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

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The pharmaceutical supply chain is responsible for ensuring the supply of medicines in the right place, at the right time and in the right quantity and the industry is being pressured by a shifting paradigm and by changes on the trends and concerns of the society. The optimising of pharmaceutical supply chain networks a promising research field. Recently, various optimisation models have been built to optimise the design of the pharmaceutical supply chain network. Firstly, a literature review on these models is performed to provide a theoretical basis. A second literature review identify the key elements to obtain an agile supply chain. In this work, a mixed integer linear programming model is proposed as an optimisation tool to design a supply chain network for the pharmaceutical industry. This model addresses a multi-product, multi-active ingredient, and multi-period network. The existence of multiple storage conditions is also proposed. The decisions supported concern the facilities' integration into a pharmaceutical supply chain, along with inventories, productions and distributions. The objective is minimising the total costs of the supply chain, guaranteeing the demand satisfaction. This model is tested through an example adapted from the literature, and then applied to a case study about the COVID-19 vaccines distribution.

***Index Terms*—Agile, Pharmaceutical Supply Chain, Optimisation, Network Design, MILP**

I. Introduction

The pharmaceutical industry is a key asset of the economies of the developed countries as major high-technology industrial employers, moving trillions of dollars annually and employing thousands of people. Its social importance must be also mentioned due to its direct impact on the quality of life and healthiness of the population, which guarantees economical sustainability of the healthcare systems [11].

To guarantee a smooth and robust connection between the pharmaceutical industry and the final customer, it is crucial to ensure that the Pharmaceutical Supply Chain (PSC) is up to the task. The PSC is being constantly challenged to improve the efficiency of the drug supply. Continuous innovation and development of new products and technologies, the emergence of legal barriers and licenses, patents and regulations, entry of new competitors with new products, and the pressure prosecuted by the government and health care providers to widen the therapeutic indications of the drugs to other areas and diseases, raising the investment costs and reducing the profit margins constitute some challenges to the industry [18]. A shortage of drugs is not tolerated because if critical drugs lack in pharmacies and hospitals, people's health and even their life are at risk.

The pharmaceutical industry can be defined as a complex set of processes, operations and organisations involved in the discovery, development and manufacture of drugs and medications [18]. The PSC comprises a network of manufacturers (primary and secondary, in-house and external contractors), packaging facilities, wholesalers, and final healthcare providers such as hospitals and pharmacies. According to [18], PSC involves four indispensable echelons: primary manufacturers, secondary manufacturers, distribution centres (DCs) and retailers.

The PSC represents the path through which essential pharmaceutical products are distributed to the end-users with the right quality, at the right place and at the right time. Therefore, PSC is complicated to manage and greatly responsible for ensuring that the appropriate drug is delivered to the right people at the right time and in the right situation to fight against sickness and sufferings [12].

II. Literature Review

Each of the reviewed models is characterised according to its more relevant characteristics, objective functions, outputs (or decision that the formulation aims to support) and solution approach, which can be exact or non-exact.

A. Exact methods

[6] proposed a multi-period mixed integer linear programming MILP model to minimise the total costs of a distribution supply chain SC considering the production processes. In order to reduce the computational time needed, the authors introduced several aggregation schemes and a novel MILP model formulation which is based on a continuous representation of time. [10] extended [15] to cope with uncertainty on the outcome of the clinical trial. [21] developed a MILP model aiming to for multi-period enterprise-wide planning in pharmaceutical industry. The model integrates procurement, production, distribution and inventory strategies on a long-term perspective, and includes inventory holding costs, material shelf-lives, and waste treatment. [13] developed a multi-period bi-objective MILP model to minimise the total costs and the unmet demand. The model aims to support decisions as locating and planning the capacity of pharmaceutical manufacturing centres and main and local distribution centres over a long-term planning, along with material flows over a mid-term planning. They used a robust possibilistic programming approach to deal with the uncertainty. The model is tested in a

case study. [23] built a multi-objective MILP model to design a PSC network. To combine sustainability and resilience in the SC, four objective functions are proposed: minimise the total cost of the system, maximise the job opportunity and economic development of the region, minimise the total environmental impact and minimise the non-resilience of the network. The authors considered five measures of resilience. The approach is validated through numerical examples and a case study. [22] presented a model to minimise the total cost and the unmet demand on a pharmaceutical supply network design problem that supports decision about facility location, and flow of products from facilities in different or in the same echelon of the SC. The authors an iterative fuzzy approach. [17] developed a MILP to minimise the costs of a location-inventory problem on a three-echelon PSC network that support both strategic and tactical decisions as opening manufacturing and distribution centres, material flows in the network, and the optimal inventory policy taking into account products' perishability. [7] proposed a bi-objective model to find an acceptable trade-off between the total cost minimisation and the greenhouse gases emission minimisation. [16] addresses crisis management in PSCs by creating a multi-objective non-linear model to minimise the network total cost and the unmet demand and maximise the satisfaction of social responsibility. Product perishability, substitutability and uncertainties are considered. To obtain the Pareto front of the three objective functions, a TH approach is used. [24] developed a bi-objective MILP model for designing a perishable PSC network under demand uncertainty. The objectives are simultaneously to minimise the total cost of the network and the lost demand. The proposed model is multi-product and multi-period and includes facilities location, vehicle routing, and inventory management decisions. A goal programming approach is developed to solve the bi-objective problem.

