded as first-stage design decisions. Then, these decisions are followed by the resolution of uncertainty, and at a second stage, recourse decisions, which are known as 'wait and see' decisions, are taken and interpreted as corrective measures at the end of the period. A conceptual representation of a two-stage stochastic problem is provided in Figure 13, as well as the corresponding scenario tree.

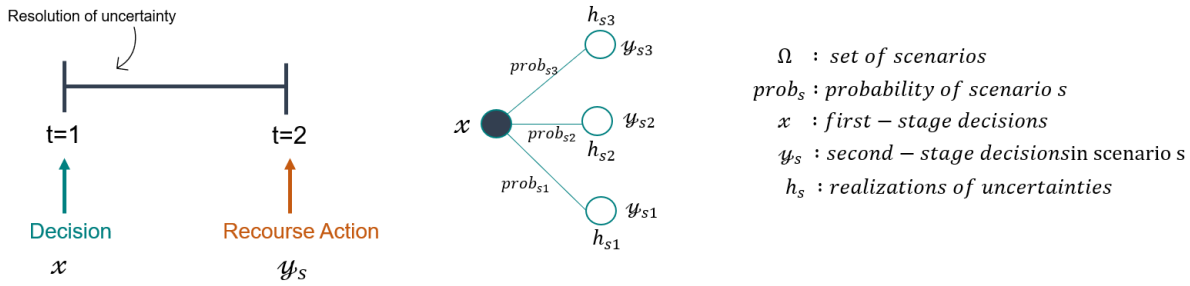


Fig.13. Conceptual representation of a two-stage problem (left) and s scenario tree (right), based on (Li and Grossmann 2021)

As demonstrated in the representation of Figure 13, Ω represents the set of scenarios being considered, h_s represents the probabilities of each scenario s, x represents the first-stage decisions and y_s represents the second-stage decisions for each scenario.

4.3 Chapter Final Remarks

In the present chapter, mathematical formulation is provided for several key points, such as the integrated supply chain design and planning optimization model integrating several interconnected supply chain decisions, namely: supplier selection; raw material purchase planning; facility location and capacity installation; technology selection; production planning; transportation network definition; and, inventory planning. Additionally, the uncertainty incorporation has also been accounted for, through the application of a two-stage stochastic optimization approach based on the scenario tree concept.

Four objective functions are presented so as to include the three pillars of sustainability. The economic pillar is accounted for through the calculation of NPV, aiming to be maximized. The environmental concerns are addressed through the application of the Life Cycle Assessment (LCA) method, being the goal to minimize the environmental impact. Finally, the social pillar is accounted for by maximizing pharmaceutical access to medicines and vaccines. Firstly, by prioritizing the location of entities in countries with higher burden of disease (using the metric DALY), and secondly, by maximizing the minimum delivery-to-demand-ratio. Moreover, a constraint is considered in order to guarantee minimum levels of access to pharmaceutical products, by respecting a minimum coverage rate, or by respecting a satisficing level defined.

Additionally, uncertainty incorporation has also been accounted for, through the application of a two-stage stochastic optimization approach based on the scenario tree concept.

5. Model Validation & Results Analysis

In this chapter, the formulated model is applied to representative case-study of the Sanofi Group, one of the biggest producers of meningitis vaccines. The results obtained are analysed and discussed in order to achieve relevant conclusions and insights on the work developed. This chapter is organized as follows. In section 5.1 the case-study is defined and characterized. In section 5.2, the results obtained with the model application to the case-study are analysed and discussed. Lastly, in section 5.3, the chapter final remarks are stated.

5.1 Case-Study: A pharmaceutical Industry supply chain

The developed model is applied to a case-study in order to serve as a basis for results analysis and validation of the model. Hence, in the present subchapter, a study concerning the supply chain of Sanofi, a French pharmaceutical company, is performed based on its provided reports of year 2020, as well as on information provided publicly by the company. However, it should be mentioned that due to the lack of substantial data, the case-study serves only as a representative study of a supply chain network.

Sanofi Pasteur is the vaccines division of Sanofi and represents a world leader in the vaccine industry and an important supplier of life-saving vaccines all over the world as well as in funded international markets such as UNICEF, the Pan American Health Organization (PAHO) and the Global Alliance for Vaccines and Immunization (GAVI). For over 45 years, Sanofi Pasteur has been crucial in the fight of meningococcal meningitis epidemics and in driving meningitis vaccine evolution. Meningococcal meningitis is a disease which anyone can get, anywhere in the world and can be prevented through vaccination. According to the Centre for Disease Control and Prevention (CDC), about 1.2 million cases of meningococcal meningitis are estimated to occur worldwide every year. Furthermore, and according to Lancet (Abbafati et al. 2020), meningitis is one of the infectious diseases in the top ten causes of DALYs in children younger than 10 years old. A global market study developed by WHO and the market information for access to vaccines refers that the forecast global demand for the year 2019 was near 170 million doses (World Health Organization and Market Information for Access to Vaccines 2019). Hence, there is still a long way to go to ensure routine, broad immunization across age groups and countries.

When looking further into details concerning company's vaccine supply chain network (Sanofi Pasteur 2021), one can note that there are 12 production sites and 5 main R&D sites around the world, being more that 2.5 million doses of vaccines produced daily and more than 500 million euros invested every year(Social 2020). Each production site is dedicated to the production of specific active pharmaceutical ingredients (API) of vaccines being manufactured by the company. For instance, Sanofi Pasteur production site in Argentina is dedicated to produce a specific hepatitis B vaccine, while in Thailand production relies on vaccines against poliomyelitis, measles, mumps, rabies and diphtheria. Currently, Sanofi Pasteur has meningococcal meningitis' vaccine being manufactured at production sites located in U.S. (Pennsylvania), Canada (Toronto), Europe (France), and Asia (India). Moreover, locations of warehouses were identified in U.S. (Pennsylvania), Canada (Toronto), Europe (France), Asia (India) and Latin America (Brazil).

By using the present representative case-study, the goal is to determine if and where a new factory dedicated to the production of meningococcal meningitis vaccine could be installed, as well as new warehouse's locations to which vaccines may flow after being produced at factories. Possible scenarios will be analysed considering the different sustainability objectives, giving a special emphasis to the social pillar since it requires an increased attention when planning and designing a vaccine supply chain network.

According to the map provided by (The World Health Organization 2020) and presented below in Figure 14, Africa, Middle east, Latin America and Asia appear to be the areas with higher incidence of meningitis per 100 000 population.

The highest incidence of meningitis disease in the so called "African meningitis belt" make this area a plausible location to install a factory. Moreover, according to a study developed by (Songane 2018), vaccination coverage in many countries in Africa is very low and vaccine supply chains are far from effective, thus contributing to constant outbreaks of vaccine-preventable diseases. The same study reveals that promoting research, development, and production of vaccines in African countries can be a potential long-term solution to improve access to this product. Therefore, the 6th market (Africa) considered by the company constitutes a potential location to install a new factory, more precisely in Kenya due to its proximity to the seaport.

Regarding possible warehouse locations, besides the ones already existent, those close to the referred global markets are included as potential sites. Hence, the locations considered in this case-study include U.S. (Pennsylvania), Canada (Toronto), Europe (France), Asia (India) and Latin America (Brazil). Two warehouses in Africa, one in Kenya (near the new possible factory location) and one in Nigeria, are included in the case-study, aiming to cover the meningitis belt area. Moreover, additional warehouse locations are considered to cover other markets: Middle East (Israel), Eurasia (Russia) and Australia.

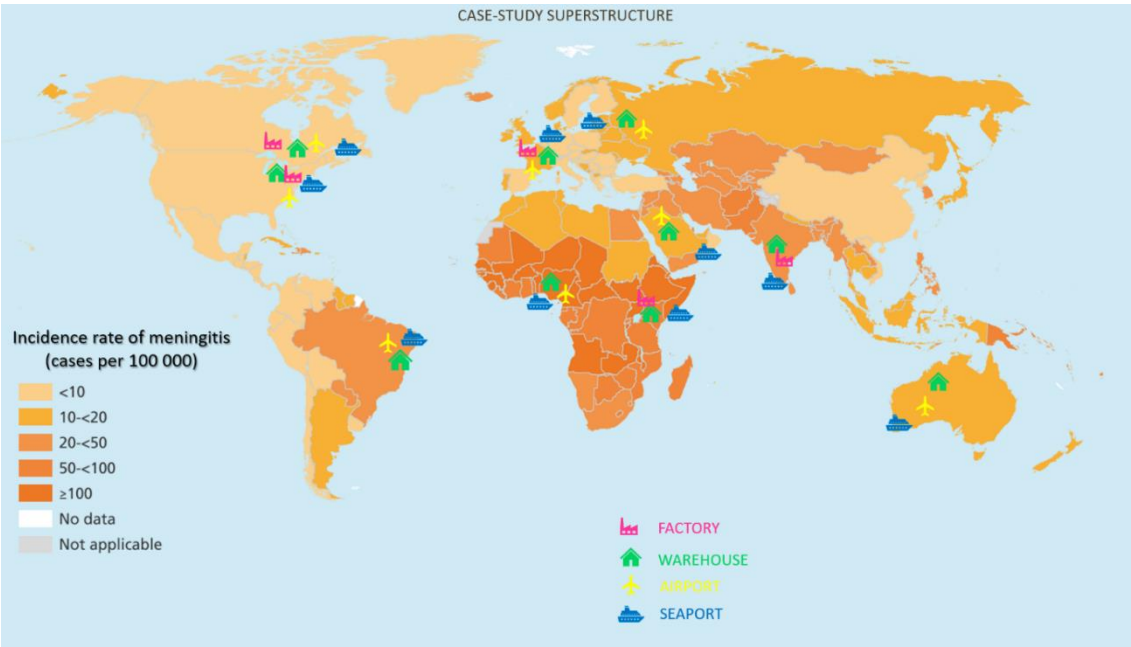


Fig.14 – Case-study superstructure and *Incidence rates of meningitis per 100.000 population by country in 2017 (WHO, 2020)*

In order to transport vaccines from factories to warehouses or directly to markets, and from warehouses to markets, transportation by road, air and sea were considered. The possibility of transporting products by plane and ship, forces a connection between airports and seaports. Regarding transportation by road, trucks of smaller and bigger capacity were considered. Rail transportation, on the other hand, is not included in the case-study to be modelled in this work, but it can be simply considered by adding/changing the model inputs and/or adding/replacing the location of the hub terminals.

Two distinct transportation options may be used by selecting different combinations: **unimodal** transportation is performed only by road (trucks), whereas **intermodal** transportation may occur with combination of road (truck), air (plane) and sea (ship) transportations. Intermodal transportation system starts with road transportation, which takes products from the entity of origin to an airport or seaport. At these places, products are transhipped to the airplane or ship and transported to another airport or seaport, where the products are transhipped to a truck, or several trucks, and transported to their destination. It is considered that transports have the appropriate storage conditions to transport vaccines, being reflected in transportation costs.

The superstructure representing this case-study is presented in Figure 14 and a code was attributed to each entity in Table 4. The time horizon considered is ten years with annual increments for planning decisions. The time window considered in each time period arises from the average manufacturing lead time for vaccines, which is, approximately, 12 months.

Table 4. Entities codification in the case-study superstructure

Suppliers	Factories	Warehouses	Airports	Seaports	Markets
U.S (Pennsylvania) **S1**	U.S (Pennsylvania) **F1**	U.S.(Pennsylvania) **W1**	Harrisburg (U.S.) **Air1**	Philadelphia (U.S) **Sea1**	U.S **C1**
Canada (Toronto) **S2**	Canada (Toronto) **F2**	Canada (Toronto) **W2**	Toronto (Canada) **Air2**	Toronto (Canada) **Sea2**	Europe **C2**
Europe (France) **S3**	Europe (France) **F3**	Europe (France) **W3**	Paris (France) **Air3**	Rotterdam (Netherlands) **Sea3**	Latin America **C3**
Asia (India) **S4**	Asia (India) **F4**	Asia (India) **W4**	Jaipur (India) **Air4**	Haldia (India) **Sea4**	Eurasia **C4**
Africa (Kenya) **S5**	Africa (Kenya) **F5**	Latin America (Brazil) **W5**	São Paulo (Brazil) **Air5**	São Paulo (Brazil) **Sea5**	Asia **C5**
		Africa (Kenya) **W6**	Isiolo (Kenya) **Air6**	Isiolo (Kenya) **Sea6**	Africa **C6**
		Africa (Nigeria) **W7**	Murtala (Nigeria) **Air7**	Ibadan (Nigeria) **Sea7**	Middle East **C7**
		Middle East (Israel) **W8**	El Arish (Israel) **Air8**	Haifa (Israel) **Sea8**	Canada **C8**
		Eurasia (Russia) **W9**	Pulkovo (Russia) **Air9**	St. Petersburg (Russia) **Sea9**	Australia **C9**
		Australia **W10**	Melbourne (Australia) **Air10**	Melbourne (Australia) **Sea10**	

Within the model, six types of entities are included, namely, suppliers, factories, warehouses, airports, seaports and markets.

