

FACULDADE DE ENGENHARIA DA UNIVERSIDADE DO PORTO

Dynamic Capacity Management in Pharmaceutical Supply Chains

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Resumo

A recente pandemia de COVID-19 destacou o papel fundamental da indústria farmacêutica e das operações da sua cadeia de abastecimento no bem estar da sociedade. Como em muitos outros setores, esta pandemia expôs importantes vulnerabilidades e fraquezas em toda a rede de distribuição farmacêutica, chamando a atenção para a importância de estratégias de resiliência, flexibilidade e sustentabilidade.

Um dos principais desafios em relação à resiliência é a capacidade de entender e antecipar o comportamento da cadeia de abastecimento sob incerteza e gerir dinamicamente a sua capacidade. Para enfrentar este desafio, este trabalho de dissertação propõe uma abordagem baseada em simulação com um duplo objetivo: i) compreender a dinâmica da cadeia de abastecimento farmacêutica, a fim de detetar vulnerabilidades e antecipar a propagação do risco pela rede; e ii) apoiar a tomada de decisão no sentido de uma maior resiliência e flexibilidade, através de decisões estratégicas de gestão de capacidade.

Neste contexto, as principais contribuições deste trabalho baseiam-se na integração e exploração de diferentes paradigmas de simulação, a fim de compreender as relações causa-efeito em sistemas complexos, sob diversos cenários de disrupção. Dessa forma, os riscos de disrupção e sua propagação são identificados em toda a rede da cadeia de abastecimento, fornecendo *insights* para o desenvolvimento proativo e atempado de planos de contingência e mitigação de riscos.

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 dissertation 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.

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Ana Carolina Tavares da Silva

*“Let us choose for ourselves our path in life,
and let us try to strew that path with flowers”*

Emilie du Chatelet

Contents

1	Introduction	1
1.1	Contextualization	1
1.2	Motivation	2
1.3	Objectives	3
1.4	Methodological approach	3
1.5	Dissertation structure	4
2	Bibliographical Review	7
2.1	Supply Chain Management	7
2.1.1	Supply chain concepts	8
2.1.2	Main challenges in supply chain management	10
2.1.3	Performance measures in SCM	13
2.1.4	Decision support tools in SCM	14
2.2	The Pharmaceutical Industry	15
2.2.1	Overview on the pharmaceutical sector	15
2.2.2	Pharmaceutical Supply Chain	15
2.2.3	Main gaps in current research and opportunities for improvement	18
2.3	Simulation	20
2.3.1	Simulation as tool for decision support systems	20
2.3.2	Simulation approaches	22
2.3.3	Case studies implementing simulation	22
3	Problem Definition and Methodological Approach	25
3.1	Problem Formulation	25
3.2	Problem Conceptualization	26
3.3	Simulation model	30
3.3.1	System Dynamics approach for overall SC modelling	32
3.3.2	Agent-Based approach for "comprehensive" SC modelling	33
3.3.3	SC configuration and deployment	44
3.3.4	SC performance evaluation	44
4	Base Case – Instance, Results & Validation	47
4.1	Base Case instance	47
4.2	Simulation results	49
4.3	Validation of the simulation model	52
4.4	Methodological framework for simulation experiments	52

5	Simulation Experiments	55
5.1	Disruption scenario 1: <i>Excess demand</i>	55
5.1.1	Simulation Results	56
5.1.2	Mitigation measure 1: <i>Increase safety stock</i>	58
5.1.3	Disruption scenario 1 assessment	60
5.2	Disruption scenario 2: <i>Reduced production capacity</i>	61
5.2.1	Simulation Results	61
5.2.2	Mitigation measure 1: <i>Increase safety stock</i>	64
5.2.3	Mitigation measure 2: <i>Outsource product</i>	65
5.2.4	Mitigation measure 3: <i>Increase production capacity</i>	68
5.2.5	Mitigation measure 4: <i>Redirect orders</i>	69
5.2.6	Disruption scenario 2 assessment	72
6	Conclusions and future work	73
6.1	Conclusions	73
6.2	Future work	74
	References	77
A	Agent-Based Approach simulation parameters	83
A.1	<i>API_productionLine</i> agent	83
A.1.1	Stocks	83
A.1.2	Flows	83
A.1.3	Variables	84
A.1.4	Parameters	84
A.2	<i>FP_productionLine</i> agent	85
A.2.1	Stocks	85
A.2.2	Flows	85
A.2.3	Variables	85
A.2.4	Parameters	86
B	Base Case Configuration Data	87
B.1	Primary Manufacturers	87
B.2	Secondary Manufacturers	87
B.3	Wholesalers	88
B.4	Retailers	89
C	Publications	91
C.1	5 th European Conference on Industrial Engineering and Operations Management	91

List of Figures

1.1	Methodology used in the development and testing of the simulation model	4
2.1	Decision levels in Supply Chain Management (adapted from [6])	9
2.2	Intersection of the development and supply chains (adapted from [31])	10
2.3	Three pillars of sustainability (based on [32])	13
2.4	Product life-cycle (adapted from [39])	16
2.5	Pharmaceutical Supply Chain (adapted from [39])	17
2.6	Seven step approach to build a valid simulation model, as presented by Law (2019) [33]	21
3.1	Pharmaceutical Supply Chain	26
3.2	Overview of the simulation entities	31
3.3	Simulation framework	31
3.4	System Dynamics Modelling	32
3.5	Modelling of a primary manufacturing facility (<i>API_manufacturer</i>)	34
3.6	Detail of the order management modelling of a primary manufacturer (<i>API_manufacturer</i>)	35
3.7	Modelling of the <i>API_productionLine</i> agent	36
3.8	Modelling of the <i>FP_productionLine</i> agent	39
3.9	Modelling of the <i>Wholesaler</i> agent	41
3.10	Modelling of the <i>Retailer</i> agent	42
3.11	Example of an Excel Configuration file	44
3.12	Statistics tab of the simulation GUI with the KPIs	45
3.13	Additional performance metric for service level analysis	46
4.1	Base-case Simulation Model - Facilities locations	47
4.2	Pharmaceutical products demand trajectory, adapted from [9]	48
4.3	Average lead time of SC facilities, by continent	51
4.4	Amount of backorders in each echelon (<i>PM_Backorder</i> , <i>SM_Backorder</i> and <i>W_Backorder</i>) and the amount of lost sales per day in retailers (<i>R_OrderLostRate</i>)	51
4.5	Methodological framework for simulation experiments	53
5.1	Pharmaceutical products demand trajectory for disruption scenario 1	55
5.2	Amount of backorders in each echelon (<i>PM_Backorder</i> , <i>SM_Backorder</i> and <i>W_Backorder</i>) and the amount of lost sales per day in retailers (<i>R_OrderLostRate</i>) for disruptive scenario 1	57
5.3	Backorders of product A at the <i>Wholesaler</i> level, for disruptive scenario 1	57
5.4	Backorders of product A at the <i>Retailer</i> level for disruptive scenario 1	58

5.5	Amount of backorders in each echelon (<i>PM_Backorder</i> , <i>SM_Backorder</i> and <i>W_Backorder</i>) and the amount of lost sales per day in retailers (<i>R_OrderLostRate</i>) for mitigation measure applied to disruptive scenario 1	59
5.6	Backorders quantities in each echelon (<i>PM_Backorder</i> , <i>SM_Backorder</i> and <i>W_Backorder</i>) and the amount of lost sales per day in retailers (<i>R_OrderLostRate</i>), for disruption scenario 2	62
5.7	Inventory level over time of European secondary manufacturer for the case of disruption scenario 2	62
5.8	Mitigation measures applied to disruptive scenario 2	63
5.9	Backorders quantities in each echelon (<i>PM_Backorder</i> , <i>SM_Backorder</i> and <i>W_Backorder</i>) and the amount of lost sales per day in retailers (<i>R_OrderLostRate</i>), for mitigation measure 1 applied to disruption scenario 2	65
5.10	Backorders quantities in each echelon (<i>PM_Backorder</i> , <i>SM_Backorder</i> and <i>W_Backorder</i>) and the amount of lost sales per day in retailers (<i>R_OrderLostRate</i>), for mitigation measure 2 applied to disruption scenario 2	67
5.11	Inventory level over time of European secondary manufacturer for the case of disruption scenario 2, along with the amount of backordered product	67
5.12	Inventory level over time of European secondary manufacturer for the case of disruption scenario 3, along with the amount of backordered product	69
5.13	Backorders quantities in each echelon (<i>PM_Backorder</i> , <i>SM_Backorder</i> and <i>W_Backorder</i>) and the amount of lost sales per day in retailers (<i>R_OrderLostRate</i>), for mitigation measure 4 applied to disruption scenario 2	71
5.14	Snapshot of database containing the register of <i>Orders</i> placed during the 5 year simulation period, for instance of mitigation measure 4 applied to disruption scenario 2	71
6.1	Methodological framework for broker implementation	75

List of Tables

3.1	Bill-of-materials for the products considered in the simulation experiments	40
3.2	Continental factor used for demands and price calculations	43
4.1	Performance metrics for the base-case scenario over the 5 years planning horizon	49
4.2	Service levels of retailers for the base-case scenario over the 5 years planning horizon	50
5.1	Performance metrics for disruptive scenario 1, over the 5 years planning horizon .	56
5.2	Service levels of <i>Retailers</i> for disruptive scenario 1, over the 5 years planning horizon	58
5.3	Performance metrics for the mitigation measure applied to disruption scenario 1, over the 5 years planning horizon	59
5.4	Service levels of <i>Retailers</i> for mitigation measure applied to disruptive scenario 1, over the 5 years planning horizon	60
5.5	Comparison of performance metrics for disruption scenario 1	60
5.6	Performance metrics for disruption scenario 2 over the 5 years planning horizon.	61
5.7	Performance metrics for mitigation measure 1 applied to disruption scenario 2, over the 5 years planning horizon	64
5.8	Performance metrics for mitigation measure 2 applied to disruption scenario 2, over the 5 years planning horizon	66
5.9	Performance metrics for mitigation measure 3 applied to disruption scenario 2, over the 5 years planning horizon	68
5.10	Performance metrics for mitigation measure 4 applied to disruption scenario 2, over the 5 years planning horizon	70
5.11	Comparison of performance metrics for disruption scenario 2	72
A.1	Description of all stocks in the API production line agent	83
A.2	Description of all flows in the API production line agent	83
A.3	Description of all variables in the API production line agent	84
A.4	Description of all parameters in the API production line agent	84
A.5	Description of all stocks in the FP production line agent	85
A.6	Description of all flows in the FP production line agent	85
A.7	Description of all variables in the FP production line agent	85
A.8	Description of all parameters in the FP production line agent	86
B.1	Configuration data for <i>API manufacturers</i> (part 1)	87
B.2	Configuration data for <i>API manufacturers</i> (part 2)	87
B.3	Configuration data for <i>API manufacturers</i> (part 3)	87
B.4	Configuration data for <i>FP manufacturers</i> (part 1)	87
B.5	Configuration data for <i>FP manufacturers</i> (part 2)	88

B.6	Configuration data for <i>FP manufacturers</i> (part 3)	88
B.7	Configuration data for <i>Wholesalers</i> (part 1)	88
B.8	Configuration data for <i>Wholesalers</i> (part 2)	88
B.9	Configuration data for <i>Retailers</i> (part 1)	89
B.10	Configuration data for <i>Retailers</i> (part 2)	89

Abbreviations and Symbols

ABM	Agent Based Modelling
API	Active Pharmaceutical Ingredient
BOM	Bill-Of-Materials
CSCMP	Council of Supply Chain Management Professionals
DPF	Drug Product Factory
DES	Discrete Event Simulation
FP	Final Product
GUI	Graphical User Interface
IT	Information Technology
KPI	Key Performance Indicator
MMU	Millions of Monetary Units
NDA	New Drug Application
OTC	Over-The-Counter
PM	Primary Manufacturing
PSC	Pharmaceutical Supply Chain
PSE	Process Systems Engineering
R&D	Research & Development
SC	Supply Chain
SD	System Dynamics
SKU	Stockkeeping Units
SM	Secondary Manufacturing

Chapter 1

Introduction

This introductory chapter aims to present the dissertation theme “Dynamic Capacity Management in Pharmaceutical Supply-Chains”. In section 1.1 a brief contextualization of the pharmaceutical industry and its supply chain is given. In section 1.2 the motivations that supported the proposition of the theme are highlighted. Then, in section 1.3, the dissertation’s proposed objectives are described and in section 1.4 it is detailed the methodological approach adopted to fulfill the proposed objectives. Finally, in section 1.5 it is described the structure of the dissertation document.

1.1 Contextualization

The pharmaceutical industry plays a key role in the health care structure of every country by providing medicines and vaccines that directly affect the quality of life of the population. In addition to bringing direct benefits to the population, medicines also help to significantly reduce the total healthcare costs, by reducing the need for expensive surgery and/or long-term hospital care [39].

Along with its direct importance in the well-being of the population, the pharmaceutical industry plays a key role in the economy of developed countries, being one of the top-performing high-technology sectors [14].

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 management of pharmaceutical supply chains greatly increase and more pressure is put on the pharmaceutical industry to become more cost-efficient and responsive when developing, making, and distributing medical drugs [39].

To address these issues, researchers and practitioners have long believed that improved data utilisation will lead to more efficient decisions. Data-driven techniques may identify changes

automatically and self-adapt models accordingly. As a consequence, facilities and supply chains are more adaptable in terms of flexibility, cost-efficiency, and long-term goals.

In this context, the *FCT FuturePharma* project was established, with the purpose of developing optimization models with practical applications for enhancing the integration of complex choices that occur at many stages of the pharmaceutical supply chain. This research project focuses on the creation of models that take into account previously overlooked features such as adaptability, cost-efficiency, and sustainability, aspects connected to the complexity and uncertainty in this highly regulated sector, as well as new technology advancements that may affect the supply chain.

The main idea of the *FuturePharma* project is to develop an optimization platform for designing a long-term responsive and sustainable pharmaceutical supply chain.

1.2 Motivation

Despite the significant progress to develop various approaches for attaining higher levels of efficiency in the pharmaceutical supply chain, current supply operations have not been significantly updated, making the overall systems inefficient, with very low levels of productivity [39].

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 the main vulnerabilities to disruptions, and refocusing decision-making processes into more resilient and sustainable SC [54]. Supply chain disruptions can be viewed as unexpected events that trigger significant changes in the SC, moving it away from its steady-state condition [55]. 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 [39]. 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 [55].

In addition to the vulnerabilities exposed, rapidly changing markets and growing political factors provided driving forces for change, as the market rapidly shifts away from blockbusters, and moves towards more specialty and personalized drug products [59].

In the context of the *FuturePharma* project described in 1.1, this dissertation aims to build a simulation-based platform to rethink the pharmaceutical supply chain, rendering it more flexible and sustainable, and able to adapt to several uncertainty scenarios.

1.3 Objectives

This work developed in this dissertation intends to address the challenges stated above 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 and under several disruptive scenarios.

1.4 Methodological approach

The main goal of the work developed in this dissertation is to build simulation-based platform, to address the challenges and high-level decision-making in PSC network design and capacity management under disruption risks.

As stated by Law [33], 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 (Figure 1.1) was pursued to address the problem.

First, in order to contextualize the problem and adequately formulate it, a thorough bibliographical review was done.

From this analysis, the problem at hand is described, along with the requirements, constraints and simplifications that lead to a sufficiently realistic and coherent model of a pharmaceutical supply chain.

After a conceptual model was built, the simulation model was designed in order to test the intended PSC.

A base case scenario is then created for model validation. The base case scenario is established by entering SC information into an Excel file, which is then fed into the simulation model, which stores this data in an internal database.

Because there is no direct comparison with real data, simulation model validation takes into account the objectives outlined in this Chapter as well as a critical review of the findings achieved.

Following model validation, disruption scenarios will be constructed, taking bibliographical review information into consideration, and then implemented to the base case instance, validated,

and extensively analysed. Mitigation measures for the disruption scenario will be designed and implemented depending on the outcomes analysis.

A more flexible and robust pharmaceutical distribution network should be produced by experimenting with various capacity management techniques and under various disruptive events.

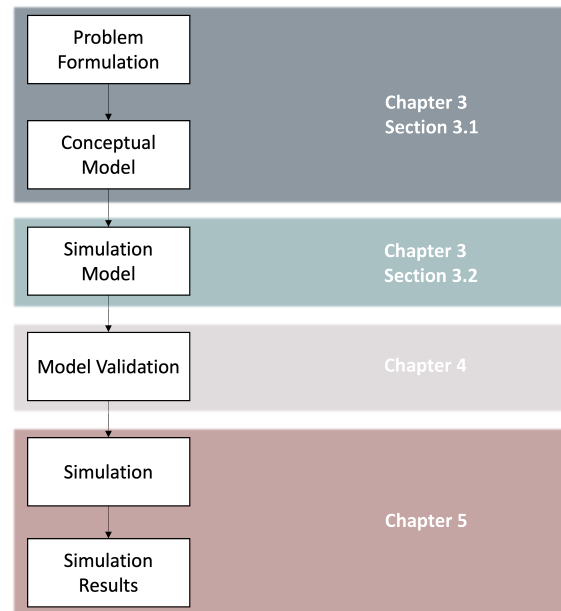


Figure 1.1: Methodology used in the development and testing of the simulation model

1.5 Dissertation structure

This dissertation is divided into six chapters, according to the sequence of work developed throughout the project.

In this first chapter, an introduction to the pharmaceutical industry is made and the objectives that are intended to be achieved with this work and the motivations that led to its realization are presented.

In chapter 2, a bibliographic review is presented on the fundamental themes to obtain the necessary knowledge for the execution of the project of this dissertation. Concepts about supply chains and their management, concepts about the pharmaceutical industry and, in particular, about supply chains in the pharmaceutical industry and the work that has been developed in this area are described. Finally, simulation concepts and the different simulation methods applied in the work developed during the dissertation are discussed.

In chapter 3, the case under study is presented in greater detail, as well as the entire procedure followed for the development of the decision support tool.

Chapter 4 refers to the definition of an instance to evaluate the developed tool, its results and extrapolations.

In chapter 5, the disruptive scenarios to be applied to the base case are presented, as well as the testing of plans created to try to mitigate the negative effects of the disruption. A small critical and comparative assessment of the tested instances is also carried out.

Finally, in Chapter 6, the conclusions of the work developed are presented, as well as the questions on which future research would be interesting.

Chapter 2

Bibliographical Review

This chapter referring to the bibliographical review is a consequence of the research carried out, with the aim of understanding most of the fundamental themes of the dissertation. Considering the objectives to be achieved and pondering all parameters of the context and motivation, the chapter was subdivided into sections.

First, in section 2.1, some concepts on supply chains and supply chain management were presented, as the main topic of this work is related to SC management.

Then, in section 2.2, some background on the pharmaceutical industry is given, as well as some of the particularities of pharmaceutical supply chains and specific gaps and innovations related to this topic.

Finally, section 2.3, presents the main concepts associated with simulation approaches, a literature analysis of some of the current solution methods, as well as some approaches to conduct a good simulation study.

2.1 Supply Chain Management

Industry and academic interest in supply chain management has exploded in recent decades and continues to do so [31]. Multiple factors have been contributing to this over the years.

Many industries realised in the 1990s that they had lowered manufacturing costs as far as they could. These industries recognised the magnitude of savings generated by planning and managing their supply chains more effectively with the implementation of recently discovered manufacturing technologies and strategies, such as just-in-time manufacturing, kanban, lean manufacturing and total quality management [31].

In the late 1990s, the development of information and communication systems led to expectations that many supply chain problems would be solved simply by employing these new technologies and business models. Nowadays, these new technologies opened new channels of communication and enabled a direct-to-consumer business model, which increased the complexity of the

supply chains. Simultaneously, deregulation of the transportation industry has resulted in the development of a variety of transportation modes and lower transportation costs, while significantly increasing the complexity of logistic systems [63].

Finally, offshoring and globalization of manufacturing operations become more common, contributing to an increase in supply chain complexity and risks. This, combined with rising energy costs and an increase in merger and acquisition activity, has prompted many industries to rethink their supply chain management strategies to better utilize existing resources and infrastructure [31].

2.1.1 Supply chain concepts

A supply chain may be defined as an integrated process wherein several business entities (i.e., suppliers, manufacturing centres, warehouses, distribution centres and retailers) work together in an effort to [31, 8]:

1. acquire raw materials,
2. convert these raw materials into specified final products, and
3. deliver these final products to retailers.

Traditionally, this chain is characterized by a forward flow of materials and a backward flow of information [8]. As result, to cut costs and improve service levels, effective supply chain strategies must consider the interactions at the various levels in the supply chain [31].

As defined by the Council of Supply Chain Management Professionals (CSCMP), supply chain management “encompasses the planning and management of all activities involved in sourcing and procurement, conversion, and all logistics management activities. Importantly, it also includes co-ordination and collaboration with channel partners, which can be suppliers, intermediaries, third-party service providers, and customers” [13]. Supply chain management, essentially, blends supply and demand management inside and between industries. Supply Chain Management is an integrating role that is primarily responsible for connecting important business units and business processes inside and between industries to create a coherent and high-performing business model. It encompasses all the aforementioned logistics management tasks, as well as manufacturing operations, and it drives process and activity coordination with and across marketing, sales, product design, finance, and information technology [13].

This definition leads to several observations:

1. Firstly, supply chain management considers every facility that has an influence on cost and plays a part in making the product conform to customer requirements, ranging from suppliers and manufacturing facilities to warehouses and distribution centres to retailers and storefronts [31, 63].

2. Second, the goal of supply chain management is to be efficient and cost-effective across the whole system. Total system-wide expenses, from transportation and distribution to raw material, work-in-process, and finished goods inventories, must be minimized. Thus, the emphasis is on applying a systems approach to supply chain management rather than merely decreasing transportation costs or reducing inventory [31, 63].
3. Finally, because supply chain management is concerned with the efficient integration of suppliers, manufacturers, warehouses, and stores, it encompasses the company's activities at multiple levels, from strategic to tactical to operational [31, 63].

The **strategic** level deals with decisions that have a long-lasting effect on the facility. This includes decisions regarding product design, what to make internally and what to outsource, supplier selection, and strategic partnering as well as decisions on the number, location, and capacity of warehouses and manufacturing plants and the flow of material through the logistics network [24, 31].

The **tactical** level includes decisions that focus on shorter planning cycle decisions. These include purchasing and production decisions, inventory policies, and transportation strategies, including the frequency with which customers are visited [24, 31].

The **operational** level refers to decisions such as demand fulfilment, production and distribution, routing, lead time quotations, scheduling and monitoring tasks that require constant control on the supply chain, being daily or weekly decisions [6, 24, 31].

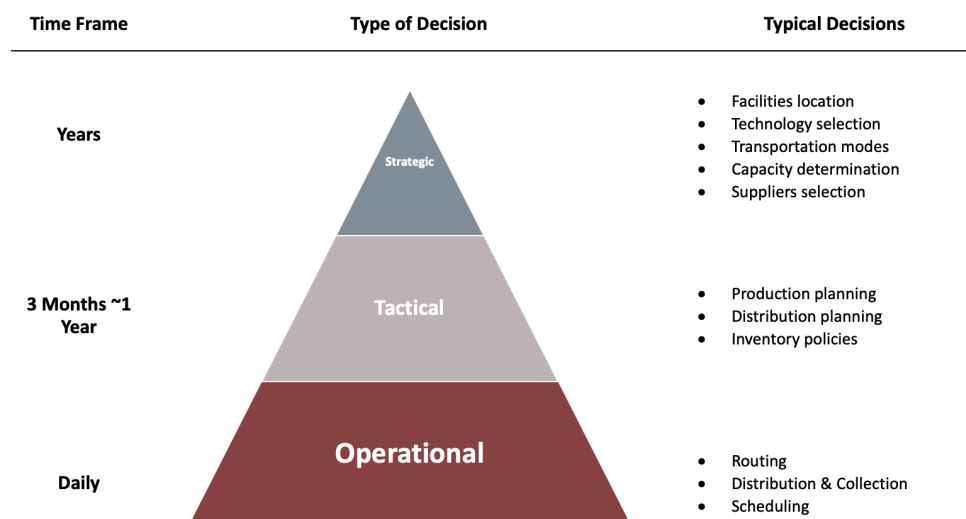


Figure 2.1: Decision levels in Supply Chain Management (adapted from [6])

2.1.2 Main challenges in supply chain management

A properly designed supply chain should be flexible, resilient and efficient, while meeting customer needs at minimum cost [6, 7]. In addition, since these systems are often associated with a high degree of resource consumption and commonly deal with non-environmentally friendly processes and products, it is necessary to pay special attention to supply chain sustainability [4, 7, 41]. Some challenges have been identified in supply chain management [4, 7, 6, 31, 41], namely:

1. **Supply chain strategies cannot be determined in isolation. They are directly affected by another chain that most organizations have, the *development chain*.** The development chain is the set of activities and procedures related to new product introduction. It comprises the product design phase, as well as the associated capabilities and knowledge that need to be developed internally, sourcing decisions, and production plans. Figure 2.2 depicts the intersection of the development and supply chains at the production point.

