



DRUG SHORTAGES

The Dynamics of Drug Shortages



CONTRACT RESEARCH REPORT
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Executive Summary

Drug shortages are an industry-wide problem. Numerous factors may be considered as contributing to drug shortages across the globe. Countries apply different processes and measures aiming to reduce the likelihood of a drug shortage and secure the future supply of medicines. However, the scale of the drug shortages issue, as well as its characteristics and drivers, have not been adequately investigated.

This report seeks to identify the causes, characteristics and scale of the drug shortage issue, focussing on the United States (US), Canada and the European Union (EU) Furthermore, we explore the measures governments and policymakers are currently taking to tackle the problem, and propose ways of addressing the underlying causes to contribute to the policy debate.

i. Finding the drivers of drug shortages

By carrying out a review of the relevant literature we document the types of drug shortage and identify their drivers, with the aim to create a starting point on what is causing these shortages.

According to the literature, the main types of drug shortage are:

1. **Disease and therapeutic area related shortages** (e.g., referring to oncology drugs, antibiotics and life sustaining/preserving drugs).
2. **Market and drug type related shortages** (e.g., referring to biosimilars and generics, injectables, on-patent drugs).

We also capture the most prevalent drivers of drug shortages which are the following:

TABLE 1: Drivers of drug shortages.

Drivers of drug shortages
Price Erosion
Supply Issues
Characteristics of the Generic Drug Market
Parallel Trade
Demand Issues
Tendering
Regulatory Issues

Source: Authors' ranking based on frequency and importance in the literature.

Moreover, we investigate and capture some of the policies that governments consider when a drug shortage occurs. We find that governments globally have been considering and implementing policies in recent months and years, attempting to address the underlying causes of drug shortages.

Below is a summary of the main EU, US and CA government responses.

FIGURE 1: Summary of government policies to tackle drug shortages.



In summary, the first part of this report suggests that:

- **Drug shortages occur globally**, across a range of therapeutic areas, but **appear to be mostly centred around the generic and biosimilar markets**.
- **The causes of drug shortages are interlinked, multifactorial**, with the **root cause often difficult to establish**.
- **The issue of low prices in the generic and biosimilar markets appears to be a key driver of drug shortages**, often underlying the causes of drug shortages.
- **Since the COVID-19** pandemic, where drug shortages have become more of a critical issue, **governments globally have been making efforts to address them, with several policy proposals** attempting to address the underlying causes. (The success of these policies has not been established yet).
- **Drug shortages can have a large economic and health impact on patients**.

ii. *Mapping of drug shortages*

In this part of the report, we:

1. **Analyse drug shortages databases to document and compare shortages** in order to identify trends, commonalities, or differences.
2. **Conduct sub-analyses** of drug shortages based on specific characteristics.
3. **Create a shortage framework** for examining trends in drug shortages and explore further through **case studies**.

- Data availability from the drug shortage databases across the three jurisdictions studied varied. All databases record the shortage reason, therapeutic area, shortage status, and drug presentation. However the EMA database does not record the companies suffering the shortage and only records shortages affecting multiple EU countries.

The **analysis of drug shortages characteristics and their differences across regions**, shows that:

- **Increases in the demand for drugs**, and the **disruption of manufacturing or discontinuation by the manufacturer**, are cited as **key reasons** for drug shortages across all the examined regional databases.
- In the **USA there are an average of two manufacturers per drug (experiencing a shortage) and almost three in Canada**, highlighting the potential vulnerability of the drug supplies.
 - In the USA, at the time of the analysis, the top three companies experiencing the most shortages had 267, 263 and 251 shortages, respectively.
 - In Canada, at the time of the analysis, the top three companies experiencing the most shortages had 2,671, 2,324, and 1,586 shortages, respectively.
- **Pediatric, Gastroenterology, Anesthesia, Nervous system, Cardiovascular and Anti-infectives are the main therapeutic classes experiencing shortages**, although there are many shortages across a range of therapeutic areas.
- In the **US and Canada, approximately 92% of shortages are for non-oncology drugs, while in Europe this is 87%**.
- **Off-patent medicines appear to be most affected**, particularly in the USA and Canada, **accounting for more than 95% of the reported drug shortages**.
- **59% of the drug shortages in the EU are biologics, compared to just 7% and 4% in Canada and USA**, respectively.
- The **EMA database records shortages affecting multiple EU countries**, but likely underestimates the scale of the problem. **During 2023, there have been 522 and 675 new shortages reported in Italy and Spain**, respectively, compared to only 10 shortages in 2023 in the EMA database.
- The **duration of a shortage** has been estimated for each region: **18 months in the USA, 5 months in the EU, and 1 month in Canada**.
- **USA seems to be heavily affected by the long duration of drug shortages**, particularly as the estimate is **2.5 times more** than reported in previous years.
- **The occurrence of drug shortages is an industry-wide problem**. Shortages are **caused by a wide range of disparate factors** not explored in detail in our study, which include active ingredient shortages, vile shortages, and supply chain issues, among other things. Among the market-based factors that we explored, we found that **price erosion is likely a strong explanatory factor driving the shortages**.

As a starting point to find solutions, we propose a framework to examine trends and explanatory factors for drug shortages based on five factors: the **price change of the originator, price change of other products with the same molecule, the market concentration, demand and competition, and patent expiration**. We apply the framework to **real-world case studies** of shortages.

In summary, the second part of this report suggests that:

- **Increased medicine demand**, particularly in recent years, as well as the **disruption or discontinuation of product manufacturer**, are identified as **major causes of drug shortages**.



- **Pediatric, Gastroenterology, Anesthesia, Nervous system, Cardiovascular and Anti-infectives** are the main therapeutic classes experiencing shortages, although there are many shortages across different therapeutic areas.
- **Infusion and Injectables followed by Tablets and Capsules** are the **most common drug presentations** to experience drug shortages.
- The **duration** of shortages has either **increased or remained the same**.
- **Price erosion does not appear to be driven by competition between manufacturers**, since the markets are highly concentrated, but instead from other dynamics that are captured in the literature (e.g., tenders).
- All the **identified factors in the literature and in our framework are related to price erosion either directly or indirectly** and therefore **price erosion is likely to be one of the most significant drivers of shortages**.
- Most **shortages affect off-patent drugs with low prices**. This means that **unattractive markets are leading to oligopolies, increasing the shortage risk significantly as there are no alternatives and no bandwidth for the other manufacturers** to pick up all the volumes.

1. Introduction

Drug shortages have affected healthcare systems for decades. Since the COVID-19 pandemic, it has risen as a critical topic, with an increasing burden and incidence across Europe and North America.

In the US, a Senate report described the drug shortages situation and how this has compared to previous years ([US Senate Committee on homeland security & governmental affairs, 2023](#)). The report indicated that there has been a growth in both the number of shortages and the impact of these shortages.

Between 2021 and 2022, drug shortages grew by close to 30% to a total of 295 active shortages, marking a five-year record. In addition, the shortages impacted patients more heavily compared to previous years, with the situation being described as an “*unacceptable national security risk*” ([US Senate Committee on homeland security & governmental affairs, 2023](#)).

In 2019/20, shortages were reported for 29% of the medicines sold in Canada (Canada, 2022). Generic drugs and drugs with a low treatment cost (<\$10,000/year) were found to have higher rates of drug shortages (Canada, 2022). Thus, addressing shortages of drugs and other health products is one of the government’s primary aims. In particular, for critical health products in shortage, such as children’s pain and fever medications (Health Canada, 2023).

In England, a record high of 165 drugs were out of stock in December 2022, according to MIMS drug shortages tracker. This represents a 30% increase compared to the same period last year (Eversana, 2022b). Additionally, data from the Medicine Shortages Index show that shortages in Ireland are worsening, as the number of out-of-stock medicines has risen to 247, following incremental increases over the past months (Azure Pharmaceuticals, 2023).

In Europe, the generic drug supply chain is said to be under huge pressure. Medicines for Europe (MFE) reported that 26% of generic medicines, 33% antibiotics, and 40% of cancer medicines in the last 10 years are no longer on European markets (Eversana, 2022a). This is said to be caused by unsustainable pricing policies, placing huge pressure on the resilience of the supply chain.

Effects of drug shortages on patients

Drug shortages have been found to have adverse economic, clinical, and humanistic outcomes on patients (Phuong et al., 2019). For example, patients were commonly reported to have increased out-of-pocket costs, rates of drug errors, adverse events, mortality, and complaints during times of shortages (Phuong et al., 2019).

The selection of alternative therapies is common practice when a shortage occurs. However, this may create safety concerns, due to adverse events from the alternative therapies or medication errors (McLaughlin et al., 2013). Also, a change in the treatment regime, as a result of a shortage, may lead to worse clinical outcomes, even when a promising substitute is available (Metzger, Billett and Link, 2012).

This report has three aims. Firstly, to identify and examine the drivers of drug shortages and relevant policies to tackle them. Secondly, to analyse drug shortage databases and document trends and characteristics of shortages in different regions. Finally, to create a shortage framework for



examining trends in drug shortages, validated by case studies with the aim to signal potential solutions.

In section 2 of the report, we examine the landscape around the drivers of drug shortages and document the types/reasons for drug shortages found in the literature. This enables us to identify and list the drivers around drug shortages, creating a starting point for the analysis. We investigate the policies that governments consider when a drug shortage is in place, particularly in the grey literature.

In section 3, we analyse drug shortages databases to document and compare shortages in order to identify trends, commonalities, or differences. Furthermore, we conduct sub-analysis of drug shortages based on specific characteristics and we create a shortage framework for examining trends in drug shortages and validate it through case studies.

2. Finding the drivers of drug shortages

In this section, we present the methods and findings regarding the types and reasons of drug shortages, as well as their drivers and indicative government policies to tackle them.

2.1 Methods

2.1.1 Targeted literature review

We conducted a targeted literature review. This approach allows us to collect evidence systemically whilst simultaneously applying search criteria restrictions. Overall, this review shows that drug shortages are a multi-factor issue and ultimately will help stakeholders in designing policy proposals to eliminate and/or managing shortages.

Scope

The main objectives of this literature review were to:

1. Document the types/reasons for drug shortages,
2. Identify and list the drivers around drug shortages and create a starting point on what is causing these shortages.
3. Investigate the factors that governments consider when trying to address shortages or the reasons underlying them, including their criteria for decide to forcing a fine on companies with drugs in shortage.

Inclusion and exclusion criteria

We conducted a preliminary search based on reviewing the titles and abstracts of potentially relevant papers.

Search strategy and databases

We considered articles published between January 2013 and May 2023 in journals indexed in Web of Science, Medline, Scopus and EconLit, amongst others, to capture literature and analysis from different research perspectives (economic, public policy, medical and others). In addition, we conducted a targeted review of sources of data and key websites (news, grey literature) and expert authors.

TABLE 2: Details of the search strategy.

Domain	Search commands	Database information	Search criteria
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Drug shortages	(drug shortages (AND (biologic OR biosimilars OR small-molecule OR branded medicines OR generics))) AND	Google Scholar hits: 9,540 Google Scholar	Since 2013, title and abstract relevance, relevance sorting, and keywords represented in the main analytical level of each study, and removal of duplicates, based on the first 10 pages of the search results. Search date: 09 May 2023
	(price erosion OR cost-containment OR supply OR supply continuity OR supply capacity OR procurement route OR competition OR drug shortage cause OR shortage reason OR drug shortage characteristics OR government policy OR government fine OR Europe OR Asia OR United States of America OR Canada OR Africa OR Oceania)		

Evidence assessment

After applying our search criteria we screened the first 100 hits, and shortlisted 69. To do so, we applied a colour scoring assessment (Table 3) to document the most critical and relevant publications. With this approach, each identified publication was assessed using two criteria: publication quality and relevance. This process is designed to provide an objective assessment, inform our decision-making, and provide transparency regarding the basis for our decisions. From the total of 100 examined papers, 31 had either a red colour scoring in both of the criteria or red colour scoring in the one criterion and amber in the other. Finally, the papers that we shortlisted were colour scored green or amber in both of the criteria or green in the one criterion and amber in the other one.

TABLE 3: Evidence assessment criteria.

	Green	Amber	Red
Publication quality	Mainly peer-reviewed papers in top field journals, journals with an impact factor of more than one, highly cited and field expert authors	Mainly peer-reviewed papers with an impact factor of less than one; less established journals, academic working papers and reports	Mainly journalism, media news, blogs, etc. on drug shortages
Publication relevance	Drivers of drug shortages, price erosion and supply chain in the selected regions	Drivers of drug shortages, price erosion and supply chain in other regions	Mainly journalism, media news, blogs, etc. on drug shortages

2.2 Results

2.2.1 Types of drug shortages

As a first step in this analysis, we document the types of drug shortages found in the literature. Table 4 presents the types of shortages, which fall under Disease and Therapeutic Area and Market Dynamics or Drug Type related shortages. Those listed under them and are in bold, appeared the most frequently in the literature. The rest are ranked based on frequency and importance in the literature.

Oncology, and life sustaining/preserving drugs more generally are ranked as the most important drugs in shortage in terms of disease and therapeutic area and they were discussed in approximately 15 papers. Regarding the Market and Drug Type related shortages, the most frequent and important shortages found in the literature are those related to biosimilars, generics and injectables. These were discussed in 45 out of the 69 shortlisted papers.

TABLE 4: Ranked list of types of drug shortages.

Disease and Therapeutic Area	Market Dynamics and Drug Type
Oncology	Biosimilar shortages
Life sustaining/life preserving drugs	Generic (sterile) injectables
Antibiotic	Generic medicines
COVID-19 treatments in hospitals	Patented drugs
Anaesthesia drugs	Oral solid forms
Palliative medicines	
Anti-infective agents	
Central Nervous System drugs	
Cardiovascular drugs	
Paediatric drugs	
Respiratory infections	

Source: Authors' ranking analysis based on review of the literature.

2.2.2 Drivers of drug shortages

We found seven drivers of drug shortages, and they are ranked (Table 5) based on frequency and importance in the literature.

TABLE 5: Ranked list of drivers of drug shortages.

Drivers of drug shortages
Price Erosion
Supply Issues
Characteristics of the Generics Drug Market
Parallel Trade
Demand Issues
Tendering
Regulatory Issues

Source: Authors' ranking analysis based on review of the literature.

Price erosion

Based on the literature identified and reviewed, price erosion is the most important driver for drug shortages. It can be attributed either to state rules (e.g., obligatory rebates, discounts, etc.) or to market dynamics (e.g., competition).

Various studies have identified commercial factors as having an important role in causing drug shortages (Chapman, Dedet and Lopert, 2022; Mattingly and Conti, 2022; Bogaert et al., 2015). For instance, low prices lead to low profit margins and then in turn supply vulnerabilities (Mattingly and Conti, 2022). For patented drugs, external reference pricing, whereby the average or lowest price of different reference countries is selected, has a large impact on the incidence of drug shortages (De Weerd et al., 2015).

In many countries there is a lack of commercial incentive in the market for antibiotics, with few companies willing or able to invest in rebuilding the supply chain and antibiotic resistance being a considerable challenge (Anderson et al., 2023; Brassel et al., 2023; Cogan, Karrar and Iyer, 2018). Also, the British Generic Manufacturers Association (BGMA) called for branded generics and biosimilars to be exempt from the voluntary scheme for branded medicines pricing and access (VPAS) scheme, as their inclusion could jeopardise launches, force withdrawals and potentially lead to shortages, due the significant price and profit pressure associated with the scheme (Wallace, 2022).

In France, a correlation has been observed between low prices and medicine shortages (Mouret et al., 2022). In addition, lower prices increase both the likelihood and magnitude of shortages in France (Dubois, Majewska and Reig, 2023).

In the US, price erosion has been identified as a potential cause of some drug shortages. Antibacterials have been found to be 42% more likely to be in shortage, compared to the average drug product, with price being identified as a key driver of these shortages (Quality Matters, 2022).

Supply issues

Supply issues are another common reason for drug shortages. This consists of manufacturing-quality problems, unavailability of raw materials, logistical issues, and business problems (Woodcock and Wosinska, 2013; Shukar et al., 2021). Often drugs with no alternatives or those that rely on single source manufacturing, can be those at highest risk of suffering from supply issues.

Across North America, Europe and globally supply issues and manufacturing problems are one of the leading causes of drug shortages (Francas, Mohr and Hoberg, 2023; Shukar et al., 2021; De Weerd et al., 2015; Li et al., 2015; Bogaert et al., 2015; Bogaert, Prokop and Bochenek, 2014; Woodcock and Wosinska, 2013). For instance, during June 2023, Canada announced shortages of leukaemia and thyroid cancer drugs, mainly due to supply issues (Otis, Writer and Contact, 2023). In Europe, manufacturing problems stem from the increased concentration and rationalisation of pharmaceutical manufacturing, in addition to globalisation (Bogaert et al., 2015).

On the other hand, in the US, the supply of generic active pharmaceutical ingredients (APIs) has caused vulnerabilities to the US pharmaceutical supply chain, where there is a heavy reliance on supply from single suppliers and from suppliers outside of the US (Socal et al., 2023; Frank, Mcguire and Nason, 2021). For example, many generic manufacturers are agreeing on exclusive contacts with a single API producer. Although this may allow for more favourable prices for APIs, there is a heightened risk of disruptions and shortages (Frank, Mcguire and Nason, 2021).

Finally, combined with the supply issues, there is a lack of incentive to upgrade production facilities and make investments. This is due to low prices and low margins, and an inability of the generic injectable market in particular to observe and reward quality (Chapman, Dedet and Lopert, 2022; Woodcock and Wosinska, 2013).

Characteristics of the generics drug market

The issues observed in the generic drug market of a lack of incentive to manufacture medicines is seen in both Europe and the North America (Woodcock and Wosinska, 2013; Elzawawy and Kerr, 2013). This lack of reward for quality can reinforce price competition and encourage manufacturers to keep costs down by minimizing quality investments (Woodcock and Wosinska, 2013).