The raw materials necessary to produce the vaccines being studied are provided by suppliers located in the surroundings of each factory location. Each supplier is characterized according to its maximum supply capacity (sc_{mi}^{max}) minimum order quantity (sc_{mi}^{min}), and cost per unit (rmc_{mi}), for each of the required raw materials. The raw materials consist in a polysaccharide antigen group and a diphtheria toxoid protein carrier (chemical material, rm_1), as well as the glass container (rm_2).

At the factories, vaccines are produced and afterwards they are transported to warehouses or directly to markets. At the warehouses, vaccines will be stored and for that reason, storing technologies may need to be installed in these facilities. These entities are characterized according to maximum (ea_i^{max}) and minimum (ea_i^{min}) installation area. For the warehouses W6 to W10, and factory F5, installation area is not pre-defined since none of them is yet constructed. Contrarily, the optimal installation area is given by the model, depending on what specific scenario the model is running. Warehouses are also characterized by inventory levels (ic_{mi}^{max} and ic_{mi}^{min}) and initial inventory (ins_{mi}) for product *fpMen* existent at the warehouse W1 to W5.

Table 5 details the average labour costs (lc_i) and construction costs ($sqmc_i$). Construction costs are applicable to factories and warehouses. The last parameter shown presents DALY values for meningitis disease, and the results were obtained through the Global Burden of Disease (GBD) Results Tool (IHME, 2021) for each geographical area included in the case-study.

Table 5. Characterization of each geographical area with entities included in the case-study according to location variable costs and DALYs.

Geographic Areas (markets)	Entities	Average Hourly labour cost (lc_i)	Construction cost ($sqmc_i$)	DALYs (Metric used: Rate per 100.000 population)
U.S (C1)	F1, W1, Air1, Sea1	89.69	-	57.18
Europe (C2)	F3, W3, Air3, Sea3	37.5	-	56.90
Latin America (C3)	W5, Air5, Sea5	13.51	-	373.78
Eurasia (C4)	W9, Air9, Sea9	6.94	470	162.65
Asia (C5)	F4, W4, Air4, Sea4	1.47	-	621.07
Africa (C6)	F5, W6, Air6, Sea6, Air7, W7, Sea7	7.14	330	3683.55
Middle East (C7)	W8, Air8, Sea8	17.4	337	344.22
Canada (C8)	F2, W2, Air2, Sea2	45.62	-	59.87
Australia (C9)	W10, Sea10, Air10	43.12	1266	53.32

The product considered in the study represents one of the vaccines manufactured and commercialized by the company, which are vaccines against meningococcal meningitis, denoted by $fpMen$.

Meningitis vaccines represent a family of vaccines that are temperature sensitive, should be refrigerated (storage at 2º to 8ºC (35º to 46ºF)) and not used if exposed to freezing. Other vaccines produced by the company need to be stored around -50º to -15ºC, which is not the case of the meningitis vaccines being studied. However, preserving the cold chain from production until the final administration is not only an expensive but a challenging task, especially in hot, large, and developing countries (Lemmens et al. 2016), (Chen et al. 2014). Regarding the product itself, $fpMen$, it is presented in a cardboard box containing 5 vials, with single doses per vial, thus each product stock keeping unit (SKU) contains 5 doses of meningitis vaccines, represented in Figure 15. Additionally, they are characterized in terms of inventory cost, price per unit sold, product weight and necessary storage volume per unit of product.

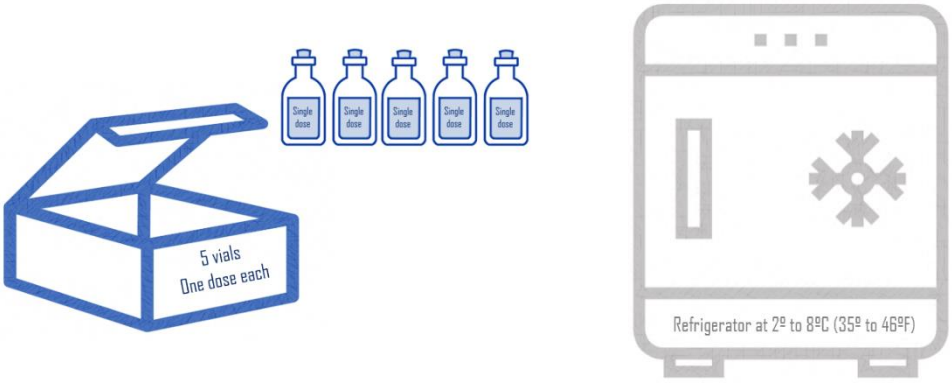


Fig 15 – *Product and storage representation for the present case-study* (Toxoid, Vaccine, and Limited 2017)

Due to their limited shelf-life, a proper collection of outdated vaccines to recycle, remanufacture or destroy through incineration processes is required and helps reducing the negative environmental impacts. Moreover, expired medicines are not only hazardous to the environment but also to humans and animals. The company being considered in this case-study encourages process optimization, regeneration when possible, and incineration with energy recovery, as an effort to reduce consumption of non-renewable raw materials.

Since using appropriate storing technologies represent an essential feature on a vaccine supply chain, production technologies (at the factories) and refrigeration technologies (to allow for cold storage at the warehouses) are the ones considered for the present case-study, according to the family of vaccines. Technologies are characterized according to levels of production (pc_g^{max} and pc_g^{min}), installation costs (tec_g), operating costs (opc_g) and necessary number of workers (w_g). All values related to the parameters considered in this analysis are provided in Appendix B.

5.2 Results' Analysis and Discussion

Given the decision-support tool detailed in chapter 4, the present section presents the results obtained from the application of the model to the case-study described in the previous subchapter. This has been implemented in GAMS 35, and the case-study solved using CPLEX 20.1, in an Intel Core i5-7300U, 2.60-2.71 Hz processor with 8GB RAM.

Moreover, and apart from validating the model presented, this section aims to provide sufficient evidence on how a pharmaceutical sustainable supply chain behaves depending on the objective function being considered, in order to comprehend how each sustainability pillar, measured by each objective function defined, affects the vaccine supply chain design and planning model.

For that purpose, different scenarios are considered using a lexicographic optimization:

- **Case A**: starting with maximizing NPV, the optimum economic solution is obtained, and the maximum NPV value is then used as a constraint when maximizing the social performance. Then, both maximum NPV and social performance values, are used as constraints when minimizing the environmental impact. Hence, case A corresponds to the non-dominated solution with optimum economic performance.
- **Case B:** starting with maximizing pharmaceutical accessibility, the optimum social solution is obtained, and the maximum pharmaceutical access value is then then used as a constraint when maximizing economic performance. Then, both maximum social performance and NPV values are used as constraints when minimizing the environmental impact. Hence, case B corresponds to the non-dominated solution with optimum social performance.
- **Case C:** starting with minimizing the environmental impact, the optimum environmental solution is obtained, and the minimum environmental impact value is then used as a constraint when maximizing economic performance. Then, both environmental impact and NPV values are used as constraints when maximizing the social performance. Hence, case C corresponds to the non-dominated solution with optimum environmental performance.

As a simplification, the following scheme summarizes the strategy being used:

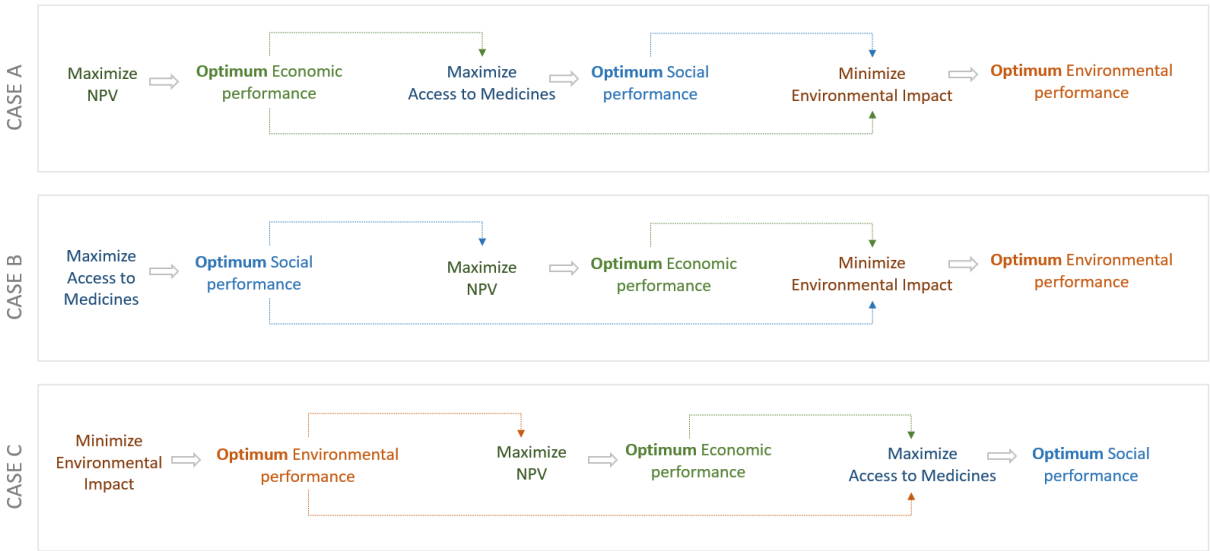


Fig 16 – *Strategy followed for the first scenarios to be studied*

For each case, the superstructure for the supply chain was obtained, shown in Figure 17, as well as the corresponding indicator values for a time horizon of ten years which are presented in Table 6. A higher value in the economic indicator means a higher profit. A higher value in the environmental indicator means a higher negative impact for the environment. A higher value in the social indicator means more equity in access to medicines, i.e., means that availability of medicines is enhanced by selecting locations in countries with higher burden of disease.

Regarding the second social objective function (*Pharma Distribution*), which is the maximization of the minimum delivery-to-demand ratio, the value 1 (corresponding to 100%) was chosen for parameter θ_{it} (coverage rate) so as to guarantee a total demand satisfaction for each market. Hence, a possible study could be done in order to evaluate how this tendency towards a more socially responsible supply chain in terms of equity in access to medicines affects the other pillars of sustainability, by varying the value of the referred parameter in constraint (40), represented below as a reminder.

$$pr_{mit} \geq \theta_{it} \times dmd_{mit} \tag{40}$$

Table 6. Performance indicator's values for scenarios A, B and C.

		Cases		
Indicator	Units	**A**	**B**	**C**
Economic	€	**7.83E+09**	7.76E+09	7.76E+09
Social (Pharma Access)	-	8.61E+03	**1.36E+04**	4.48E+03
Social 2 (Pharma Distribution)	-	1.0	1.0	1.0
Environmental Impact	-	2.92E+07	2.96E+07	**2.87E+07**

From table 6 one can observe that the most profitable solution is obtained in case A, which is not the scenario with the worst social and environmental performances. Thereby, the best economic performance is obtained at a cost of 36.6% reduction on the social indicator and an increase of 2% on the environmental impact, both situations compared with the best performances obtained in case B and case C, respectively. In case B, the best social performance is obtained, however this is also the case where environmental indicator perform its worst, at a cost of a 3% increase, approximately, on the environmental impact when compared with optimal performance obtained in case C. Economic performance doesn't perform its worst, even though it has a decrease of approximately 0.8%. As of case C, the minimum environmental impact is achieved at a cost of approximately 1% reduction in the NPV over the same period of 10 years and social performance achieves its worst value when achieving the greenest solution, with a 67% decrease in equal access of medicines comparing with the best solution obtained in case B. Thus, the greener solution has both the worst economic and social performances. Moreover, one can detect the great variation in the performance of social objective function *Pharma Access*, which solution improves by 158% when compared to case A and 303% when compared to case C. In terms of supply chain network, it can be seen that different networks are obtained (see Figure 17 and Table 7).

