Supply Chain Resiliency in the Pharmaceutical Industry – a Simulation-Based Approach

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Abstract

The recent COVID-19 pandemic has highlighted the key role of the pharmaceutical industry and its supply chain operations in society. Like in many other sectors, this pandemic has unveiled important vulnerabilities and weaknesses across the pharmaceutical distribution network, calling the attention for the importance of resiliency, flexibility, and sustainability strategies.

One of the key challenges regarding resiliency is the ability to understand and anticipate the supply chain behaviour under uncertainty and dynamically manage capacity. In order to address this challenge, this paper proposes a simulation-based approach with a twofold goal: i) to understand the pharmaceutical supply chain network dynamics, in order to fast-track vulnerabilities and anticipate risks propagation across the network; and ii) to support decision-making for enhancing resiliency and flexibility, through capacity management strategic decisions.

The main contributions of this work are grounded on the integration and exploitation of different simulation paradigms, in order to understand the cause-effect relationships in complex systems, under several disruption scenarios. In this way, the disruption risks and their propagation are identified throughout the supply chain network, providing insights for the proactive and timely development of contingency and risk mitigation plans.

Keywords
Pharmaceutical Supply Chain, Resiliency, Decision-making, Capacity management, Simulation.

1. Introduction
The pharmaceutical industry plays a crucial role in the healthcare structure of a country by providing medicines and vaccines that directly affect the quality of life of the population (Marques et al. 2020). Along with its direct importance in the population's well-being, this industry also highly impacts the economy of developed countries, by being a top-performing high-technology sector (EFPIA 2020). Supply chain efficiency and resiliency can, therefore, be considered critical to endure a long-term sustainable growth.

However, as scientific and technological breakthroughs take place, societal expectations increase, regulations become more stringent, and markets rapidly change, the complexity of managing pharmaceutical supply chains (PSC) is significantly increasing, along with the pressure to become more cost-efficient, responsive, and reliable, when developing, making, and distributing pharmaceutical drugs (Marques et al. 2020). Moreover, the ongoing COVID-19 pandemic seems to have been a critical turning point regarding Supply Chain (SC) management principles and practices, by exposing global supply chains to a significant amount of stress, uncovering their main vulnerabilities to disruptions, and refocusing decision-making processes into more resilient and sustainable SC (Renn 2020). Supply

chain disruptions can be viewed as unexpected events that trigger significant changes in the SC, moving it away from its steady-state condition (Ribeiro and Barbosa-Povoa 2018). However, these events are highly difficult to portray and forecast due to their multidimensional and irregular nature, and, therefore, adequately managing them is still a challenge.

The pharmaceutical industry is particularly vulnerable to disruptions due to its complexity and global scale. Moreover, it undoubtedly plays a pivotal role in guaranteeing a secure and continuous worldwide supply of medicines. Therefore, network disruptions management has recently emerged as a key priority for both, researchers and practitioners. But, despite the significant progress in the design of decision support tools to enhance efficiency, resiliency and sustainability in the pharmaceutical supply chain, current operations have not been significantly improved and, in general, systems are still quite inefficient and highly vulnerable (Marques, Moniz et al. 2020). Moreover, the lack of consensus in the definition of resiliency metrics, and the weaknesses of current quantitative approaches, show this research topic needs further, more sophisticated developments (Ribeiro and Barbosa-Povoa 2018).

In this context, this work intends to address these challenges by developing a *simulation-based platform* to support high-level decision-making in SC network design and capacity management under disruption risks. Such a platform is expected to considerably enhance SC flexibility and resiliency in the pharmaceutical industry context. Unlike classical mathematical programming (optimization) models, the simulation of a supply chain should allow a better understanding of the target system and an estimation/forecasting of its performance. By testing different, representative scenarios, the behaviour of the SC can be better understood, and a correlation can be established between each type of disruption and the best feasible network configuration to reduce its negative impacts.

In this perspective, the main goal of the proposed simulation-based procedure is to design a resilient (capable to withstand disruptive events) and flexible (quickly responding to outside disruptions) pharmaceutical distribution network, exploring different capacity management strategies, under several disruptive scenarios.

The rest of the paper is organized as follows. In section 2, a theoretical review is provided regarding supply chain management and decision-making approaches for the pharmaceutical industry. In section 3, the adopted research methodology is described. Preliminary results are presented and discussed in section 4. Finally, the main conclusions and possible future research developments are summarized in section 5.

