UNIVERSIDADE DE LISBOA

Faculdade de Farmácia

National Laboratory Portfolio Management System

André Filipe Lopes Morgado

Dissertation supervised by Professor Rui Miguel Dias Loureiro and co-supervised by Pharmaceutical Lieutenant Colonel Inês Milheiro Nunes Martins

Masters in Pharmaceutical Engineering

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Declaration

I declare that the present document is my original work and complies with all the requirements of the Code of Conduct and Good Practices of the University of Lisbon.

Abstract

This thesis explores the current strategies to combat disruptions in the pharmaceutical Supply Chain (SC), particularly concerning medicine and Medical Device (MD) shortages. The study evaluates how blockchain-based networks, specifically Hyperledger Fabric, can enhance the transparency, traceability, and security of healthcare SCs. For this purpose, a comprehensive literature review focused on the main determinants of medicine and MD shortages under normal and emergency circumstances was conducted.

The National Medicines Laboratory (LM) presents a critical role in producing medicines for rare diseases, generic medications for prevalent illnesses in Portugal, and managing strategic reserves for military and public health emergencies, hence its fundamental discussion throughout this project.

The feasibility of implementing a blockchain network was considered based on its ability to address key issues such as stock transparency and traceability. Using a permissioned blockchain framework like Hyperledger Fabric (HLF), the study assessed potential improvements in stock management, identifying parameters crucial for adoption, such as regulatory alignment, technological infrastructure, and stakeholder collaboration. The literature review provided evidence that blockchain could mitigate many of the existing shortcomings in the current SC, including reducing shortages and preventing counterfeiting.

Blockchain technology could substantially enhance Supply Chain Resilience (SCR), making stock management more efficient and adaptable. The implementation, however, depends on the adaptation and objectives of national and international stakeholders, and the capability of addressing barriers such as system complexity and early-stage technological adoption. This research concludes that, while challenges remain, blockchain holds promise for securing medical SCs, thus improving healthcare logistics and emergency preparedness.

Keywords: Blockchain Technology, Drug Shortages, Hyperledger Fabric, Portfolio Management, Supply Chain;

Resumo

A presente tese explora quais as estratégias atualmente utilizadas para reduzir disrupções na cadeia de abastecimento farmacêutica, particularmente no que diz respeito à escassez de medicamentos e dispositivos médicos. O estudo avalia de que forma a tecnologia blockchain, mais especificamente a tecnologia Hyperledger Fabric, pode melhorar a transparência, rastreabilidade e segurança das cadeias de abastecimento na área da saúde. Neste sentido, foi realizada uma revisão abrangente da literatura focada principalmente nas causas determinantes da escassez tanto em circunstâncias normais como de emergência.

O Laboratório Nacional do Medicamento apresenta um papel fundamental na produção de medicamentos para doenças raras, medicamentos genéricos para doenças prevalentes em Portugal, e na gestão de reservas estratégicas para emergências militares e de saúde pública, sendo por isso fundamental a sua discussão ao longo deste projeto.

A viabilidade de implementação de uma rede blockchain foi avaliada com base na sua capacidade de permitir um melhor funcionamento relativamente à transparência e rastreabilidade de stocks. Utilizando uma rede blockchain permisionada como a Hyperledger Fabric, o estudo avaliou potenciais melhorias na gestão de stocks, identificando parâmetros cruciais para a sua adoção, tais como infraestrutura tecnológica, colaboração entre os intervenientes da cadeia e questões regulamentares. A revisão da literatura evidenciou que esta tecnologia pode efetivamente minimizar as consequências inerentes às lacunas atuais, incluindo a redução da escassez de medicamentos e dispositivos médicos, preparação para cenários de alta procura como emergências, e até prevenção da falsificação de produtos médicos.

A tecnologia blockchain pode melhorar substancialmente a resiliência da cadeia de abastecimento, através de uma gestão de stocks mais eficiente. A sua implementação no entanto, depende da adaptação e objetivos dos intervenientes nacionais e internacionais, e da superação dos obstáculos, como a complexidade do sistema e a adoção de uma tecnologia ainda numa fase inicial. Apesar dos desafios existentes, a blockchain pode otimizar o desempenho das cadeias de abastecimento farmacêutico, melhorando tanto a preparação de emergências como o sistema de saúde no geral.

Palavras-chave: Cadeia de Abastecimento, Escassez de Medicamentos, Gestão de Portefólio, Hyperledger Fabric, Tecnologia Blockchain;

Abbreviations

AI - Artificial Intelligence

ANEPC - National Authority for Emergency and Civil Protection

API - Active Pharmaceutical Ingredient

ASHP - American Society of Health-System Pharmacists

CBRN - Chemical, Biological, Radiological, and Nuclear

DLA - Defense Logistics Agency

DLT - Distributed Ledger Technology

DM - Disaster Management

DRM - Disaster Risk Management

DRR - Disaster Risk Reduction

EADRCC - Euro-Atlantic Disaster Response Coordination Centre

EC - European Commission

ECHO - European Civil Protection and Humanitarian Aid Operations

EEA - European Economic Area

EMA - European Medicines Agency

ERCC - Emergency Response Coordination Centre

EU - European Union

FDA - Food and Drug Administration

FEMA - Federal Emergency Management Agency

GMP - Good Manufacturing Practice

HERA - Health Emergency Preparedness and Response Authority

HLF - Hyperledger Fabric

ICRC - International Committee of the Red Cross

IFRC - International Federation of Red Cross

INEM - National Institute of Medical Emergency

INFARMED - National Authority of Medicines and Health Products, I.P.

IoT - Internet of Things

IT - Information Technology

LM - National Medicines Laboratory

MAH - Market Authorization Holder

MD - Medical Device

MS - Member States

MSP - Membership Service Provider

NATO - North Atlantic Treaty Organization

NHS - National Health System

NSR - National Strategic Reserve

OCHA - United Nations Office for the Coordination of Humanitarian Affairs

PNRRC - National Platform for Disaster Risk Reduction

PoW - Proof of Work

PPE - Personal Protective Equipment

QR - Quick Response

R&D - Research and Development

RFID - Radio Frequency Identification

SC - Supply Chain

SCR - Supply Chain Resilience

SCV - Supply Chain Visibility

SUCH - Hospital Common Use Services

UCPM - Union Civil Protection Mechanism

UN - United Nations

UNDRR - United Nations Office for Disaster Risk Reduction

US - United States

WHO - World Health Organization

Glossary

Member States – A candidate country that meets the accession criteria as defined by the Copenhagen European Council of 1993 and signs the accession Treaty with the individual EU Member States becomes a Member State of the European Union. Now there are 27 Member States: Belgium, Bulgaria, Czechia, Denmark, Germany, Estonia, Ireland, Greece, Spain, France, Croatia, Italy, Cyprus, Latvia, Lithuania, Luxembourg, Hungary, Malta, the Netherlands, Austria, Poland, Portugal, Romania, Slovenia, Slovakia, Finland, and Sweden.

Critical/Essential Medicines - As stated by the European Commission, a certain medicine is listed as critical when it is essential to ensure the continuity of care and the provision of quality healthcare, guaranteeing a high level of public health protection in Europe, and also when their unavailability results in serious harm or risk of serious harm to patients. [21] For WHO, essential medicines are the ones that satisfy the priority healthcare needs of a population, selected with due regard to disease prevalence and public health relevance, evidence of efficacy and safety, and comparative cost-effectiveness. They are intended to be available in functioning health systems at all times, in appropriate dosage forms, of assured quality, and at prices individuals and health systems can afford.

Portfolio Management - It can be defined as a continuous process of creating portfolios based on an investor's preferred level of risk and reward and then adjusting it over time to maximize returns.

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1. Introduction

The development of new technologies, knowledge, and services provides new possibilities and brings new needs to satisfy. The impact of these shifts is widely recognized and presents significant challenges, but they are especially challenging for logistics in both military and healthcare systems. [1] Medical supply disruptions are a critical concern for defense and public healthcare systems domestically and globally. Consequences of this problem include treatment delays or interruptions, sub-optimal/alternative treatments that may have adverse medication effects and greater toxicity, or even forgoing treatment, and many other complications that tend only to increase in times of emergency. [2,3,4,5] Secure and harmonized supply chains are the foundation for strong reliable frameworks, and for that matter, ensuring the availability of medicines and MDs is paramount for organizations like the North Atlantic Treaty Organization (NATO), the World Health Organization (WHO), and European Medicines Agency (EMA), Food and Drug Administration (FDA), United Nations (UN) and other European and national authorities. [6,7,8] Despite countries' efforts to mitigate shortages routinely and in times of severe crisis, preparedness, and urgent action are needed.

The LM plays a crucial role in the production of medicines whose supply is at stake, namely medicines to treat rare diseases and generics used for diseases prevalent in Portugal, as well as logistic support for the health of the armed forces, production of specific medications for military use, and, in coordination with government health services, maintaining strategic reserves for emergencies, epidemics, and pandemics, ensuring their proper storage and management. [9] However, current systems can benefit from improving key elements such as transparency, traceability, and collaboration between SC participants.

Hence, one of the aims of this study is to analyze and gain a deeper understanding, through a comprehensive review of current literature, of the determinants and consequences of medicine and MD shortages under "normal" and emergency circumstances, such as public health, health economics, pharmaceutical regulation, SC management, and economic issues, seeking to identify effective strategies, contributing to the creation of a mechanism that can improve the LM portfolio management system, as well as the flow and management of medical products.

Seeking to address and mitigate these challenges, this thesis evaluates the possible implementation of a blockchain-based network using Hyperledger Fabric technology. A decentralized permissioned blockchain framework that can offer transparency, traceability, and security features can be the way to have a better stock management framework capable of dealing with SC issues.

The thesis further examines how viable the implementation of such a network is in the context of national and international SC stock management systems, acknowledging specific parameters that would or would not enable the deployment of such a complex and early-stage innovative system.

The main research objectives revolve around the following topics:

- Evaluate the shortage of medical products problem;
- Explore and research the current strategies used in the normal pharmaceutical framework as well as in times of emergency and disasters;
- Explore how Hyperledger Fabric Technology features and capabilities can help supply chain management;
- Evaluate the viability of utilizing Hyperledger Fabric for stock management.

2. Literature Review

2.1 Medical Shortages

The shortage of medicines and MDs has been a longstanding, chronic, and growing problem in the European Union (EU) for the last few years [10], causing a global public health concern. This constantly challenges the capacity of healthcare systems worldwide to guarantee citizens' access to adequate care and availability of medicines and MDs, which is one of the most relevant aspects of the fundamental right to health protection. [11]

According to the PGEU Medicines Shortages Report 2023, since 2019, all surveyed countries (26) have experienced shortages. [2] Compared to the previous year (2022), 65% of the responding countries affirmed that the situation worsened and 23% stayed the same. Only 3 countries, namely Cyprus, Greece, and North Macedonia, registered improvements compared to the previous year. [2] The same issue appears for MDs, as 69% of responding countries reported having shortages. [2] Despite the little information and the lack of regulation regarding drug shortages in low-middle-income countries, these experience problems such as relying on external supply due to a lack of domestic manufacturing capacity. [12,13] There is also a tendency for these countries to implement fewer measures to combat shortages, as the implementation of such measures requires resources. [14]

Although there are no consensually recognized definitions for the shortage of medicines or MDs, and even though some countries do not have an official definition, most organizations or countries have their definition for this concept. [2,5,15,16,17] De Weerdt et al. (2015) identified over 20 different definitions for drug shortages in a study including 26 countries across Europe, where a distinction is made between general definitions of drug shortages and definitions used for reporting drug shortages. The authors found some key points that could help define when a supply problem becomes a shortage, which was defined at four levels: (i) demand side, (ii) supply side, (iii) delivery of a drug, and (iv) availability of a drug. [15]

Recent work has dealt with the need for a common definition of drug shortage and calls for the European Commission (EC) to undertake action on the shortage situation. [18]

In the EU, the Member States (MS) mostly address this problem independently. Notwithstanding negotiations and agreements between countries, the organization of healthcare systems in the EU remains a national responsibility, with each country having its regulatory mechanisms to manage its system, ensuring quality and efficiency. [10] However, some initiatives are coordinated by the European Medicines Agency (EMA). [16] Examples are the guidance practices documents and the task force work program until 2025, published in 2019 and 2022 respectively. [19,20,21] The FDA tries to resolve these issues in the US. [22] WHO also plays a key role in developing assessments on the magnitude and nature of the problem of shortages of medicines and vaccines, as well as supporting countries' shortage problems. [23,24]

Economic globalization has promoted the delocalization and gathering of manufacturing sites of drug substances and medicinal products, stressing the resilience of pharmaceutical SCs. [25] Although there has been an increasing level of measures to manage and prevent shortages of medicines [14], not enough countries worldwide participate in monitoring and reporting shortages, and data availability appears to be among the most persistent challenges that need to be considered. [23]

2.2 Supply Chain

The production and distribution of medicines involve many transnational supply chains, in which most of the time, the process begins with raw materials, transformation into Active Pharmaceutical Ingredients (API) at primary manufacturing sites, with secondary sites producing the finished pharmaceutical products. [6] The same goes for MDs, relating to the activities and processes from the point of manufacture to the end of use. [26] Their distribution and management come further along the process and are also known as factors that tend not to ease logistics.

In the early stages of the SC, industries must strike a fine balance between future capacity and projected needs. This turns out to be especially challenging in the pharmaceutical sector, due to the number of significant uncertainties related to clinical trials of new drugs, competitive market dynamics, increased regulatory demands, and shrinking profit margins. These factors complicate technical decisions related to production capacity planning, non-existent products, and overall infrastructure investments [27], and disrupt other fundamental pillars like transparency and trust.

To understand the root causes of shortages, it is vital to have a good grasp of how the healthcare SC operates. Although the structure of the SC is similar to any other, it is still said to be one of the more complex SCs in the world regarding logistics coordination. With that in mind, acknowledging the different dynamics, components, and participants of the SC scheme is essential to apply effective regulatory and strategic decisions, such as requiring redundancy, or for negotiators to justify appropriate price increases in return for increased resilience [28], and to take other right approaches on how to address its issues.

Failure in any part of the SC can lead to detrimental downstream effects and issues. [29] Disruptions, from supplier failures to disasters, regularly occur, and the ability to manage them is critical to patient care. [28]

The simplicity used to describe the healthcare SC can sometimes be deceiving of its complexity and reliability. This multifactorial process can be hard to comprehend at first sight but to make it more understandable, breaking it down into sections can help. The three main key parts can be: the manufacturers, the mediators, and the stakeholders. (Figure 1) Logistics and transportation are also heavily considered as they will impact all three parts together. [29] Although not referred to in Figure 1, regulators should also be considered.

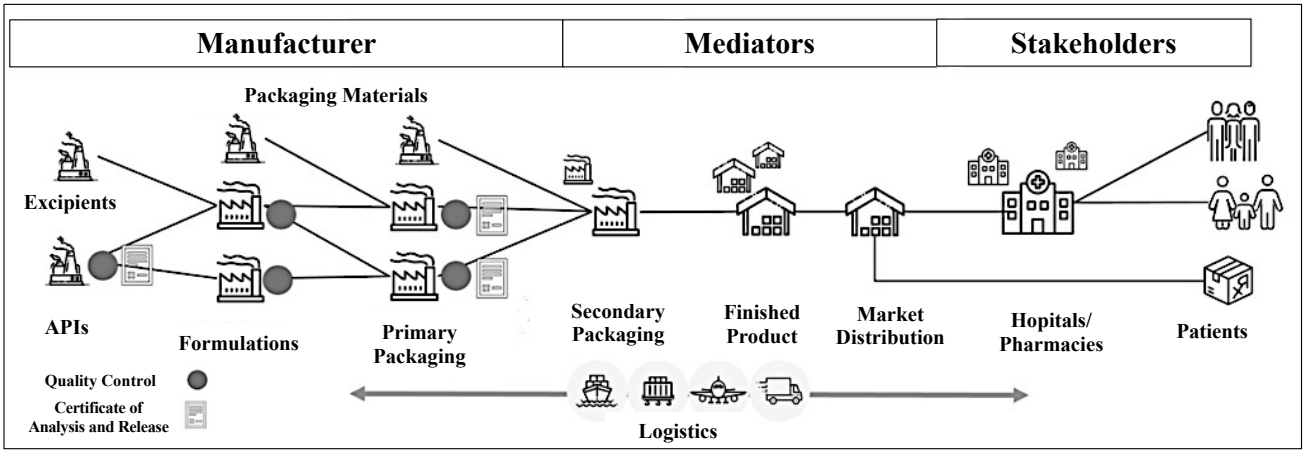

Figure 1 - Supply chain operating model. (Adapted from https://supplychainbeyond.com/pharma-brands-vs-generics-1/)

One of the main reasons that make SC logistics in the healthcare sector so complicated is the stringent regulations, which are constantly adapted and must be rigorously followed. [29] The reliability of the SC and the legislation concerning medicines and MDs encompass all participants in that chain.

Apart from the general regulations imposed by players being those national or geopolitical, such as the FDA or EMA, each country addresses the issues of its SCs by

applying legislation according to its specific problems, ensuring that the system operates as efficiently as possible, always intending to improve the procurement of healthcare products for patients and healthcare professionals, as seen in Annex 1. [6] Currently, regulations force firms in the pharmaceutical industry to provide only a certain level of transparency.

With this many complications and problems in SC management, there is a constant and urgent need to strengthen the solutions and methods used, update and evaluate them regularly, enhance the process, and achieve maximum efficiency, keeping in mind that this matter affects public health.

2.2.1 Supply Chain Vulnerabilities and Efficiency Barriers

Supply chain vulnerability is the susceptibility of the SC to the occurrence of an event that can have an impact on disruption. [26,30] It can be defined as the diminished capacity to anticipate, cope with, resist, and recover from external shocks to the SC. [41] Researchers denote that a system must be built to respond to disruptions and bounce back effectively for effective SC performance. [31-33] When discussing the vulnerability inherent to the SC, terms like SCR and Supply Chain Visibility (SCV) are often used.

SCR is the adaptive ability of the SC to prepare well for unexpected or uneven situations and further recovery options by maintaining the desired level of interconnectivity and device over structure and function. [26,33] By building resilience strategies into SCs, vulnerabilities may be reduced and the capacity of SCs to mitigate the impact of disruptive events increased. [34] In general, promoting the long-term resilience of medical SCs would benefit from collaborative approaches that balance measures best undertaken by the private sector with those more appropriately managed by governments or supranationally. [6]

Furthermore, the healthcare SC must have a clear and transparent SCV, in which the information is shared, and the best actions can be taken. SCV is the ability of an SC to keep track of the flow of goods, in this case, medicines and MDs, funds, and information, to improve its SCR and performance [35]. SCV improves SCR through information sharing between SC partners/stakeholders. [33,36] Interest in greater SCV at different points in the SC and the use of real-time sensitive and relevant transparent information has been highlighted by various stakeholders, for example by respondents to

a recent public online consultation, where the public and all health product partners and stakeholders shared their views on the topic. [37]

Many are the factors known to cause an increase in the complexity of the SC. As a first step, policymakers should consider how to harness information already reported to regulators by manufacturers to identify and assess points of vulnerability in manufacturing SCs. [6,38]

Although some work is already being done in this direction such as reports [2,7,11,38], and communications [19,20-24,39,40,41], data acquiring, and publishing should be of utmost importance since having good and clear information is key to taking steps in the right direction. [14] This type of research tends to depend on the stakeholder publishing perspective, which can result in additional complexity in determining true causes. [18] Differing perceptions of the root causes of shortages complicate the effectiveness of preventive measures. [17] Better anticipation of risks requires sharing information between stakeholders, as joint decision-making has a positive impact. In general, achieving better visibility requires constantly collecting real-time information on medical SCs' structure, content, and status [6], and maintaining close ties with key stakeholders. [33] Robust data and further analysis of the origin and extent of medicine and MD shortages, and effective measures for prevention and mitigation, are needed. [17]

Then, policy and regulation actions should focus on addressing the root causes, to mitigate (or reduce exposure to) the risk of shortages. [6] Encouraging flexibility and agility in the system can also help reduce the risks of potentially harmful supply disruptions. Trade facilitation encompasses a series of policies and border measures to reduce the time and cost of moving goods. The smooth functioning of medical SCs is enhanced through firms moving final products and inputs where needed easily. [6] The enhancement of collaborative regulation in the form of process connection and process simplicity leads to mitigating risks arising from SC vulnerabilities, thus improving SCR. [42] Process test runs, and simulations should be given emphasis.

Due to the multifactorial origin of problems and complications that involve the entire SC, the entire process of streamlining standards and resolutions that best fit becomes complicated. Therefore, it is necessary to recognize and understand the main cause of shortages that generate the greatest impact.

2.3 Causes of Shortages

2.3.1 Shortages of Medicines

The underlying causes for drug shortages are complex and multi-faceted. [10] Drug shortages result from demand and supply mismatches that can be affected by manufacturing, distribution, regulatory, economic, or even political considerations [5], for instance, social and political unrest or political shifts like Brexit. The causes of disruption in the pharmaceutical SC are multifactorial and global, involving different participants which is intrinsically often very complex, involving multiple steps, with the potential for each step to be undertaken in a different facility, and even in a different country. [11,23]

Some actions can be seen over the years relating to the implementation of measures that can somehow solve or at least lessen the size of the problems faced with drug shortages. However, these measures appear rather reactive, focusing on managing existing or upcoming shortages [14], instead of taking a long-term kind of approach, making sure that future planning is taken into consideration. Overall, drug shortage causes can be classified as supply, demand, or regulatory issues, as shown in Figure 2. One should also consider the needs coming from unforeseen demand, for instance, pandemics, outbreaks, some kind of disaster, or panic-driven buying.