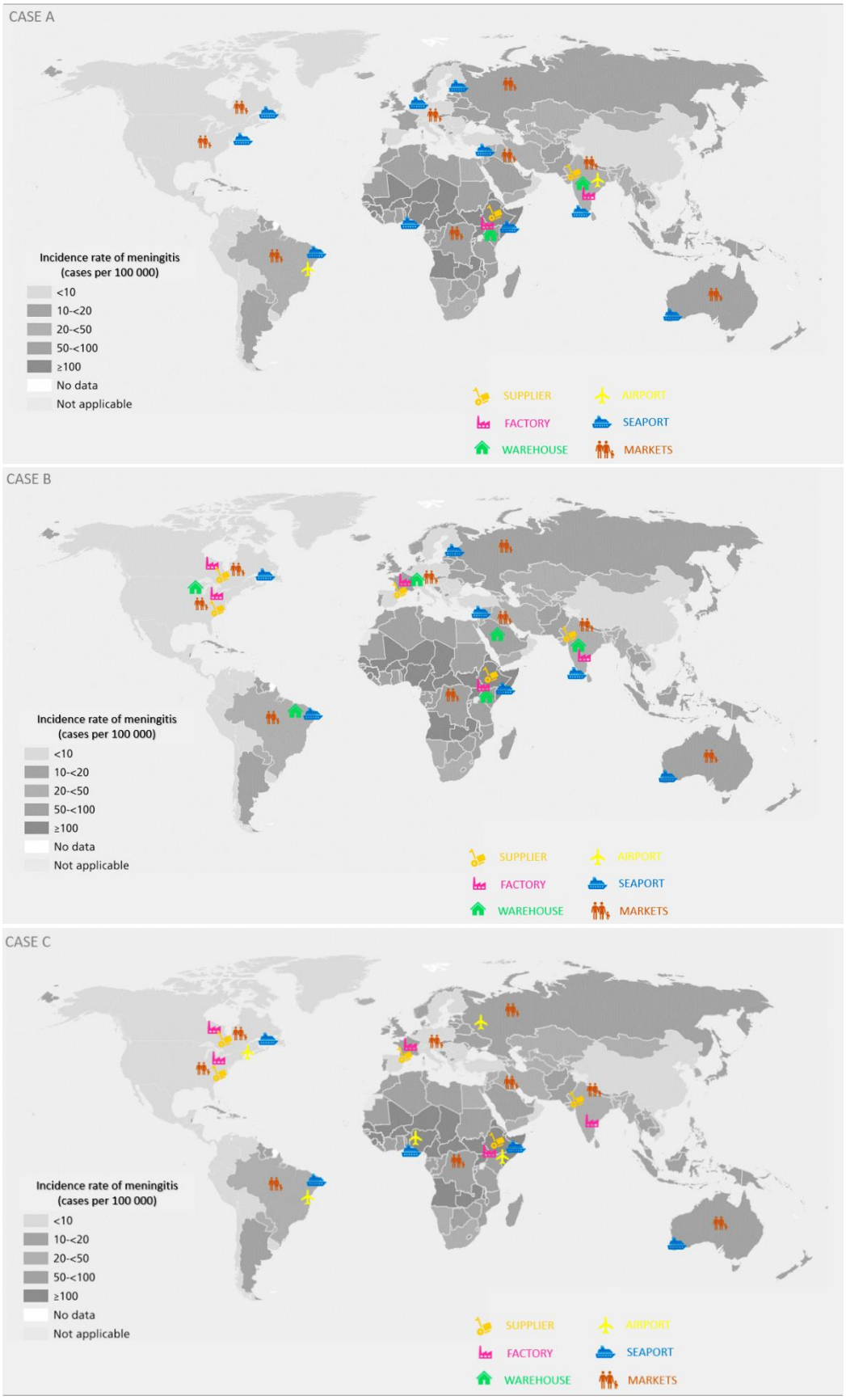


Fig. 17 – *Superstructure obtained for cases A, B and C being analysed*

Table 7. Summary results for each case being study

		Cases		
		A	**B**	**C**
Suppliers		94% supplied from Asia and 6% supplied from Africa Supplier in Asia only supplies factory in Asia (same for supplier in Africa)	38% supplied from Asia, 32% supplied from Europe, 14% from Canada, 9% from US and 7% from Africa	33% supplied from Europe, 26% supplied from Canada, 20% supplied from Africa, 12% supplied from Asia and 9% from US
Factories		Asia Africa	Europe, US, Asia, Canada, Africa	Europe, US, Asia, Canada, Africa
Production		Most production is in Asia (94%)	Most production is in Europe and Asia	Most production is in Europe and Canada
Warehouses		India Kenya	France, US, Brazil, India, Kenya, Nigeria, Middle East	No warehouses installed
Storage technology		Storage technology used is Refrigeration		None
Inventory		Divided between India and Kenya	Inventory is distributed among the seven warehouses	No inventory at warehouses
Transportation	Road	Mostly trucks of bigger capacity are used		
	Air	Used for intercontinental transportation between India and Brazil	Air transportation is not used	Intercontinental transportation between Canada and Brazil, Kenya and Russia. Intracontinental transportation between Kenya and Nigeria
	Sea	Netherlands, US, Brazil, Russia, Canada, Israel, Australia, Kenya, Nigeria	Brazil, Russia, Canada, Australia, Nigeria, Israel, India	Nigeria, Brazil, Australia, Canada, Kenya

A brief analysis of the results summarized in table 7 and displayed in figure 17 is made below so as to discuss the most relevant aspects.

- **Supply**: Across the different cases, the supplier in Asia is sourcing a great amount of units for different markets around the world. For both cases A and B, Asia is the preferred supplier, particularly for case A where more than 1,5 billion units are being sourced from this supplier compared to less than 100 million units being supplied by Africa. As for case B, around 635 million units are being supplied by Asia, 535 million from Europe and a smaller amount is being sourced from Canada, US and Africa. This preference for Asia as a supplier of raw materials may occur due to the lower costs of raw materials and lower labour and transportation costs. In Case C one can notice that raw materials are being sourced by five different suppliers and each factory is supplied by the closest supplier. This may happen because in this case the first objective being considered is the environmental performance, hence the results suggest a minimization of the environmental impact by reducing transportation costs between suppliers and factories.

- **Facilities and installed capacity**: A preference is given to factories in Africa and Asia, which are the ones installed across the three cases being analysed. In case A, factory in Asia is the one with higher production levels, being the biggest producer with an amount of 150 million SKU, which corresponds to 750 million doses of meningitis vaccines. Regarding case B, the major production of vaccines is done in Asia and Europe and in case C the installed capacity is more uniformly distributed between the five factories installed, being Europe's the one with higher production levels. Regarding warehouses installed capacity, one can note that, while in case A only two warehouses are considered, located in India and Kenya, in case B seven warehouses are included in the supply chain. This can be explained by the more socially beneficial case being analysed in situation B and being the maximization of economic objective function the second indicator considered, hence allowing for less profitable structures when comparing with case A (which corresponds to the maximization of NPV as the first indicator being maximized). Finally, in case C, no warehouses are installed, which can be due to the more evenly distribution of production across the installed factories, leading to the less need of keeping inventory in warehouses. Moreover, installation of warehouses has an impact to the environment associated, which is aimed to be minimized, as well as further costs.

  In the present case-study, one production technology and one storage technology are considered for the type of vaccines being produced at the factories and stored at warehouses, respectively. Therefore, there is an additional impact on both costs and environment from the use of these technologies at the referred entities. Regarding refrigeration, this technology is used at warehouses in order to storage meningitis vaccines at a temperature of 2ºC to 8ºC.
- **Transportation**: As shown in table 7, trucks of bigger capacity are preferred over the ones with lower capacity for road transportation between entities. This option allows for reduced costs and lower impact for the environment compared to the use of smaller trucks. In terms of intermodal transportation, sea transportation is used in the three cases, being the combination road followed by sea and followed by road transportation, the one preferred over other possible combination. Regarding air transportation, it is used for some intercontinental connections between India and

Brazil (case A) and in Case C, it is used for intercontinental transportation between the pairs of entities Canada-Brazil and Kenya-Russia and for intracontinental transportation between Kenya and Nigeria (Case C). The results obtained regarding transportation modes can be explained through its influence on the supply chain performance in terms of economic and environmental sustainability, which directly affects decision-making. These impacts on the economic and environmental performance are analysed on the next topic of the present discussion chapter.

- **Comparison between different activities of the supply chain in terms of associated costs and environmental impact:** As already mentioned, it is visible from table 6 that there's a great variation in the performance of social objective function across the three cases. On the other hand, a smaller variation is verified on both economic and environmental indicators performance across the three cases.

  The smaller variation in economic performance among the three cases can be justified by the significant contribution of production to the total costs. As it is visible from Figure 18, besides purchasing of raw materials, production activities together with refrigeration represent almost 65% of the total costs for case A, 76% total cases for case B, and 66% of total cases in case C. Moreover, by assuring a total demand satisfaction through the use of a coverage rate of 100% on the social constraint (40), the cost of production can only be minimized up to a certain point, for instance, by locating a factory in a country with lower construction and labour costs. However, according to *Our World In Data*, countries with lower labour costs are often in line with countries with higher levels of DALYs, as estimated by (Sterck et al. 2018) and explained by the same author that the average income (measured by GNI per capita) has a strong negative correlation with DALYs lost due to communicable diseases, such as meningococcal meningitis. Thus, by prioritizing the location of entities in geographical areas with higher burden of disease, markets with lower costs associated are, indirectly, being prioritized. In this way, one can notice that production at factories, as well as refrigeration at warehouses, which represent a great amount of the total costs, can only be reduced up to a certain point, partly explaining the lower difference of economic performance across the three cases being analysed. Furthermore, there is a great risk associated with opening facilities in developing countries. In a work developed by (Plotkin et al. 2017), the authors addressed risks and costs associated with vaccine manufacturing and concluded that in lower and middle income countries, not only equipment and raw materials need to be imported, but also trained and skilled labor. In the referred work, it is also discussed the option of hiring and training employees, which would be very beneficial for the country where the facility is being located, since local employment would be enhanced.

  As of transportation activity, it represents around 24% for case A, 6% for case B and approximately 5% in case C, on the overall costs of the supply chain.

The contribution of each activity to the total costs is displayed in Figure 18 as a conclusion of the main contributors for total costs (represented on the right side of the image).

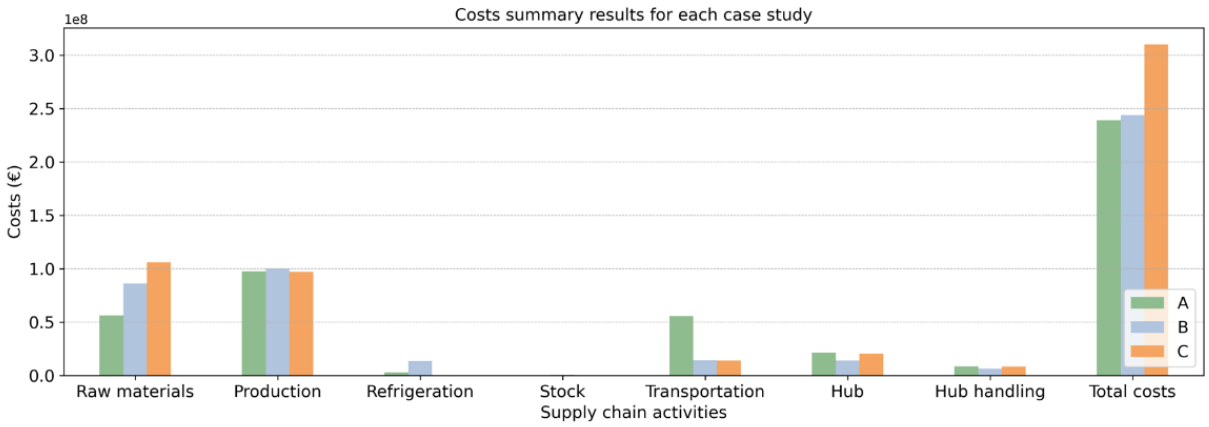


Fig 18 – *Costs' summary results for each case being study*

Aiming to identify **environmental sustainability hotspots**, the results obtained for each supply chain activity across the different scenarios being studied are represented in Figure 19 and available in Table 25 of Appendix C.

The small variation in the environmental impact across the different cases can also be justified by the major contribution of production technology to the total environmental impact, as it can be clearly seen in Figure 19. After production of pharmaceutical products at factories, transportation is the activity with larger negative impact on the environment, which is reduced 88% from case A to C and 20% from B to C. Moreover, refrigeration technology is the activity with lowest negative impact for the environment within the activities considered in the case study's supply chain. Nevertheless, further studies should be made to explore alternatives for storage technology and compare resulting values of environmental impact.

Hence, it would be important to address different options of greener production so as to minimize the impact for the environment. Interesting potential solutions would be to investigate the use of remanufacturing activities. Studies developed by (Kumar and Mukherjee 2020) and (Barbosa-Povoa, Mota, and Carvalho 2018) demonstrate that the recovery of final products allow for the improvement of environmental performance of the supply chain, although it affects other decisions and activities of the supply chain, such as raw material purchasing, flows of materials between entities, transportation capacities, necessary installation areas, among other.

Recovery and remanufacturing of pharmaceutical products are extremely challenging, not only due to their limited shelf-life, but also because of their hazardousness for the environment, humans, and animals. According to some researchers on this topic, such as (Govindan et al. 2015) and (Amaro and Barbosa-Póvoa 2008), outdated vaccines should be properly collected to recycle, remanufacture or to be destroyed at incineration centers. These three activities can potentially reduce negative environmental impacts caused by production activities of the pharmaceutical industry.

Sanofi Pasteur has been encouraging process optimization, regeneration when possible, and incineration with energy recovery, aiming to decrease non-renewable raw materials' consumption (CSR

Sanofi, 2020). Furthermore, according to the mentioned study developed by (Amaro and Barbosa-Póvoa 2008), it is important to distinguish non-recoverable medicines (which should be sent to incineration centres), remanufacture medicines (e.g. repacked medicines) and recyclable materials (e.g. glass), being the first ones referred as generators of low-added value materials, while the remanufacturing ones can be brought back to the forward pharmaceutical supply chain.