2. Theoretical review

2.1 Pharmaceutical supply chain design and planning

The pharmaceutical industry is inherently global, and consequently its supply chains are usually large and complex to manage. Like in any other industry, the pharmaceutical SC involves a complex network of interactions between different entities, such as suppliers, manufacturers, wholesalers, final healthcare providers (such as hospitals, pharmacies, etc.) and final consumers (Sousa et al. 2011). Some specific features, however, create unique management challenges that depend on the stage of the drug product life cycle. This life cycle, in the case of a pharmaceutical product, starts when a new product is discovered, and it goes on with the pre-clinical and clinical tests, market launch, and finally, the distribution into the market (Marques et al. 2020).This process follows a "Go / No Go" policy, always under rigorous monitoring by the regulatory bodies. Therefore, the pharmaceutical industry encompasses two very different types of supply chains: one covering the drug development phase; and the other for the production, distribution and marketing of the successful drugs (Azzaro-Pantel 2018; Marques et al. 2020).

When there is an authorization for a pharmaceutical product to go to the market, a whole supply chain must be established, starting with the *upscale* in production capacity. The production process is the core element in the pharmaceutical network and consists of two main stages (Sarkis et al. 2021): i) the *primary manufacturing (PM) stage*, where the Active Pharmaceutical Ingredient (API) is produced; and ii) *the secondary manufacturing stage*, where the API is converted into a consumable product (e.g., tablets, capsules, syrups) and then packaged.

The *secondary manufacturing (SM)* stage is typically highly decentralized and closer to the market, comprising several manufacturing facilities geographically distributed, in order to satisfy local markets. *Primary manufacturing,* on the other hand, is usually carried out in a very centralized way, at a few global multipurpose factories, which means that

more than one API is being produced in the same facility, sharing the available resources (Sousa et al. 2011). As the risk of cross-contamination is exceptionally high and this cannot happen under any circumstances, time-consuming and expensive cleaning and sterilization operations between product changeovers are required (Marques et al. 2020). Therefore, this manufacturing stage tends to be, not only, difficult to manage, but also highly inflexible to accommodate production to market changes. Moreover, the pharmaceutical SC network complexity is highly dependent on the nature of the final product (Sarkis et al. 2021), possibly requiring special handling conditions across the distribution chain, as it is the case, for example, of biologically based drugs (e.g., vaccines).

In this context, manufacturers need to deliver effective and safe products in quantities that meet the global demand, while ensuring that production processes are economically viable and comply with a set of strict regulations. The complexity of the overall SC planning can, therefore, increase significantly (Sarkis et al. 2021). Due to this complexity, research has been focusing on supply chain problems spanning across all decision-levels, as highlighted in several published reviews (Narayana et al. 2012; Franco and Alfonso-Lizarazo 2017; Marques et al. 2020).

Recently, Franco and Alfonso-Lizarazo (2017) identified in the literature, three main research topics for pharmaceutical SC management, namely: (1) supply chain network design; (2) inventory problems; and (3) optimization of SC networks. The authors acknowledge that most of the works in these topics are based on deterministic approaches, using classical mathematical programming models and heuristics, that do not capture important aspects of real-world pharmaceutical SC configurations. Also, Marques et al. (2020) notices that current approaches to pharmaceutical supply chain design and management are still highly fragmented, and identifies the seamless integration and coordination across the SC network as one major challenge. Moreover, those approaches seem to be mostly driven by classical optimization models, hardly addressing the real end-to-end supply chain planning problem (Laínez et al. 2012), and most of the literature still relies on operational planning and scheduling approaches based on optimization or hybrid simulation-optimization methods (Ruiz-Torres et al. 2010; Moniz et al. 2014; Marques et al. 2017).

We can therefore conclude that, although supply chain resiliency has been attracting increased interest over the years, in the pharmaceutical industry it is a fairly recent topic (Ribeiro, 2018). Nevertheless, in some noteworthy studies (Lücker and Seifert 2017; Lücker et al. 2019), pharmaceutical SC resiliency is addressed through the exploitation of strategies related to additional inventory, dual sourcing and agility capacity, that are used to minimize the negative consequences of disruptions. In their most recent work, these authors developed a mathematical model based on a single product and a single location, subject to supply chain disruptions (Lücker et al. 2019). Therefore, although some progress has been made recently, results clearly show the need for a further development of efficient approaches to simultaneously deal with the complexity and large-scale problems arising in global pharmaceutical supply chains, as well as with the exploitation of effective resilient-driven strategies.

2.2 Simulation-based strategies

In this context, simulation-based strategies as proposed in this work, seem to be able to overcome some of the hurdles observed in previous works. The use of simulation, as a key component of broader decision support systems, has been significantly increasing in the past years (Pierreval et al. 2007). The simulation of a SC allows the representation of complex constraints and interactions within the network, and is able to model the system's behaviour over time, leading to a better understanding of its dynamics (Terzi and Cavalieri 2004). In this way, simulation. models can be used to assess the performance of a system design, under uncertainty, and to evaluate alternative solutions.