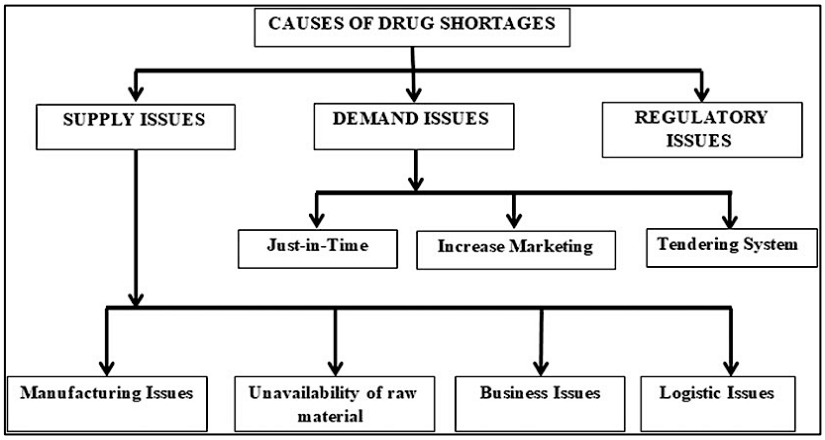

Figure 2 - General Causes of Drug Shortages. (from [14])

While battling against a "blurred view" of the shortage issue [18] can be very difficult, addressing the causes is fundamental to attacking the problem from its core.

In Table 1 there are represented in percentage the causes identified by OECD in the EEA, with corresponding data from 2015 to 2020. [6]

Table 1 - Causes of drug shortages in the EEA, data from 2015 to 2020. (Adapted from [6])

Causes of shortage	%
Quality and Manufacturing issues	51
Commercial reasons	25
Unexpected increases in demand	9
Distribution issues	8
Regulatory issues	4
Unforeseen major events or natural disasters	1
Other Issues	1

According to the information provided by OECD [6], the main causes for the shortage of medicines are the following categories: quality and production problems (51%), commercial reasons (25%), and increased demand for medicines (9%). This data seems to be congruent with the data presented in the United States market between 2017 and 2021, where the reasons found were, apart from unspecified reasons (36%), the manufacturing, packaging, or shipping issues (22%), the business decisions (15%) and the discontinuation of the drug production (10%). [43]

The percentage of countries that had problems relative to each cause of shortages for each country in 2022 is described in Table 2.

Table 2 - Percentage of countries with problems relative to each cause of shortage for each country, 3 answers per country. (Adapted from [2])

Causes of shortage	%
Disruption / Suspention of manufacturing process	65
National pricing and procurement strategies	62
Unexpected / high increases in demand	50
Quota imposed by manufacturer	31
Logistical chain inefficiencies	27
Commercial market withdrals	27
Parallel export out of my country	23

A brief analysis of the data presented shows that the issues representing the three main causes that led to shortages between 2015 and 2020 persisted as of 2022. Adversities in the manufacturing process, business and procurement strategies, and unexpected increases in demand are the three main sources of this ongoing problem. [2,6,10,11,17]

The two main reasons for the disruptions observed in Portugal in 2021 were manufacturing problems and increased demand, which is consistent with the previous data, as suggested below in Figure 3. [11]

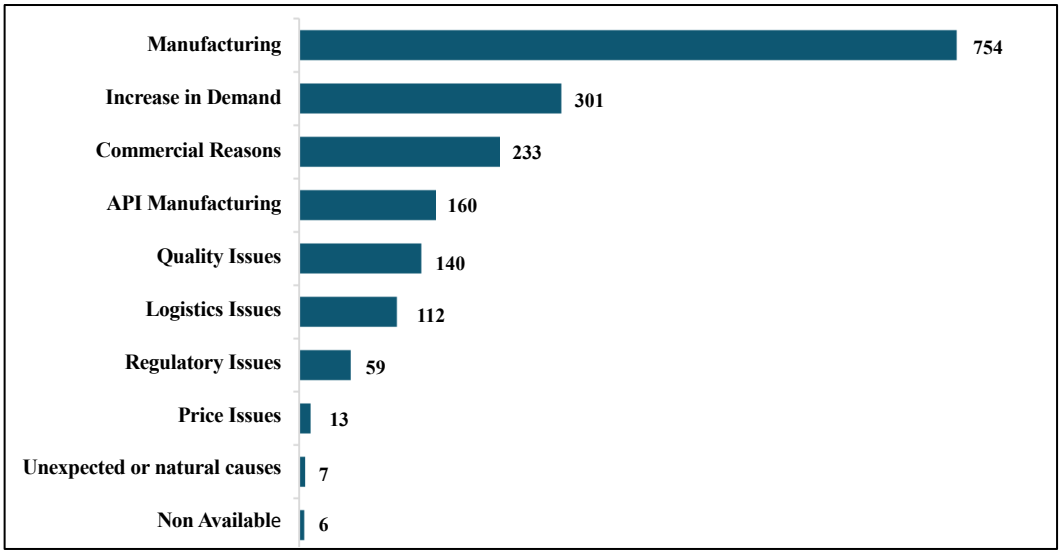

Figure 3 - Main reasons associated with the unavailability of medicines in Portugal in 2021. (from [11])

Historically, drug shortages have been prevalent in financially non-attractive domains like rare disease medicines, or non-profitable countries like developing countries. [44] The geographic concentration of manufacturing (either individual sites or small geographic areas) creates particular vulnerabilities in natural or man-made disasters. [17]

2.3.2 Shortage of Medical Devices

According to WHO, MDs "include all the health technologies (except for vaccines and medicines) required for prevention, diagnosis, treatment, monitoring, and palliation". [45] MDs and in vitro diagnostic MDs are essential for a working healthcare system, not only for patients but also for health professionals, and have a crucial role in the prevention, diagnosis, monitoring, prediction, prognosis, and treatment of acute and chronic illness and diseases, as well as rehabilitation. [46] As previously seen in drug shortages, the regulations implemented for MD shortages aim to improve the quality, safety, and reliability of MDs, strengthen patient transparency and information, and enhance vigilance and market surveillance. [46]

Before the pandemic, shortages of MDs received less attention than medicine shortages, likely due to the differences in notification requirements to some extent. [6]

Experts and industry representatives have identified several risks to the future supply of MDs, however, data on the occurrence and evidence of the causes of shortages of MDs and in-vitro diagnostics are very scant. [6]

In Europe, approximately 69% of countries experienced shortages of MDs in community pharmacies in 2023, which shows a slight increase from the previous year's situation (66%). [2] Only two countries had systems aiming at the identification of MD shortages. These shortages span across all categories of MDs. [2]

For MDs, SC issues were the most critical problem, closely followed by shortages or discontinuation of components, parts, or accessories, and in third place, the price of MDs, as seen in Figure 4. [47] More than a third of pharmacists in Europe reported that the shortages occurred one to three times for the same device, with another third reporting the issue more than 10 times for the same device. [6]

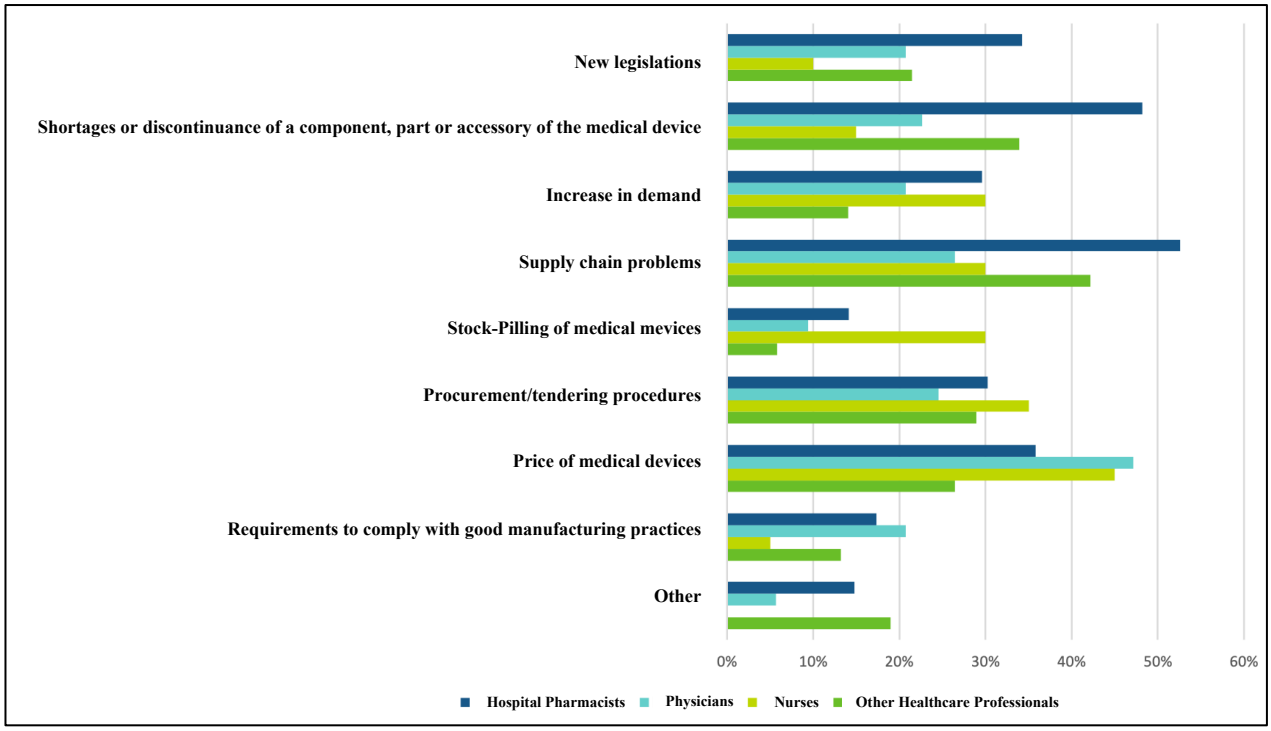

Figure 4 - Percentage of hospital pharmacists (1251), physicians (53), nurses (20) and other healthcare professionals (121) for the question "What do you see as the cause of shortages of medical devices in your hospital/country?", grouped by profession. (from [47])

The current demand for medical facilities, particularly for those related to the intensive care units, exceeds the local availability with potentially serious consequences on patients' care. [48] Getting the right balance between premarket and post-market data collection, specifically, where appropriate, having a greater reliance on post-market

collection, including real-world real-time data collection, can reduce the extent of premarket data collection and directly impact when patients will have access to high-quality, safe, and effective MDs. [49] According to the publicly available information of the EU, the overall number of registered adverse MD events has been the same for the last five years, despite the constant market growth. [50] The alignment of regional and international networks allows the timely distribution of devices where they are more in need. [48]

National healthcare agencies may encourage more publications of information about safety and shortage alerts of MDs intended for patients and consumers since EU statistics only provide limited information. It was impossible to find specific data on the severity of incidents, possible causes, class of devices, etc. This information is particularly relevant for healthcare professionals, and the general public to increase patient safety. [51]

2.4 Impact of Shortages on Patients and Healthcare Professionals

2.4.1 Impact of Medicine Shortages on Patients and Healthcare Professionals

Access to affordable essential medicines is a fundamental human right. [52] The burden of shortages on patients and pharmacies across Europe, the US, and other developed and developing countries such as Australia, has increased compared to previous years, negatively impacting patients' trust in the pharmaceutical SC. [2,52-54] WHO considers better access to essential medicines a priority health issue. [55]

While this problem continues, patients and healthcare professionals tend to be the ones most affected. Consequences include an increase in compromised treatments and their effectiveness, jeopardizing patient safety and well-being [3,4,5,14,52], higher workload imposing additional burdens for health professionals [6,14,52] and healthcare systems [2,3,11,52], and economic consequences, such as the need to procure higher-priced medicines. [5,14] These outcomes can prolong patient suffering, contribute to the progression of diseases, and even cause other adverse health outcomes that reduce patient well-being and increase morbidity. [56] Across OECD countries, medicine shortages mainly affect older, off-patent medicines, and are particularly prevalent among central nervous system, cardiovascular, and anti-infective drugs. [2] In many instances, few

medications are the only available therapy for rare diseases, and their shortages can lead to serious health deterioration and death. [57]

The data presented in the PGEU Medicine Shortages Report 2023, showcases the key points representing the impact of medicine shortages on patients in Europe, described in Figure 5. [2]

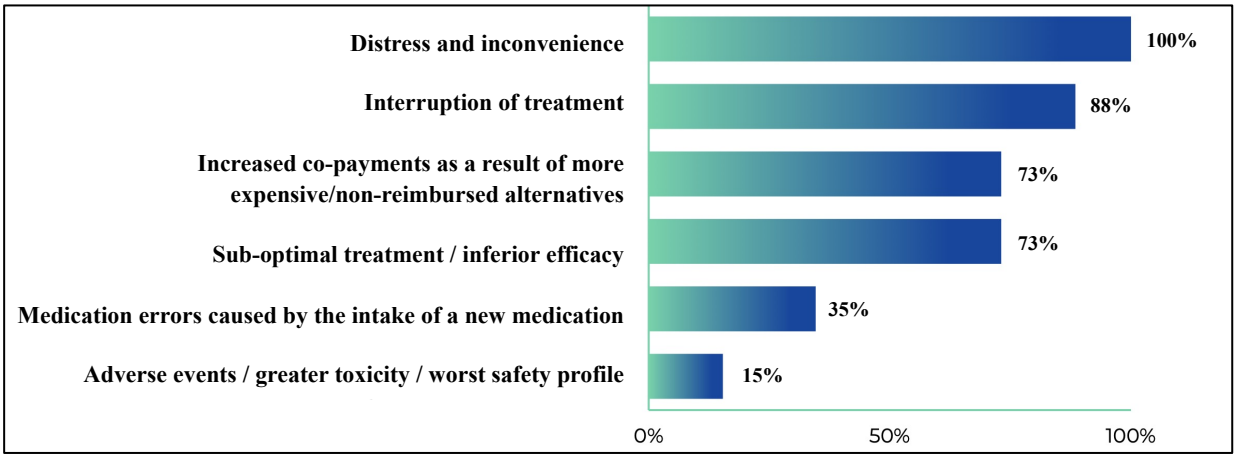

Figure 5 - Main impacts of medicine shortages on patients in European Countries in 2023. (from [3])

Drug shortages impact consumers through reduced sales and increased prices, making it more difficult for patients to fill their prescriptions, and leading to higher drug prices. [58]

This problem affects all stakeholders and has economic, clinical, and humanistic impacts. [5] In the EAHP 2023 Shortage Survey Report, only 3,5% (N=53/1497) of the surveyed healthcare professionals believed that medicine shortages are not a current problem for delivering the best patient care, and 1% could not answer. 95% of healthcare professionals believe this issue hinders the capability to provide quality and efficient care. [47]

Medication errors and adverse events continue to occur from drug shortages, often resulting in inadequate patient care, high institutional costs, and patient complaints [3], resulting from a mix-up in medicines, especially for older patients, and problems leading to therapeutic compliance.

2.4.2 Impact of Medical Device Shortages on Patients and Healthcare Professionals

Medical equipment is an essential health intervention tool to prevent, diagnose, treat disease, and rehabilitate patients. Shortage of MDs, either due to unavailability or

non-functioning, is to this date a barrier to the ability of the health system to deliver quality health services. [59] MD supply chains continue to be endangered due to many global and systemic issues, impacting multiple manufacturers and device types. [60]

Service delivery is severely compromised without proper functional medical equipment. A professional nurse from a medical ward reported: “The shortage of medical equipment is to the extent that we sometimes don’t do some of the nursing care as far as the quality nursing care is concerned”. This can be a problem concerning staff retention and knowledge deficits. [59] Another study in Greece where hospital workers were asked about shortages, revealed that 84% of the participants who experienced medical supply shortages reported that these shortages harmed the quality of healthcare provided to the patients. Medical supply shortages were significantly associated with emotional exhaustion and depersonalization among healthcare workers. [61]

The EAHP Shortage Survey Report disclosed that more than half of hospital pharmacists (61%) stressed having experienced shortages that impacted patient care in their hospital. A similar response rate was observed for physicians (59%) and other healthcare professionals (66%). [47]

Even though not defined as MDs, Personal Protective Equipment (PPE) shortages should be addressed as the extraordinary trade and industrial policy during the COVID-19 pandemic revealed significant failures in preparedness. Trade played a mixed role. [62] The neglect of this matter led to critical shortages in hospitals and pharmacies, to a point where resources required to sustain human life, prevent permanent disability, or stabilize a patient with a medical emergency, were depleted and alternative methods were exhausted.

Proper transparency, stock management, data availability, leadership, and governance are required to develop and implement procurement, maintenance, and quality control plans. [59] Otherwise, healthcare professionals cannot deliver patients with essential care, posing a serious threat to their health and general well-being.

2.5 Types of Shortages

Of all the classes of medicines, the three most frequently reported to be in short supply in Europe in 2023 were, anti-infectives for systemic use, such as antibiotics (84%), followed by nervous system (60%), and lastly cardiovascular system (56%). [2] Reminding that these percentages refer to the portion of countries that recalled having

shortages of these classes of medicines. [2] Similarly, the results presented by INFARMED in the "*Relatório Anual 2021, Gestão da Disponibilidade do Medicamento*" (2021 Annual Report, Management of Availability of Medicines), where the main classes of medicines in short supply were, central nervous system, cardiovascular, anti-infective medications, and antineoplastic, and immunomodulatory drugs, representing 21%, 17,5%, 9,25%, and 8,7%, respectively. [11]

In the US the top five classes of drugs in active shortage as of March 31st, 2024, according to the American Society of Health-System Pharmacists (ASHP) [63], were:

- Antimicrobials (which include antibiotics);
- Central nervous system drugs such as ADHD medications;
- Chemotherapy medications;
- Fluids and electrolytes;
- Hormones (such as oxytocin);

In July 2023, the ASHP Drug Shortages Resource Center was updated with the latest quarterly drug shortage statistics from the University of Utah Drug Information Service. ASHP surveyed a sample of its members to learn the severity and impact of ongoing shortages of select categories of drugs, and some of the results can be found in Figure 6. [63]

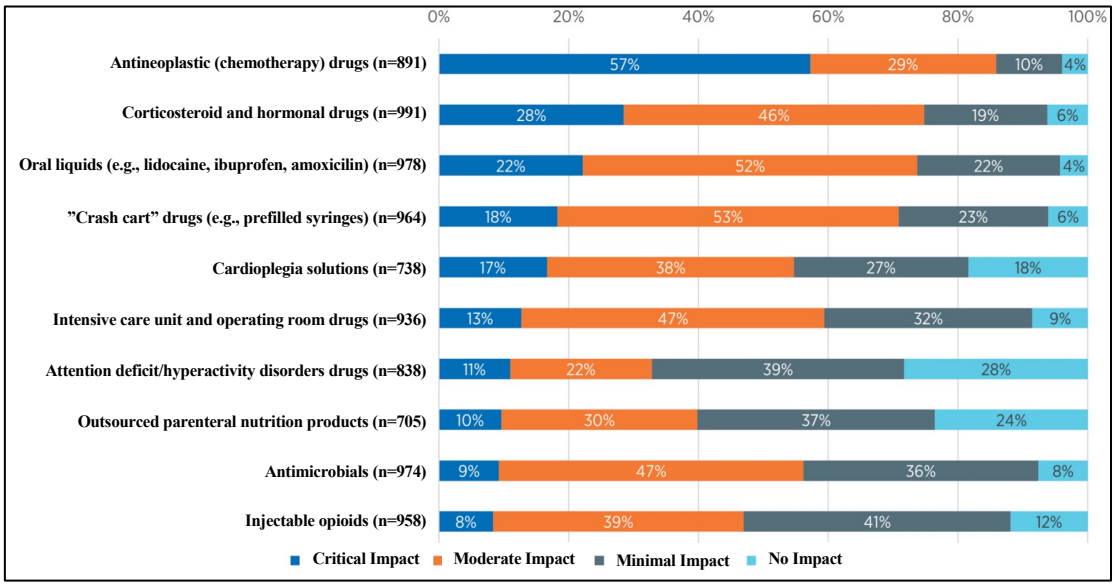

Figure 6 - Characterization of drug shortages by category. (from [64])

The different tiers of impact were defined as not experiencing a shortage, minimal impact (managing shortages through operational changes with no effect on patient care), moderate impact (managing through operational strategies but affecting patient care), or critical impact (rationing, canceling, or delaying treatments or procedures). [64] About one-third (32%) of respondents characterized drug shortages as critical and 63% as moderate. Four percent characterized shortages as having minimal impact. Only 3 out of 1123 respondents, indicated their organization was not experiencing shortages.

Different countries or areas encounter different drugs in shortage and different levels of criticality depending on health and economic conditions. [5,65-66] However, essential medicines [5,67] and emergency medicines [10,62,68-71] are almost always more likely to be in shortage than other medicines.

2.5 Times of Emergency

The increasing frequency of natural and man-made disasters imposes significant social and economic costs. [72,72] Local authorities, civil societies, and governments are key for providing immediate assistance and restoring vital public services such as water, food supplies, transportation, communication, and healthcare, which include medicines, MDs, and the necessary medical assistance. However, these disasters often exceed national capacities as no country can produce all the necessary components and medicines for its population. Internationalization could be seen as a means of reducing risks through diversification of supply channels. [17] This only highlights the importance of strategies and prevention systems in Disaster Management (DM) and recovery.

Some organizations such as NATO, the EU, the UN, the EC, and the International Federation of Red Cross (IFRC) work together to find solutions for the consequences that result from these types of disasters. Despite the differences, all of them unite in their commitment to deliver disaster response in a timely and efficient manner, meeting the needs of the affected populations.

