Pharmaceutical Industry Supply Chains: Planning Vaccines' Distribution

Inês Ralheta Duarte

Thesis to obtain the Master of Science Degree in Biomedical Engineering

Instituto Superior Técnico, University of Lisbon, Portugal

Pharmaceutical supply chains tend to be complex, and its management encounters several challenges. This, along with the importance to consider sustainability objectives, has significantly increased the complexity of network's management in this sector. Addressing equity in access has proven to be a critical concern in pharmaceutical supply chains, in particular when dealing with vaccines' distribution, thus being important to consider availability and affordability when designing and planning a vaccines' supply chains. Hence, a decision-support tool is introduced following the work developed by (Mota *et al.*, 2018), where a multi-objective mixed integer linear programming model is proposed, aiming to integrate several strategical-tactical decisions while considering the three pillars of sustainability, which are addressed as objective functions. The economic assessment is performed through the Net Present Value (NPV). The environmental impact assessment follows the Life Cycle Analysis (LCA) methodology. Accessibility of pharmaceutical products is the major focus for the social assessment, aiming to provide an equal distribution based on the burden of diseases of each country, which is made through a DALY-based metric (Disability-Adjusted Life Year). The model is applied to a real base case study aiming to discuss different optimization scenarios and allowing to understand the effect of decisions on each performance indicators.

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

1. Introduction

The 2030 Agenda of Sustainable Development comprises several goals intended to drive global and national policies in the direction of a sustainable development of our societies. Within these goals, one seeks to support well-being at all ages and guaranteeing healthy lives, while another fosters inclusive and sustainable economic growth, employment, and proper work for all.

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". This concept 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 several entities that manage products from suppliers to customers and their associated returns, always considering 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 and detailed scheduling (Shah, 2004). 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 resources needed to 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 years, especially in developing countries (Pfizer, 2015). Hence, 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 tend to be complex, and its management encounters multiple challenges. Decision-makers often struggle with the high levels of uncertainty, which together with the need to consider sustainability principles (economic, environmental and social objectives) in supply chain management, have greatly increased the complexity of the network's management in this sector.

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.

2. Pharmaceutical Industry sector and their supply chains

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),(EFPIA, 2020). This 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, enhancing, or preserving health, and to avoid exacerbation of existing illnesses. Accordingly, along with the direct benefits for population, medicines and vaccines also contribute towards a significant cost reduction in the total healthcare costs of each country by decreasing the need for long-term care services and/or costly surgeries (Pfizer, 2015).

Challenges and driving forces

Pharmaceutical supply chains are typically complex and involve a large network of manufacturers, packaging resources, wholesalers, and final healthcare providers (hospitals, pharmacies, among others), as well as 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 (Marques *et al.*, 2020).

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). Despite the improvements and progress in continuous manufacturing, support by regulators and the rising consciousness of its benefits, traditional batch operating mode still prevails in the primary manufacturing phase. Since batch processes are commonly used for low volumes and high product variability, it provides an easier quality control and decontamination measures in case of a batch is contaminated, higher flexibility as well as lot traceability and well-defined steps, thereby providing a better knowledge of the supply chain intermediaries.

Given the complex and demanding management, pharmaceutical supply chains tend to be vulnerable to **uncertainty** and more susceptible to higher levels of risk. This is due to various reasons: firstly, the considerable impact of uncertainty related with outcomes of clinical trials throughout the development process; secondly, it is important to identify the uncertainty at the raw materials supply, commercial production and distribution levels, which may lead to a higher growth in complexity. With respect to **sustainability**, concerns such as an efficient water and energy consumption, waste management, reverse flows on supply chains and social issues are being considered in some works. Moreover, the rise in unused and expired medicines is pushing pharmaceutical companies to restructure their supply chains and adopt new sustainable technologies.

An extremely complex social challenge also faced is regarding **equity**. Kochhar *et al.*, (2013) highlighted that geographical locations represent 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. Moreover, **population density** may vary across distinct regions within a country, being harder to reach people in some areas. Thus, vaccine manufacturers have been trying to expand accessibility of products, particularly in developing countries (Lemmens *et al.*, 2016).

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 challenge the traditional business model for the pharmaceutical industry. The **increasing regulatory burden** and **quality of products** were identified as major driving forces 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.