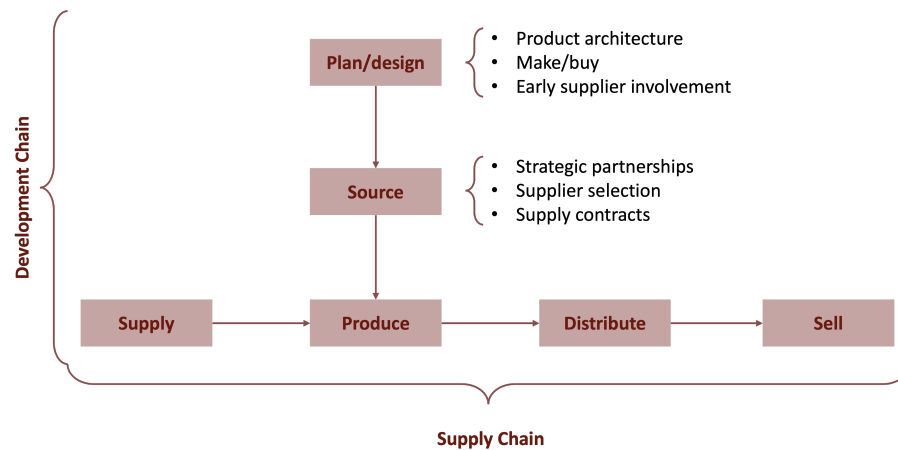


Figure 2.2: Intersection of the development and supply chains (adapted from [31])

In addition, many companies have other supply chains that also need to be considered, such as reverse logistics chains (related to the return of products or components) and spare parts chains.

The main challenge is to align the specific goals of each supply chain with the overall goals of the company, such as increasing market share or profit.

2. **It is challenging to design and operate a supply chain so that total system-wide costs are minimized, and systemwide service levels are maintained.** The challenge grows dramatically with the size of the system. A variety of factors make this a challenging problem:
 - (a) The supply chain is a complex network of facilities spread across a vast geographic area, and in many cases, across the world.
 - (b) Different facilities in the supply chain may have competing goals.

- (c) The supply chain is a dynamic system that changes over time. Not only do consumer demand and supplier capabilities vary over time, but so do supply chain relationships.
- (d) Variations in the system over time are also an essential aspect. Product demand and costs are variable over time and make it challenging to define the most efficient supply chain approach, one that reduces system-wide costs while meeting customer expectations.

Most experts would have declared just a few years ago that these two goals, enhanced service, and reduced inventory levels, could not be met at the same time. Indeed, classic inventory theory states that increasing service level requires increasing inventory and thus cost. Surprisingly, recent advances in information and communication technology, along with a greater grasp of supply chain strategies, have resulted in innovative approaches that allow the business to improve both objectives at the same time.

3. **Uncertainty and risk are inherent in every supply chain.** Customer demand can never be forecast exactly, travel times will never be certain, and machines and vehicles will break down. Similarly, recent industry trends that focus on reducing supply chain costs, such as outsourcing, offshoring, and lean manufacturing, considerably increase the level of risk in the supply chain. As a result, supply chains must be structured and managed to reduce as much uncertainty and risk as possible while also dealing efficiently with the remaining uncertainty and risk.

Global optimization is made more challenging by the fact that supply chains must be developed for and operated in unpredictable environments, posing huge risks to the organisation. This is due to a few hurdles, including:

- (a) **Matching supply and demand is a major challenge.** Obviously, this challenge stems from the fact that producers must commit to specific production levels months before demand profiles are known. These upfront commitments imply significant financial and supply risks.
- (b) Even when customer demand for specific products does not vary substantially, **inventory and back-order levels may fluctuate significantly across the supply chain.**
- (c) **Forecasting doesn't solve the problem.** Even with the most sophisticated forecasting techniques, it is difficult to estimate the precise demand for a specific product.
- (d) **Demand is not the only source of uncertainty.** Delivery lead times, manufacturing yields, transportation times, and component availability may all have a substantial impact on the supply chain.
- (e) **Recent trends such as lean manufacturing, outsourcing, and offshoring that focus on cost reduction increase risk significantly.** Similarly, outsourcing and offshoring imply that the supply chains are more geographically dispersed and, as a result, natural and man-made disasters can have a tremendous impact.

4. **Building up resilience to handle long-term and global disruptions in supply chains is a challenging task.** Supply chain resilience refers to the capacity to stay robust and adjust system behaviour in dynamic situations in the face of significant disruptions (such as catastrophes, disasters, or crises) while retaining acceptable performance [29].

The need to manage rising complexity has sparked interest in supply chain resilience, as disruptions within complex supply chains can occur from a variety of sources and result in major failures [27]. The difficulty that a SC now faces is not anticipating disruptions, but rather maintaining a low threshold of vulnerability. This can be a difficult undertaking since the unexpected frequency and severity of catastrophes, disasters, and crises that affect individuals, as well as organizations and corporations, ultimately makes a SC vulnerable [27, 75].

To prepare themselves for both unexpected happenings and risky events, supply chains must develop an adaptive capacity, by either following a proactive approach or a reactive approach [46, 50, 30, 74]. Although the capacity to anticipate and overcome disruptions reduces susceptibility and improves financial performance, it also increases costs [48]. Depending on their financial stability and resources available for resilience building, firms may apply different tools and be affected differently by a disruption [46].

Existing research shows that supply chain resilience improves performance results; however, no proactive or reactive techniques exist to handle long-term, unusual, and global disruptions such as pandemics, as current supply chain resilience techniques are focused on local and small-scale disturbances [46, 35, 71, 70]. Because such strategies are the only strategies available, organizations have been forced to adapt them. However, inventories can meet the demand only for an extremely limited time, and quarantines across the world may take subcontracting options inapplicable thus, their effectiveness is questionable [30].

5. **New energy and sustainability challenges and initiatives have reframed supply chain design difficulties.** Traditionally, supply chain optimization focused on improving the economical performance of supply chains. However, industries are currently under regulatory and societal pressure to transition from a cost-driven to a more sustainable-driven development, integrating not only economic but also environmental aspects [6, 18, 39].

A truly sustainable supply chain must be economically, environmentally, and socially sustainable [42, 43, 64]. Integrating the three sustainability pillars (Figure 2.3) has been proven to be critical for firms to be flexible and resilient, allowing them to respond to internal and external risks [1, 26, 25].

Supply chain design with sustainability concerns is clearly an ongoing study area in the field. The achievement of supply chain sustainability has mostly focused on minimizing the supply chain's environmental impacts, which are generally evaluated in terms of greenhouse gas emissions and resource usage [29, 19, 60, 72]. However, many other environmental

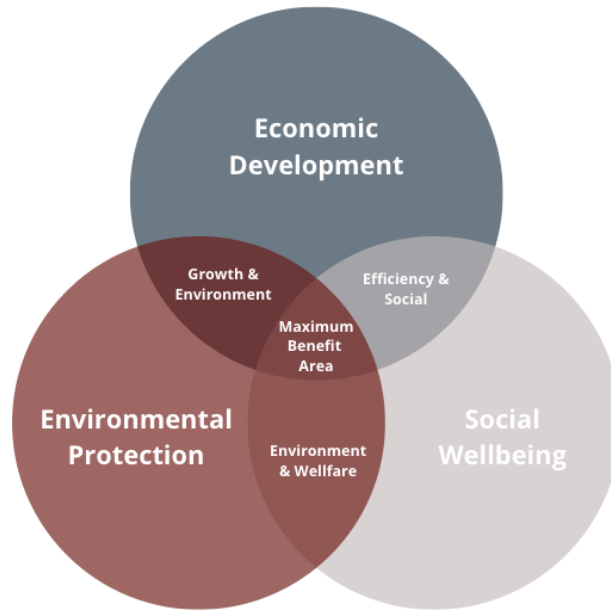


Figure 2.3: Three pillars of sustainability (based on [32])

implications, such as energy use, water consumption, agricultural land use, water contamination, and the nitrogen footprint, have also been studied [77, 76]. Social concerns must also be addressed in the design and management of a sustainable supply chain, although this area has received less attention than environmental repercussions [4, 5]. Several social implications, such as the number of local jobs created, facility location in low GDP or high unemployment areas, human health, living circumstances, and education, have been studied for inclusion in quantitative models [12, 53, 73]. However, these indicators and metrics are still in the early stages of development, presenting more research opportunities in supply chain design [18].

2.1.3 Performance measures in SCM

The establishment of appropriate performance measurements is a critical component in supply chain design and analysis. A performance measure, or collection of performance measurements, is used to determine a current system's efficiency and/or effectiveness, or to evaluate competing alternative systems [8]. Performance measures may also be used to develop proposed systems by identifying the values of the decision factors that result in the best desirable level(s) of performance. According to the available research, these metrics are classified into two types: qualitative performance measures and quantitative performance measures [8].

- **Qualitative performance measures** are those measures for which there is no single direct numerical measurement, though some parts of them might be quantified [8]. Customer satisfaction, flexibility, information and material flow integration, effective risk management,

and supplier performance are some of the qualitative performance measures identified [8].

- **Quantitative performance measures** are those measures that may be directly described numerically [8]. Quantitative supply chain performance measures may be categorized by: (1) objectives that are based directly on cost or profit, like cost minimization, sales maximization, profit maximization, inventory investment minimization or return on investment maximization and (2) objectives that are based on some measure of customer responsiveness, like product lateness minimization, customer response time minimization or lead time minimization [8].

2.1.4 Decision support tools in SCM

Improvements in decision-making regarding resilient and sustainable supply chains can be accomplished through the development of models and decision support systems [11, 20, 74].

The use of simulation for ripple impact studies in the supply chain is logical given the time aspects and dynamics in structures and flows [29]. In supply chain resilience analysis and severe disruptions, discrete event simulation has been widely employed. Ivanov (2017) examined recent simulation modelling literature and created a multi-stage supply chain design simulation model that took capacity disruptions and experimental results into account. This research illustrates the main applications of simulation to the modelling of ripple effects [29]. Additionally, the author created a framework for simulation modelling in relation to supply chain disruption management and outlined the similarities and differences between optimisation and simulation techniques within this framework [74].

Many of the approaches developed in the past in SCM are not able to consider all the features and complexities associated to real systems, such as the delays associated with the information that flows through a real SC. These approaches, which usually involve using mathematical programming models, such as mixed-integer linear programming (MILP), to address SC planning decisions, tend to over simplify the real systems, in order to reach optimal or near-optimal solutions in a reasonable amount of time. Therefore, these models are not as insightful as those in which the dynamic features of the SCs are explicitly considered. Specifically, at the operational level, models that capture the SC dynamics are particularly appealing because they assist managers in understanding complex interactions between system states, data, and decision variables [51].

Another limitation of the tools that are available for SCM is that they have traditionally focused on myopic methods for manufacturing sites, logistics and distribution tasks rather than on approaches that consider all these methods simultaneously. Specifically, a large body of literature in PSE is concerned with the analysis of manufacturing plants and the computation of optimal scheduling plans in terms of predefined criteria (usually makespan, cost or profit) that satisfy a demand that comes directly from a customer [44, 51]. However, the approaches devised to date neglect important aspects of the problem, such as the buffering effect, demand distortion and storage costs, which are all due to the distribution channels through which the materials flow.

Neglecting these aspects may result in either infeasible or suboptimal solutions for the entire SC [51].

2.2 The Pharmaceutical Industry

2.2.1 Overview on the pharmaceutical sector

Millions of citizens around the World benefit from the pharmaceutical industry's contributions [52]. Citizens can expect not only to live longer but to live better quality lives, as we are now able to treat complex diseases with greater precision and effectiveness than ever before [52, 14]. In the past 20 years, advances in research and development have paved investigation to better prevent and treat diseases, with data showing that in 2020 alone, around 7,000 drugs were in development in the key fields of oncology, immunology, neurology, and infectious diseases [52, 28].

In addition to bringing direct benefits to the population, medicines also help to significantly reduce the total healthcare expenditures by substantially reducing costs in other areas of healthcare including hospital stays and long-term care [14]. Data from EFPIA shows that medicines constitute the smallest part of healthcare costs, particularly in 2017 in Europe, only 19.5% of the total health expenditure was spent on medical goods (including pharmaceuticals), with 40.4% spent on in-patient care (hospital stays) and the final 39.1% spent on outpatient-care and other costs [14].

Moreover, the research-based pharmaceutical industry is one of the most valuable assets of the World's economy, being one of Europe's top-performing high-tech industries [52]. According to EUROSTAT data [16], the pharmaceutical industry is the high-tech sector with the highest added value per person, significantly above the average value for hi-tech and manufacturing industries, and the sector with the highest ratio of research and development (R&D) investment to net sales.

Nonetheless, the sector faces real challenges. Besides the additional regulatory hurdles and escalating R&D costs, the sector has been severely hit by the impact of fiscal austerity measures introduced by governments [14]. Accounting for the cost of failed drugs, the average cost of bringing a new drug to market is now estimated to be over \$2bn [14]. Additionally, by the time a medicinal product reaches the market, an average of 12-13 years will have elapsed since the synthesis of the new active substance, with only one or two of every 10,000 substances synthesized in laboratories successfully passing all stages of development required to become a marketable medicine [14].

2.2.2 Pharmaceutical Supply Chain

Like any other industry, the pharmaceutical supply chain involves a complex network of interactions between different entities, such as suppliers, manufacturers, wholesalers, retailers (such as hospitals, pharmacies, etc.), and final consumers (patients) [65]. Some specific features, however, create unique management challenges that are particular to this sector.

Like other supply chains of other sectors, the pharmaceutical industry can identify two different chains: the drug development chain and the drug commercialization supply chain [39, 3].

- The **Drug Development Chain** is the chain built to support the drug discovery and development phase;
- The **Drug Commercialization Supply Chain** supports the marketing, production, and distribution of successful drugs.

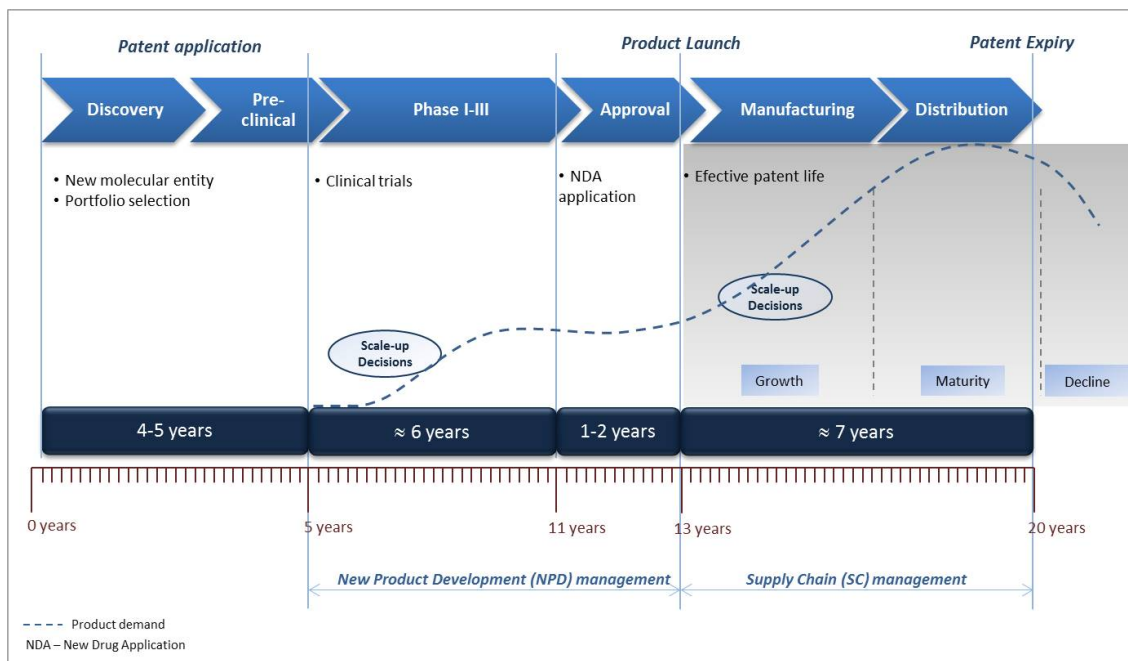


Figure 2.4: Product life-cycle (adapted from [39])

Concerning the discovery and development phase of the pharmaceutical product (represented in Figure 2.4), it typically begins in large multinational R&D facilities with thousands of chemical compounds being tested until a promising new molecule (Active Pharmaceutical Ingredient - API) is found [39]. The new API is then subjected to extensive tests (pre-clinical tests) conducted in animals to determine the toxicity and safety level for human testing in the following clinical trials stage [39, 3]. When a novel drug advances into the clinical trials stage, several considerations about upscaling production capacity must be taken. Only when all phases of clinical trials have been completed successfully is a New Drug Application (NDA) submitted for approval and market launch [39]. Furthermore, to ensure the availability of commercial-scale production capacity as soon as the new drug is approved, the investment in new production facilities for the API production (from the second supply chain) should be made around 5 years before market-launch [67, 23], which is well before clinical trials completion and market-launch approval by the regulatory bodies. These decisions, although highly risky, are necessary to avert delays in the market launch, and revenue losses because of the patent's effective life being shortened. Finally, after regulatory approval of both the product and the procedure, the new drug is introduced into the market under patent protection, via a network of production and distribution agents that make up the aforementioned drug commercialization supply chain [39, 59].

The drug commercialization supply chain will be the focus of this dissertation and it's comprised of manufacturing facilities, where the production of the pharmaceutical product takes place, wholesalers that purchase the pharmaceutical product in bulk and sell it to retailers (such as hospitals, pharmacies, etc.), the point of contact with consumers (see Figure 2.5) [39].

The manufacturing process is the backbone of the pharmaceutical industry and is divided into two main stages [59]:

- The primary manufacturing (PM) stage, where the active pharmaceutical ingredient (API) is produced.
- Followed by the secondary manufacturing (SM) stage where the API is converted into a consumable product (e.g., tablet, capsule, syrup), and then packaged.

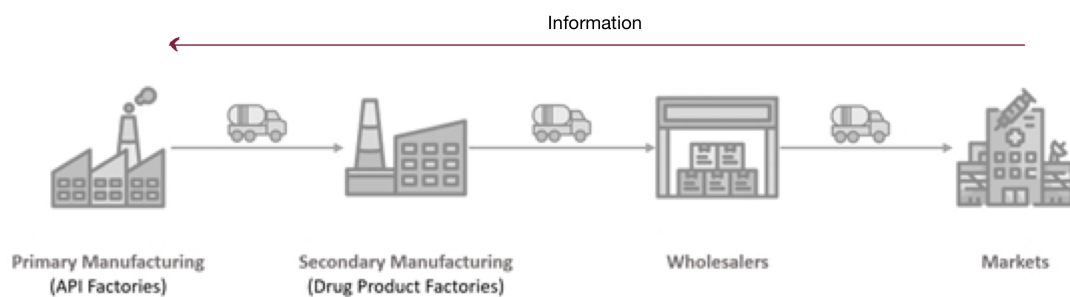


Figure 2.5: Pharmaceutical Supply Chain (adapted from [39])

The **secondary manufacturing** stage is typically highly decentralized and closer to the market, comprising several manufacturing facilities geographically distributed, 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 [65]. 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 [39]. Consequently, this manufacturing stage tends to be, not only, difficult to manage, but also highly inflexible to accommodate production to market changes, and therefore the bottleneck of this supply chain.

As pharmaceutical manufacturers are focused on delivering effective and safe products, in quantities that meet the global demand, while also ensuring that production processes are economically viable, the complexity of supply chain planning increases significantly [29]. Another feature of the pharmaceutical industry that contributes to the complexity of SC management is the reliance on the final product's nature [59].

Therapeutic drugs can be classified into two major groups, each defined by key specifications and/or formulations that dictate decisions related to its manufacturing and supply chain [59].

These groups include **small molecules** (chemically synthesised drugs and characterised by large-scale manufacturing) and biologics (products that involve components extracted from or produced by a living organism) [15]. This last group include monoclonal antibodies (mAbs), vaccines, blood products, and advanced therapy medicinal products (ATMPs). As manufacturing of biologics involves cell-based production systems and complex downstream separation trains, largely performed in batch/semi-batch mode, this often presents challenges in the optimisation and scale up of unit operations [61, 47].

In the case of an API shortage, primary manufacturing's lack of responsiveness might result in drug product shortages, affecting patients. For well-established chemically synthesized therapeutic products, stockpiling has shown to be a viable choice; however, it is not necessarily the ideal approach for more complicated and expensive biologics with limited shelf lives. Because of the high value of these items, the amount of product inventory retained must be limited to avoid tying up working capital [59]. For years, off-the-shelf manufacturing followed the above stockpiling planning paradigm, but patient-specific medicines have started to change this approach. The usage of intermediate storage facilities between drug substance and drug product production can function as a buffer against market fluctuations: the customer-facing end (hospitals and pharmacies) places orders with wholesalers, who check inventory levels and make orders upstream if necessary [59].

Furthermore, network and task coordination become of primary importance as the supply chain becomes more complex. Once the network has been designed, manufacturers need to ensure that distribution and storage conditions are met and maintained throughout the product journey, to reduce losses due to product degradation that can lead to drug shortages or reduced quality.

2.2.3 Main gaps in current research and opportunities for improvement

The pharmaceutical industry is inherently global therefore its supply chains are usually large and complex to manage. It is critical to increase the healthcare industry's worldwide operational performance since it is responsible for providing 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 [21]. Although tremendous progress has been achieved in recent years in terms of efficiency, the existing results are seldom leveraged to model and build a supply chain that is more sustainable, adaptable, and resilient [39].

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 [59]. Due to this complexity, research has been focusing on supply chain problems spanning across all decision levels, as highlighted in several published reviews [39, 17, 45].

Recently, Franco and Alfonso-Lizarazo [17] identified in the literature three main research topics for pharmaceutical SC management, namely:

- Supply chain network design;

- Inventory problems;
- 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. [39] notice that current approaches to pharmaceutical supply chain design and management are still highly fragmented, and identify 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 [34], and most of the literature still relies on operational planning and scheduling approaches based on optimization or hybrid simulation-optimization methods [39, 58, 40].

Therefore, although supply chain resiliency has been attracting increased interest over the years, in the pharmaceutical industry it is a fairly recent topic [56]. Nevertheless, in some noteworthy studies [36, 38, 37], 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 [36]. Although tremendous progress has been achieved in recent years in terms of efficiency, the existing results are seldom leveraged to model and build a supply chain that is more sustainable, adaptable, and resilient [39]. Results clearly show the need for 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.