The fundamental principle of NATO is to ensure the freedom and security of its members through political and military means. Currently, 32 countries have joined, most of which are MS, along with the USA and Canada also being part of this alliance. [74] Although DM is not one of the main focuses of NATO, this organization has also a long track of achievements in disaster response. [73] The EU serves as more of a political and

economic union of Europe. Disaster response, humanitarian and rescue missions, peacekeeping, and armed missions for crisis management, are some of the operations led by the EU. [73]

On the other hand, the UN is an intergovernmental organization that promotes international cooperation, being the main entity responsible for coordinating international disaster relief operations, more specifically, the United Nations Office for the Coordination of Humanitarian Affairs (OCHA). OCHA is the part of the UN Secretariat responsible for bringing together humanitarian actors to ensure a coherent response to emergencies. [8]

Even though the help and response actions granted by these organizations are of extreme relevance, this does not substitute the preparedness each country should hold but complements their efforts in this area. [73]

2.5.1 Healthcare Systems During Emergencies

The phenomenon of shortages tends only to increase during emergencies, catastrophes, pandemics, and other disasters. [75] Considering this, governments, and national and international authorities have been implementing measures to prevent shortages of medicines and MDs, both for regular circumstances and emergencies, where swift and effective action is crucial. [38,39,40,47] Most nations and institutions report current and past situations, showcasing the scenario publicly, while also evaluating what is working and what can be improved, having a better grasp on what to act upon, and working on the needs of patients and enhancing the functioning of healthcare systems[1,11,23,38,47].

The recent COVID-19 pandemic and the Russian military aggression against Ukraine exposed Europe's SC dependencies. These events put industries into the most formidable challenge to date [39,26], dramatically showcasing the unpreparedness to deal with a large and sudden surge in demand on already stretched SCs [2] and the risk that economic dependency could be weaponized. [39]

Local, national, and international logistics could not keep pace, particularly for medications with limited therapeutic alternatives for critical care. [10,75] The poor response to the COVID crisis raised serious questions about the performance of SCs across the globe. [26] This has also heightened awareness of the risk of medicine shortfalls,

experienced across all MS and involving both original and generic medicines. [39] A comparison of the epidemic curve with and without precautions can be seen in Figure 7.

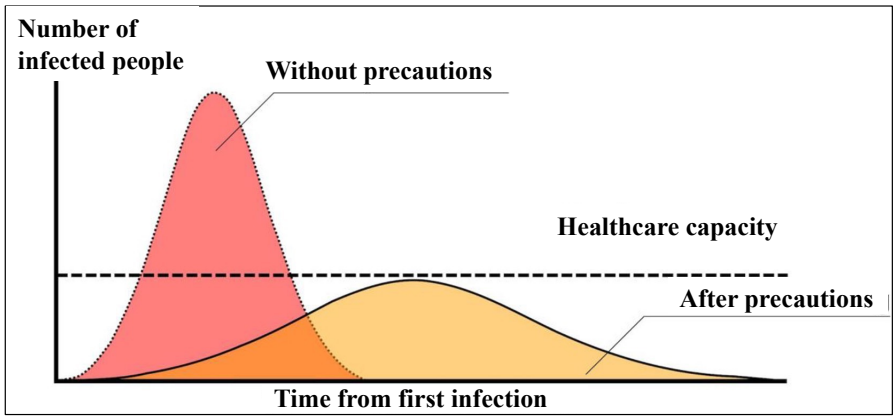

Figure 7 - A sample epidemic curve, with and without precautions taken.

Sedatives, analgesics, and paralytics needed to support critical care were particularly affected by the rapid increase in the volume of patients requiring mechanical ventilation, combined with high-dose requirements often used to manage severe hypoxemia. [75] Also, PPEs, such as masks and gloves [71], and disinfectant products, including hand sanitizers [76], were often scarce, causing difficulties in preventing the spread of the virus.

Exchanging guns for bags of food supplies and disinfectant spray, military personnel were among the first and most important responders in the pandemic. The military carried out missions to evacuate citizens and transport medical supplies and protective equipment. [77]

In Portugal, the National Laboratory of Medicines, increased its production, providing more than twenty tons of an alcohol-based antiseptic solution, as well as supply of PPEs for military units, establishments, and bodies and for national forces deployed, with more than two million units, including surgical masks, gloves, and full protection suits. [78] Support was also provided later through the diagnosis and laboratory research of SARS-CoV2, vaccination stations, material, and human resources, reaching more than seventeen thousand doses of vaccines administered. [78]

The availability of medicines is a cornerstone for the strong European Health Union. The recent Health Emergency Preparedness and Response Authority (HERA) along with the Union Civil Protection Mechanism (UCPM) supports foresight and

emergency preparedness, providing stockpiles of critical medical countermeasures to be quickly deployed when MS cannot cope with a health emergency. [39]

It became imperative for both national and international portfolio management systems to operate as efficiently as possible. There was an urgent need to prioritize resource availability for patients, forcing the development and adoption of new triage and patient management protocols or pathways. [79] Urgent measures had to be taken to ensure sufficient production and availability of the most critical medicines and components. [39]

2.6 Current Strategies and Prevention Systems

As emphasized previously, there is a tremendous need to prepare for emergencies, anticipating the harm they may bring. The advancement of DM practices has evolved since the 1970s and the world has gained a deeper understanding of the reality of disasters for a long period. [80] Integrated and holistic approaches were developed to reduce the impact of disasters. From this point on, emergency management capacity played a significant role at the national level in countries that focused on creating emergency management systems at the national level. [80]

As time unfolds, there seems to be an increasing interest in preventing this situation through acquiring new strategies, planning, preparation, and international cooperation, as no country can be self-sufficient. Many are the laws, treaties, agreements, and alliances done to try to prevent existing or potential problems that may occur.

This could be analyzed in two different levels. First, the main strategies, defense mechanisms, tools, and activities at the international level, both within the European context and among NATO countries will be discussed, and next, some of the most important measures implemented at the national level.

2.6.1 International Efforts to Prevent and Manage Emergencies

The front force of civil protection and humanitarian aid is part of the UN's work, by taking the leading role in disaster relief coordination. OCHA's main activities revolve around public and private advocacy, coordinating the flurry of response efforts, encouraging new, and more effective funding and financing mechanisms, and finally, gathering, analyzing, and sharing data and information on the entirety of a humanitarian response. [8] Unearmarked donations play a vital role for example, if there is a need to

allocate funds to kick-start a response mechanism to a sudden-onset disaster, this balance can go straight where it is in need. [81]

In 2023, OCHA promoted knowledge-sharing across the various country-based pooled funds, developing harmonized approaches, and collecting insights from past innovations and allocations. Also, the launch of the One Grant Management System (OneGMS) strengthened information-sharing and analysis capabilities, supporting the management, through the life cycle of a project granted by OCHA's pooled funds. [8,81]

Humanitarian organizations and MS have continued to exploit various tools from the OCHA-managed INFORM, a multi-stakeholder forum dedicated to developing crisis-related analysis, as part of their efforts to adapt to evolving risks. This includes the IFRC and the Red Crescent, as well as humanitarian aid operations conducted by the EC and the US. [81]

Also, within the UN, there is the United Nations Office for Disaster Risk Reduction (UNDRR), which helps decision-makers across the globe better understand and act on risk. [82] Their mission is described in the UNDRR Strategic Framework 2022-2025 as, *"to provide leadership and support to accelerate global efforts in disaster risk reduction to achieve inclusive sustainable development and the goal of the Sendai Framework."* [83] This framework is an international agreement adopted by UN member states during the Third UN World Conference on Disaster Risk Reduction (DRR), held in Sendai, Japan, in March 2015. It outlines global strategies and goals to reduce disaster risk and enhance resilience to natural and human-made hazards, encouraging countries to integrate risk reduction strategies into policies and programs, and promoting accountability and transparency. [83]

The Sendai framework envisages health at the heart of Disaster Risk Management (DRM) and, for the first time, suggests that health and DRM are significantly intertwined at the multi-sectoral global policy level. [80,83]

UNDRR is now focusing on providing enhanced support to MS to reduce risk and accelerate risk-informed development pathways, against multiple complex risks to prevent disasters and ensure sustainable development. [84] There has been an investment in developing needs-based, demand-driven approaches to strengthening Member State and stakeholder capacity, including improving the ability to convene, increasing accessible digital training platforms, and ensuring that the DRR knowledge base is openly available. [84]

UNDRR's strategic objectives are: [84]

- Countries use quality risk information and analysis to reduce risk and inform development decisions;
- DRR governance at global, regional, national, and local levels;
- Catalyze investment and action in DRR through partnerships and engagement with stakeholders;
- Mobilize governments and other stakeholders through advocacy and knowledge sharing with the DRR central to sustainable development.

While DRM strategies include risk reduction, DM is a component of a wide-ranging system. This approach comprises preventive, responsive, and recovery measures to combat unfavorable situations having a resilient approach to these adverse events. [80]

Another essential organization playing a key role in DM is NATO. The help provided by this entity is translated into the coordination of requests and assistance provided in emergencies. [85] Since the inception of NATO, preparedness has been recognized as crucial, not only in the military realm but also in the civilian field, including civil defense. [120] NATO's main emergency response mechanism is the Euro-Atlantic Disaster Response Coordination Centre (EADRCC). It coordinates disaster response efforts. [85,86] EADRCC's responsibilities include, handling the fallout from chemical, biological, radiological, or nuclear catastrophes, terrorist acts, and organizing NATO's and partner nations' responses, supporting other organizations. These activities are jointly orchestrated with organizations with which the EADRCC liaises closely such as the UN OCHA, the EU, the International Committee of the Red Cross (ICRC), and others. [85] In addition, there is constant availability of access to national civil experts to be called upon in case a major disaster takes place.

Similarly, the EU has the European Civil Protection and Humanitarian Aid Operations (ECHO) [87], which provides emergency assistance and supports disaster response and preparedness, and also the Emergency Response Coordination Centre (ERCC), responsible for coordinating the delivery of aid to disaster-stricken countries, such as relief items, expertise, civil protection teams, and specialized equipment. [88]

ERCC can assist any nation, whether within or outside the EU, impacted by a major disaster, once provided with a request by the national authorities or a UN agency. [88]

In October 2001, the EC established the EU Civil Protection Mechanism. The Mechanism aims to strengthen cooperation between the EU countries and 10 participating states on civil protection improving prevention, preparedness, and response to disasters. [89] In March 2019, the EC upgraded the UCPM and created rescEU to establish a reserve of new civil protection capabilities, including forest fighting planes, special water pumps, urban search and rescue and field hospitals and emergency medical teams [72], fully funded by the EU, to protect citizens from disasters and manage emerging risks. [90] The commission allocated around 690 million euros to seven MS, including Portugal, to further develop the rescEU strategic reserves of medical, chemical, biological, radiological, and nuclear items. [91,92]

It responds to crises in Europe and beyond by building capacities such as: [90]

- Wildfire assets;
- Medical capabilities;
- Chemical, biological, radiological, and nuclear (CBRN) capabilities;
- Strategic stockpiles of medical and CBRN items;
- Mobile shelters;
- Emergency transportation;
- Electricity supplies.

Since their establishment in 2020, the rescEU strategic reserves have been mobilized multiple times, proving to be a crucial response tool during major crises, such as COVID-19. Another example is the one following Russia's invasion of Ukraine. To tackle the medical needs of Ukrainians, the EU deployed medical evacuation services and assistance from its rescEU medical/CBRN, energy, and shelter stockpiles hosted in various locations. [90]

The EC maintains control over its operation in close cooperation with host countries. In the event of an emergency, the rescEU reserve is intended to assist all EU MS and the states participating in the Mechanism, and it can also be mobilized for neighboring countries of the EU. [90-92] This protection mechanism is significant and symbolic, given the close connection between many of these assets and the defense capacity of certain states.

As much as global, international, and regional efforts impact the preparedness and response mechanisms, DRM should be designed at the national level, based on the circumstances of each country. It is impossible to use a DRM framework that works in all countries, whereas the DRR framework can be designed internationally. [80] For this matter, countries must implement their risk management strategies, complementing that with the support and assistance given by these international organizations, collectively working to ensure better dynamics, increased preparedness and resilience, enhanced resource utilization, shared knowledge, and improved communication and coordination.

2.6.2 Strategies Adopted at the National Level

Strategies, organization, and prevention mechanisms are essential for each country to be prepared for emergencies, whether they are natural or man-made disasters. Although no country can be self-sufficient, as previously mentioned, nations mustn't rely on external help to combat certain uncomfortable situations being able to possess almost all of the necessary tools to go through these types of incidents.

The Federal Emergency Management Agency (FEMA) helps to prevent, assist, and after disasters in the US and its territories. FEMA promotes preparedness and resilience through education, coordinates federal response efforts, including disaster declarations and assistance programs, and supports recovery and mitigation to strengthen communities against future risks. [93] In April 2024, FEMA launched a guidebook about the Strategic Foresight 2050. This guidebook was designed to help emergency management organizations at every scale incorporate foresight into their planning and operations, providing an invaluable framework for systematically, creatively, and boldly accounting for the unknown. [94]

The strategic foresight process is divided into five main phases. It begins with framing, where the scope, objectives, and priorities are set. Next is scanning, which identifies external signs and analyzes trends and emerging issues. Then forecasting, where future scenarios are developed to explore potential developments and uncertainties. During the workshopping phase, stakeholders gather to discuss projected scenarios. Lastly, the findings, recommendations, and implications for decision-making are documented and communicated, tailored to the organizational context. [94]

Still in the US, the Defense Logistics Agency (DLA) is a governmental agency that manages the end-to-end global defense SC, for military services, 11 combatant commands, and other federal, state, and local agencies partner and allied nations. FEMA and DLA Distribution have worked together on emergency and disaster recovery efforts for 20 years. [95] In 2005 a formal agreement was made designating DLA as a source of services and supplies, ensuring their rapid movement, and including a deployable depot to manage and operate FEMA incident support bases. [96]

In Portugal, the National Authority for Emergency and Civil Protection (ANEPC) constitutes the central service of direct administration, guaranteeing the organization and preparedness of the State's strategic sectors to respond to crises. Although under the Ministry of Home Affairs, it has administrative and financial autonomy over its assets. [97] The main goals of the National Platform for Disaster Risk Reduction (PNRRC), a multi-sector and multi-discipline structure that houses several institutions and organizations, are to take stock of and coordinate DRR actions and establish a framework integrating initiatives that promote DRR within sector plans and programs according to the Sustainable Development Goals outlined in the Sendai Framework. Also, it intended to foster the incorporation of risk issues into local, national, and sub-regional plans ensuring sustained development. These goals move towards a cohesive and comprehensive approach to DRR, aligning with international standards such as the Sendai Framework, and promoting resilience at multiple governance levels. [97]

Organizations such as the LM, the Portuguese Red Cross, the Hospital Common Use Services (SUCH), the National Institute of Medical Emergencies (INEM), and many others collaborate with the ANEPC, to promote emergency preparedness, and enhance effectiveness in emergency response by providing specialized medical help and expertise[9,97].

Some examples of other entities responsible for the management of disasters and emergencies in Europe: in Germany, the Federal Office of Civil Protection and Disaster Assistance (BBK), in France, the Direction Générale de la Sécurité Civile et de la Gestion des Crises (DGSCGC), in Italy, the Department of Civil Protection (Dipartimento della Protezione Civile), and in Spain, the General Directorate of Civil Protection and Emergencies (Dirección General de Protección Civil y Emergencias).

National emergency and DM structures and their collaboration, transparency, and trust with other international organizations are fundamental. National and international disaster response, monitoring, preparedness, and management can reduce the impacts of

disasters that often overwhelm national coping capacities, in which case, assistance is critical to ensuring that humanitarian needs are promptly and adequately met.

2.7 Technology Incorporation in Healthcare Management

The creation of inter-organizational and multinational networks that enable the processing and exchange of information in real-time has been made possible by the development of modern Information Technology (IT) solutions. [98] The ongoing development of new IT tools allowed for numerous controls, helping to harness the data behind the monitoring of demand and supply of medicines and MDs, and traceability in SCs. [6,10,98] Introducing IT tools establishes a solid base for a robust, transparent, and efficient system for managing stocks and logistics.

Traceability is crucial in different contexts, but it is indispensable in SCs with this many partners involved and strict requirements for success. [98,99] Product traceability provides numerous verification, tracking, and alerting benefits [100], effectively addressing certain issues SC related. [98] These benefits include aspects such as real-time notifications of falsified or unfit products, tracking product recalls, alerts to product quality issues, and more, as well as other SC management aspects, such as efficient commissioning or decommissioning of products, equivalency identification, information exchange about SC actors, products, facilities, etc. [100] Radio Frequency Identification (RFID) technology has also been quite effective in providing anti-counterfeiting measures in the SC. However, the genuineness of RFID tags cannot be guaranteed in the post-supply chain since these tags can be cloned in the public space. [101] Distributors must verify all purchased medicinal products against the cross-national database whenever there is a suspicion of counterfeiting. This cross-national database is accessed to confirm the authenticity of the products in their possession. This is important not only for the protection of earnings and reputations of producers, distributors, drug stores, and hospitals but also for safeguarding public well-being and consumer safety. [6,98,100,102] One of the challenges regarding this, is the sharing of information with all relevant parties.

Lack of transparency, mistrust in collaborations, and unwillingness to share data can be huge challenges for the global healthcare industry. [103] Hence, creating a unified system of information, where all the important information is shared, can be a huge step to better functionality and efficiency, consequently strengthening SC management. A system that ensures transparency, reliability, and provenance assurance would increase

the overall trustworthiness. One solution to address all these three needs might be utilizing blockchain-based Distributed Ledger Technologies (DLTs). [104] Advanced and potentially disruptive applications from Industry 4.0 include the Internet of Things (IoT), Artificial Intelligence (AI), and big data analytics. [105,106]

Blockchain seems to be one of the upcoming systems regarding technology, smart contracts, and transactions, as it provides a decentralized, distributed, peer-to-peer network with an immutable ledger eliminating the need for centralized authority for transaction verification, and creating secure records that cannot be tampered with. [101,103,107] These networks use cryptography to ensure that solely authorized users access the data, operating under protocols to add new blocks to the chain. This decentralized DLT will be discussed in greater detail later in this work.

With the current level of science and automation, IoT has emerged as a key technology for enhancing SCR. [108-110] IoT refers to the growing network of Internet-accessible devices and their ability to exchange data. Its components can track every movement of containers, products, packaging, and goods in real-time, which permits obtaining relevant data related to the status of SC operations. [108,111,112] IoT devices, such as GPS trackers and RFID tags can provide live tracking monitoring of the location and condition of goods. [101,102,110,112] This data can be fed into a centralized system for continuous monitoring. IoT enables objects to gather and later share data about themselves and their surroundings, providing updates on stock levels, and preventing overstocking or stockouts. [108] This data is sent to a central server after being captured with a device. This is where the integration and incorporation of blockchain technology come in IoT devices. [108] More and more, the combination of IoT and blockchain technology keeps receiving scholarly attention. [101,107,108,113]

Dolgui and Ivanov [109] found that the big data sourced from IoT could be connected end-to-end with high granularity through 5G technology, which might help digitize SC processes, such as manufacturing, warehousing, and logistics. [109,114] Given the large number of devices that generate a huge amount of data, IoT technology is the driver of a special area, namely the analysis of Big Data in real-time. [115]

Big Data analytics refers to the systematic processing and analysis of large quantities of data which can be distinguished by volume, variety, velocity, veracity, variability, and value. [116] Big data can improve healthcare delivery and reduce costs while supporting advanced patient care, improving patient outcomes, and avoiding

unnecessary expenses. [117] Such analysis includes predictive analytics, business analytics, big data analytics, and SC analytics. [118] This tool can strengthen market competitiveness and improve data quality management and usage experience. There is also a positive relationship between maintaining the quality of big data and the firms' perceptions of adopting big data analytics, whether sourced internally or externally. [119]

Digital technologies, process innovations, and optimized systems and processes used by manufacturers and marketing authorization holders can utilize available information to ensure supply security. [41] Adopting new systems and technologies like these can become quite significant in a society with ever-increasing technological advancements, which tend to improve and facilitate processes, in this case, topics such as SCR and SCV.

3. National Laboratory of Medicines

3.1 National Laboratory of Medicines Role

The LM, part of the Portuguese military, has been a cornerstone of pharmaceutical services for over a century. Specializing in the production and research of medicines, this institution guarantees the health and preparation of military personnel through innovative solutions and rigorous quality standards. [9] It ensures the manufacturing of approximately seventy essential medicines for the armed forces, also contributing to the production of medical equipment whose normal supply is at stake, namely rare disease medicines, generic medication, and discontinued drugs, most used in treating and preventing diseases that are more prevalent in the national territory, with an annual production of approximately three million medications. [9,78] Additionally, this institution ensures the sanitary replenishment of the acquisition, packaging, storage, production, control, distribution, and maintenance of medicines, hygienic materials, MDs, and other health products. [9] LM is the only place in Portugal where methadone is produced, by presenting special conditions in production and transportation, producing nearly ten thousand liters annually, being used for daily support to around fourteen thousand patients enrolled in opioid substitution programs. [78] The full LM's portfolio for 2023 is present in Annex 2.

Being strictly connected with INFARMED, the National Health System (NHS), the Ministry of Health, the Ministry of National Defense, and also the Ministry of Science and Technology and Higher Education, it also plays a fundamental role in providing medicines and MDs, and in the National Strategic Reserve (NSR).

