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SUSTAINING PHARMACEUTICAL SUPPLY: STRATEGIES FOR MITIGATING AND MANAGING DRUG SHORTAGES

Ph.D. thesis

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
AMR	Antimicrobial resistance
API	Active Pharmaceutical Ingredients
AS	Antimicrobial Stewardship
ASHP	American Society of Health-System Pharmacists
ATC	Anatomical Therapeutic Chemical classification system
AUS	Australia
BEL	Belgium
cGMP	Current Good Manufacturing Practice
CH	Switzerland
CNS	Central Nervous System
COVID-19	Coronavirus Disease 2019
CV	Cardiovascular
EAHP	European Association of Hospital Pharmacists
EENT	Eye, Ear, Nose and Throat Medicines are a category of pharmaceuticals used to treat conditions affecting these sensory organs.
EMA	European Medicines Agency
ESP	Spain
EU	European Union
FAMHP	Federal Agency for Medicines and Health Products
FDA	Food and Drug Administration

GI	Gastrointestinal
GMP	Good Manufacturing Practice
Group “C”	Cardiovascular system
Group “J”	Anti-infective for Systemic Use
Group “L”	Antineoplastic and immunomodulating agents
Group “N”	Nervous system
HA	Health Authority
HCP	Healthcare Professional
HUN	Hungary
i.v.	Intravenous
IMS	Intercontinental Medical Statistics
IT	Information Technology
MA	Marketing Authorization
MAH	Marketing Authorization Holders
MWL	Medicines Watch List
N/A	Not Applicable
ND	Not Determined
NNGYK	National Center for Public Health and Pharmacy
OGYEI	National Institute of Pharmacy and Nutrition
No.	Number
p.o.	per os
TGA	Therapeutic Goods Administration
US	United States
WHO	World Health Organization
WHO AWaRe	WHO Access, Watch, Reserve

WHO CC	WHO Collaborating Centre

1. INTRODUCTION

Drug shortages occur when the available supply of drugs does not sufficiently meet the end-user level demand, despite the financial resources being available (1). Drug shortages pose a significant threat, as they directly impact patient health and safety. Already in 2012, the World Health Organization (WHO) called medicine shortages a "complex global challenge" (2). The problem affects almost all developed countries, ranging from the United States through EU member states to Australia (2, 3). In the second decade of the twenty-first century, drug shortages have increasingly become an issue with higher frequency and severity of shortages (1).

The issue has a grave impact on every stakeholder along the pharmaceutical supply chain, ranging from Marketing Authorization Holders (MAHs) through wholesalers to hospitals, community pharmacies, and ultimately patients, posing a serious threat to treatment outcomes (4, 5). The substitution, absence, or delay of safe and effective therapies can compromise medical procedures, cause errors, and additional workload, thus seriously impacting patient welfare. While MAHs and wholesalers mainly face reputational damage, shortages can severely affect the effectiveness of patient therapy, and also hinder healthcare professionals (HCPs) from doing their jobs effectively, as searching for the proper alternative medicines requires substantial additional time and workload (6). The working hours of HCPs spent mitigating the effect of shortages have already tripled between 2004 and 2010 (7). This also has a detrimental impact on the finances and personnel management of health care sites (8). Moreover, a shortage is always associated with a higher level of risk due to the discontinuation of regular care and using alternative substitutions that are less safe and cause a higher occurrence of medication errors (8). When working with unfamiliar substances, HCPs may miscalculate the dosage, thereby increasing the occurrence of overdosing or underdosing. When patients are "triaged", the medicines for which no known alternative substitute are preserved for those suggested to have the best medical prognosis (5).

Both essential and non-essential medicines are widely affected by shortages (2, 9). The WHO proposed the concept of essential medicines in 1977, which is a catalogue of every healthcare system's minimum medical needs. Essential medicines are those that satisfy the priority healthcare needs of the population. The basic concept is that high-priority

drugs should be available as part of a functioning health system for all people, guiding physicians to evidence-based and rational prescribing (10). Clinical evidence confirms that medicines included in the list can significantly improve patients' outcomes, and their shortage can have a severe negative impact on treatment quality (11). Mitigating shortages is especially important in the case of drugs included on the World Health Organization (WHO) essential medicine and/or Access, Watch, Reserve (AWaRe) list, as their shortage is more likely to have severe negative impacts on treatment outcomes (8). The WHO Essential Medicines List was updated in 2023, while the AWaRe list is from 2021 (12, 13). The Intercontinental Medical Statistics (IMS) Institute for Healthcare Informatics in November 2011 identified five disease areas that are extremely exposed to drug shortages, meaning that 63% of all cases are reported in these categories. These areas were oncology, anti-infectives, cardiovascular, central nervous system and pain management, and generic injectables. The same five disease areas that are most often exposed to shortages have also been confirmed in 2013 (14) and in 2019 (15).

Despite being a widespread global challenge, there is no single global definition yet to determine when a drug is in shortage (4). Therefore, studying the issue is complex, because of the scarcity of publicly available data and different definitions and reporting systems between countries (4). As a starting point, internationally adopted guidelines and definitions would be useful to compare shortages across countries, as currently these are lacking (16). Health Authorities (HAs) have one of the most crucial roles in handling shortages: they must ensure the continued volume of pharmaceutical products and be aware of any interruptions (17). Over the past decades, HAs worldwide have taken various actions to collect, monitor, evaluate, and prevent drug shortages and reduce their impact on the healthcare system (18). In Europe, HAs, MAHs, and distributors share the responsibility to avoid shortages. According to Article 81 of Directive 2001/83, MAHs and the distributors shall ensure appropriate and continued supplies of medicinal products to pharmacies and hospitals to address the needs of patients (19). The European Association of Hospital Pharmacists (EAHP) started investigating drug shortages in 2012 due to increased reports from its members expressing difficulties in sourcing medicine (20). In the United States (US), President Obama signed the Food and Drug Administration (FDA) Safety Innovation Act in July 2012 (21). The Act mandated manufacturers to inform the FDA of impending shortages to enable early mitigation of

the problem. In Australia, the Therapeutic Goods Administration (TGA) dedicated a website to monitoring medicine shortages in May 2014 (22).

While these were all necessary steps in the right direction, further international coordination and common best practices would be beneficial for more effective shortage prevention and management. Shortage prevention should start from understanding the causes of drug shortages and mitigating them. While causes are multifactorial and can vary between different countries, it is possible to identify main patterns and root causes (23). It is also necessary to assess shortage management practices, to identify best practices that can be adapted to international guidelines. This dissertation focuses on analysing the share of critical shortages between selected countries, the root causes of shortages, and identifies best practices in shortage management strategies on both central and local levels.

2. OBJECTIVES

The objectives of the dissertation can be divided along the quantitative and qualitative analyses.

2.1. Objective of the quantitative analysis

The objective of the quantitative analysis is to compare drug shortages in six countries (Hungary, Belgium, Spain, Switzerland, Australia, and the United States) by evaluating the frequency and criticality of shortages, particularly within four specific Anatomical Therapeutic Chemical (ATC) groups that are most severely affected by drug shortages. The analysis seeks to understand the differences in total reported shortages and critical shortages internationally, identify which ATC groups are most affected, and quantify the challenges faced by different regions regarding the availability of essential medicines.

2.2. Objectives of the qualitative analysis

The qualitative analyses focused on three objectives.

The first objective is to identify and categorise the factors causing drug shortages through a systematic literature search. The complex set of factors causing drug shortages is explored in detail, and root causes are identified.

The second objective is to analyse centrally managed mitigation strategies across countries, which are adopted by regulatory bodies or governments. The aim is to identify best practices in shortage management that could be adapted internationally to prevent and reduce the number of shortages, with particular focus on the shortages of essential medicines.

Finally, the third objective of the qualitative analysis is to study local shortage mitigation measures, that can be carried out by healthcare practitioners at the inpatient level. This is done through a deep dive into handling the shortages of antibiotics. The aim is again to identify best practices that could be adopted more widely to support the mitigation of drug shortages also at local levels.

3. METHODS

3.1. Quantitative analysis

I have selected six countries to perform the comparative quantitative analysis and to understand how total reported shortages and critical shortages compare internationally and which ATC groups are mostly affected by critical shortages. The countries and respective databases were selected according to pre-defined criteria. As a next step, databases were processed focusing on selected therapeutic categories, the shortage of which would have the most severe impact on patient care. Finally, a risk assessment was carried out to identify critical shortages. In the analysis, both total and critical shortages were compared across countries and ATC groups.

3.1.1. Country selection

Six countries have been chosen for analysis to ensure geographic diversity. The selected countries are Australia from the Pacific region, the United States from North America, Belgium, Spain, and Hungary from the European Union (EU), and Switzerland, a European country that is not part of the EU. The selection criteria have been developed to filter out countries with insufficient details to carry out risk assessment and identify the ATC group for each shortage. This is important because countries use different reporting systems and publish varied information on shortages. Throughout the country selection process, I considered several aspects to decide whether to include a country in the study.

- First-world countries, where drug shortages are not a result of the lack of available financial resources.
- Selected countries must have a profound pharmaceutical industrial background.
- Selected countries must have a publicly available reporting system, and reported shortages must be classifiable according to the ATC.
- Databases of the selected countries must contain public information regarding available substitutes to allow for the assessment of severity.
- Databases of the selected countries must list discontinued presentations separately from current shortages.

The six selected countries satisfy all the above-mentioned criteria and constitute a profound ground for analysis.

3.1.2. Therapeutic area selection

Shortages were categorized based on the ATC Classification System, which organizes the active ingredients of drugs by the organ or system they target, as well as their therapeutic, pharmacological, and chemical characteristics. This system is managed by the WHO Collaborating Centre (WHO CC) for Drug Statistics Methodology (24). The following particular ATC groups have been chosen in shortage for further examination.

- Group C: Cardiovascular system
- Group L: Antineoplastic and immunomodulating agents
- Group J: Anti-infectives for systemic use
- Group N: Nervous system

These four ATC groups have been selected for analysis, as these categories of medications play a significant role in the therapeutic arsenal. The permanent or temporary absence of these medicines would have a serious impact on patient care and the healthcare system (25-28). The selection of these groups has been confirmed with the pre-examination of the data, which showed these ATC groups are present in the highest proportions among all reported shortages. The selection of the four ATC groups for analysis did not consider the prevalence of diseases within these groups across the six selected countries.

3.1.3. No unique common definition for drug shortage

Shortages reported due to discontinued production, stopped commercialization, or interrupted commercialization were excluded from the analysis. This exclusion was necessary because there was insufficient information regarding these shortages' reason and duration. To process analogous and comparable information on shortages in the chosen countries, shortage databases of all countries were accessed in the one-week time period between the 4th and 9th of March 2021. As most databases cannot access detailed data on past shortages but only show current shortages, longitudinal analysis was not possible. In Hungary, Belgium, Spain, and Australia one national database was available, managed by the HAs (Table 1). In the United States and Switzerland, two or more databases were available, run by multiple authorities (US) or private bodies (CH). In the US, the ASHP database has been chosen (29), as it contains more details regarding the available substitutes compared to the FDA reporting system. In Switzerland, the

Martinelli database was chosen as the national HAs database focuses only on a narrow scale of medicines considered essential by law (30).

Table 1: Characteristics of notification systems in the selected countries.