The European Commission has also acknowledged that drug shortages in Europe most often involve older, off-patent, and generic medicines. This has been attributed to the low-profit margins associated with these types of products (Kent, 2021).

For generic medicines, internal or external reference pricing, tendering as well as price capping have been highlighted as causes of drug shortages (De Weerd et al., 2015; Bogaert et al., 2015). Smaller markets, particularly those for generic injectable products, often have less price competition and are more susceptible to supply disruptions (Frank, Mcguire and Nason, 2021). Over the study period, 2012-2019, the number of shortages across all generic types increased, with the rate of shortages increase being most pronounced in the market for injectable products (Frank, Mcguire and Nason, 2021).

In the USA, the drivers of drug shortages are multi-factorial but are largely economic due to a lack of incentive to produce generics (Elzawawy and Kerr, 2013). Furthermore, several changes to the

market environment in the USA may have contributed to the drug shortages issue, including the reliance on more producers outside of the US (Frank, Mcguire and Nason, 2021).

In Germany, both the market concentration and patent protection are associated with the likelihood of a drug shortage (Francas, Mohr and Hoberg, 2023)

Parallel trade

The differences in prices of drugs between member states of the EU can result in parallel trade, which can lead to drug shortages in the country with the lower price (Bart, 2008; Forrester and Dawes, 2008).

Parallel trade has been identified as an issue in Slovakia, with the Health Ministry collaborating with the State Institute for Drug Control, to analyse the causes and measures to prevent illegal re-exportation (Ministry of Health of the Slovak Republic, 2023). However, some suggest the effect of parallel trade on drug shortages is disputable (De Weerd et al., 2015).

“Taking appropriate steps to minimise the risk of parallel trade or export exacerbating shortages” is one of ten recommendations from the EMA for marketing authorisation holders, wholesalers, distributors and manufacturers to minimise the occurrence or shortages (EMA, 2023a).

When making supply and price decisions for a specific market, manufacturers consider a variety of factors, including population. Large-scale US imports of Canadian drugs are unlikely to be included into major pharmaceutical companies' inventory supply decisions, placing Canadians at risk of suffering shortages for essential medicines (The Wilson Center, 2019).

Another trade policy concern is the preservation of patents and other intellectual property (IP). Patents are territorial rights, and Canada and the United States have independent intellectual property regimes with distinct terms and conditions. Potential discrepancies in patent and other intellectual property protection periods could lead to an increase in infringement (The Wilson Center, 2019). Finally, parallel imports can distort domestic competition by reducing prices, thus leading to shortages.

Demand issues/fluctuations

Demand issues contributing to drug shortages include just-in-time inventory, higher demand for a product, seasonal demand, and unpredictable demand (Shukar et al., 2021; Park et al., 2021).

Generics manufacturers face demand-side concentration and these changes which together with other forms of policy-driven price regulation cause a downward pressure on prices (Frank, Mcguire and Nason, 2021). Although a causal effect has not been established in the study, it is said to be a contributing factor to drug shortages.

The surge in respiratory infections in Europe has been identified as a cause of some recent drug shortages. For example, in England, the surge in respiratory infections, particularly strep A, has led to Amoxicillin shortages (Eversana, 2022b)

In the US, stockpiling among medical providers in the early phase of the pandemic accounted for some of the COVID-19 drug shortages (Park et al., 2021). The buyers behaviour resulted in a concentration of sales volume in the first two months of the pandemic (Park et al., 2021).

The combined supply and demand issues in the current environment, may mean that many drugs are not profitable in certain countries. As a result, global companies may (de)-prioritise some countries against others, which may result in a shortage of that drug or stock keeping units (SKUs) in that country.

Tendering

Tendering can lead to price erosion that is driven by government policies. The low pricing associated with tendering may result in suppliers leaving tendered markets. This reduced competition has the potential to lead to drug-supply shortages, due to the weakening of the supply chain (Dranitsaris et al., 2017).

Cost is often the main determinant of success in tendering for biosimilars. This often results in low prices and a vulnerability to shortages. The development of standardised criteria and methods of assessment of tenders that go beyond price alone may encourage competition and the long-term sustainability of biosimilars (Simoens and Cheung, 2020; Bogaert et al., 2015).

In Italy, tendering procedures for biosimilars are organised at the regional level and they can allow for multiple winners (while for generics there is a single winner tender). Contracts have a 24-month duration but are re-opened following the launch of a new biosimilar (Cavaliere et al., 2023; Agenzia Italiana del Farmaco (AIFA), 2021).

Despite there being laws that promote the use of health technology assessment (HTA), cost-effectiveness and price-quality considerations for tenders in Italy, often in practice they are still awarded solely based on price (Cavaliere et al., 2023; Agenzia Italiana del Farmaco (AIFA), 2021).

The lack of incentive for the continued production of less profitable drugs in a setting of highly competitive tendering and contracting practices has been cited as a root cause of shortages (Chapman, Dedet and Lopert, 2022). Tendering can often lead to the selection of a single supplier. This carries a risk that if there is a sudden rise in demand, they may not be able to meet this increase (Bogaert et al., 2015).

In Spain, there are many multiple award tenders, in which the first company awarded, offers a more aggressive price. If that company has a supply issue, any other company should “cover” the demand and supply.

Regulatory issues

The lack of a unified definition of ‘drug shortage’ is one of the key regulatory issues related to drug shortages. There is a diversity of opinions on how a shortage should be defined (Shukar et al., 2021; Bogaert et al., 2015). There is not a consensus on the level at which all drug shortages should be assessed, the appropriate timeframe applied, the issue of linking commercialisation to shortages, and finally by the severity of the problem itself (Bogaert et al., 2015).

In order for solutions to be found, a definition for drug shortages needs to be developed (Bochenek et al., 2018). In the US, it has been found that although there is not a causal association, the increase in FDA regulatory scrutiny may arguably contribute to some of the drug shortages seen in recent years (Frank, Mcguire and Nason, 2021).

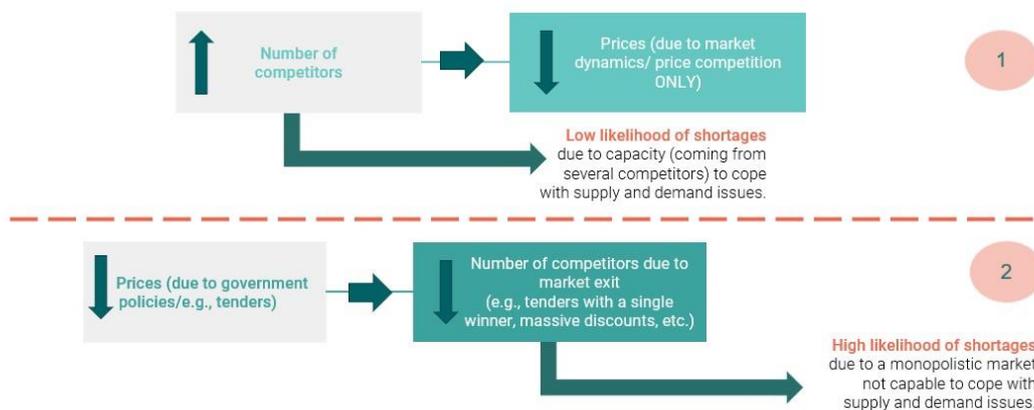
The relationship between price, competition and shortages

The literature review of the drivers of drug shortages reveals that they are directly or indirectly related to price erosion and thus can affect competition. The figure below illustrates the relationships between price, competition and shortages. We identify two types of relationship.

The first is where an increase in the number of competitors can lead to a low likelihood of shortages due to sufficient capacity to cope with supply and demand issues, and therefore any decreases in price will be mainly attributed to price competition.

The second type of relationship starts with a government induced price reduction (e.g., due to cost-containment policies, tenders, etc.), which results in a drop in the number of competitors due to market exit. This increases the likelihood of shortages due to a monopolistic market.

FIGURE 2: Graphical illustration of the relationship between price, competition, and shortages.



2.3. Policy solutions

Governments globally have been considering and implementing policies in recent months and years, attempting to address the underlying causes of drug shortages, as the issue has gained more prominence.

Most recently, the European Commission proposed measures to resolve shortages and improve supply security (European Commission, 2023). Such measure is the Voluntary Solidarity Mechanism, which aims to enable medicines redistribution within the EU to countries facing shortages. Accordingly, the EU plans to establish a Critical Medicines Alliance, which will facilitate the coordination of different stakeholders at the EU against shortages (European Commission, 2023). The Commission's Health Emergency Preparedness and Response Authority (HERA) is also working to secure the availability of medicines, particularly through cooperative procurement of pharmaceuticals. Also, strategic partnerships and a network of international partners are planned to be established (European Commission, 2023) to:

- (i) further facilitate the production of all critical medicines and mitigate the risk of shortages,
- (ii) diversify the supply chain, and

- (iii) ensure coordination and resilience of the supply chain.

Below, we have categorised policies proposed in different countries based on drivers of shortages that they aim to address.

Addressing tendering practices

The development of standardised criteria as well as a method of assessment for tenders can help manufacturers to avoid facing segmented markets, encourage competition and support the longer-term sustainability of biosimilars (Simoens and Cheung, 2020).

Current procurement is focused only on cost minimisation, often with single-winner tenders, as well as limited consideration of the security of supply. A reformed procurement process could be advantageous for biosimilars (European Health and Digital Executive Agency., 2022).

In addition, awarding multiple winners in combination with using the Most Economically Advantageous Tender (MEAT) criteria, rather than purely focusing on price, would help to generate a more sustainable market (European Health and Digital Executive Agency., 2022).

In Germany, following an introduction of new legislation, tendering for antibiotics and oncology drugs will now consider location, to promote the EU as a production location, and the manufacturers must guarantee several months of supply (Eversana, 2023b).

In Italy, the revision of tender criteria has been highlighted as a key measure in avoiding supply disruptions and shortages (Egualia, 2023b; a). Researchers have developed a forecasting algorithm in partnership with the Italian Federation of Industries for Accessible Medicines to aid in the efficiency of tender processes and the avoidance of shortages.

There are many tenders with a small number of pharmaceuticals offered and few tenders with large purchase volumes. These are more efficient but frequently end up being "deserted" due to the demand for economies of scale. The extremely low prices, particularly for multi-regional tenders, drive suppliers away, weakening the supply chain. A definition for accurate supply needs is crucial for sustainability for public system, manufacturing companies, citizens and patients (Egualia, 2023b; a).

Moreover, in Italy, there is a Framework Supply Agreement for biosimilars, which primarily aims to limit the drug shortage risk. It works through awarding contracts to multiple manufacturers and if the first awardee is not able to supply, then the second or even the third awardee can facilitate the supply. For generics, however, there is only a single-winner tender, and currently, the price is the only criteria to win a tender. This means that the problem of shortages is much more relevant for the whole generics markets than for the biosimilars (Cavaliere et al., 2023; Agenzia Italiana del Farmaco (AIFA), 2021).

Addressing price erosion

Different European countries have proposed or applied several measures to tackle price erosion.

In Italy, price renegotiation has been proposed to help reduce the likelihood of supply disruptions and withdrawal of related products from the market (Egualia, 2023b). This has been highlighted, since 26% of equivalent drugs sold in pharmacies are priced less than or equal to EUR 5 and current regulation does not allow for adjustment to inflation for drugs reimbursed by the Italian NHS (Egualia, 2023b).

A similar proposal has been seen in France, whereby the French Government has called on the economic committee for health products (CEPS) to be more flexible in approving price increases for certain drugs to preserve supply capacity (Eversana, 2023a).

The President of CEPS agreed that CEPS would be more flexible in applying price hikes, in particular for low-margin products, often generics, and where products are considered crucial (Eversana, 2023a).

In 2021, generics represent 68% of the total pharmaceutical sales, in terms of volume, in the French pharmaceutical market and this is 22% more than 2011 (DREES, 2022). The French Generic Medicines Manufacturers Association (GEMME) warns that the future of generics in France is compromised by the safeguard clause, which excludes generics and imposes payback requirements on the pharmaceutical sector if pharmaceutical spending surpasses a certain threshold. This plays a significant role in reducing healthcare costs through pricing set 60% lower than originator drugs. This pricing strategy, dictated by the regulation has resulted in annual savings of EUR 2 billion; however the sustainability of the market is arguably at risk. Instead, GEMME suggests volume-based regulation by encouraging the substitution of generics and biosimilars rather than regulation based primarily on depreciation in value.

Addressing supply issues

In the US, it has been highlighted that incentives may need to be provided in the US to support API production (O'Boyle, 2023). To address this, the Manufacturing API, Drugs and Excipients (MADE) Act has been reintroduced by the US House of Representatives. The act aims to incentivise domestic manufacturing of drugs, APIs, personal protective equipment (PPE) and diagnostics through a tax credit system (O'Boyle, 2023).

In Germany, similar measures have been proposed to diversify the supply chain and introduce location criteria for supply quality (Woodcock and Wosinska, 2013). To solve manufacturing-quality problems in the US, the FDA needs to exercise its regulatory flexibility to avoid shortages on behalf of the patients to avoid shortages (Woodcock and Wosinska, 2013) of medically necessary drugs, in particular generic sterile injectables. In turn, this may further strengthen the incentive to innovate and improve quality (Woodcock and Wosinska, 2013).

In Europe and Canada there have been proposals and laws to ensure the earlier notification of shortages (Sharma, 2023; Health Canada, 2023; Bocquet et al., 2017). For example, in France there has been an establishment of emergency call centres implemented by pharmaceutical companies for pharmacists and wholesalers to inform of shortages. In addition, pharmaceutical companies are obliged to inform health authorities of any risk of a potential shortage situation (Bocquet et al., 2017).

Moreover, with more than 3,500 reports of stockout or risk for stockout and with more than 35% of French citizens who have been affected by the drug shortages, the French regulatory agency Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM) aims to put forward a plan to anticipate and react more effectively to potential supply issues (ANSM, 2023a; b).

For this reason, the ANSM will utilise epidemiological data to better monitor the number of medical consultations, the number of visits to the emergency rooms, and the number of hospitalisations for specific diseases (e.g., COVID-19, influenza, etc.). Also, they will monitor the stocks and supplies of laboratories, wholesaler-distributors, and pharmacies, as well as their sales. In addition, they will incorporate feedback from health professionals and patients related to the difficulties that they face due to shortages (ANSM, 2023a; b).



The European commissioner for health and food safety says proposed changes to pharmaceutical law will include stronger obligations for the supply of medicines and earlier notifications of shortages (Sharma, 2023).

In May 2023, the “Critical Medicines Act” was addressed to the EU commission with goals to establish a voluntary solidarity mechanism to help alleviate shortages in member states, and create a list of critical medicines in Europe whose supply needs to be monitored and protected (European Health and Digital Executive Agency., 2022).

In Canada, the government will more proactively communicate shortages that have a potential high impact on patients (Health Canada, 2023). In particular, Canada has secured imports for children’s pain and fever medicines and has set out a policy on the importation and sale of infant formulas, human milk fortifiers and dietary products for the treatment of inborn errors of metabolism to mitigate shortages ([Health Canada, 2022](#); [News - C.B.C., 2022](#)).

In Bulgaria, in order to cope with supply issues caused by parallel trade, the government aims to implement policies enhancing its response to shortages in the supply chain and ensuring better traceability of parallel trade and shortages (Kotseva and Nikolov, 2023).

The International Generic and Biosimilar Medicines Association (IGBA) have recommended four key policies to strengthen the predictability of supply chains (IGBA, 2023) This includes establishing better collaboration between governments, industries, and international institutions to help identify supply chain risks and adopt mitigation measures, as well as a more sustainable procurement system utilising criteria beyond price to strengthen supply.

3. Mapping of drug shortages

In this section, we analyse drug shortages databases to document and compare shortages in order to identify trends, commonalities, or differences. Also, we conduct sub-analyses of drug shortages based on specific characteristics, for example if the drug is off-patent or if the drug is used to treat cancer.

3.1 Methods and Data

3.1.1 Drug shortages databases

For the analysis, we collect data on drug shortages in the USA, Europe and Canada. For the USA, we mainly use the U.S. Food and Drug Administration (FDA) drug shortages database, supplemented with information from the American Society of Health-System Pharmacists (ASHP) database (FDA, 2023; ASHP, 2023). For the EU and Canada, we use the European Medicines Agency (EMA) database and the Canada drug shortages database, respectively (EMA, 2023b; Drug Shortages Canada, 2023a). The timeframe for the FDA analysis was from 2014 to 2023, for the EMA database this was from 2013 to 2023, while for Canada we covered the years from 2014 to 2023. The following figure summarises the databases' information and limitations.

FIGURE 3: FDA, EMA, and drug shortages Canada databases information.