3.1.1 LM Assistance During Crisis

The LM activates production lines to respond to emergencies or drug shortages, to help mitigate the greater impact that these events would have otherwise. It constitutes strategic reserves for emergency, epidemic, or pandemic situations, ensuring their storage and management. [9,78] During the pandemic crisis caused by COVID-19, the laboratory demonstrated remarkable adaptability and productive flexibility to address epidemic or pandemic emergencies. This was evident through the increased capacity of its production line for hand sanitizer. The LM, anticipated and reorganized itself to adapt its hand sanitizer production, almost quadrupling its output to approximately a thousand liters per

day, thus responding effectively to the urgent need, to cover the necessities of the NHS. As above-mentioned, it supplied PPEs for military units, establishments, and bodies, and deployed national forces, more than two million units, including surgical masks, gloves, and full protection suits. [78]

3.1.2 Production of Rare Disease Medicines

Rare disease medicines are of special concern since they treat rare diseases and have a low demographic incidence. [57,120] The WHO has suggested a frequency of less than 6.5 to 10 per 10,000 people to define rare diseases. In the EU, this definition is for less than 5 in 10,000 people (or 1 in 2,000). [121]

These types of drugs do not allow for recovering the capital invested in the Research and Development (R&D) of new medicines, and in this case pharmaceutical industries do not invest in them. [120] Moreover, in the US, due to a special period of market exclusivity granted to rare disease medicine manufacturers by the FDA, one company typically produces the drug's entire supply. [57] The issue starts right at the beginning of the process, where these medicines need to undergo just like "normal drugs" in the clinical trials. Substantial evidence of clinical safety and efficacy is necessary to obtain approval. Trial design requires an appropriate sample size, control group, validated biomarkers, and clinically meaningful outcome measures. For rare diseases, there are already strategies in place to address the methodological challenges posed by these constraints. [122] On top of that, the costs inherent to these medicines are much higher than "regular" drugs. The costs for FDA-approved drugs from 1999 to 2015, were five times greater for rare disease medicines ($150,854 vs. $33,654 per year). [123] In countries where the costs of these expensive treatments are not reimbursed the problem is further exacerbated and leads to uneven access across Europe where there is a considerable variation in the costs per patient. [124] In Portugal, the expenditure of the NHS on rare disease medicines increased almost six times between 2016 and 2022, from 49 million to 286 million euros, respectively, representing 21% of the public investment in innovative medicines. [125]

The Orphan Medicinal Product Regulation of 1999 was the first European legislative text concerning rare diseases, representing the start of a commitment at the European level to develop rare disease policies aiming at improving the care of patients

with rare diseases. [126,127] Before this big step, only eight medicines had been approved to treat rare diseases. As of today, 244 designated orphan medicinal products have been granted authorization for orphan medicinal by the EC since the orphan legislation was implemented. [128]

In this context, the LM produces rare disease medicines on demand, such as copper histidine, a medication used primarily to treat a rare genetic disorder, Menkes disease, where patients have copper deficiency. Additionally, many other medicines are formulated at the request of the NHS for specific situations. The role is not to compete with the pharmaceutical industry, but rather to ensure that treatments that are essential for people, which are not produced or profitable for the industry, are available.

3.2 Portfolio Management

A general definition of portfolio management can be the continuous process of creating portfolios based on an investor's preferred level of risk and reward and then adjusting it over time to maximize returns. [129] When applied to the pharmaceutical industry context, portfolio management refers to enhancing the value of R&D portfolios through proper resource allocation. [130] This requires the evaluation of objectives, risk management, and planning aligned with the strategic concepts of a given entity, whether private or public. The portfolio management process needs to be cross-functional, involving the entire organization. [130]

This includes subsequent layers: planning, execution, and feedback. [130] But first, there is a need to define the starting point.

I. **Establish a baseline.** Before deciding where to go, figuring out the point of the situation and the existing conditions is essential.

Compiling a thorough assessment of current and potential projects in the pharmaceutical R&D portfolio, including:

- Funding status;
- Pipeline stage;
- Forecasts for internal and external development costs.

Asking questions such as, “What areas receive the most funding, and what areas are potentially under-invested?”, can make the purpose much more evident and clarify the path to reaching it.

II. **Determine the strategic goals and start planning.** Which might include:

- Breaking new ground in a specific therapeutic area;
- Addressing a short-term funding gap;
- Fostering long-term stability and growth;
- A combination of smaller goals.

Considering the preexistent strategies and assessing results may be fundamental to knowing the next steps. Identifying the goals met and future improvements.

III. **Execution.** Utilizing the data gathered till this state, it is time to start executing the plans drawn.

IV. **Feedback/Portfolio Review**

It is key that value-evaluating tools are set up, aiming to understand if the metrics used are working and improving the system in a way that is expected and beneficial working towards the organization’s goals. Portfolio reviews are inherently tough, and decisions on what to salvage and where to cut your losses can be extremely challenging. [130,131] However, determining what are the next steps is much easier when adequate information is available to guide those decisions. Effective data analysis tools facilitate the evaluation of which combinations of projects would maximize value, sales growth, or the number of new launches. [130]

V. **Restarting the whole process**

As this process is continuous, and there’s always room for improvement of processes, new projects, and new technologies that can be applied, there is a need to from

time to time to start the whole process from the beginning and evaluate if the right approach was taken and see what can be improved to be applied in the next set of actions.

3.3 National Strategic Reserve

The EU plays a significant role in DRM, among its MS and globally. [132] A common strategy for effectively using resources for access to medicines is drug formularies of essential medicines. Besides the essential medicines lists, there are other supplementary plans for emergency stockpiles, guaranteeing the supply of certain medical products. [133] Appropriate inventory strategies and coordinated stockpiling policies can help mitigate shortages due to disasters, abnormal spikes in demand, and interruptions in SCs in the short term, but are of limited effectiveness in long-term disruptions. [6]

A compilation of all the medical stocks, medicines, and MDs, present in hospitals, military pharmacies, warehouses, and other governmental facilities, which can be used, if necessary, in case of disasters and emergencies is called the NSR. These stocks aim to protect the supply of the national markets, combined with specific foreign importations, to cover gaps in national supplies. [14]

This reserve needs to be thoroughly evaluated. There is no need to buy as much as possible, just like what happened in some cases as the COVID-19 pandemic impact escalated. Unprecedented uncertainty and risk surrounding the availability, access, and affordability led to “panic buying” and stockpiling of medical supplies, creating unanticipated demand shocks, stockouts, and systematic disruptions of healthcare SCs. [134] On the other hand, the expected costs and benefits of risky behavior alternatives compared to the expected costs and benefits of safe behavior alternatives, potentially explain the buying and stockpiling of medical items during the COVID-19 pandemic. [134]

3.3.1 RescEU Program

Seeking to involve Portugal in rescEU, a consortium was formed to apply to the European Union Civil Protection Mechanism, aiming to obtain financial support for the project "Development and Maintenance of a rescEU Stockpile" (rescEU - Stockpile Project). [92] The Portuguese project objectives consisted of developing, maintaining, and ensuring the availability of strategic stockpiles of medical countermeasures capable of responding to cross-border health threats and complementing the existing rescEU reserves. The shared part for Portugal was 146 291 367,23 euros, to be distributed among

the entities participating in the consortium, in which LM is present. [92] The expected impact of this project is substantial. By enhancing Portugal's preparedness and response capabilities, the project not only improves the country's ability to handle health crises but also contributes to the overall resilience of the EU.

It also sets a precedent for future collaborations and investments in shared resources, paving the way for a more integrated and resilient European response to disasters.

3.4 National Laboratory Partnerships and Agreements

The LM collaborates with some key institutions to enhance its impact on public health and emergency response capabilities. Originally founded as the Central Pharmacy for the Army, following the change to the Military Laboratory of Chemical and Pharmaceutical Products, and finally the National Medicines Laboratory, the LM maintains as of today a very close relationship with the Ministry of National Defense, continuing to provide sanitary support and medications to the Portuguese armed forces, including military personnel, their families, and veterans. [9]

As noted earlier, the LM also works with the NHS, producing medicines on demand that are no longer manufactured by the pharmaceutical industry, rare disease medicines, some specific antidotes, other medications requested by public hospitals, and also the production of methadone for opioid substitution programs in collaboration with the Service for Intervention in Addictive Behaviors and Dependencies (ICAD). [9,135] The agreements with Infarmed and the Ministry of Health are crucial to managing the NSR, ensuring an adequate stock for emergencies or market shortages. Recently, a collaboration protocol was signed with the Directorate-General for Reintegration and Prison Services (DGRSP), which enhances the acquisition of medicines, MDs, and other health products. [136]

These types of partnerships enable the LM to play a crucial role in public health, and emergency preparedness in Portugal, contributing to military and civilian needs.

3.5 Current Situation

In May 2024, the Portuguese government issued a strategic plan specifically focused on addressing and transforming the healthcare system in response to emergencies. [137] This plan outlines measures for improving the healthcare system's resilience, efficiency, and effectiveness, particularly in public health emergencies.

The “Plan for Preparation and Response to Disasters and Public Health Emergencies” referred to in the document lists three main topics on which to act. Risk Typing, Action and Rapid Response Plan, and Surveillance and Early detection, were the main topics listed to prepare and respond to critical situations. This elaborated process involves the help, contribution, and coordination from different entities with expertise in the area, including but not limited to, the Directorate-General of Health (DGS), ANEPC, INEM, LM, and Security Forces, among others. [137]

4. Blockchain Technology

The foundation of many businesses has been the basic principle of trust among various parties. The pharmaceutical industry grapples with numerous issues, such as limited transparency, challenges in product tracking, lack of trust between stakeholders, and the distribution of expired products. Implementing blockchain technology has demonstrated promising solutions to issues related to transparency in various fields, such as healthcare and finance. One of its most significant impacts is expected in the logistics industry, particularly in the SC.

Blockchain is a clever system of decentralized trustless verification based on some of the math born in cryptography. This decentralized DLT ensures all transactions are recorded transparently and immutably, and that information is distributed and synchronized between all nodes in the network. [107,138] This functionality is provided by a consensus algorithm deployed in the system to eliminate duplicate transactions, allowing nodes to verify the truth of information before it is added to the registry. As a decentralized digital registry, each participant within the network maintains an exact copy of the ledger. [113] By 'sharing' databases between multiple parties, blockchain removes intermediaries previously required to act as trusted third parties to verify, record, and coordinate transactions. [139] There are four types of blockchain systems, the Public Blockchain (a permissionless blockchain), a Consortium Blockchain, a Hybrid Blockchain, and a Private Blockchain.

This technology can be integrated as an embedded web layer to support a range of functionalities, including but not limited to payment processing, currency exchange, token reception and distribution, transfer of digital assets, and the execution of smart contracts. [104] The main strengths linked to blockchain technology are data transparency, security, asset management, and smart contracts. [139]

4.1 Impact of Blockchain Implementation

The enterprise's use is best for processes that involve multiple parties, and each party needs access to the same data but has slightly different or out-of-data information that has to be reconciled. These processes take time and effort, and their middlemen removal via automation increases overall efficiency. Blockchain can shore up trust relative to the information related to the product's provenance.

One of the main impacts of this technology in the SC field is the reduction and simplification of bureaucracy and paperwork. As a multistakeholder network, the long easy-to-fake paper-based certificate paper trails associated with the validity of transactions, authorizations, and quality assurance can be replaced with a theoretically simple automated process for storing information in a tamper-evident digital version, enabling a more direct relationship between each participant. [139] Within the SC context, blockchain expands the number of suppliers and buyers, ensuring the integrity of data passing through the SC, thereby getting closer to the elusive goals of SC visibility and transparency. Along with IoT, this registry can track many attributes such as price, ownership, weight, geolocation, and quality, among other details. [140] While traditional digital databases employed by companies can achieve similar tracking capabilities, blockchain technology offers superior resistance to tampering. [140] In healthcare, sensitive data from all stakeholders could be shared using encryption, and data protection to improve service efficiency and quality. In logistics, data sharing across the SC could enable higher levels of transparency, empowering consumers to make better choices about the products they buy. [139]

Blockchain solutions ensure top-tier security. The tracing capabilities of blockchain represent a novel manifestation of SC tracking solutions. [104] Through the implementation of a decentralized system, healthcare providers can facilitate secured electronic health records, transparency in the SC, integrity of medical data, secure transactions, and reduction in fraud claims.

4.2 Blockchain Technology Mechanism (Public Network, Proof of Work Consensus Mechanism)

The concept of blockchain transactions can seem simple upfront but involves a lot of computational power and coding. The intention here is not to delve deeply into how the mathematical and coding part works but rather to give an idea of how it works. Taking the Bitcoin blockchain, a public blockchain, as an example, Figure 8 illustrates the overview of the transactions workflow.

Everyone generates a public key accessible for every member, and a private key, each looking like a string of bits. The digital signature is much safer than a regular password which does not change because this digital signature is different for each new message. Creating a digital signature involves using a function that depends on the

message and the private key. The digital signature is the element that will undergo validation in each transaction. [141]

The transaction process starts with informing all participants of the will to make a specific transaction. Once the transaction is formulated, it is broadcast to the entire network, disseminating the transaction details to all participants, and ensuring the information is public, among the authorized participants. [141]

The next step is validation, which works through a shared protocol for new information blocks. [142] All parties are informed, and this data must be entered into a block that will be created and then appended to the chain. These block creators, frequently called “miners”, listen for transactions, create blocks, broadcast those blocks, and get rewarded for the work. Solving the computational puzzle is difficult to solve but is easy to check. [101] The resolution of this problem is called Proof of work (PoW). [141] The transaction is deemed valid if the sender has sufficient funds and all transaction details are accurate. From the miners' perspective, each block can be seen as a series of lotteries.

Since all blocks are cryptographically linked, to change a previous block, all the subsequent blocks must be changed, which makes it computationally impractical for an attacker to change if honest nodes control a majority of CPU power. [141] The only strategy would be guessing and checking random signatures, using the public key that everyone knows. However, the number of possible signature combinations with 256 bits, would be 2^{256}. So if a signature is valid against a given message, it is extremely certain that the only way someone could have produced it is if they knew the secret key associated with the public key used for verification. [141]

Upon validation, the transaction is grouped with other validated transactions forming a new block. This block, containing multiple transactions, is then prepared for approval based on a consensus mechanism, confirming the accuracy and legitimacy of the block. [139,141,142] This eliminates duplicate transactions, allowing nodes to verify the truth of information before it is written to the registry. The PoW also assures the correct sequence, represented by the longest chain with the greatest PoW effort invested in it. [141] If most of the computational power is controlled by honest nodes, the legitimate chain will grow faster and surpass any fraudulent chains. If there's a momentary tie, the approach should be to wait until some additional blocks make one of them longer. With the general agreement to give preference to whichever blockchain has the most work put into it, there can be a decentralized consensus. [101,139,141,142]

In the end, the transaction is executed. From the initial creation of the transaction to its execution and inclusion in the blockchain, highlights the robustness, security, and transparency of blockchain technology. All steps ensure the transaction is accurate, secure, and immutable, reflecting the decentralized and trustless nature of blockchain systems. [139,141]

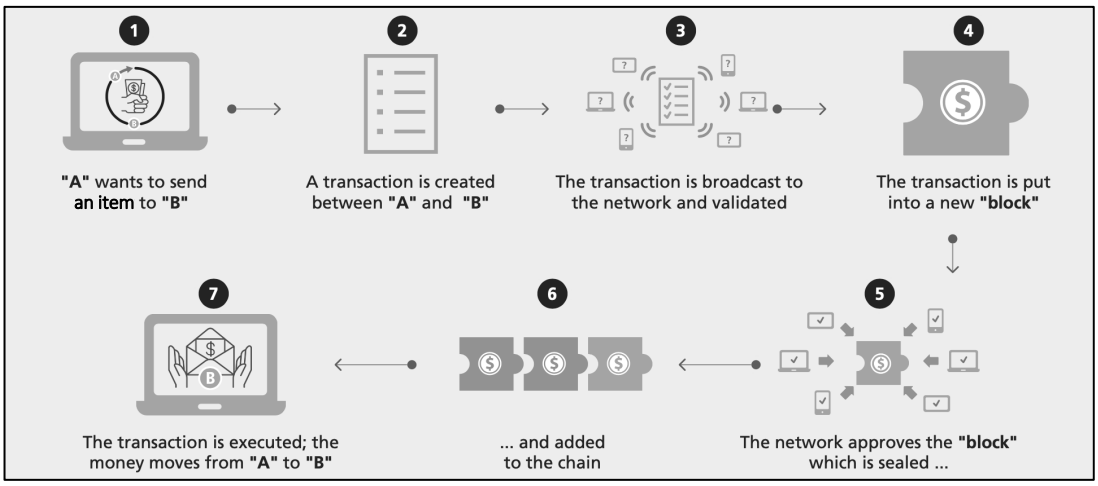

Figure 8 - Blockchain network scheme. (from [139])

4.3 Current Main Blockchain Drawbacks

Just like any new technology, blockchain offers significant advantages, however, it also comes with some drawbacks that must be addressed. The most prominent challenges within public blockchains are privacy, transaction costs, regulatory uncertainty, scalability issues, interoperability hurdles, and user complexity can hinder its widespread adoption and effective implementation. [139,143] Understanding these limitations is crucial for overcoming barriers and fully realizing blockchain's potential. Annex 3 presents the limitations found in a wide range of articles that reference and identify these limitations. [143]

Industries' adoption is one of the most critical challenges. Obtaining stakeholder commitment will be challenging, as there is a need to recognize the benefits of blockchain-based collaboration. This will be particularly difficult due to legacy processes, regulations, and laws governing various aspects of the business, as the regulatory landscape surrounding blockchain and cryptocurrencies is still evolving. Stakeholders will likely incur costs to migrate from legacy systems and integrate with new systems and practices. [105,139]

Progress in blockchain technology is necessary to overcome current technical limitations, particularly moving from pilot implementations to full-scale deployments. [139,143,144] The relative complexity adjacent to blockchain for non-technical users can also pose usability challenges, requiring education and training initiatives. [143]

Due to the mentioned issues, many observers believe permissionless (public) networks are unsuitable for large-scale non-financial applications such as SC solutions. [104,145] There is still much work to be done before this technology is fully implemented. The technology needs to mature further to address the challenges specific to each use case. [104] Addressing these concerns is key for the progress of blockchain technology incorporation, along with the cooperation between different entities such as legislators, organizations, and technology developers, which are crucial for promoting the broad adoption of blockchain technology.

4.4 Hyperledger Fabric

Permissioned blockchains have received much attention because of their fast transaction processing and privacy preservation. Hyperledger blockchain, a consortium open-source collaborative project, aims to advance cross-industry blockchain technologies by providing a modular framework, which allows custom usage of consensus mechanisms to fit particular use cases [146,147], and architecture ideal for building enterprise-grade blockchain solutions, possessing a high degree of flexibility and extensibility. [104,143,147,148]

HLF was specifically designed for enterprise use cases, providing features like scalability, privacy, and flexibility. [143,147,149] It offers channel-based privacy, enabling selective data sharing among network participants [149], and providing high control over access and permissions, making it ideal for industries and organizations that require strict privacy and compliance measures, such as governmental entities. [146] One of the many standout features of HLF is its ability to enable a network of networks. Members of a network work together, but because some organizations need data to remain private, they can maintain separate relationships within their networks. [147] Clients, peers, and orderers are further grouped into organizations, which normally represent companies or wider groups of participants. [150] Compared to public permissionless blockchains, it promises improved performance and provides certain features that address key requirements of enterprises. [140]

In this private network, all entities are known. Each peer has a unique identity provided by a Certificate Authority (CA). The certificates hold information about each node along with their function in the network, operating as their identity within the network. Each organization's CA administrator generates certificates for the organization's peers. [147] This CA is linked with a distinct Membership Service Provider (MSP) associated with its organization, which manages identities and authentication, while the CA issues digital certificates for secure communication. Peer nodes execute smart contracts known as "chaincode" [146], maintain a copy of the shared ledgers, and validate transactions. This chaincode is a program written in Go, Node.js, or Java that implements a prescribed interface. Since all nodes are known, there is no need to utilize a PoW system. Chaincodes are accessible to authenticated peers so that non-authorized peers remain unaware of them. [148] Privacy is accomplished through channels[148].

Initially, identities are generated for authentication of the peers to channels using cryptography, and just like that, channel belonging can be verified for each peer. Figures 9 and 10 illustrate how two or more channels can achieve privacy from other entities within the same network. As represented in Figure 9, the introduction of channel 2 (C2) enables peer 2 (P2) and peer 3 (P3) to transact without peer 1 (P1) being aware of smart contract 5 (S5) and without having access to ledger 2 (L2). This process requires an ordering service which is provided by the ordering nodes. Their job is to receive endorsed transactions from endorsing peers, ordering them into a consistent sequence, and packaging them into blocks. [146,148] In a practical scenario there will be multiple ordered peers. HLF supports pluggable consensus mechanisms, enabling the selection of a consensus algorithm that best fits their specific needs. Among the available algorithms used to implement the ordering service within the network are Solo, Practical Byzantine Fault Tolerance (PBFT), Raft, and Kafka. [104,148,150]

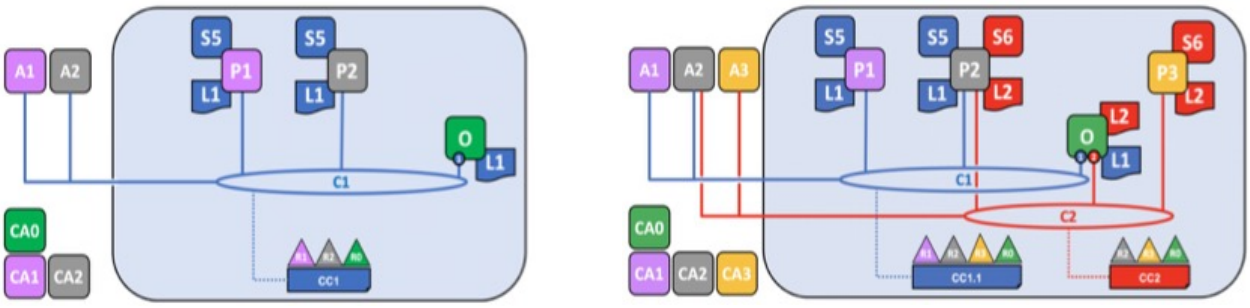

Figure 9 - Two Hyperledger Fabric network architectures, one with one channel and another with more than one channel (from [147])

Legend: Client – A1, A2, A3; Certificate Authority – CA0, CA1, CA2, CA3; Channel – C1, C2; Channel Configuration – CC1, CC1.1, CC2; Ledger – L1, L2; Orderer – O; Organization – R0, R1, R2, R3; Smart Contract – S5, S6; Peer – P1, P2, P3;

4.4.1 Hyperledger Fabric Transaction Flow

The transaction flow is split into three main phases which are the following:

1. Transaction Proposal and Endorsement
2. Transaction Submission and Ordering
3. Transaction Validation and Commitment

As showcased in Figure 10 in the processes' first phase, a client will submit a cryptographically signed transaction proposal to a trusted peer for execution. This peer can execute the transaction or pass it on to another endorsed peer within its organization. These peers will execute the transaction and return their responses to the gateway service, without updating their ledgers for the time being. Endorsers invoke a cryptographically signed endorsement known as the Endorsement System Chaincode (ESCC), which simulates the transaction proposal and creates a read and a write set for the ledger. [147,150] The write set includes all key updates from the execution, while the read set contains all keys read by peers during the initial simulation. Endorsers create a cryptographically signed endorsement with these sets and send it as a proposal response back to the client. The client collects endorsements based on the Endorsement Policy (EP) and submits them to the orderer, ending phase one. [150] This phase is important because it allows for distributed validation, preventing malicious or unauthorized transactions from entering the network.