Today, simulation modelling paradigms include Discrete Event Simulation (DES), System Dynamics (SD) and Agent-Based Simulation (ABS) (Borshchev 2014). Each of these paradigms reflect different views in mapping the real-world system (Borshchev 2014). While the DES paradigm adopts a process-oriented approach, SD reflects cause-effect relations through stocks, flows and feedback loops, and in ABS, the modeller describes the system as a set of individual objects that may interact with each other and the environment (Borshchev 2014).

In the pharmaceutical context Jetly et al. (2014), proposed a multi-agent simulation of the supply chain, replicating several important features observed in this particular type of SC. Later, Rathnasiri and Rupasinghe (2017) developed a discrete event simulation model to design the network for the whole distribution chain, from the manufacturer to the consumer. More recently Azghandi et al. (2018) proposed a simulation model to analyze the effects of product recalls in the pharmaceutical industry considering different types of disruption.

Given the advantages in using simulation to tackle large-scale problems under uncertainty, this work proposes a simulation-based approach to support the design of resilient-driven strategies. The main contribution of this work lies on the integration of different simulation paradigms in order to leverage the understanding of the cause-effect relations in highly complex systems, such as the pharmaceutical SC, under several disruption scenarios.

3. Adopted methodology

3.1 Methodological framework

As mentioned in the introductory section, the purpose of this work is to build a simulation-based platform to test the flexibility and resilience of pharmaceutical SCs. By running simulation models under different disruption scenarios, we aim at uncovering key weaknesses in the SC so that timely measures can be taken to contain possible disruptions.

As stated by Law (2019), a well-defined approach to conducting a simulation study is critical to the development of effective and successful models. Following this author's guidelines, a methodological sequential approach was pursued to address our problem.

First, the problem under consideration was described in a first stage – *Problem Formulation*. Subsequently, requirements for the model were identified, and constraints and simplifications were considered in the *Conceptual Modeling* phase, leading to a sufficiently realistic and coherent model. Then, a *Simulation Model* was constructed – in our work we have used the *Anylogic* software, considering all the pharmaceutical supply chain logic and features. Based on a comprehensive set of data collected from the literature, and on some simplifying assumptions, a *Simulation Instance* was created to test and validate the model. Finally, a set of simulation scenarios were tested, and the results analyzed in the *Simulation Results* phase.

3.2 Problem formulation (case study)

The case study presented in this paper was designed considering the behaviour of a standard global pharmaceutical supply chain. Such a SC usually involves primary manufacturers, secondary manufacturers, wholesalers, and retailers.

Primary manufacturers are responsible for producing the API (Active Pharmaceutical Ingredient) that is the result of lengthy and costly R&D activities, with a highly complex and regulated production process. This is why this manufacturing step typically follows a *Make-to-Stock* strategy, and in a limited number of facilities. The following participants of the PSC are the *secondary manufacturers* that produce final drug products, with the API provided by the primary manufacturers. This manufacturing process is typically less complex and consequently less time consuming. Therefore, secondary manufacturers are in general more than the primary manufacturers, are usually located closer to the markets, and operate in a *Make-to-Order* strategy. The next elements of the supply chain are the *wholesalers*. They buy stock of the final drug product from secondary manufacturers, and sell it to *retailers*, which are the final elements of the chain, and are the point of connection with the final consumer. Given its nature, the SC must be reliable, flexible, and resilient, this meaning that it needs to carefully satisfy the requirements of the different participants, and be capable of containing the negative effects of unexpected disruptive scenarios.

This paper proposes a simulation model capable of representing, testing and assessing the behaviour of the pharmaceutical supply chain, so that its vulnerabilities can be identified and contained by the exploitation of several strategies, such as varying the facilities' safety stock levels, or, in a later stage, by possibly outsourcing product from external facilities or investing in new production capacity.

3.3 Conceptual model

Building a realistic and coherent model starts by documenting all the case study structural and behavioural requirements and features, identifying the entities, and describing the simplifications and assumptions to be made. In our case, the following **entities** have been identified:

- *API manufacturing facilities* – representing the facilities (primary manufacturers) where the API will be produced;
- *Final Product (FP) manufacturing facilities* – group of facilities (secondary manufacturers) that will produce the consumable final product with the API provided by the above facilities;
- *Wholesalers* – facilities that sell products in bulk to retailers;
- *Retailers* – the final elements of the PSC and point of contact with the consumers;

- *Orders* – "orders" represent informational transactions between the supply chain elements (participants), in the form of inventory requests (an order is created when a facility wants to request product from a facility in an upper stage of the supply chain).