Recent trends show that adoption of digitalization in pharmaceutical production and supply chain will be critical for smooth data interchange between manufacturing facilities and supply chain networks, as it will enable the connectedness of processes, goods, and people [59]. Adoption of transactional IT solutions such as track and trace systems, as well as cloud-based and blockchain platforms, may improve communication and operations throughout the supply chain, particularly in the expanding pharmaceutical ecosystem with various actors [59]. However, these digital tools do not provide comprehensive frameworks to assist in decision-making. As a result, it is critical to build analytical IT tools to explore, analyze, and anticipate actions for the design, planning, and operation of each component of the supply chain [59]. The Process Systems Engineering (PSE) community has mostly concentrated on the development of advanced optimization and decision-support technologies in order to attain optimum performance and customer satisfaction [59].

Computer-based modelling programs and tools show great promise since they provide low-cost experimentation platforms and the capacity to determine the ideal process operating under a wide range of conditions. Such models and platforms, also known as digital twins, find use in a wide range of pharmaceutical production processes [59].

In the field of supply chain management, optimisation-based techniques have enhanced the strategies and operations of pharmaceutical and bio-pharmaceutical processes and distribution in a variety of ways. Computational tools have been developed to seek optimal long-term strategic plans, taking into account the problem of supply chain design and capacity planning, as well as mid- and short-term decisions, addressing the problem of production planning and scheduling, as well as assist with real-time monitoring of storage conditions that are critical for sensitive pharmaceutical products with short shelf-life, thus increasing drug safety [59, 22].

One of the major impediments to the rapid implementation of *Industry 4.0* concepts in pharmaceutical production is a shift in mentality [59]. Practitioners should embrace the benefits of implementing *Pharma 4.0* by replacing paper-based systems with cloud-based servers, as this will allow for major improvements in agility and productivity in the pharmaceutical sector's operations [23].

2.3 Simulation

2.3.1 Simulation as tool for decision support systems

The use of simulation as a tool for decision support systems has been increasing in the past years [49]. The simulation of a SC allows the representation of complex constraints and to represent the behavior of the system over time, therefore leading to a better understanding of the target system [69].

By testing a wide variety of scenarios, the behavior of the SC can be better understood, and a correlation can be established between the type of disruption and the best possible network configuration to contain its negative impacts. This will make the supply chain more flexible, sustainable, and resilient.

The use of a simulation model is a substitute for actual system (existing or intended) experimentation, which is generally disruptive, inefficient, or just impossible [33]. As a result, if the model is not a "near" approximation to the actual system, any inferences drawn from it are likely to be incorrect, potentially leading to costly actions. The process of establishing whether a simulation model is an accurate representation of the system for the specific aims of the research is known as validation [33].

A famous quote by Professor George Box states, "All models are wrong, but some models are useful". No matter how much effort and money is spent on model development, a simulation model of a complex system can only be an approximation to the actual system. Absolute model validity does not exist, and it is not even desired [33]. A model is, after all, intended to be an abstraction and simplification of reality. The more effort (and hence money) spent on model development, the more generalizable the model should be. The most correct model, however, is not always the most cost-effective. A simulation model should always be created with a certain set of goals in mind. In fact, a model that is valid for one goal may not be valid for another [33].

Having a clear plan for performing a simulation study is crucial to the research's overall success and the development of a valid model. In Figure 2.6 it is presented the seven-step approach for conducting a successful simulation study, formulated by Law (2019) [33].

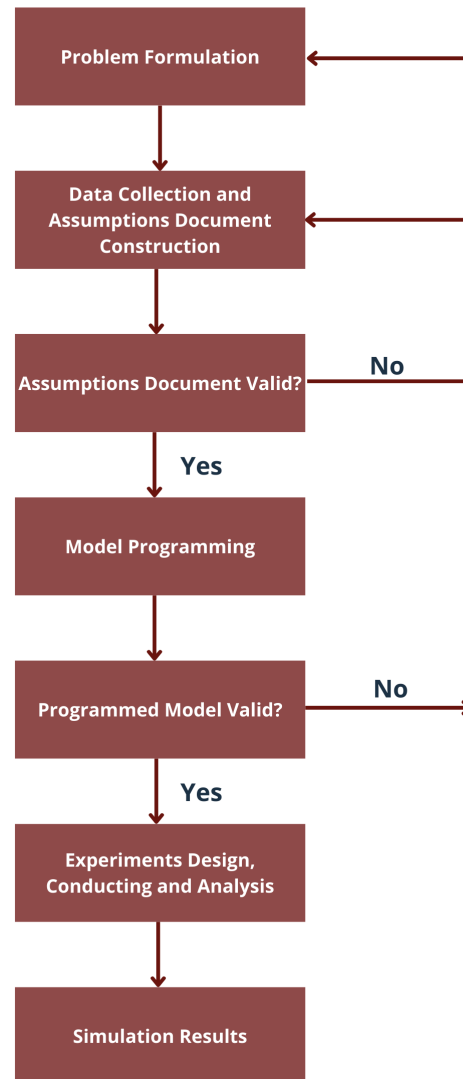


Figure 2.6: Seven step approach to build a valid simulation model, as presented by Law (2019) [33]

As portrayed in the figure, the first step is to **formulate the problem**. In this step, the problem of interest is described and the overall objectives for the study, specific questions to be answered, performance measures to be used to evaluate the efficacy of different system configurations, as well as system configurations to be modelled and time frame for the study should be clarified [33]. The next step is **data/information collection**, where data on the system structure and operating procedures should be collected and an assumptions document should be constructed.

After **validation of the assumptions document**, the **model programming** can be done with the aid of a commercial simulation-software package (*AnyLogic*, *Arena*, *ExtendSim*, *FlexSim*,

Simio, *SIMUL8*, etc.) or in a general-purpose programming language (e.g., C++ or Java).

Again, **validation needs to be ensured**, this time of the programmed model, by comparing simulation model output data for the system with the comparable data collected from the actual system (if it exists). Sensitivity analyses should be performed on the programmed model to see which factors have the greatest impact on the performance measures and, thus, have to be modelled carefully [33].

Finally, **experiments should be run** for each system configuration of interest, and **results should be collected and documented**. The assumptions document (essential for future reuse of the model), a full description of the computer program, and the outcomes of the present research should all be included in the model documentation (and the corresponding simulation study). To improve model credibility, the final presentation for the simulation research should typically contain an animation and a summary of the model building/validation process [33].

2.3.2 Simulation approaches

A model can be simulated using different simulation techniques, such as Discrete Event Simulation (DES), System Dynamics (SD), and Agent-Based Modelling (ABM). The Discrete Event Simulation approach has been the backbone of the Operational Research simulation for a long time. It's process-oriented and focuses on modeling the system in detail, to understand its behaviour. DES is most useful for problems involving queues, in which the processes can be well defined [62], and more suitable for modeling problems at an operational/tactical level [68].

As in discrete event simulation, System Dynamics is used to better understand the behavior of the system to be simulated over time. Contrarily to DES, System Dynamics model represents a system as a set of stocks and flows, where the state changes occur continuously over time. These models are more suited to modeling problems at a strategic level [68].

Agent-Based Modeling is a simulation technique that focuses on modelling entities and the interactions between them. The modelled entities can take the initiative in performing actions, operations, etc. There is no concept of queues or flow in this type of models [62].

2.3.3 Case studies implementing simulation

Some relevant simulations on Supply Chains have already been made and documented.

In 2008, Puigjaner and Guillén-Gosálbez [51] implemented a multi-objective, multi-agent framework, to get a flexible and extensible SC. Moreover, “this framework includes environmental and financial considerations that enlarge the scope of the SC analysis and assist in assessing the trade-off between diverse environmental and economic concerns”.

In 2018, Ivanov [29] tested how the resilience levers interact with corresponding sustainability factors, in a multi-stage supply chain. This work aimed at analyzing the propagation of disruption in the supply chain, taking into consideration sustainability factors. The author observed that the literature typically analyses four levers of supply chain resilience increase using backup facilities,

using inventory buffers, eliminating single-source suppliers with high-risk exposure, and using facility fortification.

By simulating a supply chain, the author confirmed that single sourcing, inventory reductions, and labor market stability in the region, are important sustainability factors.

Chapter 3

Problem Definition and Methodological Approach

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, the goal is to uncover key weaknesses in the tested SC so that timely measures can be taken to contain possible disruptions.

3.1 Problem Formulation

The aim of this dissertation is to build a decision-support tool able to test a generic pharmaceutical supply chain under several disruptive scenarios and evaluate its performance. By submitting this supply chain to disruptions, the main vulnerabilities of the PSC should become visible and mitigation measures could be explored in order to investigate which strategies perform better in containing the negative impacts observed.

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 withstand unexpected disruptive scenarios.

In this regard, this dissertation proposes a simulation model capable of representing, testing and assessing the behaviour of a generic pharmaceutical supply chain, so that its vulnerabilities can be identified and contained by the exploitation of several mitigation measures (strategies), such as varying the facilities' safety stock levels, outsourcing product from external facilities or investing in new production capacity. FAs the goal of this dissertation is to build a platform able to test any generic pharmaceutical supply chain, then a generic pharmaceutical supply chain needs to be considered. As previously detailed in Chapter 2, specifically in Section 2.2.2 for the case of the pharmaceutical sector, such a SC usually involves primary manufacturers, secondary manufacturers, wholesalers, and retailers. A simplified representation of the supply chain is represented in Figure 3.1.

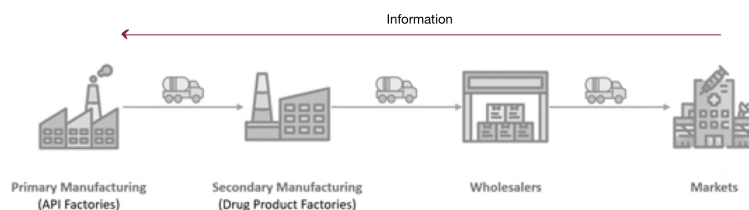


Figure 3.1: Pharmaceutical Supply Chain

Retailers (markets) are responsible for delivering drug product to the general public, so when there is demand for a specific product they (retailers) need to have available inventory to immediately deliver it to the consumer. These facilities get their inventory by placing orders with the wholesalers, that are expected to send it (via terrestrial, maritime or aerial transportation means) as soon as they have available stock. On the other end, wholesalers get drug product by placing orders directly with the secondary manufacturing facility. These facilities are usually further away so wholesalers usually buy products in bigger batches. Secondary manufacturing facilities respond to wholesaler orders by producing final product with API bought from primary manufacturing facilities.

Primary manufacturing facilities buy raw materials from suppliers and produce API to stock, for the aforementioned (Chapter 2) reasons. This supply chain, in the ideal scenario, should be able to always answer the demand, be flexible to demand fluctuations and be able to withstand the occurrence of disruptive events such as pandemics, crises, natural disasters, etc. As evidenced by the COVID-19 pandemic, however, this does not correspond to reality.

3.2 Problem Conceptualization

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 [33].

Considering that in the bibliographical review phase of the dissertation work, four echelons were identified in the typical PSC, then the first four entities of the model are: Primary manufacturers, Secondary manufacturers, wholesalers, and retailers. Each of these *entities* has its own features, requirements, and operating modes:

- *API manufacturing facilities* - representing the facilities (primary manufacturers) where the API will be produced. These entities should accommodate the following features:
 - Have a geographic location (coordinates);
 - Exist in small number of elements;

- Be located in areas of lower production costs (like Asia) or in areas with high R&D indexes (like North America);
 - Have a defined number of production lines producing multiple API products;
 - Operate in a Make-to-Stock strategy;
 - Have a maximum production capacity;
 - Have manufacturing resources with associated costs;
 - Be able to accept orders from FP manufacturing facilities;
 - Have an order management “system” capable of managing inventory requests (orders) from FP manufacturing facilities;
 - Send API product to FP manufacturing facilities;
 - Have a limited inventory capacity (to hold API stock);
 - Be able to increase production capacity (by investing in new production lines or inventory storage)
 - o Have available and limited transportation capacity to send product to the FP manufacturing facilities;
- *FP manufacturing facilities* - group of facilities (secondary manufacturers) that will produce the consumable final product with the API provided by the above facilities. These entities should accommodate the following features:
 - Have a geographic location (coordinates);
 - Exist in a bigger number of elements than the API manufacturing facilities;
 - Be equally world-wide distributed in order to be closer to major markets;
 - Have a defined number of production lines producing multiple final product;
 - Operate in a Make-to-Order strategy;
 - Have a maximum production capacity;
 - Have manufacturing resources with associated costs;
 - Accept orders from Wholesalers;
 - Have an order management “system” capable of managing inventory requests (orders) from Wholesalers;
 - Send final product to Wholesalers;
 - Have a limited inventory capacity (to hold both API product and final product);
 - Be able to increase production capacity (by investing in new production lines or inventory storage)
 - Have available and limited transportation capacity to send product to the Wholesalers;

- Be able to outsource product from facilities outside the supply chain (with associated costs);
- *Wholesalers* - facilities that sell products in bulk to retailers. These entities are even closer to the consumers and therefore in even bigger number. These entities should accommodate the following features:
 - Have a geographic location (coordinates);
 - Exist in a bigger number of elements than FP manufacturing facilities;
 - Be equally world-wide distributed;
 - Operate in a Make-to-Order strategy;
 - Have an order management “system”;
 - Accept orders (information) from Retailers;
 - Send final product to Retailers;
 - Have a limited inventory capacity (to hold final product);
 - Be able to increase storage capacity (with associated costs);
 - Have available and limited transportation capacity to send product to the Retailers;
- *Retailers* - the final elements of the PSC and point of contact with the consumers. These entities should accommodate the following features:
 - Have a geographic location (coordinates);
 - Be able to cover the entire population;
 - Be able to meet all Consumer demand;
 - Have a limited inventory capacity (to hold final product);
 - Be able to increase storage capacity (with associated costs);

Moreover, there is information flow going upstream the supply chain that will trigger a flow of product downstream. Therefore, two more entities can be identified:

- *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). These entities should have information on:
 - The origin (facility) of the order;
 - The destination (facility) of the order;
 - The type of product to be sent;
 - The amount of product to be sent;

- *Product* - physical product being transferred down the supply chain. This entity should have:
 - A time of production;
 - An expiry date;

Bearing in mind the specific features of pharmaceutical SC operations, the additional **requirements** for the simulation model have been defined:

- this being a work to test the resiliency of a supply chain, then the simulation horizon should be long enough to capture the main vulnerabilities (at least 5 years);
- the supply chain model should be customizable, this meaning the SC configuration should be easily adapted to different business contexts and environments;
- the number of products circulating in the SC 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);
- as the goal is to test SC resiliency to disruptions, it needs to be easy to introduce disruptions in the SC;
- safety stocks should be changeable and be used to ensure a given SC responsiveness level;
- as different geographical regions have different policies and economic and societal backgrounds, SC characteristics such as prices, demand, etc should vary according to facility location (facilities should be able to adapt their operations to their location);
- all customizable inputs (as stated above) should be read from an external source (e.g., an Excel file);
- the SC overall performance should be evaluated through a set of KPIs (Key Performance Indicators), namely: demand satisfaction (as a percentage of consumer met demand); order fulfilment (failed orders, backorders and response/delivery times); lead times and overall SC costs;
- it should be possible to easily identify main sources of failure in the SC (SC elements less resilient, more problematic).

Additionally, given the high complexity of the pharmaceutical SC, and after investigation on simulation tools, supply chain management concepts and optimization challenges, some **assumptions** and **simplifications** needed to be made in the model:

- given the considered long time horizon, and the complexity in accurately transportation times between locations, these were calculated using embedded GIS functions of the simulation tool used (*IGISRouteProvider* tool from the *AnyLogic* simulation software);
- manufacturing facilities work with production lines where a given production line produces a single product. Each production line has its own independent resources and can operate concurrently without restrictions (production lines are considered to be independent);
- given the considered long time horizon, set-up times in production facilities are ignored as they will not have a significant impact on the simulation results;
- when there are queues in the process, processing will follow a FIFO approach, i.e., there is no pushing, jockeying or leaving queues;
- when an order is made, there is no time limit for that order to arrive, and no order cancellations are considered, for the case of primary manufacturers, secondary manufacturers and wholesalers;
- product demand in retailers needs to be immediately met or it is considered to be lost (no waiting for stock in retailers);

3.3 Simulation model

Considering the main components associated with the present problem, namely: (i) the requirements, assumptions, and simplifications of the case study (ii) the issues in the SC that are intended to be identified, (iii) the types of decisions to be made, and (iv) the simulation paradigms reviewed in Section 2.3.2 and their features, it was 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. By studying available simulation software tools, it was concluded that *AnyLogic* would be the best solution, the main reason being the fact that it allows for simultaneously using the 3 simulation paradigms [10]. An additional factor contributing to the decision of using *AnyLogic* is that this tool is built on a java foundation so it helps the fact that all functions (or most functions) already built in Java can be used in the programming of the simulation model. Additionally, as *AnyLogic* has a java foundation, this also means that the simulation model can be compiled into a .jar file and executed on any machine that supports Java applications.

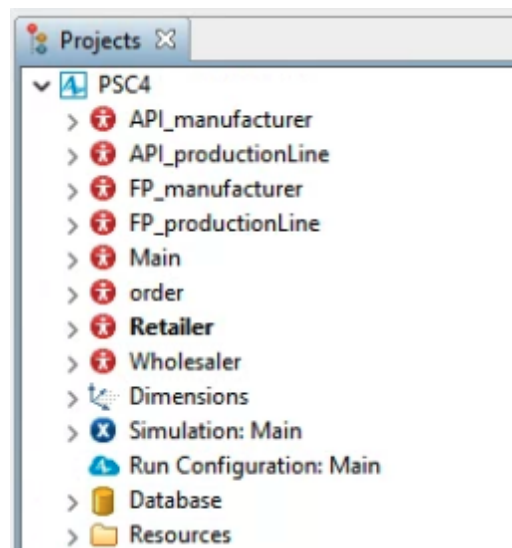


Figure 3.2: Overview of the simulation entities

Therefore, an *AnyLogic* project was created with properties presented in Figure 3.2. In this figure it is understood that in the PSC project (*PSC4*), 8 simulation agents were created. The *Main* agent is created by default and corresponds to the main stage where simulation is run. Then, 7 more agents coinciding with the entities described in Section 3.2 (apart from the entity *product* that was not modelled because of time constraints). Furthermore, there is also a section where simulation *Dimensions* are defined, a *Database* and a *Resources* folder.

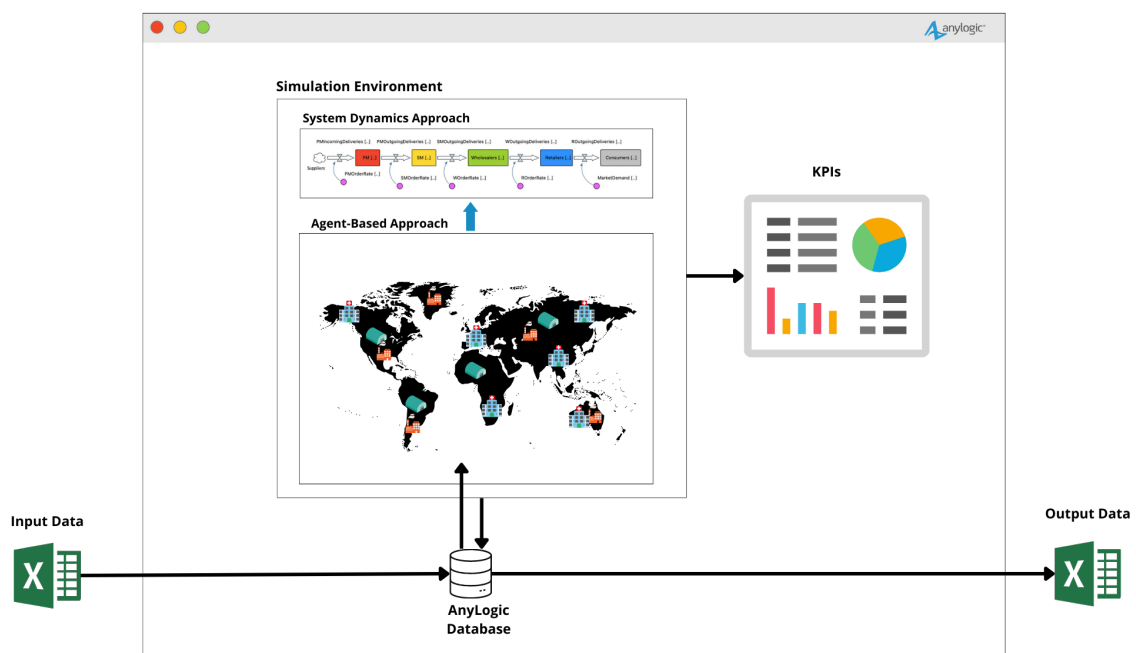


Figure 3.3: Simulation framework

As mentioned before, incorporating multiple simulation paradigms would be the best approach for the PSC modelling. Therefore, all three simulation paradigms were used: System Dynamics and Agent-based modelling for primary behaviour definitions, both integrated with an Agent-Based approach. Both paradigms were implemented in the *Main* agent of the simulation, and the simulation framework is presented in Figure 3.3.

First, the SC is configured by modifying the *Input Data Excel file*, and the information on the Excel file is then saved in the embedded *Database*. Section 3.3.3 contains more information about SC configuration and deployment.

The database information is then utilised to generate the population of agents described in detail in Section 3.3.2, which is subsequently used to create the System Dynamics behaviour described in Section 3.3.1.

Finally, SC performance can be evaluated through a series of KPIs described in Section 3.3.4. Data recorded in the *AnyLogic Database* may be exported to an Excel file for further examination.

3.3.1 System Dynamics approach for overall SC modelling

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 high level 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. This modelling follows the John Sterman's model for Business Dynamics [66], and its generic behaviour is described by Figure 3.4 and Equations 3.1 - 3.10.



Figure 3.4: System Dynamics Modelling

$$\begin{aligned} \frac{d(PM[ProductType])}{dt} &= \\ &= PMIncomingDeliveries[ProductType] - PMOutgoingDeliveries[ProductType] \end{aligned} \quad (3.1)$$

$$PMIncomingDeliveries[ProductType] = PMOrderRate[ProductType] \quad (3.2)$$

$$\begin{aligned} \frac{d(SM[ProductType])}{dt} = \\ = PMOutgoingDeliveries[ProductType] - SMOutgoingDeliveries[ProductType] \end{aligned} \quad (3.3)$$

$$PMOutgoingDeliveries[ProductType] = SMOrderRate[ProductType] \quad (3.4)$$

$$\begin{aligned} \frac{d(Wholesalers[ProductType])}{dt} = \\ = SMOutgoingDeliveries[ProductType] - WOutgoingDeliveries[ProductType] \end{aligned} \quad (3.5)$$

$$SMOutgoingDeliveries[ProductType] = WOrderRate[ProductType] \quad (3.6)$$

$$\begin{aligned} \frac{d(Retailers[ProductType])}{dt} = \\ = WOutgoingDeliveries[ProductType] - ROutgoingDeliveries[ProductType] \end{aligned} \quad (3.7)$$

$$WOutgoingDeliveries[ProductType] = ROrderRate[ProductType] \quad (3.8)$$

$$\frac{d(Consumers[ProductType])}{dt} = ROutgoingDeliveries[ProductType] \quad (3.9)$$

$$ROutgoingDeliveries[ProductType] = MarketDemand[ProductType] \quad (3.10)$$

3.3.2 Agent-Based approach for "comprehensive" SC modelling

The Agent-Based approach was developed, integrated with the SD model, to evaluate the individual performance of each facility and to understand its behaviour 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 as an autonomous element, 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 ($PMOrderRate[..]$, $SMOrderRate[..]$, $WOrderRate[..]$, $ROrderRate[..]$).

The agents created for this approach can be seen in Figure 3.2 and are: *order*, *API_manufacturer* and *FP_manufacturer*, *API_productionLine*, *FP_productionLine*, *Retailer* and *Wholesaler*. Each of these agents has its own modelling method, except for *API_manufacturer* and *FP_manufacturer* who follow a similar approach.

(a) *order*

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 modelling was required.

(b) *API_manufacturer* and *FP_manufacturer*

As stated above, both manufacturing facilities were modelled in the same manner. They were modelled following a hybrid approach of discrete-event simulation, agent-based modelling and indirectly, through the production lines agents, a system dynamics approach.