In the second phase, transaction submission and ordering, once the client gathers sufficient consistent endorsements, it consolidates them into a signed transaction and submits it to the orderers. [148,150] The ordering service then uses a pluggable consensus protocol to create the sequence of all transactions, batching them into blocks and signing them. Before submitting, the client carefully reviews, compares, and verifies that all endorsement requirements and chaincode policies have been met. The orderer subsequently verifies the transaction and sequence according to the channel's configuration. [147,148,150]

Here transaction order consensus is achieved across all network participants, guaranteeing the integrity and consistency of the blockchain by employing consensus algorithms.

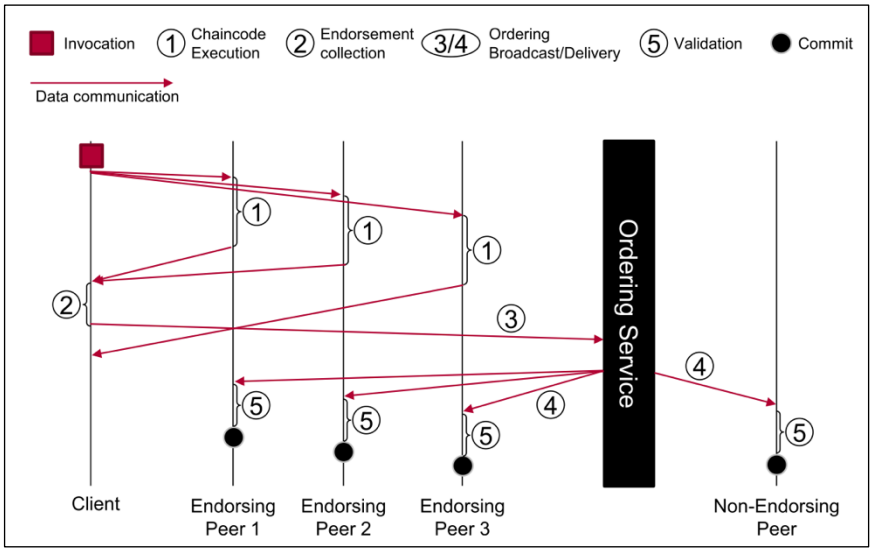

Figure 9 - Hyperledger Fabric Transaction Flow. (from [150])

Finally, the Validation System Chaincode (VSCC) validates a transaction in the validation and commitment phase, including checking endorsement policy and read-write set versioning. At the same time, a Multi-Version Concurrency Control (MVCC) ensures that valid transactions do not have read-write conflicts, preventing double-spending. [147] Blocks are then validated to ensure that the EP has been satisfied and that the ledger state remains unchanged. After validation, the blocks can be delivered by the ordering service or indirectly distributed by other peers through the gossip protocol. [147,148,150] Transactions in the block are tagged as valid or invalid [147], as then peers update their ledgers, ‘‘commit phase’’, and append the block. Each peer notifies the client application that the transaction (invocation) has been immutably appended to the chain, as well as notification of whether the transaction was validated or invalidated. [147]

4.4.2 Hyperledger Fabric Private Data Transaction Flow

For private data transactions, some slight changes in the process ensure that data privacy is maintained within the authorized peers for that specific operation, as shown in Figure 11. Although creating new channels comprising the organizations that need access to the data could be an option, this would create additional unnecessary administrative overhead. However, there is the possibility of private data collection. This acts as a

privacy policy determining which peers can process and store related data, and which organizations should have access. [147,150] This enables transactions where specific organizations store the actual data, while the rest only have access to the transaction hash.

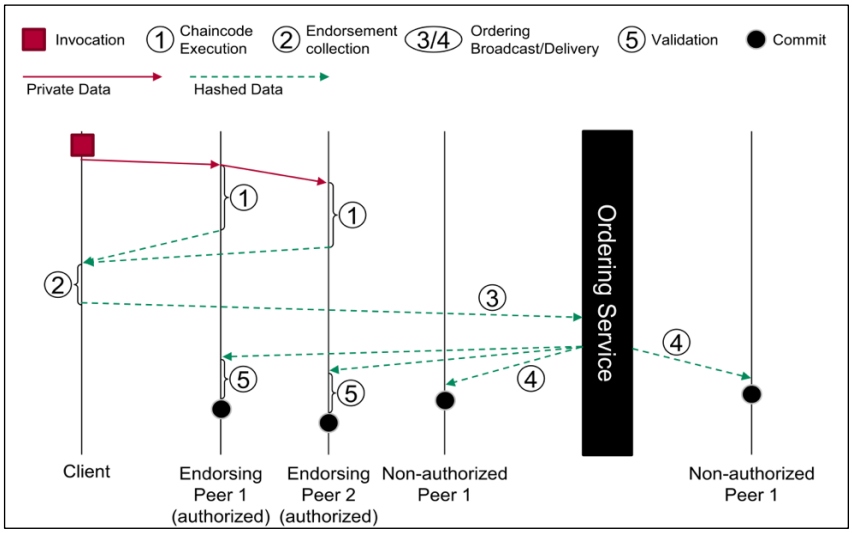

Figure 10 - Hyperledger Fabric private data transaction flow. (from [150])

At the start of a private data transaction, the transaction proposal, including the confidential data, is sent to the endorser, who then forwards the data to other authorized peers through a gossip protocol. The same read-write sets as a normal transaction are then generated, but instead of containing confidential data, they include a hash of the private data keys and values. [147,150] The endorsements are sent to the client, who forwards them to the ordering service in sequence.

The ordering phase doesn't change much from the regular transactions, as by consensus the data is collected into a block and distributed to all peers, which receive the hashes of the private data. This enables all peers on the channel to validate transactions using the hashes of the private data consistently, without accessing the actual confidential data. [147] The transactions are stored in all peers' ledgers, and the read-write sets are updated. Authorized peers will try to access the private data, first checking their local transient data store to determine if they have received it at chaincode endorsement time. If not, the peer will attempt to retrieve the data from other authorized peers. The transaction's hash values will validate the private data before committing the information to their copy of the private state database and private write set storage. [147,148,150]

4.5 Comparison with other blockchain platforms

The HLF approach for the medical SC management system has performance improvements over other technologies, such as Ethereum, as Fabric provides fine-grained control over consensus. This leads to relative performance gains for larger networks where the standard consensus algorithm that requires all nodes to reach consensus might face some bottlenecks. In addition, the usage of HLF also facilitates better performance (scalability and privacy) because of its permissioned mode of operation, flexible transparency, and ability to extend pseudo-anonymity (that is offered by Bitcoin or Ethereum blockchains) to full anonymity.

A performance improvement over other technologies, such as Ethereum is achieved as Fabric provides fine-grained control over consensus. [148] In general, Fabric outperforms Ethereum in terms of performance, but their scalability manners are similar. Organizations should determine their needs and priorities while choosing the DLT platform. [146]

5. Materials and Methods

The research process consisted of searching databases to find relevant articles, reviews, data, and questionnaires that would meet the context of the themes presented, as well as unclassified publicly available information about LM. The databases referred to were, SpringerLink, ScienceDirect, Scopus, Google Scholar, IEEE Xplore Digital Library, organizations' websites, and other documents in the form of reports, publications, statements, and dispatches. Due to the non-experimental character of this project, all the research was based on previous knowledge and a possible projection for the future.

This study is limited by its qualitative method since it cannot determine the significance and magnitude of each challenge, calling for future quantitative research studies in this area.

6. Methodology

This thesis reflects on the national portfolio management system, leveraging the current capabilities of the Hyperledger Fabric blockchain technology, to improve transparency, control, and trust among stakeholders, pursuing the creation of a blockchain-based inventory management system, mitigating the shortage of medical products in both normal times and emergencies.
Part of the purpose of this thesis is to research whether the features and capabilities of blockchain technology can be used within the pharmaceutical SC, in resonance with organizations such as the LM and Infarmed.

Blockchain technology, originally developed as the basis for a peer-to-peer digital transaction network, with Bitcoin as a notable example, offers more than simple support for cryptocurrencies. Its applications have expanded beyond this area, providing better solutions for many businesses. In the pharmaceutical and healthcare realm, blockchain can revolutionize portfolio management, addressing critical issues such as safety, traceability, trust among SC partners, drug scarcity, emergency and disaster prevention and mitigation, and overall better stock management. Understanding the applications of this fairly new technology is key to demonstrating how these aspects can be improved effectively concerning healthcare delivery.

Some articles have already described plausible applications for blockchain in healthcare, in which they discuss secure electronic records, interoperability, patient monitoring, and more recently counterfeit medicines. [101,144] For that matter, this thesis proposes the application of blockchain to enhance transparency, traceability, and security in the medical SC, reducing risks of shortages and enhancing the flow of products more efficiently.

The proposition here is to design a system capable of managing the flow of medical products, implementing a private permissioned blockchain network, intended to be administered by a state-controlled agency. For this specific purpose, the HLF platform seems to be the leading choice for the implementation of the project, as it provides a comprehensive set of tools for private blockchain networks and solves some of the problems intrinsic to other blockchain frameworks, establishing a more secure and sustainable medical processing SC system. This model considers that every participant

can manage data under the blockchain, input data, and monitor each stage of the products' management.

The analysis of medical shortages has indicated how important implementing a traceability system capable of tackling this issue can be, which leads to better stock management, quality assurance, and SC visibility. The starting point should address the key factors, stakeholders, and processes impacting the medical SC.

6.1 Supply Chain Framework based on Hyperledger Fabric

The SC starts with the raw materials suppliers or API suppliers, who provide the essential materials for production. These materials are then delivered to manufacturers, where production takes place. Once manufactured, the products are distributed to warehouses for storage. From there, they can be further distributed to healthcare institutions that dictate what actions should be taken to ensure the best management of these products, or directly to hospitals, and pharmacies, ensuring that healthcare providers and patients receive the medications efficiently and safely. Every step throughout the chain is registered to the blockchain. The suggested system would look something like what is proposed by us in Figure 12.

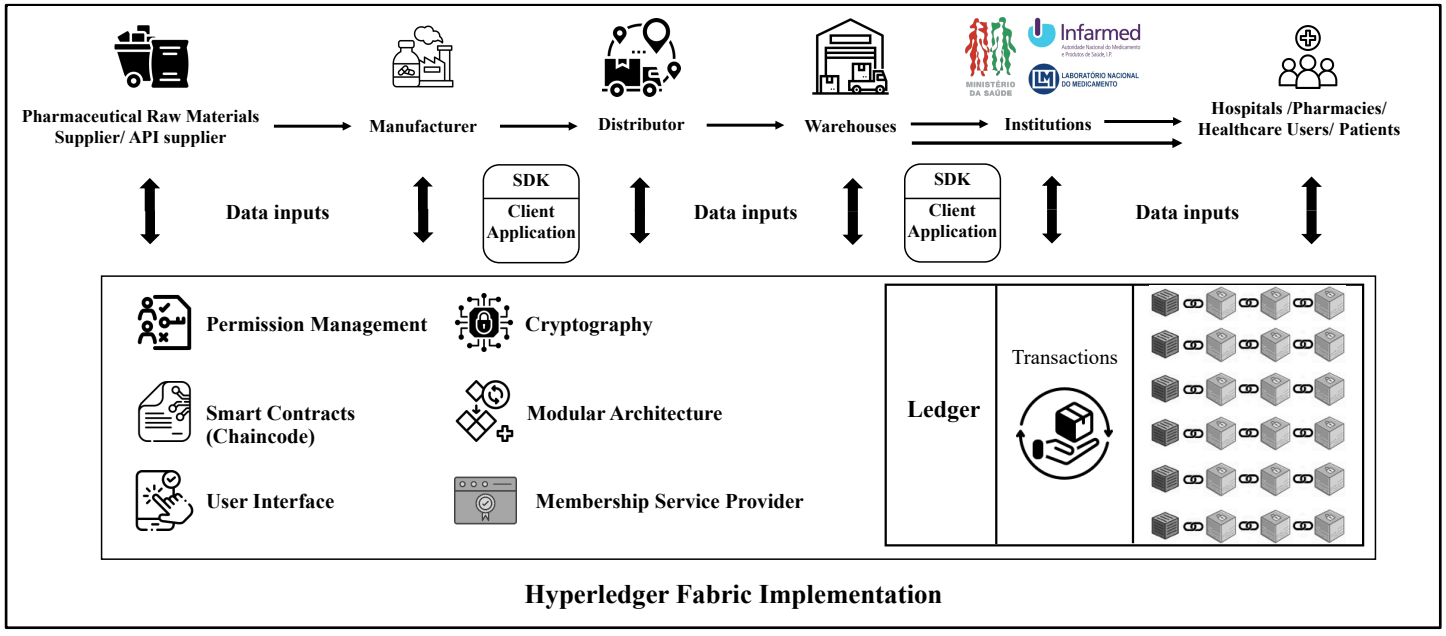

Figure 11 - Medical product supply chain information sharing on Hyperledger Fabric.

As the products flow through the SC, and transactions occur, this data generated by smart contracts (or chaincode) will be recorded, providing continuous asset monitoring. This information will be accessible by creating a dApp using SDK (Software Development Kit), identified in Figure 12 as the Client Application. Every action throughout the SC is registered to the blockchain for everyone but can only be accessible by authorized peers. Access control policies within smart contracts, along with the digital signature protocol, define who the information is to be shared with to ensure data security and integrity. In this network architecture, each entity in the SC operates within a single network, the HLF network, which can have multiple channels.

6.2 Introduction of Products into the Network

The introduction of new products (assets) into the network will involve the execution of a chaincode function that enables the creation of a new asset. The chaincode holding the specific pieces of information, which will be discussed next, about this product is deployed, and after that, a transaction is invoked to add the new product to the ledger. As of this point, the product will already be available on the client applications of peers with access to that information.

Since the members present in the network have already been issued certificates and are trusted, the creation of new items and products should not be a problem since the creation of “fake” or inexistent new products is not something to worry about.

6.3 Transaction Data Exchange for the Blockchain System

This system would involve adding a unique identifier in the packaging stage after production, such as a Quick Responder (QR) code that can be easily scanned, which contains relevant information about the product - the composition, manufacturer's name and license, manufacturing date, expiry date, batch number, logistic partner information, and other information that may be relevant. Both sender and receiving organizations' details shall be a feature of the information set as it is a critical component in developing transactional logic ensuring optimal traceability practices. All information will be incorporated into smart contracts, significantly enhancing communication between parties, and improving the overall effectiveness of the blockchain system. Some entities may not fill all parameters if it is consensual that certain details are not required. Although not all the parameters are described in the proposed mock-up (Figure 13), some other pieces of information such as storage conditions and legal classification should also be considered.

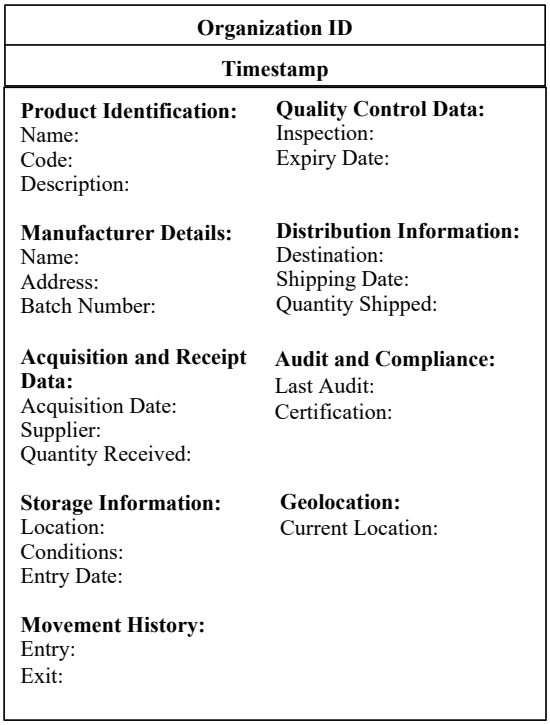

Figure 12 - Traceability information set mock-up.

Supposing a production site manufactures 50 units of a certain medicine, each with a unique identifier within the same batch. Upon handover to a registered logistics partner, the authenticity is verified and recorded on the blockchain. Subsequent handovers are similarly authenticated and updated in the ledger. Through a simple QR code system,

the authenticity of transactions, and the status of products can be verified, due to the traceability throughout the supply chain.

Although there are already rigid recording requirements, the traceability of medical products has consistently been challenging due to the complexity of large-scale data processes and diverse organizational practices. This goes away with blockchain since it requires a standardized information format, similar to Figure 13. This information set provides better communication, especially concerning products' current status and quality.

6.4 Hyperledger Fabric-based Implementation Architecture

The essential components of a simple Hyperledger Fabric network include peers (P), endorsing and committing peers, which maintain and update the ledger and execute chaincode, and ordering service (O), ensuring consensus on the order of transactions, maintaining a consistent sequence across the network, a certificate authority (CA), managing and providing digital certificates, a channel (C), enabling separate transactions and data sharing among participants within the same network for privacy, chaincode (S), for the execution and rule guaranteeing of transactions, a ledger (L), providing immutability of the transaction records, endorsement policies (EP), which ensure the integrity and validity of transactions, client applications, that serve as the interface for the final users to propose transactions and finally an MSP for the management of identities and authentication. All transactions shall occur under the chaincode associated with consensus and validation mechanisms guaranteeing reliable and consistent executions. Peers will host chaincodes and ledgers, which the client applications connect to via an SDK, enabling users to view transactions and ledgers.

For the transaction example explanation only P, O, C, L, and S will be considered for simplification purposes. Although not represented in the following figures it should be mentioned that each organization and ordering service should have been authorized previously by a CA to ensure the authenticity of the members present in the network.

In a simple network where INFARMED (Org 1) and LM (Org 2) interact, let's suppose INFARMED wants to make a transaction proposal to LM for a certain amount of a specific medical product. This network is exemplified simply in Figure 14. The transaction starts with the proposal from INFARMED via its client application (A1),

initiating a transaction proposal for the request of the medical product, which is sent to P2. The proposal is redirected to P3, which is the peer from LM linked to the same channel (C1), and the transaction is simulated to verify if the conditions of the chaincode (S1) are met, and if so, the transaction is endorsed and submitted to the ordering service (O). The ordering service will use consensus to order the transactions correctly, but since this is a simple transaction, it will only create a block and put the transaction into it, to be delivered to the peers. This block is broadcast to all of the peers that have access to channel 1, in this case, P2, and P3, and after receiving the block, peers validate it, ensuring that it satisfies the endorsement policies and all the necessary criteria. If this validation occurs, the block is committed to the peers' ledgers, updating the records of the ledger, finishing the process, and ensuring that the transaction is securely validated, ordered, and recorded on the blockchain so that all the peers present in the same channel have a copy of the transaction.

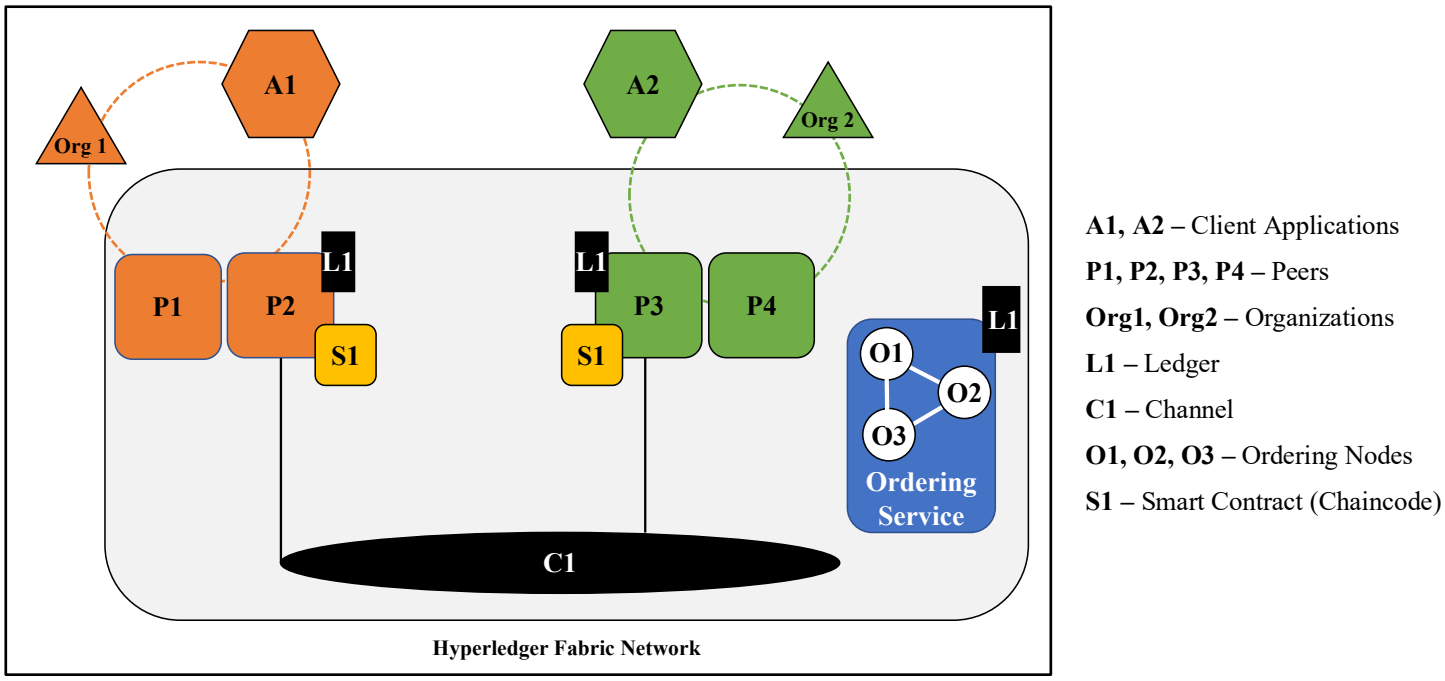

Figure 13 - Hyperledger Fabric network with two organizations sharing the same channel.