3. Supply chain optimization in the pharmaceutical context

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 et. al 2018), 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, while, in fact, real-world problems include uncertainties and difficulties when estimating key parameters. Therefore, some authors have worked on methods to 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.

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 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).

When working with various objectives in a supply chain, a multi-objective decision making (MODM) procedure may be necessary. **Goal programming** is used to model multiple, often conflicting, performance measures where undesirable deviations from the value aimed to be reached should be minimized in an achievement function. Another approach is the **weighted sum method**, where a multiple-criteria problem is converted into a scalar problem by creating a weighted sum of all the criteria (Shen, 2005). 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 (Lemmens *et al.* 2016).

Social concerns in supply chain optimization

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, and not including social concerns in the supply chain design and planning may have negative consequences to the companies involved. In the review developed by the same authors, social indicators identified as the most used were job creation, safety, health, number of working hours and discrimination, as well as indicators related to satisfaction and community development aspects.

Addressing **equity** has proven to be a critical concern when dealing with vaccine and medicines' distribution by pharmaceutical companies.

Cardoso *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 expected costs, ensuring a minimum level of demand satisfaction. Equity aspects considered include equity of access, aiming 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 level across services, avoiding a delivery of only the cheapest services; socioeconomic equity, where unsatisfied demand for lower income populations should not exceed a defined level, avoiding a lack of provision due to poverty; and geographical equity, where unsatisfied demand across geographical areas should not exceed a maximum level, so as 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.

4. Model Conceptualization

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 a decision-support tool for the design and planning of closed-loop supply chains focusing on strategic-tactical challenges is suggested. The generic supply chain representation considers a four-echelon structure (see Figure 1), 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 for the material transport from one transportation mode to the other.

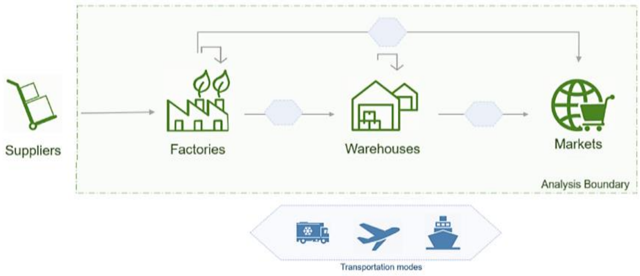

Fig 1. – Network representation

The three pillars of sustainability are introduced as objective functions. Considering the above features which account for the pharmaceutical supply chain main characteristics, a conceptual framework is defined, describing the procedure followed in this work (see Figure 2). The input data required include the overall superstructure for the location of entities, production and storage technologies available, transportation modes, 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

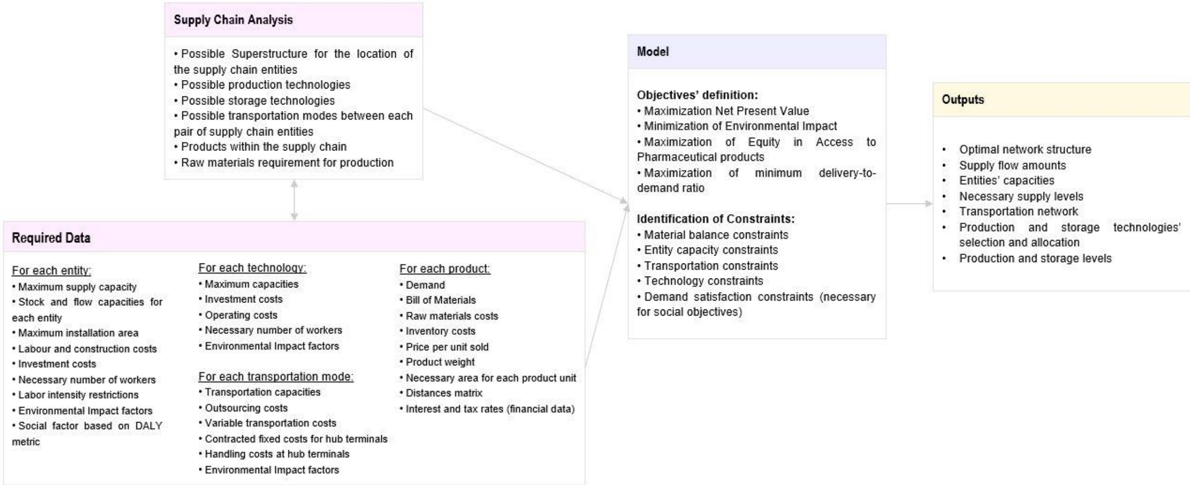

Fig 2. – Conceptual framework of the investigation procedure

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.

