Sustaining pharmaceutical supply: strategies for mitigating and managing drug shortages

PhD thesis outline

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1. Introduction

Drug shortages occur when the available supply of drugs fails to meet end-user demand despite sufficient financial resources. Drug shortages affect most developed countries. Over the past decade, the frequency and severity of shortages have increased significantly. Drug shortages impact all stakeholders in the pharmaceutical supply chain, including Marketing Authorization Holders (MAHs), wholesalers, hospitals, pharmacies, and patients, jeopardizing treatment outcomes. Delays or substitutions in therapies can lead to medical errors, increased workload, and compromised patient welfare. Both essential and non-essential medicines are affected. Mitigating shortages is critical, especially for drugs on the WHO Essential Medicines and AWaRe lists, as their availability significantly influences treatment outcomes. The therapeutic areas most affected are oncology, anti-infectives, cardiovascular, central nervous system and pain management, and generic injectables. Despite being a global issue, drug shortages lack a universally accepted definition, complicating data collection and cross-country comparisons. Standardized international guidelines are crucial to bridging this gap, and Health Authorities are key in ensuring pharmaceutical supply continuity and addressing disruptions. While global initiatives have appeared to monitor and mitigate shortages, greater international coordination is needed. Effective global mitigation strategies can be developed by understanding the multifactorial causes and identifying adaptable best practices. This study examines critical shortages, root causes, and management practices across selected countries at both central and local levels.

2. Objectives

The objectives of the dissertation can be divided into 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 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 and critical shortages, identify which ATC groups are most affected, and quantify the challenges different regions face.

2.2. Objectives of the qualitative analysis

The qualitative analyses focused on three objectives. The first objective is to identify and categorize the factors causing drug shortages through a systematic literature search.

The second objective is to analyse centrally managed mitigation strategies (regulatory bodies or governments) to identify best practices in shortage management.

Finally, the third objective of the qualitative analysis is to study local shortage mitigation measures that healthcare practitioners can carry out at the inpatient level thorough the examination of antibiotic shortages.

3. Methods

3.1. Quantitative analysis

I have selected six countries for a comparative quantitative analysis to understand the ratio of total and critical shortages in the selected ATC groups. As a next step, databases were processed focusing on selected therapeutic categories. 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

First-world countries have a profound pharmaceutical industry, a publicly available reporting system, and a system for classifying reported shortages according to the Anatomical Therapeutic Chemical (ATC) classification system. Databases of the selected countries must contain information regarding available substitutes indicating discontinued presentations separately from current shortages.

3.1.2. Therapeutic area selection

These four ATC groups have been selected for analysis, as these categories of medications play a significant role in the therapeutic arsenal:

Group C: Cardiovascular system

Group L: Antineoplastic and immunomodulating agents

Group J: Anti-infectives for systemic use

Group N: Nervous system

The pre-examination of the data also confirmed the selection of these groups, which showed higher proportions of these ATC groups among others.

3.1.3. No unique common definition for drug shortage

To process analogous and comparable information, databases were accessed in the one-week time period between March 4th and 9th, 2021 and involved only current shortages. In Hungary, Belgium, Spain, and Australia, one national database was available, managed by the HAs. In the US, the ASHP database has been chosen, as it contains more details regarding the available substitutes compared to the FDA reporting system. The Martinelli database was chosen as the national HAs database in Switzerland, focusing only on a narrow medicine scale.

3.1.4. Risk Assessment of Critical Shortages

All the posted products "currently in shortage" were investigated individually. The following criterion was set: if no domestic alternatives were available, the shortage was considered critical, as emergency imports would be necessary. In Belgium and Australia, the database already included information regarding the severity, which has been augmented to match the criteria applied for all other countries.

3.1.5. The bias-reducing steps

Three bias-reducing steps have been performed to obtain comparable data:

- Transforming the data into population-proportionate figures.
- Filtering out critical cases from all shortages.
- Comparing critical cases with the WHO Essential List.

These steps were necessary due to the lack of uniform definitions, reporting systems, and severity assessments. To avoid significant population bias, we calculated the ratio of

critical shortages relative to the country's population, rather than simply comparing the raw numbers of shortages. This ratio was determined by the number of shortages per million people.

3.1.6. Binomial Probability

For statistical analysis, the variable Critical_BI was defined, which is an indicator variable with a value of 1 for critical shortages and 0 for non-critical shortages. The null hypothesis was that the proportion of critical shortages would not significantly differ across ATC groups. As the final step, critical shortages were compared to the WHO Essential Medicine List.

3.2. Qualitative analyses

The first objective of the qualitative analysis focused on identifying the factors causing drug shortages. Between September 19, 2020, and October 12, 2020, a search through Google Scholar and Pub Med was conducted to gain a thorough understanding of the topic.