Country	Database Manager	Definition of Shortage	Source of Information	Scope of Report	Counter-measures
Belgium	FAMHP	Undeliverable for four consecutive days. (31).	MAH must notify FAMHP within 7 days if a drug will be unavailable for more than 14 days (32).	Only a specific presentation, not the entire medicine range.	-Emergency import - Greater responsibility to full-line distributors - MAH should provide a reason and compensate costs
Switzerland	Martinelli Consulting GmbH	Supplies not satisfying demand and orders (30).	The website is based on voluntary reports from companies and users (30).	Drugs officially approved in Switzerland are listed in Martinelli database.	- Emergency import - Strategic stockpiling - Define essentiality
Spain	AEMPS	The number of available units is below the level of national or local consumption needs (1).	The AEMPS database lists supply problems for different presentations, including anticipated ones (33).	Concerns about a certain presentation. The entire range of medicine is not unavailable.	- Define essentiality - Emergency import - Maintain MA and production - Delivery in 24 working hours - Export ban
Australia	TGA	Medicine supply may not meet demand for next six months (34).	MAHs are required to report all registered medicines in 2–10 days upon severity (35).	The medicines are set out in Therapeutic Goods Determination (36).	- Emergency import - Export registration - National Medical Stockpile (37) - Medicine Watch List (38)

Table 1 continued:

Country	Database Manager	Definition of Shortage	Source of Information	Scope of Report	Counter-measures
United States	ASHP	Supply issue that affects how a pharmacy prepares, dispenses a drug, or influences patient care when prescribers must use an alternative agent (8).	Voluntary reports from practitioners, patients, and others (29).	ASHP lists every drug shortage reported through the online report form as soon as it is investigated and confirmed, usually within 24–72 h (29).	- Define essentiality - Emergency import - Reevaluates voluntary recalls - Expedite changes Maintain MA and production - Drugs into smaller units - ASHP management practice
Hungary	OGYEI/ NNGYK	If MAH can't maintain supplies of a medicine or unwilling to supply it temporarily or permanently (39).	Before the final delivery to the wholesaler, but in a maximum of two months (39).	Concerns about a certain presentation. The entire range of medicine is not unavailable.	- Recommend alternatives - Shortage declaration by Health Authority - Emergency import - Export ban

FAMHP: Federal Agency for Medicines and Health Products, MAH: Marketing authorisation holder, AEMPS: Agencia Española de Medicamentos y Productos Sanitarios, TGA: Therapeutic Goods Administration, ASHP: American Society of Health-System Pharmacists, OGYEI: Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet, NNGYK: Nemzeti Népegészségügyi és Gyógyszerészeti Központ

3.1.4. Risk Assessment of Critical Shortages

All the posted products “currently in shortage” were investigated individually to determine whether the risk is considered acceptable or critical. The different presentations of a particular pharmaceutical ingredient were counted as individual shortages. Table 2 summarizes how critical shortages were identified for each country. In most of the studied countries, authorities did not publish a severity assessment, and therefore, criteria to distinguish critical cases had to be defined. The following criterion was set: if no domestic alternatives were available, the shortage was considered critical, as emergency imports would be necessary in this case. It is general practice in every country that the HA suggests a domestic alternative for every drug that is in shortage. If no domestic alternatives are available, the country can perform an emergency import from abroad, but this is considered a high-risk and high-expense solution, which is to be avoided. In Belgium and Australia, the database already included some information regarding the severity, which has been augmented to match the criteria applied for all other countries.

Table 2: Allocation of critical shortages.

Country	**Allocation of Critical Shortages**
Switzerland	If there is no domestic alternative (30).
Spain	If there is no domestic alternative (33).
Hungary	If there is no domestic alternative (40).
United States	The "shortage risk index" was defined with the ratio of unavailable and available presentations. If this number is higher than 5, the shortage is considered critical. If the database states: "there are no presentations available" or "there is insufficient supply for usual ordering," despite that the index will be lower than 5, the shortage is considered critical.
Belgium	According to the FAMHP decision tree and in case it is necessary to import from abroad (32).
Australia	According to the TGA definition, if the medicine is included on the Medicines Watch List (MWL) or if the shortage has the potential impact to have a life-threatening or serious impact on patients and there is not likely to be a sufficient supply of potential substitutes automatically considered as critical (35).

FAMHP: Federal Agency for Medicines and Health Products, TGA: Therapeutic Goods Administration

3.1.5. The bias-reducing steps

The comparison was complicated due to different definitions and reporting systems therefore three bias-reducing steps have been performed to obtain comparable data and conduct a reliable analysis. The bias-reducing steps were the following:

1. Transforming the data into population-proportionate figures.
2. Filtering out critical cases from all shortages (according to criteria in Table 2).
3. Comparing critical cases with the WHO Essential Medicine List.

These steps were all necessary so that despite the differing reporting systems, some comparative international oversight could still cover drug shortages. The lack of uniform definitions, reporting systems, and severity assessments along unified international criteria creates significant obstacles to any international comparison of shortages. The characteristics of the national reporting systems of the countries under analysis are highlighted in Table 1.

To perform the quantitative analysis of the data, the first two bias-reducing steps were carried out. Data have been transformed into population-proportionate figures for all countries, and critical cases have been filtered out from all shortages according to the predefined criteria.

To avoid significant populational bias, instead of comparing nominal shortage numbers, the proportion of critical shortages to the country's population was taken into consideration. The ratio was calculated as the number of shortages per million people (41). The proportion of critical shortages is significantly different across ATC groups. The number of shortages derived from the databases regarding the four abovementioned ATC groups have been analysed both quantitatively and qualitatively.

3.1.6. Binomial Probability

Tests of Proportion of Critical Shortages across ATC Groups Data have been analysed to obtain insights into critical shortages and understand whether the proportion of critical shortages differs across the four ATC groups studied (C, J, L, N). The software “Stata” version 17.0 was used for the analysis (StataCorp LLC 4905 Lakeway Drive, College Station, Texas, USA). For the purpose of statistical analysis, the variable Critical_BI was defined, which is an indicator variable taking the value 1 for critical shortages, and 0 for the non-critical shortages. The null hypothesis was that the proportion of critical shortages would not significantly differ across the different ATC groups.

As the final step of the analysis, critical shortages were compared to the WHO Essential Medicine List.

3.2. Qualitative analyses

To perform the qualitative analyses, several targeted literature reviews were conducted.

The first objective of the qualitative analysis focused on identifying the factors causing drug shortages. To gain a thorough understanding of the topic a search through Google Scholar and Pub Med was conducted between 19th September 2020 and 12th October 2020. The most frequent keywords and terms used included the following: *drug shortage as a global challenge, shortage impacts on stakeholders, causing factors of shortages, generics market, commonly affected products by shortages, handling of shortages, advanced protocols for shortages.* Additional information has been collected from the American Society of Health-System Pharmacists (ASHP) website, the European Association of Hospital Pharmacist (EAHP) report and the National Institute of Pharmacy and Nutrition (OGYEI), and Food and Drug Administration (FDA) database. The following professional journals have also served as a source: The New England Journal of Medicine, The Lancet Oncology, The Oncologist, Mayo Clinic Proceedings, Journal of Parenteral and Enteral Nutrition, Journal of Oncology Practice, Journal of the American Medical Association, American Journal of Health-System Pharmacy: AJHP: official journal of the American Society of Health-System Pharmacists, American Journal of Pharmaceutical Education. Original peer-reviewed research articles written in English were included (16).

The second objective of the research focused on reviewing centrally managed shortage management strategies and identifying best practices. The search was conducted between 6th March 2021 and 24th June 2021, using the databases of Google Scholar and PubMed. The included sources were either original, peer reviewed articles, legislative documents, or policy documents. Keywords included "drug shortage management", "medicine shortage management", "regulatory measures for drug shortages", "government measures for drug shortages". The analysis focused on centrally managed shortage management strategies adopted by either governments or regulatory bodies such as healthcare authorities and excluded measures that were executed locally. The analysis has also built on preliminary insights gained during the first literature review regarding root causes and focused specifically on the six countries selected for quantitative analysis: United States, Australia, Belgium, Spain, Hungary and Switzerland.

Finally, the third objective of the qualitative analysis was to conduct a thorough examination of antibiotic shortages and identify local mechanisms for addressing shortages at the inpatient level. A systematic literature review was conducted to

summarize studies on antimicrobial shortages. The review focused on five major databases: PubMed, Reaxys, Ovid, ScienceDirect and Embase. The search began on September 27, 2022, and was last updated on July 15, 2023. The search terms included "antibiotic," "shortage," and "in clinic," with the time interval set between 2000 and 2023. Only original, peer-reviewed research articles written in English were included in the review (42). The primary criterion for inclusion was that the topic should focus on antibiotic shortages. It was not sufficient to mention an existing shortage, but the article had to address the consequences of shortages, such as AMR and patient symptoms. Furthermore, the studies also had to present an adequate solution to the antibiotic shortage. In addition, the study should specifically address antibiotic shortage, it is not enough to solely address a general drug shortage. Fifty-four articles were identified in the first round of the analysis, and forty papers remained after removing duplicate descriptions. After further reading, another thirty articles had to be excluded. Of these thirty trials, fourteen looked at patients' symptoms, bacterial susceptibility, and the development of resistance rather than addressing the shortage and were not included. Of the remaining twenty-six potential articles, I excluded four studies that did not specifically describe antibiotic shortages but other drug shortages, as well as twelve articles that described shortages but did not provide a possible solution. In the end, ten studies met all the criteria selected for the review. The flowchart of the search is illustrated in Figure 1 (43).

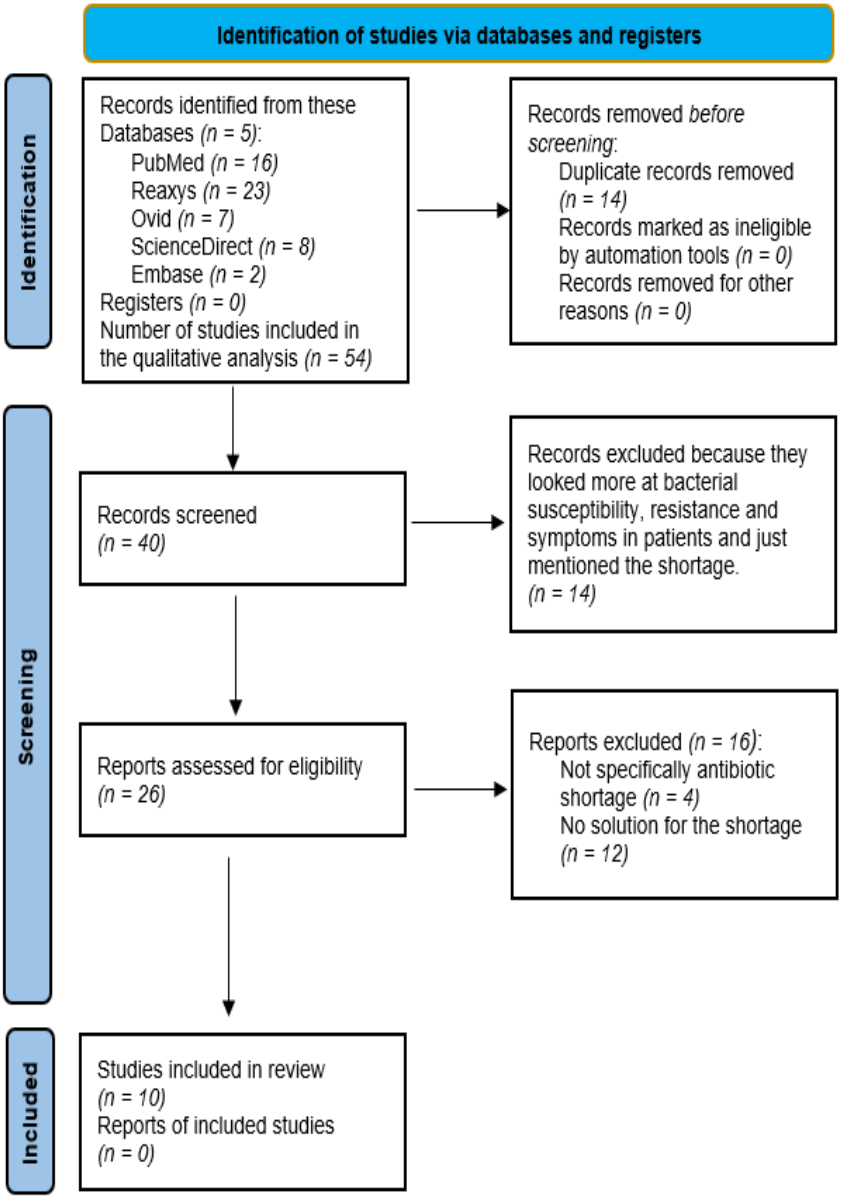

Figure 1: The flowchart of the search (42, 43).

The studies addressed the same issue but differed in several ways. Some studies looked at shortages occurring for a short period (less than half a year to a year), while others collected data on both drugs and solutions over several years. Furthermore, in some studies, only one type of antibiotic shortage was tested, while in others, a significant number of antibiotics were in shortage. As a final step in the systematic analysis, the local measured mitigate antibiotic shortages were summarised based on the analysed articles.

4. RESULTS

4.1. Quantitative analysis

Figure 2 illustrates the shortages observed in the studied countries, encompassing both general and critical cases.