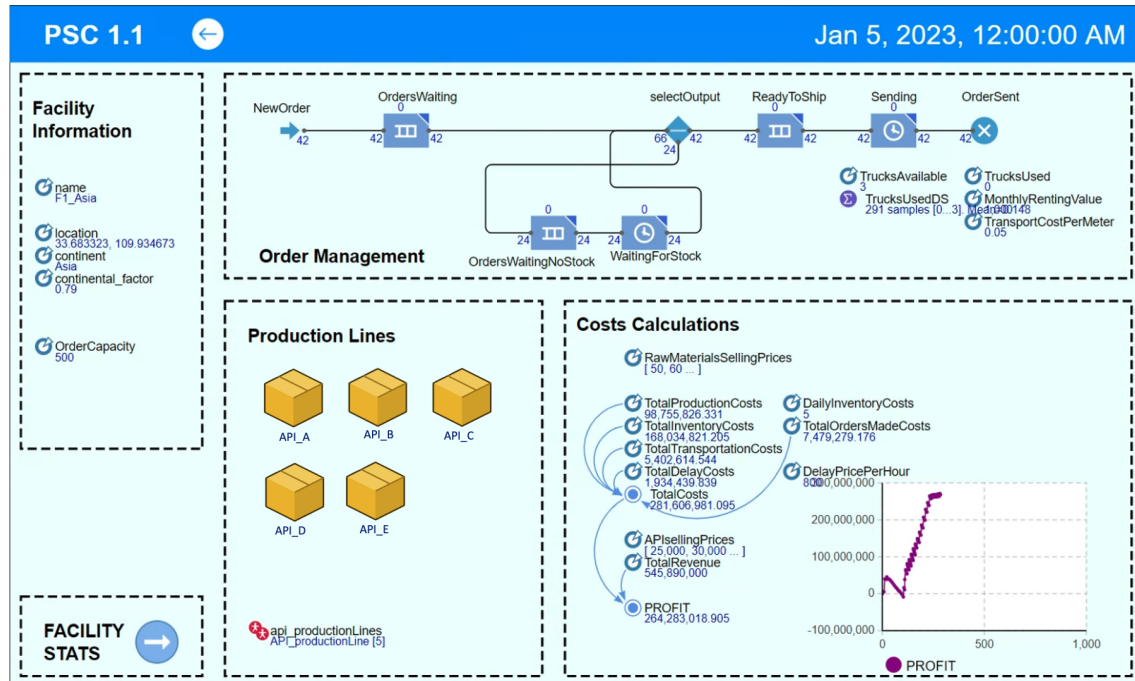


Figure 3.5: Modelling of a primary manufacturing facility (*API_manufacturer*)

The simulation environment of a primary manufacturing facility (*API_manufacturer*) is depicted in Figure 3.5. In this figure, 5 sections can be identified.

The first section, **Facility Information**, includes information received from the Excel configuration file about the facilities.

Following that are two sections relating to performance measures. First, there is the **Facility Stats** section, which redirects to the GUI page where facility performance measures are displayed. Then comes the **Costs Calculations** section, which corresponds to the facility's

financial "department," and it is in this section that the economic performance of the echelon is calculated. Section 3.3.4 delves deeper into all performance measures.

A discrete-event approach was used to model a subsystem responsible for managing incoming orders and outgoing product in the **Order Management** section.

Finally, there is the **Production Lines** section, which contains the production line agent population.

- **Order Management structure:**

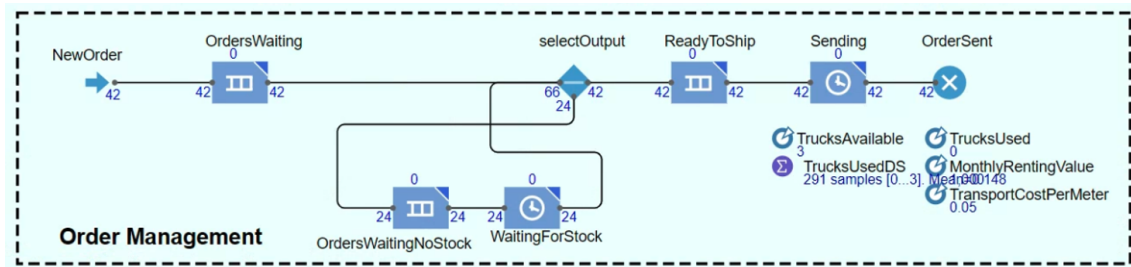


Figure 3.6: Detail of the order management modelling of a primary manufacturer (*API_manufacturer*)

When an order directed to the specific agent is received via the entry point *NewOrder*, it is routed to the queue *OrdersWaiting*. If there is enough API product inventory to fill the quantity in the order, it is redirected to another queue (*ReadyToShip*) to wait for available transport (*TrucksAvailable* > 0) to be shipped. This behaviour is seen in more detail in Figure 3.6.

Sending an order was modelled as a delay with the duration of transportation time between the source and the destination (data stored in the *order* agent). Time of transportation, or time of delay, is an approximation calculated with the information provided by the *IGISRouteProvider* tool of *AnyLogic* and the geographic coordinates of these two facilities.

- **Production Lines structure:**

As different manufacturing facilities may produce different products, the manufacturing process must be adaptable and easily upscalable/downscalable. Therefore, it was determined that developing a production line agent would be the best option as the manufacturing facility would be fairly flexible in terms of production capacity, with the ability to add new production lines (agents) or remove them from manufacturing facilities (population of agents).

Figure 3.5 depicts these production line agents as a box that, when clicked, displays the agent modeling (Figures 3.7 and 3.8).

Specifically in the example of Figure 3.5, the primary manufacturing facility located in Asia produces 5 API products (*API_A*, *API_B*, *API_C*, *API_D* and *API_E*), each of these products being produced in one production line.

On simulation startup, the production line population is created based on the information in the Excel configuration file (Section 3.3.3), and the modeling of the agents *API_productionLine* and *FP_productionLine* is detailed in subheadings (c) and (d). More detail on the parameters of the agent-based approach for these agents is presented in Appendix A.

(c) *API_productionLine*

The production line of a primary manufacturer was modelled using a system dynamics approach as it was intended to model a more generic behaviour of the system and not a very detailed modelling that a discrete-event approach could provide. The system dynamics modelling used for this agent was also based on John Sterman's model for Business Dynamics [66].

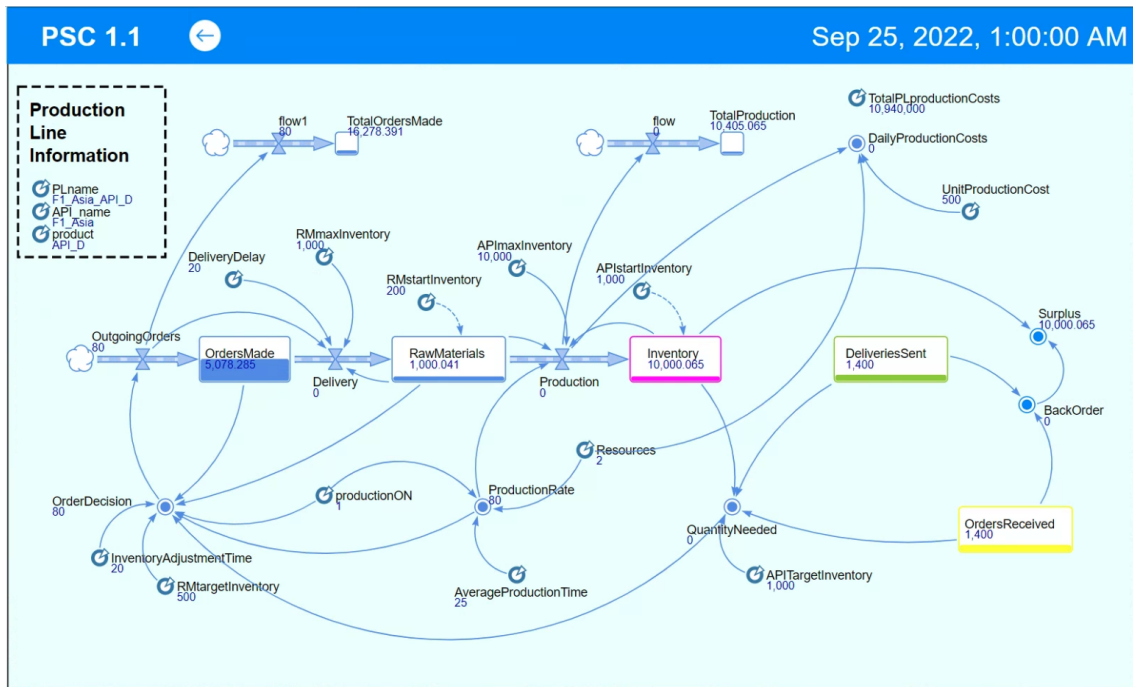


Figure 3.7: Modelling of the *API_productionLine* agent

As previously detailed in Chapter 2, a System Dynamics approach represents production line behaviour through a set of stocks and flows. The stocks used for the modelling of the production line, as well as the mathematical equations used for representing their behaviour were:

- **OrdersMade**: representing the quantity of raw material ordered from suppliers that but yet to arrive at the primary manufacturing facility storage.

$$\frac{d(OrdersMade)}{dt} = OutgoingOrders - Delivery \quad (3.11)$$

- **RawMaterials**: the quantity of raw material in storage at the primary manufacturing facility. This raw material is used to produce API.

$$\frac{d(RawMaterials)}{dt} = Delivery - Production \quad (3.12)$$

- **Inventory**: the quantity of API currently in storage at the facility.

$$\frac{d(Inventory)}{dt} = Production \quad (3.13)$$

Additionally, there are stocks *TotalOrdersMade*, that accounts for all the orders of raw material that were made, and *TotalProduction*, that accounts for all API produced in the specific production line. *DeliveriesSent* accounts for the totality of API product sent from the production line, while *OrdersReceived*, represents the total amount of API that was requested from the production line. These additional stocks are mostly used for statistical and performance analysis metrics.

In terms of flows, three major flows can be identified:

- **OutgoingOrders**: Because raw materials inventory is not a problem, it is considered a continuous flow of material coming into stock. Before arriving, materials need to be ordered. This process is modelled as a flow and follows an order rate (*OutgoingOrders*) that depends on the quantity of raw materials already in storage (*RawMaterials*), the maximum storage capacity for raw materials (*RMmaxInventory*), the rate of raw materials leaving storage (*ProductionRate*), the quantity of API that is needed (*QuantityNeeded*), it also considers a target inventory for raw materials, or safety stock (*RMtargetInventory*) and the inventory adjustment time (*InventoryAdjustmentTime*), that corresponds to the time that it takes for product to be delivered. It also considers whether the production line is active in order to avoid material stockpiling when production is halted. This flow's behaviour is defined through the following set of equations:

$$OutgoingOrders = OrderDecision \quad (3.14)$$

$$\begin{aligned} OrderDecision = & \\ & = \frac{ProductionRate}{InventoryAdjustmentTime} + \\ & + \frac{\max((RMtargetInventory - RawMaterials - OrdersMade + QuantityNeeded), 0)}{InventoryAdjustmentTime} \\ & * productionON \end{aligned} \quad (3.15)$$

$$\begin{aligned}
QuantityNeeded &= \\
&= \max((API_{TargetInventory} + OrdersReceived - DeliveriesSent - Inventory), 0)
\end{aligned} \tag{3.16}$$

- **Delivery:** This flow corresponds to the arrival of raw materials into stock. It relates to the *OutgoingOrders* flow, delayed by the value of time of transportation between supplier facilities and primary manufacturers (*DeliveryDelay*). The Java algorithm used to portray this behaviour was the one presented in 3.17, where the first term $((RawMaterials < RM_{maxInventory})?1 : 0)$ makes sure that the maximum storage capacity hasn't been reached, and the second term $(delay(OutgoingOrders, DeliveryDelay))$ corresponds to a delay of the *OutgoingOrders* flow.

$$\begin{aligned}
Delivery &= \\
&((RawMaterials < RM_{maxInventory})?1 : 0) * \\
&\quad * delay(OutgoingOrders, DeliveryDelay)
\end{aligned} \tag{3.17}$$

- **Production:** API production is done by processing the *RawMaterials* in stock and transforming them into API product. Production rate (*ProductionRate*) depends on the number of resources allocated to the production line (*Resources*), the average time of production (*AverageProductionTime*), the product already produced and in storage, and the maximum available storage capacity. Production rate also assumes that the production line is active (*ProductionON* = TRUE). The Java algorithm used to portray this behaviour was the one presented in 3.18, where the first term $((Inventory < API_{maxInventory})?1 : 0)$ makes sure that the maximum storage capacity hasn't been reached, the second term $((RawMaterials > 0)?1 : 0)$ assures that there is Raw Material in storage to be used for API production, and the third term (*ProductionRate*) depends on the available number of resources (*Resources*) and the average time of production (*AverageProductionTime*), while also making sure that the production line is operational (*productionON*).

$$\begin{aligned}
Production &= ((Inventory < API_{maxInventory})?1 : 0) * \\
&\quad * ((RawMaterials > 0)?1 : 0) * ProductionRate
\end{aligned} \tag{3.18}$$

$$ProductionRate = \frac{Resources}{AverageProductionTime} * productionON \tag{3.19}$$

Two more flows can be identified, these flows ($flow = Production$ and $flow1 = OutgoingOrders$) are only supplementary flows as they allow for the control of stocks *TotalOrdersMade* and *TotalProduction*.

Additionally, some other parameters and variables are in the model for statistics and performance analysis.

(d) *FP_productionLine*

The modelling of the secondary manufacturer production line agent was done using the same SD approach as the primary manufacturer production line and is depicted in Figure 3.8.

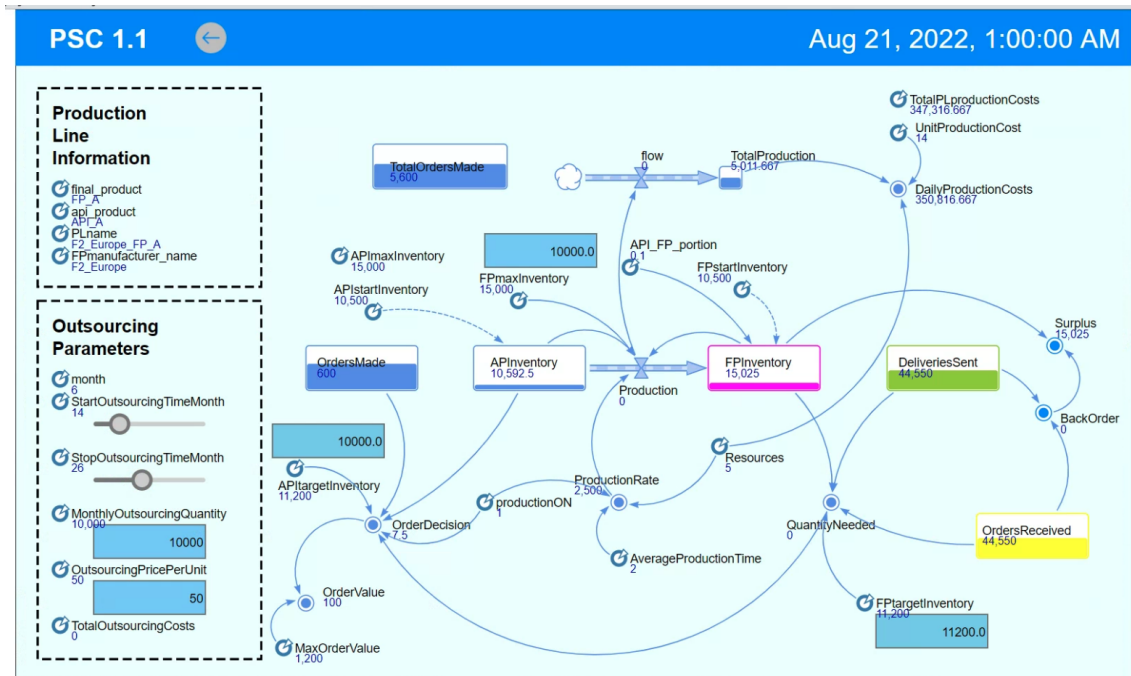


Figure 3.8: Modelling of the *FP_productionLine* agent

However, in this agent only one main flow is identified, the *Production* flow that follows equation 3.20. The flows *OutgoingOrders* and *Delivery* used in the modelling of the *API_productionLine* have been replaced with an event, to coordinate with the discrete-event approach of the order management “system” described by Figure 3.6.

This discrete-event approach still relies on variable *OrderDecision*, following Equation 3.21, but it exists in the form of a condition-triggered event that creates an order agent and sends it to the closest working primary manufacturer agent, with the quantity discriminated in variable *OrderDecision*.

$$Production = ((FPInventory < FPmaxInventory)?1:0) * ((APIInventory > 0)?1:0) * ProductionRate \quad (3.20)$$

$$OrderDecision = (max((APItargetInventory + QuantityNeeded - APIInventory - OrdersMade), 0) * productionON \quad (3.21)$$

Additionally, as the production doesn't necessarily follow a 1:1 ratio from API to FP, a Bill-Of-Materials was created (Table 3.1) and the *Inventory* stock now follows Equation 3.22.

$$\frac{d(Inventory)}{dt} = \frac{Production}{API_FP_portion} = \frac{Production}{BOM} \quad (3.22)$$

Finally, this agent includes a section for specifying outsourcing parameters. This is done on a monthly basis, with the quantity defined arriving at the secondary manufacturing facility. These values can be changed by the user during simulation using the simulation GUI's input fields.

Table 3.1: Bill-of-materials for the products considered in the simulation experiments

APIs produced	FPs produced	BOM
API_A	FP_A	0.1
API_B	FP_B	0.25
API_C	FP_C	0.5
API_D	FP_D	0.2
API_E	FP_E	0.3

(e) **Wholesaler**

The modeling of this agent is similar to that of the primary manufacturer, with the exception of inventory management.

While talking about production lines made sense in manufacturing facilities, because wholesalers are only inventory holding and distribution facilities, the concept of production line, or even "distributionLine" doesn't make sense.

To replace that modeling, an array approach of System Dynamics elements was used, despite the fact that the concept and functionalities of System Dynamics were not used (main

benefits/reasons for using System Dynamics). It makes more sense to talk about a discrete-event approach because the dynamics in the model are created by events rather than flows (as seen in Figure 3.9, there are no flows in this agent modelling). System Dynamics is only used for its element features, specifically the option to use as arrays, and the ability to visualize the mathematical functions for the agent's dynamics.

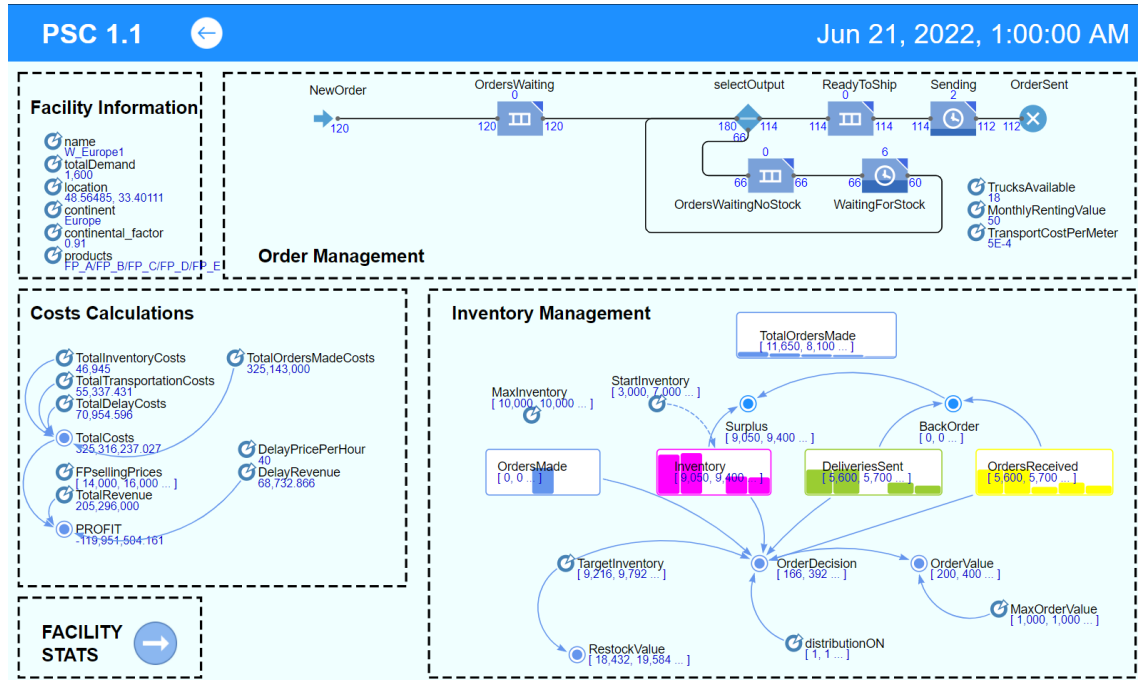


Figure 3.9: Modelling of the *Wholesaler* agent

With that in mind, the variable *OrderDecision* continues to be similar to the one in Equation 3.21, and the event that triggers the order of new product is also similar to the one used for modelling of the production lines of secondary manufacturers (*FP_productionLine*). The difference now is that the event must listen to an array of values that can be triggered concurrently. As a result, there must be an event for each dimension of the array (one event for each type of product handled in the wholesaler agent).

(f) *Retailer*

Finally, there is agent *Retailer*. This agent doesn't have an order management system as these facilities don't receive orders from consumers. Instead, there is an *OutgoingDeliveries* flow that is dictated by *MarketDailyDemandRate*. Similarly to the other agents, the retailers' behaviour can be described through a set of algorithms.