Regarding transportation modes, alternatives such as exploring different hub locations or other transportation modes such as rail transportation should be considered in order to find strategies capable of reducing environmental impact of transportation.

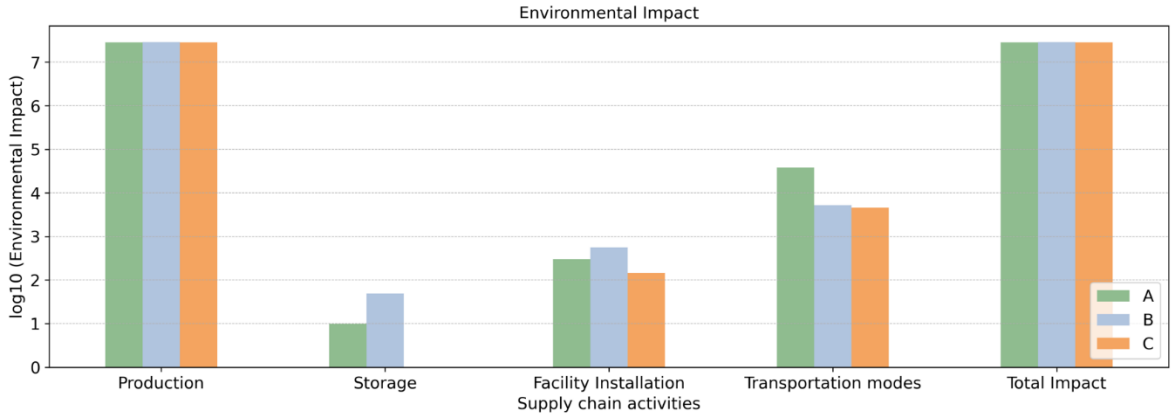


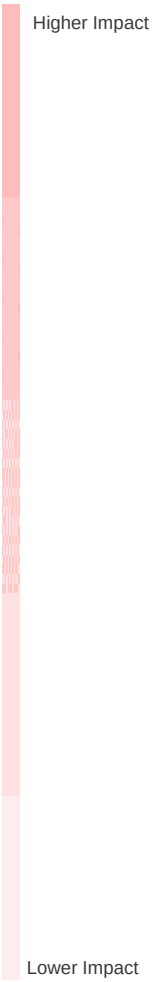
Fig. 19 – Environmental Impact of the considered supply chain activities across the scenarios

Furthermore, by looking closer to the results on the environmental impact per midpoint category in table 8, it is possible to identify **environment sustainability concern points**, which allows for an opportunity to explore more specific strategies to enhance supply chain sustainability. When analyzing the obtained results, one can compare each category' results and point out that categories FE (freshwater eutrophication), HT (human toxicity), MET (marine toxicity) and FET (freshwater ecotoxicity) are the ones mostly affected by pharmaceutical supply chain activities. Looking closer to the results obtained for the environmental impact of each activity of the supply chain (available in Table 26 of Appendix C), one can note that production is the major contributor for human and marine toxicity. Regarding refrigeration, CC (climate change) is the category with bigger percentage associated. As of transportation modes, environmental impact relies mostly on CC category.

Therefore, alternative strategies should also be explored in order to reduce the impact of these activities in the specific mentioned categories and, consequentially, in the final environmental impact result.

Table 8. Environmental Impact per category across the scenarios

	Cases		
Environmental Impact	**A**	**B**	**C**
FE	9.21E+06	9.42E+06	9.11E+06
HT	8.06E+06	8.20E+06	7.99E+06
MET	7.15E+06	7.33E+06	7.11E+06
FET	2.00E+06	2.03E+06	1.97E+06
MRD	1.71E+06	1.75E+06	1.69E+06
PMF	2.15E+05	1.44E+05	1.39E+05
TA	1.73E+05	1.27E+05	1.23E+05
CC	1.50E+05	1.06E+05	1.05E+05
FRD	1.33E+05	1.16E+05	1.12E+05
POF	1.18E+05	6.23E+04	6.03E+04
IR	1.01E+05	9.34E+04	9.03E+04
TET	6.76E+04	6.70E+04	6.51E+04
ME	6.53E+04	5.09E+04	4.93E+04
ULO	3.68E+04	2.33E+04	2.26E+04
ALO	3.48E+04	3.11E+04	2.88E+04
NLT	2.56E+04	1.08E+04	1.03E+04
OD	1.60E+03	5.81E+02	5.61E+02
Total normalized	2.92E+07	2.96E+07	2.87E+07



5.2.1 Supply Uncertainty Analysis

As mentioned before, uncertainty is often considered in the design and planning of supply chains in parameters such as demand. While some types of vaccines, such as influenza and tropical diseases' vaccines, or other pharmaceutical products, may have uncertainty associated to demand, meningitis is a disease that should be included in routine immunization programmes of every country in order to eradicate the disease. Hence, uncertainty can be present in steps of the supply chain such as raw materials supply, facilities construction, production times, storage resources used. The first step that may be affected by uncertainty in the course of a supply chain network is factory's suppliers of raw materials. Therefore, the goal at this point of the study is to understand how profit margin and the supply chain network is affected in face of a decline in the amount of raw materials supplied and a rise in this same amount.

A stochastic approach was developed, and different scenarios s were designed and added to the decision variables X_{maijt}, S_{mit}, YCT_{it}, P_{mgit} and S_{mgit}. The new stochastic parameters include sc_{mis}^{max} for the maximum supply quantity of product m by supplier i under scenario s and ρ_s as the probability of occurrence of scenario s, where $\sum_{s\in S}\rho_s = 1$.

Moreover, constraints were adjusted in order to meet the changes performed in the decision variables mentioned and the objective functions are also adjusted, being the new equations given below.
The stochastic economic objective function is given below in equation (41) to (43).

$$\max NPV = \sum_{s} prob_s \left(\sum_{t\in T} \frac{CF_{st}}{(1+ir)^t} - \sum_{\gamma} FCI_{\gamma} \right) \tag{41}$$

$$CF_{st} = \begin{cases} NE_{st} & t = 1, \dots \dots NT-1\,, s \in S \\ NE_{st} + \sum_{\gamma} (sv_{\gamma} + FCI_{\gamma}) & t = NT\ \,, s \in S \end{cases} \tag{42}$$

$$\begin{aligned} NE_{st} = (1-tr)\Bigg[& \sum_{\substack{(m,i,j)\in F_{INCFP} \\ (a,m,i,j)\in NetP}} psu_m X_{maijts} - \Bigg(\sum_{\substack{(m,i,j)\in F_{OUTSUPRM} \\ (a,m,i,j)\in NetP}} rmc_{mi} X_{maijts} + \sum_{\substack{(m,g)\in H_{prod} \\ i\in I_f}} opc_g P_{mgits} \\ & + \sum_{\substack{(m,g)\in H_{stor} \\ i\in (I_f \cup I_w)}} opc_g S_{mgits} + \sum_{\substack{(a,m,i,j)\in NetP \\ a\in (A_{plane}\cup A_{boat}\cup A_{trucks})}} tc_a . pw_m . d_{ij} . X_{maijts} \\ & + \sum_{\substack{(a,m,i,j)\in NetP \\ (j\in I_{plane} \wedge i\notin I_{plane}) \cup (j\in I_{boat} \wedge i\notin I_{boat})}} hhc_j . X_{maijts} + \sum_{i\in (I_{plane}\cup I_{boat})} cfp_i . Y_i + \sum_{(m,i)\in V} sc_m S_{mits} \\ & + \sum_{i\in (I_f \cup I_w)} w_i . lc_i . wwh . wpt . Y_i + \sum_{i\in (I_f \cup I_w)} wpsq . lc_i . wwh . wpt . YC_i \\ & + \sum_{\substack{(m,g)\in H \\ i\in I_f}} w_g . lc_i . wwh . wpt . Z_{gmi} \Bigg] + tr . DP_t \end{aligned} \tag{43}$$

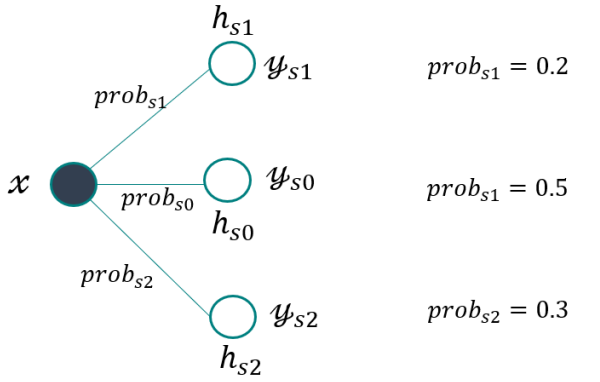
The stochastic environmental objective function is given by the new equation (44) below.

$$\begin{aligned} \min EnvImpact = \sum_{s} prob_s \Bigg(\sum_{c} \eta_c \Bigg(& \sum_{\substack{t\in T \\ (m,g)\in H}} ei_{mgc} pw_m P_{mgits} + \sum_{\substack{t\in T \\ (m,g)\in H}} ei_{mgc} vpu_m S_{mgits} \\ & + \sum_{\substack{t\in T \\ (a,m,i,j)\in H}} ei_{ac} pw_m d_{ij} X_{maijts} + \sum_{\substack{t\in T \\ (a,m,i,j)\in H}} ei_{ic} YC_i \Bigg) \Bigg) \end{aligned} \tag{44}$$

Three different scenarios were considered in the stochastic case D:

- The base scenario, $s0$, with the original supply amounts of raw materials.
- Scenarios $s1$ and $s2$, which represent scenarios where supply was increased by 20% and reduced by 30%, respectively.

The probabilities assigned were 50% to the base scenario $s0$, 20% to scenario $s1$ and 30% to scenario $s2$, being the decision tree considered for the analyses represented in figure 19 . With these probabilities for each scenario considered, the model was optimized towards the maximization of the NPV value.



x : $first - stage\ decisions$; y_s : $second - stage\ decisions$ in scenario s
h_s : $realizations\ of\ uncertainties$

Fig 20 – Decision tree considered to study uncertainty in supply

The results are shown in Table 9, where the results with uncertainty in supply were compared with Case A that aimed at the maximizing the economic goa Comparing the results displayed in table 9, for both cases A (first deterministic case analysed) and case D (stochastic case), it is possible to conclude that economic and environmental pillars of sustainability are not substantially affected by uncertainty in supply of raw material, with a decrease of less than 1% in the economic performance and an improvement of less than 1% in the environmental performance.

However, social indicator has decreased approximately 42% compared do case A. This is observed because Cases A to C were analysed considering lexicographic optimization, where objectives were considered based on their importance to the company Sanofi Pasteur, being maximization of economic indicator the most important, followed by social indicator of pharmaceutical access, and finally the minimization of environmental impact. So, it can be concluded that uncertainty in raw materials highly influences the social component if an economic goal is targeted, so a deeper study on how uncertainty can affect social goals should be performed as an extension of the current work

In terms of supply chain network, the model chooses to produce vaccines at the factory located in Asia and Africa, although the last one represents only 5% of the total production by the company, which is very similar to the case A results. Regarding warehouses location, only the one in India is installed. Intercontinental transportation by plane is made only between India-Brazil, India-Canada, while by boat connections are made between, India and Netherlands, Russia, Kenya, Israel, as well as between Brazil and US, Australia.

Table 9. Performance indicator's values for scenarios A, D.

		Cases	
Indicator	Units	**A**	**D**
Economic	€	7 826 185 535	7 825 635 753
Social (Pharma Access)	-	8 609.24	4 925.69
Social 2(Pharma Distribution)	-	1.0	1.0
Environmental Impact	-	29 213 570	29 157 614

5.3 Chapter Final Remarks

The present chapter focuses on the validation of the developed model dedicated to the design and planning of sustainable supply chains in the pharmaceutical industry sector, through its application into a representative case study of the company Sanofi Pasteur.

Different scenarios were designed in order to perform a multi-objective lexicographic analysis. In Case A, economic objective function was the first being emphasized, followed by social objective and being the environmental one the last being considered. Thus, in this case, the maximum value for economic performance was obtained, as well as the second-best value for social indicator. In Case B, social objective function has been the first one being maximized, followed by economic objective and, lastly, environmental performance was determined. For this case B, the best social performance was obtained, along with the worst environmental performance across the three cases. Case C was performed in order to analyse the differences that would result by giving the first emphasis on the minimization of the environmental objective function, followed by maximization of economic objective, and being the social objective the last one being considered. This case C resulted in the best environmental performance, as expected, with the worst economic performance, although without significant losses in profit, and a major decrease in the social performance. The lexicographic analysis performed enabled the understanding of the performance of combined indicators across the supply chain. Moreover, the obtained supply chain structure and decisions' results for each case A to C is presented and discussed, allowing for the understanding on how each performance indicator is affected by decisions, as well as connections between supply chain activities, such as production, storage and transportation.

Within the result's analysis and discussion, environmental sustainability hotspots were identified, being production the supply chain activity with higher negative influence on the environment, followed by transportation. Climate change, human and water toxicity were identified as the categories with higher contribute for the obtained environment negative impact. Hence, results indicate a possible future research path to follow in order to minimize the impact of these activities on the environment, particularly on the identified midpoint impact categories.