Taking into account the specific features of pharmaceutical SC operations, the following main **requirements** of the simulation model have been defined:

- the simulation horizon should be of at least 5 years in order to capture main vulnerabilities;
- the supply chain model should be customizable, this meaning the SC configuration should be easily adapted to different business contexts (allowing a variable number of SC entities);
- the number of products considered should also be changeable, thus allowing to change the SC complexity;
- times and costs of production in the manufacturing facilities should be easily configurable;
- product demand should also be configurable and depend on the type of product (as different products may be in different stages of their life cycle);
- the SC performance should be evaluated through a set of KPIs (Key Performance Indicators), namely: demand satisfaction as a percentage of consumer met demand; order fulfillment (failed orders, backorders and response/delivery times); lead times and overall SC costs.

Additionally, given the high complexity of the pharmaceutical SC, some **simplifications** were made in the model:

- given the considered time horizon, transportation times between locations were approximated based on the IGISRouteProvider;
- manufacturing facilities work with production lines (one given production line produces a single product);
- given the considered long time horizon, *set-up* times in production facilities are ignored as they will not have a significant impact in the simulation results;
- when there are *queues* in the process, we will consider they follow a FIFO rule (*First-In-First-Out*);
- when an order is made, there is no time limit for that order to arrive, and no order cancelations are considered.

3.4 Simulation model

Considering the simulation paradigms mentioned above and the characteristics of the different methods, we have concluded that integrating multiple methods and designing a model to address the PSC behaviour at different decision levels would likely lead to more powerful and useful planning tools. This is one of the main contributions of this work. To develop our models, we have chosen the Anylogic software, the main reason being the fact that it allows for simultaneously using the 3 above simulation paradigms (Borshchev and Filippov 2004).

First, a System Dynamics (SD) approach was used to model the overall behaviour of the pharmaceutical supply chain, representing each echelon (*primary_and secondary_manufacturers*, *wholesalers,* and *retailers*) as a stock of pharmaceutical products and the transaction of products between each echelon represented as a flow. This approach allows for a strategic assessment of the overall material flows along the network and service level evaluation, which is critical for the fast identification of possible disturbances occurring in each SC echelon. The overall model behaviour is represented through Figure 1 and the following equations.

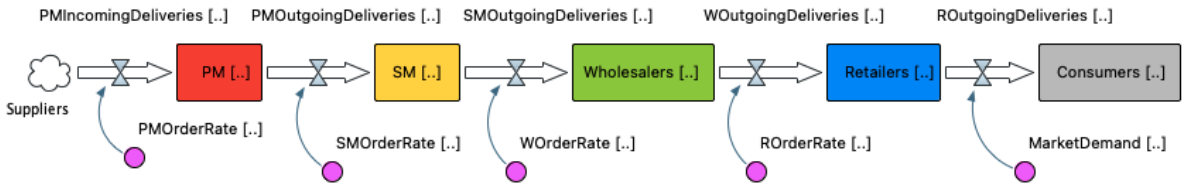

Figure 1. System Dynamics model

$$\frac{d(Consumers[ProductType])}{dt} = ROutgoingDeliveries[ProductType] = MarketDemand[ProductType]$$

(…)

$$\frac{d(PM[ProductType])}{dt} = PMIncomingDeliveries[ProductType] - PMOutgoingDeliveries[ProductType]$$

Second, an Agent-Based approach was developed, integrated with the SD model, in order to evaluate the individual performance of each facility, and to understand the behavior of these facilities and the key factors influencing the overall performance of the system. Therefore, the agent-based approach was used to model each individual entity of the SC, bringing to the model the ability to easily simulate different capacity and inventory management strategies locally, including adding/removing new elements to the network. In this context, the simulation is based on populations of agents (*primary_and secondary_manufacturers*, *wholesalers,* and *retailers*) that interact with each other through a fifth agent: the *order*. The role of this agent is to control the rate of each flow between the stocks of the System Dynamics model. Figure 1 shows the modeling details of the *wholesaler* agents.