The second objective of the research focused on reviewing centrally managed shortage management strategies and identifying best practices. The search was conducted between March 2021 and June 22421. The analysis focused on strategies adopted by either government or regulatory bodies such as healthcare authorities. The analyst of the six countries selected for quantitative analysis.

Finally, the third objective was to investigate antibiotic shortages and identify locally applicable shortage-handling mechanisms. To this end, a systematic literature review was conducted to summarize the studies. The search began on September 27, 2022, and was last updated on July 15, 2023.

4. Results

4.1. Quantitative analysis

Figure 1 illustrates the shortages observed in the studied countries, encompassing both general and critical cases.

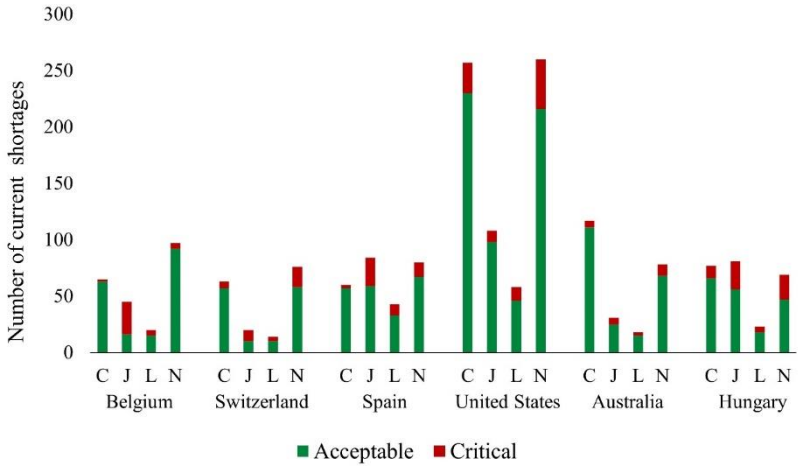

Figure 1: Number of shortages per country, per ATC group (critical and non-critical). C: Cardiovascular system, L: Antineoplastic and immunomodulating agents, J: Anti-infectives for systemic use, N: Nervous system (Turbucz, 2022).

As a result, Table 1 was developed. Column (d) of Table 1 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. The proportion of critical shortages per million people has been calculated in column (e) to reduce the

bias due to the population differences. 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 1: Number of shortages per million people in the studied countries, including critical cases (Turbucz, 2022).

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 2 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 indicated significant differences in the shortage proportions of certain ATC groups.

Table 2: Proportion estimation of critical shortages over the whole dataset. Binomial probability tests of the proportion of critical shortages across ATC groups (Turbucz, 2022).

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 2 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) was 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 the same as the average across the sample (17.0% vs. 16.9%). Looking at critical shortages per country and ATC group, Figure 2 reflects that the proportion of critical shortages per population is higher in every European country than the non-European figures (Figure 2).

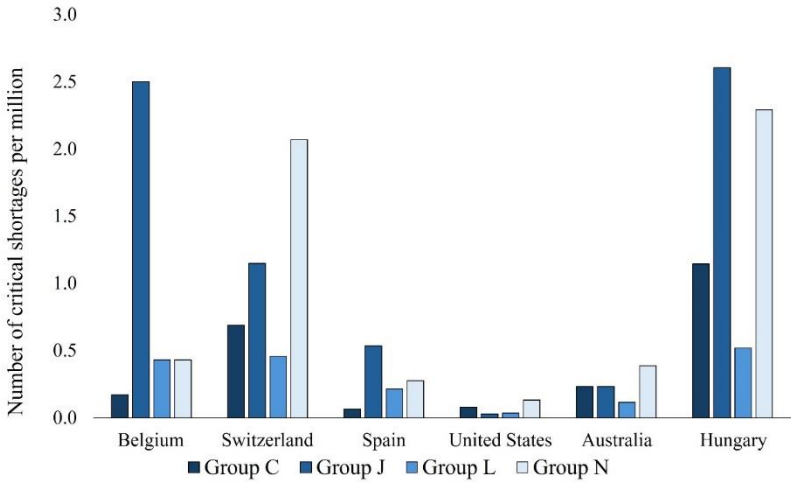

Figure 2: Comparison of critical shortages in various countries by ATC groups. C: Cardiovascular system, L: Antineoplastic and immunomodulating agents, J: Anti-infectives for systemic use, N: Nervous system (Turbucz, 2022).

Table 3 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 3: Summary of critical shortages of the examined countries according to the WHO Essential Medicine List (Turbucz, 2022).