B. Non-exact methods

[20] proposed a global SC network optimisation procedure for pharmaceuticals. The authors developed a model that aims to maximise the NPV to solve the problem of allocating and determining product flows. They solved the problem using two decomposition algorithms: a Lagrangian decomposition method. [19] expanded the investigation of [20]. The authors explored two decomposition algorithms to reduce the solution time. In the first method, the SC is decomposed into two sub-problems, one for each echelon and solve the MILP. [8] designed a single-period distribution network under demand uncertainty. To consider the uncertainty, a set of possible scenarios and for each scenario, the distribution network was optimised using a genetic algorithm. [3] proposed an approach to optimise product flows between facilities. The authors consider the oligopolistic competition across wholesalers that drives price and demand fluctuations. They try to maximise the profit of the company and propose the solution by determining the Nash Equilibrium, and, then, using the interior-point barrier algorithm. [1] proposed a location-allocation model for pharmaceutical centres, trying to locate a set of new facilities to minimise the transportation cost from these facilities to the customer. They considered two objectives: minimisation of costs and maximisation of customer satisfaction. [2] presented a bi-level bi-objective model for a PSC that assigns distribution centres to retailers, respective product flows and appropriate vehicles to perform the transport, aiming to minimise total costs along with the unmet demand. Uncertainty is considered in demand, inventory levels and shipping costs. Then a robust approach was used based on the Benders decomposition algorithm. [9] develop a multi-period multi-objective model to design a pharmaceutical distribution network while minimising the costs and the adverse environmental effects and maximising the welfare of society. Location, allocation and distribution decisions are supported by the model. The authors use the NSGA-II algorithm to find the Pareto front. A case study on a pharmaceutical distribution company is solved. [25] studied a facility location and vehicle routing problem on a distribution pharmaceutical network. The authors considered two types of distribution centres: depots (main) and satellites (secondary). They model the problem as a linear function that aims to minimise the total cost. To solve the problem, a technique is developed which iterates between an upper bound and a lower bound, based on Lagrangian relaxation combined with a branch-and-cut approach. [14] developed a four-echelon multi-period approach to design a pharmaceutical distribution network allowing the flow of products inside one level of the SC considering fuzzy uncertainty on the demand. The bi-objective model aims to maximise the service level while minimising costs. The authors developed an NSGA-II algorithm. [5] proposed a model to design a multi-product multi-period PSC network. The authors create a multi-objective approach to minimise the total costs, minimise the delivery time and maximise the reliability of the transportation system with the objective of determining both strategic, tactical and operational decisions. The authors compare five metaheuristics.

III. Model formulation

This section describes the formulation of the proposed model. Firstly, the characteristics considered in the model are defined. Then, an appropriate mathematical formulation as a MILP is presented by characterising the model parameters, decision variables, constraints, and objective function.

A. Problem definition

The present model features a typical SC of the pharmaceutical industry, approaching location, allocation, inventory and production decisions on a five-level SC:the primary manufacturers, the secondary manufacturers, the main DC, the local DC and the retailers (or demand zones). Two sets of goods are considered: the set of APIs (Active Pharmaceutical Ingredients), which are carried from the Primary Manufacturer to the Secondary Manufacturer; and the products, which are the actual drugs, that are carried from the Secondary Manufacturer downwards on the SC. The model allows the design of a PSC considering the flow of multiple API and multiple products. The pharmaceutical products have strict storage rules to prevent the damage to the product itself. For that reason, considering a general inventory for all the products can become insufficient when planning and designing a PSC.

The current model support the existence of various storage conditions in the inventory of each facility. It is considered that each product must be stored under a specific storage condition along the SC.

A concept of network is established in the present SC. This is a group of entities that will work together to accomplish the objective, which is to meet the demand with the least cost possible. Entities that integrate the network will incur in integration costs, henceforth designated *fixed costs*. Those costs can be considered as the investments that each facility will need to perform in order to enter in the distribution network. Those investments may involve process integration technologies that enable the cooperative relationships, partnerships, adaptation of processes or acquisition of new technologies necessary to enter a specific SC. Inventories exist in four levels of the SC. In the Primary Manufacturer, an inventory of finished API can be kept. In the Secondary Manufacturer, Main DC and Local DC, there are inventories of finished products. Each primary manufacturers and secondary manufacturers have their own production capacity and their storage capacity. Each main and local DC have their own handling capacity and storage capacity

B. Model parameters

Let A be the set of API that must be carried from the set of Primary Manufacturers, denoted by F to the set of Secondary Manufacturers, denoted by S. In those Secondary Manufacturers, the API are converted into a set of pharmaceutical products P. Those pharmaceutical products are then shipped to the main DC M and therefore to the local DC L. Finally, the products are transported from the local DC to the retailers R, according to its demand. Let T be the set of time-periods. On this problem, all entities have a cost to integrate the consortia, except the Primary Manufacturers. Integration costs of the Secondary Manufacturer s, the Main DC m and Local DC are denoted by fc_s^S, fc_m^M and fc_l^L, respectively.