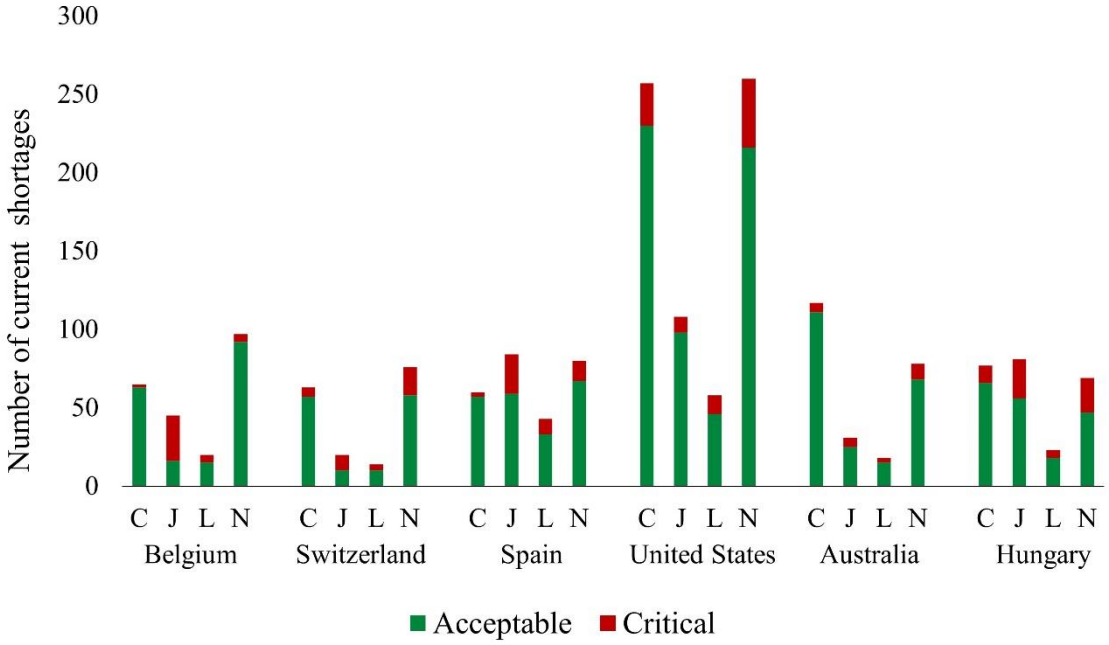

Figure 2: Number of shortages per country, per ATC group (including both critical and non-critical) (44). C: Cardiovascular system, L: Antineoplastic and immunomodulating agents, J: Anti-infectives for systemic use, N: Nervous system

The four ATC groups represented 68.7% of all reported shortages in the analyzed countries, indicating a significant concentration of shortages within these categories. This finding is remarkable, considering that there are 14 ATC groups in total. Column (d) of Table 3 shows the calculated proportion of total shortages per million people for each country. The highest proportion was recorded in Hungary and the lowest in the US. The average of the European countries for total shortages per million people (d) is significantly higher than non-European figures. The Spanish figure is an outlier compared to other European countries, as shortages per million people (d) are at least 75% less than any other European country. However, comparing shortages per million people across

countries still does not afford unbiased results, as the total number of shortages reported can largely differ across countries due to the reporting system in use. To obtain less biased and more relevant results, the proportion of critical shortages per million people has been calculated in column (e). The percentage of critical shortages among all reported cases is shown in column (f). On average, the percentage of critical shortages is two times higher in Europe than in the US or Australia.

Table 3: Number of shortages per million people in the studied countries, including critical cases.

Country	**Date**	**Shortages (a)**	**Critical (b)**	**Population in Million (c)**	**Shortage per Million (d)**	**Critical Shortage per Million (e)**	**Percentage of Critical Shortages (f)**
Belgium	4 Mar 2021	227	41	11.6	19.57	3.53	18.1%
Spain	6 Mar 2021	267	51	46.7	5.72	1.09	19.1%
Hungary	9 Mar 2021	250	63	9.6	26.04	6.56	25.2%
Switzerland	6 Mar 2021	173	38	8.7	19.89	4.37	22.0%
Average of European countries	-	229.25	48.25	-	17.805*	3.89	21.1%
United States	9 Mar 2021	683	93	332.9	2.05	0.28	13.6%
Australia	8 Mar 2021	244	25	25.8	9.46	0.97	10.2%

*The European average values were calculated from the data of individual European countries examined. Mar: March

Table 4 shows that the proportion of critical shortages is 16.87% across the whole sample. In contrast to my hypothesis, the binomial probability tests performed for each ATC group (ATC group is denoted by ATC_ID) indicated significant differences in the shortage proportions of certain ATC groups.

Table 4: Proportion estimation of critical shortages over the whole dataset. Binomial probability tests of the proportion of critical shortages across ATC groups.

Critical_BI	**Proportion**	**Std. Err.**	**Logit (95% Conf. Interval)**			
0	0.83134	0.00872	0.81355	0.84776		
1	0.16866	0.00872	0.15224	0.18645		
ATC	**Number of All Shortages (N)**	**Observed nr of critical shortages (k)**	**Expected nr of critical shortages (k)**	**Expected (p) % of critical shortages**	**Observed (p) % of critical shortages**	**Difference (Expected vs Observed p)**
C	639	55	107.77061	0.16866	0.08607	0.08259
J	369	105	62.23373	0.16866	0.28455	0.11589
L	176	39	29.68330	0.16866	0.22159	0.05293
N	660	112	111.31237	0.16866	0.16970	0.00104

Table 4 displays the result that the observed proportion (Observed p) is substantially different from the expected proportion (Expected p) for 3 out of 4 groups. In the therapeutic group related to the cardiovascular system (ATC group C), only 8.6% of total shortages were critical, compared to the expected 16.8%. In comparison, the group of anti-infectives for systemic use (ATC group J) were the most affected by critical cases (28.5% of observed shortages were critical). The proportion of critical shortages observed was also higher than expected, 22.2% for antineoplastic and immunomodulating agents (ATC group L). For nervous system drugs (ATC group N), the observed proportion of

critical shortages was almost exactly the same as the average across the sample (17.0% vs. 16.9%).

Looking at critical shortages per country and per ATC group, Figure 3 reflects that that the proportion of critical shortages per population is higher in every European country than the non-European figures (Figure 3).

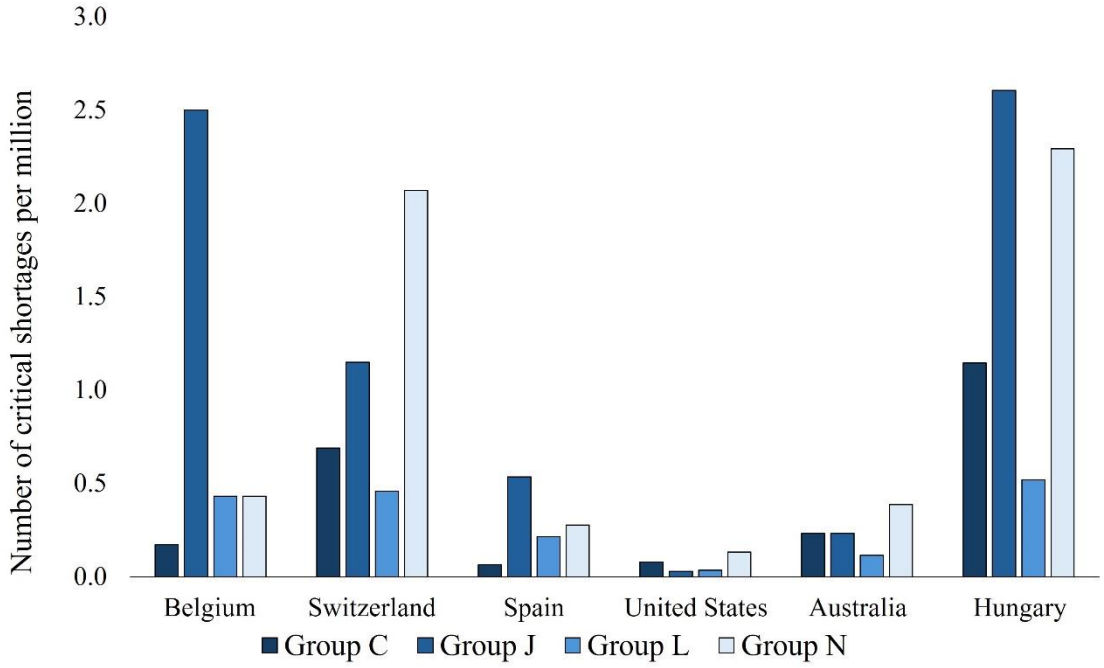

Figure 3: Comparison of critical shortages of various countries by ATC groups (44). C: Cardiovascular system, L: Antineoplastic and immunomodulating agents, J: Anti-infectives for systemic use, N: Nervous system

Table 5 shows that Switzerland and the US have the lowest ratio with 36.8% and 45.1% of critical shortages being WHO essential medicines, respectively. Belgium displays the worst result, with over 90% of its critical shortages being WHO essential.

Table 5: Summary of critical shortages of the examined countries according to the WHO Essential Medicine List.

Country	**No. of critical shortages/million people**	**No. of critical shortages on WHO Essential List/million people**	**No. of WHO Essential/No. of all critical shortages (%)**
Belgium	3.53	3.19	90.24
Switzerland	4.37	1.61	36.84
Spain	1.09	0.75	68.63
Hungary	6.56	3.96	60.32
Average of Examined European Countries	3.89	2.38	64.25
United States	0.28	0.28	45.16
Australia	0.97	0.74	76.00

The results show no correlation between the volume of critical shortages per population and the percentage of WHO essential medicines among critical shortages.

4.2. Qualitative analysis

4.2.1. Causes of drug shortages

The first objective of the qualitative analysis was to identify the factors causing drug shortages. The review of literature has uncovered a complex set of factors underlying such shortages, but various stakeholders of the supply chain agree that they mainly derive from three root causes, according to Figure 4:

– Business and economic issues

– Requirements of mature quality management systems

– Logistical and regulatory challenges (45, 46).

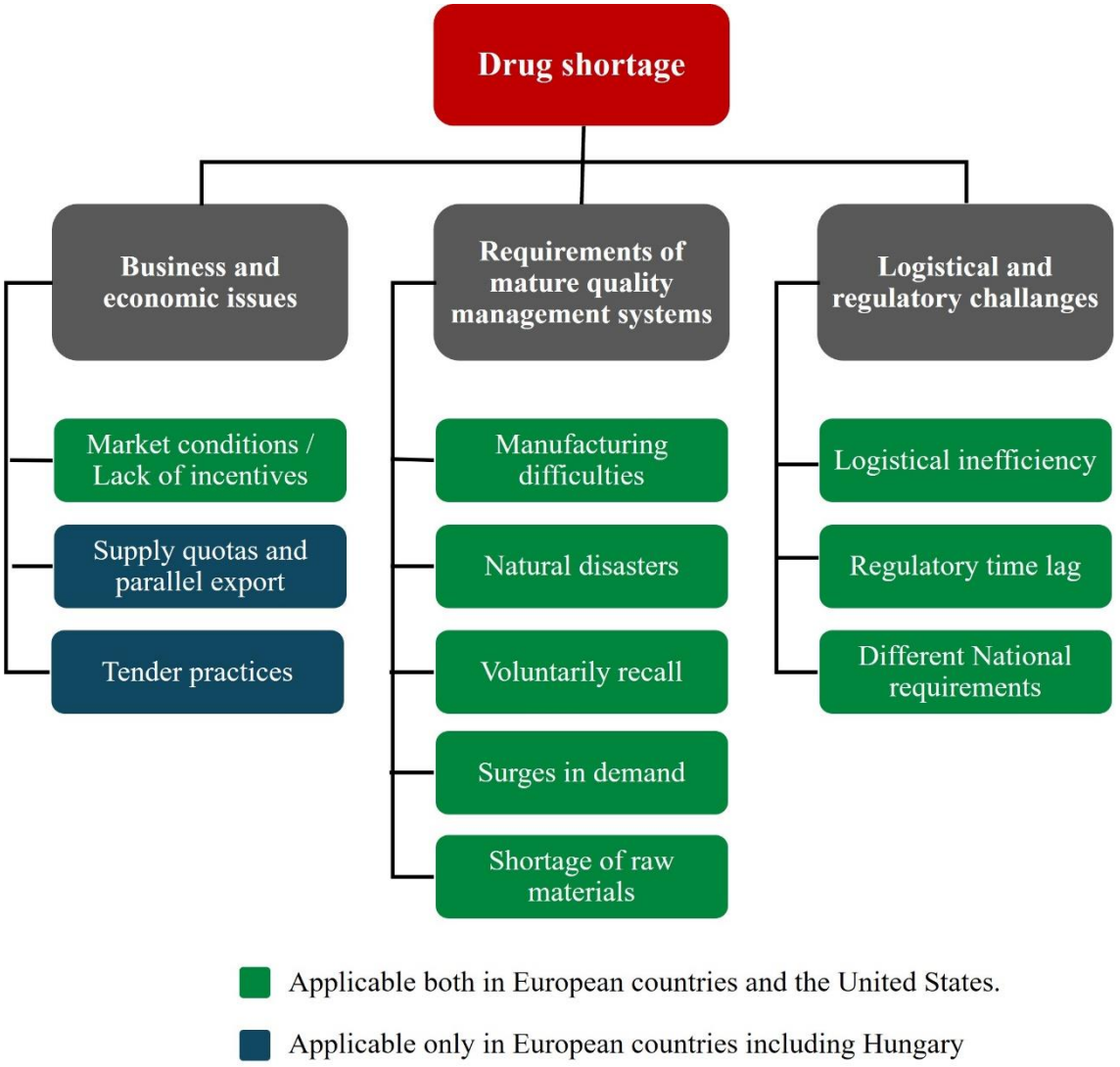

Figure 4: Potential root causes of shortages and derived factors (16, 45, 46).