Country	**No. of critical shortages/million people**	**No. of critical shortages on WHO Essential List/million people**	**WHO Essential/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. Shortages mainly derive from three root causes, according to Figure 3:

Business and economic issues.

- Business and economic issues.
- Requirements of mature quality management systems.
- Logistical and regulatory challenges.

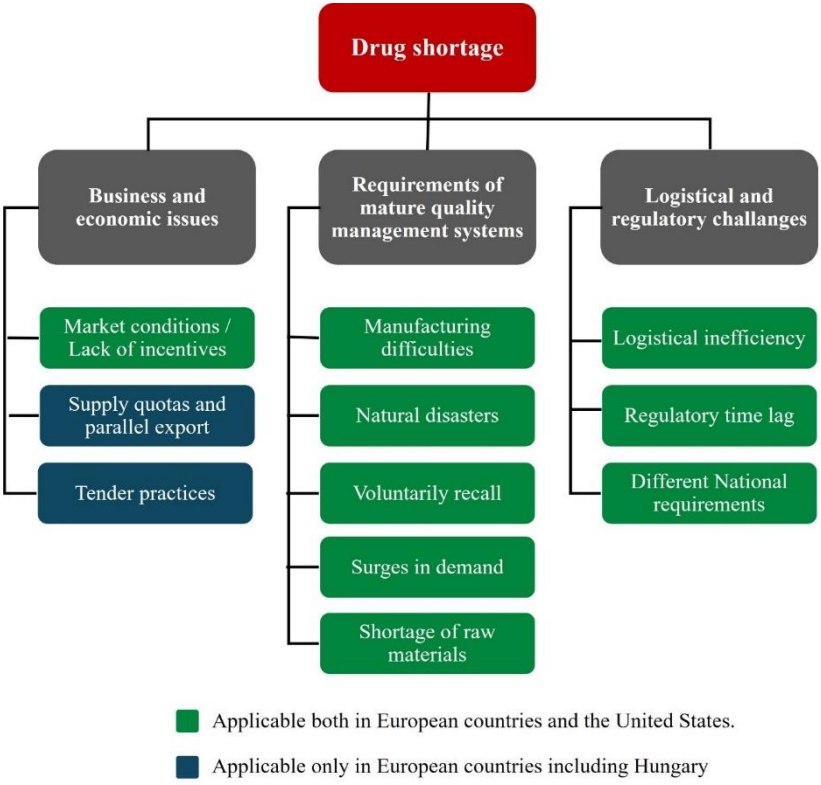

Figure 3: Potential root causes of shortages and derived factors (Turbucz, 2020).

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. 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 root causes that were only pertinent in the EU. On the other hand, no root causes were identified that would only be applicable to the US. 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 4.

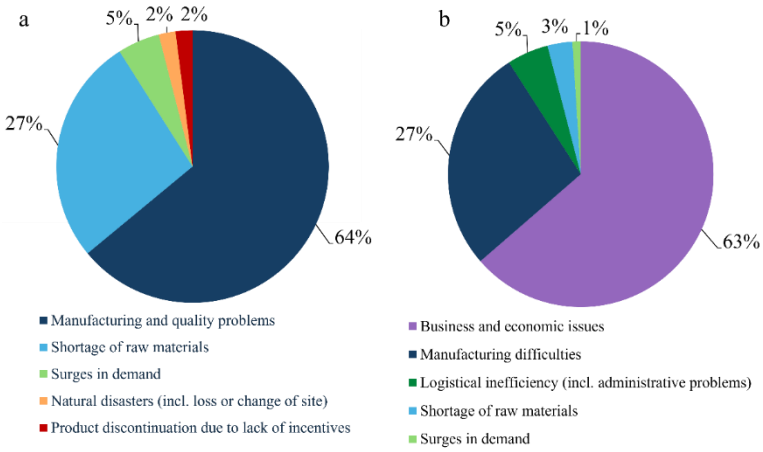

Figure 4: Causing factors behind the shortages reported by MAHs a) in the United States from 2013 to 2017 and b) in

Hungary from January 13, 2020, to January 20, 2020. (Turbucz, 2020).

In the United States, 64% of shortages were attributed to manufacturing and quality problems, which involve delays due to capacity issues and voluntary recall due to bacterial contamination or any other foreign matter found in the current batch. The second most reported root cause was a 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 for shortages are Business and Economic issues, which account for 63% of all shortages, indicating that this root cause poses a more severe risk there than in the US. Manufacturing difficulties also significantly impact Hungarian shortages, 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%).

4.2.2. Centrally managed shortage management strategies

This section analyzes shortage management strategies currently in place, focusing on six countries. The countermeasures discussed here are centrally managed by regulatory bodies or health authorities, not local actions of healthcare practitioners (Turbucz 2022).