Finally, uncertainty in supply activities is introduced to the model in order to study the impact of this source of uncertainty, which resulted in no significant changes on economic and environmental performances, but a great difference in the social indicator has been detected.

Thereby, when addressing multiple objectives, such as the ones tackled in the present thesis on the three pillars of sustainability, it is important and useful to perform a multi-objective lexicographic analysis so as to better understand the influence on the supply chain of compromising one objective over another. Moreover, dealing with uncertainty is crucial, particularly in pharmaceutical industry sector, thus being important for decision-makers to consider it, together with sustainability objectives, when designing and planning pharmaceutical supply chains.

6. Conclusion & Future Work

The last chapter of this work is focused on providing a final conclusion of the work developed, highlighting relevant findings, in section 7.1. In section 7.2, important aspects and limitations to be studied in future research are identified.

6.1 Final Conclusion

As referred at the beginning of the present dissertation, the United Nations established 17 Sustainable Development Goals for the 2030 Agenda of Sustainable Development, pointing towards an improvement in equity and overall quality of life for everyone. Although sustainability has been gaining significance over the years, it is strongly encouraged by economic and environmental challenges faced by society. On the other hand, including social objectives remains an essential gap to be explored when working on supply chain decision-making tools, such as optimization models, especially in the pharmaceutical sector.

The present dissertation stresses common challenges that decision-makers are confronted with when designing and planning a sustainable supply chain, focusing on the social pillar of sustainability and the inevitable uncertainty often present. Hence, and to provide the necessary information on the topic, a comprehensive literature review has been done in both second and third chapters. The main contributions to the literature were identified, potentially identifying research gaps that need to be explored, which include integrating social objectives when designing and planning sustainable supply chains (particularly regarding accessibility to pharmaceutical products).

In the second chapter, the pharmaceutical industry sector was characterized as well as its supply chains. From the review, one can firstly conclude that the special and demanding characteristics of pharmaceutical products make this supply chains very complex and challenging for decision-makers to design and plan in an efficient and sustainable way. The main challenges identified for decision-makers to cope, within the pharmaceutical industry sector, were regarding the different levels of uncertainty at each stage of the supply chain and the increasing need to integrate sustainability aspects, in particular regarding social objectives, such as equity in access to medicines. As of the main driving forces, the increasing regulatory burden and the growth of personalized medicines are encouraging a shift to a more proactive and patient-centric approach, thus focusing on prevention and early treatments.

In the third chapter, along with a brief review on the main concepts and considerations regarding sustainable supply chain management, the commonly used optimization methods were identified and

described. From this chapter, one can conclude that, although several articles explore supply chain networks under uncertainty, there is still a gap to fill regarding the integration of sustainability objectives as well, where a particular emphasis to include different social objectives should be given. Moreover, it has also been concluded that, as social indicators, job creation is most found one in literature, followed by safety and health of workers, while aspects such as providing equity in access remains a research gap. With respect to possible sources of uncertainty, demand has been the most studied when modelling supply chains under uncertainty, being stochastic programming identified as the preferred optimization model (Govindan et al. 2017).

Given the above, and in order to contribute with relevant advances to the topic being addressed, a decision-support tool has been developed with the aim of integrating economic, environmental and social sustainability objectives, in a context of uncertainty. Following the work developed by (Mota et al. 2018), the presented decision-support tool provides support for strategic-tactical decisions, allowing to study and comprehend the effect of each decision on the performance indicators. Hence, the mentioned generic model has been adapted to better include specific characteristics of the pharmaceutical industry, such as the demanding storage conditions required for the stability of these products. Moreover, the economic evaluation has been achieved through the Net Present Value, aiming to maximize profit, while the environmental assessment is through the minimization entities, technologies, and transport modes' impact in the environment, using the Life Cycle Analysis methodology. Moreover, the social pillar of sustainability has been the major focus of this work, where the aim is to contribute with an approach which is able to, in a quantitative way, consider aspects of equity in access to pharmaceutical products. Therefore, the Access to Medicine Index (AtMI) was the starting point, where its qualitative indicators were studied and grouped into categories: Registration and coverage (1), Donation programs (2) and Equitable pricing strategies (3). With the social indicators within each group, AtMI aims to improve equity in access to pharmaceutical products, by ensuring both availability and affordability, and being these concepts addressed by prioritizing countries with the highest burden of disease and with lower ability to pay for medicines. Hence, the goal was to, in a quantitative way, consider these aspects that Access to medicine foundation finds as the most important when tackling equity in access to medical products. The suggestions described in the fourth chapter aim to, firstly, prioritize the location of entities (suppliers, factories and warehouses) in countries with higher burden of disease, using the metric DALY and secondly, to maximize the minimum delivery-to-demand ratio in each country, thus enforcing equal access to pharmaceutical products among countries. Moreover, while the social objective functions aim to maximize equity in access, a social constraint is also used to respect a satisficing level of equity.

Lastly, the model is applied to a real base case study of Sanofi Pasteur, a division of the French company Sanofi dedicated to vaccines, aiming to discuss different optimization scenarios and to study trade-offs among the three pillars of sustainability. A lexicographic optimization approach was chosen in order to analyse the different outcomes and impacts of having the three objective functions varying in emphasis on one (or more) over other(s), hence, avoiding having to assign specific weights to each objective function. This analysis is firstly dedicated to the objective functions' results discussion, followed by a

discussion on the superstructures and decisions obtained for three of the cases considered and, lastly, a study dedicated to uncertainty considerations is also done.

The application of the developed model enables the understanding of the effect of decisions on each performance indicators, as well as allowing for the comprehension of connections among different supply chain activities, providing an opportunity to better understand the performance of the combined indicators across the supply chain. Moreover, an approach to integrate crucial social concerns is suggested in order to consider equity in access to medicines, by improving both availability and affordability of pharmaceutical products across different geographical areas in the world. Moreover, environmental sustainability hotspots were identified, and from these, potential strategies to reduce supply chain activities on the environment can be identified. Finally, the developed model allows to design and plan a pharmaceutical sustainable supply chain accommodating uncertainty in supply through a stochastic approach. Furthermore, as an important note, the final model has been made in a sufficient generic way so as to allow for different types of medicines, different types of storing technologies, such as freezers, *Walk In Colder Rooms*, *Walk In Freezer Rooms*, solar refrigerators/freezers, among others.

6.2 Future Work

The present work provides a decision support tool to design and plan pharmaceutical supply chains, where sustainable objectives are considered, focusing on the social pillar due to its extreme importance when dealing with vaccines' equal access across different countries. Even though important steps were taken on this subject, future research is foreseen so as to continue the work developed.

Firstly, it is important to continue exploring different social indicators as well as studying different supply chains within the pharmaceutical industry. Further research on these topics may help with better conclusions on the best suited indicators.

One important aspect to consider in future research is regarding the recovery of products such as medicines. Comparing with products from other industrial sectors, recovery and remanufacturing of pharmaceutical products is very challenging. Due to their limited shelf-life, a proper collection of outdated vaccines to recycle, remanufacture or destroy through incineration processes is required and helps reducing the negative environmental impacts. Moreover, expired medicines are not only hazardous to the environment but also to humans and animals. Some pharmaceutical companies, such as Sanofi Pasteur, encourages process optimization, regeneration when possible, and incineration with energy recovery, as an effort to reduce consumption of non-renewable raw materials. Furthermore, according to a study developed by (Amaro and Barbosa-Póvoa 2008), when studying closed loop supply chains in the pharmaceutical industry, one can distinguish non-recoverable medicines that must be sent to incineration centres and recyclable (e.g. glass) or remanufacture medicines (e.g. repacked medicines), being the first ones referred as generators of low-added value materials, while the remanufacturing ones can be brought back to the forward pharmaceutical supply chain.

On this topic of reverse logistics supply chains, studies developed by (Mota et al. 2018) and (Kumar and Mukherjee 2020), being the last one a study developed in the pharmaceutical industry context.,

demonstrate that the recovery of final products allows for the improvement of environmental performance of the supply chain, although it affect other decisions and activities of the supply chain, such as raw material purchasing, flows of materials between entities, transportation capacities, necessary installation areas, among others. Therefore, supply chain networks need to be properly designed and planned.

As future challenges, ways to better plan inventory may be explored, such as other storing technologies already mentioned. Within the research on alternative storing technologies, it is important to study their costs (both purchasing costs and operational costs) and environmental impact, since these may both be reduced by, for instance, renewable energy.

Furthermore, the developed model may still be improved to better craft uncertainty in other parameter than supply, since one can identify other sources of uncertainty in the pharmaceutical industry supply chains, including facilities construction, production times, storage resources used, and also regarding the transportation modes used.

Finally, future research is ought to be made in order to measure resilience's effects in pharmaceutical supply chains and help decision-makers reducing supply chain's vulnerability. Redundancy in production capacity, lead time ratio, shortages or losses caused by disruptions are examples of resilience concerns to be considered in the design and planning of supply chains. Some authors have already explored this topic and came to the conclusion that resilience policies represent a possible way to minimize costs and maximizing sustainable performance during disruptions.

References

Abbafati, , Stephen S. Lim, and Christopher J. L. Murray. 2020. “Global Burden of 369 Diseases and Injuries in 204 Countries and Territories, 1990–2019: A Systematic Analysis for the Global Burden of Disease Study 2019.” *The Lancet* 396(10258):1204–22. doi: 10.1016/S0140-6736(20)30925-9.

Agrawal, Gaurav, Michael Conway, Jennifer Heller, Adam Sabow, and Gila Tolub. 2021. “On Pins and Needles : How Accessible and Effective Will COVID-19 Vaccines Be?” *Mckinsey & Company* (February).

Ahi, Payman, and Cory Searcy. 2013. “A Comparative Literature Analysis of de Fi Nitions for Green and Sustainable Supply Chain Management.” *Journal of Cleaner Production* 52:329–41. doi: 10.1016/j.jclepro.2013.02.018.

Amaro, A. C. S., and A. P. F. D. Barbosa-Póvoa. 2008. “Planning and Scheduling of Industrial Supply Chains with Reverse Flows: A Real Pharmaceutical Case Study.” *Computers and Chemical Engineering* 32(11):2606–25. doi: 10.1016/j.compchemeng.2008.03.006.

Archibald, Thomas W., and Sarah E. Marshall. 2018. “Review of Mathematical Programming Applications in Water Resource Management Under Uncertainty.” *Environmental Modeling and Assessment* 23(6):753–77. doi: 10.1007/s10666-018-9628-0.

Association for Accessible Medications. 2017. “Introduction to the Generic Drug Supply Chain and Key Considerations for Policymakers.”

Azaron, A., K. N. Brown, S. A. Tarim, and M. Modarres. 2008. “A Multi-Objective Stochastic Programming Approach for Supply Chain Design Considering Risk.” *International Journal of Production Economics* 116(1):129–38. doi: 10.1016/j.ijpe.2008.08.002.

Badri, Masood A. 1999. “Combining the Analytic Hierarchy Process and Goal Programming for Global Facility Location-Allocation Problem.” *International Journal of Production Economics* 62(3):237–48. doi: 10.1016/S0925-5273(98)00249-7.

Barbosa-Póvoa, Ana Paula. 2012. “Progresses and Challenges in Process Industry Supply Chains Optimization.” *Current Opinion in Chemical Engineering* 1(4):446–52. doi: 10.1016/j.coche.2012.09.006.

Barbosa-Povoa, Ana Paula, Bruna Mota, and Ana Carvalho. 2018. “How to Design and Plan Sustainable Supply Chains through Optimization Models?” *Pesquisa Operacional* 38(3):363–88. doi: 10.1590/0101-7438.2018.038.03.0363.

Barbosa-Póvoa, Ana Paula, and José Mauricio Pinto. 2018. “Challenges and Perspectives of Process Systems Engineering in Supply Chain Management.” Pp. 87–96 in *Computer Aided Chemical Engineering*. Vol. 44. Elsevier B.V.

Barbosa-Póvoa, Ana Paula, Cátia da Silva, and Ana Carvalho. 2018. “Opportunities and Challenges in Sustainable Supply Chain: An Operations Research Perspective.” *European Journal of Operational Research* 268(2):399–431. doi: 10.1016/j.ejor.2017.10.036.

Bing shen How, Hon Loong Lam. 2018. “Sustainability Evaluation for Biomass Supply Chain Synthesis: Novel Principal Component Analysis (PCA) Aided Optimisation Approach.”

Blos, Mauricio F., Robson M. Da Silva, and Paulo E. Miyagi. 2015. “Application of an Agent-Based Supply Chain to Mitigate Supply Chain Disruptions.” *IFAC-PapersOnLine* 28(3):640–45. doi: 10.1016/j.ifacol.2015.06.154.

Bui, Tat Dat, Feng Ming Tsai, Ming Lang Tseng, Raymond R. Tan, Krista Danielle S. Yu, and Ming K. Lim. 2020. “Sustainable Supply Chain Management towards Disruption and Organizational Ambidexterity: A Data Driven Analysis.” *Sustainable Production and Consumption* 26:373–410. doi: 10.1016/j.spc.2020.09.017.