4.2.1.1. Root Cause 1 – Requirements of mature quality management systems

The pharmaceutical market does not acknowledge nor reward MAHs' efforts of investing in quality management systems (46). Mature quality systems conform to Current Good Manufacturing Practice (cGMP) principles and are based on performance and a patient-focused approach, incorporating technology, statistical process control, and planning activities to ensure medicines are produced and supplied transparently (47). However, because of their strict guidelines, they can also contribute to the rise of drug shortages.

Voluntarily recall

Recall refers to not distributing a specific batch of products because of a lack of confidence in safety or any other defect (48). These recalls may have a fast and severe effect on accessibility, especially if certain drugs are marketed only by a few MAHs. A dilemma may arise if it is predicted that a voluntary recall will cause a drug shortage, while for example only the packaging is damaged (49). However, to conform with the guidelines of mature quality management systems, MAHs often opt for a voluntary recall.

Manufacturing difficulties

Pharmaceutical manufacturers often subcontract production to third parties in geographically distant locations to take advantage of significantly lower production costs (50). Every party involved in the production process is responsible for working according to cGMP, creating an additional responsibility for MAHs, who must ensure that subcontractors also comply (51). The EU introduced the new Active Pharmaceutical Ingredients (API) Regulation in 2013 to ensure these global guidelines are met. As a result, MAHs and regulatory authorities need to perform more personal audits (52). Bottlenecks can arise at various stages of the production process; for example, due to aged and inefficient equipment, the lack of competent workforce, or resources shifted toward business areas with higher profit potential, such as research and development. Moreover, MAHs often use the same equipment to produce various products, therefore it is difficult to quickly increase production of one product without compromising the supply of another (53).

Shortage of raw materials

Shortage of raw materials has a critical impact on the supply chain because even if multiple MAHs produce the same medicinal product, they may have only one common source of raw materials (5). Historically, the manufacturing of drugs for US citizens has been inland-based (54). However, the import of raw materials, particularly for APIs, is continuously on the rise, making the stability of these channels essential for the whole supply chain (54). As of August 2019, only 28% of US manufacturers procured APIs as raw materials from the domestic market, while the remaining 72% has been imported from overseas (54). As materials are largely procured from non-European countries such as China or India, the stable drug supply of developed countries is highly dependent on

these dominant producers (5). In addition, there is a low number of suppliers capable of meeting quality standards required by EU or US legislation, and many of them are affected by operative risks of countries with frequent natural disasters, armed conflicts, or political instability. Problems also may arise due to trade arguments, damage during transport, changing climate conditions, or a decreased yield of plants that are a source of materials (5).

Natural disasters

Production or shipment capacity can be significantly reduced by natural disasters, such as fires, hurricanes, tornadoes, and floods. If a certain manufacturer is the sole source of a product, a long-term shortage might occur. Sometimes disasters generate shortages as the treatment of victims creates an unexpected spike in the demand for certain medicines (8).

4.2.1.2. Root Cause 2 – Business and economic issues

Lack of incentives to market barely profitable medicines

MAHs frequently remove less profitable products from their portfolio, potentially causing short supply (55). If market conditions limit the profitability of MAHs they are undermotivated to continue the production and invest more efforts in improving its quality (45). There is strong price competition in the pharmaceutical market, also referred to as the „race to the bottom in pricing" (56). As another economic factor, mergers and acquisitions of pharmaceutical companies since the 1980s often lead to decreased product quantity and contribute to shortages (57). Cost-containment actions such as reference pricing, payback mechanisms, or discounts, introduced by some countries to control public expenditures on pharmaceuticals also limit profitability and thereby, the incentives of MAHs to produce certain medications (45).

Parallel distribution

Occasionally, parallel distribution is also mentioned as a potential cause of medicine shortages; however, it is a highly controversial aspect. Parallel distribution refers to business transactions between wholesalers registered in different markets, which leverage the difference in prices among their countries (58). If a country's manufacturers produce the quantity necessary to meet the needs of their market, but a wholesaler exports a

proportion of the products to a foreign market where they can gain a higher profit, a shortage may occur in the domestic market (59). In response to this ethically questionable practice of wholesalers, MAHs introduced quotas to control the amount of certain medicinal products available to countries to limit parallel trade. However, if quotas are not set at the right levels to cover domestic demand, they can contribute to drug shortages (60).

Tendering practices

Public tendering is used to increase price competition to reduce prices. In 2009, 18 European Union (EU) member states used tendering practices for procuring medicinal products, mostly for hospitals. In Hungary, "Act CXLIII of 2015 on Public Procurement" regulates tender practices (61). The single-winner approach introduces the risk that the chosen company may not be able to supply the right quantity at the right time, which is then sanctioned by fines. To mitigate this issue, when selecting the winner, besides the most important criterion, the price, the second alternative criterion should be the availability of the medicine. The single-winner approach leaves hospitals highly dependent on one firm, which could be resolved by including second or third winners based on such multifactorial criterion, which could automatically supply if the first winner cannot do so (45).

4.2.1.3. Root Cause 3 - Logistical and regulatory challenges

The pharmaceutical supply chain has become highly complex and disintegrated over the past decades as numerous industries have transmitted a higher portion of their production overseas (54). Normally, markets would respond to an upcoming shortage by raising production levels; however, logistical and regulatory burdens resulting from the overly complex supply chain often limit the ability and speed of MAHs to raise production (45).

Supply chain difficulties

The "just-in-time" stock management allows fewer goods "on hand". Benefits include optimized cash flow and storage capacity (62). This inventory strategy and frequent delivery issues result in higher exposure to unforeseen shortages (45).

Supply and demand issues

The level of demand for a certain drug can rise over general expectations due to a various reason, such as a new indication being approved regarding the product, a disease being in a high spread, or growing media attention around a product (8). During the coronavirus disease 2019 (COVID-19), several important factors led to increased demand and supply chain challenges:

- Panic buying and stockpiling,
- A shift to home consumption,
- Increased demand for health and safety products,
- The rise of e-commerce and delivery services,
- Supply chain disruptions (63).

Regulatory Issues

If the HA inspectors find non-compliance with GMP, the authority may seize involved products and schedule another facility inspection until the violation has been corrected. Further regulatory-related issues if a medicine previously approved on a certain market and its MA was invalidated, pending MA approval, or a previously approved medicine must wait for MA renewal so-called "regulatory time lag" (45).

4.2.1.4. Root causes: US vs EU comparison

Based on the findings detailed above, it was possible to draw a comparison between the United States and the European Union, to show how each of the root causes are present in these markets. Table 6 summarises this comparison. Out of the three main categories of causes identified (Business and Economic issues, Requirements of mature quality management systems, Logistical and regulatory challenges), only among the Business and Economic issues category were found root causes that are only pertinent in the EU. On the other hand, no root causes were identified that would only be applicable to the US.

Table 6: Comparing Root causes of shortages in EU/Hungary and the US (45, 46).

Root causes	**Derived shortage factor**	**United States**	**EU including Hungary**
Business and Economic issues	Market conditions/ Lack of incentives	Economic incentives favour highly profitable drugs; therefore, MAHs might discontinue the production of those with low-profit margins.	
	Tender practices	N/A	Single-winner structure leaves hospitals highly dependent on one firm, which might not be able to meet the whole demand.
	Supply quotas and parallel export	N/A	Due to exporting to more profitable markets, discrepancy arises between the volume manufacturers release on a given market and the ability of the wholesalers to satisfy patients' needs from the said market.
Requirements of Mature quality management systems	Manufacturing difficulties	Manufacturers cannot provide sufficient quantity or quality.	
	Natural disasters	Production facilities have to discontinue production and/or have to meet increased demand for particular medicinal products which would be essential to treat disaster victims.	
	Voluntarily recall	The supply of medicines could be significantly reduced because of GMP issues.	
	Surges in demand	Due to unpredicted increases in the use of a particular product, supply cannot meet the market needs, e.g., COVID-19.	
	Shortage of raw materials	Due to the limited availability of ingredients, production is forced to be lower than normal manufacturing capacity, e.g. Valsartan case.	

Table 6 continued:

Root causes	**Derived shortage factor**	**United States**	**EU including Hungary**
Logistical and regulatory challenges	Logistical inefficiency	Medicine would be available; however, patients cannot acquire it due to various reasons.	
	Regulatory time lag	Medicine waits for Marketing Authorization renewal.	
	Different National requirements	Specific requirements by authorities, e.g., specific label requirements, pharmacovigilance system, and Falsified Medicines Directive regulation.	

After identifying the root causes behind drug shortages, it was also interesting to briefly compare how the share of these root causes behind medicine shortages differ between the United States and European markets. As data on various European countries was limited, the United States and Hungary were compared. The comparison is shown in Figure 5.

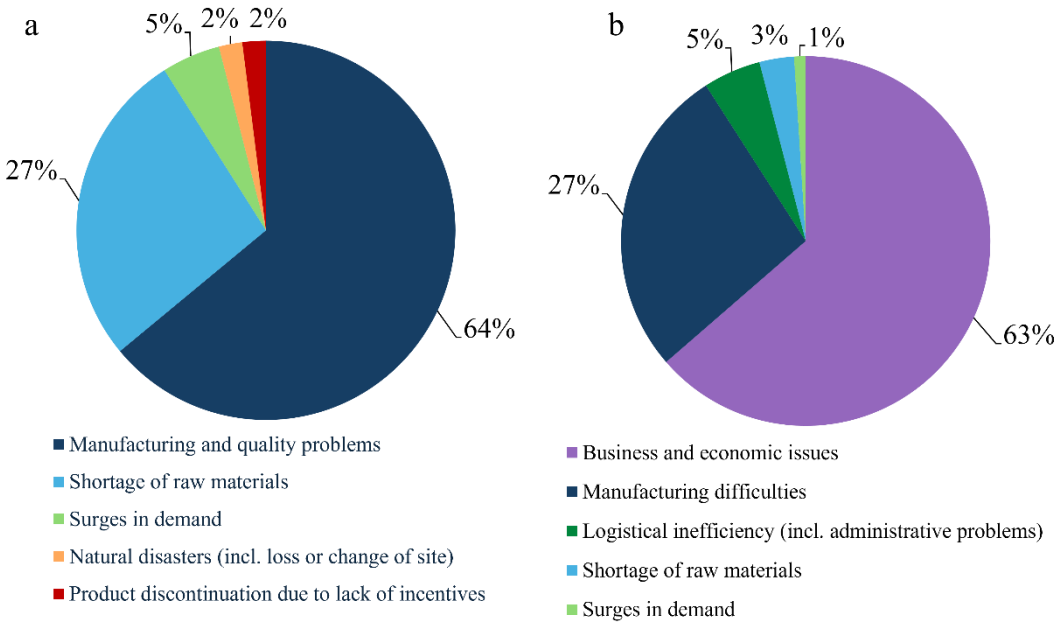

Figure 5: Causing factors behind the shortages reported by MAHs a) in the United States from 2013 to 2017 (64) and b) in Hungary from 13th January 2020 to 20th January 2020 (16, 40).