3.2. Results

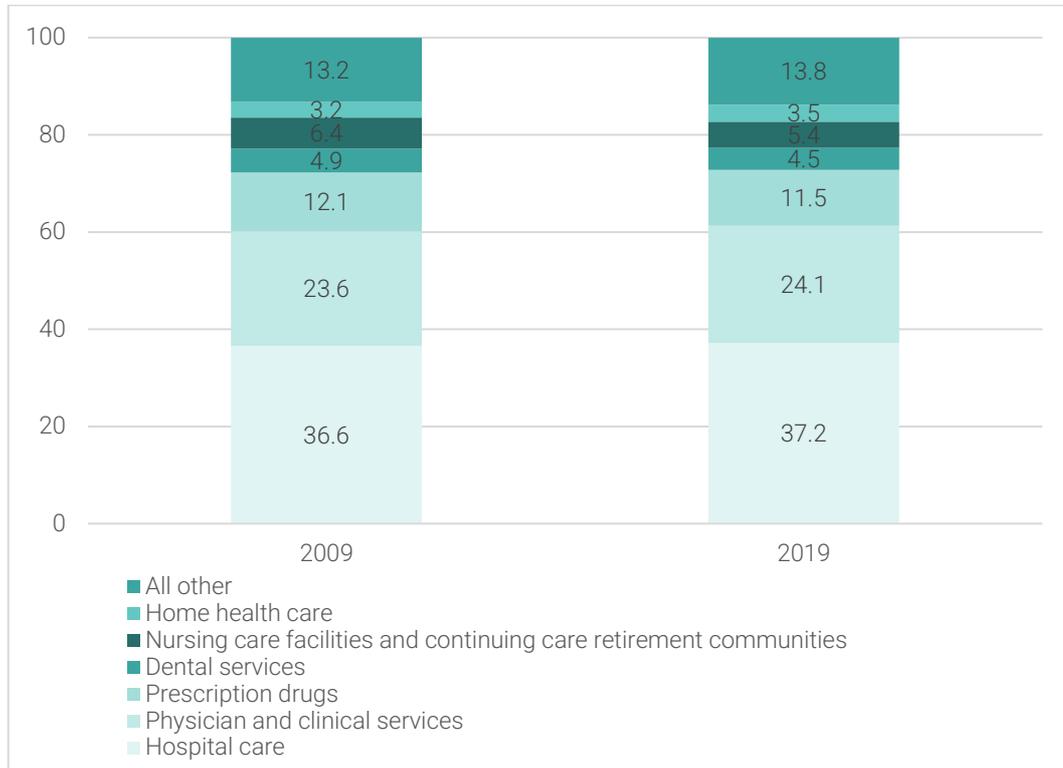
3.2.1 FDA drug shortage database analysis

Overview of health care expenditures in the USA

Personal healthcare expenditures account for 85% of the total national health care expenditures in the USA and in 2019, the national health expenditures were approximately \$3,795 billion, from which, 11.5% or \$436 billion was spent on prescription drugs, while 61% on hospital care and physician and

clinical service (National Center for Health Statistics, 2023a; b; ASPE, 2022). Figure 4 breaks down the expenditures by category.

FIGURE 4: Personal healthcare expenditures, by type of expenditure in the US (2009 and 2019).

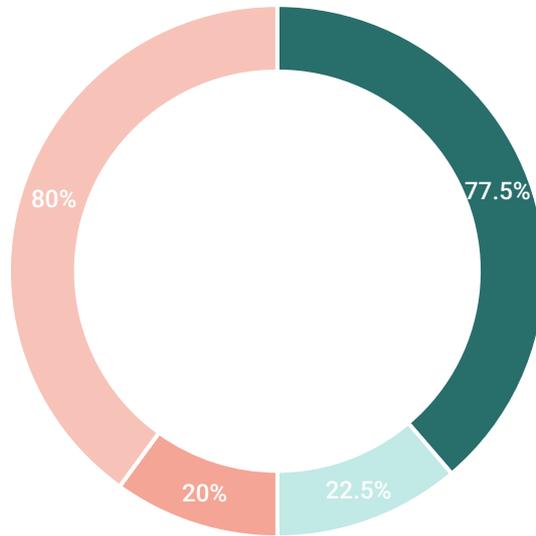


Adapted from: Centers for Medicare & Medicaid Services, National Health Expenditures Accounts. See (National Center for Health Statistics, 2023b) and *Health, United States, 2020–2021*.

According to (ASPE, 2022), the US health-care system spent \$603 billion on prescription medications in 2021, before rebates, with \$421 billion spent on retail drugs. Drug cost increased primarily due to increases in spending per prescription, and to a lesser extent due to greater utilisation (i.e., more prescriptions). Non-retail drug spending grew at a faster rate (25%) than retail expenditures (13%). Furthermore, it has been found that drug spending is substantially influenced by a relatively small number of high-cost products. The cost of speciality medications (those used to treat chronic, rare, or complex disorders) has risen steadily, reaching \$301 billion in 2021, a 43% increase since 2016.

Figures 4a and 4b use ASPE (2022) data and depict the average share of total prescriptions and brand-name drug expenditures between 2016 and 2021. Neither measure changed significantly during this time span. Despite accounting for only 20% of retail and non-retail prescriptions, brand name medications accounted for 80% of prescription drug expenditures in both retail and non-retail settings, with little change over time. Further data analysis, reveals that there was a substantial decrease in non-retail prescriptions in 2020, which was most likely due to a decrease in office visits during the early phases of the COVID19 pandemic. However, there was no equivalent decrease in non-retail drug spending (ASPE, 2022).

FIGURE 4a. Average share of all retail prescription drug spending and prescriptions (branded vs generics, 2016-2021).

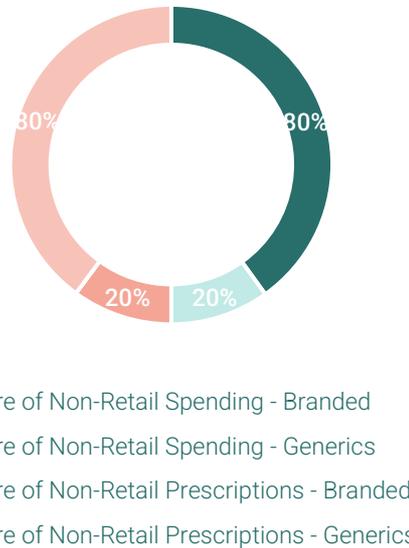


- Share of Retail Spending - Branded
- Share of Retail Spending - Generics
- Share of Retail Prescriptions - Branded
- Share of Retail Prescriptions - Generics

Source: ASPE (2022) and authors' calculations.

Therefore, we find that generics account for 80% of retail and non-retail prescriptions, generic and biosimilar medications accounted for 20% of prescription drug expenditures in both retail and non-retail settings, with little change over time.

FIGURE 4b. Average share of all non-retail prescription drug spending and prescriptions (branded vs generics, 2016-2021).



Source: ASPE (2022) and authors' calculations.

In 2021, specialty medications accounted for 50% of overall drug spending. While generic medications account for the majority of prescriptions filled in the United States (80%-90%) (Office of Generic Drugs, 2022; ASPE, 2022), brand name drugs account for 80% of prescription drug spending in both retail and non-retail settings, with little change over time. Finally, the top 10% of most expensive pharmaceuticals account for less than 1% of all prescriptions but 15% of retail spending and 20%-25% of non-retail spending. These statistics can be particularly useful for governments and manufacturers to weight the product-specific (e.g., branded vs generics) relationship between drug shortages, expenditures, and potential patient impact.

Summary results

The data from the FDA database has been filtered by Generic Name and Company. This is to ensure the same drug in different strengths, dosage forms, or presentations is not duplicated and only captured once. The timeframe of the FDA drug shortages analysis is from 1st of January 2014 to July 2023.

Since 2019, the number of shortages reported in the FDA database has increased year on year, from 72 to 232 in 2022 (and 160 in 2023). Shortages have been particularly high since 2020.

We found that the primary reason for drug shortages is a demand increase for the drug, followed by discontinuation of manufacturing, and manufacturing delay. Paediatric, Gastroenterology, and Anaesthesia are the top three therapeutic classes experiencing shortages, although there are many shortages across many therapeutic areas.

In terms of other drug-specific characteristics, injectables are the most common drug presentation to experience drug shortages, accounting for 55% of drug shortages, followed by Tablets and Capsules.

The database shows that the mean number of manufacturers per drug is two. Furthermore, 3.66% of drugs experiencing a shortage are biologics, and approximately 95% of the drugs in shortage are off-patent. Drug shortages in oncology represent 7.92% of total shortages, and Paediatric drugs represent 10.62% of shortages. In terms of manufacturers experiencing shortages, the top 10 manufacturers reporting the greatest number of shortages can be found in the appendix (Table A10).

Incidence, status, and reason of drug shortages

The FDA database incidence analysis is presented in figure 5. The figure shows that the number of shortages reported in the FDA database are more than double in 2020 compared to 2019, with shortages being particularly high since 2020. In 2022 there is the peak of the shortages' incidence, with the number of shortages having increased year on year, from 72 in 2019 to 232 in 2022 (and 160 in 2023).

In the first half of 2023, there have been 160 shortages, and if the shortages continue at this rate they will be doubled by the end of the year and be the highest year on record (*shown in figure 5). Moreover, for the covered period, 43.3% of the shortages are current/ongoing, while 18.5% have been resolved and 38.2% of the drugs in shortage have been discontinued.

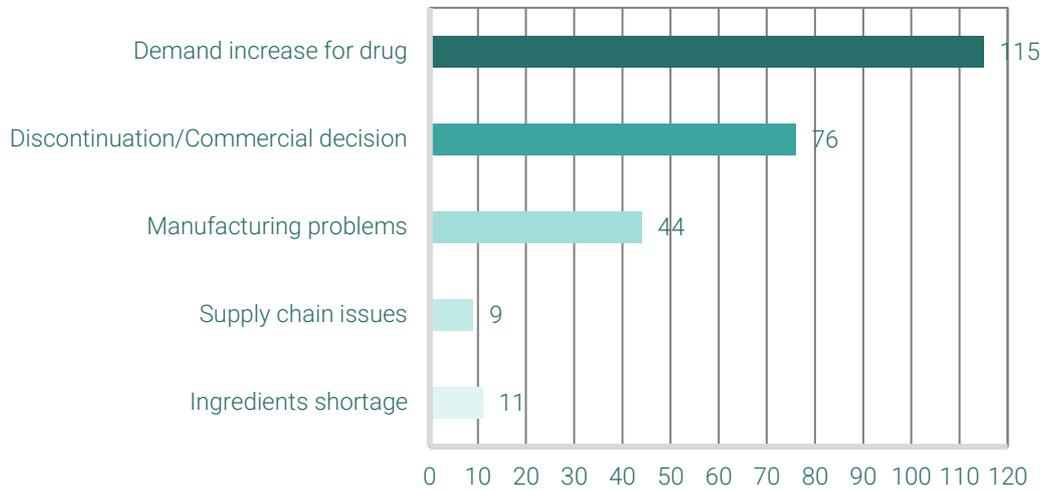
FIGURE 5: FDA: Incidence of shortages (2014-2023, filtered by Generic & Company name).



***Projection based on current rate of shortages in 2023.**

In terms of the shortage reason, demand increase for the drug is cited as the leading cause of shortages, accounting for approximately 45% of shortages; however, the database does not record the reasons consistently, with the majority of shortages having no reason cited. Discontinuations, including those for business reasons, account for 30% of shortages. Figure 6 presents the reasons for shortages.

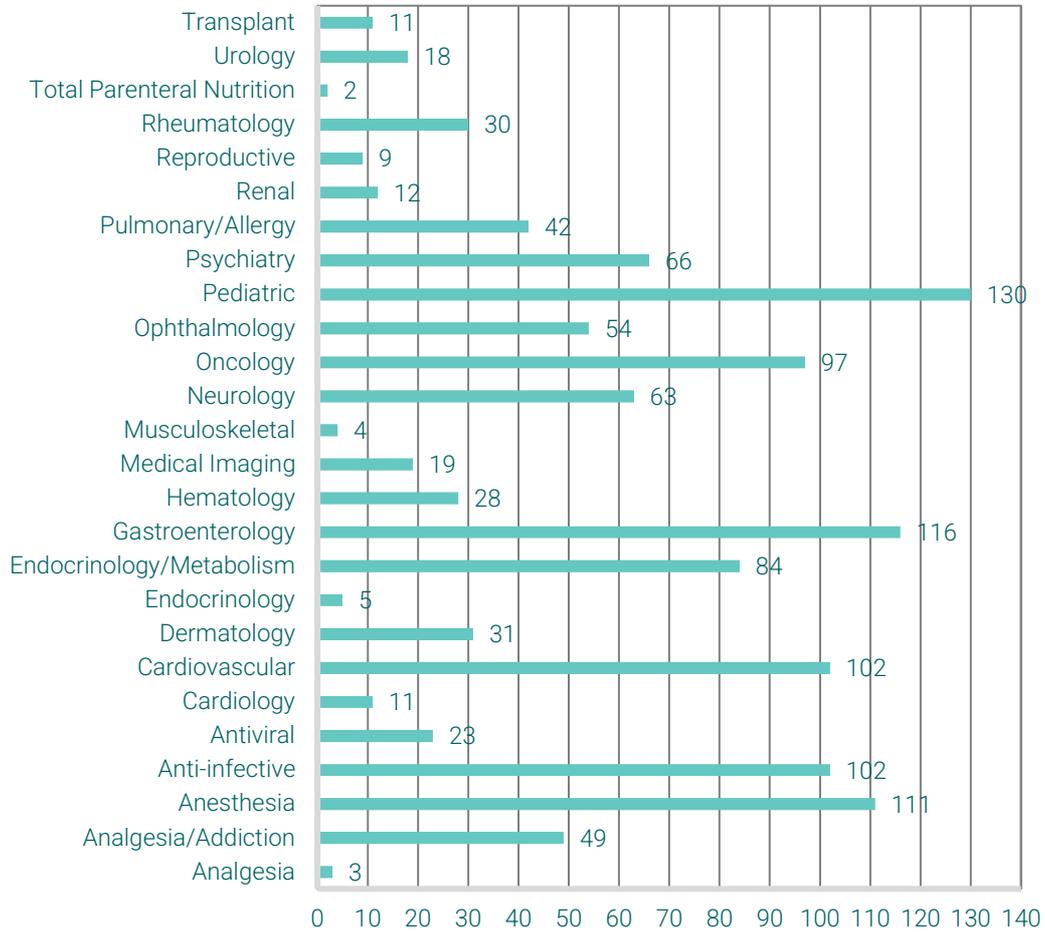
FIGURE 6: FDA: Reason for shortage (2014-2023, filtered by Generic & Company name).



Therapeutic area and drug presentation in shortage

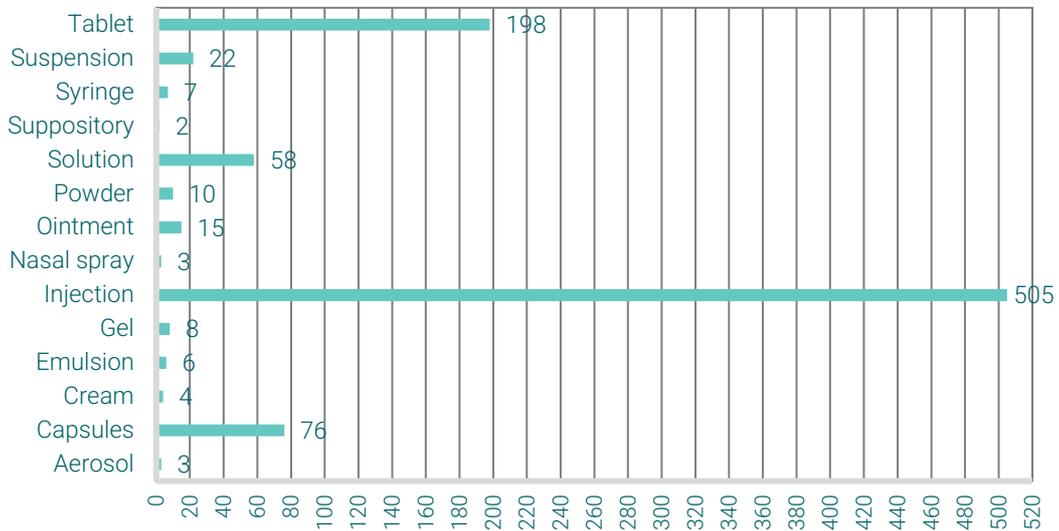
There are drugs from many therapeutic areas experiencing shortages, affecting many diseases. The therapeutic classifications are based on the descriptions provided in the database. The therapeutic areas most affected by shortages US are: Paediatric, Gastroenterology, and Anaesthesia.

FIGURE 7: FDA: Therapeutic area shortages (2014-2023, filtered by Generic & Company name).



Shortages have been seen in a variety of drug presentations, although injectables account for over half of the reported shortages (figure 8).

FIGURE 8: FDA: Shortages based on drug presentation (2014-2023, filtered by Generic & Company name).



Other characteristics of drug shortages

Further examination of the US drug shortages shows that 7.92% of drugs in shortage are oncological (figure 9) and 10.62% are pediatric drugs (figure 10). Moreover, 5.26% of drugs in shortage for the three main shortage ATCs in 2023 are on-patent (figure 11).

FIGURE 9: FDA: Oncology vs Non-Oncology shortages (filtered by Generic & Company name).

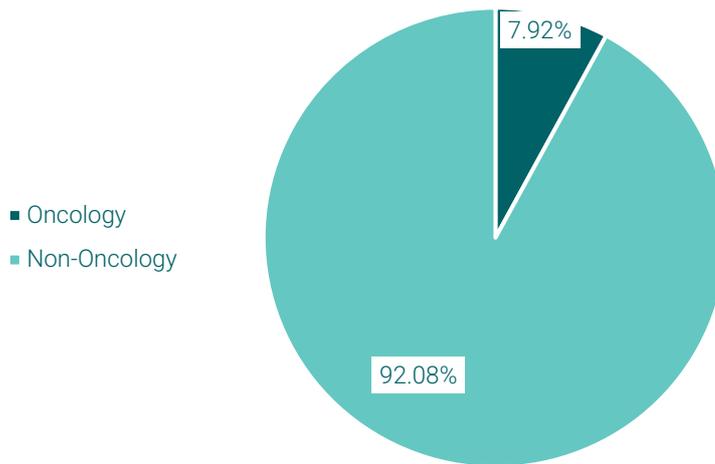


FIGURE 10: FDA: Pediatric vs Non-Pediatric shortages (filtered by Generic & Company name).