Cardoso, Teresa, Mónica Duarte Oliveira, Ana Barbosa-Póvoa, and Stefan Nickel. 2015. “An Integrated Approach for Planning a Long-Term Care Network with Uncertainty, Strategic Policy and Equity Considerations.” *European Journal of Operational Research* 247(1):321–34. doi: 10.1016/j.ejor.2015.05.074.

Chandra, Dheeraj, and Dinesh Kumar. 2020. “Prioritizing the Vaccine Supply Chain Issues of Developing Countries Using an Integrated ISM-Fuzzy ANP Framework.” *Journal of Modelling in Management* 15(1):112–65. doi: 10.1108/JM2-08-2018-0111.

Chardine-Baumann, Emilie, and Valérie Botta-Genoulaz. 2014. “A Framework for Sustainable Performance Assessment of Supply Chain Management Practices.” *Computers and Industrial Engineering* 76(1):138–47. doi: 10.1016/j.cie.2014.07.029.

Charmondusit, K., S. Phatarachaisakul, and P. Prasertpong. 2014. “The Quantitative Eco-Efficiency Measurement for Small and Medium Enterprise : A Case Study of Wooden Toy Industry.” 935–45. doi: 10.1007/s10098-013-0693-4.

Chen, Sheng I., Bryan A. Norman, Jayant Rajgopal, Tina M. Assi, Bruce Y. Lee, and Shawn T. Brown. 2014. “A Planning Model for the WHO-EPI Vaccine Distribution Network in Developing Countries.” *IIE Transactions (Institute of Industrial Engineers)* 46(8):853–65. doi: 10.1080/0740817X.2013.813094.

Danese, Pamela, Pietro Romano, and Marco Formentini. 2013. “The Impact of Supply Chain Integration on Responsiveness: The Moderating Effect of Using an International Supplier Network.” *Transportation Research Part E: Logistics and Transportation Review* 49(1):125–40. doi: 10.1016/j.tre.2012.08.002.

Devika, K., A. Jafarian, and V. Nourbakhsh. 2014. “Designing a Sustainable Closed-Loop Supply Chain Network Based on Triple Bottom Line Approach : A Comparison of Metaheuristics Hybridization Techniques.” *European Journal of Operational Research* 235(3):594–615. doi: 10.1016/j.ejor.2013.12.032.

DHL Research and Innovation. 2020. “Delivering Pandemic Resilience How To Secure Stable Supply Chains for Vaccines and Medical Goods During the Covid-19 Crisis.” *September, 2020*.

EFPIA. 2020. “The Pharmaceutical Industry : A Key Asset To Scientific and Medical Progress the Pharmaceutical Industry.” 28.

Ekambaram, Anand. 2014. “Facility design for vaccine manufacturing—regulatory, business, and technical considerations and a risk-based design approach.” Vaccine Development and Manufacturing, First Edition

EMA. 2020. “COVID-19 Vaccines: Development, Evaluation, Approval and Monitoring.” Retrieved (https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-development-evaluation-approval-monitoring).

Farrokh, Mojtaba, Adel Azar, Gholamreza Jandaghi, and Ehsan Ahmadi. 2018. “A Novel Robust Fuzzy Stochastic Programming for Closed Loop Supply Chain Network Design under Hybrid Uncertainty.” *Fuzzy Sets and Systems* 341:69–91. doi: 10.1016/j.fss.2017.03.019.

Federsel, Hans Jürgen. 2009. “Chemical Process Research and Development in the 21st Century: Challenges, Strategies, and Solutions from a Pharmaceutical Industry Perspective.” *Accounts of Chemical Research* 42(5):671–80. doi: 10.1021/ar800257v.

Fengqi You and Belinda Wang. 2011. “Life Cycle Optimization of Biomass-to-Liquid Supply Chains with Distributed–Centralized Processing Networks.” doi: doi.org/10.1021/ie200850t.

Franca, Rodrigo B., Erick C. Jones Ã, Casey N. Richards, and Jonathan P. Carlson. 2010. “Int . J . Production Economics Multi-Objective Stochastic Supply Chain Modeling to Evaluate Tradeoffs between Profit and Quality.” *Intern. Journal of Production Economics* 127(2):292–99. doi: 10.1016/j.ijpe.2009.09.005.

Garcia, Daniel J., and Fengqi You. 2015. “Supply Chain Design and Optimization: Challenges and Opportunities.” *Computers and Chemical Engineering* 81:153–70. doi: 10.1016/j.compchemeng.2015.03.015.

Gartner, The, Healthcare Supply, and Chain Top. 2020. “The Gartner Healthcare Supply Chain Top 25 for 2020.”

Ghaderi, Hamid, Alireza Moini, and Mir Saman Pishvaee. 2018. “A Multi-Objective Robust Possibilistic Programming Approach to Sustainable Switchgrass-Based Bioethanol Supply Chain Network Design.” *Journal of Cleaner Production*. doi: 10.1016/j.jclepro.2017.12.218.

Govindan, Kannan, Mohammad Fattahi, and Esmaeil Keyvanshokooh. 2017. “Supply Chain Network Design under Uncertainty : A Comprehensive Review and Future Research Directions.” 263:108–41. doi: 10.1016/j.ejor.2017.04.009.

Govindan, Kannan, Hamed Soleimani, and Devika Kannan. 2015. “Reverse Logistics and Closed-Loop Supply Chain: A Comprehensive Review to Explore the Future.” *European Journal of Operational Research* 240(3):603–26. doi: 10.1016/j.ejor.2014.07.012.

Günther, H., M. Kannegiesser, and N. Autenrieb. 2015. “The Role of Electric Vehicles for Supply Chain Sustainability in the Automotive Industry.” *Journal of Cleaner Production* 90(2015):220–33. doi: 10.1016/j.jclepro.2014.11.058.

Hammami, Ramzi, Yannick Frein, and Atidel B. Hadj-alouane. 2009. “Int . J . Production Economics A Strategic-Tactical Model for the Supply Chain Design in the Delocalization Context : Mathematical Formulation and a Case Study.” *Intern. Journal of Production Economics* 122(1):351–65. doi: 10.1016/j.ijpe.2009.06.030.

Hao, Peng, Bo Wang, Gang Li, Zeng Meng, Kuo Tian, and Xiaohan Tang. 2014. “Thin-Walled Structures Hybrid Optimization of Hierarchical Stiffened Shells Based on Smeared Stiffener Method and Fi Nite Element Method.” *Thin Walled Structures* 82:46–54. doi: 10.1016/j.tws.2014.04.004.

Heintz, Juliette, Jean Pierre Belaud, and Vincent Gerbaud. 2014. “Chemical Enterprise Model and Decision-Making Framework for Sustainable Chemical Product Design.” *Computers in Industry* 65(3):505–20. doi: 10.1016/j.compind.2014.01.010.

Hickey, Anthony J., and David Ganderton. 2001. *Pharmaceutical Process Engineering (Drugs and the Pharmaceutical Sciences)*.

Hoek, Albert Jan Van, Mwanajuma Ngama, Amina Ismail, Jane Chuma, Samuel Cheburet, David Mutonga, Tatu Kamau, and D. James Nokes. 2012. “A Cost Effectiveness and Capacity Analysis for the Introduction of Universal Rotavirus Vaccination in Kenya : Comparison between Rotarix and RotaTeq Vaccines.” 7(10). doi: 10.1371/journal.pone.0047511.

IHME. n.d. “GDX Health Data.” Retrieved August 10, 2021 (http://ghdx.healthdata.org/gbd-results-tool).

John M. Mulvey; Robert J. Vanderbei. 1995. “Robust Optimization of Large-Scale Systems.” *Automatica* 6(2):315–31. doi: 10.1016/0005-1098(70)90103-2.

Johnston, R. B. 2016. “Arsenic and the 2030 Agenda for Sustainable Development.” *Arsenic Research and Global Sustainability - Proceedings of the 6th International Congress on Arsenic in the Environment, AS 2016* 12–14. doi: 10.1201/b20466-7.

Kannegiesser, M., H. Günther, and N. Autenrieb. 2015. “The Time-to-Sustainability Optimization Strategy for Sustainable Supply Network Design.” *Journal of Cleaner Production* 108:451–63. doi: 10.1016/j.jclepro.2015.06.030.

Keeble, Brian R. 1988. “The Brundtland Report: ‘Our Common Future.’” *Medicine and War* 4(1):17–25. doi: 10.1080/07488008808408783.

Keith Collins and Josh Holder. 2021. “See How Rich Countries Got to the Front of the Vaccine Line - The New York Times.” *New York Times*. Retrieved May 27, 2021 (https://www.nytimes.com/interactive/2021/03/31/world/global-vaccine-supply-inequity.html).

Khanna, Ish. 2012. “Drug Discovery in Pharmaceutical Industry: Productivity Challenges and Trends.” *Drug Discovery Today* 17(19–20):1088–1102. doi: 10.1016/j.drudis.2012.05.007.

Klutz, Stephan, Jorgen Magnus, Martin Lobedann, Peter Schwan, Benjamin Maiser, Jens Niklas, Maike Temming, and Gerhard Schembecker. 2015. “Developing the Biofacility of the Future Based on Continuous Processing and Single-Use Technology.” *Journal of Biotechnology* 213:120–30. doi: 10.1016/j.jbiotec.2015.06.388.

Kochhar, Sonali, Barbara Rath, Lea D. Seeber, Gabriella Rundblad, Ali Khamesipour, and Mohammad Ali. 2013. “Introducing New Vaccines in Developing Countries.” *Expert Review of Vaccines* 12(12):1465–78. doi: 10.1586/14760584.2013.855612.

Kosaka, Tatsuro. 2021. “Chugai Announces 2020 Full Year Results and Forecasts for 2021.” 2020(April 2020):7–10.

Kravanja, Zdravko. 2013. “Multi-Objective Optimisation for Generating Sustainable Solutions Considering Total Effects on the Environment ˇ Uc.” 101:67–80. doi: 10.1016/j.apenergy.2012.04.025.

Kumar, Anup, and Kampan Mukherjee. 2020. “Lean Manufacturing in Pharmaceutical Closed-Loop Supply Chain.” *International Journal of Environment and Waste Management* 26(1):14–38. doi: 10.1504/IJEWM.2020.108062.

Lemmens, Stef, Catherine Decouttere, Nico Vandaele, and Mauro Bernuzzi. 2016. “A Review of Integrated Supply Chain Network Design Models: Key Issues for Vaccine Supply Chains.” *Chemical Engineering Research and Design* 109:366–84. doi: 10.1016/j.cherd.2016.02.015.

Li, Can, and Ignacio E. Grossmann. 2021. “A Review of Stochastic Programming Methods for Optimization of Process Systems Under Uncertainty.” *Frontiers in Chemical Engineering* 2(January):1–20. doi: 10.3389/fceng.2020.622241.

Marques, Catarina M., Samuel Moniz, Jorge Pinho de Sousa, Ana Paula Barbosa-Povoa, and Gintaras Reklaitis. 2020. “Decision-Support Challenges in the Chemical-Pharmaceutical Industry: Findings and Future Research Directions.” *Computers and Chemical Engineering* 134:106672. doi: 10.1016/j.compchemeng.2019.106672.

Max Roser and Hannah Ritchie. n.d. “Burden of Disease, Our World in Data.” *2016*. Retrieved (https://ourworldindata.org/burden-of-disease).

Menou, Veronique, Allison Hornstein, and Elizabeth Lipton-McCombie. 2021. “Access to Medicine Index 2021.” 1–72.

Messmann, Lukas, Victoria Zender, Andrea Thorenz, and Axel Tuma. 2020. “How to Quantify Social Impacts in Strategic Supply Chain Optimization : State of the Art.” *Journal of Cleaner Production* 257:120459. doi: 10.1016/j.jclepro.2020.120459.

Mota, Bruna, Maria Isabel Gomes, Ana Carvalho, and Ana Paula Barbosa-povoa. 2018. “Sustainable Supply Chains : An Integrated Modeling Approach under Uncertainty R.” *Omega* 77:32–57. doi: 10.1016/j.omega.2017.05.006.

Mota, Bruna, Maria Isabel, Ana Carvalho, and Ana Paula Barbosa-povoa. 2015. “Towards Supply Chain Sustainability : Economic , Environmental and Social Design and Planning.” *Journal of Cleaner Production* 105:14–27. doi: 10.1016/j.jclepro.2014.07.052.

Mukhamedjanova, Kamola A. 2020. “Concept of Supply Chain Management.” *Journal of Critical Reviews* 7(2):759–66. doi: 10.31838/jcr.07.02.139.

Munir, Manal, Muhammad Shakeel Sadiq Jajja, Kamran Ali Chatha, and Sami Farooq. 2020a. “Supply Chain Risk Management and Operational Performance: The Enabling Role of Supply Chain Integration.” *International Journal of Production Economics* 227(January):107667. doi: 10.1016/j.ijpe.2020.107667.