In the United States, 64% of shortages were attributed manufacturing and quality problems, which involve both delays due to capacity issues and voluntary recall due to bacterial contamination or any other foreign matter found in the current batch (65). The second most reported root cause was shortage of raw materials, in 27% of cases. Surges in demand for certain products accounted for 5% of shortages, followed by natural disasters (2%) and product discontinuation due to the lack of financial incentives (2%) (64, 66).

The picture in Hungary looks quite different, as the leading reason of shortages are Business and Economic issues, which account for 63% of all shortages. This indicates that this root cause poses a more severe risk there compared to the US. Manufacturing difficulties also have significant impact on Hungarian shortages, being the second most reported cause, with 27% of the cases. Further causes reported are logistical inefficiency (5%), shortage of raw materials (3%) and surges in demand (1%) (40).

4.2.1.5. Adding more severity: Imperfect reporting systems

Despite not being an explicit root cause, the lack of sufficient information due imperfect warning systems contributes to the issue of drug shortages to a great extent (5). In the US, drug manufacturers must inform the FDA 6 months in advance if they intend to stop the production of a certain medicinal product (67). However, there is no financial or administrative fine for missing the report to the FDA (68). The HA cannot mandate a MAH to produce a particular product (69). In case the medicinal product being in shortage is produced only by one MAH, which would be the only source for wholesalers or hospitals, the situation is even more severe (1). Drugs being short in supply are often only noted when patients walk into the pharmacy and try to purchase medicine, but it is no longer available, whereas the pharmacist behind the counter should have reliable and timely information to manage patients' therapy (70).

In the EU, the situation is similar, but also varies greatly across countries. Almost all European member states obligate stakeholders to notify a specific institution according to Directive 2001/83/EC Article 81 and 23a of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (19). However, the requirements for reporting systems are not unified. Table 7 summaries the various characteristics of reporting systems in European countries.

Table 7: Comparison of National Drug Shortage Reporting Systems Across Selected European Countries (1, 16, 71, 72).

Country	**Reportable products**	**Frequency of database updating**	**Short Description**
Austria	Products with marketing authorization	Weekly	The voluntary list provided by MAHs regarding their products.
Belgium	If unavailability poses a risk to public health/ no therapeutic alternative available	Daily	MAHs have to report by law any shortage that will last for two weeks.

Table 7 continued:

Country	**Reportable products**	**Frequency of database updating**	**Short Description**
Croatia	Only reimbursed products	Monthly	A list is available for download on the website.
England	Products for community pharmacy only	Monthly	Pharmacists via direct email.
Estonia	Unlimited	On-call basis	It changes with new information every day.
France	If unavailability poses a risk to public health/ no therapeutic alternative available	Daily	Pharmacists and hospitals can upload information.
Germany	If unavailability poses a risk to public health/ no therapeutic alternative available	In cases assumed to be of special interest to HCPs	MAHs should report to different institutions. The list is often not up to date, and not all shortages are listed here because it is not mandatory.
Hungary	Products with marketing authorization	Weekly	Based on MAHs information also have a national website where they propose a solution for substitutions.
Italy	Products with marketing authorization	Weekly	MAHs, health care providers, health departments, patients, or associations.

Table 7 continued:

Country	**Reportable products**	**Frequency of database updating**	**Short Description**
Latvia	Products with marketing authorization	Daily	Anyone (hospital, pharmacy, patient) could use this website to report.
Norway	Products with marketing authorization	Weekly	Both the Norwegian Authority and the national centre of shortage of drugs in hospital has webpages open to everyone.
Poland	Products with marketing authorization	At least bimonthly	Chef Pharmaceutical Inspectorate collects data from the pharmacists who are obliged to report online by giving details of the nature of the shortage.
Spain	Products with marketing authorization	On-call basis	MAHs or health authorities of autonomous communities.
The Netherlands	Products with marketing authorization	Daily	MAHs, wholesalers, pharmacists.

The comparison shows that although they share a common purpose, reporting systems across Europe are based on different principles and function in distinct ways, making them incomparable. It is also clear that in many European countries, the reporting system is not fit to deliver timely warnings to stakeholders if shortages occur. Therefore, the lack of information can also contribute to the severity of shortages.

4.2.2. Centrally managed shortage management strategies

After examining the root causes of shortages, it is also important to understand what shortage management strategies are already in place. There are currently no international shortage management guidelines, and even practices within the EU are not unified. To mitigate shortages more effectively, countries should adopt a wider range of transparent, unified shortage management measures. The aim of this section is to analyse what shortage management strategies are currently in place, focusing on the six countries selected for the quantitative analysis, and identifying best practices that could be adopted as part of international guidelines. The countermeasures discussed here are centrally managed by either regulatory bodies or health authorities, i.e. not local actions of healthcare practitioners.

The current forms of countermeasures by country are reported in Table 8 and can be grouped under the six following categories:

1. Compulsory stockpiling
2. Measures for essential medicines
3. Notification responsibility
4. Measures affecting wholesalers
5. Export bans
6. Emergency imports

Table 8: Countermeasures introduced by countries. *N/A means that no relevant literature on this topic was obtained.

Country	**Compulsory Stockpiling**	**Measures for Essential Medicines—Legal Definitions**	**Notification Responsibility—Legal Background**
Belgium	Full-line wholesalers required to have a range of products in stock for the needs of the given geographic territories (73).	Not defined.	Not providing the exact reasons is considered a clear legal violation (74).
Switzerland	Delegated to companies at a defined level of stocks in Ordinance (75).	Compounds for which there are no or only limited substitutes have been affected by a supply shortage over the previous three years (75).	Determined in 531.215.32 Ordinance (75).
Spain	Health Authority may demand commercialization to grant the suspension, or the revocation of the product (76).	Essential if the pharmaceutical gap cannot fully cover or have a high economic impact. Critical if it has no available therapeutic alternatives and has a complex manufacturing process, and/or has only one supplier (77).	Spanish Medicine and Products Devices Agency Circular No. 3/2011(78).

Table 8 continued:

Country	Compulsory Stockpiling	Measures for Essential Medicines—Legal Definitions	Notification Responsibility—Legal Background
United States	Food and Drug Administration supports MAHs to maintain production (79).	If used to treat or prevent a serious disease or condition, and there is no other adequate available source (80).	Safety and Innovation Act in 2012 (21).
Australia	National Medical Stockpile maintains the strategic reserve of products (81).	Included on Medicines Watch List, has a potential life-threatening or serious impact, or has no potential substitutes (35).	Therapeutic Goods (Reportable Medicines) Determination 2018 (36).
Hungary	Products decreed by the minister should be available in the quantity defined therein (39).	Not defined.	Act XCV of 2005 on Medicinal Products for Human Use (39).

Table 8 continued:

Country	Measures Affecting Wholesalers	Export Bans	Emergency Imports
Belgium	Full-line wholesalers are assigned besides regular ones with special responsibilities and privileges (77) (73).	Temporarily to medicinal products for which a shortage is notified (74).	Based on a doctor's request wholesalers may temporarily import medicine from the EU, if no substitutes are available in BE, in specific quantities requested by the doctor (82).
Switzerland	Managing the strategic level of inventory stock delegated by the federal government in local law (75).	Parallel export does not become significant due to high prices (83).	Upon application for temporary import submission (84).
Spain	All wholesalers are required to deliver within 24 working hours (77).	If lack of medicinal products causes a pharmaceutical gap (85).	The Spanish Agency of Medicinal Products and Medical Devices can also approve the import of medicines labelled in other languages or with an expiry date shorter than 6 months (77).

Table 8 continued:

Country	Measures Affecting Wholesalers	Export Bans	Emergency Imports
United States	* N/A	* N/A	Food and Drug Administration may allow emergency importation (79).
Australia	Wholesalers also have a duty to notify authorities about the expected duration of a discontinuation(37).	Only for MAH or designated entity (86).	Therapeutic Goods Act has been amended to assist import (34).
Hungary	Authorized wholesale distributors shall be required to procure and supply the medicinal products as their authorization for wholesale distribution pertains (39).	The active substances decreed by the minister for a period not exceeding one year (39).	On the wholesaler's request "contingent-approval" (87) or the physician statement "individual approval of the Hungarian Health Authority"(88).

4.2.2.1. Compulsory Stockpiling

In Australia, the National Medical Stockpile must maintain "key medicines" to avoid critical shortages of essential drugs (38). A similar system exists in Switzerland, where the government defines medications that are subject to compulsory stockpiling in the appendix to the Ordinance and the level of such stock that would satisfy average domestic consumption for three months without any import (75).

4.2.2.2. Measures for Essential Medicines

To mitigate the number of critical shortages, it is crucial to implement targeted countermeasures that address critical drugs. Specifically, the focus should be reducing the scarcity of WHO essential drugs by implementing sustainable solutions. In Spain, the government can demand production and commercialization from MAHs to bridge supply gaps concerning essential products (89). This seems to be an effective measure to cut back shortages, as critical shortages per million people in Spain were significantly the lowest among European countries. The US shortage management system works similarly. In response to the shortage of a medically necessary drug, the FDA can suggest and support establishing a new manufacturing site or even involving a new supplier. If a MAH decides on a voluntary recall, the FDA may conduct a risk evaluation and encourage other MAHs to initiate, maintain, or increase production of the drug (79). They can also facilitate the review of new generic applications that are potential alternatives (79). The regulation also permits hospitals within the same health facility to repackage drugs into smaller units to alleviate drug shortages (21). In Spain, MAHs that stop distributing a medicinal product without the authorities' permission face heavy fines (90).

4.2.2.3. Notification Responsibility

In the US, authorities maintain an apparent oversight of shortages. They, therefore, can handle them very effectively—the quantitative analysis clearly reflected that the critical shortages per million people are the lowest in the US. The criteria for products reported in the central systems are strict and well-defined, so authorities can monitor developing shortages from an early stage and address them accordingly (29). For example, MAHs are mandated to inform the FDA of impending shortages six months in advance when they plan to stop producing a single-source or medically necessary (life-supporting, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including emergency medical care or during surgery) drug (21). This effectively helps maintain a low percentage of shortages that become critical. The FDA may also oblige the MAHs to conduct periodic risk assessments to address vulnerabilities in its supply chain. It was a significant step forward in the EU that in July 2019, the European Medicines Agency (EMA) published the "Guidance on detection and notification of shortages of medicinal products for MAHs in the European Union" (91).

The document contains the effort to facilitate the more uniform reporting and communication of drug shortages and harmonize the "drug shortage" definition. The document "Good Practice Guidance for Communication to the Public on Medicines' Availability Issues" (92) contains communication guidelines for the national authorities and the EMA for patients and HCPs.

4.2.2.4. Measures Affecting Wholesalers

In Belgium and Spain, some countermeasures specifically target wholesalers, who are obliged to ensure continued and adequate supply. In Spain, all wholesalers are required to deliver within 24 working hours (77). In Belgium, to reduce the cases where shortages arise due to "distribution problems", distributors were assigned as full-line and regular wholesalers. MAHs are obliged to supply full-line wholesalers within a shorter period. Full-line distributors are required to deliver emergency shipments in 24 hours. They must have a range of specified medicines in stock to supply the needs of defined geographic areas. Moreover, full-line distributors are only allowed to supply strictly determined wholesalers, domestic pharmacies, and hospitals; thereby, parallel export is not permitted (73).

4.2.2.5. Export Bans

In Australia, exports can only be performed by MAHs or designated distributors acting on behalf of the MAHs, not by most wholesalers, as in many European countries (86). This is highly important, as parallel export is usually a key factor in causing shortages, mostly affecting countries with low drug prices compared to international averages. In Spain, AEMPS can restrict exportation only to medicinal products without therapeutic equivalents (93). There are serious penalties and fines of up to 1 million euros for distributors who export medicines when this activity has been forbidden.

4.2.2.6. Emergency Imports

When there is no other possibility of resolving a critical shortage as no substitution is available domestically, emergency imports must be performed. The conditions of an emergency import are determined by national laws. In most countries, this is contingent on the approval of the HA, such as the FDA in the US, the NNGYK in Hungary, or the Spanish Agency of Medicinal Products and Medical Devices in Spain (Table 8). In

Belgium, wholesalers may also perform emergency imports from the EU based on a doctor's request in the specific quantities necessary for the given treatment (82).

