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A Simulation Approach for the Design of More Sustainable and Resilient Supply Chains in the Pharmaceutical Industry

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Abstract: In a world facing unprecedented challenges, such as climate changes and growing social problems, the pharmaceutical industry must ensure that its supply chains are environmentally sustainable and resilient, guaranteeing access to key medications even when faced with unanticipated disruptions or crises. The core goal of this work is to develop an innovative simulation-based approach to support more informed and effective decision making, while establishing reasonable trade-offs between supply chain robustness and resiliency, operational efficiency, and environmental and social concerns. Such a decision-support system will contribute to the development of more resilient and sustainable pharmaceutical supply chains, which are, in general, critical for maintaining access to essential medicines, especially during times of crises or relevant disruptions. The system will help companies to better manage and design their supply chains, providing a valuable tool to achieve higher levels of resilience and sustainability. The study we conducted has two primary contributions that are noteworthy. Firstly, we present a new advanced approach that integrates multiple simulation techniques, allowing for the modeling of highly complex environments. Secondly, we introduce a new conceptual framework that helps to comprehend the interplay between resiliency and sustainability in decision-making processes. These two contributions provide valuable insights into understanding complex systems and can aid in designing more resilient and sustainable systems.

Keywords: pharmaceutical supply chain; resiliency; sustainability; decision-support systems; simulation

Citation: Silva, A.C.; Marques, C.M.; de Sousa, J.P. A Simulation Approach for the Design of More Sustainable and Resilient Supply Chains in the Pharmaceutical Industry. *Sustainability* **2023**, *15*, 7254. https://doi.org/10.3390/su15097254

Academic Editor: Mirco Peron

Received: 10 March 2023
Revised: 21 April 2023
Accepted: 23 April 2023
Published: 27 April 2023

1. Introduction

The importance of resiliency and sustainability in the design and management of supply chains (SC) is consistently growing, with researchers and practitioners attempting to take into account these two aspects simultaneously.

Sustainability concerns in SC management are not new and have been evolving over the past decades along the triple bottom line (i.e., economic, environmental, and social dimensions) [1]. Together with the traditional economic goals, research activities have been mostly driven by increasing awareness about environmental impacts and social issues. Despite the fact that supply chains (SCs) have been experiencing disruptions for decades, recent global events have sparked a new level of awareness regarding their vulnerability and the pressing need to implement not just more sustainable, but also more resilient SCs [2].

Being highly tied to the notion of business continuity, the resiliency of a system has been broadly defined as its ability to withstand disturbances and rapidly converge to the original or a new desirable state [3,4].

Therefore, the concepts of sustainability and resiliency are clearly associated with complex and multidimensional decisions that hinder their joint implementation in such dynamic systems as supply chains [3,5]. Moreover, despite the existing lack of consensus, it is becoming clearer that sustainability and resiliency influence each other in many complex ways, either leading to different types of trade-offs or by mutually reinforcing each other [6–8].

When developing resilient SC operations, current approaches are mainly grounded on flexibility and redundant strategies with reserved capacity, inventory, and resources for pro-actively dealing with future disruptions [7,9]. These strategies, however, typically configure sub-optimal conditions for sustainability, with these redundancies having important environmental and economic impacts. Understanding the level of these influences in both dimensions is critical to seize opportunities for developing new decision-making approaches toward improved SC resiliency and sustainability.

This is particularly relevant in the pharmaceutical industrial context, not only due to its global scale and complexity, but also due to its major social and environmental impacts [10]. As medicines directly affect people's lives, the social dimension becomes very important, with the need to ensure medicines' affordability and availability in a long-run perspective. In that sense, resiliency strategies are critical to prevent medicine shortages under SC disruptions. However, some critical challenges such as the limited shelf-life of medicines and costly waste disposal processes, tend to hinder the effective implementation of most resilience-driven strategies. In that sense, a careful balance between the resiliency and the sustainability dimensions in pharmaceutical SC operations is particularly challenging and is still very poorly explored.

Therefore, this study aims to address the integration of both concepts (resiliency and sustainability) in a decision-support system with a twofold goal: (1) to understand how resilience-driven strategies impact the pharmaceutical SC operations under several scenarios; and (2) to find synergies between the multiple conflicting criteria, as a way to drive the decision-making process toward a sound balance between resiliency, and environmental (waste generation) and social (global access of medicines) issues.

Following the authors' previous work [11], a simulation-based approach is proposed here considering the integration of Agent-Based Simulation (ABS) and Discrete-Event-Simulation (DES) techniques, for the design and planning of the pharmaceutical supply chain. The proposed methodology allows an assessment of the impacts of resilience-driven strategies on the SC's overall performance to be made, and can be used to guide the decision-making process toward trade-off solutions, leading to waste reduction and increased access to medicines in low-income regions.

The findings of the present study are in line with prior research results, in particular with new conceptual frameworks that help us understand the interplay between resiliency and sustainability in decision-making processes. Moreover, this work is based on an advanced approach, integrating multiple simulation techniques that enable the modeling of highly complex environments, and that can be used to enhance the resilience and sustainability of supply chains. This approach has an enormous potential in identifying critical variables, their mutual influences, and the trade-offs that decision makers must consider to ensure the sustainability and resilience of supply chains in complex and dynamic environments, therefore contributing to the ongoing discourse in the field.

The rest of the paper is organized as follows. In Section 2, a background is provided covering the most recent studies that address the integration of sustainability and resiliency in SC decision-making approaches. In Section 3, a detailed description of the problem is presented. In Section 4, the methodological approach is described. The main results are presented in Section 5, and final conclusions and future developments are drawn in Section 6.

2. Background

The literature on the concepts of sustainability and resiliency in SC operations is vast and has recently greatly expanded, particularly regarding decision-support approaches based on optimization and simulation methods [4,12,13]. Yet, both concepts seem to have been evolving independently, disregarding their interactions and, sometimes, the conflicting associated goals [3,6]. In this context, sustainability refers to the ability of the pharmaceutical supply chain to meet the needs of the present while focusing on maintaining environmental, economic, and social stability for long-term sustainable growth [14,15].

Sustainable supply chain management involves managing the flow of materials, information, and capital among entities within a supply chain, with the aim of achieving sustainable development goals across the economic, social, and environmental dimensions [15].

Resilience, on the other hand, refers to the ability of the pharmaceutical supply chain to withstand and recover from disruptions, such as natural disasters, political instability, or pandemics. A resilient supply chain is able to adapt quickly to changing conditions and continue to deliver critical drugs and medical supplies to patients in need. This may entail integrating redundancy into the supply chain, diversifying raw material suppliers, and developing contingency plans for a range of potential disruptions [3,4,6].

The significant complexity of today's supply chains and business context, however, is boosting the emergence of a new paradigm for decision-making processes based on the interface between sustainability and resiliency. As highlighted by several thorough reviews ([2,5,6,16]), the integration of both concepts is critical for strengthening SC operations in a long-run perspective and is calling more and more attention from researchers and practitioners ([17–19]).

Ivanov et al. [20] developed a multi-objective hybrid "linear programming/system dynamics" model for return flow minimization in a supply chain under disruptions. The proposed method compares SC recovery policies after a disruption and designs a more resilient and sustainable SC. Later, the same authors [7] proposed a Discrete-Event Simulation model to study the performance impact of disruption propagation in the supply chain, considering sustainability factors, in order to design a resilient SC. Jabbarzadeh et al. [21] proposed a hybrid approach for the joint consideration of resilience and sustainability on sourcing decisions. The authors developed a fuzzy c-means clustering approach for the sustainability assessment, and a stochastic bi-objective optimization model to determine the resilience strategies that maintain the required sustainability performance. Ramezankhani et al. [22] proposed a mixed sustainability and resilience approach to assess the SC performance, based on a dynamic network data envelopment analysis (DEA). The methodology was applied to an automotive manufacturing company.

Asghari et al. [23] developed a dynamic nonlinear programming model to appraise financial incentives in reverse logistics, with a focus on assessing the effect of the incentives on the return quantity of used products. Such a model was used in designing reverse logistics networks. The motivation for this research mainly comes from the rising environmental concerns that have compelled manufacturers to retrieve and recover products that have reached the end of their life cycle.

Duminy and Grosser [24] developed a causal model based on System Dynamics simulation to identify the appropriate social and economic sustainability performance indicators for resilient supply chains in the pharmaceutical industry. The study shows the underlying supply chain structure and the impacts of the most common causes of medicine shortages. Roostaie et al. [25] developed an assessment framework for the integration of both concepts, based on a systematic literature review and a case study. Zavala-Alcívar et al. [8] proposed a conceptual framework, integrating the key management components of resiliency, to enhance sustainability operations in the supply chain. More recently, Owida et al. [26] proposed a decision-making framework for integrating resiliency and sustainability, based on a literature review and on an industrial case study in the food industry. All these studies [8,25,26] acknowledge the need for new conceptual frameworks to support a better understanding of the synergies of resiliency and sustainability in decision-making processes.

Despite these important contributions, it seems clear that an effective integration of both concepts into a practical decision-support approach is still far from being achieved. In this regard, simulation techniques stand in a privileged position to tackle these new challenges by enabling the deployment of complex SC structures and the assessment of their behavior under several scenarios without disrupting actual operations. The use of simulation as a tool for decision support has been increasing in the past years [27]. By manipulating input variables such as production capacity, demand, and distribution

channels, simulation can provide valuable insights into the potential consequences of implementing changes, and can help identify areas of improvement or optimal solutions.

Moreover, recent research has demonstrated its unique capabilities in the exploitation and analysis of multiple trade-offs in decision making, regarding SC resiliency and/or sustainability [11,24,28,29].

In this context, this work expects to leverage the potential of simulation techniques, such as ABS and DES, in the analysis, in the pharmaceutical industry, of key trade-offs between resiliency and sustainability metrics. A special focus will be given to the still poorly explored social dimension of these problems, by explicitly integrating it into the decision process.

3. Problem Definition

In this work, we consider a global pharmaceutical supply chain configuration as depicted in Figure 1. Independently of the market dimension and complexity, we assume this network is a typical pharmaceutical SC structure [10], characterized by five echelons: primary manufacturers; secondary manufacturers; wholesalers; donation centers; and retailers.