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

Then, the API are transported to the secondary manufacturers with a tc_{afs} cost per unit. In each second manufacturer, there is not inventory of API, but products p can be stocked, under different conditions also. Regarding the storage of products under condition c, a maximum storage capacity of the secondary manufacturer s is defined as s_{sc}^S and a cost of storing a storage unit of a product p is defined as ic_{sc}^S. A unit of product p occupied σ_{pc} number of units of storage space. Each secondary manufacturer s has an initial inventory of product p, ii_{sp}^S, and a maximum production capacity of product p, pc_{sp}^S. To produce a unit of product p, ρ_{ap} must be consumed.

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

Then, the product p are transported to the local DC with a tc_{pml} cost per unit. In each local DC, each product p can be stocked under a certain storage conditions c, so, a maximum storage capacity of the local DC l is defined as s_{lc}^L and a cost of storing a storage unit of a product p is defined as ic_{lc}^L. Each local DC has an initial inventory of product p, ii_{lp}^L, and a maximum handling capacity, h_{lp}^L. Finally, the product p are transported to the retailers with a tc_{plr} cost per unit. There are not storage of products. The products are received according the demand of product p in the retailer m at time-period t, d_{prt}.

C. Decision variables

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

- X_s^S, X_m^M and X_l^L are equal to 1 if the secondary manufacturer s, the main DC m and the local DC l, respectively, integrate the consortia and 0 otherwise;
- Q_{afst}^{α} is the quantity of API a shipped from the manufacturer f to the secondary manufacturer s at period t;
- Q_{psmt}^{β}, Q_{pmlt}^{γ} and Q_{plrt}^{δ} are the quantity of product p at period t shipped from the secondary manufacturer s to the main DC m, from the main DC m to the local DC l and from the local DC l to the retailer r, respectively;
- I_{fat}^F is the inventory of API a in the primary manufacturer f at the end of the period t;
- I_{spt}^S, I_{mpt}^M and I_{lpt}^L are the inventory of product p at the end of the period t in the secondary manufacturer s, in the main DC m, and in the local DC l, respectively;
- P_{fat}^F is the quantity of API a produced in the primary manufacturer f, in the period t;
- P_{spt}^S is the quantity of product p produced in the secondary manufacturer s, in the period t.

D. Constraints

1) Demand Satisfaction

The demand satisfaction constraints set the minimum value for the outgoing flows at Local DC. The demand satisfaction group of constraints guarantee that the total flow of products from all the Local DC to each Retailer is greater or equal than

the demand existing on that retailer. The inequality must be verified for all retailers, products and time-periods. The group of constraints is expressed in Equation 1.

$$\sum_{l} \Psi^{\delta}_{plrt} \geq d_{prt} \quad \forall\ p,\ r,\ t > 0 \tag{1}$$

2) Production Capacity

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

Equation 2 guarantees that the quantity of API a produced in the primary manufacturer f, does not exceed the capacity of that facility for each API and time-period.

$$P^{F}_{fat} \leq pc^{F}_{fa} \quad \forall\ f\ , a\ , t > 0 \tag{2}$$

Equation 3 guarantees that the quantity of product p produced in the secondary manufacturer s, does not exceed the capacity of that facility, if it integrates the consortia, for each product and time-period.

$$P^{S}_{spt} \leq X^{S}_{s} * pc^{S}_{sp} \quad \forall\ s,\ p,\ t > 0 \tag{3}$$

3) API Consumption

In the secondary facility, API are used sole or combined to produce pharmaceutical products. This conversion respects to the proportionality parameter ρ. Since the secondary manufacturer receives API just-in-time and the consumption is considered immediate for the purposes of the present model, the inflow of each API at each Secondary Manufacturer and time-period will be equal to the consumption of that API. Also, all the API consumed are considered to be converted to pharmaceutical products (there is no waste). The consumption of an API will, therefore, be the total production of products in that facility and time-period multiplied by the parameter that stores the ratio between products and API. The constraints regarding this API to Product Conversion in expressed in Equation 4.

$$\sum_{p} (P^{S}_{spt} * \rho_{ap}) = \sum_{f} \Psi^{\alpha}_{afst} \qquad \forall\ s,\ a,\ t > 0 \tag{4}$$

4) Storage Capacity

Storage capacity constraints guarantee that the storage capacity for each storage condition of each facility is never exceeded in any facility, time-period and storage condition. The inventory of API a, stored under condition c in the primary manufacturer f, in the end of the period, cannot exceed the storage capacity of that facility under that condition on each time period t, as expressed in Equation 5.

$$\sum_{a} (I^{F}_{fat} * \sigma_{a,c}) \leq s^{F}_{fc} \qquad \forall\ f,\ c,\ t > 0 \tag{5}$$