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

Compulsory Stockpiling

The National Medical Stockpile in Australia must maintain "key medicines" to avoid critical shortages of essential drugs. A similar system exists in Switzerland, where the government defines medications subject to compulsory stockpiling.

Measures for Essential Medicines

In Spain, the government can demand production and commercialization from MAHs; in the US, the shortage management system works similarly. The regulation also permits hospitals within the same health facility to repackage drugs into smaller units to alleviate drug shortages.

Notification Responsibility

In the US, authorities maintain an apparent oversight of shortages. They, therefore, can handle them very effectively—the quantitative analysis 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 early and address them accordingly. 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”. The document contains communication guidelines for the national authorities and the EMA for patients and HCPs.

Measures Affecting Wholesalers

In Spain, all wholesalers are required to deliver within 24 working hours. 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.

Export Bans

In Australia, exports can only be performed by MAHs or designated distributors acting on behalf of the MAHs. In Spain, AEMPS can restrict the exportation of medicinal products without therapeutic equivalents. There are serious penalties and fines of up to 1 million euros for distributors who export medicines when this activity has been forbidden.

Emergency Imports

National laws determine the conditions of an emergency import. 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. In Belgium, wholesalers may also perform emergency imports from the EU based on a doctor's request in the specific quantities necessary for the treatment.

4.2.3. Inpatient-level shortage management strategies through the example of antibiotics

To explore these measures, I focused on a selected therapeutic group, antibiotics, 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. The high number of antibiotic shortages often arise from inappropriate and excessive prescribing and use, especially of broad-spectrum medicines, a decrease in bacterial susceptibility, and the development of antimicrobial resistance (AMR). These causes can be categorized under "Surges in demand" among the above-discussed root causes (Lőrinczy, Turbucz, 2023).

Therapeutic alternatives and protocol development

The initial step to tackle drug shortages is to find suitable alternative therapies currently available. Clear therapeutic exchange policies allow healthcare professionals to follow guidelines without wasting time on case-by-case research. Pure active ingredients may still allow customized local preparations if no alternative products are available. In Hungary, pharmacists can produce magistral medicinal products under official Pharmacopoeia regulations and Council of Europe standards for patient-specific needs. A risk-based framework could expand magistral medicinal production beyond GMP regulations. It would require oversight from Health Authorities and HCPs, focusing on manufacturing steps, validation, and physician-approved therapeutic protocols. While production outside GMP carries risks, the unavailability of essential medicines poses an even greater risk to patients.

Prioritization and Allocation Policies

When developing therapeutic protocols, healthcare professionals should assess preliminary risk factors like age, comorbidities, allergic profiles, resistance patterns, and concomitant medications. These factors can all inform patient-specific therapy planning. Healthcare professionals should review the patient's profile if shortage risk is high to identify potential alternative treatments. This approach ensures continuity of care while limited supplies are saved for those who need them most.

Emergency import

Emergency imports also serve as a local strategy to mitigate drug shortages when domestic supplies are insufficient. 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.

Education and Training for Healthcare Professionals

Educating healthcare professionals on shortage management ensures everyone is prepared. Specifically for antimicrobials, AS programs are coordinated activities to develop and measure optimal antibiotic use, helping healthcare professionals use the right agent at the right dose, for the right time, and in the right way. These programs include, for example, training on the correct use of antibiotics, particularly the avoidance of excessive or frequent use of broad-spectrum antibiotics.

Communication matrix protocol and stakeholder engagement

Local healthcare professionals, who are closest to the patient, play a critical role. Multiple studies highlight the need for effective communication channels among healthcare workers, regulators, suppliers, and policymakers to allow coordinated responses. Adapting a communication matrix protocol can ensure that stakeholders are contacted quickly when they need to be involved in critical situations.

5. Conclusions

This dissertation addresses the global challenge of drug shortages, which can disrupt healthcare delivery, compromise patient safety, and place additional burdens on the pharmaceutical supply chain.

The lack of essential medicines greatly impacts treatment outcomes, so their shortages constitute a particular threat.

A mixed-methods approach was chosen, combining quantitative and qualitative analyses.

The quantitative analysis examines the frequency and severity of shortages in six selected countries, particularly in the 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, including business and economic issues, requirements of mature quality management systems, and logistical and regulatory challenges. 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 shortages through harmonized international practices and adaptable local solutions.

Standardized definitions, reporting systems, and clear collaborative frameworks would reduce the number of shortages. Together, these measures can help health systems maintain access to essential medicines while increasing resilience against future supply chain challenges. These measures could enhance access to essential medicines and strengthen supply chain resilience.

6. Bibliography of the candidate's publications

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