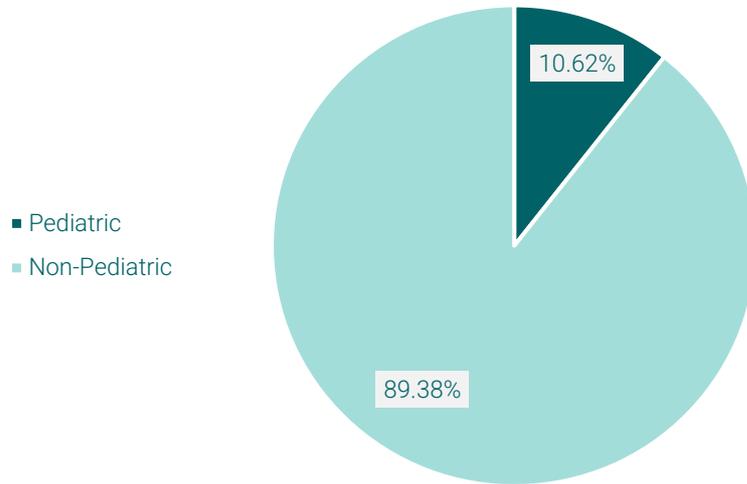
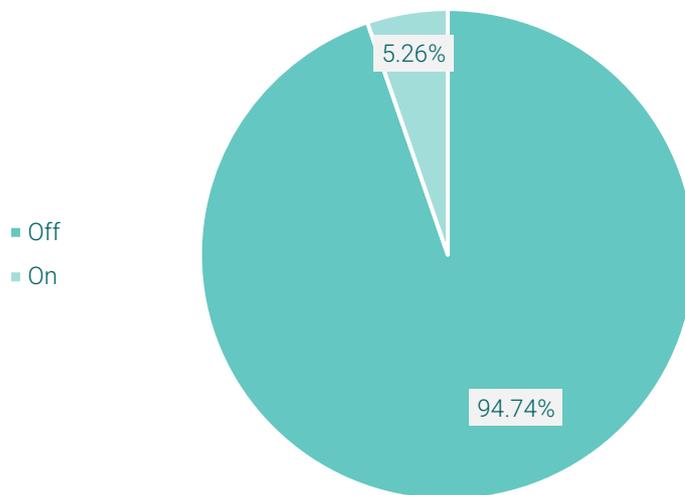


FIGURE 11: FDA: On-patent vs Off-Patent shortages (for the top three ATCs in shortage during 2023).



3.2.2 EMA drug shortage database analysis

Summary results

The EMA database includes medicine shortages, but does not record the manufacturer/s. The shortages recorded are those that affect more than one EU country, with the average number of countries affected per drug shortage being 16.57. This means, however, that shortages affecting one or a small number of EU nations are not recorded here, so the database is likely to be underrepresenting the scale of the problem.

The EMA assess each shortage and provide recommendations, on shortage management as well as information for health care professionals. The timeframe of the EMA drug shortages analysis is from 1st of January 2013 to July 2023.

The number of shortages reported in the EMA database increased following the COVID-19 pandemic, and 2023 has seen the most reported shortages of any year. Infusion and Injectables, of different forms (suspension, solution, powder), are the drug presentations accounting for the most shortages. Quality issues and demand increases are the main reported reasons for drug shortages.

58.7% of the drug shortages are biologics, compared to just 6.98% and 3.66% in Canada and USA respectively. This may be partially explained by a higher rate of biosimilar approvals in the EU compared to the US and Canada (Harston, 2021; Smart & Biggar, 2020).

Incidence, status, and reason of drug shortages

The EMA database incidence analysis is presented in figure 12. A key finding is that the number of shortages reported is already 10 for 2023, the highest year on record despite only including data up until July 2023. With the same rate of shortages for the remaining months of 2023, it is expected there will be 16 shortages (*shown in Figure 12). In 2019 there were no shortages recorded in the EMA database for many EU countries at the same time. Moreover, from all the analysed shortages, 43.5% are current/ongoing, while 50% of the shortages have been resolved.

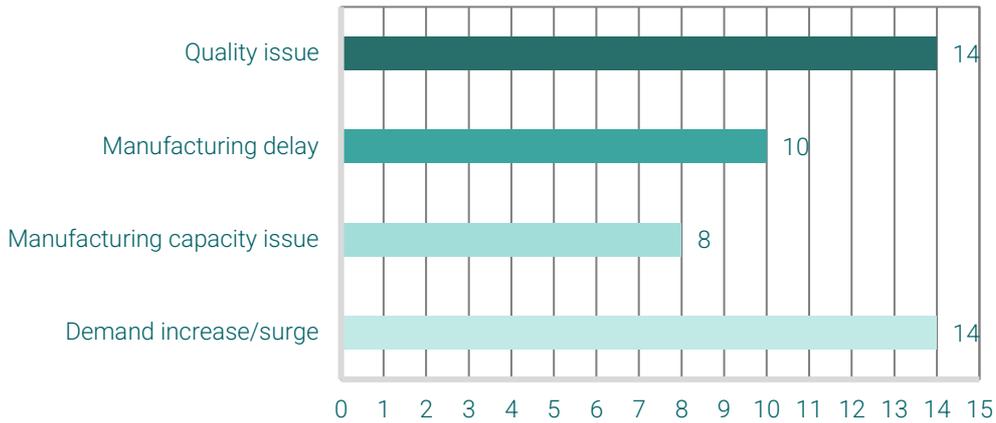
FIGURE 12: EMA: Incidence of shortages (2013-2023).



*Projection based on current rate of shortages in 2023.

In terms of the shortage reason, issues related to manufacturing, whether a delay, quality issue, or capacity issue are responsible for many of the shortages. Demand increase for the drug has become a growing cause in recent years.

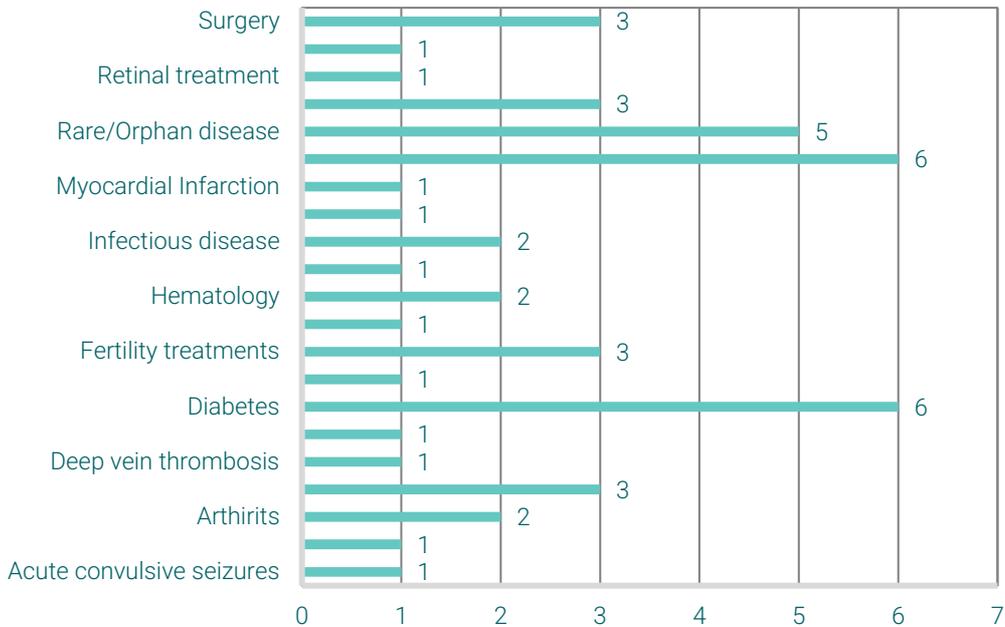
FIGURE 13: EMA: Reason for shortage (2013-2023).



Therapeutic area and drug presentation in shortage

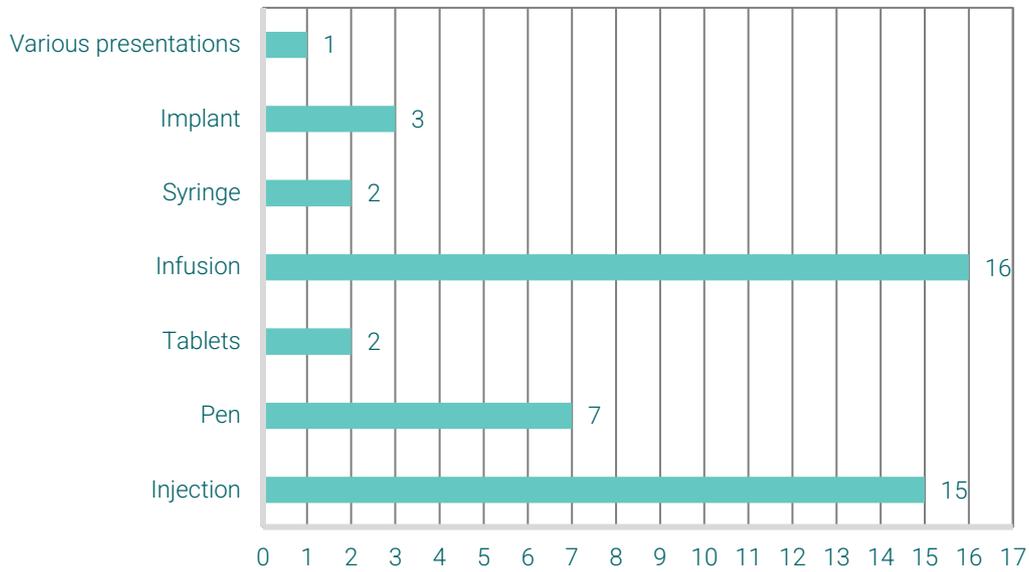
The documentation of the therapeutic areas is based on the description given in the shortage report, with no area disproportionately suffering more shortages.

FIGURE 14: EMA: Therapeutic area shortages (2013-2023).



Injectables are responsible for two-thirds of reported shortages (figure 15).

FIGURE 15: EMA: Shortages based on drug presentation (2013-2023).



Other characteristics of drug shortages

Further examination of the EU drug shortages shows that 13.04% of drugs are oncology medicines (figure 16) and approximately 60% of drugs in shortage are biologics. Finally, 27% of drugs since 2020 have been on-patent, the highest proportion of the three databases (figure 17).

FIGURE 16: EMA: Oncology vs Non-Oncology shortages (2013-2023).

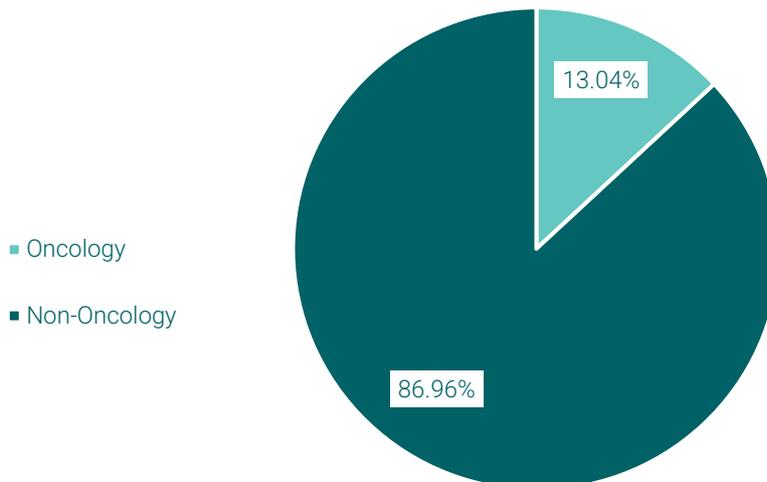
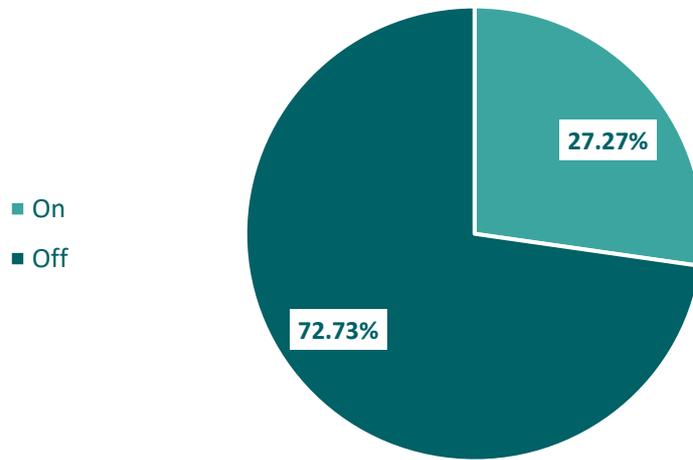


FIGURE 17: EMA: On-patent vs Off-Patent shortages (Drug shortages since 2020).



3.2.3 Canadian drug shortage database analysis

Summary results

The data from the Canadian database has been filtered by the Drug Ingredients (in the FDA this is called “generic name”) and Company. This filtering ensures that the same drug in different strengths, dosage forms, or presentations is not duplicated. The timeframe of the analysis is from 1st of January 2014 to July 2023.

In the last two years, 2022 and 2023 the incidence of drug shortages reported in the Canadian Drug Shortages database has been particularly high, increasing from 390 in 2021 to 825 in 2023.

The primary reason for drug shortages is the ‘disruption of the manufacturer of the drug’, responsible for approximately 59% of the reported reasons for shortages. Nervous system, Cardiovascular and Anti-infective for systemic use are the top three therapeutic classes experiencing shortages.

Tablets are the most common drug presentation to experience drug shortages, followed by solution. The database shows that the mean number of manufacturers per drug is 2.9. In addition, 7% of drugs experiencing a shortage are biologics and drug shortages in oncology represent 7.1% of total shortages.

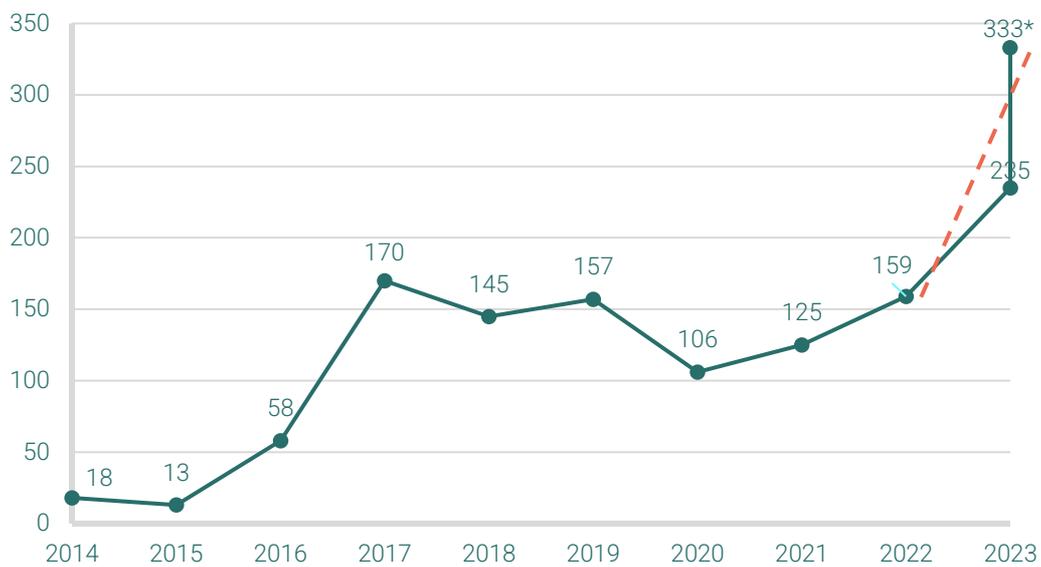
Tier 3 shortages are defined as those that have the greatest potential impact on Canada’s drug supply and health care system. Seventy-five incidences of ‘tier 3 shortages’ have occurred in Canada (involving 30 active ingredients), with 22 of these 75 occurring in 2023 alone.

Finally, the companies experiencing the most shortages in Canada are presented in the appendix (Table A16).

Incidence, status, and reason of drug shortages

The Canadian database incidence analysis is presented in figure 18. The analysis shows that the number of shortages that have rapidly increased since 2021, with the number of shortages more than doubled in that period. There have been 235 drug shortages in 2023, and if the current rate of shortages continues at the same rate, it is expected there will be 333 shortages in 2023 (*shown in figure 18). However, 77% of the reported shortages have been resolved, while 23% are still current/ongoing.

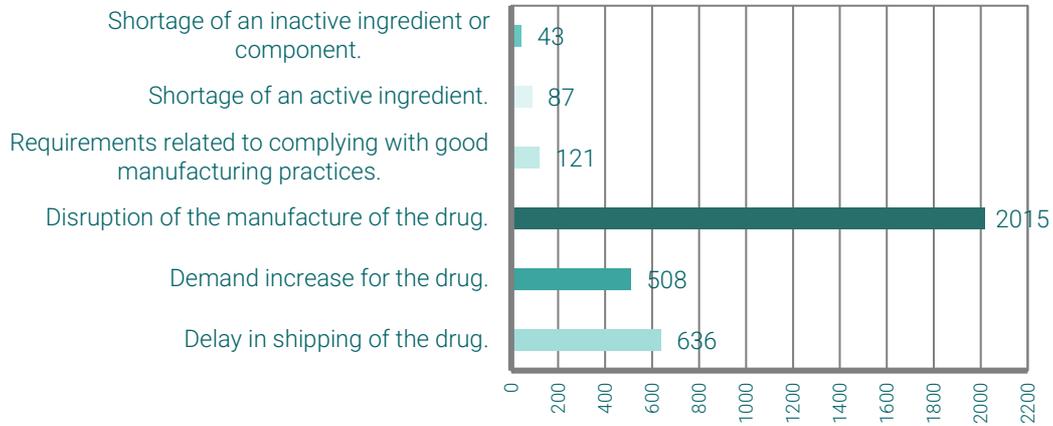
FIGURE 18: Canada: Incidence of shortages (2014-2023).



***Projection based on current rate of shortages in 2023.**

In terms of the shortage reason, 'disruption to the manufacturer of the drug' is the leading cause of drug shortages. However, the database does not include additional information on a case-by-case basis on the shortage reason. Figure 19 documents the reasons for shortages in Canada.