Equation 6 guarantees that the inventory of product p, stored under condition c in the secondary manufacturer s, in the end of the period t, does not exceed the storage capacity of that facility under that condition (if it integrates the consortia) on each time period. Similar equations apply also to main DCs (equation 7) and local DCs (equation 8).

$$\sum_{p} (I^{S}_{spt} * \tau_{p,c}) \leq X^{S}_{s} * s^{S}_{sc} \qquad \forall\ s,\ c,\ t > 0 \tag{6}$$

$$\sum_{p} (I^{M}_{mpt} * \tau_{p,c}) \leq X^{M}_{m} * s^{M}_{mc} \qquad \forall\ m,\ c,\ t > 0 \tag{7}$$

$$\sum_{p} (I^{L}_{lpt} * \tau_{p,c}) \leq X^{L}_{l} * s^{L}_{lc} \qquad \forall\ l,\ c,\ t > 0 \tag{8}$$

5) Handling capacity

Handling capacity constraints are intended to limit the flow exiting the distribution centres. The handling capacity is the maximum quantity of products that the distribution centres can handle in each time-period, since distribution centres have limited resources. Equations 9 and 10 guarantee that the outflow from each main DC and local DC, respectively, cannot exceed their handling capacity for all products, in each time period.

$$\sum_{p} \sum_{l} \Psi^{\gamma}_{pmlt} \leq X^{M}_{m} * h^{M}_{m} \qquad \forall\ m,\ t > 0 \tag{9}$$

$$\sum_{p} \sum_{r} \Psi^{\delta}_{plrt} \leq X^{L}_{l} * h^{L}_{l} \qquad \forall\ l,\ t > 0 \tag{10}$$

6) Mass-balance

Mass-balance constraints guarantee that the inputs and outputs of each facility are equal in all facilities and time-periods, and for all products. In primary manufacturers, the inputs are the API productions and the inventory that comes from the last period. The outputs are the final inventory and the outflow to secondary manufacturers. In secondary manufacturers, the inputs are the product productions (restricted by Equation 4) and the inventory that comes from the last period. The outputs are the final inventory and the outflow to main DC. In main DC, the inputs are the inflow from secondary manufacturers and the inventory that comes from the last period. The outputs are the final inventory and the outflow to local DC. In local DC, the inputs are the inflow from main DC and the inventory that comes from the last period. The outputs are the final inventory and the outflow to retailers.

Equation 12 guarantees that the initial inventory of API a, plus the quantity of API produced, in the primary manufacturer f, in the period t, is equal to the final inventory plus the outflow of that API in that facility.

$$I^{F}_{fat-1} + P^{F}_{fat} = I^{F}_{fat} + \sum_{s} \Psi^{\alpha}_{afst} \qquad \forall\ f,\ a,\ t > 0 \tag{11}$$

Equation 12 guarantees that the initial inventory of product p, plus the quantity of product produced, in the secondary manufacturer s, in the period t, is equal to the final inventory plus the outflow of that product in that facility.

$$I^{S}_{spt-1} + P^{S}_{spt} = I^{S}_{spt} + \sum_{m} \Psi^{\beta}_{psmt} \qquad \forall\ s,\ p,\ t > 0 \tag{12}$$

Equation 13 guarantees that the difference in inventories of product p in the main DC m at the end of the period t corresponds to the balance of flows of that product in that facility and period. A similar equation applies to the local DCs (equation 14).

$$I^M_{mpt-1} + \sum_j \Psi^\beta_{psmt} = I^M_{mpt} + \sum_l \Psi^\gamma_{pmlt} \quad \forall\ m,\ p,\ t > 0 \tag{13}$$

$$I^L_{lpt-1} + \sum_k \Psi^\gamma_{pmlt} = I^L_{lpt} + \sum_r \Psi^\delta_{plrt} \quad \forall\ l,\ p,\ t > 0 \tag{14}$$

7) Initial inventory

Initial inventory constraints guarantee that the initial inventory of the first period matches the initial inventory stipulated in the model input parameters. Equations 15, 16, 17 and 18 guarantee that the inventory in the end of the time period zero are equal to the initial inventory defined.

$$I^F_{f,a,0} = ii^F_{fa} \tag{15}$$

$$I^S_{s,p,0} = ii^L_{sp} \tag{16}$$

$$I^M_{m,p,0} = ii^M_{mp} \tag{17}$$

$$I^L_{l,p,0} = ii^L_{lp} \tag{18}$$

8) Binary variables

Equations 19 defines the binary decision variables of the present model: the integration or not of a given facility in the network.

$$X^S_s\ X^M_m\ ,\ X^L_l\ \in\ \{\ 0\ ,\ 1\ \} \tag{19}$$

9) Non-negative variables

Equations 20, 21 and 22 defines the non-negatives variables: flows, inventories and productions cannot take negative values.