However, if LM decides against proceeding with the transaction due to stock availability, internal approvals, business rules, or any other reason, it can refuse to endorse the transaction. In this case, the transaction will not meet the required endorsement policy, so it cannot be submitted to the ordering service, and as a result will not proceed.

For instance, if this network was joined by a third organization (Org 3), who would want to transact with INFARMED (Org 1), and not want other organizations to know

about the specific details of their transactions, they could do so using a different channel (C2) within the same network, since peers can participate in multiple channels, as represented in Figure 16. Both organizations would have to be connected to C2. Now P1 (Org 1) and P5 (Org 3), will have a different ledger (L2) from the one shared between the peers connected to C1 (L1), where the records resulting from transactions between peers in C2 occur. Members from the same channel may agree to cooperate in sharing and managing copies of the ledger related to a channel, as our scheme suggests in Figure 15.

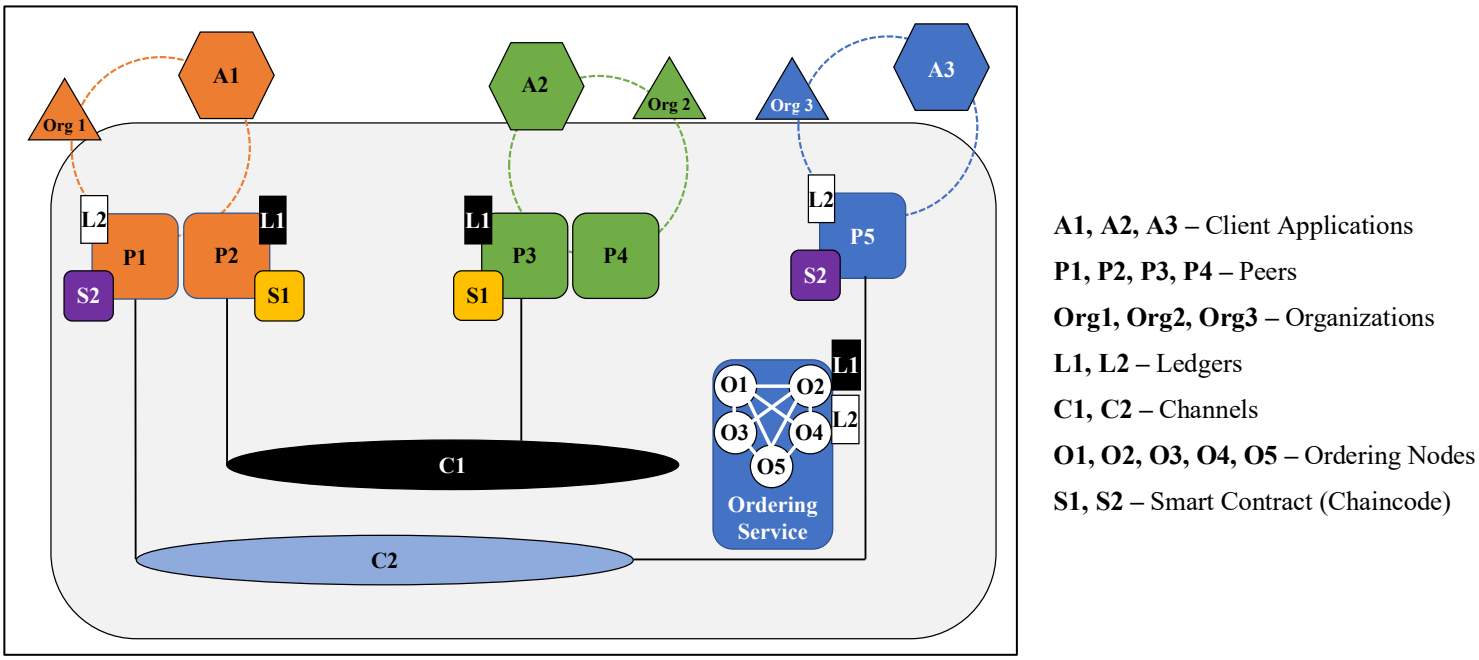

Figure 14 - Hyperledger Fabric network with three organizations sharing different channels.

Any data such as transaction, member, and channel information, is not accessible to network members who have not been explicitly granted access to a particular channel. It is important to mention the increase from 3 to 5 ordering nodes, from the simplest network to the multiple channel network, to introduce the idea that as the network grows and depending on what consensus mechanism is implemented, the number of ordering nodes may vary. This number should be uneven (odd) to ensure optimal fault tolerance, prevent deadlocks, and provide majority decisions. Having at least five nodes is a good notion to have, since the loss of function of two nodes, which might happen during a normal maintenance cycle or for any other failure reason, still leaves 3 nodes available to form a quorum, which is needed for the consensus mechanism to work. With a five-node configuration, the network can tolerate losing two nodes, whereas, in the four-node scenario, only one of the nodes can fail because the loss of a second node would impair

the forming of a quorum. The possibility of having multiple private channels within the same HLF network enables transaction privacy and confidentiality for a specific subset of network members. This framework allows for scalability while preserving privacy.

On this note, with a better network capability, this system could be adapted for a much bigger network where organizations from different countries would be involved. This system could be a connecting mechanism between countries that share the same values, regulations, and treaties, and the list goes on, enabling them to have privacy for their systems within a single network. For example, if a Member State requires a specific set of medical products, perhaps due to a disaster, it could just go and check the shared information of stock inventories between countries and ask for the transactions to fight the sudden surge in demand for that specific product. Countries would be able to transact much more freely and within the contracts shared throughout channels

Although this work might already be done by central authorities, such as the EC, this system would provide a much faster, automated, and secure response to these and other events. The system can provide multiple possibilities, as countries could have their own channel, in which they transact without being concerned if other nations or organizations are aware of their business. The privacy obtained by the multiple channel's mechanisms, and the traceability provided by the encryption of records kept in the peers' ledgers grants organizations an easier and more agile framework for managing their products and stock reserves. Our prototype for this network is shown below in Figure 16.

For minimalization purposes, the peers of each organization are not represented, along with the ledgers, the smart contracts, and the client applications. However, every organization will hold at least one client application, to interact with the network. For every channel engaged, the entities will possess a ledger where the information originating from the transactions within the specific channel is recorded. And at least one smart contract per channel.

Channel 1 (C1) **–** Portugal's National Health Authorities
Channel 2 (C2) **–** EU MS
Channel 3 (C3) **–** Portugal's National Strategic Reserve
Channel 4 (C4) **–** RescEU program members for strategic reserve
Channel 5 (C5) **–** Health Authorities and Hospitals

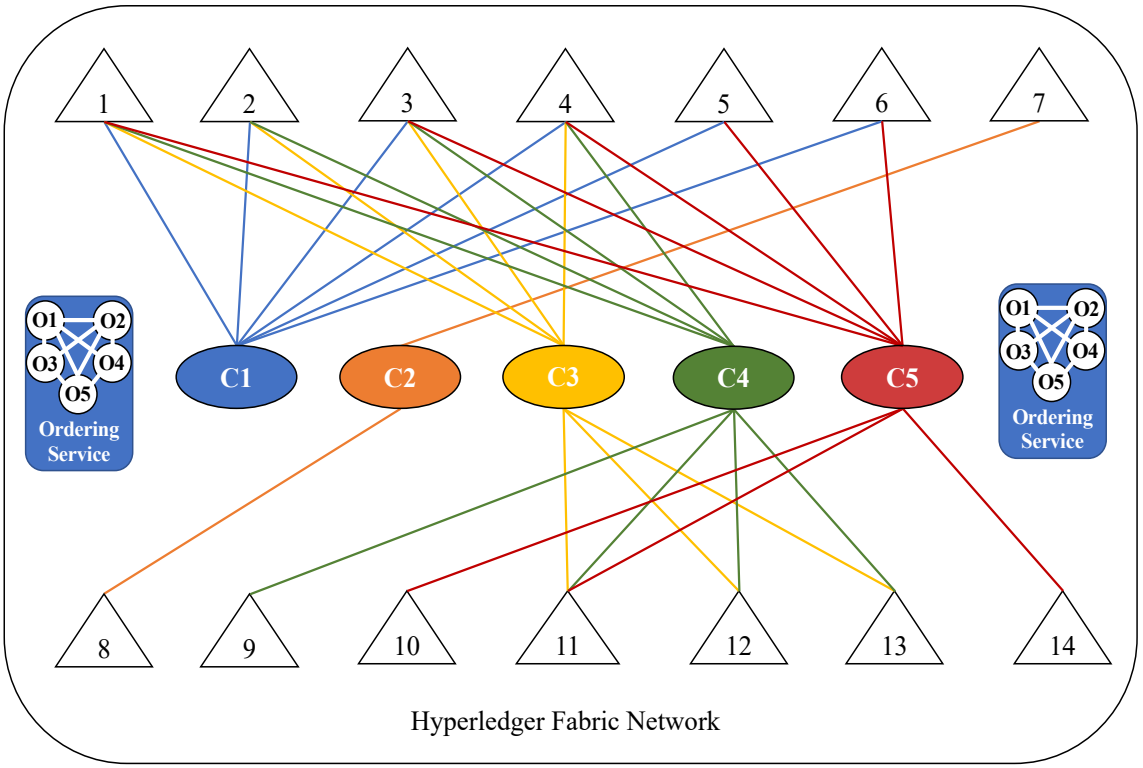

Figure 15 - Hyperledger Fabric network prototype architecture for the supply management of medical products.

1 - INFARMED **2 -** LM **3 -** DGS **4 -** INEM **5 -** Ministry of Health	**6 -** SNS **7 -** Member State's Representatives **8 -** EC **9 -** ECHO **10 -** SUCH	**11 -** SPMS **12 -** INSA **13 -** Armed Forces **14 -** Hospitals

C1 - 1, 2, 3, 4, 5 and 6;

C2 - 7 and 8;

C3 - 1, 2, 3, 4, 11, 12, and 13;

C4 - 1, 2, 3, 4, 9, 11, 12, 13;

C5 - 1, 3, 4, 5, 6, 10, 11, 14;

6.5 Value Proposition

While product management strategies are always evolving and the approaches keep improving for the optimization of processes in general, the current stock management systems for medical products still bear a lot of inefficiencies, such as lack of transparency and traceability, poor coordination and communication, lack of diversified sourcing, and are often vulnerable to fraud and tampering. The combination of these problems can lead to another set of problems, for instance, stockouts, overstocking, expired products, and regulatory non-compliance scenarios. Although the mitigating measures to these problems may be on the downstream side including, production, regulators, and SC participants, the most affected are patients and healthcare providers, who have little control over what measures are implemented and bear almost all the consequences of these issues.

In an attempt to solve, or at least, reduce the magnitude of these problems, implementing an HLF network can be a good option since having a permissioned blockchain-based framework that is tamper-proof and transparent network, can enable the tracing of the source and flow of the products, for a more efficient management of medical product inventories, across all stakeholders, from raw materials to patients.

This fairly recent technology can provide a list of benefits when compared to traditional databases and information sharing. The immutability and transparency of information shared between stakeholders through this DLT can be managed and defined in terms of privacy, through the channels' mechanisms mentioned before. This enables the secure tracking of products along the SC, reducing the chances of counterfeit products entering the chain and improving regulatory compliance. This could also help minimize single points of failure within the SC. The fact that the information recorded on the ledgers is immutable, provides reliable, undeniable, and easily auditable records of transactions, which can simplify regulatory and auditing processes. Then, from the security aspect, a permissioned blockchain network where only authorized participants can access sensitive data brings down the chances of data breaches and theft. The modular structure of HLF can provide extensive functionalities and customization flexibility, which enables organizations to tailor their transactions and smart contracts to suit their specific needs and requirements best. This also provides useful tools for scalability. Automation and digitalization of processes with smart contracts will reduce manual

intervention, speeding up the transactions, and minimizing the possibility of human-induced errors and delays.
This can lead to improved collaboration by facilitating data-sharing, better coordination, and better and faster decision-making for more effective and precise responses to SC disruptions regardless of source.

HLF provides several competitive advantages over most commonly used traditional databases and data-sharing platforms. These often use fragmented data which can differ if there are different sources of information, unlike the DLT where everyone keeps a copy of the same information, giving a much more precise track record, allowing every entity to have a truthful source of information. This can be a huge problem regarding compliance assurance and auditing processes, if every entity can manage its data records, it can alter the true information and present it in a manner that may be most convenient. Traditional platforms get outperformed by this DLT from a security standpoint as centralized databases are vulnerable to unauthorized access. The scalability of information sharing is also very limited and costly in centralized databases. On the other hand, HLF can scale by adding nodes, effectively handling more transactions, for a cost-effective scaling.

Although this technology may have some limitations which will be discussed further next, the inherent benefits make it a compelling option for a new and enhanced strategy mechanism for stock management.

6.6 Limitations

Even though HLF shows promising benefits, several current limitations ought to be carefully addressed to have a better foundation for a successful deployment, which requires a solid strategy, planning, and careful assessment of all the parameters.

First of all, the high complexity of setting up the HLF network might be an issue, because this would require organizations to have specialized personnel with expertise in blockchain technologies, development of smart contracts, more precisely chaincode in HLF, for the flawless implementation, execution, management, and ongoing maintenance

of the network, which could turn out to be costly due to its specificity. Another big challenge is to get entities to agree on policies, technical mechanisms, and a new framework. This shift would have to happen gradually. It is commonly known that adaptability to new systems most often poses great discomfort unless it demonstrates without a doubt that the latest proposal is far better than the system utilized at the moment. Having to restructure workflows usually is not well-accepted in most cases. The most prominent example was the introduction of Bitcoin into monetary transactions, which left many people skeptical and caused a lot of misunderstanding. Since then many of those perceptions have shifted with many believing this system can be a revolution in digital finance and DLTs.

Organizations may be hesitant to share their data on a shared ledger, even though this ledger would respect all privacy requirements imposed, which is achievable due to the modular capabilities of HLF. Another challenge is the scalability aspect. Although from a theoretical standpoint, it is feasible, in reality, the performance of the network tends to decrease as more participants join [150], which can be a problem since with the high volume of transactions that might occur, this system may require optimizations to improve throughput and latency aspects, both critical for the SC flowability.

Legal frameworks are an obstacle too as this is still a very premature evolution of blockchain technology applications in general, being equally underdeveloped in the medical product distribution sector. The pre-established conceptions and regulations for trade between entities would change and be re-evaluated for reconciliation with the presented framework.

While the limitations and drawbacks are clear, the potential advantages of such a system outweigh the efforts and the work required to be put into, solving these aspects, and most importantly, creating a solution that remedies SC problems that impact numerous people worldwide constantly.

7. Conclusions

While medical product shortages are a serious common knowledge concern to healthcare systems worldwide, their impact on treatment quality, patient safety, overall costs, and patients' well-being is far beyond the desired state. Effective SC management is crucial to averting and lessening this phenomenon caused by various disruption factors. Building a robust SC system requires the implementation of key tactics to guarantee the timely supply of quality medical products and the protection of public health.

Emphasizing the publication of studies, reports, and relevant data related to the shortage of medical products, allows a better evaluation of current situations, and consequently enhances the measures adopted to solve or prevent these issues. Demand issues and procurement strategies were two of the main causes of shortages. Similarly, MD SC issues were the top cause, and the demand during the COVID-19 pandemic only exacerbated demand problems.

Although major organizations are already doing some work at the domestic and international levels, the interconnectivity between the stakeholders in the chain can increase SCR and SCV. In times of emergency, having already set adequate strategies is vital to ensure a quick and effective response and recovery in the aftermath. DRM and DM are critical to promoting sustainable and resilient development, where stock reserves have a special preparedness role. However, open communication and transparency amongst all parties involved lead to better coordination, efficient resource allocation, and the development of trust, which consequently ensures thorough and tailored measures for the communities.

The National Laboratory of Medicines is a fundamental organization when it comes to the management of essential medicines and medical supplies. Thus, having good portfolio management and product visibility is crucial for having a comprehensive picture of essential and in-demand medicines to prioritize effectively, supporting public health by maintaining a safe and reliable supply of necessary pharmaceuticals.

Introducing innovative technologies that can provide new alternatives and solutions to SC problems, can change how SCs are managed. Enhancing visibility, improving coordination between stakeholders, and optimizing inventory levels should be prioritized to reduce the likelihood of major shortages happening. This approach will lead to a more resilient and responsive SC network.

The work developed in this project can be considered a starting point for the inception of more advanced solutions in pharmaceutical SC management automation, to achieve a higher level of reliability, robustness, and trust in information sharing, security, and privacy. The potential for automating the pharmaceutical SC and enhancing its transparency and traceability is especially great when combining the HLF blockchain with other state-of-the-art technologies. For this all stakeholders must work together, focusing on the future of healthcare by putting their interests aside and embracing new and innovative solutions that enhance collaboration to guarantee the accessible, fair, and high-quality availability of medical products to everyone.

8. Future Work

There is still a lot of work to be done to turn the proposed solution into a fully functional system that could leverage the HLF capabilities. To understand better how this complex technology network system would apply in the real world, implementing a pilot project that could provide real data would add valuable information about the feasibility of such a system. Although assessing parameters like transaction flow, scalability, and overall performance can be a difficult task, undertaking a few experiments and small projects could provide valuable insights, point out any possible bottlenecks, and lead in the right direction in terms of optimizations that might be required for the full deployment development. A thorough cost-benefit analysis to determine the return on investment and also in comparison to the benefits.

In a further stage, the integration of IoT sensors could also be a valuable idea since the real-time data this system may deliver is crucial for tracking and monitoring the condition parameters of medical products. The introduction of AI could also provide tools for predictive analysis for SC optimization, and anomaly detection among others.

To utilize the full potential of HLF and blockchain technologies in general, and to create more transparent and resilient medical SCs, comprehensive research and in-depth studies are essential to handle the existent challenges and guarantee a future successful technology establishment.