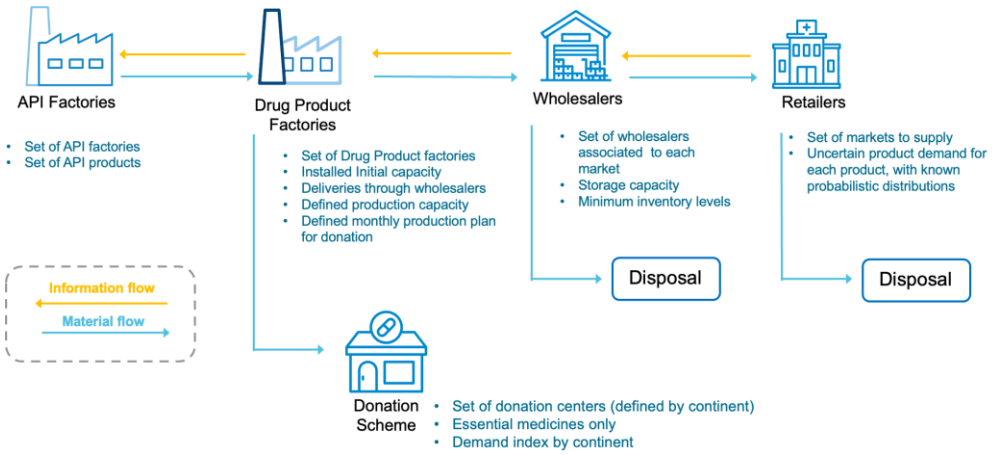


Figure 1. Pharmaceutical Supply Chain.

In the primary manufacturing stage, raw materials are converted into an API (Active Pharmaceutical Ingredient) product. Production here is the outcome of extensive and costly R&D initiatives, framed by very complex and regulated manufacturing processes [30]. For these reasons, this manufacturing stage is typically very inflexible, following a Make-to-Stock strategy, and located in a limited number of facilities.

In the secondary manufacturing stage, the final drug product is produced, based on the API provided by the primary manufacturers. This step usually involves combining the API with other non-therapeutic ingredients, further processing of the formulation into a particular dosage form, and then packaging to ensure integrity and prevent deterioration during commercialization [10]. Because this manufacturing process is often less complex and with reduced lead times, secondary manufacturers are more responsive to market changes and, therefore, are often located closer to the markets, adopting a Make-to-Order strategy [30,31]. Moreover, we will consider that, as part of their social responsibility activities, the secondary manufacturers implement a "donation program" [32]. In that sense, a pre-defined percentage of the monthly production at the secondary manufacturers is directed for donation centers. The donation centers are characterized by a product demand that depends on the product type and on the specific needs for that product at the moment the product is available.

Wholesalers play a crucial role in the supply chain, as they acquire inventory of the final drug product from secondary manufacturers, and distribute that product to the

retailers. Retailers are the final echelon in the supply chain, and represent the healthcare providers (pharmacies, hospitals) that dispense the drug product to the end-consumer.

All these facilities are connected through a set of transportation resources, and two main flows are considered: an upstream flow of information, and a downstream flow of materials.

The fact that drug products have a precise expiration date, together with the uncertainty on market demand and production rates, can lead to significant pharmaceutical waste; i.e., a considerable amount of discarded or expired drugs that are no longer needed or usable. This type of waste has become a growing concern due to its potential to cause harm to the environment and human health [33,34]. The improper disposal of pharmaceutical waste can result in the release of these drugs into the environment, where they can contaminate water sources, soil, and food [34,35]. This can lead to adverse effects on aquatic life, on wildlife, and potentially on humans [34–36]. The presence of these drugs in the environment can also impact the efficacy of antibiotics, leading to the development of drug-resistant bacteria [34,35].

The safe disposal of these materials is, therefore, critical, in reducing the potential for harm to the environment and human health, and thus disposal facilities are a crucial element to be considered in the pharmaceutical supply chain.

These SC attributes, combined with the number of entities, resources, and operations involved, result in quite large and complex design and management problems.

Given its specific nature, the pharmaceutical SC must be reliable, flexible, and resilient, this meaning that it must carefully fulfill the requirements of the different participants, while also being capable of mitigating the adverse effects of unanticipated system disruptions. To achieve these requirements, SCs often rely on network redundancy strategies, such as redundant capacity and backup upstream sources. However, these strategies come with trade-offs that may not always result in an increased benefit, particularly regarding sustainability aspects.

This work will explore the strategies related to risk-mitigating inventory levels [9] in which a reserve inventory is built up to fulfill market demand in face of a supply chain disruption.

Based on these strategies companies seek to ensure an adequate level of inventory that, not only, meets the expected customer demand, but also prevents stockouts and lost revenue during unforeseen events. Yet, increasing inventory levels involves, not only, significant financial resources related to production, holding, labor, and capital costs, but also yields important environmental impacts, with increased waste generation and resource consumption. As pharmaceutical products have limited shelf-life, additional inventory becomes a critical issue to manage as it increases the potential of waste generation due to expired and/or unused medicines.

In this context, a natural research question arises: "How can the pharmaceutical supply chain be managed to effectively balance both resiliency and sustainability?"

This question stems from (1) the need to assess the impact of resilience-driven strategies, such as the ones based on risk-mitigating inventory for the supply chains operations; and (2) better understand how this impact affects the environmental and social performances, in order to guide the decision-making process to a sound balance between these criteria in SC design and planning.

This question is of great importance as it has far-reaching implications for the pharmaceutical industry from economic, environmental, and public health perspectives. By finding ways to balance resiliency and sustainability in the pharmaceutical supply chain, we can contribute to a more robust, responsible, and sustainable future for the industry itself and for the overall society.

4. Methodological Approach

4.1. Simulation-Based Decision-Support Framework

The aim of this work is to develop a hybrid simulation approach, based on ABS and DES, to be part of a decision-support platform for enhanced supply chain resiliency and sustainability. The adopted decision-support conceptual framework encompasses five main stages as depicted in Figure 2.

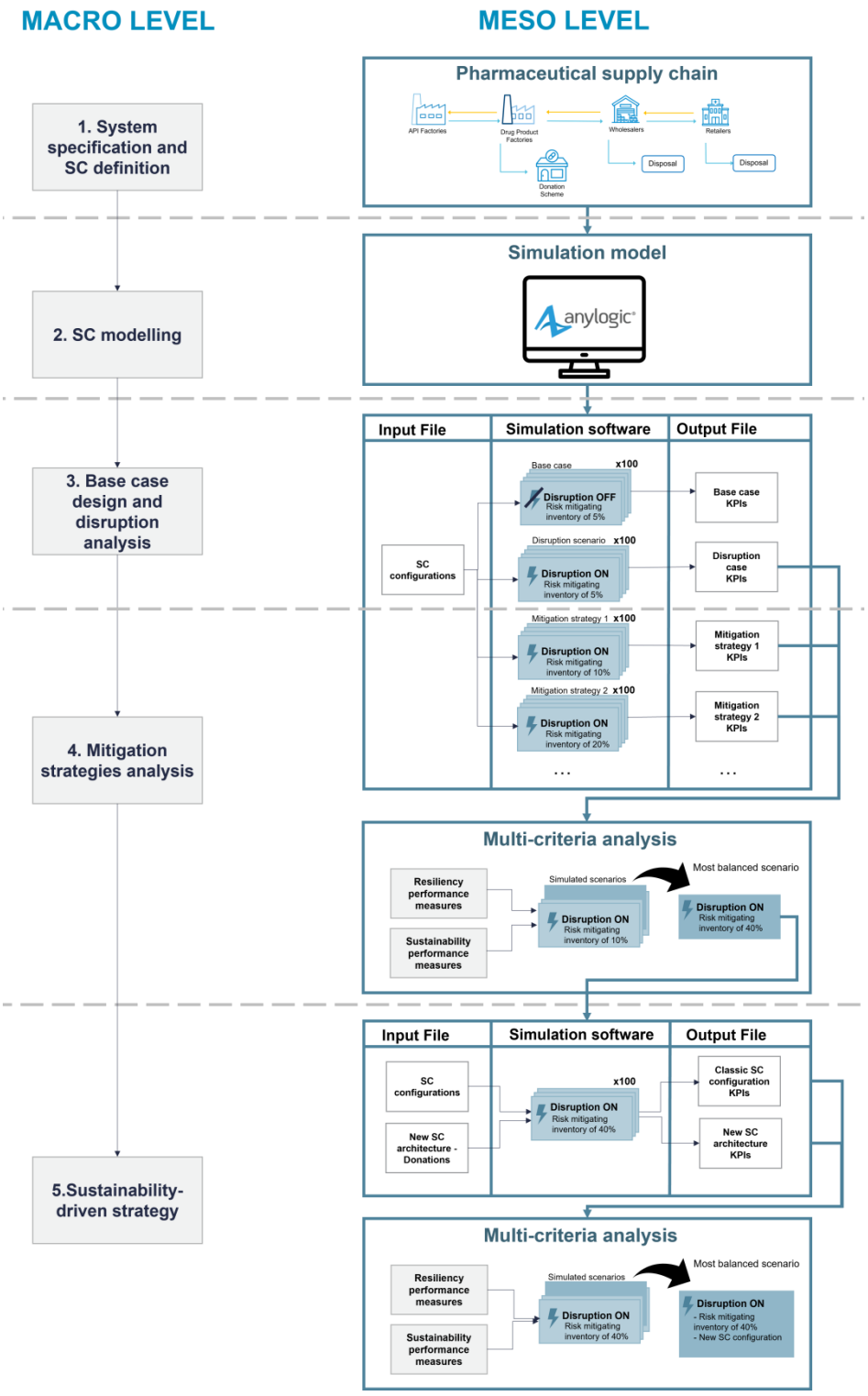


Figure 2. Hybrid simulation-based decision-support framework.

First, the SC structure under consideration is defined, as well as the related parameters, system constraints, and network dynamics. Based on this information, in the second stage, a simulation model of the SC is built using the Anylogic software. The following stage consists of the generation of a problem instance for the base case and a disruptive scenario, considering a set of data from the literature and some simplifying assumptions. The main goal here is to establish the SC operational performance under demand uncertainty, and its behavior in face of a disruption event.

The next two stages are focused on the SC resiliency (stage 4) and sustainability (stage 5) aspects of the SC.