$$\Psi^\alpha_{pfst}\ ,\ \Psi^\beta_{psmt}\ ,\ \Psi^\gamma_{pmlt}\ ,\ \Psi^\delta_{plrt}\ \in\ \mathbb{N}^0 \tag{20}$$

$$I^F_{fat}\ ,\ I^S_{spt},\ I^M_{mpt},\ I^L_{lpt}\ \in\ \mathbb{N}^0 \tag{21}$$

$$P^F_{fat}\ ,\ P^S_{spt},\ \in\ \mathbb{N}^0 \tag{22}$$

E. Objective function

For the case in hands, the objective of the model will be the minimisation of the SC costs, as the sum of the fixed costs, distribution costs and inventory costs, and is expressed in equation 23.

$$\begin{aligned}\text{minimise}\quad z = \text{Fixed costs + Transportation costs +}\\ \text{+ Inventory costs}\end{aligned} \tag{23}$$

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

$$\begin{aligned}\text{Fixed costs} = \sum_s X^S_s fc^S_s + \sum_m X^M_m fc^M_m +\\ + \sum_l X^L_l fc^L_l\end{aligned} \tag{24}$$

Transportation costs are calculated as the sum for all products, time-periods, origin facilities and destination facilities of the number of products transported from each origin facility to each destination facility multiplied by the cost of transporting that product in that path. The transportation costs are expressed in Equation 25.

$$\begin{aligned}\text{Transportation costs} = \sum_a \sum_f \sum_s \sum_t \Psi^\alpha_{afst} * dc^\alpha_{afs} +\\ + \sum_p \sum_s \sum_m \sum_t \Psi^\beta_{psmt} * dc^\beta_{psm} +\\ + \sum_p \sum_m \sum_l \sum_t \Psi^\gamma_{pmlt} * dc^\gamma_{pml} +\\ + \sum_p \sum_l \sum_r \sum_t \Psi^\delta_{plrt} * dc^\delta_{plr}\end{aligned} \tag{25}$$

Inventory costs are the costs of storing an API in the primary manufacturer or a product in other facilities for one period of time. The inventory costs are calculated as the sum for all storage conditions, facilities and time-periods of the final inventory of each product in each facility and time-period, multiplied by the storage space that that product requires for the storage condition considered, and multiplied by cost of one storage space under the storage condition considered, in each facility. The inventory costs are calculated as expressed in Equation 26

$$\begin{aligned}\text{Inventory costs} = \sum_t \sum_f \sum_c (\sum_a I^F_{fat} * \sigma_{ac}) * ic^F_{fc}) +\\ + \sum_t \sum_s \sum_c (\sum_p I^S_{spt} * \tau_{pc}) * ic^S_{sc}) +\\ + \sum_t \sum_m \sum_c (\sum_p I^M_{mpt} * \tau_{pc}) * ic^M_{mc}) +\\ + \sum_t \sum_l \sum_c (\sum_p I^L_{lpt} * \tau_{pc}) * ic^L_{lc})\end{aligned} \tag{26}$$

IV. Computational experiments

In this section, computational experiments are performed to validate the model proposed. First, the problem data will be contextualised and explained. Secondly, the results are presented and analysed. Finally, a discussion on the topic is performed.

A. Data gathering

This computational experiment is inspired by the problem addressed by [13]. The authors' model is tested via an empirical case study, based on the data collected from Iran's National Organisation of Food & Drug about the distribution of Amoxicillin. Despite their model approaches a multi-product problem, the authors used a single product problem

for simplification. According to the authors, designing the SC for a single product does not limit the application of the model, since, in the proposed model, different products are just interconnected by sharing the same facilities. The conversion of API to a product in these experiments will be considered as one to one ratio. The storage requirement will be one unit of storage space for one tonne of amoxicillin, and it will be considered only one storage condition. Amoxicillin must be stored at room temperature.

Regarding the possible locations for facilities and infrastructures, [13] considered the existence of 8 secondary manufacturers. I will be assumed the existence of 4 primary manufacturers, each one located near one of the biggest cities of Iran. Ten locations for main DC are considered in the same publication. Each province can be considered a demand zone and also have a local DC candidate to enter the network.

Two experiments will be performed in this section:

- Experiment 1 is to test the model by analysing the outputs for the empirical example developed by [13], considering a network with one product only, one API and one storage condition;
- Experiment 2 proposes the validation of the model with a multi API and multi-product problem, with also multiple storage conditions.

To analyse the sensibility of the model, a set of scenarios will be analysed for each experiment: baseline scenario, half the demand, double the demand and fixed costs variations are performed.