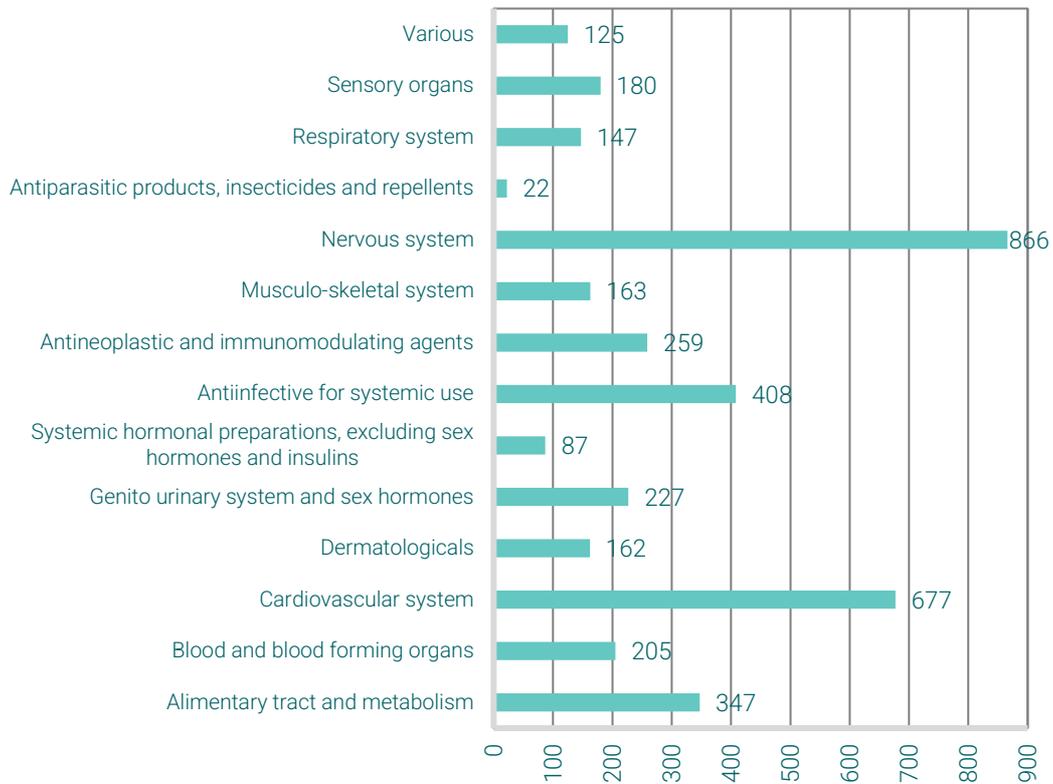
FIGURE 19: Canada: Reason for shortage (2014-2023).



Therapeutic area and drug presentation in shortage

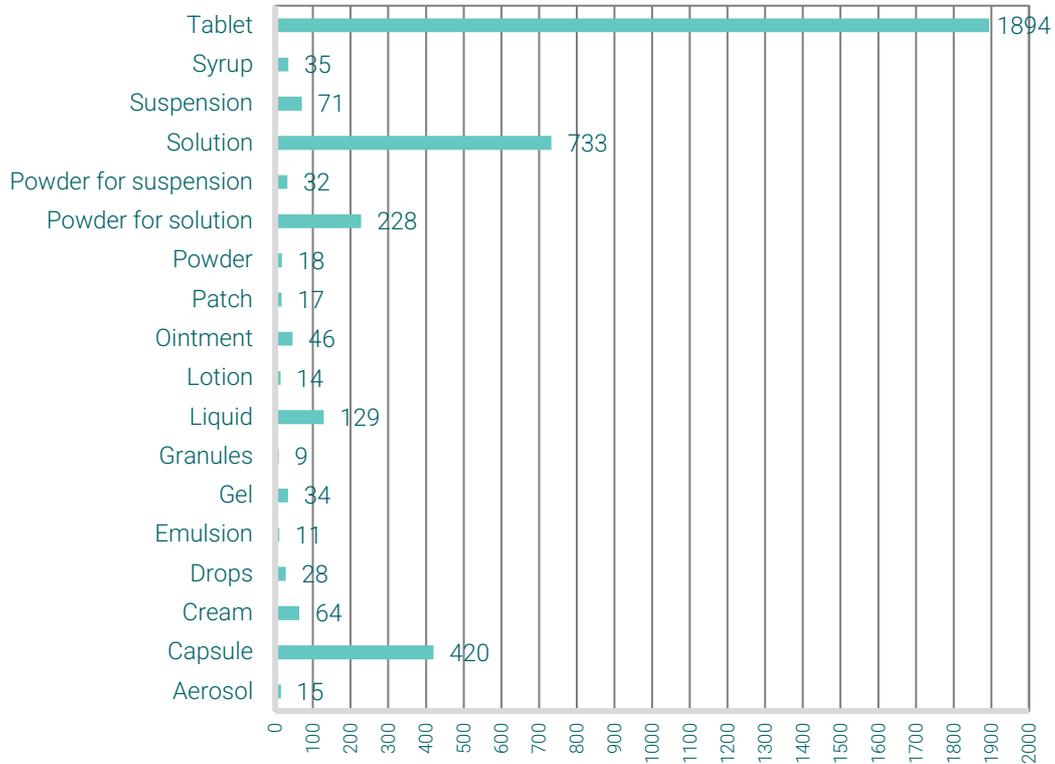
In Canada, the nervous and cardiovascular system ATCs are the areas which experience most shortages, as shown in figure 20.

FIGURE 20: Canada: Therapeutic area shortages (2014-2023).



In terms of drug presentation, tablets are the most common one found in shortage in the Canadian database, followed by Solutions and Capsules (figure 21).

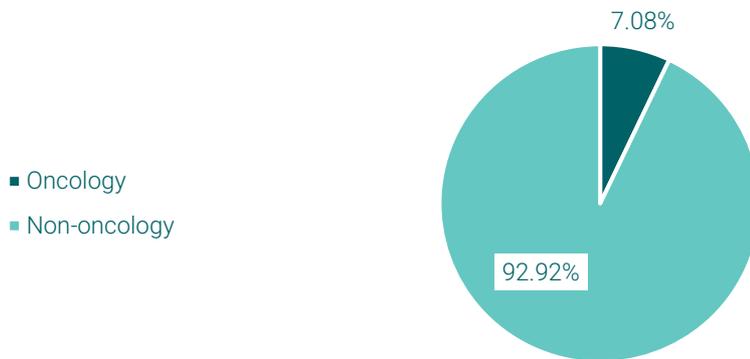
FIGURE 21: Canada: Shortages based on drug presentation (2014-2023).



Other characteristics of drug shortages

Further examination of the Canadian drug shortages shows that 7% of drugs in shortage are oncology drugs (figure 22), of the ATCs: L01, L02, L03. In addition, 7% of drugs in shortage are biologics. Finally, from all drugs of the drug shortages documented in the three main therapeutic classes in 2023, only one was a drug on-patent.

FIGURE 22: Canada: Oncology vs Non-Oncology shortages.



3.2.4 Duration of drug shortages

Previous evidence

In the US, between 2001-2016, the median duration for resolved shortages was 7.2 months (varying from 2.8 to 17.3) and the median duration for active shortages was 13.6 months (varying from 5.8 to 58.4) (Mazer-Amirshahi et al., 2017).

A study conducted in 2013 with a focus on European countries (Belgium, Italy, Spain, England, Germany, and France) drug shortages found that the duration of a drug shortage is 139 days (appx. 4.6 months) (Pauwels et al., 2014).

In Canada, the median duration of a shortage was calculated to be 32 days (appx 1.1 months) (Videau et al., 2019).

The table below summarises the studies and the duration of shortage found in the USA, Europe and Canada.

TABLE 6: Past evidence on the duration of drug shortages.

Study	Time period	Region	Median duration of shortages
Mazer-Amirshahi et al. (2017)	2001-2016	USA	7.2 months
Pauwels et al. (2014)	2013	Europe	4.6 months
Videau et al. (2019)	2018	Canada	1.1 months

New estimates

In the table below, we provide updated estimates around the duration of drug shortages. To do so, we analysed the FDA, EMA, and Drug Shortages Canada databases (FDA, 2023; EMA, 2023b; Drug Shortages Canada, 2023a)

TABLE 7: New estimates on the duration of drug shortages.

Time period	Region	Median duration of shortages
2014-2023	USA	18 months
2013-2023	Europe	5 months
2017-2023	Canada	1 months

Source: Authors' calculations.



We find that the median shortage duration for Europe and Canada has remained almost the same compared to studies examining previous years. Interestingly, the USA seems to be heavily affected by the duration of drug shortages which is 2.5 times more than reported in previous years.

Although the cause of this was not able to be established, a possible reason for this might be the manufacturing disruption caused by COVID-19, as well as price erosion. Specifically, we expect price erosion to be one of the main causes of the increased shortage duration, as it has been reported that a change of appx. 14% in the drug price could lead to more than 18 months of shortage duration in the USA (Dave et al., 2018).

4 Framework for examining trends and multi-factor relationships in drug shortages

In this section, we conduct a descriptive analysis examining the correlation/trends between a set of biosimilar shortages and their explanatory factors/drivers as identified by the literature. This allows us to explore their relationship and create a shortage framework, thereby providing an indication of what drives the occurrence of a shortage.

4.1 Drug shortages framework

We used the literature review outcomes to inform our framework. Specifically, we propose a framework consisting of five correlated factors that can be used in this and future research in the field in determining shortages' factors value ranges. To validate this, we apply three case studies.

FIGURE 22: Drug shortage framework.



4.1.1 Case studies

We use case studies to apply the framework and get indicative values for determining the relationship between shortages and their drivers.

Methods, data and variables

For the European shortages of the case studies, Organon shared price data for etanercept, adalimumab and bevacizumab, obtained from IQVIA. Moreover, when the shortage is characterised/considered as being “temporary”, then it is likely not be included in the EMA database.

For the US, OHE calculated the average prices per milligram (mg), demand measured by standard units consumed, patent expiration, competition based on the number of firms, and the therapeutic class concentration (measured by the Herfindahl–Hirschman index (HHI)) by exploiting Medicare’s Part D data and several publicly available sources (more details can be found in the appendix). Moreover, we assume that the pharmaceutical market is global and government and/or firm decision in one country can cause spillover effects to other countries.

The case studies are based on the following drugs and shortages:

TABLE 8: Case studies.

Biologic drug	Shortage	Reason/status	Product info	Country
Etanercept	Feb to April 2014 (EMA, 2023b)	Resolved (Supply disruptions due to capacity constraints at the packaging facility occurred in some EU Member States)	Pre-filled pen and pre-filled syringe. Name: Enbrel Indication: Enbrel is an anti-inflammatory medicine. It is used to treat certain arthritic diseases and psoriasis in adults and children.	
	Dec 2022 (Drug Shortages Canada, 2023c)	Discontinued (for business reasons)	Enbrel	
Adalimumab	2020 (FDA, 2023)	Discontinuation	Adalimumab (Humira) Pre-filled Syringe Therapeutic Categories: Dermatology; Gastroenterology; Ophthalmology; Rheumatology	
	Nov 2020 (Drug Shortages Canada, 2023e)	Discontinued (for business reasons)	Humira	
	Oct-Nov 2022 (Drug Shortages Canada, 2023d)	Resolved (Disruption of the manufacture of the drug).	Hulio	
	December 2022 (Drug Shortages Canada, 2023b)	Avoided shortage (Disruption of the manufacture of the drug)	Abrilada	

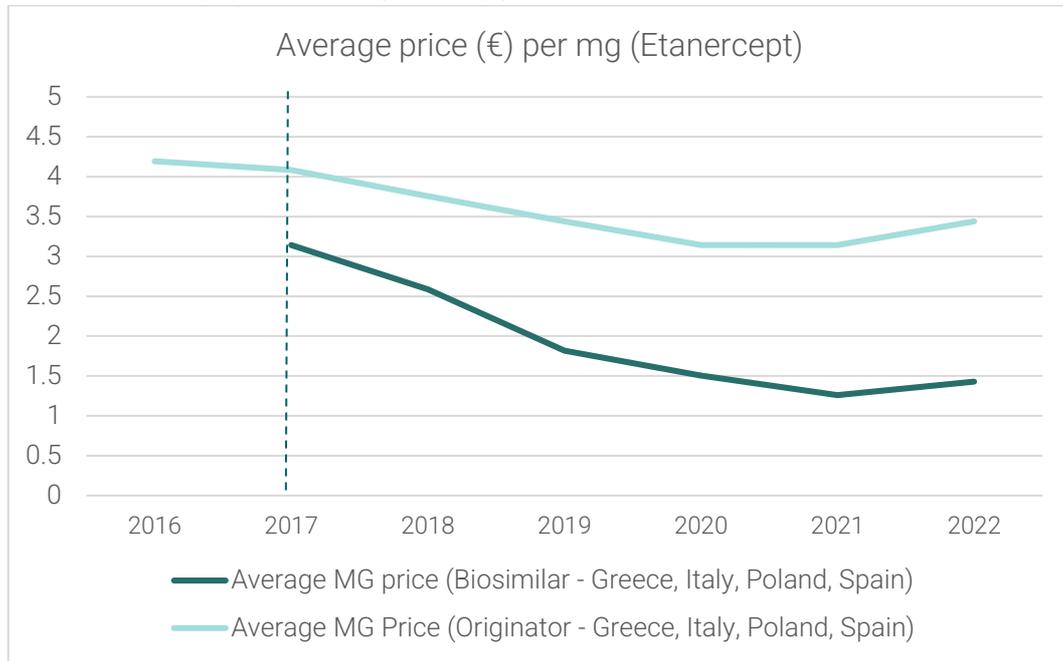
Bevacizumab	April 2023 - (AIFA, 2023)	Ongoing	Oyavas	
	September – November 2022 March - April 2023 (Agencia Española de Medicamentos y Productos Sanitarios, 2023)	Resolved	Aybintio	
	August 2020 - July 2021 March - May 2022 March 2023 (Agencia Española de Medicamentos y Productos Sanitarios, 2023)	Resolved	Zirabev	

Note: The shortages above that are referring to Italy and Spain are not reported in the EMA database because, as it has been mentioned earlier in this report, it is required to report it only when it is likely to affect more than one EU country.

Summary results

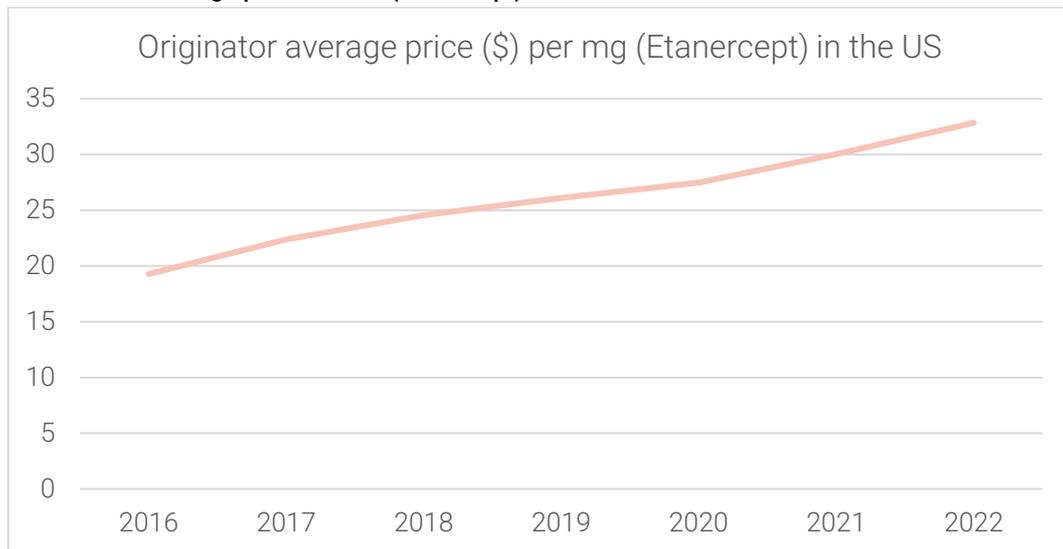
Figures 23, 24, and 25 illustrate the price erosion across time for Etanercept, Adalimumab and Bevacizumab, respectively.

FIGURE 23: Average price erosion (Etanercept).



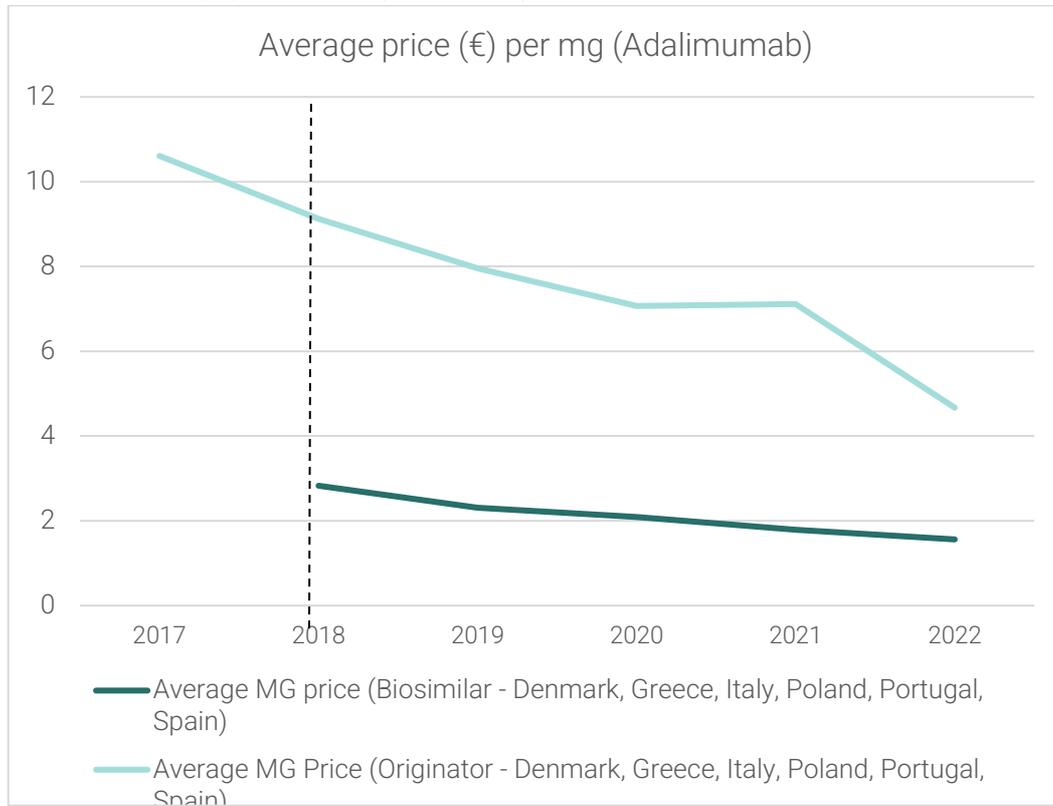
Source: Authors' calculations based on prices in Greece, Italy, Poland, and Spain. Note: The dashed line indicates the data point when the first biosimilar of our data entered in the market.