Munir, Manal, Muhammad Shakeel Sadiq Jajja, Kamran Ali Chatha, and Sami Farooq. 2020b. “Supply Chain Risk Management and Operational Performance: The Enabling Role of Supply Chain Integration.” *International Journal of Production Economics* 227(March 2019):107667. doi: 10.1016/j.ijpe.2020.107667.

Musamih, Ahmad, Khaled Salah, Raja Jayaraman, Junaid Arshad, Mazin Debe, Yousof Al-Hammadi, and Samer Ellahham. 2021. “A Blockchain-Based Approach for Drug Traceability in Healthcare Supply Chain.” *IEEE Access* 9:9728–43. doi: 10.1109/ACCESS.2021.3049920.

Papageorgiou, Lazaros G., Guillermo E. Rotstein, and Nilay Shah. 2001. “Strategic Supply Chain Optimization for the Pharmaceutical Industries.” *Industrial and Engineering Chemistry Research* 40(1):275–86. doi: 10.1021/ie990870t.

Pfizer. 2015. “The Value of Medicines in Offsetting Healthcare Costs.” Retrieved (Pfizer.com/ValueOfMedicines)

Pfizer. 2019. “The Value of Vaccines in Disease Prevention:A Global Perspective.” 298(18):2155–63.

Pishvaee, M. S., J. Razmi, and S. A. Torabi. 2012. “Robust Possibilistic Programming for Socially Responsible Supply Chain Network Design: A New Approach.” *Fuzzy Sets and Systems* 206:1–20. doi: 10.1016/j.fss.2012.04.010.

Pishvaee, M. S., J. Razmi, and S. A. Torabi. 2014. “An Accelerated Benders Decomposition Algorithm for Sustainable Supply Chain Network Design under Uncertainty: A Case Study of Medical Needle and Syringe Supply Chain.” *Transportation Research Part E: Logistics and Transportation Review* 67:14–38. doi: 10.1016/j.tre.2014.04.001.

Pishvaee, Mir Saman, and Jafar Razmi. 2012. “Environmental Supply Chain Network Design Using Multi-Objective Fuzzy Mathematical Programming.” *Applied Mathematical Modelling* 36(8):3433–46. doi: 10.1016/j.apm.2011.10.007.

Plotkin, Stanley, James M. Robinson, Gerard Cunningham, Robyn Iqbal, and Shannon Larsen. 2017. “The Complexity and Cost of Vaccine Manufacturing – An Overview.” *Vaccine* 35(33):4064–71. doi: 10.1016/j.vaccine.2017.06.003.

Privett, Natalie, and David Gonsalvez. 2014. “The Top Ten Global Health Supply Chain Issues: Perspectives from the Field.” *Operations Research for Health Care* 3(4):226–30. doi: 10.1016/j.orhc.2014.09.002.

Rastegar, Mehdi, Madjid Tavana, Afshin Meraj, and Hassan Mina. 2021. “An Inventory-Location Optimization Model for Equitable Influenza Vaccine Distribution in Developing Countries during the COVID-19 Pandemic.” *Vaccine* 39(3):495–504. doi: 10.1016/j.vaccine.2020.12.022.

Reinhardt, Ingrid Carla, Dr Jorge C. Oliveira, and Dr Denis T. Ring. 2020. “Current Perspectives on the Development of Industry 4.0 in the Pharmaceutical Sector.” *Journal of Industrial Information Integration* 18(July 2019):100131. doi: 10.1016/j.jii.2020.100131.

Richardson, Julie. 2013. “The Triple Bottom Line: Does It All Add up?: Assessing the Sustainability of Business and CSR.” *The Triple Bottom Line: Does It All Add Up* 1(1986):1–186. doi: 10.4324/9781849773348.

RobecoSAM AG. 2021. *The Sustainability Yearbook 2021*. ISBN: 9783952538500

Rommelfanger, Heinrich J. 2004. “The Advantages of Fuzzy Optimization Models in Practical Use.” *Fuzzy Optimization and Decision Making* 3(4):295–309. doi: 10.1007/s10700-004-4200-6.

Sabri, Ehap H., and Benita M. Beamon. 2000. “A Multi-Objective Approach to Simultaneous Strategic and Operational Planning in Supply Chain Design.” 28.

Sadjadi, Seyed Jafar, Zahra Ziaei, and Mir Saman Pishvaee. 2019. “The Design of the Vaccine Supply Network under Uncertain Condition: A Robust Mathematical Programming Approach.” *Journal of Modelling in Management* 14(4):841–71. doi: 10.1108/JM2-07-2018-0093.

Saffar, Mohammad Mahdi, G. Hamed Shakouri, and Jafar Razmi. 2015. “A New Multi Objective Optimization Model for Designing a Green Supply Chain Network under Uncertainty.” *International Journal of Industrial Engineering Computations* 6(1):15–32. doi: 10.5267/j.ijiec.2014.10.001.

Sahinidis, Nikolaos V. 2004. “Optimization under Uncertainty: State-of-the-Art and Opportunities.” *Computers and Chemical Engineering* 28(6–7):971–83. doi: 10.1016/j.compchemeng.2003.09.017.

Sanofi Pasteur. 2021. “Sanofi Pasteur Profile 2021.” *Steve Debenport | May 2021*, 2.

Sazvar, Zeinab, Keivan Tafakkori, Nastaran Oladzad, and Sina Nayeri. 2021. “A Capacity Planning Approach for Sustainable-Resilient Supply Chain Network Design under Uncertainty: A Case Study of Vaccine Supply Chain.” *Computers and Industrial Engineering* 159(June):107406. doi: 10.1016/j.cie.2021.107406.

Settanni, Ettore, Tomás Seosamh Harrington, and Jagjit Singh Srai. 2017. “Pharmaceutical Supply Chain Models: A Synthesis from a Systems View of Operations Research.” *Operations Research Perspectives* 4:74–95. doi: 10.1016/j.orp.2017.05.002.

Shah, Nilay. 2004. “Pharmaceutical Supply Chains: Key Issues and Strategies for Optimisation.” *Computers and Chemical Engineering* 28(6–7):929–41. doi: 10.1016/j.compchemeng.2003.09.022.

Simchi-Levy, D., Kaminsky, P. and Simchi-Levy, E. 2008. “Designing and Managing the Supply Chain.” 22(1):259–61.

Social, Corporate. 2020. “Corporate Social Responsibiliy - Chapter 4 of 2020 Document d’Enregistrement Universel - Sanofi.”

Songane, Mario. 2018. “Challenges for Nationwide Vaccine Delivery in African Countries.” *International Journal of Health Economics and Management* 18(2):197–219. doi: 10.1007/s10754-017-9229-5.

Sterck, Olivier, Max Roser, Mthuli Ncube, and Stefan Thewissen. 2018. “Allocation of Development Assistance for Health: Is the Predominance of National Income Justified?” *Health Policy and Planning* 33:i14–23. doi: 10.1093/heapol/czw173.

Tancrez, Jean-sébastien, Jean-charles Lange, and Pierre Semal. 2012. “A Location-Inventory Model for Large Three-Level Supply Chains.” 48:485–502. doi: 10.1016/j.tre.2011.10.005.

Taylor, David. 2016. *The Pharmaceutical Industry and the Future of Drug Development*. Vols. 2016-January.

The World Health Organization. 2020. *Defeating Meningitis by 2030: A Global Road Map (26th October 2020)*.

Thompson, Kimberly M., and Radboud J. Duintjer Tebbens. 2016. “Framework for Optimal Global Vaccine Stockpile Design for Vaccine-Preventable Diseases: Application to Measles and Cholera Vaccines as Contrasting Examples.” *Risk Analysis : An Official Publication of the Society for Risk Analysis* 36(7):1487–1509.

Toxoid, Diphtheria, Conjugate Vaccine, and Sanofi Pasteur Limited. 2017. “Product Monograph.” 1–41.

Tsang, K. H., N. J. Samsatli, and N. Shah. 2006. “Modelling and Planning Optimization of a Complex Flu Vaccine Facility.” *Food and Bioproducts Processing* 84(2 C):123–34. doi: 10.1205/fbp.05001.

Tsang, K. H., N. J. Samsatli, and N. Ã. Shah. 2007. “Capacity investment planning for multiple vaccines under uncertainty.” 85:120–28. doi: 10.1205/fbp06001.

Tsao, Yu Chung, Vo Van Thanh, Jye Chyi Lu, and Vincent Yu. 2018. “Designing Sustainable Supply Chain Networks under Uncertain Environments: Fuzzy Multi-Objective Programming.” *Journal of Cleaner Production* 174:1550–65. doi: 10.1016/j.jclepro.2017.10.272.

Wang, Min, and Lindu Zhao. 2021. “Cold Chain Investment and Pricing Decisions in a Fresh Food Supply Chain.” *International Transactions in Operational Research* 28(2):1074–97. doi: 10.1111/itor.12564.

WHO. 2020. “Vaccines-and-Immunization.” Retrieved (https://www.who.int/health-topics/vaccines-and-immunization)

World Health Organization, and Market Information for Access to Vaccines. 2019. “Global Market Study: Meningococcal Meningitis Vaccines.” (May):1–4.

Yabuta, Keisho, Haruka Futamura, Koji Kawasaki, Masahiko Hirao, and Hirokazu Sugiyama. 2018. “Design-Oriented Regression Models for H2O2 Decontamination Processes in Sterile Drug Product Manufacturing Considering Rapidity and Sterility.” *International Journal of Pharmaceutics* 548(1):466–73. doi: 10.1016/j.ijpharm.2018.06.055.

Yazdian, Seyed Ahmad, and Kamran Shahanaghi. 2011. “A Multi-Objective Possibilistic Programming Approach for Locating Distribution Centers and Allocating Customers Demands in Supply Chains.” *International Journal of Industrial Engineering Computations* 2(1):193–202. doi: 10.5267/j.ijiec.2010.03.003.

Zahiri, Behzad, Jun Zhuang, and Mehrdad Mohammadi. 2017. “Toward an Integrated Sustainable-Resilient Supply Chain : A Pharmaceutical Case Study.” *Transportation Research Part E* 103(2017):109–42. doi: 10.1016/j.tre.2017.04.009.

Zhao, Liang, Chao Ning, and Fengqi You. 2019. “Operational Optimization of Industrial Steam Systems under Uncertainty Using Data-Driven Adaptive Robust Optimization.” *AIChE Journal* 65(7). doi: 10.1002/aic.16500.

Zuo-Jun Max Shen, Mark S. Daskin. 2005. “Trade-Offs Between Customer Service and Cost in Integrated Supply Chain Design.” *Manuf. Serv. Oper. Manage.7* 188–207. doi: doi.org/10.1287/msom.1050.0083.

APPENDIX A - Corporate Sustainability Assessment (CSA)

Table 10- Corporate Sustainability Assessment (CSA) for the five companies that accomplished highest scores in DOW Jones Sustainability Index (RobecoSAM AG 2021)

		Company name				
Sustainability Dimensions	Measured Criteria	Roche Holding AG	GSK	AstraZeneca PLC	Chugai Pharm.	Sanofi
Environmental	Strategy to improve Access to drugs or products	94	97	97	64	86
	Product Quality & Recall Management	96	88	93	94	74
	Operational Eco-Efficiency	100	100	87	88	92
	Health outcome contribution	100	100	98	100	100
	Codes of Business conduct	82	89	90	94	89
	Climate strategy	100	100	99	96	96
	Addressing cost burden	90	88	79	100	79
Social	Talent Attraction and retention	86	96	90	87	82
Governance & Economic	Innovation management	90	86	75	85	100

APPENDIX B – Considerations and parameters on the case-study elements

Table 11- Represents all entities accounted for the present case-study

Entities Names and Definitions: Superstructure						
Suppliers	Factories	Warehouses	Airports	Seaports	Markets	Technologies
sUS (I_{sup})	fUS (I_f)	wPennsylvania (I_w)	airUS (I_{air})	portUS (I_{port})	cUS (I_c)	Production (gp)
sCanada (I_{sup})	fCanada (I_f)	wToronto (I_w)	airCanada (I_{air})	portCanada (I_{port})	cEurope (I_c)	Refrigeration (gr)
sEurope (I_{sup})	fEurope (I_f)	wFrance (I_w)	airFrance(I_{air})	portNetherlands (I_{port})	cLatinAmerica (I_c)	
sAsia(I_{sup})	fAsia (I_f)	wIndia (I_w)	airIndia (I_{air})	portIndia (I_{port})	cEurasia (I_c)	
sAfrica(I_{sup})	fAfrica (I_f)	wBrazil (I_w)	airBrazil (I_{air})	portBrazil (I_{port})	cAsia (I_c)	
		wKenya (I_w)	airKenya(I_{air})	portKenya (I_{port})	cAfrica (I_c)	
		wNigeria (I_w)	airNigeria(I_{air})	portNigeria (I_{port})	cMiddleEast (I_c)	
		wMiddle East (I_w)	airIsrael (I_{air})	portIsrael (I_{port})	cCanada (I_c)	
		wRussia (I_w)	airRussia (I_{air})	portRussia (I_{port})	cAustralia (I_c)	
		wAustralia (I_w)	airAustralia (I_{air})	portAustralia (I_{port})		

Entities Names and Definitions: Materials	
Raw Materials	Final Products
rm1 (M_{rm})	fpMen (M_{fp}) 1SKU (5 vials of meningitis vaccines)
rm1 (M_{rm})	

Entities Names and Definitions: Transportation Modes		
Land Transportation	Air Transportation	Sea Transportation
atruck1 (A_{truck}) Smaller Truck	aplane (A_{plane})	Aship (A_{ship})
atruck2 (A_{truck}) Bigger Truck		

Parameters and respective assigned values related to the entities considered in the case-study, namely: maximum and minimum supply capacities; raw materials unit costs; maximum and minimum installation areas; hourly labour costs per entity; construction costs per entity; number of necessary workers per entity; maximum flow considered in the network; maximum and minimum allowed inventory levels per entity; and initial stock per entity.