B. Results analysis

1) Experiment 1: baseline

The CPLEX solver engine took 244 seconds to solve the MILP and returned a total cost as an objective function of €147982.40. The optimal number of facilities under this scenario is 2 primary manufacturers, 2 secondary manufacturers, 3 main DCs, 11 local DCs and 31 retailers. The demand is higher than the capacity of opened manufacturing facilities in winter seasons, which correspond to periods 4, 8, 12, and 16. Thus, to satisfy the demand for all the seasons, two secondary manufacturers are required to open. Despite the production capacity of a secondary manufacturer being half of the production capacity of a primary manufacturer, as depicted in section 5.2, two primary manufacturers are still open to minimise the transportation costs between primary and secondary manufacturers. This event happens because there are no fixed costs to open a new primary manufacturer, and, therefore the model tends to connect the primary and secondary manufacturers with the lowest transportation costs possible. Those transportation costs vary according to the distances between facilities and the far the cities where the facilities a located, the higher the transporting costs between them. Therefore, to supply API to a specific secondary manufacturer, the closest primary manufacturer possible is chosen. In the winter season, the demand exceeds the production capacity of those periods. To balance this excess of demand, inventories are built in local DC is the period previous to winter. The local DC which are integrating the network are the facilities with lower inventory costs of the entire network and, therefore those are chosen to store products that will be supplied in winter. The time-period with the highest demand is time-period 16, and in that period the demand only exceeds the production capacity of the primary and secondary manufacturers by 12.5%. The decision to stock products in local DC to guarantee the demand satisfaction in winter is preferred rather than opening new secondary manufacturing facilities which would carry significant fixed integration costs to supply only a total of 225 tonnes of product in the entire temporal horizon. Storing 225 tonnes of product represents, in the worst case, a cost of € 9562.50, but choosing another secondary manufacturer to reinforce the capacity of the network would carry a minimum fixed integration cost of € 23400.

2) Experiment 1: half demand

The network is composed of 1 primary manufacturer, 1 secondary manufacturer, 2 main DCs, 6 local DCs and 31 retailers. As expected, less facilities integrate the network to satisfy the minor demand. The objective function cost value achieved is € 85724.16. An objective function with a cost 42% lower than the baseline objective function was achieved to supply the demand 50% lower. This represents an increase of 15.7% in the total cost per tonne of product supplied. Similarly to the baseline scenario, in the winter periods (4, 8, 12 and 16) the demand is higher than the total production capacity. Therefore, the network planning model proposes the built-up of inventory on local DC in periods that precede winter (3, 7, 11 and 15).

3) Experiment 1: double demand

Considering the scenario in which the demand is duplicated, the network is composed of 4 primary manufacturers, 4 secondary manufacturers, 7 main DC, 22 local DC and 31 retailers. The total cost of the network is € 282887.54 and comparing it with the baseline scenario, represents an increase of 91%. However, the total costs per tonne of product provided to the retailer are around 5% lower. Therefore, the network can respond to an increase of 100% of the demand, and its efficiency increases since the cost per tonne supplied decreases. Similarly to the baseline scenario, in the winter periods (4, 8, 12 and 16) the demand is higher than the total production capacity. Therefore, the network planning model propose the built up of inventory on local DC in periods that precede winter (3, 7, 11 and 15).

4) Experiment 1: varying fixed costs

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

lower, it carries fewer costs to add facilities into the network than storing products to guarantee the supply in peak demand periods. However, when the fixed integration costs are higher, incurring in inventory costs reveals less expensive than adding more facilities into the network, which leads to an increase in the usage of inventory and to a reduction in the usage of capacity.

5) Experiment 2: baseline

In the baseline instance of experiment 2 an objective function of € 153206.04 was achieved. The optimal solution contemplates the integration in the network of 3 primary manufacturers, 3 secondary manufacturers, 7 main DCs, 22 local DCs and 31 retailers. In the present scenario, the inventory is only required on period 15 to store 4 tonnes of product A. This happens since the total demand on period 16 is 844 tonnes of products and the total capacity of the 7 main DC in the network is only 840 tonnes. Therefore, the solution that carries fewer costs to the SC is to store 4 units of product 1 in one of the local DC. The fixed integration costs of opening one more main DC would be higher than keeping 4 units of product in inventory.

6) Experiment 2: half demand

Considering the scenario in which the demand was reduced to one half, or 50% less, of the original baseline demand, the network is composed of two primary manufacturers, four secondary manufacturers, seven main DC and eleven local DC. The optimal objective function cost is € 146300.88. In the optimal solution, integrate the network 2 primary manufacturers, 2 secondary manufacturers, 4 main DCs, 11 local DCs and 31 retailers. In this scenario the optimal solution considers inventories equal to zero in all the facilities and in all the time-periods, meaning that in this scenario, opening more facilities is preferable rather than accumulating inventories.

7) Experiment 2: double demand

A problem with twice the demand as considered in the baseline scenario was loaded into the optimisation model developed. However, an infeasible situation was achieved due to the excess of demand or lack of capacity in the SC facilities. In order to be able to analyse a scenario in which the demand is over the baseline demand, the demand was iterative from the original demand on steps of 10% until a feasible problem is achieved. With a demand 40% above the demand of the baseline scenario, a feasible solution to the problem was found. However, with a demand 50% above the baseline scenario, the model becomes infeasible. The number of facilities integrating the PSC network when the demand is 40% above the baseline scenario is 4 primary manufacturers, 4 secondary manufacturers, 11 main DCs and 31 local DCs. On this scenario, the total cost of the optimal network is € 353177.84. A demand 40% above the baseline scenario can be fulfilled without the use of inventories, but a demand of 50% above the baseline scenario cannot be fulfilled by the network. This happens because in this scenario, all the facilities available are integrating the network, which corresponds to a handling capacity of 1200 tonnes per time-period in main DC, and 1240 tonnes per time-period in local DC.