In the fourth stage, different risk-mitigating inventory levels will be tested to determine which inventory level performs better, regarding the risk mitigation objective, and without excessively compromising the economic, environmental, and social performances. In terms of the environmental dimension, since the considered resiliency strategy has a great impact on waste generation, the quantity of waste will be used to assess environmental performance. The social dimension will be monitored through global medicine availability, with a special focus on the medicine access of underserved markets. It should be noted that this is a fairly unexplored metric in the literature.

Finally, the last stage (stage 5) will focus on the sustainability performance of the system, and on how to offset the drawbacks of the implemented mitigation strategies in the previous stage. Here, the focus will be on building a sustainable-driven strategy that benefits from the adopted risk-mitigating strategy, by anticipating the excess waste generation and redirecting it to donation programs in underserved markets.

In this stage, a new base case will be simulated, considering an additional reverse flow of medicines with expiring risk from retailers and wholesalers, intended to integrate the donation stream. Medicines with a close expiry date are considered to have a high probability of being wasted, either because they do not meet the regulations for the regular market or because they will not be sold on time. Either way, this expected waste can be anticipated and avoided by redirecting such medicines to donation programs. As these medicines are close to expiring, we assume that donations will only occur if there is a great need for those medicines, which means they will be immediately consumed.

By running several simulations on the base case with reverse flows, it is possible to determine the environmental and social gains that are achieved under the risk-mitigating inventory strategy.

4.2. Simulation Model

To model the supply chain considered in this work, agent-based and discrete-event simulation techniques were integrated into a single approach.

In an agent-based simulation setting, the components of a system, such as suppliers, manufacturers, distributors, and customers, are represented as individual "agents". These agents are modeled to make decisions and interact with one another, based on specific rules and behaviors. This approach allows for modeling the interactions and interdependencies between different components of the supply chain. By simulating the behavior of individual agents, agent-based simulation can provide insights into the collective behavior of the supply chain.

The integration of this approach with discrete-event simulation can provide a comprehensive and detailed view of the behavior of individual agents. Discrete-event simulation is a simulation approach that models the behavior of a system as a sequence of events occurring at discrete points in time. By integrating agent-based simulation with discrete-event simulation, the behavior of individual agents can be tracked over time, and this includes the events the agents participate in and the decisions they make. This information can be used to better understand the interplay between individual agents and the system, and to analyze the impact of various events on the supply chain's performance.

The simulation model was developed as an extension of the authors' previous work [11], using the AnyLogic software as shown in the conceptual framework presented in Figure 3.

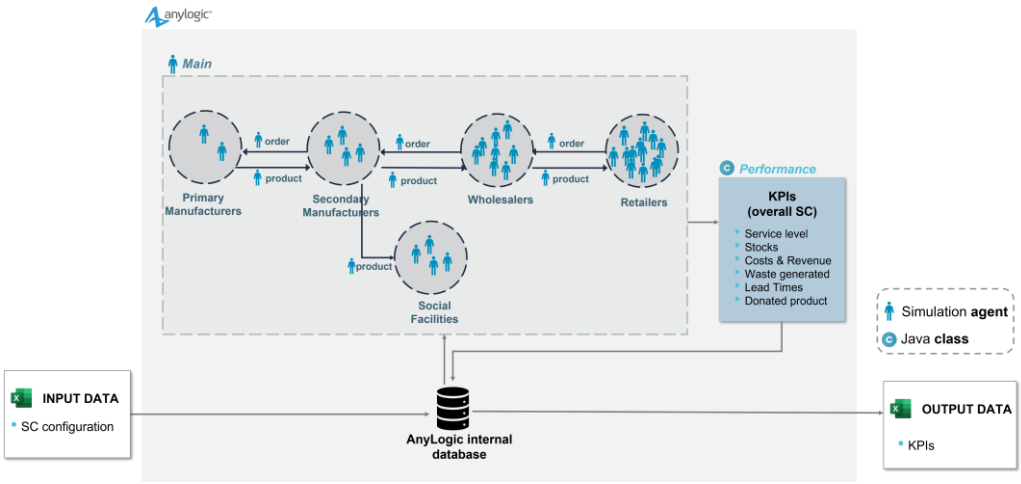


Figure 3. Simulation conceptual framework.

4.2.1. An Agent-Based Approach for SC Modeling

The supply chain is configured in a simulation start-up stage, using information from an Input Data Excel File (see Figure 3). This file provides information such as facility locations, products handled/produced in each facility, product demand profiles, production times, or initial stock values. At the start-up step, this information is loaded into the software's internal database and used to generate the populations of agents for the SC configuration under analysis.

During the simulation, the supply chain key performance indicators (KPIs) are displayed, and when the simulation is over, these KPIs can be exported to an Output Data Excel File.

In total, the simulation model comprises 8 agents, that can be divided into 3 different groups: the Main agent, the Facility agents, and the Flow agents.

The Main agent is created by default and it is the core of the simulation. This agent houses the agents representing the SC and is used to oversee/control the entire simulation. This agent also groups the information on all facilities' current state and performance data.

Facility agents model the behavior of the SC echelons, with a discrete-event approach. In this category, we have the following agents:

- Primary_manufacturer: models the behavior of the facilities where the API will be produced;
- Secondary_manufacturer: models the behavior of the facilities that will produce the consumable final product with the API provided by the primary manufacturers;
- Wholesaler: models the behavior of wholesalers;
- Retailer: models the behavior of retailers, and it is in this agent that the demand from consumers is considered;
- Social: models the behavior of a special type of retailer; this agent will be the recipient of the donations from the secondary manufacturer, and will serve a specific part of the population that cannot afford to buy medications.

Flow agents are used for communication between Facility agents, and are created to be delivered and handled by those agents. In this category, we have the following agents:

- Order: this agent carries information about the type, quantity, and destination of the ordered products, as well as additional information such as the times of orders and deliveries;
- Product: this agent represents the (pharmaceutical) product at the end of secondary manufacturers that will be delivered to final consumers; a product agent has a type (of product), a quantity, and a production batch identification (id) for product traceability.

The behavior of these agents, as well as their interactions, is dictated by the discrete-event modeling component of each agent.

4.2.2. Discrete-Event Modeling of the Facility Agent

Each agent's behavior is modeled using a discrete-event approach, this model being specific to each echelon. However, some behavioral patterns may be drawn, and as a result, some common subsystems can be defined and implemented.

The first of these subsystems is responsible for managing incoming and outgoing orders; the second subsystem handles inventory management; and finally, a third subsystem implements the donation scheme. This third subsystem is exclusive to the secondary manufacturing facility agent, as depicted in Figure 4.

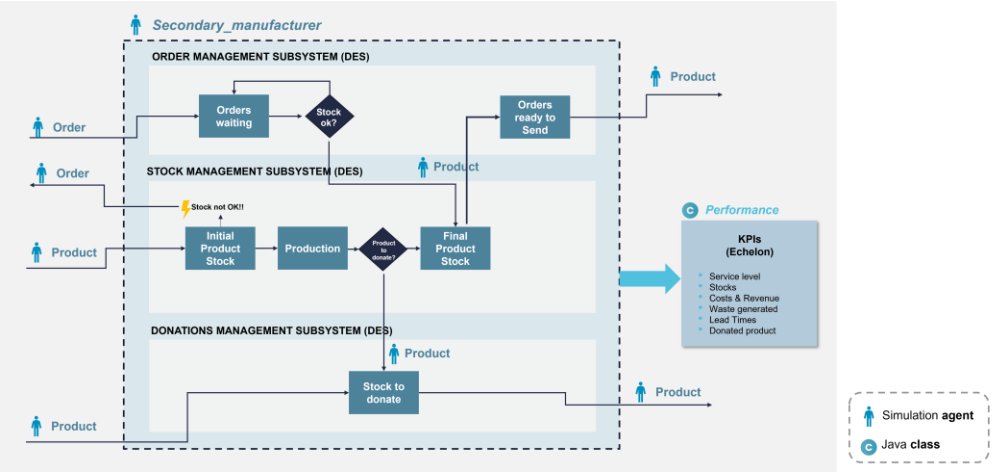


Figure 4. A secondary manufacturer agent.

The order management subsystem has an entry block that receives order agents, followed by a queue with all the orders waiting for stock. When there is enough stock to fulfill the order, product agents from the inventory management subsystem are attached to the corresponding order agent, and moved to a queue with the orders ready to be shipped. Finally, there is a "delay", representing the time of transport, and then the product agents are sent to their destination.

The inventory management subsystem is dependent on whether manufacturing exists at that echelon. This subsystem also has an entry block, where the product arrives from the supplier. The product is then sent into a queue of product stock. If the echelon is a manufacturing echelon, this product is moved to a delay block, at a cadence determined by the production schedule. After this production delay, the product is sent to another queue of final product stock. If the echelon is not a manufacturing echelon, the product enters directly into this queue. Product agents stay in this queue until they are requested by an order agent, from the order management subsystem. In this subsystem, there is also a monthly event that checks the level of the current inventory, and when the stock is below a pre-defined value, an order agent is created and sent to the supplier. For the case of wholesaler and retailer agents, there is also an event that checks for the expiry date and sends the product to the secondary manufacturer, when it is close to that date.

Finally, the donations subsystem receives products from the inventory subsystem and from the other agents, and sends them to the underserved retailer facilities.

4.2.3. Key Performance Indicators

In order to assess the supply chain resilience, we have adopted the metrics proposed by [37] as presented below (Figure 5). This diagram shows the service level evolution when the supply chain is in the presence of a disruptive event. The service level is in the original steady state until time period t_0, the moment when the disruptive event occurs. The SC is

assumed to be able to withstand the disruption for some time, until its impact starts to be felt at period t_d. The impact of the disruption leads to a decrease in the service level, until a stabilization stage is reached. At period t_r, the supply chain enters the recovery stage and the service level starts increasing until reaching a new steady state at t_f.