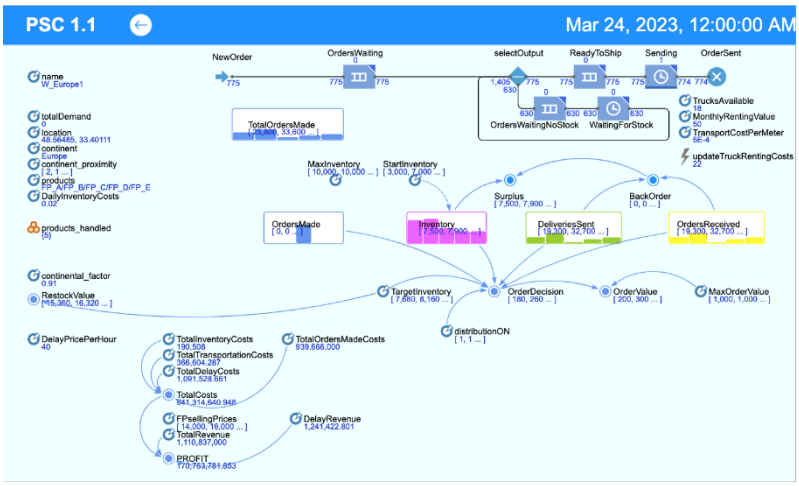

Figure 2. *Wholesaler* agent model.

The configuration of the populations of agents is made in a simulation startup step, with the information contained in a *Configuration Excel File*. This file contains: the agents' location (latitude and longitude); the drug products handled in each element of the SC; production costs and times for the different manufacturing facilities; and the final consumers' demand. Using this model, different supply chain designs can be tested and evaluated, by changing the parameters in the input configuration file.

The *order* agent carries information about the type, quantity and destination of the ordered product. This agent was created simply to be transported and handled by the other agents and, therefore, no additional modeling was required. Modeling the behavior of the other agents was done with a hybrid approach of System Dynamics and Discrete-Event Simulation, where: (a) stock management is defined with System Dynamics; and (b) the management of orders is done by a Discrete-Event approach.

Stock management varies according to the type of facility. However, a *safety stock* of products is always considered, taking into account the backlogged and ongoing orders (orders that have been made but have not yet arrived), and the product already in inventory. In the case of manufacturing facilities, the production time is also a parameter to consider.

The supply chain performance, in its multiple dimensions, can be visualized using different *dashboards* in the Stats tab of the simulation GUI (Graphical User Interface) of *Anylogic*. Additionally, for each of the SC facilities, the evolution of product in stock, the backordered product quantities, and some other statistics such as average lead time or average inventory level, are computed and shown. Moreover, a database of all the orders in the supply chain was also created, with their origin, destination, quantity, type of product, as well as the times of creation and delivery. This database can be exported to an *excel file* after the simulation, thus allowing further subsequent analysis.

3.5 Base-case simulation (*Initial operating conditions*)

A scaled-down case of a global pharmaceutical supply chain was used to demonstrate the applicability of the developed simulation tool. The PSC network can be found in Figure 2 in which the facilities and their locations are depicted.

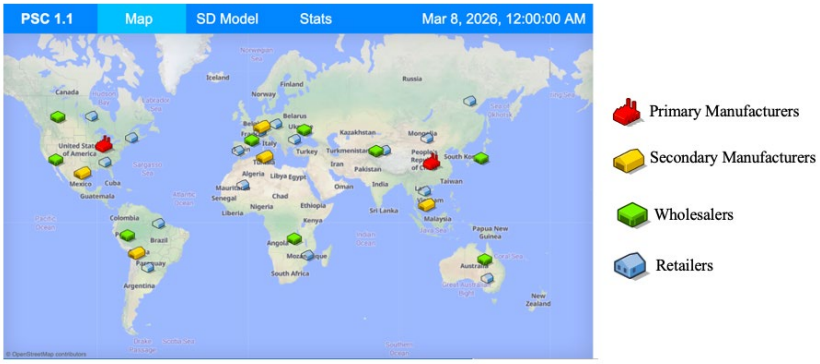

Figure 3. Base-case simulation model.

The following facilities and assumptions were considered: 2 primary manufacturers located in Asia and North America, operating in a Make-to-Stock strategy; 5 secondary manufacturers, located in North America, South America, Africa, Europe, and Asia, operating in a Make-to-Order strategy; 8 wholesalers (distributed through 6 continents); and 16 retailers. Orders for raw-materials and final products are placed to the closest upstream facility, preferably in the same continent. At the retailers, when demand cannot be met, we assume it is lost (no backorders).

Additionally, the final products considered in this case and their demand are based on the recent work by Blossey et al. (2022). Therefore, five products (P1-P5) are considered, and all quantities are given in SKU (stockkeeping units) where here 1 SKU means 1,000 boxes (50 pills each) of the associated pharmaceutical product. The products are in different life cycle stages with corresponding expected demand profiles as depicted in Figure 3.