Three flows control the dynamics of the agent:

- **LostOrders**: follows equation from variable *OrderLostRate* and represent the amount of demand that can't be met;

- **OutgoingDeliveries**: represents the amount of product being sold at the retailer facility (product delivered to the consumers). It is described by Equation 3.23, where the first term $((Inventory[ProductType] > 0)?1 : 0)$ assures that there is product in storage, before leaving the facility.

$$\begin{aligned}
 OutgoingDeliveries[ProductType] = \\
 &= ((Inventory[ProductType] > 0)?1 : 0) * \\
 &\quad * OutgoingDeliveryRate[ProductType] \quad (3.23)
 \end{aligned}$$

- **IncomingOrders**: represents the daily consumer demand profile and follows the value of variable *IncomingOrderRate*;

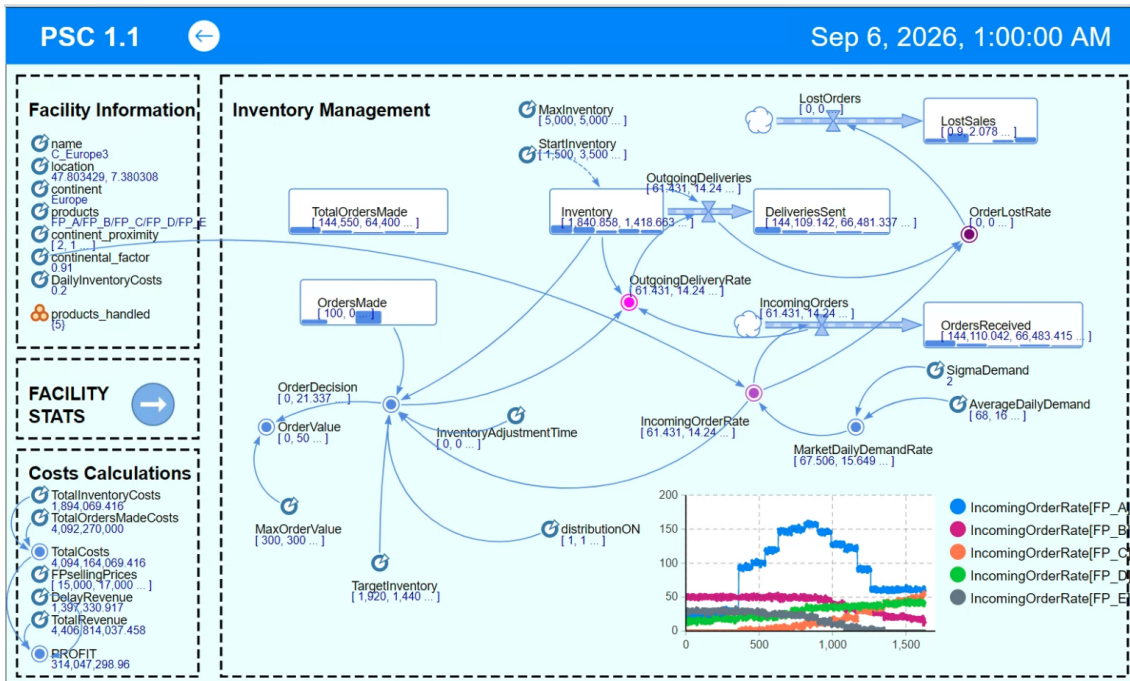


Figure 3.10: Modelling of the *Retailer* agent

Some important variables for the system modelling:

- **OrderDecision**: already detailed in previous sections;
- **MarketDailyDemandRate**: daily demand profile of consumers. This follows a normal distribution with mean value following the profile from the Excel sheet and a configurable sigma value. This distribution intends to simulate the variation and uncertainty in consumer demand and is one of the main advantages of using simulation over other decision-support tools.

$$\begin{aligned}
MarketDailyDemandRate[ProductType] = \\
&= abs(normal(((AverageDailyDemand[ProductType] > 0)?1 : 0)* \\
&\quad * SigmaDemand, AverageDailyDemand[ProductType]))) \quad (3.24)
\end{aligned}$$

- **IncomingOrderRate**: daily demand rate that arrives at the specific retailer facility. Takes into consideration the location of the facility and therefore there is a continental factor to take into consideration. This continental factor is configurable in the Excel sheet but for the work presented in this dissertation, values in Table 3.2 were used, following research presented in [reference].

$$\begin{aligned}
IncomingOrderRate[ProductType] = \\
&= MarketDailyDemandRate[ProductType] * continental_factor \quad (3.25)
\end{aligned}$$

Table 3.2: Continental factor used for demands and price calculations

Continent	Consumption Factor	Continental Factor
Asia	0.17	0.79
Africa	0.05	0.67
North America	0.38	1
South America	0.06	0.68
Europe	0.29	0.91
Oceania (Australia)	0.05	0.67

- **OutgoingDeliveryRate**: considers the product in storage and the incoming order rate.

$$\begin{aligned}
OutgoingDeliveryRate = \\
&= min(IncomingOrders[ProductType], \\
&\quad Inventory[ProductType] + OrderDecision[ProductType]) \quad (3.26)
\end{aligned}$$

Like *Wholesalers*, product orders are made through condition-triggered events that “listen” to the *OrderDecision*.

3.3.3 SC configuration and deployment

The configuration of the Supply Chain 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.

Variables in the Excel file are also used to introduce disruptive scenarios and associated mitigation measures.

Data used for definition of the base case introduced in Chapter 4 is presented in Appendix B

	A	B	C	D	E	F	G	H	I
	Name	Latitude	Longitude	Products	TargetInventory	MaxInventory	StartInventory	StartConsuming	StopConsuming
2	C_Africa1	-18,49803	35,52196	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000	1500/3500/0/1000/2500	0/0/90/0/0	1900/1900/1900/
3	C_Asia1	39,85081	81,53998	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000	1500/3500/0/1000/2500	0/0/80/0/0	1900/1900/1900/
4	C_Asia2	18,93957	105,38082	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000	1500/3500/0/1000/2500	0/0/90/0/0	1900/1900/1900/
5	C_America1	53,68261	-93,03091	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000	1500/3500/0/1000/2500	0/0/80/0/0	1900/1900/1900/
6	C_Europe2	39,695369	-5,777918	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000	1500/3500/0/1000/2500	0/0/90/0/0	1900/1900/1900/
7	C_Oceania	-30,81518	142,80871	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000	1500/3500/0/1000/2500	0/0/80/0/0	1900/1900/1900/
8	C_Asia3	45,14825	106,87251	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000	1500/3500/0/1000/2500	0/0/90/0/0	1900/1900/1900/
9	C_Samerica1	-25,19872	-59,57517	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000	1500/3500/0/1000/2500	0/0/80/0/0	1900/1900/1900/
10	C_Namerica2	34,279063	-85,032205	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000	1500/3500/0/1000/2500	0/0/90/0/0	1900/1900/1900/
11	C_Europe3	47,803429	7,380308	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000	1500/3500/0/1000/2500	0/0/90/0/0	1900/1900/1900/
12	C_Europe4	44,6865	27,887137	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000	1500/3500/0/1000/2500	0/0/80/0/0	1900/1900/1900/
13	C_Africa2	22,3791	-2,8278	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000	1500/3500/0/1000/2500	0/0/90/0/0	1900/1900/1900/
14	C_Namerica3	45,364666	-69,254042	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000	1500/3500/0/1000/2500	0/0/80/0/0	1900/1900/1900/
15	C_Asia4	58,660257	132,36479	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000	1500/3500/0/1000/2500	0/0/90/0/0	1900/1900/1900/
16	C_Europe1	50,83976	16,82374	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000	1500/3500/0/1000/2500	0/0/80/0/0	1900/1900/1900/
17	C_Samerica2	0,1345	-53,15877	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000	1500/3500/0/1000/2500	0/0/90/0/0	1900/1900/1900/

Figure 3.11: Example of an Excel Configuration file

3.3.4 SC performance evaluation

Overall supply chain performance, in its multiple dimensions, can be visualized using different dashboards and tables in the *STATS* tab of the simulation GUI (Figure 3.12). Four main performance measures are used in order to evaluate SC performance.

First, the service level is assessed. The overall SC service level, the service level by product type, and service level by location are all presented in this section. This performance metric is obtained by dividing total product delivered by demand.

The second performance metric is stock levels. This metric corresponds the quantity of product in inventory, at all SC levels.

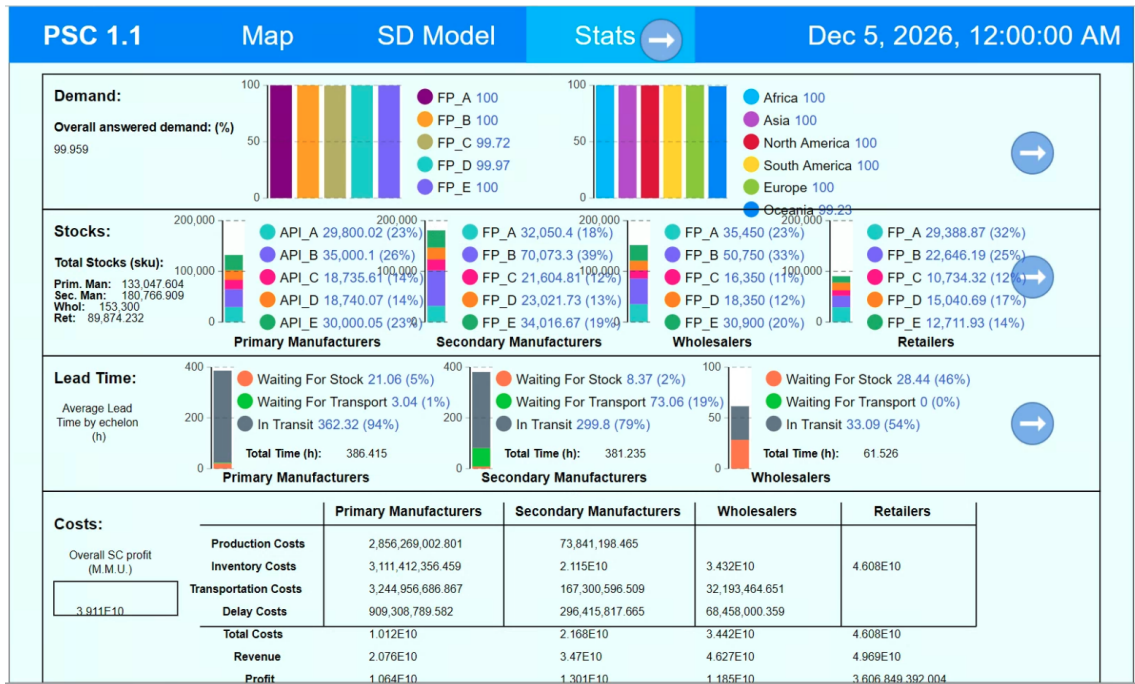


Figure 3.12: Statistics tab of the simulation GUI with the KPIs

Then a lead time analysis is made. The average lead time by echelon is shown, as well as the percentage of that time that is spent *Waiting For Stock*, *Waiting For Transport* and *In Transit*.

Finally, the last performance metric evaluated is the profit of the SC. This metric was calculated through the following set of equations:

$$Profit = Revenue - TotalCosts \quad (3.27)$$

$$Revenue = SalesRevenue + DelayRevenue \quad (3.28)$$

$$\begin{aligned}
 TotalCosts = & ProductionCosts + InventoryCosts + \\
 & + TransportationCosts + OutsourcingCosts + \\
 & + IncreasingCapacityCosts + DelayCosts \quad (3.29)
 \end{aligned}$$

A second service level metric is presented in Figure 3.13. The four graphs in this figure depict the evolution of the quantity of backordered product for each type of product at primary manufacturers ($PM_Backorder[FP_X]$), secondary manufacturers ($SM_Backorder[FP_X]$), wholesalers ($W_Backorder[FP_X]$), as well as the evolution of the daily amount of lost demand for retailers ($R_OrderLostRate[FP_X]$)

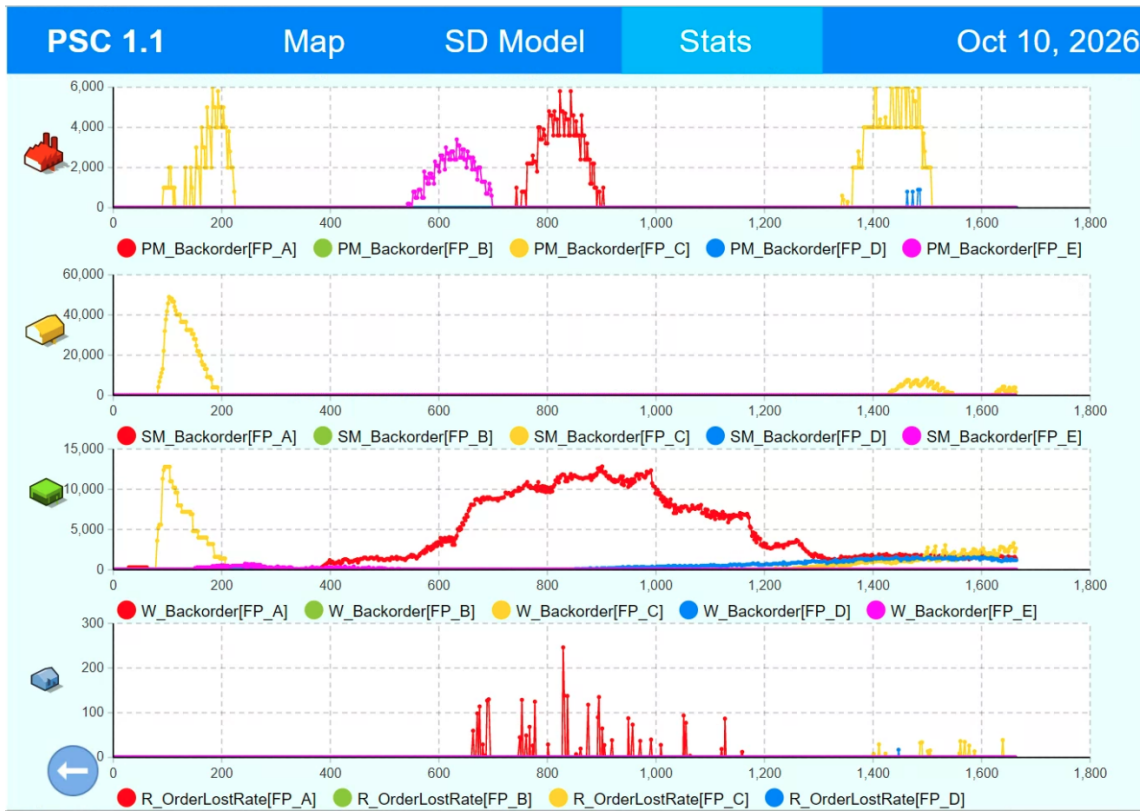


Figure 3.13: Additional performance metric for service level analysis

Moreover, a database of all the orders in the supply chain was 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 subsequent analysis.

Finally, it is worth mentioning that all the metrics presented in Table 4.1 can be drawn for every facility in the SC network allowing a more detailed assessment of the individual performances. Some of these metrics will be presented in the chapters that follow.

Chapter 4

Base Case – Instance, Results & Validation

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 4.1 in which the facilities and their locations are depicted.

4.1 Base Case instance



Figure 4.1: Base-case Simulation Model - Facilities locations

The following facilities and assumptions were considered:

- 2 primary manufacturers located in Asia and North America, operating in a Make-to-Stock strategy:
 - $F1_Namerica$; $F1_Asia$.
- 5 secondary manufacturers, located in North America, South America, Africa, Europe, and Asia, operating in a Make-to-Order strategy:
 - $F2_Namerica$; $F2_Samerica$; $F2_Africa$; $F2_Europe$; $F2_Asia$.
- 8 wholesalers (distributed through 6 continents):
 - $W_Namerica1$; $W_Namerica2$; $W_Samerica$; W_Africa ; $W_Europe1$; $W_Europe2$; $W_Oceania$; W_Asia1 ; W_Asia2 .
- 16 retailers:
 - $C_Namerica1$; $C_Namerica2$; $C_Namerica3$; $C_Samerica1$; $C_Samerica2$; $C_Africa1$; $C_Africa2$; $C_Europe1$; $C_Europe2$; $C_Europe3$; $C_Europe4$; C_Asia1 ; C_Asia2 ; C_Asia3 ; C_Asia4 .

Orders for raw materials and final products are placed to the closest upstream facility, if the facility is currently active (normal conditions, no disruption scenario) and that is preferably located in the same continent. At the retailers, when demand cannot be met, it is assumed to be 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) [9]. Therefore, five products (FP_A - FP_E) 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 4.2.

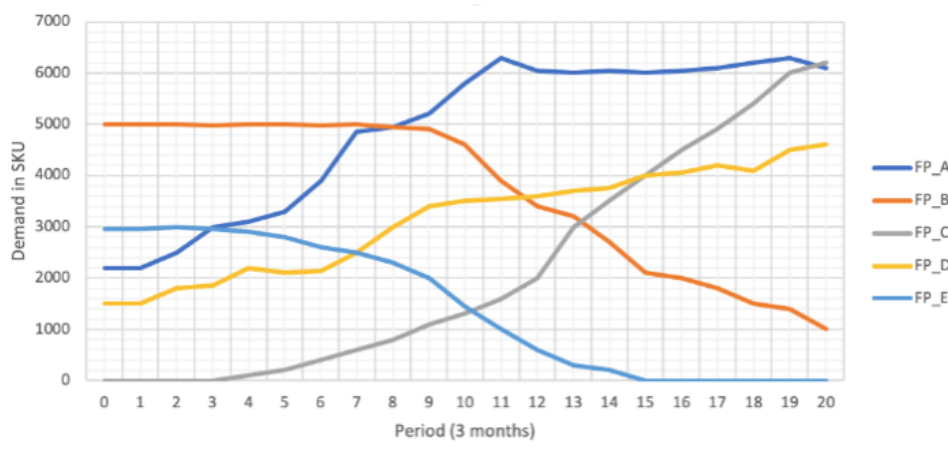


Figure 4.2: Pharmaceutical products demand trajectory, adapted from [9]

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. All results presented in Chapters 4 and 5 correspond to the average of 5 simulation experiments, and all simulation snapshots (Figures) correspond to one of the simulations run.

4.2 Simulation results

Overall Supply Chain performance is presented in Table 4.1, 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, outsourcing costs if applicable and order delays costs, over the 5-year planning horizon.

Table 4.1: Performance metrics for the base-case scenario over the 5 years planning horizon

		PM	SM	Wholesalers	Retailers
Overall service level (%)		99.96%			
Inventory level of final product at the end of the 5 years (SKU)		—	180 767	153 300	89 874
Average Lead Time by facility (h)	Waiting For Stock	21.06 (5%)*	8.37 (2%)*	28.44 (46%)*	—
	Waiting For Transport	3.04 (1%)*	73.06 (19%)*	0 (0%)*	—
	In Transit	362.32 (94%)*	299.80 (79%)*	33.09 (54%)*	—
	Average lead time in each type of facility	386.42	381.23	61.53	—
Profit at the end of 5 years (MMU)	Total Costs by echelon	10 120	21 680	34 420	46 080
	Revenue by echelon	20 760	34 700	46 270	49 690
	Profit by echelon	10 730	13 010	11 870	3 733
	Overall profit	39 260			

* Percentage of the total average lead time per facility.

Table 4.2: Service levels of retailers for the base-case scenario over the 5 years planning horizon

	FP_A	FP_B	FP_C	FP_D	FP_E	
Africa	100%	100%	100%	100%	100%	100%
Asia	100%	100%	100%	100%	100%	100%
North America	100%	100%	100%	100%	100%	100%
South America	100%	100%	100%	100%	100%	100%
Europe	100%	100%	100%	100%	100%	100%
Australia	100%	100%	94.58%	99.35%	100%	99.23%
	100% %	100%	99.72%	99.97%	100%	
Overall service level (%)	99.96%					

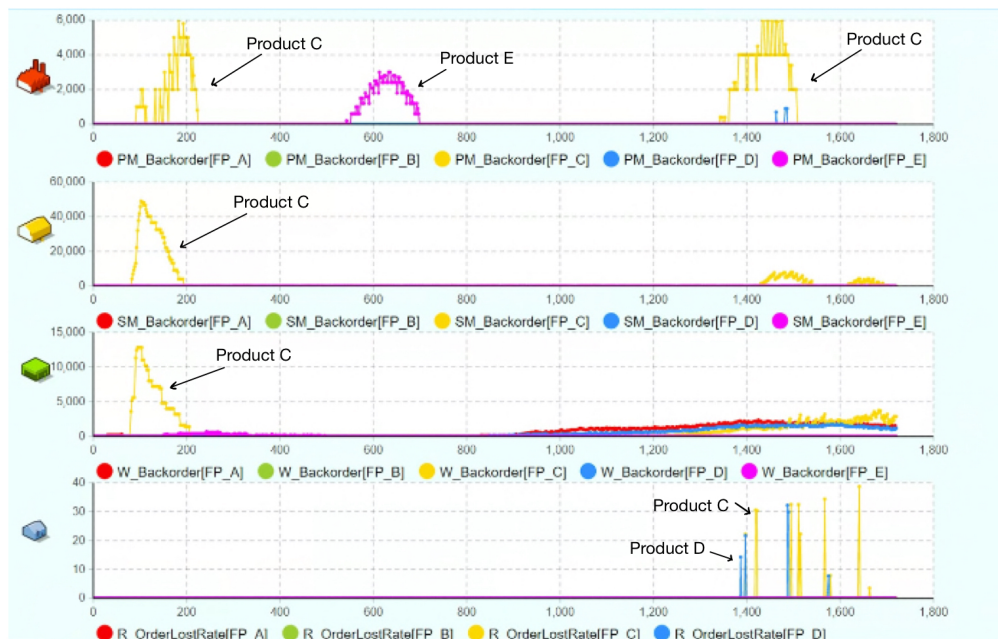
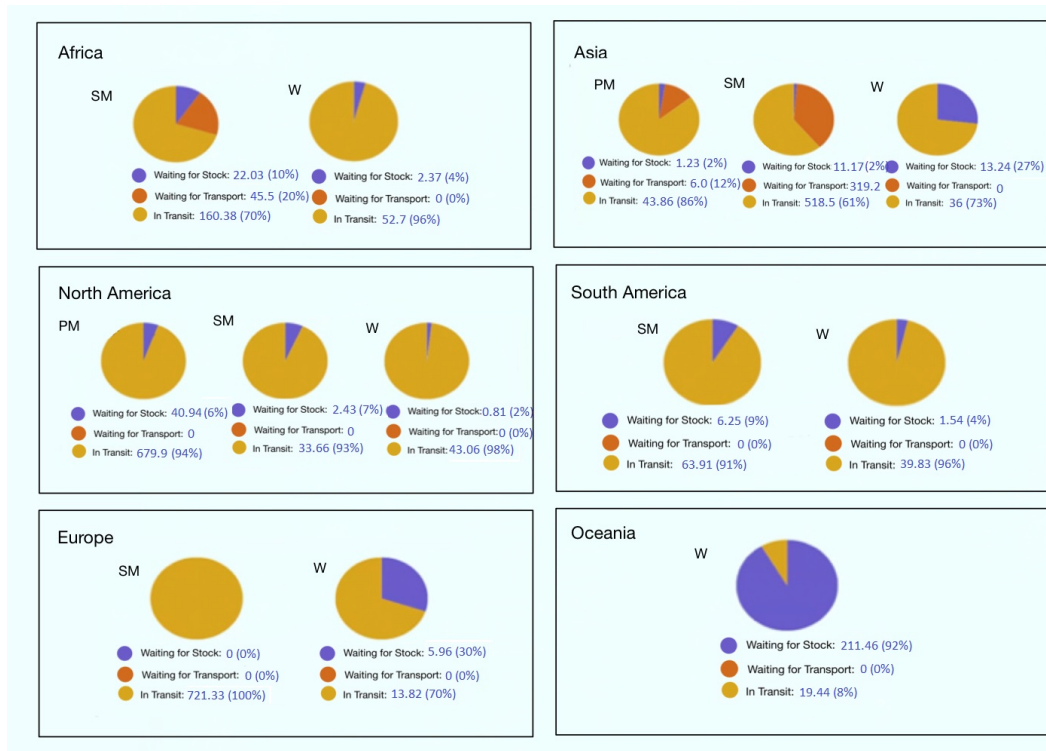
The preliminary results suggest that, under normal conditions, the designed SC network is highly effective with demand satisfaction close to 100% in every retailer (Table 4.2). Moreover, these results clearly show the bullwhip effect observed by the progressively larger inventory levels along the upstream supply chain.

Nevertheless, two potential reasons for concerns with SC performance can be found by paying closer attention to the average lead times section of Table 4.1. The average amount of time that secondary manufacturers (*SM*) keep the finished product in stock before shipping it to a wholesaler is 73 hours, or 18% of the overall lead time. This suggests that an improvement in the transportation options would be beneficial for at least one of the secondary manufacturing plants. Furthermore, a considerable portion of the lead time for *Wholesalers* (47%) is spent waiting for product to become available, which may indicate that one of the facilities has problems managing its inventory.

Further analysis on the lead times (presented in Figure 4.3) reveals that:

- For secondary manufacturers (*SM*), facilities in Africa and Asia are the ones that wait longer for transportation, particularly the one in Asia, which waits an average of 319 hours for transportation to become available.
- When it comes to managing its inventory, the wholesaler in Australia (Oceania in the figure) is fairly ineffective, waiting 92% of the lead time for products to arrive from its supplier, the Secondary manufacturer in Asia.

Figure 4.4 shows that the “most significant failure” that caused the 0.04% decrease in service level was observed after around 4 years (around day 1400). More detailed analysis of service levels presented in Table 4.2 indicates that the main issue is the Australian retailer with an overall service level of 99.23%, and considerable shortage of products C and D. This outcome is comprehensible given that it is the only continent that does not have a secondary manufacturer and needs to rely on the Asian secondary manufacturer (closest facility). Figure 4.4 also demonstrates the upward trend in backordered product and lost sales, which affects Australian wholesalers and retailers. If this SC were to be simulated for a longer period, the service level would likely decline even more. The free version of *AnyLogic* has limitations that prevent the simulation timeframe from being longer.