Mathematical Formulation

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

Economic objective function

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

$$. CF_t = \begin{cases} NE_t & t = 1, \ldots \ldots NT-1 \\ NE_t + \sum_\gamma (sv_\gamma + FCI_\gamma) & t = NT \end{cases} \tag{2}$$

$$\begin{aligned} NE_t = (1-tr)\Bigg[& \sum_{\substack{(m,i,j)\in F_{INCFP} \\ (a,m,i,j)\in NetP}} psu_m X_{maijt} \\ & - \Bigg(\sum_{\substack{(m,i,j)\in F_{OUTSUPRM} \\ (a,m,i,j)\in NetP}} rmc_{mi} X_{maijt} + \sum_{\substack{(m,g)\in H_{prod} \\ i\in I_f}} opc_g P_{mgit} \\ & + \sum_{\substack{(m,g)\in H_{stor} \\ i\in (I_f\cup I_w)}} opc_g S_{mgit} + \sum_{\substack{(a,m,i,j)\in NetP \\ a\in (A_{plane}\cup A_{boat}\cup A_{trucks})}} tc_a . pw_m . d_{ij} . X_{maijt} \\ & + \sum_{\substack{(a,m,i,j)\in NetP \\ (j\in I_{plane} \wedge i\notin I_{plane})\cup (j\in I_{boat}\wedge i\notin I_{boat})}} hhc_j . X_{maijt} + \sum_{i\in (I_{plane}\cup I_{boat})} cfp_i . Y_i \\ & + \sum_{\substack{(m,g)\in H_{stor} \\ (m,i)\in V}} sc_m S_{mgit} + \sum_{i\in (I_f\cup I_w)} w_i . lc_i . wwh . wpt . Y_i \\ & + \sum_{i\in (I_f\cup I_w)} wpsq . lc_i . wwh . wpt . YC_i + \sum_{\substack{(m,g)\in H \\ i\in I_f}} w_g . lc_i . wwh . wpt . Z_{gmi} \Bigg) \\ & + tr . DP_t \Bigg] \end{aligned} \tag{3}$$

$$DP_t = \sum_\gamma DP_{\gamma t} FCI_\gamma \tag{4}$$

$$FCI_\gamma = \begin{cases} \sum_{i\in I_f\cup I_w} sqmc_i . YC_i & \gamma = 1 \\ \sum_{(m,g)\in H} tec_g . Z_{gmi} & \gamma = 2 \end{cases} \tag{5}$$

Equation (1) 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 (2), 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 (3), 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_{mgit}) times the unitary operating cost of storage technology (opc_g); transportation costs (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 products in stock (S_{mit}) times the unitary stock cost, (sc_m); labour costs at entities (eighth and ninth terms), labour costs for production and remanufacturing technologies (tenth term)- varying with the fixed (w_i) and the variable ($wpsq$) number of workers at each entity, the number of workers needed for each technology (w_g), respectively. Moreover, a factor is the labour cost at each location (lc_i), the weekly working hours (wwh) and the number of weeks per time period (wpt).

The last term of equation (3) describes the depreciation of the invested capital, DP_t, with the tax rate represented by tr. Depreciation is calculated for each type of investment considered, γ , as represented in equation (4). Finally, fixed capital investment, FCI, is described in equation (5) 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

$$\min EnvImpact = \sum_{c} \eta_c \left(\sum_{\substack{t\in T \\ (m,g)\in H}} ei_{mgc} pw_m P_{mgit} + \sum_{\substack{t\in T \\ (m,g)\in H}} ei_{mgc} vpu_m S_{mgit} + \sum_{\substack{t\in T \\ (a,m,i,j)\in H}} ei_{ac} pw_m d_{ij} X_{maijt} + \sum_{\substack{t\in T \\ (a,m,i,j)\in H}} ei_{ic} YC_i \right) \quad (6)$$

According to equation (6), the environmental impact of four supply chain activities is calculated for each midpoint category c, namely: environmental impact of production (first term)- 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)- 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}); 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}); 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 times the normalization factor η_c . The use of normalisation factors is done so as to obtain results of each impact category in the same units.