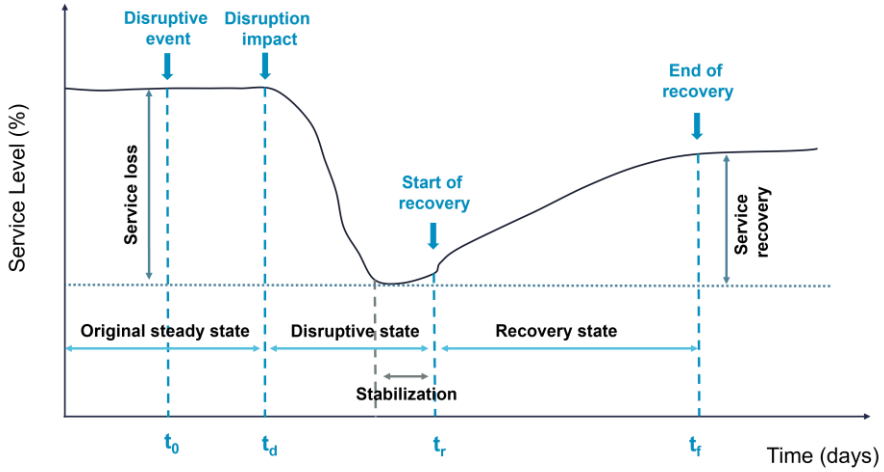


Figure 5. Service level typical behavior in the presence of a disruptive event (adapted from [37]).

To analyze and measure the SC resilience, the service loss and the disruptive state duration are compared for different scenarios.

In summary, the following measures will be used in the supply chain assessment:

- Service level (SL): will be monitored considering the overall SC service level, the service level by product type, and the service level by location; this performance metric is computed by the following expression:

$$\text{Service Level} = \frac{\text{Product Delivered}}{\text{Demand}} \times 100\% \quad (1)$$

- Disruption Time *(t_d):* time in which the disruption impact is felt at the retailer level.
- Recovery Time *(t_r)*: time in which the recovery stage starts.
- Service loss: in the disruptive state, given by the following expression:

$$\text{Service loss} = \text{SL}(\text{t}_\text{d}) - \text{SL}(\text{t}_\text{r}) \quad (2)$$

- Disruptive State Duration (DSD): period of time in which the service level is in decline, given by the following expression:

$$\text{DSD} = \text{t}_\text{r} - \text{t}_\text{d} \quad (3)$$

For the sustainability aspect of supply chain performance, the following indicators were computed:

- Waste generated: the total amount of waste generated, in SKUs; it can also be presented as a percentage of the total amount of product handled in the facility, as well as the time evolution of this value.
- Total Costs: this metric is computed considering the production costs, inventory costs, transportation costs, delay costs, and discarded costs.

Finally, it should be noted that all the metrics can be drawn for every facility in the SC network, allowing a more detailed assessment of its individual performances.

4.3. Experiments Design

To demonstrate the applicability of the simulation framework developed in this work (and presented in Figure 2), the following experiments were designed.

First, a "base case" was created, intended to be representative of a pharmaceutical supply chain with the general configuration of Figure 1. To this base case, a disruption scenario was "applied". This disruption scenario tries to replicate a possible realistic scenario, in a pharmaceutical supply chain, where an accident in a secondary production plant forces operations to stop for a year. As the results presented in the next section show, this disruption scenario will result in a decline in the overall supply chain service level. As a mitigation measure, trying to decrease these negative effects on the service level and to increase the system resilience, we will increase the safety stock and assess the resulting effects on the several KPIs.

Finally, the new network design was implemented to increase supply chain sustainability, which had been lowered due to the mitigating measures used to strengthen the supply chain's resilience.

4.3.1. Base Case

A scaled-down example of a global pharmaceutical supply chain was used as a base case (Figure 6), considering the following facilities and assumptions:

- Two primary manufacturers located in Asia and North America, operating in a Make-to-Stock strategy;
- Five secondary manufacturers, located in North America, South America, Africa, Europe, and Asia, operating in a Make-to-Order strategy;
- Nine wholesalers (distributed through six continents);
- Sixteen retailers;
- Five donation centers;
- Orders for raw materials and final products are placed at the closest upstream facility if the facility is active (normal conditions, no disruption scenario) and preferably located in the same continent;
- Five products (A/E) are considered, and all quantities are given in SKU (stockkeeping units) with 1 SKU meaning 1000 boxes (50 pills each) of the product;
- Supplier/client interactions are depicted in Figure 7;
- The products are in different life cycle stages with corresponding expected demand profiles based on the authors' previous work [11] and depicted in Figure 8;
- The demand is triggered at the retailers and is subject to uncertainty (modeled with a normal probability distribution with standard deviation of 10%);
- Demand that cannot be met by the retailers is considered to be lost (no backorders);
- In all other echelons, when an order is made, and if there is no stock, the demand is backlogged until there is stock available (backorders);
- Inventory is evaluated every month and orders are placed to maintain a stock value estimated to accommodate 1 month of expected average demand, with an additional 5% of safety stock;
- Secondary manufacturing facilities have a monthly quota of production to donate, and, therefore, 10% more is added for donations;
- Retailers and wholesalers can only sell products with an expiry date that is greater than 6 months, and if this period is reached, they are forced to dispose the product, and cover the associated costs;
- The simulation was run for a 5-year period, with a time unit of 1 day;
- All simulated scenarios were run 100 times, with the results presented in this work corresponding to the average of those experiments.

Figure 6. Supply chain configuration for the base case, as viewed in the simulation-based decision support tool developed.

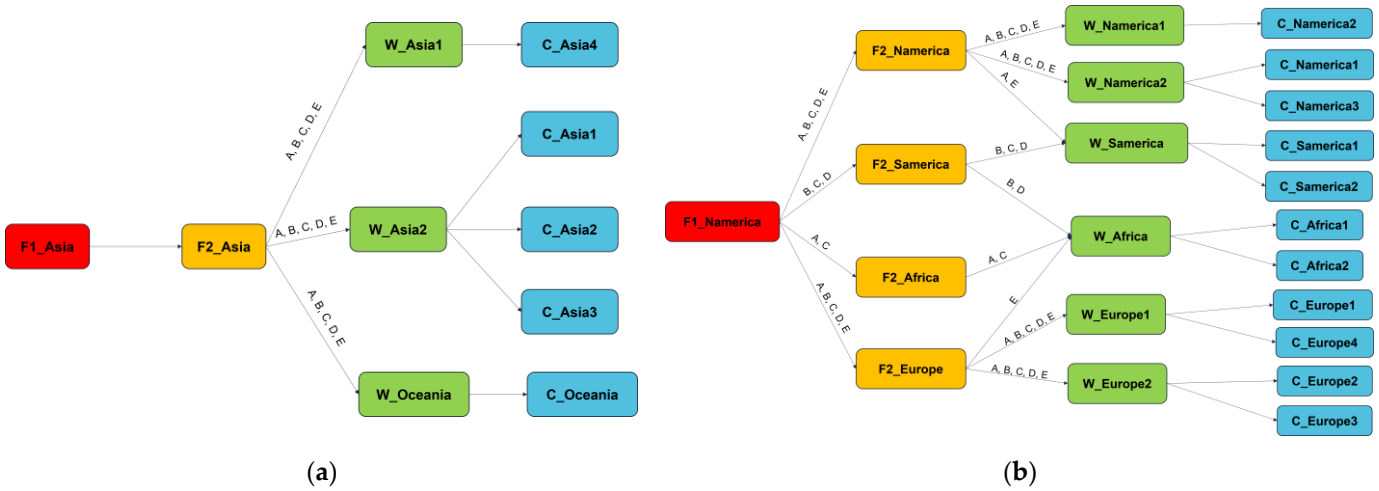


Figure 7. Supplier/Client interactions: (**a**) Asian primary manufacturer; (**b**) North American primary manufacturer.

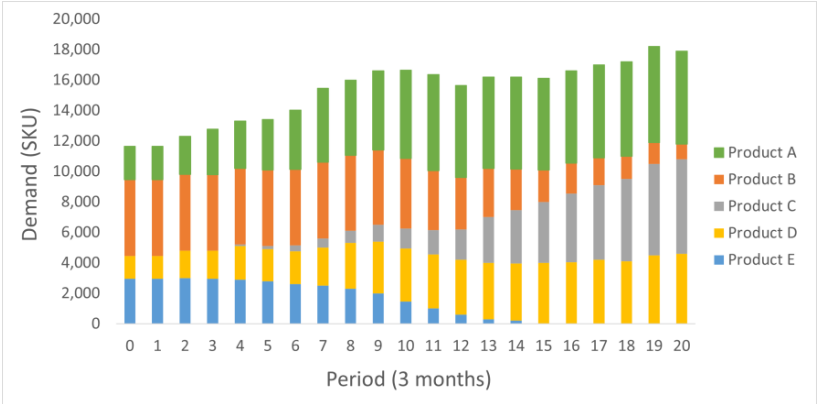


Figure 8. Pharmaceutical product demand profiles.

Figure 7 shows the SC interactions: in red, the primary manufacturers; in yellow, the secondary manufacturers; in green, the wholesalers; and in blue, the retailers. The arrows represent product flows/transactions. If there is no reference to products in the arrow, then all products are supplied by the upstream facility to the downstream facility.

4.3.2. Disruption Scenario

To test the supply chain's resilience, a disruption scenario was considered in the base case described above. This scenario replicates an accident in a secondary manufacturing facility that forces production to stop and causes all facility inventory to be lost. This event occurred in the secondary manufacturing facility located in North America, two years after the start of the simulation, and lasted for one year (Figure 9).

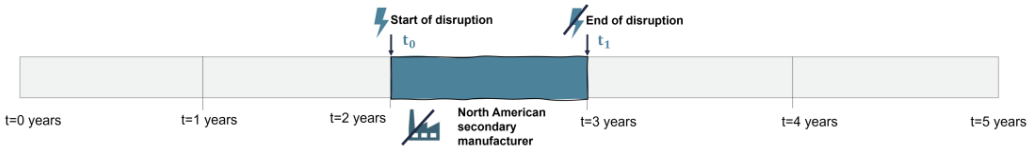


Figure 9. Simulation timeframe with the introduction of the disruption scenario.

Except for the existence of an event that disables the secondary manufacturer agent, all the settings and data are the same as in the disruption-free scenario.

4.3.3. Resiliency Strategies

In order to mitigate the disruption impacts, a resiliency strategy, based on building up reserve inventory, was implemented and tested.

Four alternative mitigation measures were created, by adding 10%, 20%, 40%, and 60% of inventory to the expected monthly demand. These extra inventory levels were applied to all supply chain echelons at the beginning of the simulation.