FIGURE 23a: Average price erosion (Etanercept) – United States.



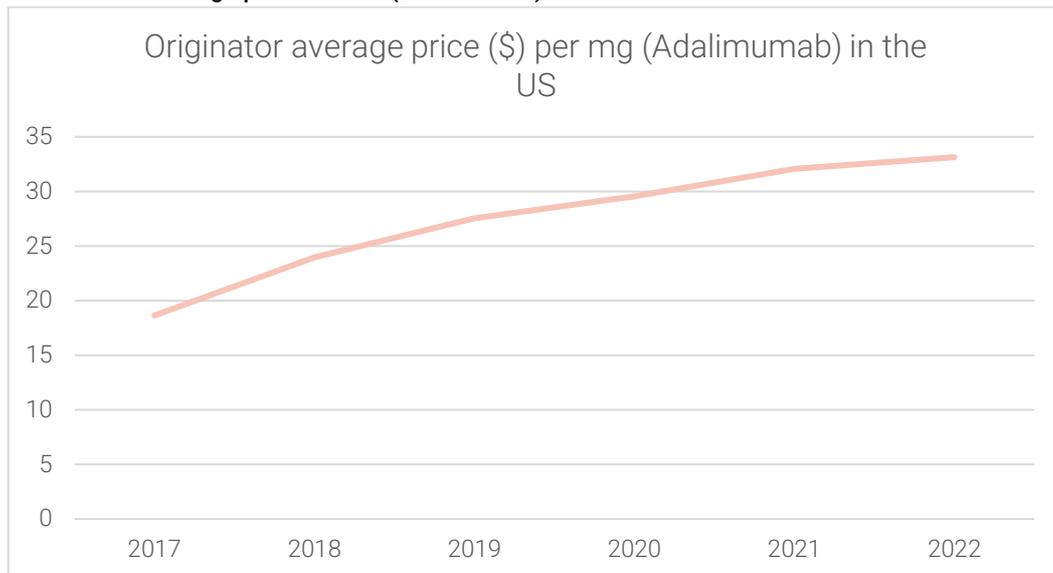
Source: Authors' calculations based on Medicare Part D sales in the US.

FIGURE 24: Average price erosion (Adalimumab).



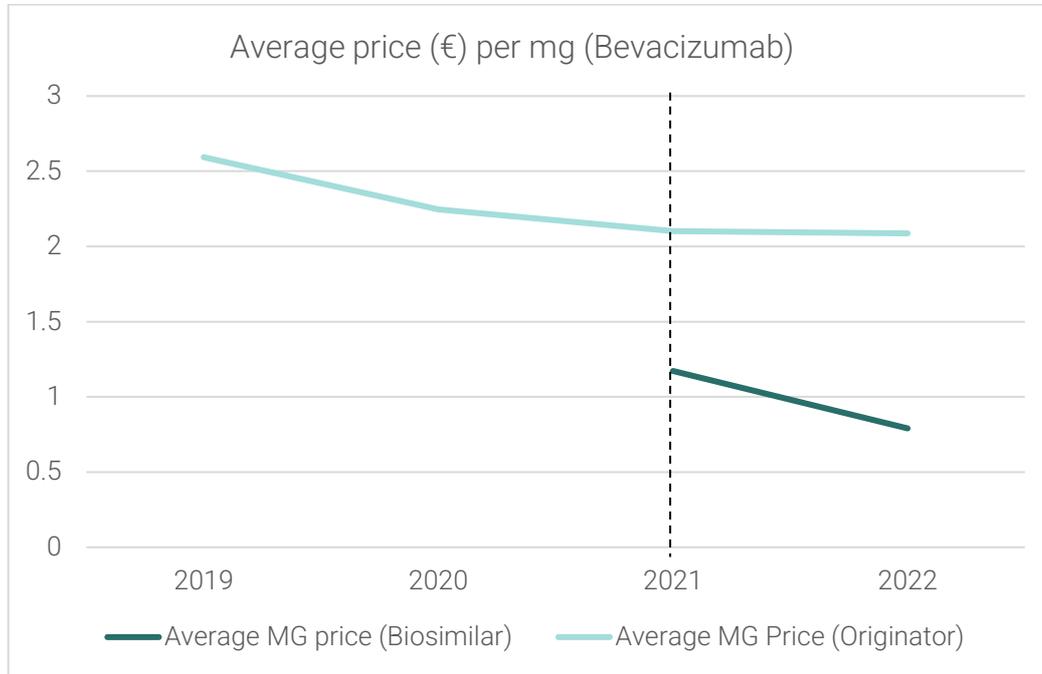
Source: Authors' calculations based on prices in Denmark, Greece, Italy, Poland, Portugal, and Spain.
Note: The dashed line indicates the data point when the first biosimilar of our data entered in the market.

FIGURE 24a: Average price erosion (Adalimumab) - United States.



Source: Authors' calculations based on Medicare Part D sales in the US.

FIGURE 25: Average price erosion (Bevacizumab).



Source: Authors’ calculations based on prices in Denmark, Greece, Italy, Poland, Portugal, Romania, Serbia, Slovenia, and Spain. Note: The dashed line indicates the data point when the first biosimilar of our data entered in the market.

The table below shows the values, and relationship between the case studies’ related shortages and their main drivers. Detailed analysis for each case study can be found in the appendix.

TABLE 9: Case studies: summary results.

	Average price change of the originator (e.g., biologic)	Price change ¹ of other products with the same molecule (e.g., biosimilars)	Market concentration (in the year or the previous year of the shortage/discontinuation) <u>Herfindahl-Hirschman Index</u>	Demand and competition	Patent expiration (of the originator)
Etanercept	+ 25%	- 60%	(4,446 , 4,853) Concentrated market	Shortage occurred when there was the highest demand for biosimilars	USA: 2012 EU: 2015

				and 4 competitors	
Adalimumab	- 14%	- 81%	(3,155 , 6,684) Concentrated market	Shortage occurred when there was the highest demand for biosimilars and > 6 competitors	USA: 2016 EU: 2018
Bevacizumab	- 24%	- 48%	(2,084 , 6,920) Concentrated market	Shortage occurred when there was the highest demand for biosimilars and > 4 competitors	USA: 2019 EU: 2022

Note 1: Price change between the year of shortage and since the year of entrance of the drug or based on the earliest point of data availability.

Note 2: We consider that the drug market is global and policy changes or/and strategic decisions in one country have spillover effects (in terms of prices, market size, and other factors) to other countries.

Note 3: More details on the analysis for each case study can be found in the appendix.

4.1.1 Range for documenting drug shortages/discontinuations

We utilise the case studies results to capture trends around current and upcoming shortages/discontinuations caused by price erosion and other explanatory factors. Based on the case studies, we find the relationship and a benchmark range where the explanatory factors for a given shortage are correlated with the shortage in a disease area.

TABLE 10: Case studies: Indicative benchmark ranges to capture trends around drug shortages.

Explanatory factors for a shortage in a disease area	Range
Price change of the originator (e.g., biologic).	(-24% , +25%) in the year or the previous year of the shortage/discontinuation occurrence.
Price change of other products with the same molecule (e.g., biosimilars).	(-48% , -81%) in the year or the previous year of the shortage/discontinuation occurrence.

Market concentration	Herfindahl-Hirschman Index (HHI): between 2,084 and 6,920 , in the year or the previous year of the shortage/discontinuation, which means that there is a (moderately and highly) concentrated market (i.e. prices go down due to government policies e.g., tenders and not because of competition)
Demand and competition	Shortages when the highest demand for biosimilars and >=4 competitors occur.
Patent expiration	Originator's lowest price in (1 year, 5 years) after patent expiration.

5 Discussion and Conclusion

In the first part of this report, we document and discuss the types and drivers of drug shortages from both the academic and grey literature. In addition, we examine some of the current and proposed government policies aimed at addressing the shortages.

In the second part of the report, we analyse drug shortages databases and provide descriptive evidence regarding the characteristics of drug shortages. We perform further analysis, where we measured the average duration of drug shortages and proposed a framework, which is validated through real-world case studies, for examining trends and multi-factor relationships in drug shortages.

In summary, this research finds that drug shortages are a global and industry-wide phenomenon, in which the generic and biosimilar markets are most heavily affected. The causes of drug shortages are interlinked, multifactorial, with the root cause often difficult to establish. Shortages are caused by a wide range of disparate factors not explored in detail in our study, which include active ingredient shortages, vile shortages, and supply chain issues, among other things. Among the market-based factors that we explored, we found that price erosion is likely a strong explanatory factor driving the shortages; low prices in the generic and biosimilar markets in particular appears to be a key driver of drug shortages, since it often underlines many of the causes of drug shortages. For example, supply issues may be partly due to sustained underinvestment in manufacturing facilities, as low profits and low prices may lead to a lack of incentive to invest.

Moreover, drug shortages can have a large economic and health impact on patients. On the patient-side, this can be due to adverse events from taking a substitute drug or prescribing errors. The economic impacts can be greater out-of-pocket costs for patients, as well as greater resources being diverted to managing shortages, rather than on other healthcare resource use. These impacts should be explored further in future research.

Since the COVID-19 pandemic, where drug shortages have become more of a critical issue, governments globally have been making efforts to address drug shortages, with some policy proposals attempting to address the underlying causes. However, the success of these policies has not been proven yet. The European Commission has proposed measures against shortages, which on the one hand do aim to target several causes of shortages, but on the other hand are questionable in terms of how feasible they are or how they (e.g., the Voluntary Solidarity Mechanism) will be perceived by governments. Other potential policies (e.g., on partnerships and diversification of supply chain), could be more effective if they consider other aspects too, such as price levels and manufacturer incentives in their design.

From the database analysis, we show that increased medicine demand, particularly in recent years, as well as the disruption or discontinuation of product manufacture, are major causes of drug shortages. Furthermore, in most instances, drug shortages affect off-patent medicines, demonstrated by the high proportion of off-patent drugs in shortage in each database, as well as the manufacturers suffering the most shortages being primarily generic/biosimilar manufacturers.

Paediatric, Gastroenterology, Anaesthesia, Nervous system, Cardiovascular and Anti-infectives are the main therapeutic classes experiencing shortages, although there are many shortages across



different therapeutic areas. Infusion and Injectables followed by Tablets and Capsules are the most common drug presentations to experience drug shortages and the duration of shortages has either increased or remained the same.

Finally, in order for different stakeholders and policy makers to be able to better understand the relationship between shortage drivers (e.g., price erosion) and actual shortages, we propose a framework consisting of five correlated factors. These are outlined and identified in Section 2, and they have been used in this analysis. The framework could also be applied in future research in the field, when capturing trends in drug shortages and determining shortages' factors value ranges.

Also, we populate the framework with three case studies that allow us to capture trends around current and upcoming shortages/discontinuations caused by price erosion and other explanatory factors.

We find that price erosion is unlikely to be driven by competition between manufacturers, as the markets are concentrated, but instead from other dynamics that are captured in the literature (e.g., tenders). As a result of price erosion, the pharmaceutical market's sustainability and competitiveness is under threat (Francois et al., 2023). Thus, there is a need to monitor the level of competition in off-patent medicinal markets on a regular basis in order to identify market sustainability and competition related issues.

Overall, it seems that all the identified factors in the literature and in our framework are related to price erosion either directly or indirectly and therefore price erosion is likely to be one of the most significant drivers of shortages.

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Appendix

ADDITIONAL FIGURES

FIGURE A1: FDA: Incidence of shortages (2014-2023, filtered by Generic name).



*Projection based on current rate of drug shortages in 2023.

FIGURE A2: FDA: Status of shortages (filtered by Generic name).

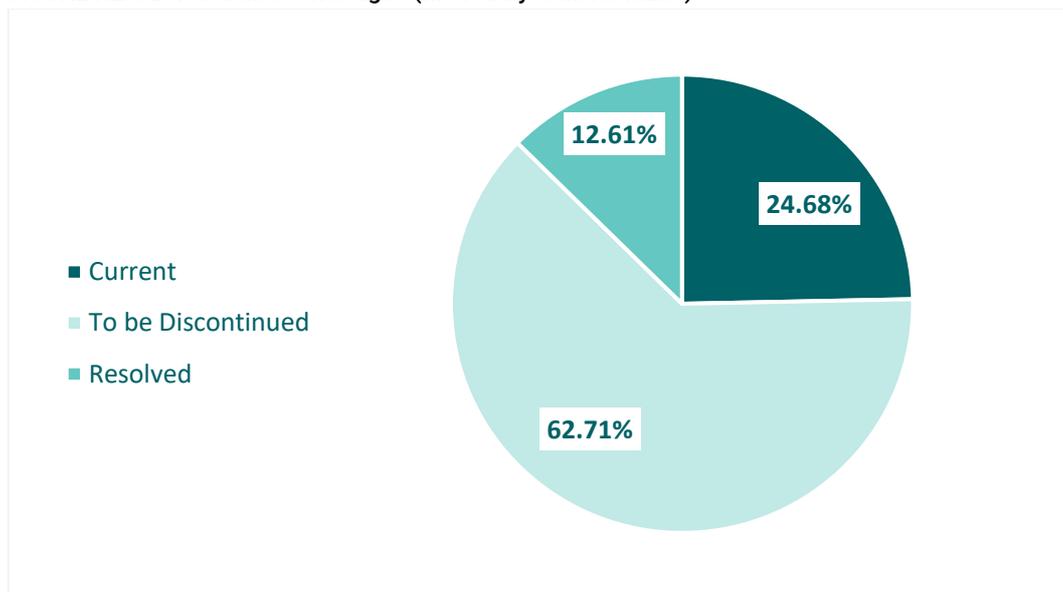


FIGURE A3: FDA: Reason for shortage (2014-2023, filtered by Generic name).

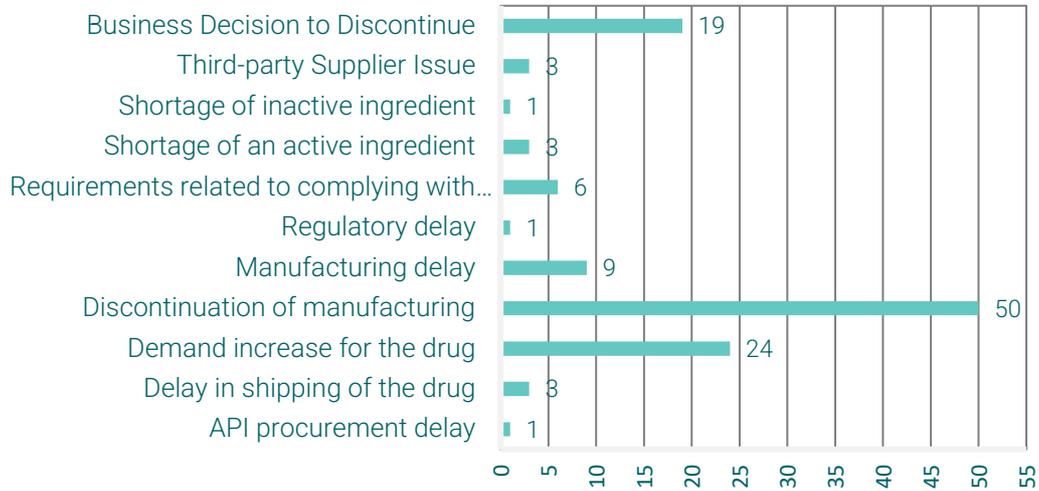


FIGURE A4: FDA: Therapeutic area shortages (2014-2023, filtered by Generic name).