Social assessment approach

Access to Medicines Index (AtMI) 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 (3). 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 1 organizes the main ideas behind these three groups of qualitative indicators.

Table 1. 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?
Resgistration Coverage strategies	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.
Ad hoc donations Long-term donation programmes	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.
Supranationally procured products: access strategies Health practitioner-administered products: access strategies Self- administered 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.

Two important questions arise at this point: firstly, it is important to understand how the index addresses the qualitative indicators mentioned in Table 1. Afterwards, it is needed to construct a quantitative way to account for these aspects that Access to Medicine Foundation (AtMF) defines as the most important when tackling equity in access.

- **Registration and coverage:** the index looks 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 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. 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,* 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. Henceforth, the above-mentioned metric is incorporated into an objective function, obtained through the maximization of pharmaceutical accessibility, as represented in equation (7):

$$\max PharmaAccess = \left(\sum_{i \epsilon (I_f \cup I_w)} e_i^{DALY} \, . \, Y_i \right) \qquad (7)$$

According to equation (7), 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 (8):

$$\max PharmaDistribution = min \left(\frac{pr_{mit}}{dmd_{mit}} \right) = \min(r) \qquad (8)$$

This second objective function distributes pharmaceuticals equitably by maximizing the minimum-delivery-to-demand ratio 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 mount 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):

$$\left(1-\frac{pr_{mit}}{dmd_{mit}}\right) \leq \delta_{it} \quad \leftrightarrow \quad pr_{mit} \geq \theta_{it} \times dmd_{mit} \qquad (9)$$

By analysing social constraint (9), one can note that, on the left side, the percentage of demand that is not satisfied should not exceed the satisficing level defined δ_{it} , while the contraint on the right is used to guarantee that pharmaceuticals are assigned to each location at least at a coverage rate (θ_{it}).

Optimization Method Selection

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.

5. Model Validation & Results Analysis

The developed model is applied to a representative case-study concerning the supply chain of meningococcal meningitis' vaccine produced by Sanofi Pasteur, based on its provided reports of year 2020, as well as on information provided publicly by the company (Sanofi Pasteur, 2020). 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). 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.

According to (WHO, 2020), 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 these countries can be a potential long-term solution to improve access to this product. Regarding warehouses' locations, besides the ones already existent, two warehouses in Africa, one in Kenya 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. The product considered in the study, denoted by $fpMen$, need to be refrigerated (2º to 8ºC) and 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.

Results' Analysis and Discussion

Different cases are designed using a lexicographic optimization:

Case A: starting with maximizing NPV, the <u>optimum economic solution</u> 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 <u>optimum social solution</u> 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 <u>optimum environmental solution</u> 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.

Table 2. 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**

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.

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.

Facilities: In case A, factory in Asia is the one with higher production levels. 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, thus 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.

Transportation: 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 below.

Comparison between different activities of the supply chain

The smaller variation in economic performance among the three cases can be justified by the significant contribution of production to the total costs. 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 (9), 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 DALY's, 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. 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 conclude 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 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.

Hence, it would be important to address different options of greener production so as to minimize the impact for the environment.
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, Soleimani and Kannan, 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.

Supply Uncertainty Analysis

As mentioned before, uncertainty is often present at several 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}. Three different scenarios were considered in the stochastic case D: 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.
With these probabilities for each scenario considered, the model was optimized towards the maximization of the NPV value.
Results were compared with case A (first deterministic case analysed) and 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.

5. Final conclusion & Future work

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. 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. The application of the developed model allows for the comprehension of connections among different supply chain activities, providing an opportunity to better understand the performance of combined indicators across the supply chain. Finally, the developed model allows to design and plan a pharmaceutical sustainable supply chain accommodating uncertainty in supply through a stochastic approach.

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.

As future challenges, ways to better plan inventory may be explored, such as other storing technologies. 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 of raw materials, 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.

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