4.3.4. Sustainability Strategies

In order to address the drawbacks, in terms of increased costs and waste, of the resiliency measures, a new network is designed to integrate the sustainability dimension in the decision-making process.

This new network structure includes a donations scheme based on a reverse flow that reintroduces products close to expiry, back into the supply chain (Figure 10). By doing so, two sustainability factors, social and environmental, can be addressed simultaneously.

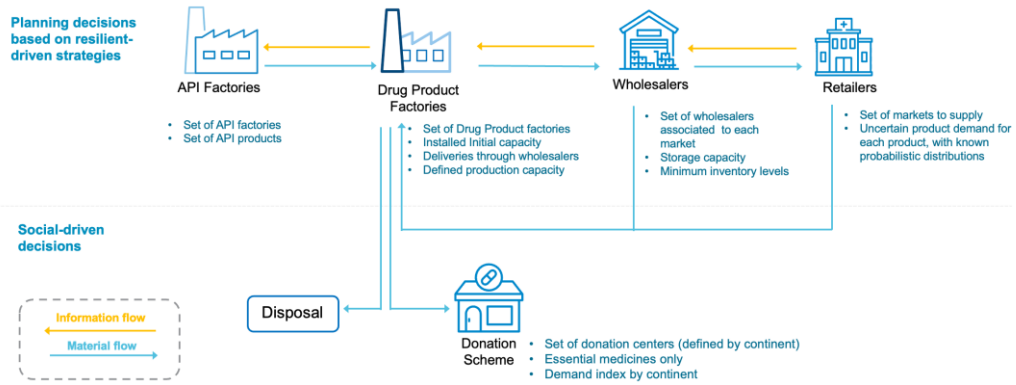


Figure 10. Revised Supply Chain architecture.

This new SC considers that products at the wholesaler and retailer level are at risk of being wasted when in stock for an extended period, and attempts to anticipate this waste generation by reintroducing this product back into the supply chain through a donations scheme regulated by the secondary manufacturer.

In this new setting, the secondary manufacturers play a pivotal role in managing the overall excess inventory. They will be responsible for selecting the product that is eligible for donation and for disposing the product that can no longer be sold. Given that the sector is highly regulated, some requirements need to be fulfilled for a product to be donated, such as guaranteeing a certain minimum shelf life; being a medicine considered essential; and having a demand that guarantees immediate consumption.

In this study, a product is considered at risk to expire if its validity is 6 months or less. In this case, it is not possible to guarantee that the product will be sold or reach the final consumer within an acceptable validity time.

5. Computational Results and Discussion

Experimental procedures were designed and carried out to understand how resilience-driven strategies may be exploited in order to also yield benefits regarding sustainability metrics. Therefore, these experiments are used to assess the overall SC performance under several scenarios and SC configurations, and to identify impacts regarding a set of resiliency and sustainability metrics (as defined above).

The simulations were performed using the Anylogic software and considered a 5-year horizon, in order to accommodate both the disruption event and the recovery time.

The base case was first tested under a free-disruption scenario as a way to establish the performance baseline for the subsequent scenario analysis. All the scenarios were tested on 100 simulation runs, in order to effectively deal with the system uncertainty.

5.1. Impact of Disruptions

After establishing the performance baseline of the pharmaceutical supply chain under study, a disruption event was simulated, considering the inoperability for one year of the secondary manufacturer in North America. Based on the first results, it was possible to observe an immediate decline in the overall service level from 96.9% (base case) to 92.6%, as depicted in Figure 11. These values were computed at the end of the simulation run, thus illustrating the service level loss over a five-year period.

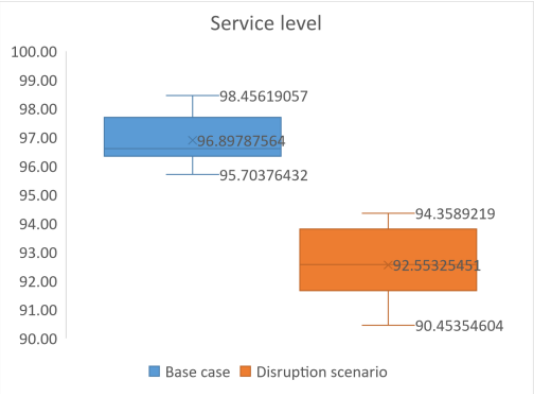


Figure 11. Service level for the base case (blue) and the disruption case (orange).

However, in order to understand the major impacts of this disruption over time, a more in-depth analysis is required. Figure 12 shows the evolution of the service level of the entire supply chain over the 5-year simulated time horizon.

As expected, the SC service level, under a disruption, follows the behavior depicted in Figure 5. During the initial steady state phase (from t = 0 to t_d = 770), the service level coincides with the base case's value. The supply chain maintains a constant service level during this period, except for a minor decline that occurs for both scenarios around t_C = 366. This decline results from the introduction of product C in the market (see Figure 8). At that time, facilities are still trying to adjust their inventory management policies to the demand and cannot fully respond to the market demand.

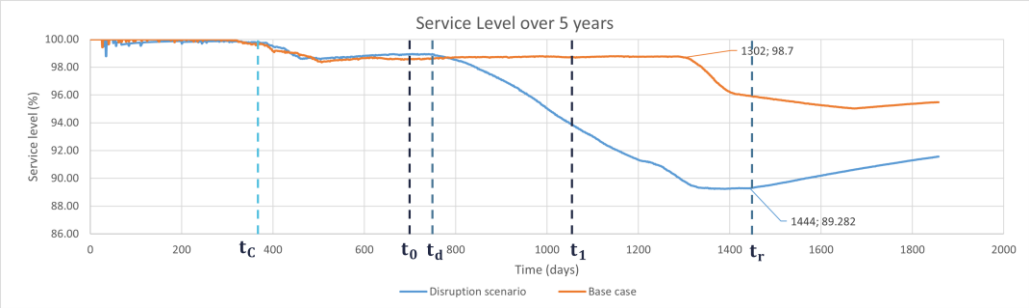


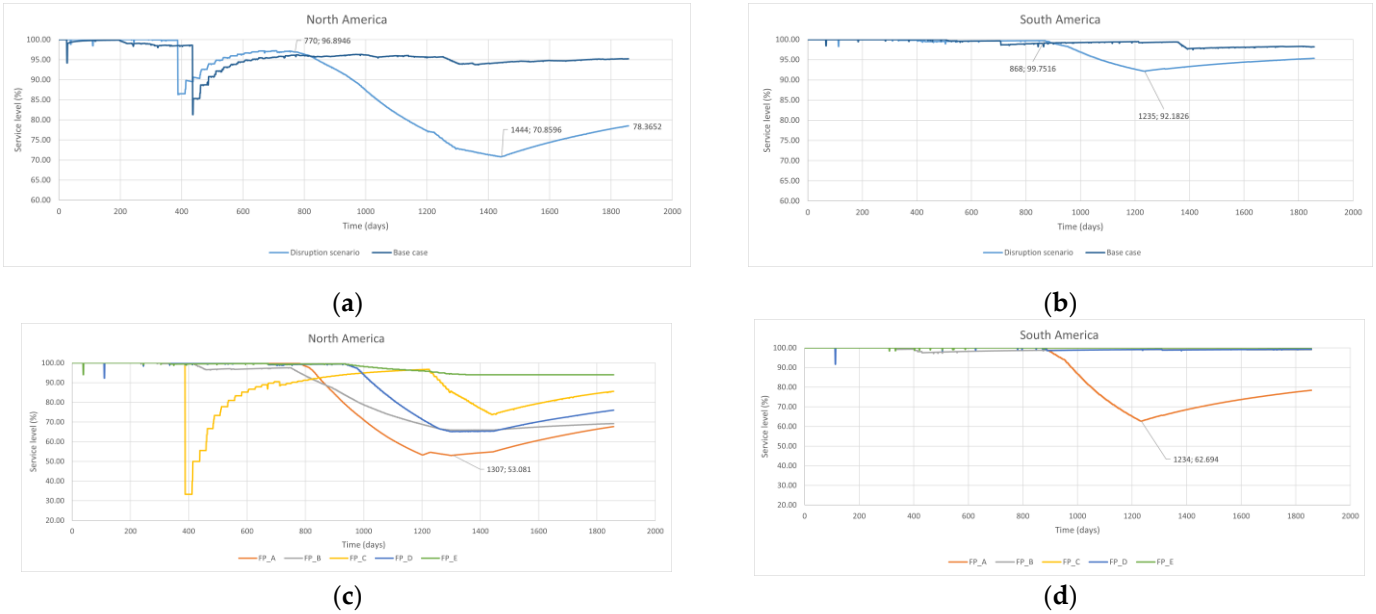
Figure 12. Service level for the base case (orange) and the disruption scenario (blue): t_C—introduction of product C in the market; t_0—start of disruptive event; t_d—disruption felt at the retailers; t_1—end of disruption; tr—start of recovery phase.

The disruptive state starts at t_d = 770, around 68 days after disruption (t_0 = 702). The decline in service level stabilizes at t_r = 1444, with a drop in service level to 89.3%. The disruptive state lasts for 674 days, entering the recovery state 297 days after the end of the disruption, at t_1 = 1068.

In the base case, a drop in service level is observed at t = 1302, due to an increase in demand for products A, C, and D, and this increase also happens when a large production lot expires.

Figure 12 shows the overall supply chain service loss is 9.5% at the turning point and 4.4% at the end of the simulation (still in the recovery state). However, as the disruptive event happens in a very specific position of the SC, thus affecting a particular section of the network, the major impacts are expected to occur within that section.

As the secondary manufacturer that stopped producing was responsible for supplying all products to the North American markets, and products A and E to the South American markets (Figure 7), a more in-depth analysis of these markets was performed (see Figure 13).



(**a**) (**b**)

(**c**) (**d**)

Figure 13. Service-level time for the base and the disruption scenario: (**a**) North American markets, in the base case (darker blue) vs. the disruption case (lighter blue); (**b**) South American markets, in the base case (darker blue) vs. the disruption case (lighter blue); (**c**) North American markets, for each type of product, in the disruption case; (**d**) South American markets, for each type of product, in the disruption case.