4.2.3. Inpatient shortage management strategies through the example of antibiotics

While the section above discussed shortage management strategies that are managed centrally (by health authorities or other regulatory bodies), there are also shortage management measures that can be executed locally. To also explore these measures, we focused on a selected therapeutic group, antibiotics. They were selected because the proportion of critical shortages of their ATC Group, J, was highest compared to other therapeutic groups in all examined EU countries. The impact of antibiotic shortages on patients at the individual level can be particularly severe and various (94). The frequent shortage of antibiotics is often linked to excessive and inappropriate prescribing (95, 96), particularly of broad-spectrum agents, along with a decrease in bacterial susceptibility and the rise of antimicrobial resistance (AMR). These drivers align with the "Surges in demand" category of root causes discussed earlier. To explore effective mitigation strategies, a focused literature review was conducted. The selected studies, summarised in Table 9, detail the affected antibiotics, duration of shortages, clinical settings, and study methodology.

Table 9: Antibiotic shortages, duration, settings, and location of each study.

Type of Antibiotic	**Interval**	**Inpatient Unit and Settings**	**Reference**
amoxicillin, gentamicin, linezolid, meropenem, teicoplanin, piperacillin/tazobactam, tobramycin, aztreonam, cefepime, cefamandole, ticarcillin	2013–2020	European hospitals; European Association of Hospital Pharmacist surveys	(95)
cloxacillin, benzathine, benzylpenicillin, erythromycin	In 2018, for a half-year	South African public-sector hospitals; Descriptive surveys and quantitative research approaches	(96)
meropenem, imipenem, piperacillin/tazobactam	2015–2016	Barnes-Jewish Hospital in St. Louis, Missouri, USA; Retrieving and analysing data, creating models	(97)
effect of piperacillin–tazobactam deficiency on meropenem	In 2015, for a half-year	University of Mississippi Medical Center, Department of Medicine-Division of Infectious Diseases, Jackson, USA; Quality improvement retrospective review	(10)
Trimethoprim-sulfamethoxazole, amikacin, aztreonam, foscarnet	2011	US hospitals surveyed by the Infectious Diseases Society of America; A nine-question survey	(98)
penicillin, cefazolin, clofazimine, dapsone, rifabutin, piperacillin–tazobactam, ceftolozane–tazobactam, cloxacillin	2020–2021	Some of the Hospitals from India, United Kingdom, South Africa, Switzerland; Database analysis	(94)

Table 9 continued:

Type of Antibiotic	Interval	Inpatient Unit and Settings	Reference
cefazolin	2019	Tokyo Metropolitan Tama Medical Center, Tokyo, Japan; Database analysis	(99)
amikacin, foscarnet, streptomycin, isoniazid, clindamycin, gentamicin and trimethoprim-sulfamethoxazole	2011	Northwestern Memorial Hospital (Chicago, IL, US); Prospective follow-up	(100)
amoxicillin, gentamicin, linezolid, meropenem, teicoplanin, piperacillin/tazobactam, tobramycin, aztreonam, cefepime, cefamandole, ticarcillin	2017–2018	Public maternity hospitals in the city of Fortaleza;	(101)
cefazolin	2016–2020	Japanese Hospitals; Database analysis	(102)

When selecting the articles during the literature review, it was a key criterion that the studies also have to discuss the mechanisms by which the shortage was handled. Table 10 reflects the pharmaceutical formulation, the substitutability of the specific product, and the adapted shortage handling mechanisms in each case.

Table 10: Possible solutions to alleviate the shortage of antibiotics based on the studies searched. i.v. for intravenous and p.o. for per os.

Shortage Product(s)	Pharmaceutical Formulation	Substitutability	Handling the Shortage	Reference
amoxicillin, gentamicin, linezolid, meropenem, teicoplanin, piperacillin/tazobactam, tobramycin, cefepime, cefamandole	i.v. p.o.: amoxicillin	substitutability depending on alternatives	Alternatives-dependent substitution and antibiotic stewardship programs through shortage warning systems	(95)
benzylpenicillin, cephalosporins, erythromycin	i.v., erythromycin: p.o.	substitution was not the applied solution	Antibiotic stewardship programs, national monitoring programs (supply management), exchange policies	(96)
meropenem, imipenem, piperacillin/tazobactam	i.v.	cefepime	Antibiotic stewardship programs, including awareness campaigns, active inventory tracking, and audits	(97)
piperacillin/tazobactam	i.v.	meropenem	Substitution policies, antibiotic stewardship programs, including identification consultations, collaboration between pharmacists and doctors	(10)

i.v. = intravenous; p.o. = per os.

Table 10 continued:

Shortage Product(s)	Pharmaceutical Formulation	Substitutability	Handling the Shortage	Reference
trimethoprim-sulfamethoxazole, amikacin, foscarnet	i.v.	trimethoprim-sulfamethoxazole (p.o.), pentamidine	Antibiotic stewardship programs, including general communication on drug shortages, electronic lists of alternatives	(98)
benzylpenicillin, cefazolin, piperacillin/tazobactam	i.v.	substitution was not the applied solution	Organized, coordinated, and strengthened foresight, facilitation of regulatory processes, local pharmaceutical production, importing	(94)
cefazolin	i.v.	ceftriaxone, ampicillin/sulbactam, vancomycin	Antibiotic stewardship programs, including optimizing current antimicrobial prescribing practices in hospitals, promoting the development of an action plan, a policy of offering financial incentives	(99)

i.v. = intravenous; p.o. = per os.

Table 10 continued:

Shortage Product(s)	Pharmaceutical Formulation	Substitutability	Handling the Shortage	Reference
foscarnet, streptomycin, isoniazid, clindamycin, gentamicin	i.v., p.o.: isoniazid, clindamycin	substitution was not the applied solution	Antibiotic stewardship programs, including tracking updated information, maintaining local inventories of critical antimicrobial stocks, importing	(100)
derivatives of penicillin	i.v.	ceftriaxone, cefazolin	Treatment with other therapeutic schemes, search for alternatives, use of ceftriaxone	(101)
cefazolin	i.v.	ceftriaxone, cefotiam, ampicillin/sulbactam	Antibiotic stewardship programs, trade promotion, national government involvement, improving forecasting systems	(102)

i.v. = intravenous; p.o. = per os.

In the study by Míljković et al., a survey of antibiotic shortages was carried out with the help of pharmacists working in European hospitals and found that several antibiotics such as amoxicillin, gentamicin, linezolid, meropenem, teicoplanin, piperacillin/tazobactam, tobramycin, cefepime, and cefamandole were among the shortage items between 2013 and 2020. To alleviate the shortages, most pharmacists used substitution as part of appropriate AS programs, depending on the availability of alternatives, although they found fault with the availability and timeliness of information in the shortage reporting systems. It was noted that it would be important to keep the shortage reporting

Information Technology (IT) software up to date and detailed, and to ensure good communication between healthcare professionals (95).

In the study by Chigome A. K. et al., antibiotic shortages in public-sector hospitals in South Africa were assessed using electronic questionnaires over six months in 2018. The drugs most cited in stock-outs were benzylpenicillin and cephalosporin, and inadequate supply systems were identified as the cause of the shortages. It was described that certain steps should be taken to address the shortage, such as the use of therapeutic exchange policies, increased communication with both stockists and prescribers, and participation in national monitoring programs (96).

The study by Hsueh K. et al. looked at meropenem, imipenem, and piperacillin-tazobactam shortages at Barnes-Jewish Hospital in the US in 2015. AS programs were implemented to conserve antibiotics, which included some guidelines and changes in decision support and appropriate communication. Additional AS programs included prospective auditing, active inventory tracking, and substitution with alternatives, even if the drug in shortage was currently available (97).

In a 2015 study, Barber et al. at the University of Mississippi Medical Center in the US examined the impact of piperacillin-tazobactam antibiotic shortages on meropenem consumption. Measures such as appropriate physician–pharmacist communication, targeted medication alerts, and changes in dosage or frequency of drug administration were used alongside intensive meropenem substitution to alleviate the shortage, but there was still a 111% increase in meropenem consumption (10).

In 2011, a study by Gundlapalli et al., trimethoprim-sulfamethoxazole (i.v.), amikacin, and foscarnet shortages were studied in US hospitals using a questionnaire-based survey. The solution to reducing the shortage was primarily substitution, and the agents used to do this were trimethoprim-sulfamethoxazole (p.o.) and pentamidine. Although practitioners indicated that alternatives were often less effective, it is worthwhile using additional initiatives in addition to substitution, such as improving doctor–pharmacist communication and timeliness of the databases and messages indicating shortages so that the shortage is communicated more quickly to prescribers and treatment planners. It is also important that more information on alternatives is available and accessible so that colleagues in clinics do not have to spend a lot of time researching the literature (98).

In a study by Shafiq et al., a survey was conducted between 2020 and 2021 in hospitals in several countries, including India, the United Kingdom, Switzerland, and South Africa. Antibiotics on the shortage list included penicillin, cefazolin, piperacillin-tazobactam, and others. The study recommends several mitigation tactics, including organized, coordinated, and strengthened forecasting of drug shortages, cooperation and exchange of medicines between countries, greater financial incentives for manufacturing, development of generic medicines, faster and easier licensing, and promotion of local production of medicines (94).

The study by Hitoshi Honda et al. looked at cefazolin shortages in a medical centre in Tokyo. In addition to substitution, AS programs have been used and suggested to mitigate shortages, such as optimizing prescribing in terms of duration of therapy and frequency of administration, encouraging a switch from intravenous to oral formulations as soon as possible, and making the transmission of information about shortages faster and more efficient, not least because logistical planning and regulation are essential for national access. It is also important that the professionals involved in each AS program receive appropriate, structured training to facilitate and improve their efforts to alleviate the shortage. Finally, manufacturers should be encouraged to stockpile the active substance or the raw material from which the active substance is synthesized, thereby increasing local production (99).

In the study by Griffith et al., antimicrobial shortages at Memorial Hospital in Chicago were tracked for three months in 2011. The shortages included foscarnet, streptomycin, gentamicin, and trimethoprim-sulfamethoxazole, all of which were involved in nationwide shortages. Another interesting finding of the research was that 2/3 of the drugs involved in the shortage were generic, and only 1/3 were originator products. To reduce these shortages, AS programs were implemented, including appropriate communication, continuous monitoring of the FDA and ASHP drug shortage websites, monitoring of local stock levels, and changes in drug therapy such as dosage dilution or shortening of treatment duration. Other efforts have included allowing imports into the US and reserving a particular antibiotic for patients whose pathogens have become resistant to other agents (100).

In a study conducted by Rocha et al. between 2017 and 2018, a maternity hospital in the city of Fortaleza investigated the lack of penicillin and its synthetic derivatives, which

was a serious problem in the treatment of women and children with syphilis, the first-choice drug for this disease. Penicillin was conserved by substitution, in most cases with ceftriaxone and cefazolin or a combination of drugs, and only newborns who were symptomatic at birth, premature, or with other conditions were treated with penicillin (101).

In a study by Nagano et al., cefazolin deficiency in Japan was examined at interrupted intervals from 2016 to 2020. They studied which parenteral drugs would be chosen as a result of the drug shortage and how the cost of these drugs would change over this period. The most common option was substituting alternative drugs (ceftriaxone, cefotiam, ampicillin/sulbactam). Due to the low prices of ceftriaxone and cefotiam, there was no significant increase in costs, but consumption of these drugs was high. Other suggestions were made to alleviate the shortage, such as financial incentives for manufacturers, regular use of shortage forecasting programs, and publication of adequate information on the alternatives listed (102).

4.2.3.1 Local Strategies to Address Antibiotic Shortages

In this section, the countermeasures are summarised based on the above literature review that do not depend directly on central decision-makers, e.g., health authorities and legislation, but local actors in hospitals and pharmacies can execute themselves. From the patient's point of view, it is not important that the shortage management was successful due to central or local mitigation strategies; strategies must complement each other. Based the literature review, local practices are demonstrated through antibiotic’s shortages.