References:

[1] Pawelczyk, M. (2018). Contemporary challenges in military logistics support. Security and Defence Quarterly, 20(3). https://doi.org/10.5604/01.3001.0012.4597

[2] European Community Pharmacists (2023). PGEU Medicine Shortages Report 2023. PGEU. https://www.pgeu.eu/wp-content/uploads/2024/01/PGEU-Medicine-Shortages-Report-2023.pdf

[3] McLaughlin, M., Kotis, D., Thomson, K., Harrison, M., Fennessy, G., Postelnick, M., & Scheetz, M. H. (2013). Effects on patient care caused by drug shortages: A survey. Journal of Managed Care Pharmacy, 19(9). https://doi.org/10.18553/jmcp.2013.19.9.783

[4] Romano, S., Guerreiro, J. P., & Teixeira Rodrigues, A. (2022). Drug shortages in community pharmacies: Impact on patients and on the health system. *Journal of the American Pharmacists Association*, *62*(3). https://doi.org/10.1016/j.japh.2021.12.017

[5] Shukar, S., Zahoor, F., Hayat, K., Saeed, A., Gillani, A. H., Omer, S., Hu, S., Babar, Z. U. D., Fang, Y., & Yang, C. (2021). Drug Shortage: Causes, Impact, and Mitigation Strategies. In *Frontiers in Pharmacology* (Vol. 12). https://doi.org/10.3389/fphar.2021.693426

[6] OECD. (2024). Securing Medical Supply Chains in a Post-Pandemic World. OECD Health Policy Studies. OECD Publishing. Paris. https://doi.org/10.1787/119c59d9-en

[7] European Healthcare Distribution Association. (2022). Annual Report 2021-2022. European Healthcare Distribution Association. GIRP. https://www.girp.eu/sites/default/files/2022-06/GIRP%20Annual%20Report%202021-2022.pdf

[8] United Nations Office for the Coordination of Humanitarian Affairs. (n.d.). OCHA. Accessed on July 15, 2024. Retrieved from: https://www.unocha.org/ocha

[9] Presidência do Conselho de Ministros, Decreto-Lei n.º 13/2021. (2021). Diário da República n.º 28/2021, Série I de 2021-02-10, páginas 3 – 19. Defesa Nacional. https://diariodarepublica.pt/dr/detalhe/decreto-lei/13-2021-156974201

[10] Scholz, N. (2020). Addressing shortages of medicines. European Parliament, (April), 12. Retrieved from: https://www.europarl.europa.eu/RegData/etudes/BRIE/2020/649402/EPRS_BRI(2020)649402_EN.pdf

[11] National Authority of Medicines and Health Products, I.P. (2022). Annual Report, GESTÃO DA DISPONIBILIDADE DE MEDICAMENTOS. https://www.infarmed.pt/documents/15786/4326055/Relatório+anual+sobre+a+gestão+da+disponibilidade+de+medicamentos+de+2021/d6729605-96aa-7b0c-e702-d59e0e7e863e

[12] Bashaar, M., Hassali, M. A., & Saleem, F. (2015). Community pharmacists' attitudes toward the quality and price of locally manufactured generic medicines in Kabul, Afghanistan. *Journal of Pharmaceutical Policy and Practice*, *8*(1). https://doi.org/10.1186/s40545-015-0037-3

[13] Hasen, G., Edris, R., Chala, G., Tefera, Y., Hussen, H., Tekassa, T., & Suleman, S. (2021). Medicines dispensing practice during the era of COVID-19 pandemic: a commentary. In *Journal of Pharmaceutical Policy and Practice* (Vol. 14, Issue 1). https://doi.org/10.1186/s40545-020-00285-5

[14] Vogler, S., & Fischer, S. (2020). How to address medicines shortages: Findings from a cross-sectional study of 24 countries. *Health Policy*, *124*(12). https://doi.org/10.1016/j.healthpol.2020.09.001

[15] de Weerdt, E., Simoens, S., Casteels, M., & Huys, I. (2015). Toward a European definition for a drug shortage: A qualitative study. *Frontiers in Pharmacology*, *6*(OCT). https://doi.org/10.3389/fphar.2015.00253

[16] Bochenek, T., Abilova, V., Alkan, A., Asanin, B., Beriain, I. de M., Besovic, Z., Bonanno, P. V., Bucsics, A., Davidescu, M., de Weerdt, E., Duborija-Kovacevic, N., Fürst, J., Gaga, M., Gailite, E., Gulbinovič, J., Gürpinar, E. U., Hankó, B., Hargaden, V., Hotvedt, T. A., … Godman, B. (2018). Systemic measures and legislative and organizational frameworks aimed at preventing or mitigating drug shortages in 28 European and Western Asian Countries. *Frontiers in Pharmacology*, *8*(JAN). https://doi.org/10.3389/fphar.2017.00942

[17] Chapman, S., G. Dedet and R. Lopert (2022), "Shortages of medicines in OECD countries", OECD Health Working Papers, No. 137, OECD Publishing, Paris. https://doi.org/10.1787/b5d9e15d-en

[18] Troein, P. et al. (2020). Reporting of Medicine Shortages in Europe [White Paper]. IQVIA. Accessed on: June 5, 2024. Retrieved from: https://www.iqvia.com/library/white-papers/reporting-of-medicine-shortages-in-europe

[19] European Medicines Agency. (2019). Good practice guidance for communication to the public on medicines' availability issues. Retrieved from: https://www.ema.europa.eu/system/files/documents/regulatory-procedural-guideline/good_practice_guidance_for_communication_to_the_public_on_medicines_availability_issues_en.pdf

[20] European Medicines Agency (2019). Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA). Retrieved from: https://www.ema.europa.eu/system/files/documents/regulatory-procedural-guideline/guidance_for_mahs_on_the_detection_and_notification_of_shortages_en.pdf

[21] European Medicines Agency (2022). Work programme until 2025 of the HMA/EMA task force on availability of authorised medicines for human and veterinary use. Available online at: https://www.ema.europa.eu/system/files/documents/work-programme/work_plan_of_hma-ema_task_force_availability_ver_2_en.pdf

[22] Food and Drug Administration. (2024). Drug Shortages. FDA. https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages

[23] World Health Organization. Regional Office for Europe. (2020). Assessing the magnitude and nature of shortages of essential medicines and vaccines: focus on the WHO European Region. WHO. Regional Office for Europe. https://iris.who.int/handle/10665/337965

[24] World Health Organization. WHO Drug Information. Vol. 30. (2016). https://iris.who.int/bitstream/handle/10665/331012/DI303-eng.pdf?sequence=1

[25] Musazzi, U. M., di Giorgio, D., & Minghetti, P. (2020). New regulatory strategies to manage medicines shortages in Europe. *International Journal of Pharmaceutics*, *579*. https://doi.org/10.1016/j.ijpharm.2020.119171

[26] Qader, G., Junaid, M., Abbas, Q., & Mubarik, M. S. (2022). Industry 4.0 enables supply chain resilience and supply chain performance. *Technological Forecasting and Social Change*, *185*. https://doi.org/10.1016/j.techfore.2022.122026

[27] Shah, N. (2004). Pharmaceutical supply chains: Key issues and strategies for optimisation. *Computers and Chemical Engineering*, *28*(6–7). https://doi.org/10.1016/j.compchemeng.2003.09.022

[28] Tucker, E. L., & Daskin, M. S. (2022). Pharmaceutical supply chain reliability and effects on drug shortages. *Computers and Industrial Engineering*, *169*. https://doi.org/10.1016/j.cie.2022.108258

[29] Procurement Partners. (n.d.). Healthcare supply chain: everything you need to know. Accessed on: 20 May 2024, https://procurementpartners.com/healthcare-supply-chain/

[30] Chowdhury, M. M. H., & Quaddus, M. (2017). Supply chain resilience: Conceptualization and scale development using dynamic capability theory. International Journal of Production Economics, 188. https://doi.org/10.1016/j.ijpe.2017.03.020

[31] Kusi-Sarpong, S., Gupta, H., & Sarkis, J. (2019). A supply chain sustainability innovation framework and evaluation methodology. International Journal of Production Research, 57(7). https://doi.org/10.1080/00207543.2018.1518607

[32] Khan, S. A. R., Piprani, A. Z., & Yu, Z. (2023). Supply chain analytics and post-pandemic performance: mediating role of triple-A supply chain strategies. International Journal of Emerging Markets, 18(6). https://doi.org/10.1108/IJOEM-11-2021-1744

[33] Mubarik, M. S., Naghavi, N., Mubarik, M., Kusi-Sarpong, S., Khan, S. A., Zaman, S. I., & Kazmi, S. H. A. (2021). Resilience and cleaner production in industry 4.0: Role of supply chain mapping and visibility. Journal of Cleaner Production, 292. https://doi.org/10.1016/j.jclepro.2021.126058

[34] Yaroson, E. V., Breen, L., Hou, J., & Sowter, J. (2021). Advancing the understanding of pharmaceutical supply chain resilience using complex adaptive system (CAS) theory. Supply Chain Management, 26(3), 323–340. https://doi.org/10.1108/SCM-05-2019-0184

[35] Xie, Y., Yin, Y., Xue, W., Shi, H., & Chong, D. (2020). Intelligent supply chain performance measurement in Industry 4.0. Systems Research and Behavioral Science, 37(4). https://doi.org/10.1002/sres.2712

[36] Faisal, M. N., Banwet, D. K., & Shankar, R. (2006). Supply chain risk mitigation: Modeling the enablers. Business Process Management Journal, 12(4). https://doi.org/10.1108/14637150610678113

[37] Government of Canada. (2023). "What we heard: Improving access to drugs and other health products in Canada". Government of Canada. Accessed on: 4 June 2024. Retrieved from: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-shortages/what-we-heard-report.html

[38] Food and Drug Administration. (2019). *Drug Shortages: Root Causes and Potential Solutions.* FDA. https://wayback.archive-it.org/7993/20191216101654/https:/www.fda.gov/media/132059/download

[39] European Commission. (2023). Addressing medicine shortages in the EU. In *COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL, THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE AND THE COMMITTEE OF THE REGIONS* (Issue COM (2023) 672 final). https://commission.europa.eu/system/files/2023-10/Communication_medicines_shortages_EN_0.pdf

[40] European Parliament, Council of the European Union. (2022). *Regulation (EU) 2022/123 of the European Parliament and of the Council of 25 January 2022 on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical device,* European Parliament. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32022R0123

[41] European Commission. (2022). Commission Staff Working Document, Vulnerabilities of the global supply chains of medicines, Structured Dialogue on the security of medicines supply. European Commission. https://health.ec.europa.eu/system/files/2022-10/mp_vulnerabilities_global-supply_swd_en.pdf

[42] Aigbogun, O., Xing, M., Fawehinmi, O., Ibeabuchi, C., Ehido, A., Ahmad, R. B., & Abdullahi, M. S. (2022). A supply chain resilience model for business continuity: The way forward for highly regulated industries. Uncertain Supply Chain Management, 10(1). https://doi.org/10.5267/j.uscm.2021.11.001

[43] Callaway Kim, K., Rothenberger, S. D., Tadrous, M., Hernandez, I., Gellad, W. F., Devine, J. W., Hershey, T. B., Maillart, L. M., & Suda, K. J. (2024). Drug Shortages Prior to and During the COVID-19 Pandemic. JAMA network open, 7(4), e244246. https://doi.org/10.1001/jamanetworkopen.2024.4246

[44] Huys, I., & Simoens, S. (2013). Editorial: European drug shortages: A call for action! In *International Journal of Pharmacy Practice* (Vol. 21, Issue 1). https://doi.org/10.1111/ijpp.12012

[45] World Health Organization, (n.d.). Nomenclature of medical devices. WHO. https://www.who.int/teams/health-product-policy-and-standards/assistive-and-medical-technology/medical-devices/nomenclature

[46] Windisch F, Zimmermann N, Habimana K, Knoll V, Fischer S, Vogler S (2023). One-pager (long version) on "Study supporting the monitoring of the availability of medical devices on the EU market (MD Availability)". Gesundheit Österreich GmbH: Vienna. Available at: https://ppri.goeg.at/Study_MD_Availability

[47] European Association of Hospital Pharmacists. (2023). EAHP 2023 Shortage Survey Report, Shortages of medicines and devices in the hospital sector – prevalence, nature and impact on patient care. EAPH. https://www.eahp.eu/sites/default/files/shortages_survey_report_final.pdf

[48] Garzotto, F., Ceresola, E., Panagiotakopoulou, S., Spina, G., Menotto, F., Benozzi, M., Casarotto, M., Lanera, C., Bonavina, M. G., Gregori, D., Meneghesso, G., & Opocher, G. (2020). COVID-19: ensuring our medical equipment can meet the challenge. Expert Review of Medical Devices, 17(6). https://doi.org/10.1080/17434440.2020.1772757

[49] Badnjevic, A. (2023). Evidence-based maintenance of medical devices: Current shortage and pathway towards solution. In Technology and Health Care (Vol. 31, Issue 1). https://doi.org/10.3233/THC-229005

[50] European Commission. (n.d.). Market surveillance (NCARs sent by country - EU statistics): vigilance statistics on medical devices 2007 to 2017. Accessed on: March 28, 2024. Retrieved from: https://doi.org/10.20344/amp.13419

[51] Pires, C., Duarte, D., & Cavaco, A. (2021). Analysis of medical device alerts issued by the Portuguese medicines agency: Scoping the purpose of new regulatory recommendations. Acta Medica Portuguesa, 34(3). https://doi.org/10.20344/amp.13419

[52] Atif, M., Sehar, A., Malik, I. et al. What impact does medicines shortages have on patients? A qualitative study exploring patients' experience and views of healthcare professionals. BMC Health Serv Res 21, 827 (2021). https://doi.org/10.1186/s12913-021-06812-7

[53] Tan, Y. X., Moles, R. J., & Chaar, B. B. (2016). Medicine shortages in Australia: causes, impact, and management strategies in the community setting. International Journal of Clinical Pharmacy, 38(5). https://doi.org/10.1007/s11096-016-0342-1

[54] Heiskanen, K., Ahonen, R., Kanerva, R., Karttunen, P., & Timonen, J. (2017). The reasons behind medicine shortages from the perspective of pharmaceutical companies and pharmaceutical wholesalers in Finland. PLoS ONE, 12(6). https://doi.org/10.1371/journal.pone.0179479

[55] Creese A, Gasman N, Mariko M: World Health Organization—The World Medicines Situation. WHO/EDM/PAR/2004.5. http://apps.who.int/medicinedocs/pdf/s6160e/s6160e.pdf

[56] Ventola CL. The drug shortage crisis in the United States: causes, impact, and management strategies. P T. 2011 Nov;36(11):740-57. PMID: 22346307; PMCID: PMC3278171.

[57] Jarosławski, S., Azaiez, C., Korchagina, D., & Toumi, M. (2017). Quantifying the persisting orphan-drug shortage public health crisis in the United States. Journal of Market Access and Health Policy, 5(1). https://doi.org/10.1080/20016689.2017.1269473

[58] Assistant Secretary for Planning and Evaluation. (2023). ASPE Report to Congress: Impact of Drug Shortages on Consumer Costs. ASPE. https://aspe.hhs.gov/reports/drug-shortages-impacts-consumer-costs

[59] Moyimane, M. B., Matlala, S. F., & Kekana, M. P. (2017). Experiences of nurses on the critical shortage of medical equipment at a rural district hospital in South Africa: A qualitative study. Pan African Medical Journal, 28. https://doi.org/10.11604/pamj.2017.28.100.11641

[60] Food and Drug Administration. (2023). Annual Report. Center for Devices and Radiological Health, FDA. https://www.fda.gov/media/175479/download?attachment

[61] Rachiotis, G., Kourousis, C., Kamilaraki, M., Symvoulakis, E. K., Dounias, G., & Hadjichristodoulou, C. (2014). Medical supplies shortages and burnout among greek health care workers during economic crisis: A pilot study. International Journal of Medical Sciences, 11(5). https://doi.org/10.7150/ijms.7933

[62] Bown, C. P. (2022). How COVID-19 Medical Supply Shortages Led to Extraordinary Trade and Industrial Policy. In Asian Economic Policy Review (Vol. 17, Issue 1). https://doi.org/10.1111/aepr.12359

[63] American Society of Health-System Pharmacists. (2024). Current Drug Shortages. ASHP. Accessed on: March 31, 2024. Retrieved from: https://www.ashp.org/drug-shortages/current-shortages

[64] American Society of Health-System Pharmacists. (2023). Severity and impact of current drug shortages. ASHP. https://www.ashp.org/-/media/assets/drug-shortages/docs/ASHP-2023-Drug-Shortages-Survey-Report.pdf

[65] Mazer-Amirshahi, M., Pourmand, A., Singer, S., Pines, J. M., & van den Anker, J. (2014). Critical drug shortages: Implications for emergency medicine. Academic Emergency Medicine, 21(6). https://doi.org/10.1111/acem.12389

[66] Rinaldi, F., de Denus, S., Nguyen, A., Nattel, S., & Bussières, J. F. (2017). Drug Shortages: Patients and Health Care Providers Are All Drawing the Short Straw. Canadian Journal of Cardiology, 33(2). https://doi.org/10.1016/j.cjca.2016.08.010

[67] Global approaches to addressing shortages of essential medicines in health systems. (2016). WHO Drug Information, 30(2). https://iris.who.int/bitstream/handle/10665/331028/DI302-180-185-eng.pdf?sequence=1&isAllowed=y

[68] Dill, S., & Ahn, J. (2014). Drug shortages in developed countries - Reasons, therapeutic consequences, and handling. In European Journal of Clinical Pharmacology (Vol. 70, Issue 12). https://doi.org/10.1007/s00228-014-1747-1

[69] Alsirafya, S. A., & Faraga, D. E. (2016). A shortage of oral morphine in Egypt. In Bulletin of the World Health Organization (Vol. 94, Issue 1). https://doi.org/10.2471/BLT.15.156240

[70] Fox, E. R., & McLaughlin, M. M. (2018). ASHP guidelines on managing drug product shortages. American Journal of Health-System Pharmacy, 75(21). https://doi.org/10.2146/ajhp180441

[71] Rubio-Romero, J. C., Pardo-Ferreira, M. del C., Torrecilla-García, J. A., & Calero-Castro, S. (2020). Disposable masks: Disinfection and sterilization for reuse, and non-certified manufacturing, in the face of shortages during the COVID-19 pandemic. Safety Science, 129. https://doi.org/10.1016/j.ssci.2020.104830

[72] European Commission (2017). Press release, rescEU - a new European system to tackle natural disasters. https://ec.europa.eu/commission/presscorner/api/files/document/print/en/ip_17_4731/IP_17_4731_EN.pdf

[73] Jacuch, A. (2019). Disaster response mechanisms in EU and NATO. Przegląd Europejski, 3. https://doi.org/10.5604/01.3001.0013.5842

[74] NATO. (n.d.). Welcome to NATO. NATO. Accessed on July 15, 2024. Retrieved from: https://www.nato.int/nato-welcome/index.html

[75] Burry, L. D., Barletta, J. F., Williamson, D., Kanji, S., Maves, R. C., Dichter, J., Christian, M. D., Geiling, J., & Erstad, B. L. (2020). It Takes a Village…: Contending With Drug Shortages During Disasters. In *Chest* (Vol. 158, Issue 6). https://doi.org/10.1016/j.chest.2020.08.015

[76] Nissen, C. T. N., Bangerter, N. B., Tran, L., Bobke, M. T., & Awwad, M. (2020). Disinfectant shortage: A multicountry comparison of breweries and distilleries responses to the covid-19 pandemic. Proceedings of the International Conference on Industrial Engineering and Operations Management, August.

[77] Lațici, T. (2020). The role of armed forces in the fight against coronavirus. *The Role of Armed Forces in the Fight against Coronavirus*, *April*. https://www.europarl.europa.eu/RegData/etudes/BRIE/2020/649401/EPRS_BRI(2020)649401_EN.pdf

[78] National Laboratory of Medicines. (n.d.). Apoio do LM no combate à pandemia. LM. Accessed on: June 18, 2024. Retrieved from: https://lm.exercito.pt/comunicacao/apoio-do-lm-no-combate-a-pandemia/

[79] Bhaskar, S., Tan, J., Bogers, M. L. A. M., Minssen, T., Badaruddin, H., Israeli-Korn, S., & Chesbrough, H. (2020). At the Epicenter of COVID-19–the Tragic Failure of the Global Supply Chain for Medical Supplies. *Frontiers in Public Health*, *8*. https://doi.org/10.3389/fpubh.2020.562882

[80] Rajabi, E., Bazyar, J., Delshad, V., & Khankeh, H. R. (2022). The Evolution of Disaster Risk Management: Historical Approach. Disaster Medicine and Public Health Preparedness, 16(4). https://doi.org/10.1017/dmp.2021.194

[81] United Nations Office for the Coordination of Humanitarian Affairs. (2024). *"OCHA Annual Report 2023"*. OCHA. https://www.unocha.org/publications/report/world/ocha-annual-report-2023

[82] United Nations Office for Disaster Risk Reduction. (n.d.). Our work. UNDRR. https://www.undrr.org/our-work

[83] United Nations Office for Disaster Risk Reduction. (2015). Sendai Framework for Disaster Risk Reduction 2015-2030. Retrieved from: https://www.undrr.org/media/16176/download?startDownload=20240722

[84] United Nations Office for Disaster Risk Reduction. (n.d.). UNDRR strategic framework 2022-2025. UNDRR. https://www.undrr.org/media/49267/download?startDownload=20240722

[85] NATO. (n.d.). NATO's response to terrorism. North Atlantic Treaty Organization. Accessed on: July 23, 2024. Retrieved from: https://www.nato.int/cps/en/natohq/topics_52057.htm

[86] Jacuch, A. (2019). Disaster response mechanisms in EU and NATO. Przegląd Europejski, 3. https://doi.org/10.5604/01.3001.0013.5842

[87] European Commission. (n.d.). Civil protection and humanitarian aid. European Union Civil Protection and Humanitarian Aid. Accessed on: July 24, 2024. Retrieved from: https://civil-protection-humanitarian-aid.ec.europa.eu/index_en

[88] European Commission. (n.d.). Emergency Response Coordination Centre (ERCC). European Union Civil Protection and Humanitarian Aid. Accessed on: July 24, 2024. Retrieved from: https://civil-protection-humanitarian-aid.ec.europa.eu/what/civil-protection/emergency-response-coordination-centre-ercc_en

[89] European Commission. EU Civil Protection Mechanism. European Commission. Accessed on June 30, 2024. Retrieved from: https://civil-protection-humanitarian-aid.ec.europa.eu/what/civil-protection/eu-civil-protection-mechanism_en

[90] European Commission. rescEU. European Commission. Accessed on June 30, 2024. Retrieved from: https://civil-protection-humanitarian-aid.ec.europa.eu/what/civil-protection/resceu_en

[91] European Commission. (2023). EU funds further strategic reserves for medical, chemical, biological and radio-nuclear emergencies worth €690 million. European Commission. Accessed on: June 30, 2024. Retrieved from: https://civil-protection-humanitarian-aid.ec.europa.eu/news-stories/news/eu-funds-further-strategic-reserves-medical-chemical-biological-and-radio-nuclear-emergencies-worth-2023-12-20_en

[92] Presidência do Conselho de Ministros, Resolução do Conselho de Ministros n.º 55/2024. (2024). Diário da República n.º 63/2024, Série I de 2024-03-28. https://diariodarepublica.pt/dr/detalhe/resolucao-conselho-ministros/55-2024-857838656

[93] Federal Emergency Management Agency. (2024, July 24). Strategic foresight initiative. U.S. Department of Homeland Security. Accessed on July 24, 2024. Retrieved from: https://www.fema.gov/emergency-managers/practitioners/strategic-foresight

[94] Federal Emergency Management Agency. (2024). FEMA Strategic Foresight 2050 - Foresight Applications for Emergency Managers. https://www.fema.gov/sites/default/files/documents/fema_strategic-foresight-2050_guidebook-final.pdf

[95] Defense Logistics Agency. (n.d.). Defense Logistics Agency. Defense Logistics Agency. Accessed on July 24, 2024. Retrieved from: https://www.dla.mil

[96] Defense Logistics Agency. (2023, July 21). FEMA logisticians, leaders, DLA Distribution share quest for speed. Defense Logistics Agency. Accessed on July 24, 2024. Retrieved from: https://www.dla.mil/About-DLA/News/News-Article-View/Article/3341908/fema-logisticians-leaders-dla-distribution-share-quest-for-speed/

[97] Portuguese National Authority for Emergency and Civil Protection. (n.d.). The National Authority. Accessed on: July 24, 2024. Retrieved from: https://prociv.gov.pt/en/the-national-authority/about-us/the-national-authority/

[98] Gaurav Kumar. (2023). Optimizing pharmaceutical supply chain with digital technologies. International Journal of Science and Research Archive, 9(2). https://doi.org/10.30574/ijsra.2023.9.2.0666

[99] di Ciccio, C., Cecconi, A., Mendling, J., Felix, D., Haas, D., Lilek, D., Riel, F., Rumpl, A., & Uhlig, P. (2018). Blockchain-Based Traceability of Inter-organisational Business Processes. Lecture Notes in Business Information Processing, 319. https://doi.org/10.1007/978-3-319-94214-8_4