As expected, the impact on North American markets is more substantial than on the South American markets (Figure 13a,b) and affects all products in North America, while only affecting product A in South America (Figure 13c,d). In North America, a service loss of about 26% is registered, starting at day 770 and entering the recovery stage at t_r = 1444, with a more substantial impact on product A. In South America, an overall service loss of approximately 8% was observed, caused by a decline in service of product A of about 37% from day 868 to day 1235.

The impact on product E is negligible in both markets, as product demand gradually declines because the product is being phased out of use (Figure 8).

5.2. Resiliency Strategies

Considering the disruption impacts observed above, a set of mitigating measures was tested. As previously detailed, these measures are based on building up reserve inventory, and four stock levels were considered for simulation: 10%, 20%, 40%, and 60% of additional inventory.

The main goal is, on one hand, to understand how these strategies enhance SC resiliency by restraining the disruption effects, and, on the other hand, to assess how they impact the sustainability performance of the SC.

The results obtained are presented in Figures 14 and 15, in which the service levels for the overall SC (Figure 14) and for the North and South American markets (Figure 15) are depicted over time, for each stock level considered.

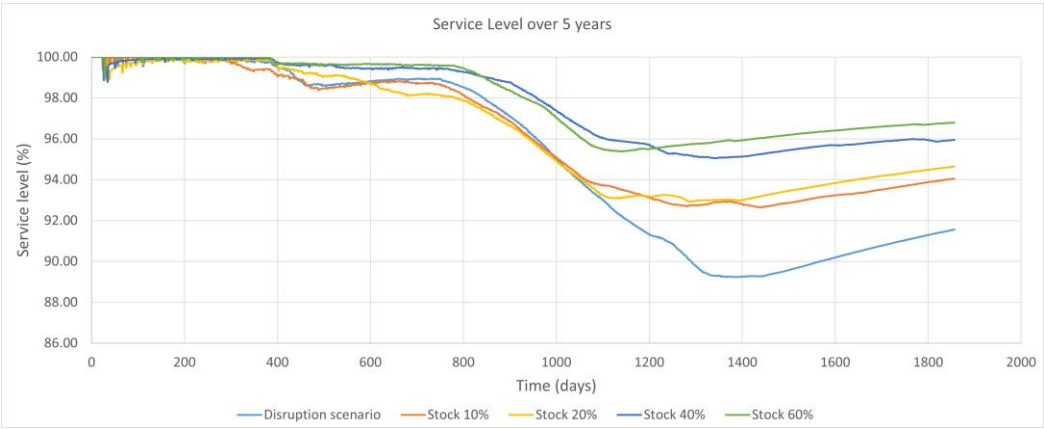
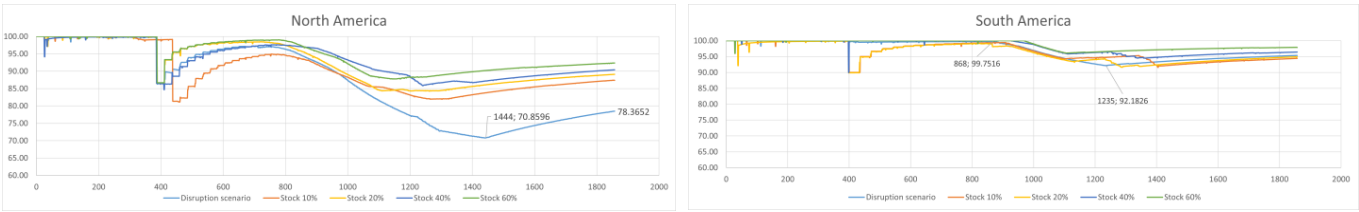


Figure 14. Service-level time for the disruption scenario with no mitigation measure (lighter blue), and with safety stocks of 10% (orange), 20% (yellow), 40% (darker blue), and 60% (green).



(**a**) (**b**)

Figure 15. Service-level time for the disruption scenario with no mitigation measure (lighter blue), and with safety stocks of 10% (orange), 20% (yellow), 40% (darker blue), and 60% (green). (**a**) North American markets; (**b**) South American markets.

Moreover, the most relevant resilience-related KPIs regarding the overall supply chain performance are summarized in Table 1.

Table 1. Resilience-related KPIs considering the overall SC.

Scenario	t_d (Days)	t_r (Days)	DSD (Days)	SL(t_d) (%)	SL(t_r) (%)	Service Loss (%)
Disruption scenario	770	1444	674	98.78	89.28	9.50
Stock 10%	771	1437	665	98.70	92.64	6.05
Stock 20%	772	1396	624	98.09	92.99	5.09
Stock 40%	777	1346	569	99.38	95.07	4.32
Stock 60%	781	1146	365	99.59	95.40	4.19

From these results, it is possible to draw some valuable insights regarding the supply chain performance.

First, with an increase in inventory, the impact on the service level of introducing product C in the market decreases. This was expected as facilities started building higher inventories, better cushioning the sudden rise in demand. Consequently, there is an increase in service levels at the beginning of the disruption state (SL(t_d)).

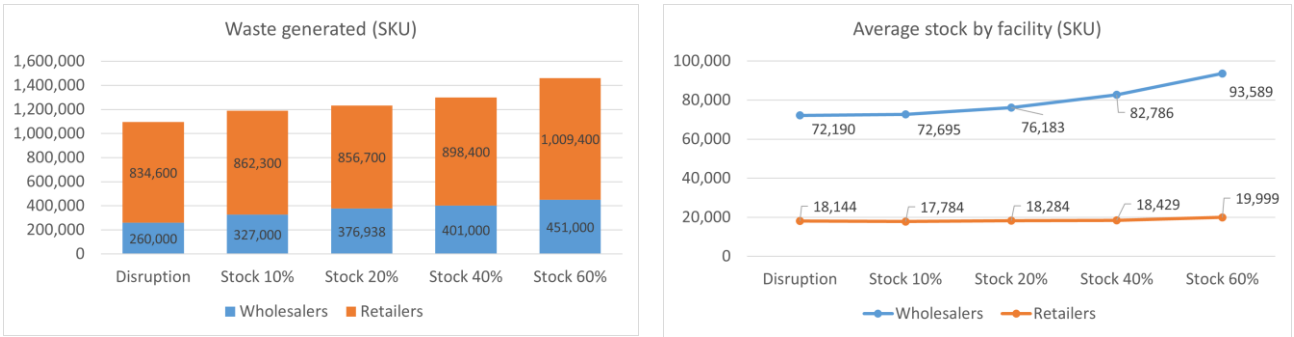
Second, increasingly higher stock values also decrease the duration of the disruption state, anticipating the start of recovery (t_r). This anticipation also translates into decreased service loss. On the other hand, the start of the disruption state (t_d) is not significantly affected by the stock increase. For instance, increasing the safety stock to 60% pushes the beginning of the disruption state by 11 days, decreases its duration by 309 days, and decreases service loss from 9.5% to 4.2% in the overall SC.

Finally, a minor increase in the safety stock of 10% is enough to significantly improve the SC performance, bringing service loss to two-thirds of its value in the disruption scenario (safety stock of 5%).

From the analysis of Figure 15, the conclusions are similar. Furthermore, it is also possible to see that the impact of increasing inventory is significantly higher in North America than in South America. This is expected as the South American market only depends on two products from the North American secondary manufacturing facility.

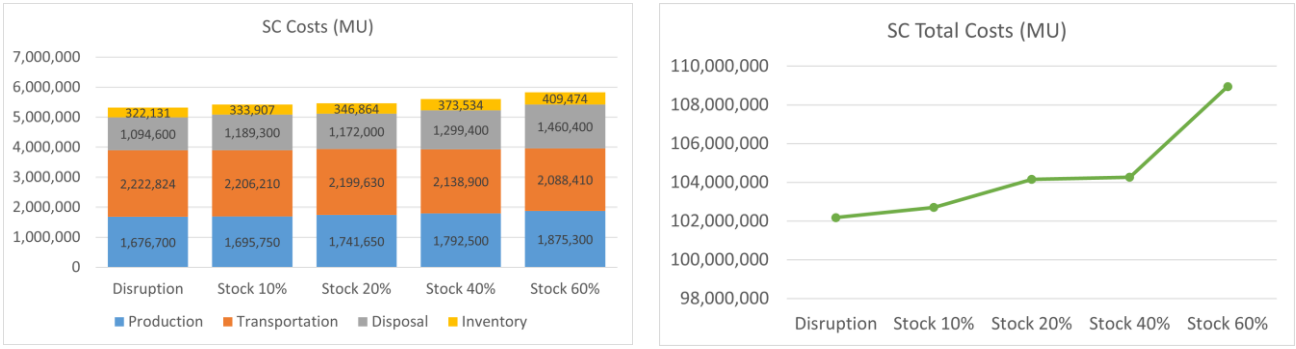
We can say that the supply chain is more resilient under these mitigating measures, as the deployment of a reserve safety stock decreases the impact of the disruptive event on the supply chain service loss, as well as on the time to start to recover.

This improvement in resilience, however, comes at the expense of increasing waste generation and total SC costs. Figures 16 and 17 present the total waste generation (Figure 16) and cost (Figure 17) for each scenario and mitigation measure.



(**a**) (**b**)

Figure 16. (**a**) Waste generated by wholesalers and retailers, for each of the mitigation scenarios; (**b**) average stock at each retailer and wholesaler facility, for each of the mitigation scenarios.



(**a**) (**b**)

Figure 17. Overall supply chain costs at the end of the 5-year horizon, for each scenario: (**a**) in terms of manufacturing costs, transportation costs, disposal costs, and inventory holding costs; (**b**) total costs of the entire supply chain.

As the safety stock increases, the available inventory at each facility also increases (Figure 16b), putting more products at risk of being unused and wasted. Additionally, higher inventory levels yield higher production costs and holding costs, and even higher disposal costs due to the higher levels of waste generated, as highlighted in Figure 16a.

On the other hand, transportation costs decrease, as higher inventory values cushion the slight variations in demand, avoiding the need for small inventory orders (Figure 17a). Nevertheless, this decrease does not compensate for the other costs, resulting in an overall increase in SC costs with the increase in safety stock levels (Figure 17b).

When compared to the disruption scenario, increasing safety stock to 60% (the most risk-averse measure) results in more than 365,800 SKUs of waste (+33%) and 6.76 MMU of additional SC costs (+7%). It should be noted that these costs correspond to the entire supply chain operation.