Therapeutic alternatives and protocol development

In general, the possible first step to mitigate the shortage is substitution with available therapeutic alternatives (10, 95, 97-99, 101, 102). It is best when therapeutic exchange policies are created, so healthcare professionals can follow clear guidelines for every scenario and no time is wasted researching alternatives on a case-by case-basis (10, 96). Even if no alternative products are available to substitute with, some pure active ingredients may still be available on the market, allowing to create a customized patient presentation locally. In several countries, it is allowed to compound medicines in clinical and retail pharmacies. For example, in Hungary, magistral medicinal products are those that the pharmacist produces, packages, and dispenses in the pharmacy following the official Pharmacopoeia regulations in accordance with the principles set out in the

resolution issued by the Council of Europe on the quality and safety assurance requirement for medicinal products prepared in pharmacies for the special needs of patients. If the pure active ingredient is available in the country, there is a potential solution if parties along the supply chain collaborate.

By establishing a risk-based framework, enhancing the expanded production of magistral medicinal products is possible beyond the scope of GMP regulations. This framework should involve the direct oversight of HCPs from Health Authorities, specifically focused on the circumstances of the manufacturing steps, including analytical support and manufacturing validation, and the physicians who should also approve therapeutic protocols before approving these medicines. This risk-based framework should be well defined and regulate potential patient population (individual therapy planning) and production circumstances. It is evident that that producing medicinal product outside of GMP puts a higher risk on the final products; however, the absolute lack of a particular product can put a higher risk instead on patients (42).

Prioritization and Allocation Policies

It is highlighted in the literature on multiple occasions how effective prioritization and allocation can help in managing drug shortages, ensuring that the most vulnerable patients retain access to essential medications (100, 101). Healthcare professionals should assess preliminary risk factors— like age, comorbidities, allergic profiles, resistance patterns, and concomitant medications—when developing therapeutic protocols. These factors can all inform patient-specific therapy planning. If shortage risk is high, healthcare professionals should review the patient's profile to identify potential alternative treatments. This approach ensures continuity of care, while limited supplies are saved for those who need it most. Consequently, the need for mid-therapy switches and the risk of developing resistant bacterial strains are both reduced.

Emergency import

Emergency imports also serve as a local strategy to mitigate drug shortages when domestic supplies are insufficient. While central frameworks regulate the legal and logistical aspects of imports, and therefore import possibilities had already been described among the centrally managed countermeasures, healthcare professionals play a vital role in leveraging this measure proactively at the local level (94, 96, 100). Emergency imports can be initiated locally, and by maintaining close communication with national regulatory

authorities, they can advocate for expedited import approvals when a shortage is imminent. Healthcare professionals can also support the preparation of the necessary documentation, including justifications for import and evidence of medical need, which will be needed for securing import permits from regulatory bodies.

Education and Training for Healthcare Professionals

Providing education on shortage management to healthcare professionals ensures everyone is prepared to implement alternative therapies and manage patient expectations. Specifically for antimicrobials, Antimicrobial Stewardship (AS) programs are often mentioned in literature, and also evolves around education and training not only to manage, but also to prevent shortages. AS programs are coordinated activities to develop and measure optimal antibiotic use, helping healthcare professionals to use the right agent at the right dose, for the right time, and in the right way. These programs include, for example, trainings on the correct use of antibiotics, particularly the avoidance of excessive or frequent use of broad-spectrum antibiotics (97, 99, 100, 103). This can also help to reduce shortages while reducing the development of resistance mechanisms (95). While AS programs focus on antimicrobials, similar educational initiatives can also be adopted to other categories of medicines.

Communication matrix protocol and stakeholder engagement

Drug shortages can only be effectively managed through well-coordinated communication and stakeholder engagement at all levels of the health system. Local healthcare professionals, who are closest to the patient, play a critical role. The need for effective channels of communication among health care workers, regulators, suppliers and policy makers in order to allow coordinated responses is highlighted in multiple studies (96, 98, 100). Adapting a communication matrix protocol can ensure that stakeholders are contacted fast when they need to be involved in critical situations. The right protocols could ensure clinical and administrative teams within the organization coordinate effectively on resource allocation, and that healthcare authorities or supplies are contacted quickly and efficiently. This could be facilitated by an open access common reporting system that enables all stakeholders to access real-time information on stock levels and report shortages. Such a reporting system and communication matrix protocols would improve transparency and speed up the mitigation steps if shortages arise (95, 98, 100).

5. DISCUSSION

5.1. Quantitative analysis

The quantitative analysis demonstrated that the proportion of critical shortages relative to population size is higher in Europe than in other investigated regions worldwide. This affects every ATC group under examination, but anti-infective (J) and nervous system (N) drugs show drastically higher critical shortage levels in Europe. My research results agree with the 2018 study conducted by Videau in hospitals (18). In their findings Switzerland was one of the most affected countries, and Spain was the least affected country by shortages in both studies (18). In addition, the anti-infective medications were the most affected therapeutic group (18). The critical shortages of medicines on the WHO Essential Medicine List need to be reduced and prevented.

A pattern can be observed regarding the relative distribution of shortages across the investigated ATC groups, except for a few outstanding data points. It is in line with expectations based on the total number of critical shortages in Table 3 that the proportion of critical shortages per million people was significantly higher in Switzerland and Hungary in each ATC group, even compared to the European average. Similarly, the lowest proportion of critical cases for each ATC group was observed in the US. A pattern that can be observed is that the distribution of critical shortages across ATC groups for the US and Australia is relatively steady, and no ATC group shows significantly higher proportions of critical shortages. The opposite is true for Belgium, Hungary, and Switzerland, where the proportion of critical shortages is outstandingly higher in therapeutic groups J and N, anti-infectives for systemic use, and nervous system drugs. It is apparent that in European countries with high total numbers of shortages per population, these two groups are causing critical pharmaceutical gaps. These results are in agreement with the surveys from the EAHP (20) and the ASHP (104) , who state that in the group of anti-infectives, shortages are particularly an outstanding issue due to the high ratio of medication errors, the increasing AMR, the substandard patient outcome, and the lack of development of new antibiotics (105).

Table 5 demonstrates what percentage of all critical shortages are included on the WHO Essential Medicine List by country. The goal of every healthcare system should be to keep this ratio as low as possible, as a WHO essential drug being in critical shortage

would mean that the country has no domestic alternative to replace the medication, and an emergency import is necessary.

5.2. Qualitative analysis

5.2.1. Causes of drug shortages

The three root causes identified behind drug shortages are Business and Economic issues, Requirements of mature quality management systems, and Logistical and regulatory challenges. Based on exploring the various issues belonging to each root cause, it is possible to suggest action steps to governmental and regulatory bodies to decrease the number of shortages stemming from each of these problems.

Firstly, to address Business and Economic issues, incentives and potentially government subsidies would be necessary to ensure that essential drugs remain on the market even when it becomes less profitable to produce and market them. The concentration of markets (which often happens through mergers and acquisitions) should also be avoided, as if more than one MAHs supplies a product, there is a lower chance for a shortage. Reasonable market conditions, including foreseeable pricing, payback, and reimbursement mechanisms, would help keep MAHs in a particular market or willing to enter the market. When introducing cost-containment actions such as reference pricing or discounts to limit public expenditure on drugs, governments also need to analyse the potential impact of such economic pressure on MAHs to mitigate potential shortages in advance. In countries where parallel distribution is an issue (particularly EU markets because of the common market without domestic borders), setting and controlling quotas is necessary to ensure that the supply of drugs produced in a country is sufficient to meet local demand. If wholesalers don't respect these quotas and export more because higher profits are achievable abroad, the risk of domestic shortages can increase significantly. To also ensure that the utilisation of tendering practices doesn't contribute to shortages due to high dependency on a single winner, the process could also identify substitute providers, who are able to supply if the winner is not able to meet their obligations.

The second root cause, Requirements of Mature Quality Management Systems may be more difficult for governments and authorities to grapple with because these issues are less related to economic incentives. Mature cGMP compliant quality management systems are indispensable to ensure safe and effective drug supply; however, rigid

requirements can unintentionally amplify supply chain challenges, particularly during voluntary recalls and manufacturing problems. Regulators could take a risk-based approach and offer conditional waivers or extensions for minor non-compliances with no patient safety implications. For good practice, one example can be that of the Hungarian Health Authority, the National Center for Public Health and Pharmacy (native abbreviation NNGYK) which may allow to put a specific batch onto the market even when it only formally differs in comparison to marketing authorisation guidelines but is still safe for market. The process and other related matters are set out in 35§ of Decree No. 52 of 18 November 2005 of the Minister of Health (106). Another way to address such root causes of drug shortages would be offering a financial incentive or tax rebate for manufacturers who invest in new equipment, technology, and personnel training. This could encourage MAHs to maintain higher production standards without compromising supply.

For the third root cause, Logistical and Regulatory Challenges, health authorities and governments should aim at making supply chain processes more efficient to reduce regulatory bottlenecks. The simplifications and harmonisation of regulatory requirements across countries could accelerate the movement of products across borders, minimizing the time and resources required to ensure compliance. In addition, governments could incentivize the development of more comprehensive supply chain management by encouraging manufacturers to rely on dual sourcing and maintain emergency stockpiles for critical drugs. Better communication between manufacturers, distributors and regulators could also help enable a quick reaction to sudden disruptions. New communication channels should be established where all stakeholders can quickly and efficiently be made aware of disturbances in supply. The use of risk-based approach can also help in expediting regulatory approvals such as approval or renewal of MAs. By mitigating the regulatory time lags and improving coordination in the supply chain, authorities have an opportunity to create a more resilient system with greater ability to absorb shocks such as natural disasters and rapid changes in demand.

When looking at the differences between the US and Hungary comparing the root causes of shortages, it is evident that the dominating root causes are quite different. While in the US, the two main driver of shortages are manufacturing and quality problems (64%) and the shortage of raw materials (27%), while shortages in Hungary are mostly caused by

business and ecconomic issues (63%), and manufacturing problems only account for less than third of shortages (27%). Such differences can be influenced by distinct regulatory environments, market structures, and supply chain dependencies. The US has a larger and more diverse pharmaceutical industry, but its heavy dependence on imported active pharmaceutical ingredients (APIs), particularly from countries like China and India, makes the market vulnerable to global supply chain disruptions. In Hungary, the pharmaceutical market is smaller and more centralized, often relying heavily on imports from larger manufacturers within the EU, which can be affected by cross-border regulatory issues (e.g. parallel export).

5.2.2. Centrally managed shortage management strategies

The analysis of drug shortage management strategies highlighted significant variability across the examined countries. Six categories of shortage management practices were identified, which are present in each of the countries, and are managed centrally by regulators or health authorities: compulsory stockpiling, measures for essential medicines, notification responsibility, measures affecting wholesalers, export bans, and emergency imports. This discussion synthesizes overarching insights from these six categories of measures, identifying key themes that can inform the further development of both national and international shortage management guidelines.

Firstly, a proactive planning and prevention approach was essential across all categories. Compulsory stockpiling (e.g. the National Medicine Stockpile in Australia) demonstrates how advance preparation ensures a safety net for critical medicines during supply disruptions. The US notification system also is a best practice in this regard, where early reporting of potential shortages is required, allowing authorities to proactively mitigate. Periodic risk assessments of the supply chain as required by the FDA for MAHs can also help identify vulnerabilities and prevent critical shortages. These practices demonstrate the importance of anticipation to detect and mitigate risks before they evolve into crises.

Moreover, shortage management should be flexible and risk-based to prioritize resources and interventions. Examples of this flexibility include Spain approving medicines with labelling in other languages or shorter shelf lives to fill urgent needs, or the FDA expediting reviews for alternative generic applications in the US to mitigate shortages. Such flexible responses work best when underpinned by a risk-based framework, which

allows allocation of the limited resources to high-priority cases, such as essential medicines with no available alternatives. Agility and systematic prioritization allows drug shortages to be addressed efficiently.

To enable such a risk-based approach, defining and prioritizing essential medicines is highly important. The WHO Model List of Essential Medicines should be internationally adopted as foundation of the list of essential medicines. All discussed shortage management strategies are especially critical when essential drugs are in shortage. Some of the best practices for the priorisation of essential medicines is in Spain, where MAHs must maintain production and commercialization for essential medicines, facing penalties for non-compliance, and the US, in which FDA may assist in establishing a new manufacturing site if production of an essential medicine was endangered. In addition, essential medicines are included in strategic stockpiling programmes in Australia and Switzerland to ensure access to them if supply chain disruptions occur.