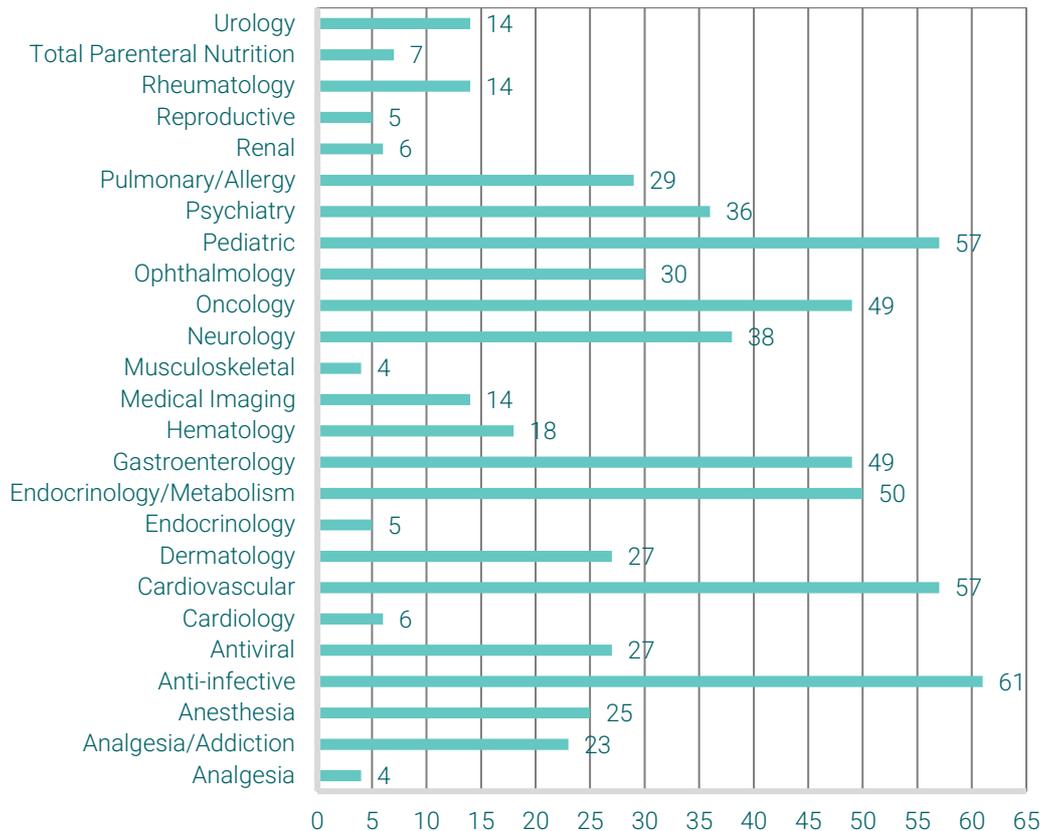


FIGURE A5: FDA: Shortages based on drug presentation (2014-2023, filtered by Generic name).

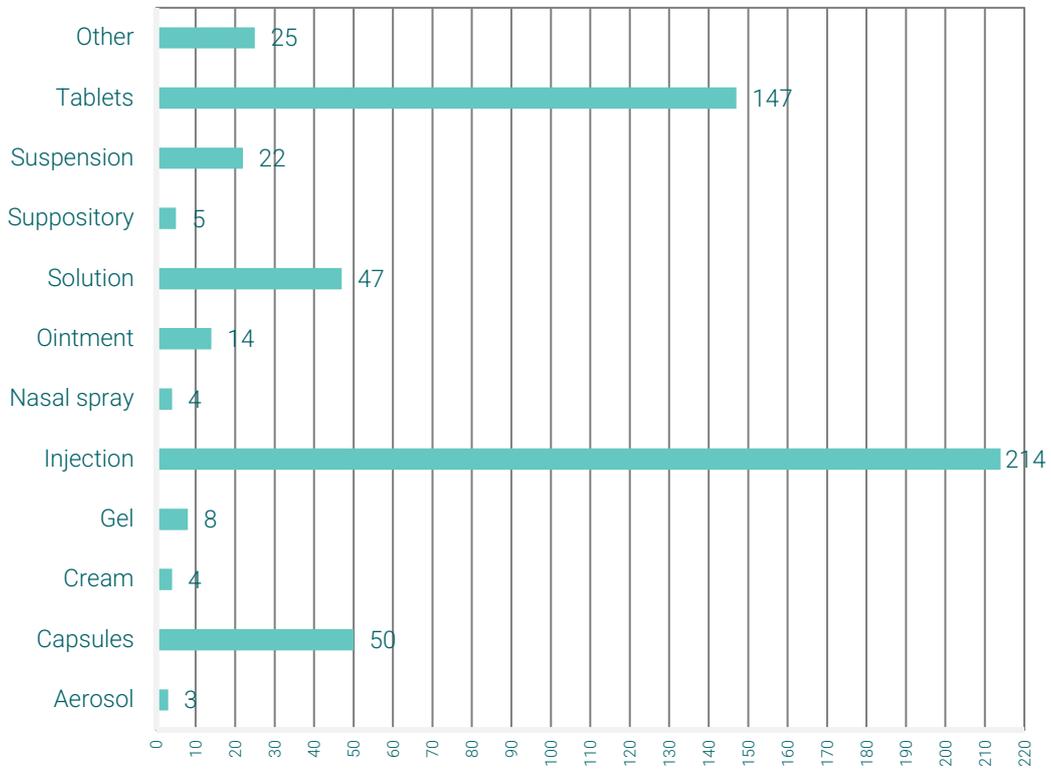


FIGURE A6: FDA: Oncology vs Non-Oncology shortages (filtered by Generic name).

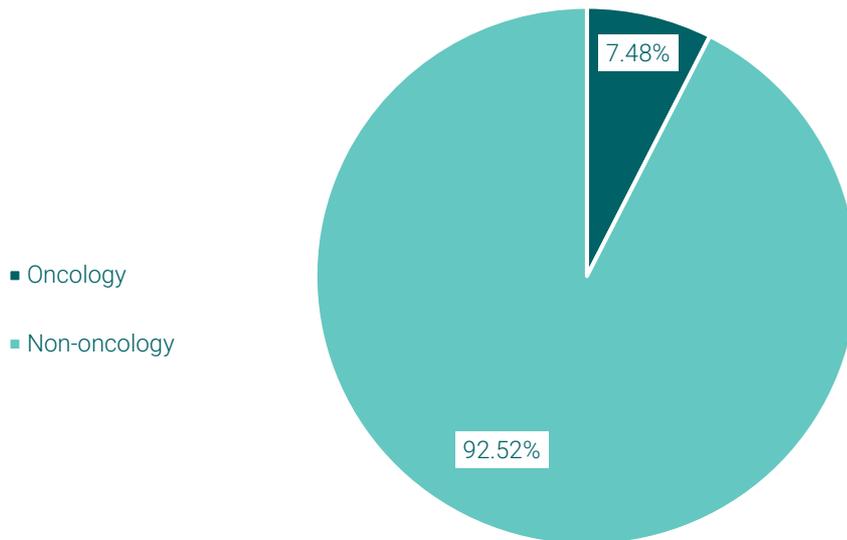


FIGURE A7: FDA: Pediatric vs Non-Pediatric shortages (filtered by Generic name).

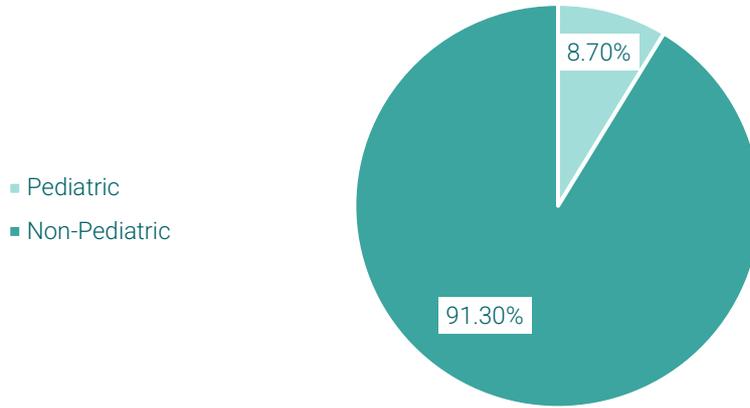
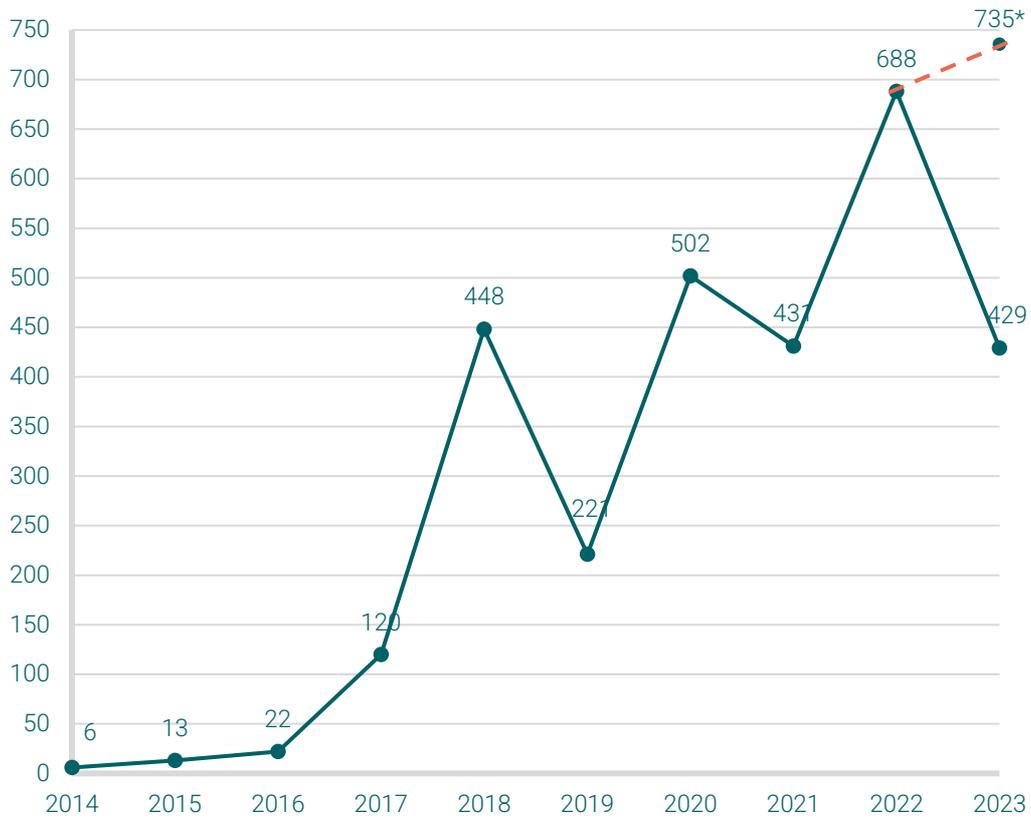


FIGURE A8: FDA: All shortages entries.



*Projection based on current rate of shortages in 2023.

FIGURE A9: FDA: Status of all shortages entries.

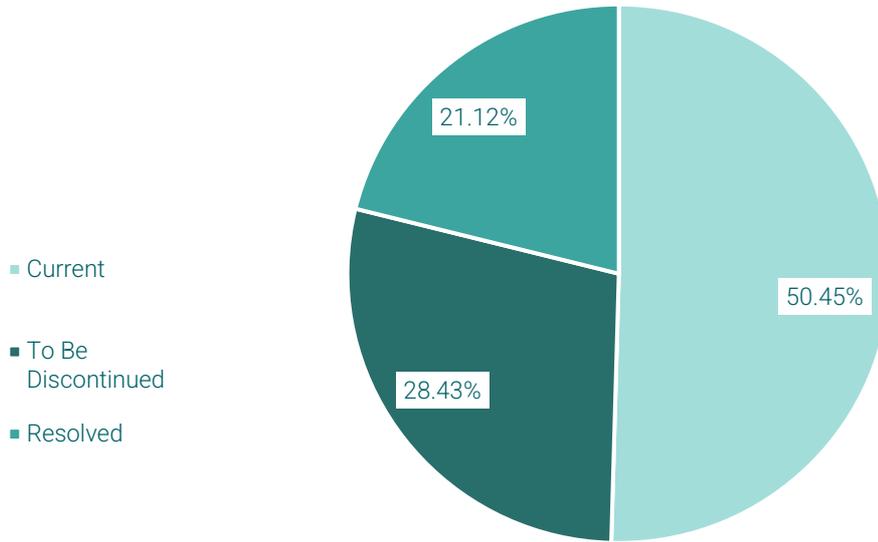
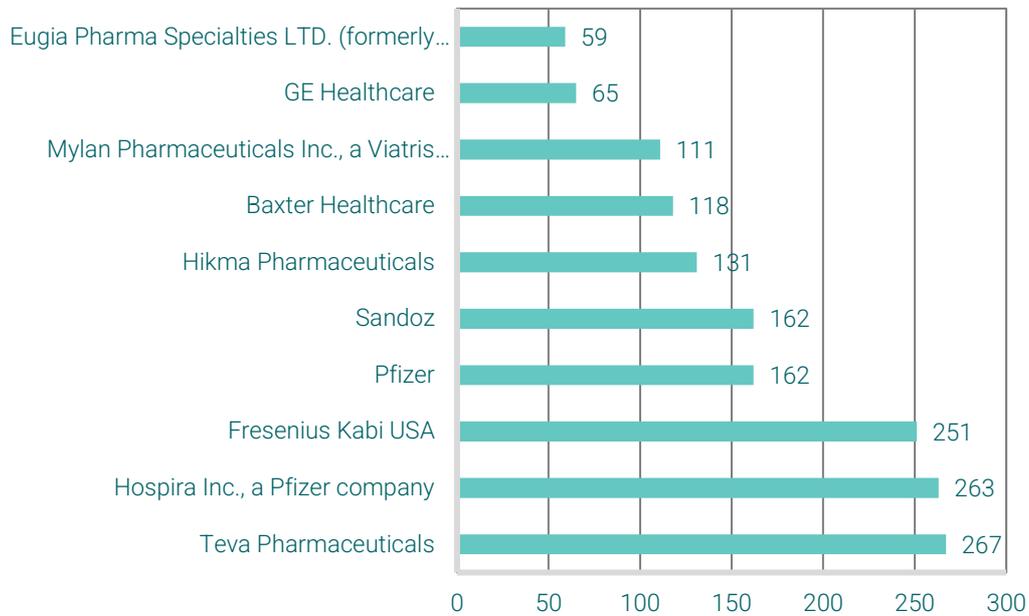


FIGURE A10: FDA: Top 10 companies experiencing the most shortages (2014-2023, no filter) at the time of the analysis.



Note: Authors' calculations based on FDA (2023). For the calculations, the number of shortages of subsidiaries have been included to the to the shortages of the parent company. Also, this graph

calculates the number of the shortages based on the different forms, strengths, etc of a drug. For example, if a drug is in shortage and the manufacturer produces it in three different forms which are also in shortage, then we consider this to our analysis as three shortages.

FIGURE A11: Canada: Incidence of shortages (2014-2023, filtered by ingredient).

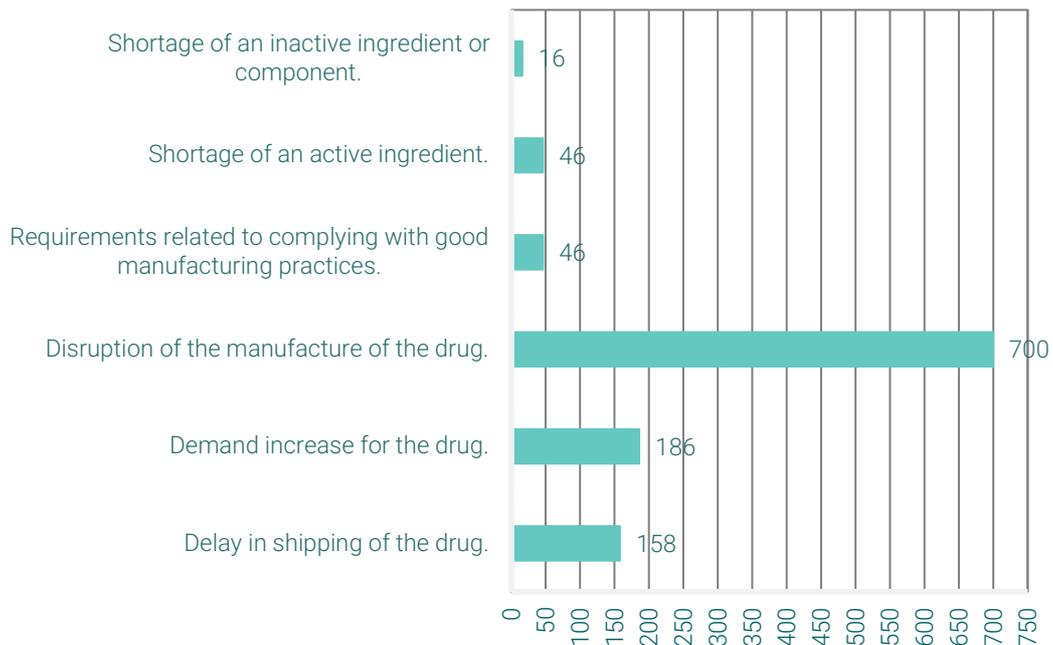


FIGURE A12: Canada: Therapeutic area shortages (2014-2023, filtered by ingredient).

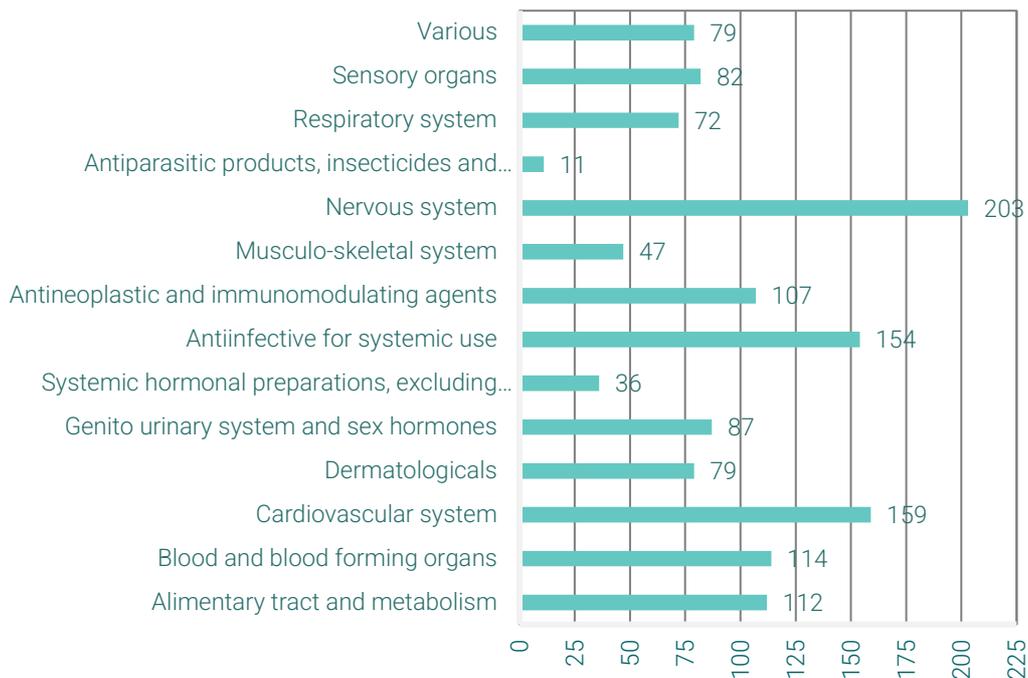


FIGURE A13: Canada: Shortages based on drug presentation (2014-2023, filtered by ingredient).