As expected, increasing inventory levels make the SC more resilient, but also more wasteful, and less profitable, i.e., less sustainable. In that sense, finding the right balance between the level of additional inventory and the increased costs and waste generated can in fact be viewed as a multicriteria decision problem. Therefore, a simple, preliminary multicriteria analysis considering the service loss, the duration of the disruptive state, waste generated, and total SC costs as the main criteria was performed (Table 2).

Table 2. Supply chain performance indicators.

Experimentation Scenario	Service Loss (%)	DSD (Days)	Waste (SKU)	Total Costs (MMU)
Disruption	9.50	674	1.09	102.1
Stock 10%	6.05	665	1.19	102.7
Stock 20%	5.09	624	1.23	104.2
Stock 40%	4.32	569	1.30	104.3
Stock 60%	4.19	365	1.46	108.9

After data normalization to ensure a fair comparison and accurate evaluation of the performance metrics, each scenario was evaluated considering all criteria equally relevant (i.e., equally weighted). The results of these analyses are presented in Table 3 in which the best compromise is obtained for the scenario implementing 40% safety stock. Under these assumptions, a 40% level of reserve inventory will be considered as the resilient strategy to be adopted in the next step of the proposed simulation-based decision-support framework (Figure 2). However, it should be noted that a more comprehensive sensitivity analysis needs to be performed, in particular, regarding what concerns the criteria weights.

Table 3. Normalization of performance indicators and multi-criteria analysis.

Experimentation Scenario	Service Loss	DSD	Waste	Total Costs	Performance
Disruption	0	0	1	1	0.5
Stock 10%	0.65	0.03	0.74	0.92	0.59
Stock 20%	0.83	0.16	0.62	0.71	0.58
Stock 40%	0.98	0.34	0.44	0.69	0.61
Stock 60%	1	1	0	0	0.5

5.3. Sustainability Strategies

Considering the selected resilience-driven strategy of an additional 40% inventory level, and the associated impact on economic and environmental metrics, a new SC design is investigated based on a donation scheme for the unused inventory.

Regarding the service level (see Figure 18 and Table 4), the implementation of the donations scheme yields results that are similar to those obtained with the scenario where the safety stock is 40% of the monthly incoming demand. This result is natural, as the donations scheme was implemented with the 40% safety stock scenario as a baseline and does not interfere with service delivery activities in the traditional markets.

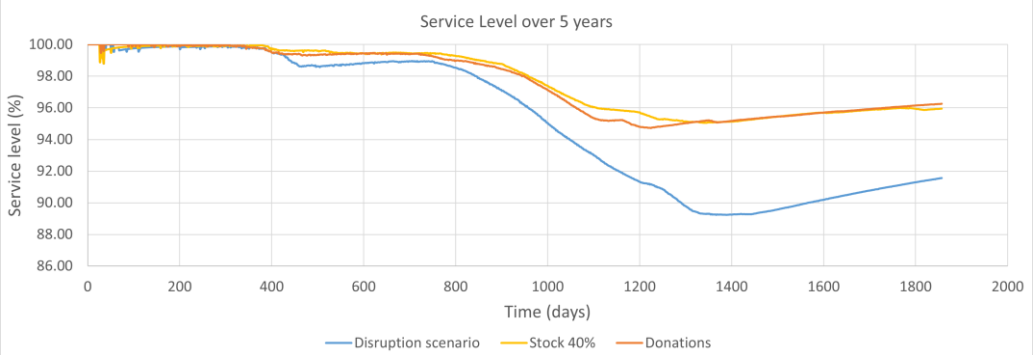


Figure 18. Service-level time for the disruption scenario (blue), with a safety stock of 40% (yellow), and for the scenario with the implementation of the donations architecture (orange).

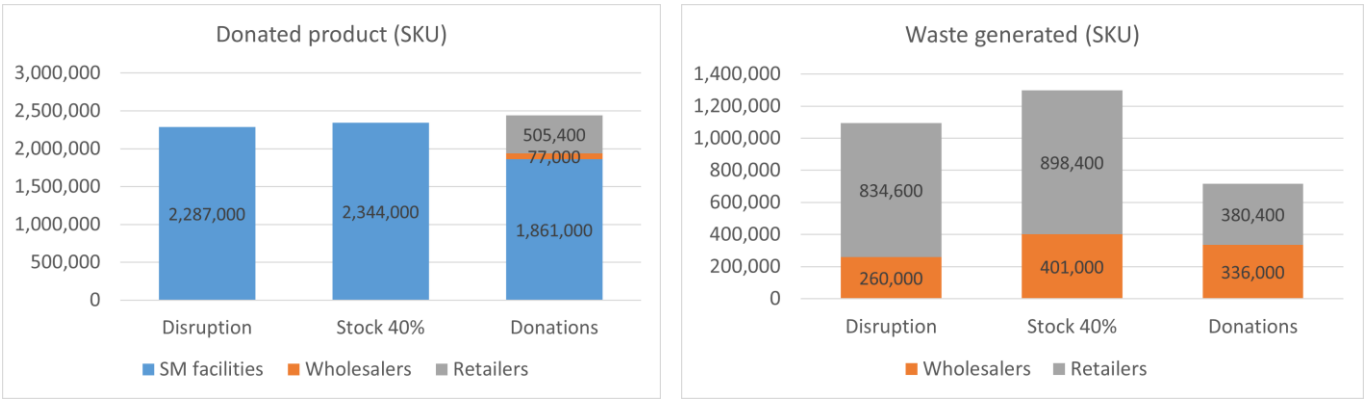
Table 4. Service levels related to underserved markets, measured at the end of the simulation.

Experimentation Scenario	Service Level					
	Africa	Asia	North America	South America	Europe	Overall
Disruption scenario	4.96%	23.69%	77.60%	8.63%	55.23%	19.66%
Stock 40%	6.07%	23.94%	80.51%	9.59%	55.77%	20.43%
Donations	11.67%	24.73%	82.78%	11.72%	57.81%	21.78%

However, a more significant impact can be observed when looking at the demand satisfaction of the underserved markets (see Table 4). The supply of additional 99,400 SKUs resulted in an approximately 2% increase in overall service level.

The enhanced service level observed in underserved markets can be attributed to an increase in donations (see Figure 19a) due to the donation scheme that has been implemented. Under this scheme, wholesalers and retailers periodically assess their inventory and identify products that have been in stock for a long period and are approaching their marketable limit. These items are subsequently donated, thus generating a "reverse flow", from the wholesalers and retailers to the secondary manufacturers. Because of this scheme, secondary manufacturers can reduce their production for donation purposes by offsetting

their monthly donation percentage with received donated products. Despite this decrease, secondary manufacturers remain the primary contributors of inventory to underserved markets, accounting for 76% of the donated products. Another expected observation is that retailers donate more products than wholesalers due to their position further down the supply chain, where they are more likely to encounter items at a more advanced stage of their life cycle.



(**a**) (**b**)

Figure 19. Supply chain sustainability metrics: (**a**) pharmaceutics donated (in SKU); (**b**) waste generated in the supply chain (in SKU).

In addition to the aforementioned benefits, the newly implemented donation scheme has resulted in a reduction in waste to approximately 48% of its value in the 40% safety stock scenario (Figure 19b), which represents a positive outcome regarding the environmental impact of these redundant measures.

Finally, Figure 20 depicts the detailed costs of the donation scenario, compared to the base case and the selected mitigation strategy. First, disposal costs have dropped as waste generation has decreased. Second, there is a slight decrease in production costs as a result of the minor decrease in production by secondary manufacturing facilities for the donation component. Finally, there is an increase in transportation costs as, in this new scenario, a new flow of material is considered, from the retailer to the underserved market facilities. Since these products are at risk of expiration, they can only be used to fulfill an immediate need, and therefore transportation is considered a priority with no possibility of load consolidation.

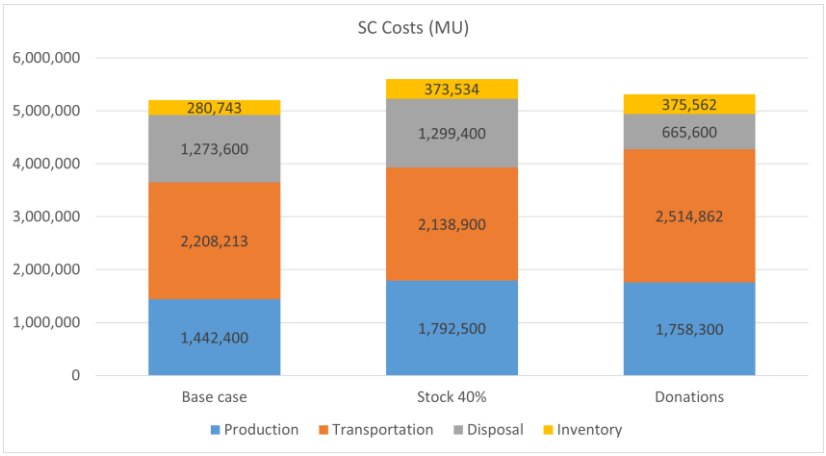


Figure 20. Supply chain costs.

In general, the proposed approach successfully shows that it is possible to find solutions with a sound balance between the levels of resiliency and sustainability. In particular, the final solution not only adequately addresses the environmental issues, but also the critical and poorly explored social dimension, by providing a larger coverage of medicine access.

6. Conclusions and Future Research

The pharmaceutical industry is highly dependent on the resilience of its supply chains, which can be impacted by a wide range of factors such as natural disasters, geopolitical problems, and pandemics.

To address these challenges, a decision-support tool was developed based on a hybrid-simulation framework that combines Agent-Based Simulation (ABS) and Discrete-Event Simulation (DES) models. This tool supports decision makers in evaluating the impact of different strategies on complex pharmaceutical supply chains, operating under various scenarios, and in the design and planning of such chains, making them more resilient and sustainable.

The study also identifies critical variables and trade-offs between resiliency and sustainability, and proposes an architecture for large-scale multi-objective simulation models that can be used in supply chain design.

The obtained results show that this methodology can help in identifying synergies between resiliency and sustainability, and finding the right balance between these two dimensions. The final solution, combining a redundant inventory strategy with a donation scheme, proves to be a good solution to achieve the required levels of resiliency without compromising the economic and environmental dimensions. Moreover, by anticipating waste generation through the redirection of products to markets in need, a step forward toward a more socially responsible use of medicines has been given.