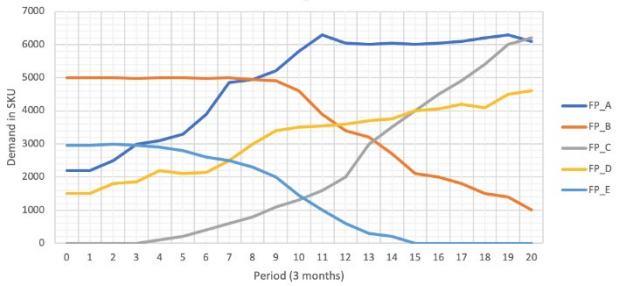

Figure 4. Pharmaceutical products demand trajectory, adapted from (Blossey et al. 2022).

The simulation was made for a 5-year period, considering a safety stock value estimated to accommodate 1 month of expected average demand. Furthermore, taking into account one of the main strengths of simulation, that is its ability to effectively deal with the uncertainty nature of real systems, all scenarios considered comprise uncertainty in product demand. This uncertainty is modelled considering demand probability distributions for each product and market.

Table 1 shows the SC performance, detailing the overall service level, average lead time by facility and SC profit in MMU (millions of monetary units). The service level corresponds to the percentage of consumer demand that can be met over the 5 year planning horizon. The average lead time corresponds to the average time that an order arriving at a specific facility takes until reaching its final destination, and the SC profit is computed considering the costs of production, material, inventory, transportation and order delays costs, over the 5 year planning horizon.

The preliminary results suggest that, under normal conditions, the designed SC network is highly effective with demand satisfaction close to 100% in every retailer. The most significant failure was observed after 4 years in Australia with an overall service level of 99,22%. This result is understandable as it is the only continent that does not have a

secondary manufacturer. Moreover, Table 1 clearly shows the *bullwhip effect* observed by the progressively larger inventory levels along the upstream supply chain.

Additionally, it is worth mentioning that all the metrics presented in Table 1 can be drawn for every facility in the SC network allowing a detailed assessment of the individual performances.

Table 1. Performance metrics for the base-case scenario over the 5 years planning horizon

		PM	SM	Wholesalers	Retailers
Overall service level (%)		99.9%			
Inventory level of final product at the end of the 5 years (SKU)		--	181 450	149 750	79 957
Average Lead Time by facility (h)	**Waiting For Stock**	16.94 (4%)*	8.67 (2%)*	29.67 (47%)*	----
	Waiting For Transport	3.36 (1%)*	73.08 (18%)*	0 (0%)*	----
	In Transit	366.89 (95%)*	316.50 (79%)*	33.06 (53%)*	----
	Average lead time in each type of facility	387.19	398.25	62.73	----
Profit at the end of 5 years (MMU)	**By echelon**	10 730	12 930	11 870	3 733
	Overall	39 260			

* Percentage of the total average lead time per facility.

4. Preliminary experimental results

As the main goal of our work is to build a simulation tool able to test the resiliency of a pharmaceutical supply chain, 2 disruptive scenarios will be presented as illustrative examples. The two scenarios are intended to put the base-case instance under some *stress* condition and test its performance, in order to identify critical points in the SC and proactively define target-specific strategies to enhance overall resiliency.

4.1 Disruption scenario 1: *Excess demand*

The first scenario is intended to test a small disturbance in order to assess the performance of the SC under such type of circumstances. As highlighted above, the main driver of this work was the COVID-19 pandemic and the vulnerabilities that it unveil in the pharmaceutical supply chain. One of the scenarios that happened during this outbreak was the increase in demand of OTC analgesics such as paracetamol, especially during the beginning stages of the pandemic (Andalo 2021). In that sense, a simulation instance was created where the demand of product A doubles its value of the base case scenario, from day 365 to day 1095 (2 years of duration).

Preliminary results regarding the SC performance under an increase in demand for product A are depicted in Table 2 and Figure 4. Although this scenario has a very limited impact as it addresses only one product, it is possible to already see some impacts on the SC.

Despite the overall service level only observed a slight decrease, backorders were registered in Asia (service level = 99,7%) and Australia (service level = 98,0%) with a total value of approximately 3 200 000 SKU. According to Figure 4, increasing the product demand of product A during 2 years caused an increase in backorders at the wholesalers starting, approximately, one month after the beginning of the disruption. Moreover, the backorders occurring at the wholesalers impacted the retailers only 1,5 years later when the first lost sales occur. This means that during this time retailers were able to manage their demand through the available inventory.

We can also see that at the secondary manufacturers (SM) the inventory slightly decreased, showing that the current safety stock level at SM serves as a cushion for the increase in demand.

Overall, these preliminary results seem to show that the SC is sensitive to relatively small disturbances on the normal conditions, but in this scenario the production capacity and inventory levels seem to be able to withstand the increase in demand of product A.