8) Experiment 2: varying fixed costs

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

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

C. Discussion

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

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

V. Case study: COVID-19 vaccines distribution

COVID-19 is a pandemic disease that can cause light to severe symptoms or even death; it has unknown long-term consequences in people of all ages, including in healthy people. Since the first moments of the pandemic, big pharmaceutical companies raced to devise a product that could cure or prevent the disease. COVID-19 vaccines are medicines that are intended to prevent the disease caused by the novel coronavirus SARS-CoV-2 [4].

In October 2021, four vaccines are available in the European Union to prevent COVID-19, produced by Pfizer, Moderna, AstraZeneca and Janssen. Modelling a problem of network design for the COVID-19 Vaccine Distribution Network is a complex process. Despite the demand data, location of the secondary manufacturers, distribution centres and product characteristics being publicly available, other parameters such as costs and capacities can be challenging to collect.

The problem, in particular, addressed the distribution of vaccines from the big pharmaceutical manufacturers located in Central Europe to the Portuguese districts. The four vaccines approved in Europe were considered as the four products, which are produced by dedicated primary and secondary manufacturers located in France, Belgium, Netherlands, Germany, Switzerland and Austria. Before reaching the retailer (or demand zone, located in the 20 Portuguese districts plus 2 autonomous regions), the vaccines must pass on one of the main DCs (located in Porto, Coimbra, Lisbon, Évora and Faro) and on one of the local DCs (located in each Portuguese district). To produce each one of those products, one API is required, and its storage must be under two different storage conditions. The demand is the population electable for vaccination in Portugal and it is distributed by the eighteen districts and two autonomous regions accordingly. The demand is also distributed along the eight time-periods of one quarter each following the 3-phases vaccination campaign approved by the Portuguese government.

The issue contemplates the allowance of backorders which is the possibility of delaying the delivery of doses of vaccines to the retailer. To solve the problem, a reformulation of the model is proposed to enable the analysis of the trade-off between backorder minimisation and cost minimisation. A multi-objective MILP will be considered, with the second objective function of minimising the number of backorders, as expressed in equation 27.

$$\text{minimise} \quad w = \sum_{t} \sum_{r} \sum_{p} B_{prt} \tag{27}$$

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

$$B_{prt} = 0 \quad , \quad t = \text{last period} \quad , \quad \forall \;\; p, r \tag{28}$$

To obtain a set of optimal solutions for the multi-objective MILP, the ϵ-constraint method is used to obtain an approximation of the Pareto front. The ϵ-constraint which will be added to the cost minimisation model is formulated in equation 29.

$$\sum_{l} \Psi^{\delta}_{plrt} \geq d_{prt} + B_{prt-1} - B_{prt} \quad \forall \;\; p, r, t \tag{29}$$

A. Results Analysis

The plot shown in figure 1 illustrates the approximation of the Pareto front which contains the set of non-dominated solutions for the problem in hands.

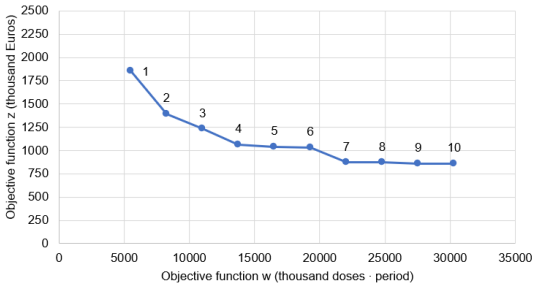

Fig. 1: Pareto front

Solution 1 corresponds to the case in which the minimal number of backorders is achieved. Due to the excess of demand in the first periods, it is not possible to fulfil all the demand without delays even if all facilities integrate the network, and therefore, 5493 thousand backorders still exist. For this case, a total SC cost of approximately 1.86 million Euros is achieved. To achieve this scenario, four of the secondary manufacturers that can produce Pfizer vaccines must integrate the network, one secondary manufacturer that produces Moderna does not integrate the network and all facilities that can produce the other vaccines must open. All main DCs and all local DCs must also integrate the network. Solutions 2 to 9 corresponds to intermediate scenarios in which a trade-off between backorders and costs must be considered.

From solution 1 to solution 2, the backorders increase 50%, and the costs decrease 25% with the closure of 2 secondary manufacturers (one of Pfizer and one of Johnson do not integrate the network), 4 main DCs (only Coimbra main DC remains in the network) and 5 local DCs are also out of the network.

From solution 2 to solution 3, the number of backorders increase 33%, while the costs reduced 12% with the closure of one secondary manufacturer producing the AstraZeneca vaccine. The unique main DC continues Coimbra. From solution 3 to solution 4, the number of backorders increase 25% and the costs reduce 14%. To achieve this, the local DC located in Faro, Vila Real and Castelo Branco also do not integrate the network, but the local DC located in Portalegre reintegrate the network.