Figure 4.4: 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*)

It is also important to note the abrupt rise in product C backorders around day 70 in all levels of the SC, except for the retailers, as seen in Figure 4.4. This increase occurs because the launch of product C on the market happened around that period (Figure 4.2).

4.3 Validation of the simulation model

There is no entirely conclusive method for verifying the suggested system's model. If there was, there might not have been a need for a simulation model in the first place [33]. The most convincing measure of a simulation model's validity is demonstrating that its output data closely reflects that of the current system [33].

Although a pharmaceutical industry supply chain is a real system, gathering information from a specific supply chain and collecting performance data is extremely difficult since this industry is highly controlled and confidential. Therefore, no direct comparison of simulation data with real data can be made.

Regardless, simulation results should be reviewed for reasonableness. If the results are consistent with how system's operations are perceived (Section 3.2), and the model is accurate for the proposed objectives, then the simulation model is said to have face *validity* [33, 57]. Depending on the model's intended usage and the utility function of the decision-maker, different levels of accuracy will be needed [57].

Considering: (i) all the requirements and assumptions collected after extensive bibliographical research on the pharmaceutical industry presented in Section 3.2; (ii) the simplifications, also detailed in Section 3.2, for an adequate level of abstraction such that model is useful; (iii) that the goal is to identify supply chain vulnerabilities and inefficiencies so that proactive measures can be applied; (iv) SC behavior shows evidence of being realistic enough through concepts normally observed in SC;

We can consider that, for the objectives presented for the dissertation, the model is considered valid.

4.4 Methodological framework for simulation experiments

In order to understand how proactive risk mitigating strategies can be used to cope with disruptive scenarios, the following methodological framework for simulation experiments was developed (Figure 4.5).

Some disruptive scenarios relating to events that might affect a pharmaceutical supply chain were established after testing and confirming the base case scenario.

The primary areas of concern were discovered after an analysis of the effects on PSC. Following some careful examination, mitigation strategies to limit these consequences were developed and implemented for the disruptive scenario's SC setup.

The optimum SC configuration was determined after analysing and comparing mitigation strategies in light of decision-maker goals.

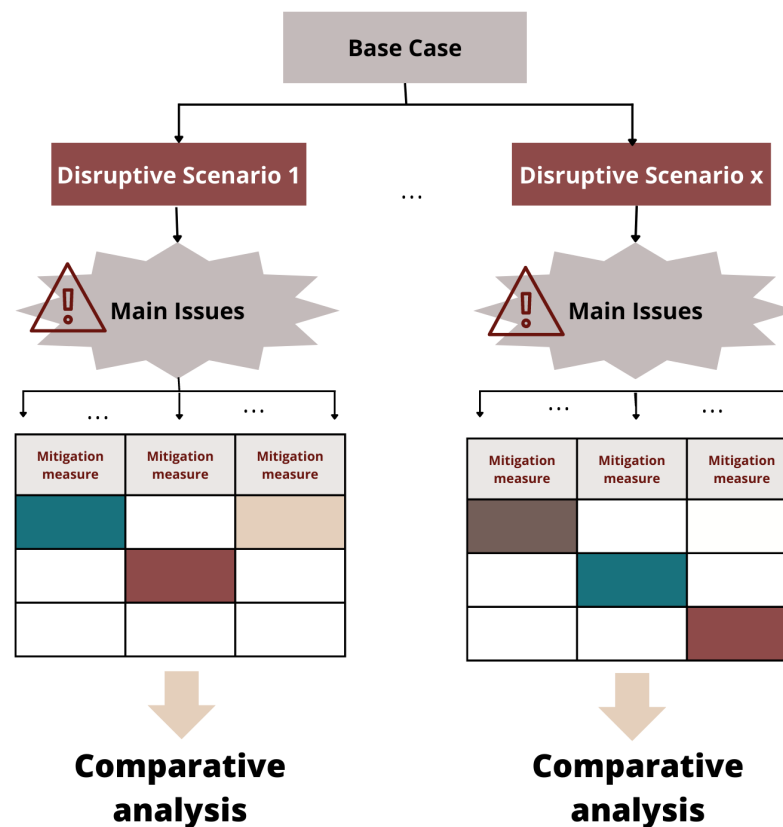


Figure 4.5: Methodological framework for simulation experiments

Possible mitigation measures considered in this work are:

- Increasing safety stock;
- Outsourcing product from facilities outside SC, at the secondary manufacturing level (with higher costs associated);
- Increasing production capacity, by investing in new production lines at the secondary manufacturing level.

Other possible measures that do not correspond to upscale/downscale in production capacity:

- Increasing available transport in facilities;
- Redirect orders to facilities that are less restricted.

Chapter 5

Simulation Experiments

As the main goal of the work proposed in this dissertation 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.

5.1 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 [2]. 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). The new demand profile is the one presented in Figure 5.1.

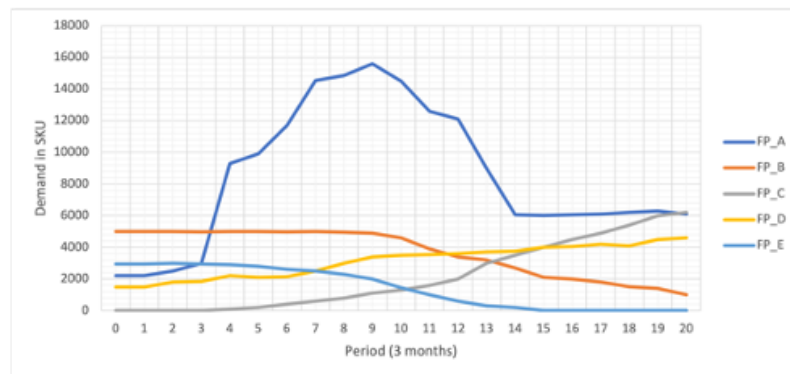


Figure 5.1: Pharmaceutical products demand trajectory for disruption scenario 1

5.1.1 Simulation Results

Preliminary results regarding the SC performance under an increase in demand for product A are depicted in Table 5.1 and Figure 5.2. 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.

Table 5.1: Performance metrics for disruptive scenario 1, over the 5 years planning horizon

		PM	SM	Wholesalers	Retailers
Overall service level (%)		99.76%			
Inventory level of final product at the end of the 5 years (SKU)		—	179 168	154 600	90 505
Average Lead Time by facility (h)	Waiting For Stock	32.52 (5%)*	8.65 (2%)*	34.8 (51%)*	—
	Waiting For Transport	3.72 (1%)*	69.12 (19%)*	0 (0%)*	—
	In Transit	368.01 (91%)*	277.08 (78%)*	33.44 (49%)*	—
	Average lead time in each type of facility	404.25	354.86	68.14	—
Profit at the end of 5 years (MMU)	Total Costs by echelon	10 130	23 080	41 320	55 780
	Revenue by echelon	22 030	41 590	55 950	60 100
	Profit by echelon	11 900	18 510	14 630	4 322
	Overall profit	49 370			

* Percentage of the total average lead time per facility.

Firstly, despite the reduced decrease in overall service level, a significant number of backorders in wholesalers were registered (Figure 5.2). Further analysis presented in Figure 5.3 shows that the backorders start to occur in the Australian wholesaler just one month after disruption, around 9 months after disruption in the South American wholesaler, and in wholesaler *W_Asia1* around 1.5 years after, with a total value of 6 500 000 SKU.

Moreover, the backorders occurring at the wholesalers impacted the retailers in Asia (service level = 99,39%) and Australia (98,27%) only 9 months later, when the first lost in sales occurred (Figure 5.4 and Table 5.2). This means that during the 9 month period, retailers were able to

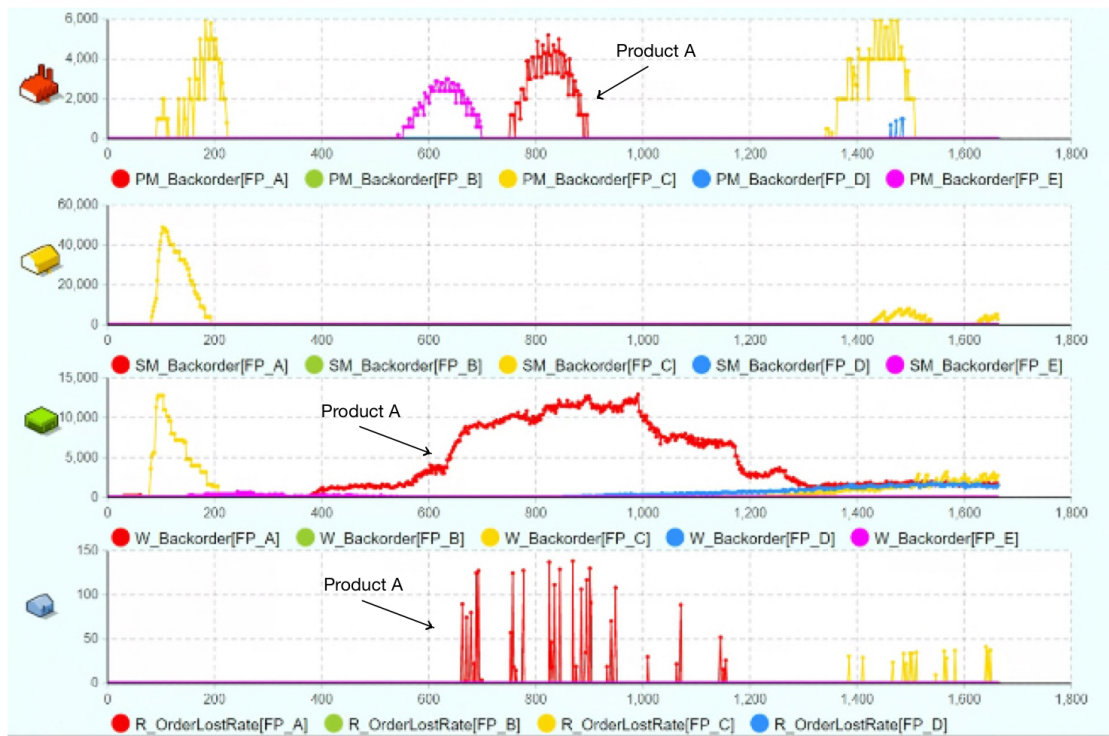


Figure 5.2: Amount of backorders in each echelon (*PM_Backorder*, *SM_Backorder* and *W_Backorder*) and the amount of lost sales per day in retailers (*R_OrderLostRate*) for disruptive scenario 1

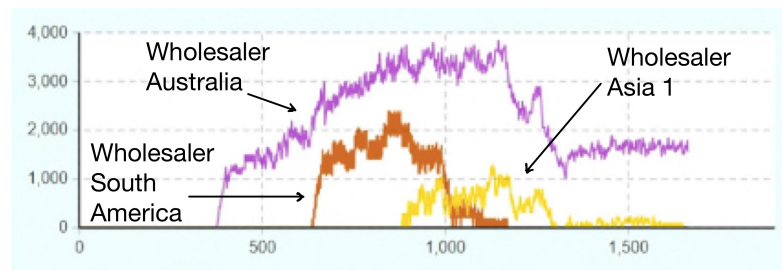


Figure 5.3: Backorders of product A at the *Wholesaler* level, for disruptive scenario 1

manage their demand through the available inventory, and the inventory of the South American Retailer was enough to prevent this market to be affected.

Table 5.1 also shows that inventory at secondary manufacturers (*SM*) has marginally dropped, indicating that the current safety stock level at *SM* is sufficient to serve as a buffer for this specific case of rise in demand.

Finally, despite a little drop in service level, SC profit increased (Table 5.1). This is reasonable, as increased demand ultimately leads to more sales and, as a result, more revenues. Even though costs increased, there was still a reasonably higher profit across all SC levels.

Overall, these results seem to show that the SC is sensitive to relatively small disturbances in

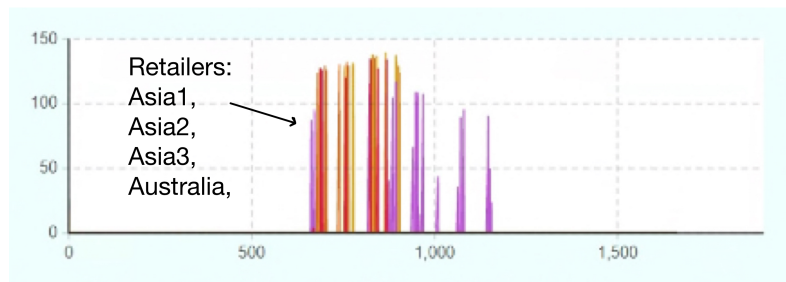


Figure 5.4: Backorders of product A at the *Retailer* level for disruptive scenario 1

Table 5.2: Service levels of *Retailers* for disruptive scenario 1, over the 5 years planning horizon

	FP_A	FP_B	FP_C	FP_D	FP_E	
Africa	100%	100%	100%	100%	100%	100%
Asia	98.68%	100%	100%	100%	100%	99.39%
North America	100%	100%	100%	100%	100%	100%
South America	100%	100%	100%	100%	100%	100%
Europe	100%	100%	100%	100%	100%	100%
Australia	97.2%	100%	95.09%	99.92%	100%	98.27%
	99.54%	100%	99.75%	100%	100%	
Overall service level (%)	99.76%					

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.

Nevertheless, it may still be worth to try to improve SC performance. As only wholesalers and retailers were affected by this specific scenario, measures involving the secondary manufacturing level, like increasing production capacity, shouldn't be applied as they won't produce significant improvements. As a result one mitigation measure was designed where the safety stock for product A is increased in 20% its original value, in all wholesalers and retailers affected by the disruption (C_Asia1 , C_Asia2 , C_Asia3 , $C_oceania$, $W_Oceania$, $W_Samerica$ and W_Asia1).

5.1.2 Mitigation measure 1: *Increase safety stock*

The results in Table 5.3 and Table 5.4 reveal an overall improvement in service level, with product shortages at retailers practically eliminated.

Backorders at wholesalers have also decreased (Figure 5.5), falling from 6 500 000 to 4 700 000 (decrease in 28%). However, this improvement in service level comes at a cost to wholesalers and retailers, as an increase in safety stock translates into an increase in inventory costs.

In terms of profit, since more demand was satisfied and the number of backorders decreased dramatically, the overall profit increased, despite the increase in inventory costs caused by the increase in safety stock.

Table 5.3: Performance metrics for the mitigation measure applied to disruption scenario 1, over the 5 years planning horizon

		PM	SM	Wholesalers	Retailers
Overall service level (%)		99.89%			
Inventory level of final product at the end of the 5 years (SKU)		—	179 337	156 950	93 067
Average Lead Time by facility (h)	Waiting For Stock	40.17 (10%)*	9.69 (3%)*	34.8 (51 %)*	—
	Waiting For Transport	4.07 (1%)*	63.78 (18 %)*	0 (0%)*	—
	In Transit	359.91 (89%)*	272.01 (79%)*	33.13 (54%)*	—
	Average lead time in each type of facility	404.15	345.48	61.01	—
Profit at the end of 5 years (MMU)	Total Costs by echelon	10 140	23 060	41 380	55 840
	Revenue by echelon	22 090	41 660	56 010	60 130
	Profit by echelon	11 950	18 600	14 630	4 293
	Overall profit	49 480			

* Percentage of the total average lead time per facility.

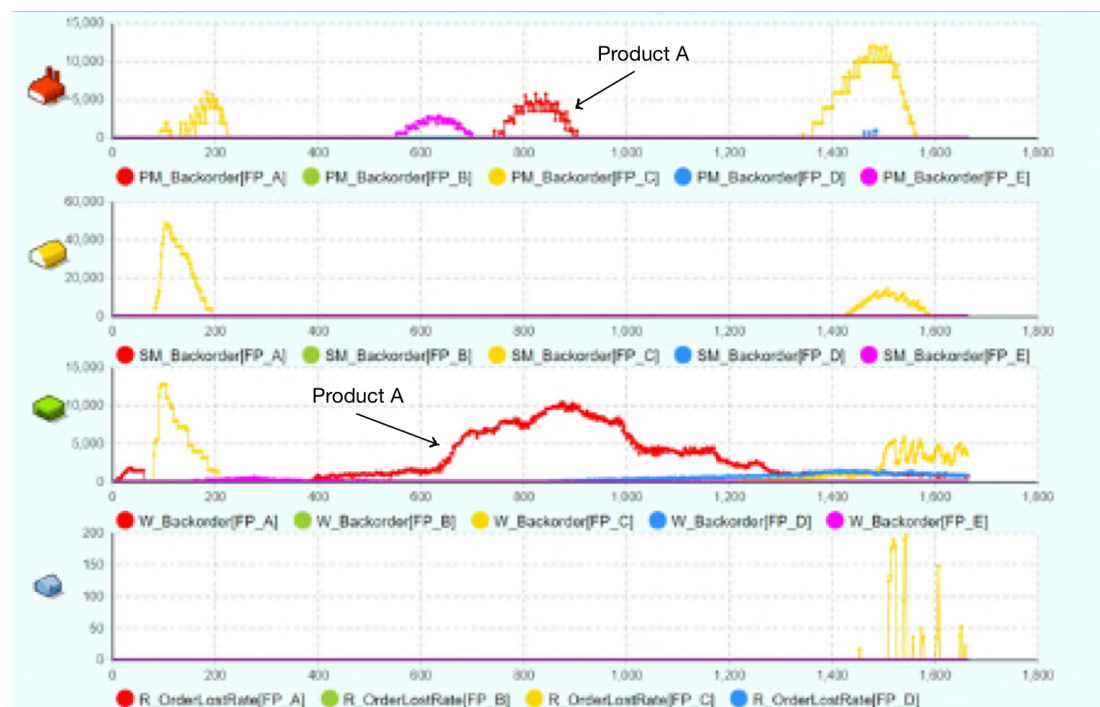
Figure 5.5: Amount of backorders in each echelon (*PM_Backorder*, *SM_Backorder* and *W_Backorder*) and the amount of lost sales per day in retailers (*R_OrderLostRate*) for mitigation measure applied to disruptive scenario 1

Table 5.4: Service levels of *Retailers* for mitigation measure applied to disruptive scenario 1, over the 5 years planning horizon

	FP_A	FP_B	FP_C	FP_D	FP_E	
Africa	100%	100%	100%	100%	100%	100%
Asia	100%	100%	100%	100%	100%	100%
North America	100%	100%	100%	100%	100%	100%
South America	100%	100%	100%	100%	100%	100%
Europe	100%	100%	100%	100%	100%	99.67%
Australia	99.66%	100%	97.72%	99.94%	100%	99.63%
	99.98%	100%	98.83%	100%	100%	
Overall service level (%)	99.89% (+0.13%*)					

* In relation to the results from disruptive scenario 1

5.1.3 Disruption scenario 1 assessment

Table 5.5: Comparison of performance metrics for disruption scenario 1

(Difference to the base case)		Base Case	Disruptive scenario	Mitigation measure 1
Service level		99.96%	99.76% (-0.20%*)	99.89% (-0.07%*)
Stocks (SKU)	SM	180 767	179 168	179 337
	W	153 300	154 600	156 950
	R	89 874	90 505	93 067
Lead Times (h)	PM	386.42	404.25	404.15
	SM	381.23	354.86	345.48
	W	61.53	68.14	61.01
Profit (MMU)		39 260	49 370	49 480

* In relation to the results from the base case.

Table 5.9 compares the key performance indicators for the base case instance, the disruptive scenario in which there is an increase in demand, and the corresponding mitigation strategy of raising safety stock by 20% in impacted facilities.

The findings appear to indicate that increasing safety stock at affected wholesalers and retailers mitigates the disruption caused by increased demand. Testing the base case with other scenarios of increasing demand should be undertaken to see whether a 20% increase was sufficient to cover all situations or whether a different increase value would be preferable.

It is also worth mentioning that increasing safety stock results in more product on hold. One factor that is not addressed in this paper but is critical to PSCs is the fact that medications have expiry dates. As a result, greater inventory may be undesirable since it will have to be discarded.

As for the lead times, increased safety stock at wholesalers and retailers means more orders are sent from primary manufacturers. As a result, there has been an increase in primary production lead times.

In terms of costs, increase in demand naturally results in increase sales, therefore more revenue. Applying mitigation measure 1 to the disruptive scenario eliminates some of the lost sales, so additional revenue is added.

5.2 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).

5.2.1 Simulation Results

The main results depicted in Table 5.6 and Figure 5.6, show a more significant decrease in the overall service level with a value of 96.15%. 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 5.6: Performance metrics for disruption scenario 2 over the 5 years planning horizon.

		PM	SM	Wholesalers	Retailers
Overall service level (%)		96.15%			
Inventory level of final product at the end of the 5 years (SKU)		—	179 265	156 650	93 499
Average Lead Time by facility (h)	Waiting For Stock	20.22 (5%)*	23.41 (6%)*	33.93 (50 %)*	—
	Waiting For Transport	3.01 (1%)*	92.66 (23%)*	0 (0%)*	—
	In Transit	361.29 (94%)*	290.08 (71%)*	33.33 (50%)*	—
	Average lead time in each type of facility	384.52	406.15	67.26	—
Profit at the end of 5 years (MMU)	Total Costs by echelon	10 380	22 910	35 200	47 050
	Revenue by echelon	21 720	35 430	47 320	50 720
	Profit by echelon	11 340	12 530	12 120	3 668
	Overall profit	39 650			

* Percentage of the total average lead time per facility.

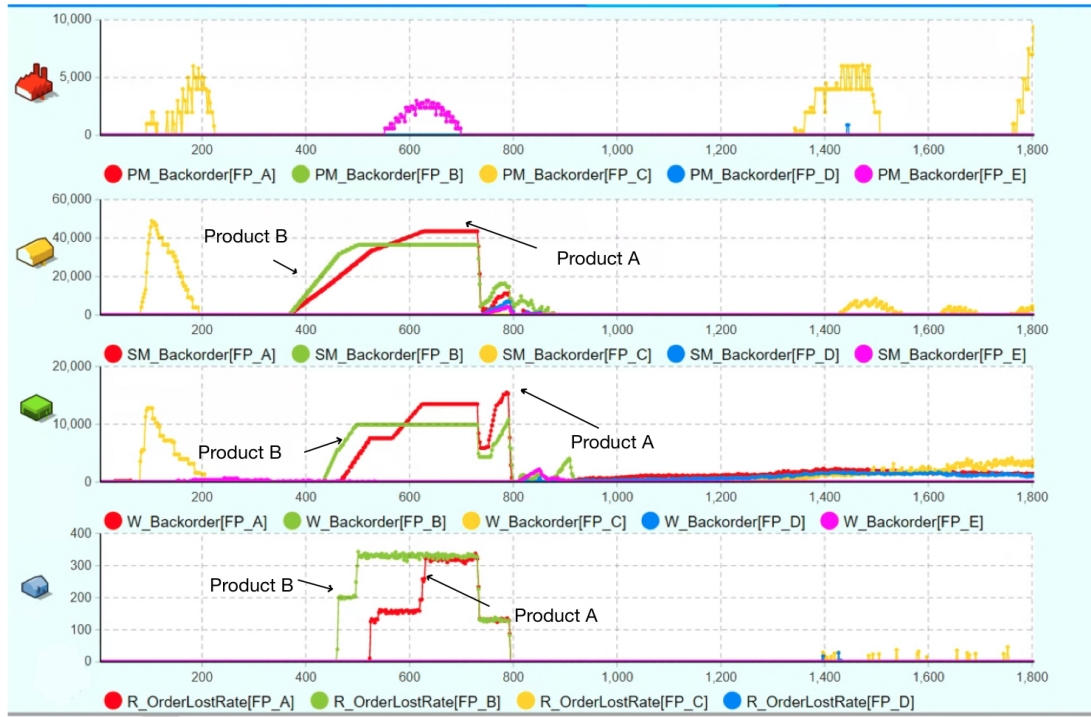


Figure 5.6: Backorders quantities in each echelon ($PM_Backorder$, $SM_Backorder$ and $W_Backorder$) and the amount of lost sales per day in retailers ($R_OrderLostRate$), for disruption scenario 2

As presented in Figure 5.6, 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 5.6 and Figure 5.7).