Table 12- Characteristics of each supplier i, for each raw material m

		sUS	sCanada	sEurope	sAsia	sAfrica
Maximum supply capacity, sc_{mi}^{max}	rm1	$BigM$	$BigM$	$BigM$	$BigM$	$BigM$
	rm2	$BigM$	$BigM$	$BigM$	$BigM$	$BigM$
Minimum order quantity sc_{mi}^{min}	rm1	0	0	0	0	0
	rm2	0	0	0	0	0
Raw material unit Cost (€), rmc_{mi}	rm1	0,0195	0,0195	0,0195	0,0100	0,0195
	rm2	0,1	0,1	0,1	0,05	0,1

Table 13- Maximum and minimum installation areas for factories and warehouses

i	F1	F2	F3	F4	F5	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11
ea_i^{max}	18000	18000	18000	18000	18000	5000	50000	5000	5000	5000	5000	5000	5000	5000	5000	5000
ea_i^{min}	-	-	-	-	0	-	-	-	-	-	100	100	100	100	100	100

Table 14- Inventory levels of product *fpMen* at the warehouses

i	W1	W2	W3	W4	W5	W6 to W11
ic_{mi}^{max}	50,000,000	50,000,000	50,000,000	50,000,000	60,000,000	50,000,000
ic_{mi}^{min}	500,000	500,000	500,000	500,000	600,000	500,000
ins_{mi}	0	0	0	0	0	-

Table 15- Number of workers per type of entity, fixed and per square meter if installed capacity (WHO 2017)

	Fixed workers per entity, w_i	Workers per sqm, $wpsq$
Factories	20	0,01
Warehouses	1	0,01

Table 16- Products characterization – General Information

Product	Inventory cost per unit (€) (sc_m)	Price per unit sold (€) (psu_m)	Product weight (mg) (pw_m)	Necessary area per unit of product (m^2)	Necessary volume per unit of product (cm^3)
rm1	-	-	6.285 mg	0,001	0.5
rm2	-	-	13000 mg	0,001	5.5
fpMen	1.98	113.55	65031 mg	0,006	27.5

Table 17- Product bill of materials (BOM_{mng}^{prod} and BOM_{mng}^{rem})

Relation between materials at factories		Final product
		fpMen
Raw material	rm1	5
	rm2	5
Final product	fpMen	1
Relation between final products at warehouses, airports and seaport		Final product
		fpMen
Final product	fpMen	1

Table 18- Technology characterization - Production

Technology	Maximum Production Capacity (units) (pc_g^{max})	Minimum Production Capacity (units) (pc_g^{min})	Installation Costs (€) (tec_g)	Operational costs per unit produced (€) (opc_g)	Fixed necessary workers (w_g)
Production	300,000,000	0	150,000	0,6	67

Table 19- Technology characterization - Storage

Technology	Maximum Storage quantity of technology g (units) (sc_g^{max})	Minimum Storage quantity of technology g (units) (sc_g^{min})	Necessary Area of technology g (cm^2) (at_g)	Installation Costs (€) (tec_g)	Operational costs per unit stored (€) (opc_g)	Fixed necessary workers (w_g)
Refrigerator	50000	0	2084	1000	0,27	1

Table 20- Transportation Modes Characterization

Transportation Mode Characteristics	Maximum Transportation Capacity (units) (ct_a^{max})	Minimum Transportation Capacity (ct_a^{min})	Maximum Contracted Capacity per time period (units) (cca_a^{max})
Truck 1	52 900	0	40 000 000
Truck 2	79 350	0	80 000 000
Plane	600,000	0	8 000 000
Boat	800,000	0	8 000 000

Table 21- Transportation Modes - Fixed Costs

Transportation Mode Fixed Costs	Fixed Costs – Monthly Payment to Carrier (€)	Handling Costs at hub terminals per unit (€)
Air- US	252,000	0,125
Air2- Canada	252,000	0,125
Air3- France	252,000	0,118
Air4- India	100,000	0,050
Air5- Brazil	144,000	0,075

Table 21- Transportation Modes - Fixed Costs (Continuation)

Transportation Mode Fixed Costs	Fixed Costs – Monthly Payment to Carrier (€)	Handling Costs at hub terminals per unit (€)
Air6- Kenya	180,000	0,075
Air7- Nigeria	180,000	0,075
Air8- Israel	200,000	0,120
Air9- Russia	250,000	0,120
Air10- Australia	220,000	0,125
Boat1- US	252,000	0,125
Boat2- Canada	252,000	0,125
Boat3- France	252,000	0,118
Boat4- India	100,000	0,050
Boat5- Brazil	144,000	0,075
Boat6- Kenya	180,000	0,075
Boat7- Nigeria	180,000	0,075
Boat8- Israel	200,000	0,120
Boat9- Russia	252,000	0,120
Boat10- Austrralia	252,000	0,125

Table 22- Economic Data

Economic Data	
Interest Rate, ir	10%
Tax rate, tr	30%
Salvage value, sv	20%

APPENDIX C – Environmental Module Characterization

Table 23- Midpoint environmental impact categories and their units

Abbreviation	Midpoint impact categories Climate	Units	Abbreviation	Midpoint impact categories Climate	Units
CC	Climate Change	kg CO_2 eq	FET	Freshwater Ecotoxicity	kg 1,4-DB eq
OD	Ozone Depletion	kg CFC-11 eq	MET	Marine Ecotoxicity	kg 1,4-DB eq
TA	Terrestrial Acidification	kg SO_2 eq	IR	Ionising Radiation	kg U235 eq
FE	Freshwater Eutrophication	kg P eq	ALO	Agricultural Land Occupation	m^2a
ME	Marine Eutrophication	kg N eq	ULO	Urban Land Occupation	m^2a
HT	Human Toxicity	kg 1,4-DB eq	NLT	Natural Land Transformation	m^2a
POF	Photochemical Oxidant Formation	kg NMVOC	MRD	Metal Depletion	kg Fe eq
PMF	Particulate Matter Formation	kg PM10 eq	FRD	Fossil Depletion	kg oil eq
TET	Terrestrial Ecotoxicity	kg 1,4-DB eq			

Table 24- Environmental Impact and normalization factors

	CC	OD	TA	FE	ME	HT	POF	PMF	TET	FET	MET	IR	ALO	ULO	NLT	MRD	FRD
Entity, per m2	3,55E+02	3,31E-05	4,02E+00	9,23E-03	1,06E-01	5,10E+01	1,74E+00	9,76E-01	5,60E-02	1,33E+00	7,80E-01	1,29E-01	1,02E+02	6,42E+00	6,42E+00	3,54E+00	1,10E+02

	CC	OD	TA	FE	ME	HT	POF	PMF	TET	FET	MET	IR	ALO	ULO	NLT	MRD	FRD
gp	5,36E+02	1,96E-05	4,93E+00	2,51E+00	3,43E-01	1,10E+04	3,23E+00	1,85E+00	5,02E-01	8,51E+00	4,57E+03	1,14E+02	1,49E+02	1,65E+01	1,15E-01	7,17E+02	1,38E+02

	CC	OD	TA	FE	ME	HT	POF	PMF	TET	FET	MET	IR	ALO	ULO	NLT	MRD	FRD
gr	3,27E+01	1,26E-06	1,48E-01	2,76E-03	3,03E-03	1,18E+00	8,04E-02	1,21E-01	7,42E-04	9,29E-03	1,28E-02	2,75E+00	5,74E-01	2,11E-01	2,51E-03	2,18E-01	6,78E-01

Transport modes, per kg.km	CC	OD	TA	FE	ME	HT	POF	PMF	TET	FET	MET	IR	ALO	ULO	NLT	MRD	FRD
truck1	1,29E-01	2,39E-08	6,42E-04	4,32E-06	2,93E-05	3,37E-02	8,81E-04	3,91E-04	7,33E-05	9,38E-05	5,47E-04	7,09E-03	1,92E-02	9,16E-03	5,02E-05	9,37E-04	6,19E-03
truck2	2,40E-02	4,44E-09	1,19E-04	8,03E-07	5,45E-06	6,27E-03	1,64E-04	7,27E-05	1,36E-05	1,74E-05	1,02E-04	1,32E-03	3,56E-03	1,70E-03	9,33E-06	1,74E-04	1,15E-03
plane	5,26E-02	1,76E-09	6,14E-04	1,00E-06	1,53E-05	1,17E-03	2,83E-04	8,62E-04	1,28E-06	7,15E-05	1,09E-05	5,47E-03	6,34E-03	4,95E-03	1,62E-05	2,58E-04	1,39E-03
boat	6,31E-02	9,52E-09	5,05E-04	2,07E-06	2,83E-05	1,66E-03	7,93E-04	2,58E-04	4,14E-06	2,69E-05	3,75E-05	3,04E-03	7,71E-03	2,68E-03	4,48E-05	5,04E-04	6,20E-03

	CC	OD	TA	FE	ME	HT	POF	PMF	TET	FET	MET	IR	ALO	ULO	NLT	MRD	FRD
Normalization factor	1,81E-04	2,66E+01	2,37E-02	3,45E+00	1,36E-01	6,89E-04	1,76E-02	7,11E-02	1,23E-01	2,20E-01	1,48E-03	7,59E-04	1,84E-04	1,29E-03	8,31E-02	2,25E-03	7,75E-04

Table 25. Environmental Impact of the considered supply chain activities across the scenarios

Environmental Impact/ Cases	A	B	C
Production	2.88E+07	2.95E+07	2.86E+07
Storage	9.93	49.65	0
Facility installation	306.23	569.92	146.19
Transportation modes	37 823.00	5 264.41	4 302.40
Total environmental impact	2.88E+07	2.95E+07	2.86E+07

Table 26- Environmental impact results for production and refrigeration for each midpoint impact category

CASE A			
Production		Refrigeration	
CC	5.67643e+08	CC	8995.6549
OD	20.7498	OD	0.0003
TA	5.22016e+06	TA	40.8306
FE	2.65806e+06	FE	0.7593
ME	363558	ME	0.8336
HT	1.1648e+10	HT	325.6058
POF	3.41755e+06	POF	22.1165
PMF	1.96027e+06	PMF	33.3392
TET	531420	TET	0.2041
FET	9.00958e+06	FET	2.5554
MET	4.83376e+09	MET	3.5264
IR	1.20257e+08	IR	757.0539
ALO	1.5742e+08	ALO	157.8820
ULO	1.74669e+07	ULO	58.0892
NLT	121729	NLT	0.6909
MRD	7.59053e+08	MRD	59.9675
FRD	1.45797e+08	FRD	186.4675
CASE B			
CC	5.81586e+08	CC	44978.2743
OD	21.2595	OD	0.0017
TA	5.34838e+06	TA	204.1529
FE	2.72335e+06	FE	3.7965
ME	372489	ME	4.1678
HT	1.19341e+10	HT	1628.0289
POF	3.5015e+06	POF	110.5826
PMF	2.00842e+06	PMF	166.6960
TET	544474	TET	1.0206
FET	9.23089e+06	FET	12.7770
MET	4.9525e+09	MET	17.6321
IR	1.23211e+08	IR	3785.2696
ALO	1.61287e+08	ALO	789.4098
ULO	1.7896e+07	ULO	290.4460
NLT	124719	NLT	3.4545
MRD	7.77698e+08	MRD	299.8375
FRD	1.49378e+08	FRD	932.3375

Table 26- (Continuation)- Environmental impact results for production and refrigeration for each midpoint impact category

CASE C			
Production		Refrigeration	
CC	5.64157e+08	CC	-
OD	20.6224	OD	-
TA	5.1881e+06	TA	-
FE	2.64174e+06	FE	-
ME	361326	ME	-
HT	1.15765e+10	HT	-
POF	3.39656e+06	POF	-
PMF	1.94823e+06	PMF	-
TET	528157	TET	-
FET	8.95425e+06	FET	-
MET	4.80408e+09	MET	-
IR	1.19519e+08	IR	-
ALO	1.56453e+08	ALO	-
ULO	1.73596e+07	ULO	-
NLT	120982	NLT	-
MRD	7.54391e+08	MRD	-
FRD	1.44901e+08	FRD	-