[100] International Coalition of Medicines Regulatory Authorities. (2021). *"*Recommendations on common technical denominators for traceability systems for medicines to allow for interoperability*"*. ICMRA. https://icmra.info/drupal/sites/default/files/2021-08/recommendations_on_common_technical_denominators_for_T&T_systems_to_allow_for_interoperability_final.pdf

[101] Toyoda, K., Takis Mathiopoulos, P., Sasase, I., & Ohtsuki, T. (2017). A Novel Blockchain-Based Product Ownership Management System (POMS) for Anti-Counterfeits in the Post Supply Chain. IEEE Access, 5. https://doi.org/10.1109/ACCESS.2017.2720760

[102] Yang, K., Botero, U., Shen, H., Forte, D., & Tehranipoor, M. (2017). A split manufacturing approach for unclonable chipless RFIDs for pharmaceutical supply chain security. Proceedings of the 2017 Asian Hardware Oriented Security and Trust Symposium, AsianHOST 2017, 2018-May. https://doi.org/10.1109/AsianHOST.2017.8353996

[103] Abdallah, S., & Nizamuddin, N. (2023). Blockchain-based solution for Pharma Supply Chain Industry. Computers and Industrial Engineering, 177. https://doi.org/10.1016/j.cie.2023.108997

[104] Nawaz, A., Wang, L., Irfan, M., & Westerlund, T. (2024). Hyperledger sawtooth based supplychain traceability system for counterfeit drugs. Computers and Industrial Engineering, 190. https://doi.org/10.1016/j.cie.2024.110021

[105] Kouhizadeh, M., Zhu, Q., & Sarkis, J. (2020). Blockchain and the circular economy: potential tensions and critical reflections from practice. Production Planning and Control, 31(11–12). https://doi.org/10.1080/09537287.2019.1695925

[106] Kristoffersen, E., Aremu, O. O., Blomsma, F., Mikalef, P., & Li, J. (2019). Exploring the Relationship Between Data Science and Circular Economy: An Enhanced CRISP-DM Process Model. Lecture Notes in Computer Science (Including Subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics), 11701 LNCS. https://doi.org/10.1007/978-3-030-29374-1_15

[107] Emmanuel, A. A., Awokola, J. A., Alam, S., Bharany, S., Agboola, P., Shuaib, M., & Ahmed, R. (2023). A Hybrid Framework of Blockchain and IoT Technology in the Pharmaceutical Industry: A Comprehensive Study. In Mobile Information Systems (Vol. 2023). https://doi.org/10.1155/2023/3265310

[108] Chen, X., He, C., Chen, Y., & Xie, Z. (2023). Internet of Things (IoT)—blockchain-enabled pharmaceutical supply chain resilience in the post-pandemic era. Frontiers of Engineering Management, 10(1). https://doi.org/10.1007/s42524-022-0233-1

[109] Tu, M. (2018). An exploratory study of internet of things (IoT) adoption intention in logistics and supply chain management a mixed research approach. International Journal of Logistics Management, 29(1). https://doi.org/10.1108/IJLM-11-2016-0274

[110] Lam, C. Y., & Ip, W. H. (2019). An Integrated Logistics Routing and Scheduling Network Model with RFID-GPS Data for Supply Chain Management. Wireless Personal Communications, 105(3). https://doi.org/10.1007/s11277-019-06122-6

[111] Huang, S. C., & Chang, H. Y. (2016). Energy-aware supply route data collecting methods using wireless sensor networks. Wireless Communications and Mobile Computing, 16(8). https://doi.org/10.1002/wcm.2574

[112] Tian, F. (2016). An agri-food supply chain traceability system for China based on RFID & blockchain technology. 2016 13th International Conference on Service Systems and Service Management, ICSSSM 2016. https://doi.org/10.1109/ICSSSM.2016.7538424

[113] Al-Rakhami, M. S., & Al-Mashari, M. (2021). A blockchain-based trust model for the Internet of Things supply chain management. Sensors, 21(5). https://doi.org/10.3390/s21051759

[114] Dolgui, A., & Ivanov, D. (2022). 5G in digital supply chain and operations management: fostering flexibility, end-to-end connectivity and real-time visibility through internet-of-everything. International Journal of Production Research, 60(2). https://doi.org/10.1080/00207543.2021.2002969

[115] Sokolović, V., & Marković, G. (2023). Internet of Things in military applications. Vojnotehnicki Glasnik, 71(4). https://doi.org/10.5937/vojtehg71-46785

[116] Sivarajah, U., Kamal, M. M., Irani, Z., & Weerakkody, V. (2017). Critical analysis of Big Data challenges and analytical methods. Journal of Business Research, 70. https://doi.org/10.1016/j.jbusres.2016.08.001

[117] Sharma, S., & Mangat, V. (2015). Technology and trends to handle big data: Survey. International Conference on Advanced Computing and Communication Technologies, ACCT, 2015-April. https://doi.org/10.1109/ACCT.2015.121

[118] Schoenherr, T., & Speier-Pero, C. (2015). Data science, predictive analytics, and big data in supply chain management: Current state and future potential. Journal of Business Logistics, 36(1). https://doi.org/10.1111/jbl.12082

[119] Raman, S., Patwa, N., Niranjan, I., Ranjan, U., Moorthy, K., & Mehta, A. (2018). Impact of big data on supply chain management. International Journal of Logistics Research and Applications, 21(6). https://doi.org/10.1080/13675567.2018.1459523

[120] Pita, J. R., & Pereira, A. L. (2022). Medicamentos órfãos em Portugal no contexto internacional (séculos XX-XXI). Dynamis, 42(2). https://doi.org/10.30827/dynamis.v42i2.27717

[121] Derayeh, S., Kazemi, A., Rabiei, R., Hosseini, A., & Moghaddasi, H. (2018). National information system for rare diseases with an approach to data architecture: A systematic review. In Intractable and Rare Diseases Research (Vol. 7, Issue 3). https://doi.org/10.5582/irdr.2018.01065

[122] Pizzamiglio, C., Vernon, H. J., Hanna, M. G., & Pitceathly, R. D. S. (2022). Designing clinical trials for rare diseases: unique challenges and opportunities. In Nature Reviews Methods Primers (Vol. 2, Issue 1). https://doi.org/10.1038/s43586-022-00100-2

[123] Chambers, J. D., Silver, M. C., Berklein, F. C., Cohen, J. T., & Neumann, P. J. (2020). Orphan Drugs Offer Larger Health Gains but Less Favorable Cost-effectiveness than Non-orphan Drugs. Journal of General Internal Medicine, 35(9). https://doi.org/10.1007/s11606-020-05805-2

[124] Schey, C., Milanova, T., & Hutchings, A. (2011). Estimating the budget impact of orphan medicines in Europe: 2010 - 2020. Orphanet Journal of Rare Diseases, 6(1). https://doi.org/10.1186/1750-1172-6-62

[125] Associação Portuguesa da Indústria Farmacêutica, (2024), "Indústria Farmacêutica em Números 2022", APIFARMA, https://apifarma.pt/wp-content/uploads/2024/04/IF_em_Numeros_2022.pdf

[126] The Council of the European Union. (2000). Regulation (EC) No 141/2000. Official Journal of the European Union, L18(1).

[127] Rodwell, C., & Aymé, S. (2015). Rare disease policies to improve care for patients in Europe. Biochimica et Biophysica Acta - Molecular Basis of Disease, 1852(10). https://doi.org/10.1016/j.bbadis.2015.02.008

[128] European Medicine's Agency. (2024). *"Annual report on the use of the special contribution for orphan medicinal products".* EMA. https://www.ema.europa.eu/en/documents/report/annual-report-use-special-contribution-orphan-medicinal-products-2023_en.pdf

[129] Sutiene K, Schwendner P, Sipos C, Lorenzo L, Mirchev M, Lameski P, Kabasinskas A, Tidjani C, Ozturkkal B and Cerneviciene J (2024) Enhancing portfolio management using artificial intelligence: literature review. Front. Artif. Intell. 7:1371502. doi: https://doi.org/10.3389/frai.2024.1371502

[130] Bode-Greuel, K. M., & Nickisch, K. J. (2008). Value-driven project and portfolio management in the pharmaceutical industry: Drug discovery versus drug development - Commonalities and differences in portfolio management practice. Journal of Commercial Biotechnology, 14(4). https://doi.org/10.1057/jcb.2008.6

[131] Büssgen, M., & Büssgen, M. A. (2023). Pipeline progress and portfolio management of the top 30 pharma companies over the past two decades. Journal of Pharmaceutical Policy and Practice, 16(1). https://doi.org/10.1186/s40545-023-00612-6

[132] Faulkner, H., Hopkins, W. J., & Clausing, S. (2024). To the RescEU? Disaster Risk Management as a Driver for European Integration. European Public Law, 30(1).

[133] Angelis, A., Montibeller, G., & Kanavos, P. (2023). A structured methodology for essential medicines lists and health emergency stockpiles: Experience with the Emergency Medicines Buffer Stock in the United Kingdom. Social Science and Medicine, 337. https://doi.org/10.1016/j.socscimed.2023.116236

[134] Friday, D., Savage, D. A., Melnyk, S. A., Harrison, N., Ryan, S., & Wechtler, H. (2021). A collaborative approach to maintaining optimal inventory and mitigating stockout risks during a pandemic: capabilities for enabling health-care supply chain resilience. Journal of Humanitarian Logistics and Supply Chain Management, 11(2). https://doi.org/10.1108/JHLSCM-07-2020-0061

[135] RTP. (2022). Laboratório Nacional do Medicamento produz metadona e antibióticos para pinguins. RTP Notícias. https://www.rtp.pt/noticias/pais/laboratorio-nacional-do-medicamento-produz-metadona-e-antibioticos-para-pinguins_n1395789

[136] Diretoria-Geral de Reinserção e Serviços Prisionais. (2024). DGRSP celebra protocolo com o Laboratório Nacional do Medicamento. Retrieved from: https://dgrsp.justica.gov.pt/Noticias-da-DGRSP/DGRSP-celebra-protocolo-com-o-Laboratório-Nacional-do-Medicamento

[137] República Portuguesa. (2024). Plano de Emergência da Saúde: Um Plano de Emergência e Transformação. https://www.sns.gov.pt/wp-content/uploads/2024/06/Plano-de-Emergencia-da-Saude.pdf

[138] Ur Rahman, M., Guidi, B., & Baiardi, F. (2020). Blockchain-based access control management for Decentralized Online Social Networks. Journal of Parallel and Distributed Computing, 144. https://doi.org/10.1016/j.jpdc.2020.05.011

[139] DHL. (2018). Blockchain in logistics: Perspectives on the upcoming impact of blockchain technology and use cases for the logistics industry. DHL. https://www.dhl.com/content/dam/dhl/global/core/documents/pdf/glo-core-blockchain-trend-report.pdf

[140] Akram, W., Joshi, R., Haider, T., Sharma, P., Jain, V., Garud, N., & Singh, N. (2024). Blockchain technology: A potential tool for the management of pharma supply chain. In Research in Social and Administrative Pharmacy (Vol. 20, Issue 6). https://doi.org/10.1016/j.sapharm.2024.02.014

[141] Nakamoto, S. (2008). Bitcoin: a peer-to-peer electronic cash system, October 2008. Cited On. https://bitcoin.org/bitcoin.pdf

[142] Nair, P. R., & Dorai, D. R. (2021). Evaluation of performance and security of proof of work and proof of stake using blockchain. Proceedings of the 3rd International Conference on Intelligent Communication Technologies and Virtual Mobile Networks, ICICV 2021. https://doi.org/10.1109/ICICV50876.2021.9388487

[143] Zakari, N., Al-Razgan, M., Alsaadi, A., Alshareef, H., al saigh, H., Alashaikh, L., Alharbi, M., Alomar, R., & Alotaibi, S. (2022). Blockchain technology in the pharmaceutical industry: a systematic review. PeerJ Computer Science, 8. https://doi.org/10.7717/PEERJ-CS.840

[144] Nagar, G., Manoharan, A. (2022). Blockchain Technology: Reinventing Trust And Security In The Digital World. https://www.irjmets.com/uploadedfiles/paper//issue_5_may_2022/23989/final/fin_irjmets1711954442.pdf

[145] Wamba, S. F., & Queiroz, M. M. (2020). Blockchain in the operations and supply chain management: Benefits, challenges and future research opportunities. In International Journal of Information Management (Vol. 52). https://doi.org/10.1016/j.ijinfomgt.2019.102064

[146] Ucbas, Y., Eleyan, A., Hammoudeh, M., & Alohaly, M. (2023). Performance and Scalability Analysis of Ethereum and Hyperledger Fabric. IEEE Access, 11. https://doi.org/10.1109/ACCESS.2023.3291618

[147] Hyperledger Fabric. (n.d.). What is Hyperledger Fabric?. Retrieved from: https://hyperledger-fabric.readthedocs.io/en/latest/whatis.html#hyperledger-fabric

[148] Ravi, D., Ramachandran, S., Vignesh, R., Falmari, V. R., & Brindha, M. (2022). Privacy preserving transparent supply chain management through Hyperledger Fabric. Blockchain: Research and Applications, 3(2). https://doi.org/10.1016/j.bcra.2022.100072

[149] Androulaki, E., Barger, A., Bortnikov, V., Muralidharan, S., Cachin, C., Christidis, K., de Caro, A., Enyeart, D., Murthy, C., Ferris, C., Laventman, G., Manevich, Y., Nguyen, B., Sethi, M., Singh, G., Smith, K., Sorniotti, A., Stathakopoulou, C., Vukolić, M., … Yellick, J. (2018). Hyperledger Fabric: A Distributed Operating System for Permissioned Blockchains. Proceedings of the 13th EuroSys Conference, EuroSys 2018, 2018-January. https://doi.org/10.1145/3190508.3190538

[150] Guggenberger, T., Sedlmeir, J., Fridgen, G., & Luckow, A. (2022). An in-depth investigation of the performance characteristics of Hyperledger Fabric. Computers and Industrial Engineering, 173. https://doi.org/10.1016/j.cie.2022.108716

Annexes

Annex 1 - Regulatory authorities' visibility of supply chains of medicines and medical devices

From: [2]

Based on responses to the 2023 OECD country survey on supply chain visibility																										
		EU/EEA countries															Non-EU/EEA countries									
		EMA	BEL	BGR	CZE	DNK	EST	FIN	DEU	LTU	LUX	NLD	NOR	POL	ESP	SWE	AUS	CAN	CRI	ISR	JPN	KOR	MEX	TUR	CHE	USA
Medicines	RA requires information on production sites	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√		√	√	√	√	√	√	√	√	√
	Changes in suppliers must be notified to the RA	√	√	√	√	√	X		√	√	√	√	√	√	√	√		√	√	√	√	√	√	√	√	√
	RA requires information on production volumes	√	√	X	X	X	√	X	√	X	X	√	X	X	√	√	√	X	X	X	X	√	X	√	X	√
	Changes in production volumes must be notified to the RA	√	√				√		√			√			√	√	√	X				√		X		X
	RA can share data on sites and/or volumes to third parties to address shortages	√	X	√	√	√	X	X	√	√	X	X	X		√	√	X	√	X	√	X	√	X	√		X
	RA conducts site inspections for GMP	X	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	RA is part of an international co-operation network for mutual recognition of site inspections	√		√	√	√	√	√	√	√	√	√	√		√	√	√	√	X	√	√	√	√	√	√	√
	The country implemented a full national track-and-trace system	X		√		X	√	X				X	√					X	X	X	X	√	X	√	X	√
	The country implemented an end-to-end national track-and-trace system	X	√		√	X		X	√	√	√	X			√	√		X	X	X	X		X		X	
Medical Devices	RA/NB requires information on component manufacturers and production sites	√	X	X		X	X	X	√	√	X	√	X		√	√	X		√		√	√	√	X	√	
	RA can share information on component manufacturers and production sites to address shortages	√						X	X	X		X			√	√	√		X		X	X	X		X	
	Quality inspections performed for sites involved in production		√	X	√	√	√	√	√	X	√	√	√		√	√	√		X		√	√	√	X	√	
	The country implemented a UDI system	√	√	X	X	√	√	√	√	X	√	√	√		√	√	X		X	X	√	√	X	√	√	

Notes: √ indicate that the answer was "Yes" in dark cells, or "Yes, partly" in lighter cells. X indicates that the answer was "No". Empty cells mean that the country did not answer.

Annex 2 - National Medicines Laboratory Portfolio 2023

From: [152]

CÓDIGO	SOLUÇÕES ORAIS	PREÇO SEM IVA	IVA	PVP
1200000	CITRATO CAFEINA 1% 10ML	3,52 €	6%	3,73 €
1200001	CLORETO POTÁSSIO 5% 100 ML	8,14 €	6%	8,63 €
1200002	CLORETO POTÁSSIO 20% 100ML	8,46 €	6%	8,97 €
1200003	HIDRATO CLORAL 5% 50ML	8,57 €	6%	9,08 €
1200004	ISONIAZIDA 0,68% 180ML	5,25 €	6%	5,57 €
	POMADAS			
1200005	ANTIMICOTICO 30GR	*Preço sob consulta*	6%	
1200006	BALSAMO MENTOL COMPOSTO 18G	*Preço sob consulta*	6%	
1200007	PASTA DE COCAINA 10% 3GR	24,36 €	6%	25,82 €
1200008	VASELINA ESTERILIZADA 18GR	*Preço sob consulta*	6%	
1200009	VITAMINA A 25GR	*Preço sob consulta*	6%	
	DESINFETANTES/CONSERVANTES			
1200010	ALCOOL 80º 500ML	2,00 €	23%	2,46 €
1300312	ALCOOL 70º 125ML	1,87 €	23%	2,30 €
1300311	ALCOOL 70º 500ML	1,99 €	23%	2,45 €
1300310	ALCOOL 90º 500ML	2,08 €	23%	2,56 €
	CÁPSULAS			
1200014	ISONIAZIDA 300MG CX 30 CÁPS.	2,73 €	6%	2,89 €
	PÓS			
1200015	ANTIMICOTICO PÓ 80GR	*Preço sob consulta*	6%	
	TESTES			
1200016	TESTES DROGA A CX10 (HEROÍNA/MORFINA/OPIO/CODEINA/DEMEROL/ANFETAMINAS)	29,81 €	23%	36,67 €
1200017	TESTES DROGA B CX10 (CODEINA/MORFINA/HEROINA)	29,81 €	23%	36,67 €
1200018	TESTES DROGA C CX10 (BARBITURICO)	29,15 €	23%	35,85 €
1200019	TESTES DROGA E CX10 (LIAMBA/HAXIXE)	39,27 €	23%	48,30 €
1200020	TESTES DROGA F CX10 (COCAINA)	39,27 €	23%	48,30 €
	MANIPULADOS			
VAR.	ÁCIDO TRICLOROACÉTICO SOLUÇÃO (VAR. DOSAGEM)	*Preço sob consulta*	6%	
1200032	CARBONATO DE CÁLCIO 125MG CÁPS.	*Preço sob consulta*	6%	
1200031	CARBONATO DE CÁLCIO 250MG CÁPS.	*Preço sob consulta*	6%	
1200033	CARBONATO DE CÁLCIO 500MG CÁPS.	*Preço sob consulta*	6%	
1200509	CLORIDRATO METADONA 1% 100ML SOL. ORAL FRS.	*Preço sob consulta*	6%	
1200046	DEXAMETASONA 4MG CÁPS.	*Preço sob consulta*	6%	
1200024	HIDRATO CLORAL 10% 50ML SOL. ORAL	*Preço sob consulta*	6%	
1200515	LACTATO MAGNÉSIO CÁPS.	*Preço sob consulta*	6%	
1200045	NISTATINA E LIDOCAÍNA 100ML SOL. ORAL FRS.	*Preço sob consulta*	6%	
1200042	PANTOCAÍNA 2% 100ML SOL. ORAL	*Preço sob consulta*	6%	
1200025	VASELINA LÍQUIDA ESTERILIZADA 10ML	*Preço sob consulta*	6%	
1200026	XAROPE COMUM S/CONSERVANTES 1L	*Preço sob consulta*	6%	
1200027	XAROPE COMUM C/CONSERVANTES 1L	*Preço sob consulta*	6%	

Annex 3 - Overview of the limitations of blockchain technology in the pharmaceutical industry previous studies

From: [141]

Limitation & future research	Categories	Papers
The mediator between patient and manufacturer has not been removed due to the absence of smart contracts in the proposed system.	Safety and security	1
The result of the proposed system may not reflect real-world performance.	Product distribution	7
Cannot track counterfeit drugs distributed through routes outside of official distribution chains.	Counterfeit drug prevention, Product distribution	7
Network size and performance were not tested in a real-world environment, and the accuracy of the machine learning modules was limited.	Counterfeit drug prevention	12
Network size limitations were not tested in a real-world deployment.	Counterfeit drug prevention	10
Noticeable latency because adding the QR code requires transaction confirmation, which is considered slow in Ethereum.	Counterfeit drug prevention	13
Challenges in adopting the blockchain technology for the pharmaceutical supply chain are discussed: 51% attacks, trust, transparency, scalability, integration, and cost.	Counterfeit drug prevention, Tracking & Tracing	18, 27
Immaturity of a still-emerging technology.	Counterfeit drug prevention	11
Total transactions per second limited to 1600; a lack of technical experts.	Counterfeit drug prevention, Tracking & Tracing	20
Scalability challenge.	Counterfeit drug prevention, Tracking and Tracing, Safety and Security	21, 27, 33, 39
Information authentication still needs verification.	Tracking and Tracing	21
Gas high-cost issue.	Tracking and Tracing, Safety and Security	13, 35
Large memory utilization.	Tracking and Tracing	21
Absence of universal guidelines, rules, and code to guide implementation of blockchain technology.	Tracking and Tracing	8
Many facets of the prototyping environment currently seem lacking.	Safety and Security	31