Finally, transparency is a repeated features of successful shortage management strategies. Robust, reliable reporting systems accessible at all levels of the supply chain can enable stakeholders to identify and respond to shortages quicky by collaboration. The US demonstrate some best practices with its well-defined criteria for reporting shortages. MAHs are obliged to inform the FDA at least six months before stopping the manufacturing of single-source or essential medicines, providing authorities an opportunity for proactive action. It is likely that this system, used together with the periodic risk assessments that MAHs needed to perform contributed to the US having the lowest rate of critical shortages per million people, as there is a lower change that shortages escalate to be critical. On the other hand, in the EU there are no unified definitions or reporting systems, which makes it hard to address shortages efficiently and also holds back coordination across borders to mitigate shortages. The European Medicines Agency (EMA) has taken significant steps to close this gap. The 2019 EMA guidance aims to harmonize definitions of shortages and reporting practices across the European Union, while the “Good Practice Guidance for Communication to the Public on Medicines’ Availability Issues” presents a framework to support transparent communication with healthcare professionals and patients. If fully implemented, these efforts could improve the EU's ability to address shortages more effectively.

5.2.3. Inpatient shortage management strategies through the example of antibiotics

The assessment of how antibiotic shortages can be handled by healtchcare professionals on the inpatient level highlights the need for local actions to address drug shortages and how they can complement central actions described above. Five key local measures were identify to mitigate shortages locally: Therapeutic alternatives and protocol development, Prioritization and allocation policies, Emergency import, Education and training for healthcare professionals, and Communication matrix protocols. From these results, some key learnings can be highlighted.

Firstly, central guidelines are needed for local measures to function. Such central guidelines have to provide some flexibility for local action, for example the production of magistral medicinal products if the active ingredient is available, or the ability to initiate emergency imports locally. With a risk-based approach, the guidelines can be set to ensure that these measures are implemented in an orderly and safe manner. Central frameworks can offer pre-defined criteria on when certain local mitigation steps should take place, reducing the need for local teams to spend time assessing risks on a case-by-case basis. This would accelerate decision-making and reduces the risk of errors from inconsistent or ad hoc risk assessments. Risk factors that can be used as criteria for evaluation include the extent of the shortage, the importance of the affected drug in treatment and characteristics of patient population at risk. For example, drugs without therapeutic alternatives pose a higher risk and may require immediate action. Additionally, patient-specific factors such as age, comorbidities and allergic profiles need to be taken into consideration when deciding how quickly the intervention needs to occur and in what form. The risk of poor outcomes including treatment failure or emergence of resistant strains can also inform prioritization. A centrally designed framework enables local practitioners to assess the risks and implement focused actions faster.

The findings also reflect that communication is key in drug shortage management, both with other domestic actors and internationally. On a local level, effective communication between healthcare facilities, regulators and local suppliers is needed for early identification and rapid management of shortages. To enable this, communication matrix protocols should be set up and followed. Such protocols could provide details on relevant contact points for each category of shortage, allowing healthcare professionals to quickly

reach out to the right parties and reduce the time needed to procure alternatives or redistribute existing stock. When local shortages could be filled with medicines available in foreign markets, cross-border communication can also become critical, while the regulatory requirements of multiple jurisdictions have to be navigated. Unified national reporting systems based on shared definitions and guidelines would make such international communication possible. Still, it was demonstrated earlier that in the European Union, shortage reporting systems are based on totally different definitions and requirements. Having these systems harmonised and interconnected would aid both local-level and international efforts by providing up-to-date data on the areas affected by shortages and where resources could be available, thus enhancing transparency and speeding up decision making.

5.3. Limitations

5.3.1. Quantitative analysis

The quantitative research has some limitations that confine the findings to the high degree of incomparability of data on drug shortages across countries. Since the reporting criteria and the reporting systems used in the various countries studied differ greatly, it has been difficult to establish a comprehensive comparison of national shortages. European countries are over-represented in the study, as the focus was identifying best practices that could be adopted for the European Union – therefore, analysing practices that are already present in one or more of the European countries was prioritised.

The quantitative analysis period of six days (March 4–9, 2021) also limits the representativeness of the findings. This timeframe shows only a "snapshot" of drug shortages instead of trends in an extended period. As a result, my thesis may not fully represent the precise dynamics of shortages in the six countries or the effectiveness of the implemented central management mechanisms. This analysis does not contain deep statistical research to support insights because only publicly available databases, which contain fragmented and categorical data across different countries, could be relied on. Standardized, open access, real-time databases containing numerical data (such as duration of shortage, costs of alternative therapy, number of patients using the drug, and quantified effectiveness of adopted countermeasures) would be required for more rigorous statistical assessment. Although the binomial probability test was performed, as

the data sampling was not random, the generalizability of the results can be limited, as it cannot be fully excluded that some shortages are dependent due to the same root causes. Standardization with population may introduce bias in the calculated ratio of shortages and critical shortages as the underlying causal factors driving drug shortages may be similar across European countries and the United States, regardless of population size.

The definition of reported shortages can create large discrepancies in the analysis, e.g. in Spain shortages do not appear on the report if a "quick solution is at hand" which may significantly change results of cross-country comparisons. The lower proportion of critical shortages in Australia may be attributed to the definition of complexity, which takes into account the number of alternatives and resultant impact on patients. In Switzerland and in the US, there are multiple shortage databases with different objectives supported by various authorities (FDA and ASHP) or organizations (Federal Office of Public Health, Swissmedic, Federal Office for National Economic Supply Martinelli Consulting). This lack of standardized definitions and reporting has resulted in enormous differences in databases which has ultimately limited the ability to generate a clear, transparent international comparison.

5.3.2. Qualitative analysis

The analysis on the root causes of drug shortages also has several limitations. As it is based on literature, it might not capture the full complexity of current shortages, and the use of historical data can lead to overlooking emerging trends. Moreover, the qualitative method introduces some subjectivity, particularly in categorizing overlapping root causes. The broader applicability of the findings is limited as they centre largely around the US and Hungary. The weight of each root cause, or their significance over time was also not studied. These limitations highlight the necessity for additional research utilizing real-time data and wider contextual investigations.

The analysis on central drug shortage management strategies is also subject to several limitations. First, the scope is limited by published data availability and quality as some countries do not have comprehensive documentation on measures. This gap limits the ability to draw fully representative conclusions. Studying only six countries can overlook greater diversity in other regions (especially low- and middle-income countries). The analysis also focuses on legal and regulatory frameworks, which might not reflect the

effectiveness of these measures in practice. It also doesn't consider important contextual factors, including healthcare system structures, economic conditions and cultural differences that will inform the implementation of these measures. While best practices have been identified within this study, there is no quantitative assessment of their impact which prohibits understanding which strategies are most affective.

The analysis of local antibiotic shortage management also has some limitations. The exclusion criteria, such as focusing only on antibiotic shortages has limited the comprehensiveness of the findings. Furthermore, the differences in design, scope and reporting among studied articles led to a challenge in synthesizing consistent conclusions. Comparisons are complicated by differences in the timeframe of shortages, the number or type of antibiotics considered, and healthcare settings. As with the analysis of centrally driven shortage management practices, the qualitative approach did not allow us to provide a quantitative assessment of the impact and effectiveness of measures. Further research could address the effectiveness of different shortage management strategies, including quantification.

6. CONCLUSIONS

Drug shortages are a global threat to health systems and the safety of patients. The proportion of critical medicine shortages relative to population size is much higher in Europe than other regions investigated, anti-infectives and nervous system drugs being particularly affected. These results suggest that shortage management should prioritise essential medicines. Although the definition of essential medicine is not unified, the WHO Model List identifies them as drugs that are critical for addressing the most pressing health needs. Adopting this list as an international benchmark to identify essential medicines could assist regulators in prioritizing action to maintaining their availability and minimise the risk of their shortages.

The root causes of drug shortages can be categorised into three groups: business and economic issues, quality management challenges, and logistical and regulatory challenges. Proactive measures addressing these issues can significantly mitigate shortages. For example, incentives to retain low-margin essential pharmaceuticals in the market, dual sourcing to mitigate over-dependency of single manufacturers, and parallel export regulation can address business and economic issues. To tackle quality management challenges, governments can provide tax benefits or grants for upgrading manufacturing facilities, while regulators can introduce a risk-based approach that allows conditional approvals for minor non-compliance if safety is not compromised. Logistical issues, especially regulatory time lags, can be mitigated by harmonizing international requirements, simplifying cross-border regulations, and speeding up the approval or renewal of marketing authorizations, ensuring faster responses to sudden supply chain disruptions. Together, these measures can prevent shortages from arising, or mitigate them at their roots.

Shortage management requires a dual-level approach, combining centralized and local actions. Central regulatory bodies play a key role by implementing measures such as mandatory stockpiling, stringent notification systems and risk-based regulatory frameworks. Shortage management responses of regulatory bodies in the EU could be taken to the next level by adopting the EMA's guidelines which aim at harmonizing definitions, reporting, and communication guidelines, which would facilitate cross-border coordination. Regulatory bodies should also develop risk-based frameworks and

guidelines that allow systematic responses of local stakeholders to help the mitigation of shortages.

Local healthcare professionals complement these efforts by implementing targeted interventions, particularly when critical shortages arise. Risk-based central frameworks should grant the flexibility to act locally, but also ensure the safe execution of local measures such as prioritization policies, substitution with magistral products, or emergency. Effective communication matrices are needed, both within and across borders, to ensure real-time updates on shortages and facilitate efficient resource redistribution. Collaboration between central and local levels ensures that shortages are addressed systematically, with high-risk patient groups being prioritised.

Healthcare systems can build resilience against drug shortages by fostering transparency, risk-based prioritization, and robust communication among stakeholders. Coordinated responses are necessary to mitigate the impact of shortages, ensuring continuity of care, and maintaining the availability of critical medicines for patients globally.

7. SUMMARY

This dissertation addresses the global challenge of drug shortages, which can disrupt healthcare delivery, compromise patient safety, and place additional burdens on the entire pharmaceutical supply chain. The lack of essential medicines has the largest impact on treatment outcomes, so their shortages constitute a particular threat. Understanding the root causes of drug shortages and how to mitigate them, as well as identifying best practices among shortage management strategies are critical for improving healthcare resilience and safeguarding patient outcomes.

A mixed-methods approach was chosen, combining quantitative and qualitative analyses. The quantitative analysis compares drug shortages across six countries—Hungary, Belgium, Spain, Switzerland, Australia, and the United States. It examines the frequency and severity of shortages, particularly in four therapeutic categories most affected by critical shortages. Findings reveal substantial disparities in shortage rates and reporting systems, with European countries experiencing higher proportions of critical shortages per population. Anti-infectives and nervous system drugs appear to be particularly affected, as they demonstrate a higher proportion of critical shortages compared to other ATC groups.

The qualitative analysis explores the root causes of shortages, with business and economic issues, requirements of mature quality management systems, and logistical and regulatory challenges being the three main categories of root causes. It is also discussed how each of these causes can be addressed, so shortages are prevented or mitigated early on. Furthermore, shortage management strategies are also studied. Best practices are identified both among centrally managed measures for regulatory bodies and locally managed measures for healthcare professionals.

The dissertation concludes with recommendations for addressing pharmaceutical shortages through a combination of harmonized international practices and adaptable local solutions. Standardized definitions and reporting systems, and clear collaborative frameworks would enable stakeholders to reduce the number of shortages. Together, these measures can help health systems maintain access to essential medicines while also increasing resilience against future supply chain challenges.

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9. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

9.1. Publications related to the PhD thesis

Turbucz, B.; Hankó, B. Overview of the Causes and Management of Drug Shortages in the United States and in Hungary. Acta Pharm Hung 2020, 90, 170-184.

Turbucz, B.*;* Major, M.; Zelko, R.; Hanko, B. Proposal for Handling of Medicine Shortages Based on a Comparison of Retrospective Risk Analysis. Int. J. Environ. Res. Public Health 2022, 19, 4102. https://doi.org/10.3390/ijerph19074102

Lőrinczy, L.; **Turbucz, B**.; Hankó, B.; Zelkó, R. Managing Antibiotic Shortages in Inpatient Care—A Review of Recent Years in Comparison with the Hungarian Status. Antibiotics 2023, 12, 1704. https://doi.org/10.3390/antibiotics12121704

9.2. Publications unrelated to the PhD thesis

Magramane, S.; Pápay, Z.; **Turbucz, B**.; Antal, I. Formulation and Characterization of Pulmonary Drug Delivery Systems. Acta Pharm Hung 2019, 89, 63-83.

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