Table 2. Performance metrics for scenario 1 over the 5 years planning horizon

		PM	SM	Wholesalers	Retailers
Overall service level (%)		99.8%			
Inventory level of final product at the end of 5 years (SKU)		--	179 124	152 350	80 840
Lead Time (h) by facility	**Waiting For Stock**	21.89 (6%)*	10.10 (3%)*	23.70 (42%)*	----
	Waiting For Transport	3.83 (1%)*	47.64 (14%)*	0 (0%)*	----
	In Transit	369.01 (93%)*	284.83 (83%)*	33.11 (58%)*	----
	Average lead time in each type of facility	394.73	342.57	56.81	----
Profit (MMU)	**By echelon**	9 604	13 970	11 320	3 607
	Overall	38 500			

* Percentage of the total average lead time per facility.

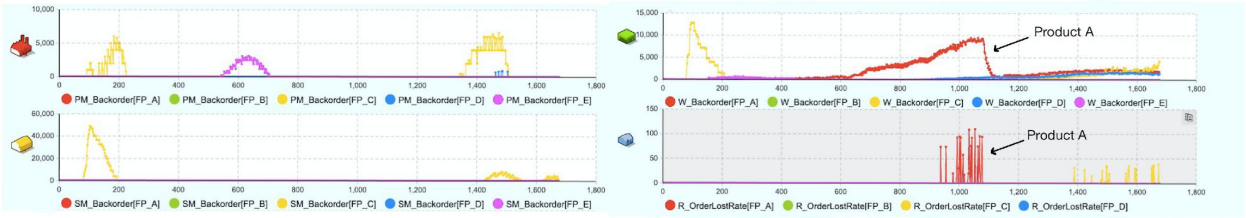

Figure 5. Amount of backorders in each echelon (PM_Backorder, SM_Backorder and W_Backorder) and the amount of lost sales per day in retailers (R_OrderLostRate).

4.2 Disruption Scenario 2: *Reduced production capacity*

A second realistic scenario is the occurrence of an accident in a manufacturing facility forcing production to stop. A specific instance was therefore created considering production of products A and B in the European secondary manufacturing facility is stopped from day 365 to day 730 (1 year of no production).

The main results depicted in Table 3 and Figure 5, show a more significative decrease in the overall service level with a value of 95,93%. As expected, the effect of this disruption is immediately felt on the secondary manufacturing facilities with the main backorders occurring in SM, wholesalers, and retailers.

Table 3. Performance metrics for scenario 2 over the 5 years planning horizon

		PM	SM	Wholesalers	Retailers
Overall service level (%)		95.9%			
Inventory level of final product at the end of 5 years (SKU)		--	179 402	151 300	84 609
Lead Time (h) by facility	**Waiting For Stock**	20.89 (5%)*	18.05 (5%)*	34.48 (51%)*	----
	Waiting For Transport	3.22 (1%)*	86.57 (22%)*	0.03 (0%)*	----
	In Transit	369.39 (94%)*	291.76 (74%)*	33.30 (49%)*	----
	Average lead time in each type of facility	393.50	396.38	67.81	----
Profit (MMU)	**By echelon**	10 472	11 579	11 262	3 512
	Overall	36 800			

* Percentage of the total average lead time per facility.

As presented in Figure 5, after production stops in the European secondary manufacturer, backorders immediately start occurring, with orders being fulfilled from inventory until running out of stock, after approximately 50 days for product B and 80 days for product A (Figure 5 and Figure 6). We can also see that, at the wholesalers, backorders related to the other products start occurring sometime later. At the retailers, product shortages are felt approximately 92 and 148 days after disruption for product B and A respectively, with a total unsatisfied demand of approximately

62 800 SKU (product A) and 96 700 SKU (product B). Moreover, results show that when production recovers, retailers need around 70 days to be able to satisfy 100% of the demand.

These results clearly show the main vulnerabilities of the SC to face the considered disruption, and highlight the importance of some key performance indicators in exploring proactive capacity and inventory management strategies to minimize the negative impacts observed. In this line, a third experiment is presented in the next sub-section in order to understand how resilient-driven management strategies are able to cope with this disruptive scenario.