However, one weakness of the used methodology is that the simulation models allow for the evaluation of supply chain performance, but they are quite limited in generating improvement actions. While simulation provides valuable insights into the potential outcomes of various supply chain decisions, it does not necessarily offer a clear path for optimization. The implementation of effective solutions obtained with simulation requires additional forms of analysis. Therefore, while simulation models are a valuable tool for evaluating supply chain performance, for supply chain optimization, they should be viewed as a complementary tool to be used in conjunction with other approaches.

Along these lines, future work is foreseen to enhance the developed simulation model, by integrating it with an optimization model. That model could be used to generate a supply chain design, to be then tested with the simulation model and assessed in terms of resilience and sustainability. By combining simulation and optimization models, supply chain designers can identify the optimal set of decisions that maximize supply chain performance while accounting for uncertainties and risks.

Author Contributions: Conceptualization, C.M.M. and A.C.S.; methodology, A.C.S.; validation, A.C.S., C.M.M. and J.P.d.S.; data curation, A.C.S.; writing—original draft preparation, A.C.S. and C.M.M.; writing—review and editing, C.M.M. and J.P.d.S.; supervision, C.M.M. and J.P.d.S. All authors have read and agreed to the published version of the manuscript.

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

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study is available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Hakovirta, M.; Denuwara, N. How COVID-19 redefines the concept of sustainability. *Sustainability* **2020**, *12*, 3727. [CrossRef]
2. Renn, O. The Call for Sustainable and Resilient Policies in the COVID-19 Crisis: How Can They Be Interpreted and Implemented? *Sustainability* **2020**, *12*, 6466. [CrossRef]
3. Fahimnia, B.; Jabbarzadeh, A. Marrying supply chain sustainability and resilience: A match made in heaven. *Transp. Res. Part E Logist. Transp. Rev.* **2016**, *91*, 306–324. [CrossRef]
4. Ribeiro, J.P.; Barbosa-Povoa, A. Supply Chain Resilience: Definitions and quantitative modelling approaches—A literature review. *Comput. Ind. Eng.* **2018**, *115*, 109–122. [CrossRef]
5. Negri, M.; Cagno, E.; Colicchia, C.; Sarkis, J. Integrating sustainability and resilience in the supply chain: A systematic literature review and a research agenda. *Bus. Strategy Environ.* **2021**, *30*, 2858–2886. [CrossRef]
6. Fahimnia, B.; Sarkis, J.; Talluri, S. Design and management of sustainable and resilient supply chains. *IEEE Trans. Eng. Manag.* **2019**, *66*, 2–7. [CrossRef]
7. Ivanov, D. Revealing interfaces of supply chain resilience and sustainability: A simulation study. *Int. J. Prod. Res.* **2018**, *56*, 3507–3523. [CrossRef]
8. Zavala-Alcívar, A.; Verdecho, M.-J.; Alfaro-Saiz, J.-J. A conceptual framework to manage resilience and increase sustainability in the supply chain. *Sustainability* **2020**, *12*, 6300. [CrossRef]
9. Lücker, F.; Seifert, R.W. Building up resilience in a pharmaceutical supply chain through inventory, dual sourcing and agility capacity. *Omega* **2017**, *73*, 114–124. [CrossRef]
10. Marques, C.M.; Moniz, S.; de Sousa, J.P.; Barbosa-Povoa, A.P.; Reklaitis, G. Decision-support challenges in the chemical-pharmaceutical industry: Findings and future research directions. *Comput. Chem. Eng.* **2020**, *134*, 106672. [CrossRef]
11. Silva, A.C.; de Sousa, J.P.; Marques, C.M. Supply Chain Resiliency in the Pharmaceutical Industry–a Simulation-Based Approach. In Proceedings of the 5th European International Conference on Industrial Engineering and Operations Management, Rome, Italy, 26–28 July 2022. [CrossRef]
12. Moreno-Camacho, C.A.; Montoya-Torres, J.R.; Jaegler, A.; Gondran, N. Sustainability metrics for real case applications of the supply chain network design problem: A systematic literature review. *J. Clean. Prod.* **2019**, *231*, 600–618. [CrossRef]
13. Peron, M.; Sgarbossa, F.; Ivanov, D.; Dolgui, A. Impact of Additive Manufacturing on Supply Chain Resilience during COVID-19 Pandemic. In *Supply Network Dynamics and Control*; Springer: Cham, Switzerland, 2022; pp. 121–146.
14. Hong, J.; Zhang, Y.; Ding, M. Sustainable supply chain management practices, supply chain dynamic capabilities, and enterprise performance. *J. Clean. Prod.* **2018**, *172*, 3508–3519. [CrossRef]
15. Seuring, S.; Müller, M. From a literature review to a conceptual framework for sustainable supply chain management. *J. Clean. Prod.* **2008**, *16*, 1699–1710. [CrossRef]
16. Shashi; Centobelli, P.; Cerchione, R.; Ertz, M. Managing supply chain resilience to pursue business and environmental strategies. *Bus. Strategy Environ.* **2020**, *29*, 1215–1246. [CrossRef]
17. Kayani, S.A.; Warsi, S.S.; Liaqait, R.A. A Smart Decision Support Framework for Sustainable and Resilient Supplier Selection and Order Allocation in the Pharmaceutical Industry. *Sustainability* **2023**, *15*, 5962. [CrossRef]
18. Sirisomboonsuk, P.; Burns, J. Sustainability in Supply Chains through Rapid Capacity Increases and Minimized Disruptions. *Sustainability* **2023**, *15*, 5629. [CrossRef]
19. Zhu, X.; Wu, Y.J. How Does Supply Chain Resilience Affect Supply Chain Performance? The Mediating Effect of Sustainability. *Sustainability* **2022**, *14*, 14626. [CrossRef]
20. Ivanov, D.; Pavlov, A.; Pavlov, D.; Sokolov, B. Minimization of disruption-related return flows in the supply chain. *Int. J. Prod. Econ.* **2017**, *183*, 503–513. [CrossRef]
21. Jabbarzadeh, A.; Fahimnia, B.; Sabouhi, F. Resilient and sustainable supply chain design: Sustainability analysis under disruption risks. *Int. J. Prod. Res.* **2018**, *56*, 5945–5968. [CrossRef]
22. Ramezankhani, M.J.; Torabi, S.A.; Vahidi, F. Supply chain performance measurement and evaluation: A mixed sustainability and resilience approach. *Comput. Ind. Eng.* **2018**, *126*, 531–548. [CrossRef]
23. Asghari, M.; Abrishami, S.J.; Mahdavi, F. Reverse logistics network design with incentive-dependent return. *Ind. Eng. Manag. Syst.* **2014**, *13*, 383–397. [CrossRef]
24. Duminy, L.; Grosser, S.N. Resilience as basis for sustainability: Shortages in production supply chains for essential consumer goods. In *Innovative Solutions for Sustainable Supply Chains*; Springer: Cham, Switzerland, 2018; pp. 223–262.
25. Roostaie, S.; Nawari, N.; Kibert, C. Integrated sustainability and resilience assessment framework: From theory to practice. *J. Clean. Prod.* **2019**, *232*, 1158–1166. [CrossRef]
26. Owida, A.; Galal, N.M.; Elrafie, A. Decision-making framework for a resilient sustainable production system during COVID-19: An evidence-based research. *Comput. Ind. Eng.* **2022**, *164*, 107905. [CrossRef] [PubMed]
27. Terzi, S.; Cavalieri, S. Simulation in the supply chain context: A survey. *Comput. Ind.* **2004**, *53*, 3–16. [CrossRef]
28. Moosavi, J.; Hosseini, S. Simulation-based assessment of supply chain resilience with consideration of recovery strategies in the COVID-19 pandemic context. *Comput. Ind. Eng.* **2021**, *160*, 107593. [CrossRef] [PubMed]
29. Hoffa-Dabrowska, P.; Grzybowska, K. Simulation modeling of the sustainable supply chain. *Sustainability* **2020**, *12*, 6007. [CrossRef]

30. Sousa, R.T.; Liu, S.; Papageorgiou, L.G.; Shah, N. Global supply chain planning for pharmaceuticals. *Chem. Eng. Res. Des.* **2011**, *89*, 2396–2409. [CrossRef]
31. Hansen, K.R.N.; Grunow, M. Modelling ramp-up curves to reflect learning: Improving capacity planning in secondary pharmaceutical production. *Int. J. Prod. Res.* **2015**, *53*, 5399–5417. [CrossRef]
32. Bradley, M.; Taylor, R.; Jacobson, J.; Guex, M.; Hopkins, A.; Jensen, J.; Leonard, L.; Waltz, J.; Kuykens, L.; Sow, P.S.; et al. Medicine donation programmes supporting the global drive to end the burden of neglected tropical diseases. *Trans. R. Soc. Trop. Med. Hyg.* **2021**, *115*, 136–144. [CrossRef]
33. Jones, O.H.; Voulvoulis, N.; Lester, J.N. Human pharmaceuticals in wastewater treatment processes. *Crit. Rev. Environ. Sci. Technol.* **2005**, *35*, 401–427. [CrossRef]
34. Kümmerer, K. Pharmaceuticals in the environment. *Annu. Rev. Environ. Resour.* **2010**, *35*, 57–75. [CrossRef]
35. Okeke, E.S.; Ezeorba, T.P.C.; Okoye, C.O.; Chen, Y.; Mao, G.; Feng, W.; Wu, X. Environmental and health impact of unrecovered API from pharmaceutical manufacturing wastes: A review of contemporary treatment, recycling and management strategies. *Sustain. Chem. Pharm.* **2022**, *30*, 100865. [CrossRef]
36. Romdhani, S.; Nouaouri, I.; Tounsi, J.; Gattoufi, S.; Allaoui, H. Two-echelon Inventory Management for Sustainable Pharmaceutical Supply Chain through Waste Reduction. *IFAC-PapersOnLine* **2022**, *55*, 1380–1385. [CrossRef]
37. Henry, D.; Emmanuel Ramirez-Marquez, J. Generic metrics and quantitative approaches for system resilience as a function of time. *Reliab. Eng. Syst. Saf.* **2012**, *99*, 114–122. [CrossRef]