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.

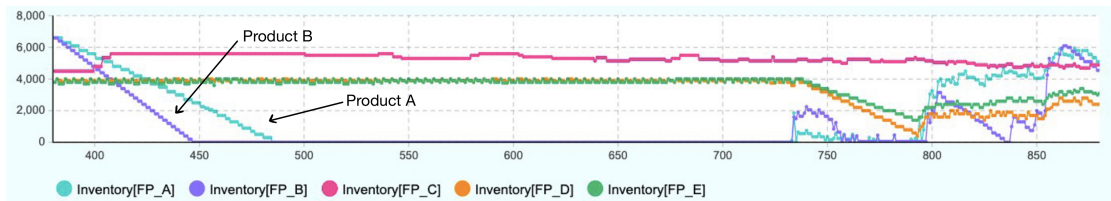


Figure 5.7: Inventory level over time of European secondary manufacturer for the case of disruption scenario 2

To conclude this analysis, three main issues have been identified:

1. a decrease in service level of products A and B in European and Asian retailers;
2. backorders of product A and B in wholesalers located in Asia and Europe;
3. backorders of products A and B in the affected facility (Europe).

To contain these negative effects, mitigation measures presented in Figure 5.8 were implemented.

<u>Main issues identified:</u>	<u>Mitigation measure 1:</u>
- Decrease of service level of products A and B in European and Asian retailers	Increase safety stock of products A and B by 20% in retailers, wholesalers and secondary manufacturers affected by disruption.
- Backorders in European (<i>W_Europe1</i> and <i>W_Europe2</i>) and Asian (<i>W_Asia1</i> and <i>W_Asia2</i>) wholesalers	<u>Mitigation measure 2:</u>
- Backorders of products A and B in European secondary manufacturing facility	Outsourcing of products A and B in secondary manufacturer located in Europe from day 455 until day 820.
	<u>Mitigation measure 3:</u>
	Increase production capacity in Europe through the opening of new production lines of products A and B
	<u>Mitigation measure 4:</u>
	Redirect orders of products A and B to other facilities.

Figure 5.8: Mitigation measures applied to disruptive scenario 2

These measures try to contain the disruptions through different strategies:

- The first mitigation measure attempts to counteract the reduced manufacturing capacity of products A and B by increasing safety stock. Therefore, safety stocks of products A and B are increased by 20% of its value in affected facilities:
- The second mitigation measure attempts to contain disruption by intervening directly at the source of disruption, the secondary manufacturing facility located in Europe. This measure consists in outsourcing products A and B around the time that disruption is noticed (It is assumed that a disruption is noticed about 2 months after it has effectively started).
- The third mitigation measure is a different measure for increasing producing capacity, this time by opening new production lines of products A and B in European secondary manufacturing facility. It is assumed that the order for production line construction is given at the beginning of simulation ($t = 0$), and that it takes 6 months for the production line to be operational.

- Finally, one last mitigation measure where disruption is attempted to be contained by redirecting orders of products A and B to other facilities, when the production lines of the European facility are affected.

5.2.2 Mitigation measure 1: *Increase safety stock*

The results in Table 5.7 show an overall increase in service level, with the product shortages at the retailers being delayed for approximately one month for product A and 20 days for product B (Figure 5.9). 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 analysis, the increased costs were compensated by the slight increase in the demand satisfaction.

Table 5.7: Performance metrics for mitigation measure 1 applied to disruption scenario 2, over the 5 years planning horizon

		PM	SM	Wholesalers	Retailers
Overall service level (%)		96.67%			
Inventory level of final product at the end of the 5 years (SKU)		—	182 369	171 600	100 600
Average Lead Time by facility (h)	Waiting For Stock	20.01 (5%)*	41.39 (9%)*	28.24 (46%)*	—
	Waiting For Transport	7.89 (2%)*	94.29 (21%)*	0 (0%)*	—
	In Transit	363.22 (93%)*	304.02 (69%)*	33.07 (54%)*	—
	Average lead time in each type of facility	391.12	439.69	61.36	—
Profit at the end of 5 years (MMU)	Total Costs by echelon	10 120	22 950	35 320	46 990
	Revenue by echelon	21 720	35 490	47 290	50 580
	Profit by echelon	11 340	12 540	11 980	3 581
	Overall profit	39 710			

* Percentage of the total average lead time per facility.

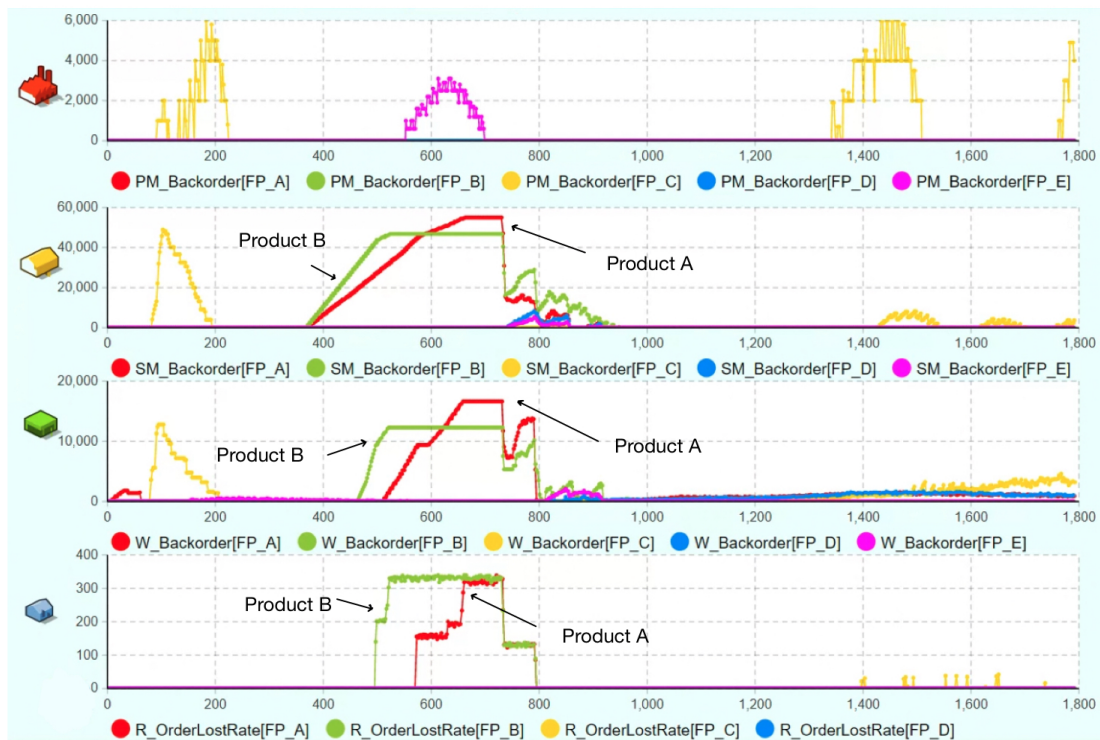


Figure 5.9: Backorders quantities in each echelon (*PM_Backorder*, *SM_Backorder* and *W_Backorder*) and the amount of lost sales per day in retailers (*R_OrderLostRate*), for mitigation measure 1 applied to disruption scenario 2

5.2.3 Mitigation measure 2: *Outsource product*

The results in Table 5.8 and Figure 5.10 show that, outsourcing 10 000 SKU of product A and B on a monthly basis translates into an overall increase in service level, with disruption being contained directly in the source.

This translates into a decrease in lead times at the secondary manufacturing level, as product availability increases with the monthly arrival of outsourced product.

Even though outsourcing product comes with associated costs, that are higher than the ones associated with the manufacturing process, overall profit is still comparable to the one of previous scenarios. For this specific case, outsourcing alone accounted for 12 MMU of the total costs presented in SM column of Table 5.7.

Table 5.8: Performance metrics for mitigation measure 2 applied to disruption scenario 2, over the 5 years planning horizon

		PM	SM	Wholesalers	Retailers
Overall service level (%)		99.97%			
Inventory level of final product at the end of the 5 years (SKU)		—	180 018	155 200	90 431
Average Lead Time by facility (h)	Waiting For Stock	22.35 (6%)*	10.60 (3%)*	27.38 (45%)*	—
	Waiting For Transport	3.26 (1%)*	74.11 (20%)*	0 (0%)*	—
	In Transit	362.87 (93%)*	293.57 (78%)*	33.05 (55%)*	—
	Average lead time in each type of facility	391.12	378.28	60.44	—
Profit at the end of 5 years (MMU)	Total Costs by echelon	10 000	20 870	34 420	46 090
	Revenue by echelon	19 980	34 680	46 290	49 690
	Profit by echelon	9 978	13 810	11 860	3 605
	Overall profit	39 260			

* Percentage of the total average lead time per facility.



Figure 5.10: Backorders quantities in each echelon (*PM_Backorder*, *SM_Backorder* and *W_Backorder*) and the amount of lost sales per day in retailers (*R_OrderLostRate*), for mitigation measure 2 applied to disruption scenario 2

Figure 5.11 clearly captures the monthly outsourcing pattern, and its influence on the inventory levels of the European manufacturing facility. The amount outsourced for product A appears to be sufficient to prevent backorders; however, the quantity outsourced for product B is insufficient as a clear pattern of backordered product can be seen in Figure 5.11.

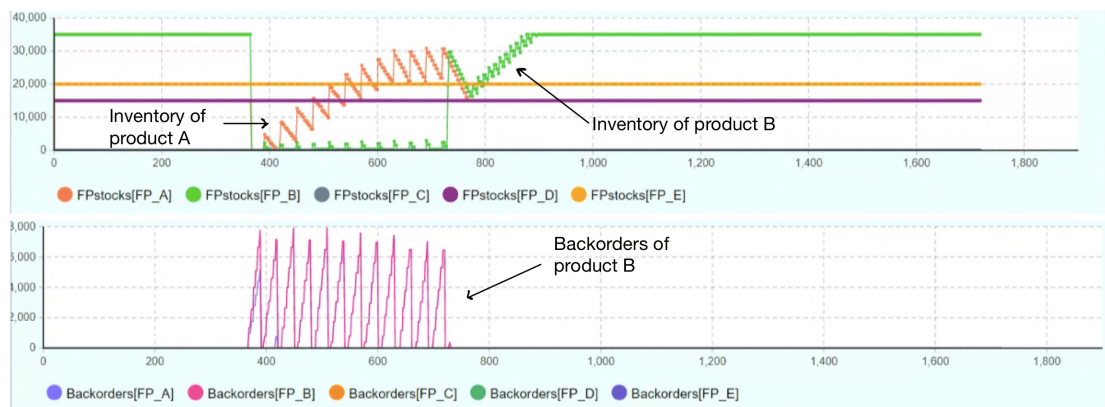


Figure 5.11: Inventory level over time of European secondary manufacturer for the case of disruption scenario 2, along with the amount of backordered product

5.2.4 Mitigation measure 3: *Increase production capacity*

Results in Table 5.9 and Figure 5.13 show that increasing production capacity also translates into an overall service level, with disruption being contained.

This increase in production capacity is obtained by opening production lines at the European manufacturing facility for products A and B. The order to open this production line is given at simulation startup, but these lines are only operational 6 months after.

The beginning of operations can be identified in Figure 5.13 with the sudden increase in back-orders of product at the secondary manufacturing level, caused by the stabilization of production line operations.

These new production lines cause the increase in inventory observed in Table 5.9, as well as the increase in costs at SM level.

It is also worth noting that the costs associated with opening the production lines are not taken into account in the data shown in Table 5.9, so the actual PSC profit needs to be decreased in the value associated with construction of 2 new production lines.

Table 5.9: Performance metrics for mitigation measure 3 applied to disruption scenario 2, over the 5 years planning horizon

		PM	SM	Wholesalers	Retailers
Overall service level (%)		99.97%			
Inventory level of final product at the end of the 5 years (SKU)		—	190 175	172 800	95 486
Average Lead Time by facility (h)	Waiting For Stock	24.55 (8%)*	11.80 (3%)*	21.80 (40%)*	—
	Waiting For Transport	7.84 (3%)*	68.47 (17%)*	0 (0%)*	—
	In Transit	276.2 (90%)*	320.94 (80%)*	32.91 (60%)*	—
	Average lead time in each type of facility	308.58	401.21	54.71	—
Profit at the end of 5 years (MMU)	Total Costs by echelon	10 920	19 000	34 540	46 030
	Revenue by echelon	21 650	28 470	46 200	49 550
	Profit by echelon	10 720	9 469	11 670	3 517
	Overall profit	35 370			

* Percentage of the total average lead time per facility.



Figure 5.12: Inventory level over time of European secondary manufacturer for the case of disruption scenario 3, along with the amount of backordered product

5.2.5 Mitigation measure 4: Redirect orders

The last mitigation measure applied to this disruptive scenario corresponds to the redirecting of orders to a different facility, when manufacturing is halted. Therefore, between days 365 and 730, orders of products A and B that were directed at the secondary manufacturing facility located in Europe will be placed with the closest secondary manufacturing facility that has product in inventory.

The results in Table 5.10 and Figure 5.13 show that this new placing of orders translates into an overall increase in service level, with disruption being contained.

In Figure 5.14, data collected from the simulation database is displayed. Information depicted in this figure relates to the log of orders made during the simulation. The specific instance of Figure 5.14 corresponds to applying a filter to only show products A and B, and for destination to be the affected facilities (W_Asia2 , $W_Europe2$ and $W_Europe1$).

After order with id=8352, the shift in the origin facilities is evident. After 1 year of simulation, orders of product A and B that were directed to Europe are now handled by secondary manufacturing facilities located in Asia, Africa and North America. These facilities can accommodate these new orders, without resulting in backorders.

In table 5.10 it is also noted that this measure translates into an increase in the primary manufacturing lead times, specifically in the time that an orders spends being transported between

facilities. This is understandable as orders for product A and B are no longer being made to the closest facility.

Table 5.10: Performance metrics for mitigation measure 4 applied to disruption scenario 2, over the 5 years planning horizon

		PM	SM	Wholesalers	Retailers
Overall service level (%)		99.96%			
Inventory level of final product at the end of the 5 years (SKU)		—	181 048	154 000	90 040
Average Lead Time by facility (h)	Waiting For Stock	23.32 (8%)*	9.22 (2%)*	30.28 (48%)*	—
	Waiting For Transport	3.48 (1%)*	94.66 (22%)*	0 (0%)*	—
	In Transit	377.3 (93%)*	320.64 (76%)*	33.11 (52%)*	—
	Average lead time in each type of facility	404.10	424.52	63.39	—
Profit at the end of 5 years (MMU)	Total Costs by echelon	10 060	21 930	34 420	46 090
	Revenue by echelon	20 990	34 670	46 280	49 690
	Profit by echelon	10 930	12 740	11 860	3 601
	Overall profit	39 130			

* Percentage of the total average lead time per facility.



Figure 5.13: Backorders quantities in each echelon (*PM_Backorder*, *SM_Backorder* and *W_Backorder*) and the amount of lost sales per day in retailers (*R_OrderLostRate*), for mitigation measure 4 applied to disruption scenario 2

	id	origin	destination	product_ordered	quantity	time_of_order	stock_ok	time_stock_ok	delay_stock	sent	time_sent	delay
494	8,229	F2_Europe	W_Asia2	FP_B	400	20-03-2023 00:00:00	✓	20-03-2023 00:00:00	0	✓	20-03-2023 00:00:00	
495	8,230	F2_Europe	W_Asia2	FP_A	300	20-03-2023 00:00:00	✓	20-03-2023 00:00:00	0	✓	20-03-2023 00:00:00	
496	8,248	F2_Europe	W_Europe2	FP_B	400	20-03-2023 00:00:00	✓	20-03-2023 00:00:00	0	✓	20-03-2023 00:00:00	
497	8,249	F2_Europe	W_Europe2	FP_A	200	20-03-2023 00:00:00	✓	20-03-2023 00:00:00	0	✓	20-03-2023 00:00:00	
498	8,253	F2_Europe	W_Europe1	FP_B	400	20-03-2023 00:00:00	✓	20-03-2023 00:00:00	0	✓	20-03-2023 00:00:00	
499	8,254	F2_Europe	W_Europe1	FP_A	200	20-03-2023 00:00:00	✓	20-03-2023 00:00:00	0	✓	20-03-2023 00:00:00	
500	8,352	F2_Asia	W_Asia2	FP_B	650	24-03-2023 00:00:00	✓	24-03-2023 00:00:00	0	✓	24-03-2023 00:00:00	
501	8,353	F2_Asia	W_Asia2	FP_A	300	24-03-2023 00:00:00	✓	24-03-2023 00:00:00	0	✓	24-03-2023 00:00:00	
502	8,370	F2_Namerica	W_Europe2	FP_B	400	24-03-2023 00:00:00	✓	24-03-2023 00:00:00	0	✓	24-03-2023 00:00:00	
503	8,371	F2_Africa	W_Europe2	FP_A	350	24-03-2023 00:00:00	✓	24-03-2023 00:00:00	0	✓	24-03-2023 00:00:00	
504	8,375	F2_Namerica	W_Europe1	FP_B	400	24-03-2023 00:00:00	✓	24-03-2023 00:00:00	0	✓	24-03-2023 00:00:00	
505	8,376	F2_Africa	W_Europe1	FP_A	400	24-03-2023 00:00:00	✓	24-03-2023 00:00:00	0	✓	24-03-2023 00:00:00	
506	8,494	F2_Namerica	W_Europe1	FP_B	400	28-03-2023 01:00:00	✓	28-03-2023 01:00:00	0	✓	28-03-2023 01:00:00	
507	8,490	F2_Africa	W_Europe2	FP_A	200	28-03-2023 01:00:00	✓	28-03-2023 01:00:00	0	✓	28-03-2023 01:00:00	
508	8,489	F2_Namerica	W_Europe2	FP_B	400	28-03-2023 01:00:00	✓	28-03-2023 01:00:00	0	✓	28-03-2023 01:00:00	
509	8,495	F2_Africa	W_Europe1	FP_A	200	28-03-2023 01:00:00	✓	28-03-2023 01:00:00	0	✓	28-03-2023 01:00:00	
510	8,474	F2_Asia	W_Asia2	FP_B	400	28-03-2023 01:00:00	✓	28-03-2023 01:00:00	0	✓	28-03-2023 01:00:00	
511	8,475	F2_Asia	W_Asia2	FP_A	300	28-03-2023 01:00:00	✓	28-03-2023 01:00:00	0	✓	28-03-2023 01:00:00	
512	8,604	F2_Africa	W_Europe1	FP_A	300	01-04-2023 01:00:00	✓	01-04-2023 01:00:00	0	✓	01-04-2023 01:00:00	
513	8,603	F2_Namerica	W_Europe1	FP_B	400	01-04-2023 01:00:00	✓	01-04-2023 01:00:00	0	✓	01-04-2023 01:00:00	
514	8,600	F2_Africa	W_Europe2	FP_A	350	01-04-2023 01:00:00	✓	01-04-2023 01:00:00	0	✓	01-04-2023 01:00:00	
515	8,583	F2_Asia	W_Asia2	FP_B	650	01-04-2023 01:00:00	✓	01-04-2023 01:00:00	0	✓	01-04-2023 01:00:00	
516	8,584	F2_Asia	W_Asia2	FP_A	300	01-04-2023 01:00:00	✓	01-04-2023 01:00:00	0	✓	01-04-2023 01:00:00	
517	8,599	F2_Namerica	W_Europe2	FP_B	400	01-04-2023 01:00:00	✓	01-04-2023 01:00:00	0	✓	01-04-2023 01:00:00	
518	8,691	F2_Asia	W_Asia2	FP_B	300	05-04-2023 01:00:00	✓	05-04-2023 01:00:00	0	✓	05-04-2023 01:00:00	
519	8,692	F2_Asia	W_Asia2	FP_A	300	05-04-2023 01:00:00	✓	05-04-2023 01:00:00	0	✓	05-04-2023 01:00:00	
520	8,707	F2_Namerica	W_Europe2	FP_B	400	05-04-2023 01:00:00	✓	05-04-2023 01:00:00	0	✓	05-04-2023 01:00:00	
521	8,708	F2_Africa	W_Europe2	FP_A	200	05-04-2023 01:00:00	✓	05-04-2023 01:00:00	0	✓	05-04-2023 01:00:00	
522	8,711	F2_Namerica	W_Europe1	FP_B	400	05-04-2023 01:00:00	✓	05-04-2023 01:00:00	0	✓	05-04-2023 01:00:00	
523	8,712	F2_Africa	W_Europe1	FP_A	200	05-04-2023 01:00:00	✓	05-04-2023 01:00:00	0	✓	05-04-2023 01:00:00	
524	8,830	F2_Namerica	W_Europe1	FP_B	400	09-04-2023 01:00:00	✓	09-04-2023 01:00:00	0	✓	09-04-2023 01:00:00	
525	8,826	F2_Africa	W_Europe2	FP_A	300	09-04-2023 01:00:00	✓	09-04-2023 01:00:00	0	✓	09-04-2023 01:00:00	
526	8,825	F2_Namerica	W_Europe2	FP_B	400	09-04-2023 01:00:00	✓	09-04-2023 01:00:00	0	✓	09-04-2023 01:00:00	
527	8,831	F2_Africa	W_Europe1	FP_A	300	09-04-2023 01:00:00	✓	09-04-2023 01:00:00	0	✓	09-04-2023 01:00:00	

Figure 5.14: Snapshot of database containing the register of *Orders* placed during the 5 year simulation period, for instance of mitigation measure 4 applied to disruption scenario 2

5.2.6 Disruption scenario 2 assessment

Table 5.11: Comparison of performance metrics for disruption scenario 2

		Base Case	Disruptive scenario	Mitigation measure 1	Mitigation measure 2	Mitigation measure 3	Mitigation measure 4
Service level		99.96%	96.15% (-3.81%)	96.67% (-3.29%)	99.97% (+0.01%)	99.97% (+0.01%)	99.96% (=)
Stocks (SKU)	SM	180 767	179 265	182 369	180 018	190 175	181 048
	W	153 300	156 650	171 600	155 200	172 800	154 000
	R	89 874	93 499	100 600	90 431	95 486	90 040
Lead Times (h)	PM	386.42	384.52	391.12	388.49	308.58	404.10
	SM	381.23	406.15	439.69	378.28	401.21	424.52
	W	61.53	67.26	61.36	60.44	54.71	63.39
Profit (MMU)		39 260	39 650	39 710	39 260	35 370	39 130

Table 5.11 compares the key performance indicators for the base case instance, the disruptive scenario in which one of the manufacturing sites ceases producing products A and B for a year, and the corresponding mitigation strategies used.

The results seem to show that, while raising the overall service level, a substantial percentage of lost sales is confirmed for *Mitigation Measure 1* (increasing safety stock at affected wholesalers and retailers). On the other hand, this metric is the one that generates the most SC profit.

As for the rest of the mitigation measures, all 3 of them seem to successfully contain disruption, but at different costs/benefits. *Mitigation Measure 2* leads to the shortest lead time at secondary manufacturers, *Mitigation Measure 3*, leads to the shortest lead times at the primary manufacturers and at the wholesalers, but is the measure that results in less profit for the SC. Regarding *Mitigation Measure 4*, it leads to reasonable values at all KPIs, but none of them are optimal.

Because various decision-makers may have different goals and perspectives on SC performance, decisions regarding which mitigation measure to apply to better contain disruption might vary depending on the decision-maker.

A multi-objective approach can also be taken, allowing the decision-makers to choose among different trade-off solutions, by expressing their appreciation on the relative importance of the objectives (that are clearly of quite different nature).

Chapter 6

Conclusions and future work

The conclusions relating to the work developed throughout this dissertation are detailed in this chapter. In addition to displaying the contributions made by this work and reviewing whether the objective initially outlined were reached, some ideas for future work are provided.

6.1 Conclusions

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.

Moreover, this work demonstrates the benefits in integrating different simulation paradigms to address highly complex and dynamic systems. On one hand, an aggregate view with SD to capture high level temporal and spatial changes along the network, and on the other hand, a disaggregate perspective with ABS to capture individual and autonomous decisions and its influence in determining the state of the system.