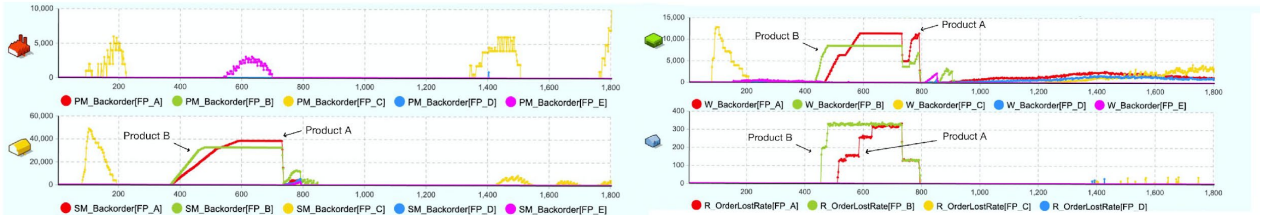

Figure 6. Backorders quantities in each echelon (PM_Backorder, SM_Backorder and W_Backorder) and the amount of lost sales per day in retailers (R_OrderLostRate).

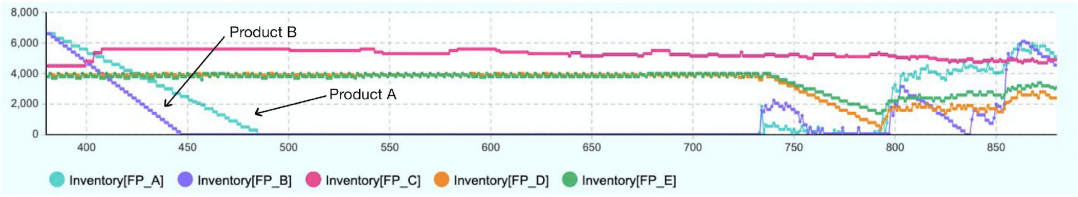

Figure 7. Inventory level over time (wholesalers).

4.3 Scenario 3: *Risk mitigating inventory level*

In order to understand how proactive risk mitigating strategies can be used to cope with disruptive scenario 2, a new simulation was run for scenario 2, considering an increase in the safety stock levels of 20% for products A and B in secondary manufacturers and wholesalers. The results in Table 4 show an overall increase in the service level, with the product shortages at the retailers being delayed for approximately one month for product A and 20 days for product B. In this case, the total unsatisfied demand is approximately 55 000 SKU (product A) and 89 800 SKU (product B), representing a decrease of 12% and 7% respectively.

Although increasing inventory represents additional costs for the SC operations, in this preliminary analysis the increased costs were compensated by the increase in the demand satisfaction.

Table 4. Performance metrics for scenario 3 over the 5 years planning horizon

		PM	SM	Wholesalers	Retailers
Overall service level (%)		96.5%			
Inventory level of final product at the end of 5 years (SKU)		--	179 162	163 100	94 021
Lead Time (h) by facility	**Waiting For Stock**	17.54 (5%)*	22.91 (5%)*	32.69 (50%)*	----
	Waiting For Transport	3.45 (1%)*	89.51 (21%)*	0.04 (0%)*	----
	In Transit	361.58 (94%)*	304.61 (73%)*	33.15 (49%)*	----
	Average lead time in each type of facility	382.56	417.037	65.875	----
Profit (MMU)	**By echelon**	11 310	12 570	12 040	3 658
	Overall	39 580			

* Percentage of the total average lead time per facility.

5. Conclusion

In this work, a new simulation-based approach was developed to support decision-making for the design and capacity management of the pharmaceutical Supply-Chain (SC), aiming to enhance its flexibility and resiliency. This approach integrates two simulation methods, not only allowing a strategic analysis of the SC (through System Dynamics) but also identifying its main vulnerabilities by evaluating the performance of each individual agent. In this context, the developed approach has proven to be effective in meeting the main specific goals defined for the research, namely: i) understanding the SC behavior under different operational scenarios; ii) identifying the SC vulnerabilities when disruptions occur; iii) quantifying the impacts of disruptions and their consequences; iv) predicting the propagation of the disruption impacts along the SC; and finally, v) easily adapting the model to test different proactive management strategies to contain the disruption risks.

As part of a wider on-going project, future work is foreseen to enhance the model by implementing a "broker" agent capable of evaluating the SC performance and dynamically manage its capacity, by either increasing safety stock levels implementing outsourcing strategies, or investing in new capacity. Furthermore, the model will be extended to include the ability to manage and track product expiration dates, to effectively meet pharmaceutical industry requirements, and to enhance the overall SC sustainability.

Although the model was developed for the specific case of the pharmaceutical industry, it can be easily generalized and adapted to other industrial sectors, and this generalization will surely be exploited in future developments of the work.

Aknowledgments

This work is partially financed by National Funds through the Portuguese funding agency, FCT - Fundação para a Ciência e a Tecnologia within the project LA/P/0063/2020 and the project "FuturePharma - Pharmaceutical supply chain of the future" - PTDC/EME-SIS/6019/2020

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