From solution 4 to solution 5, a lack of supply in the interior regions is observed, which can be confirmed by an increase of 20% in the number of doses in backorder, but only a decrease of 2% in the costs. From solution 5 to solution 6, the local DC located in Viana do Castelo joins the group of local DC that will not integrate the network, causing an increase of 17% in the number of backorders and a decrease of 1% in the costs.

From solution 6 to solution 7, the minimum number of secondary manufacturers is achieved. The local DC located in Setúbal joins the group of facilities that will not participate in the network. These events cause an increase of 14% in the number of backorders, but a decrease of 16% in the costs.

Indeed, increasing the number of backorders from 19273 to 22029 is the only time that the relative decrease in costs is higher than the relative increase in backorders.

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

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

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

In solution 1, a concentration of the productions is observed in the first four periods, following the demand profile, is perceived. This is justified because the number of facilities open haven the capacity required to fulfil the demand, leaving a reduced number of backorders in comparison to the other solutions. In the first two periods, the demand is below the production capacity, justifying the inventory built up to prepare the third period in which the demand is higher than the production capacity. In solution 2, the large reduction in the number of facilities when compared to solution 1, makes the model suggest the use of more inventory in the first periods. The quantity of products being stored increased from 4792 thousand vaccines to 5726 thousand vaccines. In solution 3, the higher number of backorders allowed the SC to save costs on inventories. With one less secondary manufacturers and one less local DC, the manufacturing facilities will need to produce also in periods 5 and 6 to guarantee that all the doses accumulated in backorders will arrive on the retailers.

According to solution 4, the primary manufacturers no more need to store API in inventory. The higher number of backorders allowed the number of facilities and inventories to decrease even more. In contrast, the production in manufacturing facilities goes on until time-period 6 to satisfy the pending demand that still did not receive its vaccine. In solution 6, 19273 backorders are allowed, which even higher than the demand. This means that it is allowed to delay more than one unit of demand for one period. In this situation, the inventory is only 98 thousand doses in the main DC. Since having backorders carries any cost, the model is now trying to save costs by reducing inventories the much as possible. In solution 7 the inventory is used to allow the reduction of one more secondary manufacturer and one local DC without delaying the demand in the first two time-periods. In this scenario, the network is becoming to much compact and backorders until the sixth time-period are necessary. It can be noticed that in time-period where the network is only supplying backorders, the inventory is null. This happens since there is no cost to have a backorder in the cost minimisation function, but an inventory cost exists.

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

With this case study, it is found that while minimising backorders allow the population to be vaccinated sooner, more facilities must integrate the network to satisfy all the demand in time. This carries extra costs which the decision-maker may not consider investing. Also, the reduction in the number of facilities is many times balanced by the increase in inventory in the remaining facilities. In solutions that are biased for cost minimisation, the vaccination campaign tends to get delayed to the last periods. In any solution it is possible to satisfy all the demand in the pretended time-period, meaning that backorders are always necessary. This occurs since all the demand is placed at the beginning of the temporal horizon.

VI. Conclusion

The study of models to enable the optimisation of the PSC network design become a pertinent academic interest. In this thesis, a model to optimise the PSC network is formulated and proposed. The objective of the proposed model is to minimise the total costs of the SC. The decisions considered encompass decisions at the strategic level, specifically the number and location of facilities, distribution, inventory positioning and production.

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

to guarantee that pharmaceutical products arrive to the final customer with the maximum quality, in the right quantity and with the necessary flexibility.

Finally, an application of the model to a COVID-19 vaccine SC network is performed. In this problem, backorders are allowed and the minimisation of backorders becomes a second objective. It is found that while minimising backorders enables the population to be vaccinated sooner, more facilities must integrate the network to satisfy all the demand in time, carrying extra costs to the SC. In the solutions that tend for cost minimisation, the vaccination campaign gets delayed.

Using an optimisation model as the proposed one to perform the PSC network design allows the determination of an optimum number and location of facilities, having into account inventories, productions and distribution flow. In the computational experiment performed, lower costs enabled higher variations in the network design. Trying to model an agile PSC considering facility construction costs or expensive technological investments as fixed costs can limit the agility of network; to model an agile PSC, working over a pool of facilities already existing and considering only integration or adaptation costs might reveal a good path. Another recommendation is to consider the use of multi-objective approaches to compare cost-minimisation with other indicators that consider customer satisfaction. In fact, the objective of minimising the delays of delivering vaccine doses is a benefit to the patient, revealing itself also a good driver for agility: regarding the set of solutions of the multi-objective problem analysed, solutions more restrictive about the delay of delivering vaccine doses also seems to allow more flexible networks.

As a future research proposal, including demand uncertainty in the optimisation model parameters should be considered. The PSC is very susceptible to market volatility, even more under an ongoing paradigm shift. Other topic for future work is the development of heuristic methods to address SC network design problems, since when large scale problems are considered, the computational time required to solve them may become unreasonable. Finally, including additional particularities of the PSC that are gaining importance in the modern world, as product perishability and customisation can be integrated in the SC optimisation models.

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