Finally, the approach developed paves the way for the further development of a methodology that allows decision-makers to proactively define contingency plans in face of disruptive events that, although less frequent, can have severe consequences in the medium and long-term planning.

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.

The work developed in this dissertation resulted in a paper submitted and accepted in the 5th European Conference on Industrial Engineering and Operations Management, where the theme of the conference is fostering Sustainable, Human-Centric and Resilient Manufacturing (in Appendix C).

6.2 Future work

Future work is foreseen to enhance the model by implementing a “broker” agent capable of evaluating the SC performance and dynamically manage its capacity. Figure 6.1 shows the methodological approach for this broker implementation. The work of this dissertation covered the top half of the methodology, but further testing with more disruptive scenarios and more specific scenarios with more instances should be made in order to improve the set of “rules” created.

With these “rules”, the goal is to create a set of proactive measures that should be implemented through a “broker” agent managing the SC.

Another feature that would benefit this model is the implementation product traceability. This might be accomplished by implementing an agent *Product* that travels through the SC. This agent should contain production date, expiration date, and further production information so that not only expiry dates can be maintained, but if an issue with a certain manufacturing batch is discovered, the product can be quickly identified in the SC.

Furthermore, another important feature to implement is the sustainability factor, specifically the social aspect of sustainability. As seen in Chapter 5, some of the measures implemented lead to a significant increase in inventory levels. As pharmaceuticals have an expiry date, an excess level of inventory may lead some product being discarded. This “broker” agent should be able to detect excess product in inventory and direct it to areas that (i) currently have product shortage; or (ii) have a reduced purchasing power.

Still regarding the sustainability factor, for the case of a decision that involves upscaling production capacity by opening a new manufacturing facility, this “broker” agent should also take social and environmental aspects into consideration in terms of new facility locations.

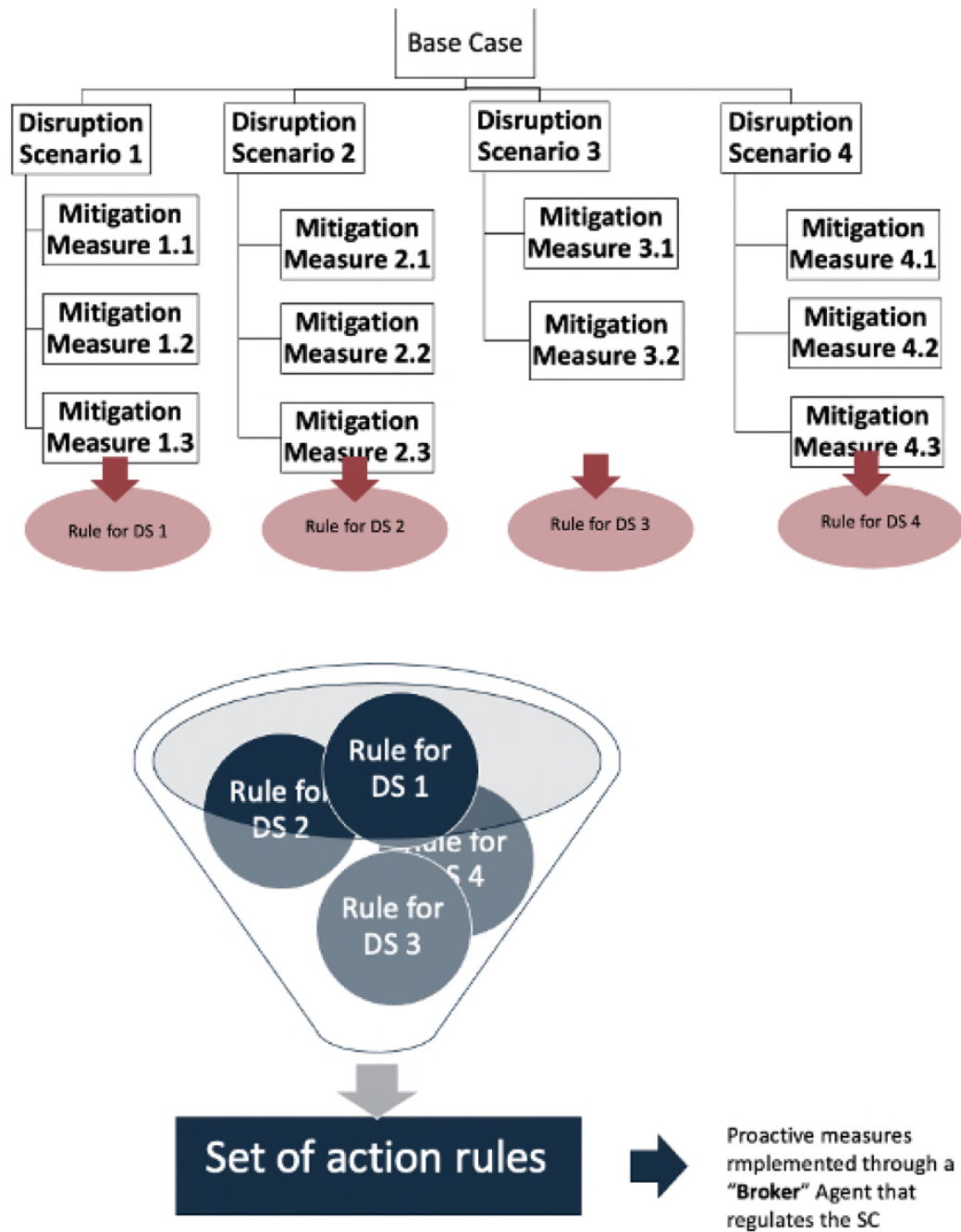


Figure 6.1: Methodological framework for broker implementation

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Appendix A

Agent-Based Approach simulation parameters

A.1 *API_productionLine* agent

A.1.1 Stocks

Table A.1: Description of all stocks in the API production line agent

Name	Description
OrdersMade	Orders of raw materials placed with suppliers that haven't arrived to the facility yet
RawMaterials	Quantity of Raw Materials in inventory
Inventory	Quantity of API product in inventory
DeliveriesSent	Quantity of API sent from the production line
OrdersReceived	Total quantity of API requested from the production line
TotalOrdersMade	Total quantity of Raw Material orders placed to suppliers
TotalProduction	Total quantity of API produced in the production line

A.1.2 Flows

Table A.2: Description of all flows in the API production line agent

Name	Description	Units
OutgoingOrders	Daily quantity of raw materials orders being placed to suppliers	API SKU/day
Delivery	Daily quantity of raw materials arriving to the primary manufacturing facility	API SKU/day
Production	Daily quantity of API being produced in the production line	API SKU/day
flow	Daily quantity of API being produced in the production line	API SKU/day
flow1	Daily quantity of raw materials orders being placed to suppliers	API SKU/day

A.1.3 Variables

Table A.3: Description of all variables in the API production line agent

Name	Description	Units
OrderDecision	Daily quantity of Raw Materials to order to suppliers	API SKU/day
ProductionRate	Desired production rate	API SKU/day
QuantityNeeded	Quantity of API needed to satisfy orders received	API SKU
BackOrder	Quantity of API in backorder	API SKU
Surplus	Extra quantity of API product in inventory	API SKU
DailyProductionCosts	Daily production line costs related with API production	MU/day

A.1.4 Parameters

Table A.4: Description of all parameters in the API production line agent

Name	Description	Units
PLname	Production line name	<i>string</i>
API_name	Primary manufacturing facility name	<i>string</i>
product	Product type	<i>string</i>
DeliveryDelay	Time between placing order to supplier and raw materials arrival at PM facility	days
RMmaxInventory	Maximum raw materials inventory	SKU
RMstartInventory	Raw materials in storage at simulation startup	SKU
APImaxInventory	Maximum API product inventory	SKU
APIstartInventory	API product in storage at simulation startup	SKU
TotalPLproductionCosts	Total production line cost related with API production	MU
UnitProductionCost	Costs of producing one SKU of API	MU
InventoryAdjustmentTime	Time between placing order to supplier and raw materials arrival at PM facility	days
RMtargetInventory	Safety stock for raw materials	SKU
productionON	TRUE if production is active or FALSE if production is halted	<i>boolean</i>
AverageProductionTime	Average time for producing 1 SKU of API	days
Resources	Number of resources available for API production	<i>int</i>
APItargetInventory	Safety stock for API product	SKU

A.2 FP_productionLine agent

A.2.1 Stocks

Table A.5: Description of all stocks in the FP production line agent

Name	Description
OrdersMade	Orders of API placed with primary manufacturers that haven't arrived to the facility yet
APIInventory	Inventory of API product
FPInventory	Inventory of final drug product
DeliveriesSent	Quantity of final drug product sent from the production line
OrdersReceived	Total quantity of final drug product requested from the production line
TotalOrdersMade	Total quantity of API product orders placed to primary manufacturers
TotalProduction	Total quantity of final drug product produced in the production line

A.2.2 Flows

Table A.6: Description of all flows in the FP production line agent

Name	Description	Unit
Production	Daily quantity of final drug product being produced in the production line	SKU/day
flow	Daily quantity of final drug product being produced in the production line	SKU/day

A.2.3 Variables

Table A.7: Description of all variables in the FP production line agent

Name	Description	Units
OrderDecision	Daily quantity of API to order to primary manufacturers	API SKU/day
ProductionRate	Desired production rate	API SKU/day
QuantityNeeded	Quantity of FP needed to satisfy orders received	API SKU
BackOrder	Quantity of FP in backorder	API SKU
Surplus	Extra quantity of FP product in inventory	API SKU
DailyProductionCosts	Daily production line costs related with FP production	MU/day

A.2.4 Parameters

Table A.8: Description of all parameters in the FP production line agent

Name	Description	Units
PLname	Production line name	<i>string</i>
FPmanufacturer_name	Secondary manufacturing facility name	<i>string</i>
API_product	API product type	<i>string</i>
final_product	Product type	<i>string</i>
APImaxInventory	Maximum API inventory	SKU
APItargetInventory	Safety stock for API product	SKU
APIstartInventory	API in storage at simulation startup	SKU
FPmaxInventory	Maximum FP inventory	SKU
FPstartInventory	FP in storage at simulation startup	SKU
TotalPLproductionCosts	Total production line cost related with FP production	MU
UnitProductionCost	Costs of producing 1 SKU of FP	MU
productionON	TRUE if production is active, FALSE if production isn't active	<i>boolean</i>
AverageProductionTime	Average time for producing 1 SKU of FP	days
Resources	Number of resources available for FP production	<i>int</i>
month	simulation month	months
StartOutsourcingTimeMonth	Month which facility starts outsourcing product	months
StopOutsourcingTimeMonth	Month which facility stops outsourcing product	months
MonthlyOutsourcingQuantity	Monthly outsourcing quantity	SKU
OutsourcingPricePerUnit	Outsourcing proce per SKU	MU
TotalOutsourcingCosts	Total production line costs related with outsourcing product	MU

Appendix B

Base Case Configuration Data

B.1 Primary Manufacturers

Table B.1: Configuration data for *API manufacturers* (part 1)

Name	Latitude	Longitude	Production	ProductionTimeDays	ProductionCost
F1_Asia	33,68332	109,93467	API_A/API_B/API_C/API_D/API_E	20/15/17/25/35	300/400/600/500/300
F1_Namerica	41,8742	-85,31355	API_A/API_B/API_C/API_D/API_E	20/15/17/25/35	800/1000/1600/1200/600

Table B.2: Configuration data for *API manufacturers* (part 2)

RMTargetInventory	RMMaxInventory	RMStartInventory	APITargetInventory	APIMaxInventory
500/500/500/500/500	1000/1000/1000/1000/1000	200/200/200/200/200	1600/1200/3000/1000/500	10000/10000/10000/10000/10000
2000/2000/2000/2000/2000	5000/5000/5000/5000/5000	200/200/200/200/200	11200/8400/7200/7000/3500	20000/25000/10000/10000/20000

Table B.3: Configuration data for *API manufacturers* (part 3)

APIStartInventory	TransportersAvailable	StartProduction	StopProduction	RestartProduction
1400/3400/0/1000/2000	3	0/0/80/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900
9800/20400/0/7000/12000	50	0/0/50/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900

B.2 Secondary Manufacturers

Table B.4: Configuration data for *FP manufacturers* (part 1)

Name	Latitude	Longitude	Production	ProductionTimeDays	ProductionCost
F2_Namerica	28,586918	-98,412973	FP_A/FP_B/FP_C/FP_D/FP_E	2/1/3/2/1.5	16/20/25/12/14
F2_Europe	49,615975	8,433826	FP_A/FP_B/FP_D/FP_E	2/1/2/1.5	14/17/12/11
F2_Samerica	-17,43172	-66,168685	FP_B/FP_C/FP_E	1/3/1.5	15/22/10
F2_Asia	10,794334	106,63451	FP_A/FP_B/FP_C/FP_D/FP_E	2/1/3/2/1.5	13/15/20/10/12
F2_Africa	36,689818	10,202233	FP_A/FP_C	2/3	15/23

Table B.5: Configuration data for *FP manufacturers* (part 2)

APITargetInventory	APIMaxInventory	APIStartInventory	FPTargetInventory	FPMMaxInventory
8000/5600/3600/5000/3500	10000/15000/10000/3000/4000	7500/10500/0/5000/6000	8000/3600/7200/5000/1500	10000/15000/10000/3000/4000
11200/8400/9000/5500	15000/35000/15000/20000	10500/24500/9000/14000	11200/10400/9000/3500	15000/35000/15000/20000
4800/4600/3000	10000/6000/3000	7000/0/4000	4800/4600/2000	10000/5000/3000
3200/3400/4000/2000/2000	2000/10000/8000/5000/7000	3000/7000/0/2000/4000	3200/2400/6000/2000/1000	2000/10000/5000/5000/7000
3200/4800	5000/8000	3000/0	3200/4800	5000/5000

Table B.6: Configuration data for *FP manufacturers* (part 3)

FPStartInventory	TransportersAvailable	StartProduction	StopProduction	RestartProduction
7500/10500/0/5000/6000	40	0/0/90/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900
10500/24500/9000/14000	80	0/0/0/0	1900/1900/1900/1900	2900/2900/2900/2900
7000/0/4000	50	0/100/0	1900/1900/1900	2900/2900/2900
3000/7000/0/2000/4000	35	0/0/80/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900
3000/0	20	0/80	1900/1900	2900/2900

B.3 Wholesalers

Table B.7: Configuration data for *Wholesalers* (part 1)

Name	Latitude	Longitude	Products	TargetInventory	MaxInventory
W_Namerica1	35,54724	-114,639	FP_A/FP_B/FP_C/FP_D/FP_E	1600/1600/1800/1000/1000	5000/5000/5000/5000/5000
W_Samerica	-6,88362	-71,9566	FP_A/FP_B/FP_C/FP_D/FP_E	6400/6400/5600/4000/5000	10000/10000/5000/5000/5000
W_Africa	-8,8299	27,43964	FP_A/FP_B/FP_C/FP_D/FP_E	6400/10400/3200/4000/6400	10000/15000/5000/5000/5000
W_Europe1	48,56485	33,40111	FP_A/FP_B/FP_C/FP_D/FP_E	6400/6800/5600/4000/4000	10000/10000/5000/5000/5000
W_Europe2	44,34072	2,12658	FP_A/FP_B/FP_C/FP_D/FP_E	6400/6800/5600/4000/4000	10000/10000/5000/5000/5000
W_Oceania	-20,706	140,9509	FP_A/FP_B/FP_C/FP_D/FP_E	1600/1800/1200/1000/1000	5000/5000/5000/5000/5000
W_Namerica2	53,44786	-113,43487	FP_A/FP_B/FP_C/FP_D/FP_E	6400/6800/4000/4000/4000	10000/10000/5000/5000/5000
W_Asia1	36,243422	138,780167	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1920/1200/1000/1000	5000/5000/5000/5000/5000
W_Asia2	39,612674	76,260058	FP_A/FP_B/FP_C/FP_D/FP_E	17280/12960/9200/9000/4500	20000/15000/10000/10000/10000

Table B.8: Configuration data for *Wholesalers* (part 2)

StartInventory	TransportersAvailable	StartDistribution	StopDistribution	RestartDistribution
1500/3500/0/1000/2000	15	0/0/90/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900
3000/7000/0/2000/4000	18	0/0/80/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900
3000/9000/0/2000/6000	18	0/0/90/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900
3000/7000/0/2000/4000	18	0/0/80/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900
3000/7000/0/2000/4000	13	0/0/90/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900
1500/4000/0/1000/4000	15	0/0/80/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900
3000/7000/0/2000/4000	20	0/0/90/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900
1500/3500/0/1000/2000	15	0/0/80/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900
4500/10500/0/3000/6000	20	0/0/90/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900

B.4 Retailers

Table B.9: Configuration data for *Retailers* (part 1)

Name	Latitude	Longitude	Products	TargetInventory	MaxInventory
C_Africa1	-18,49803	35,52196	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000
C_Asia1	39,85081	81,53998	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000
C_Asia2	18,93957	105,3808	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000
C_Namerica1	53,68261	-93,03091	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000
C_Europe2	39,69537	-5,777918	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000
C_Oceania	-30,81518	142,8087	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000
C_Asia3	45,14825	106,8725	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000
C_Samerica1	-25,19872	-59,57517	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000
C_Namerica2	34,27906	-85,03221	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000
C_Europe3	47,80343	7,380308	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000
C_Europe4	44,6865	27,88714	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000
C_Africa2	22,3791	-2,8278	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000
C_Namerica3	45,36467	-69,25404	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000
C_Asia4	58,66026	132,3648	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000
C_Europe1	50,83976	16,82374	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000
C_Samerica2	0,1345	-53,15877	FP_A/FP_B/FP_C/FP_D/FP_E	1920/1440/800/1000/800	5000/5000/5000/5000/5000

Table B.10: Configuration data for *Retailers* (part 2)

StartInventory	StartConsuming	StopConsuming	RestartDistribution
1500/3500/0/1000/2500	0/0/90/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900
1500/3500/0/1000/2500	0/0/80/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900
1500/3500/0/1000/2500	0/0/90/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900
1500/3500/0/1000/2500	0/0/80/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900
1500/3500/0/1000/2500	0/0/90/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900
1500/3500/0/1000/2500	0/0/80/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900
1500/3500/0/1000/2500	0/0/90/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900
1500/3500/0/1000/2500	0/0/80/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900
1500/3500/0/1000/2500	0/0/90/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900
1500/3500/0/1000/2500	0/0/90/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900
1500/3500/0/1000/2500	0/0/80/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900
1500/3500/0/1000/2500	0/0/90/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900
1500/3500/0/1000/2500	0/0/80/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900
1500/3500/0/1000/2500	0/0/90/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900
1500/3500/0/1000/2500	0/0/80/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900
1500/3500/0/1000/2500	0/0/90/0/0	1900/1900/1900/1900/1900	2900/2900/2900/2900/2900

Appendix C

Publications

C.1 5th European Conference on Industrial Engineering and Operations Management

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 (Láinez 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.

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.

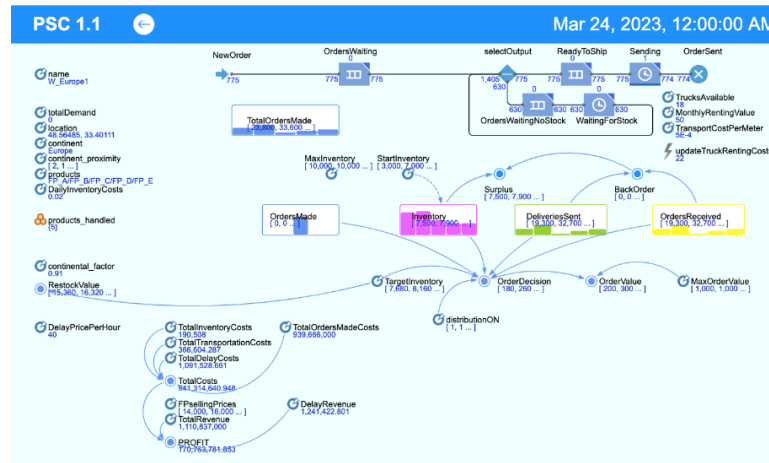


Figure 1. Wholesaler agent model.

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 2. 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.

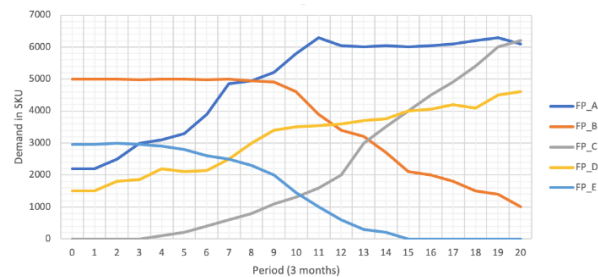


Figure 3. Pharmaceutical products demand trajectory, adapted from (Blossey et al. 2022).

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 BMU (billions 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 (BMU)	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 (BMU)	By echelon	9 604	13 970	11 320	3 607
	Overall	38 500			

* Percentage of the total average lead time per facility.

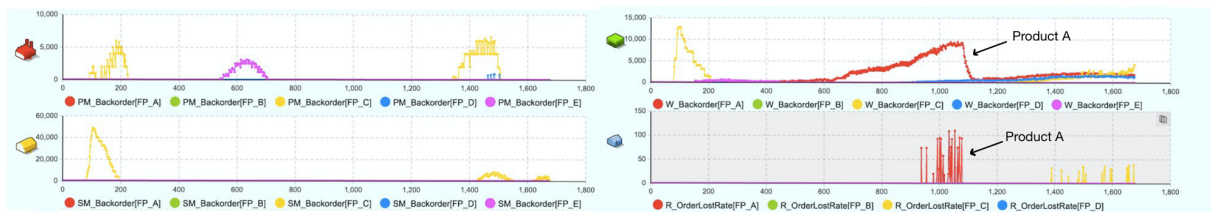


Figure 4. Amount of backorders in each echelon (PM_Backorder, SM_Backorder and W_Backorder) and the amount of lost sales per day in retailers (R_OrderLostRate).

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 (BMU)	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.

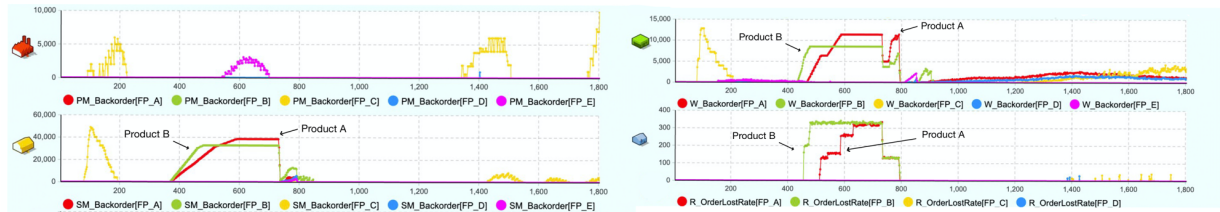


Figure 5. Backorders quantities in each echelon (PM_Backorder, SM_Backorder and W_Backorder) and the amount of lost sales per day in retailers (R_OrderLostRate).

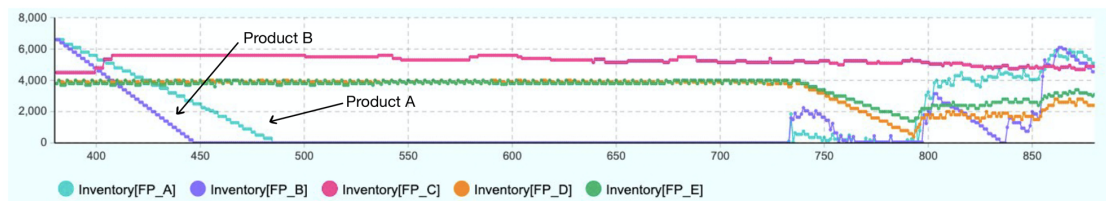


Figure 6. Inventory level over time (wholesalers).

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 (BMU)	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.

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