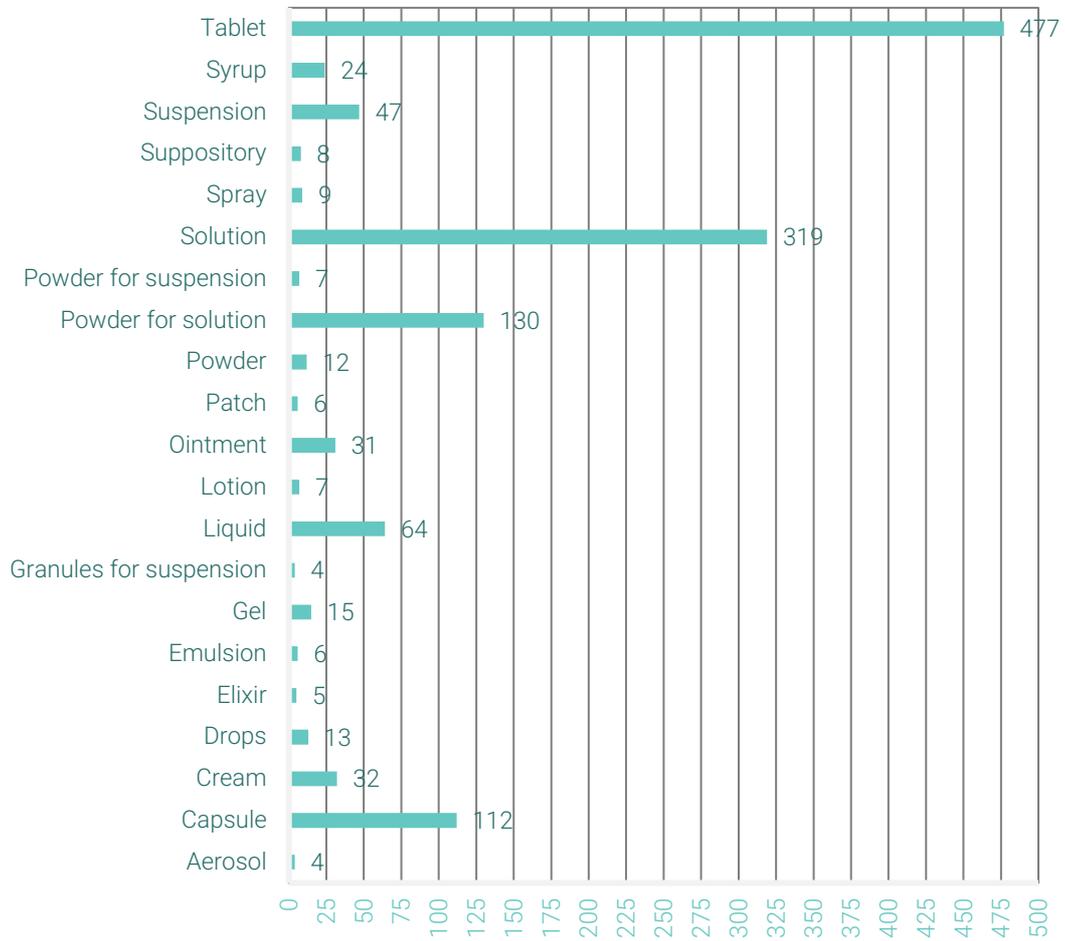
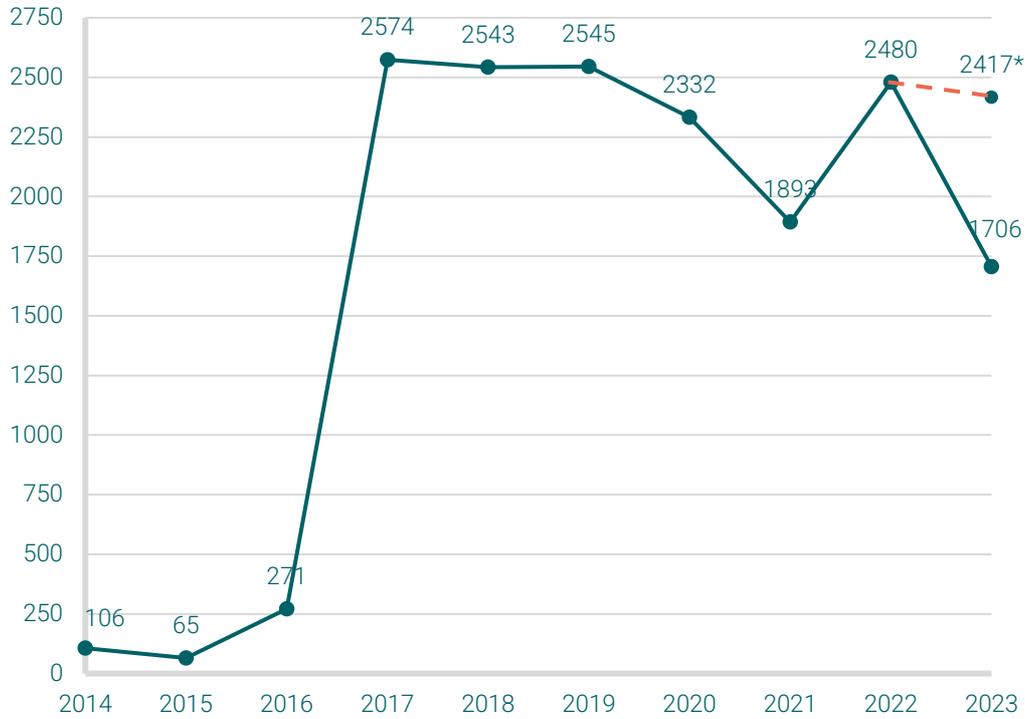


FIGURE A14: Canada: All shortages entries.



*Projection based on the current rate of shortages in 2023.

FIGURE A15: Canada: Status of all shortages entries.

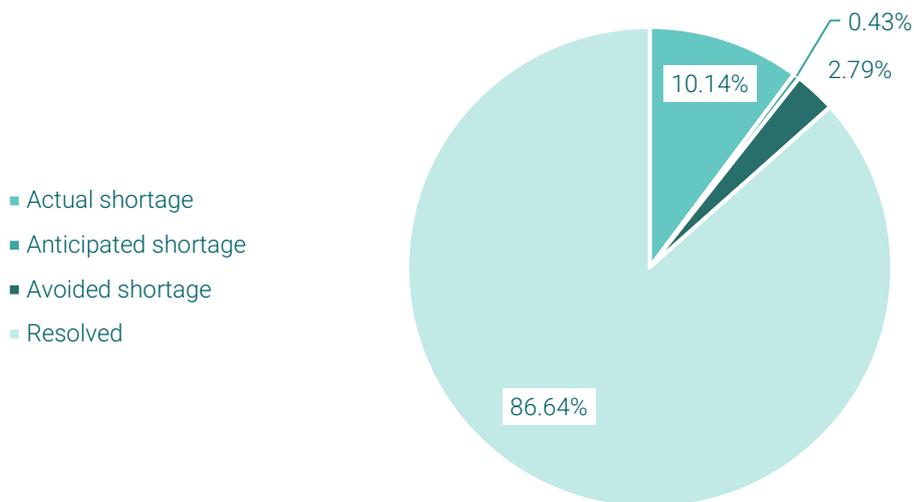
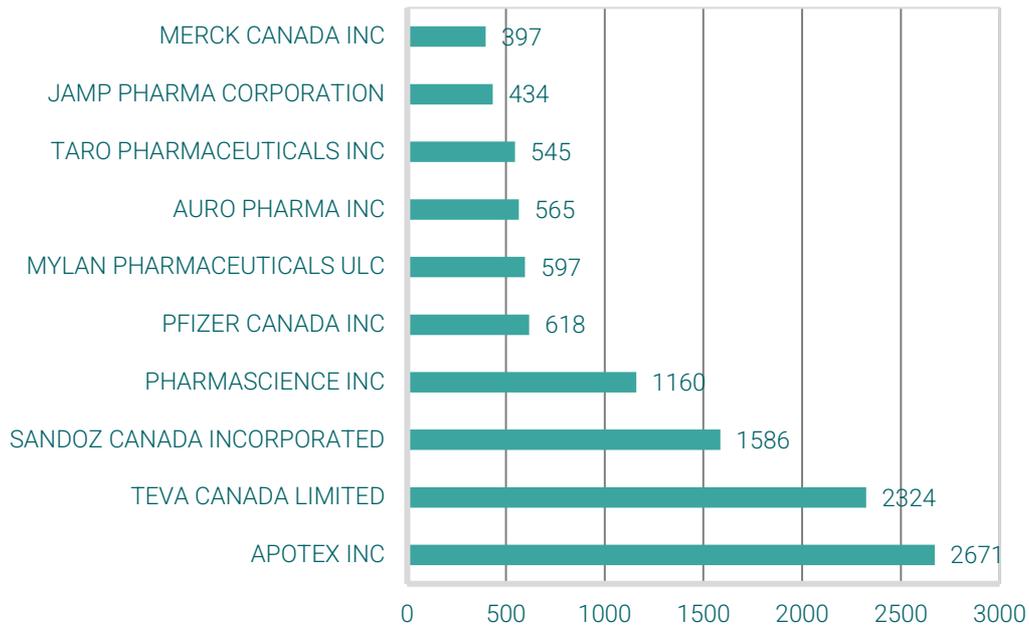


FIGURE A16: Canada: Top 10 companies experiencing the most shortages (2014-2023, no filter) at the time of the analysis.



Note: Authors' calculations based on [Drug Shortages Canada \(2023\)](#). For the calculations, the number of shortages of subsidiaries have been included to the to the shortages of the parent company. Also, this graph calculates the number of the shortages based on the different forms, strengths, etc of a drug. For example, if a drug is in shortage and the manufacturer produces it in three different forms which are also in shortage, then we consider this to our analysis as three shortages.

Etanercept

For the Etanercept case study, we collected data from: **Greece, Italy, Poland, Spain, and the United States**. The last average price of the biologic before the biosimilars entered the market was approximately 4.2 euros per mg and 35% higher than the average price per mg of the first biosimilars, in the examined EU countries.

TABLE A1: Average MG price (Etanercept).

Year	Average MG price (Biosimilar – Greece, Italy, Poland, Spain,)	Average MG Price (Originator – Greece, Italy, Poland, Spain)	Average MG Price (Originator – United States)	Average MG Price (Originator – Greece, Italy, Poland, Spain, and the US)
2016		4.19	19.28	11.74
2017	3.14	4.08	22.39	13.24
2018	2.59	3.76	24.57	14.16
2019	1.82	3.44	26.11	14.78

2020	1.51	3.14	27.49	15.32
2021	1.26	3.14	30.04	16.59
2022	1.43	3.44	32.85	18.14

For the biosimilars there was a 60% decrease in the average price from 2017 to 2021 (one year before the shortage). From 2016Q1 to 2017Q2, there was one biosimilar; from 2017Q3 to 2020Q2 there were two biosimilars; and from 2020Q3, there were three biosimilars. Moreover, 2021 is the year that average prices for both the originator and the biosimilars were the lowest in the EU (this is one year before the shortage).

Also, we notice that it was at the point (i.e., 2022) that the demand for the biosimilars peaked that shortages discontinuation for the biologic were faced. This is the year that in the US the average price per mg for Enbrel was the highest. So, an explanation for the discontinuation in Canada is probably to serve the demand in the US due to the high price.

TABLE A2: Demand: Average number of standard units (Etanercept).

Year	ENBREL - PFIZER	BENEPALI - BIOGEN	ERELZI - NOVARTIS	NEPEXTO - VIATRIS
2016	3,606,726			
2017	3,446,350	558,069	7,374	-
2018	3,136,328	857,676	93,175	-
2019	2,920,453	980,418	201,379	-
2020	2,768,396	1,045,025	277,089	1,126
2021	2,643,677	1,085,701	385,674	10,702
2022	2,477,570	1,079,612	541,765	23,726

Note: This table includes the average number of standard units based on Greece, Italy, Poland, Spain, and the US.

In order to calculate the market concentration in all of our case studies, and based on our available data, we calculated the average number of standard units consumed every year based for each product competitor/manufacturer and then for each of them we divided it from the total number of standard units consumed in a given year to get the relevant market share. Then we applied the Herfindahl–Hirschman index (HHI): $HHI = \sum_{i=1}^n \text{Market share}^2$ to estimate the concentration of the market. In order to characterise the concentration levels, we used the U.S. Department of Justice definition (U.S. Department of Justice (Antitrust Division), 2018).

The market concentration in the year or the previous year of the shortage/discontinuation for Etanercept, was the following:

TABLE A3: Market concentration (Etanercept).

Year of or before the shortage	Herfindahl–Hirschman index (HHI)	Market concentration (Greece, Italy, Poland, Spain, and the US)
2021	4,853	Concentrated

2022	4,446	Concentrated
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Notes: Based on average calculations for all of the examined countries.

Adalimumab

For the Adalimumab case study, we collected data from: **Denmark, Greece, Italy, Poland, Portugal, Spain, and the United States**. The last average price of the biologic before the biosimilars entered the market was approximately 11 euros per mg and is approximately 40% times higher than the average price per mg of the first biosimilars, in the examined EU countries. Based on the average price of all the examined countries (including the US), there is the lowest increase (3.1%) in the average price of the originator from 2019 to 2020 (when the first shortage occurred) and a 34% decrease in the average price of the originator from 2021 to 2022 (when there were disruptions in manufacturing biosimilars). Accordingly, for the biosimilars Hulio and Abrilada there was a disruption in 2022, when the average MG price was the lowest. For the biosimilars, there was a 26% decrease in the average price from 2018 to 2020 and a 18% decrease in the average price of the originator from 2018 to 2019 (one year before the first shortage occurred).

TABLE A4: Average MG price (Adalimumab).

year	Average MG price (Biosimilar - Denmark, Greece, Italy, Poland, Portugal, Spain)	Average MG Price (Originator - Denmark, Greece, Italy, Poland, Portugal, Spain)	Average MG Price (Originator - United States)	Average MG Price (Originator - Denmark, Greece, Italy, Poland, Portugal, Spain, and the US)
2017		10.61	18.64	14.62
2018	2.83	9.12	23.98	16.55
2019	2.31	7.96	27.54	17.75
2020	2.09	7.07	29.56	18.32
2021	1.79	7.12	32.06	19.59
2022	1.56	4.67	33.14	12.66

From 2018Q4 to 2019Q1, there were four biosimilar competitors, while from 2019Q2 to 2021Q1, there were five biosimilar competitors. In 2021Q2, we have six biosimilar competitors, while between 2021Q3 and 2022Q1 there are seven biosimilar competitors. After that there are eight biosimilar competitors. 2022 is the year that average prices for both the originator and the biosimilars were the lowest.

When the price for the originator stopped to increase significantly, more biosimilars entered the market. We notice that at the point (i.e., 2022) that the demand for the biosimilars peaked, shortages were faced.

TABLE A5: Demand: Average number of standard units (Adalimumab).

Year	HUMIRA - ABBVIE	AMGEVITA - AMGEN	HYRIMOZ - NOVARTIS	IMRALDI - BIOGEN	HULIO - VIATRIS	IDACIO - FRESENIUS	YUFLYMA - KERN PHARMA	HUKYNDRA - STADA	XILBRILADA - PFIZER	ADALIMUMAB L.U. - LAB UNKNOWN
2017	3,186,793	-	-	-	-	-	-	-	-	-
2018	3,384,928	6,906	5,409	10,964	783	-	-	-	-	-

2019	3,106,690	287,330	123,108	262,963	39,928	1,506	-	-	-	-		
2020	2,853,431	484,275	344,524	422,482	105,092	21,136	-	-	-	-		
2021	2,776,246	629,683	557,887	464,802	162,004	97,793	1,425	-	183	-		
2022	1,116,045	704,436	756,273	497,614	198,925	219,225	33,036	2,706	3,441	-		

Note: This table includes the average number of standard units based on Denmark, Greece, Italy, Poland, Portugal, Spain, and the US.

The market concentration in the year or the previous year of the shortage/discontinuation, was the following:

TABLE A6: Market concentration (Adalimumab).

Year of or before the shortage	Herfindahl–Hirschman index (HHI)	Market concentration (Denmark, Greece, Italy, Poland, Portugal, Spain, and the US)
2019	6,684	Concentrated
2020	3,955	Concentrated
2021	4,891	Concentrated
2022	3,155	Concentrated

Notes: Based on average calculations for all of the examined countries.

Bevacizumab

For the Bevacizumab case study, we collected data from: Bulgaria, Denmark, Greece, Italy, Poland, Portugal, Romania, Serbia, Slovenia, and Spain.

The last average price of the biologic before the biosimilars entered the market was approximately 2.5 euros per mg and is double than the average price per mg of the biosimilars. For the biosimilars there was a 48% decrease in the average price between 2021 and 2022 and a 24% decrease in the average price of the originator from 2019 to 2022 (2022 is the year when two shortages occurred and Avastin’s patent expired in Europe). For the biologic drug, the price decreased 15% when the first shortage occurred.

TABLE A7: Average MG price (Bevacizumab).

Year	Average MG price (Biosimilar)	Average MG Price (Originator)
2019		2.59

2020		2.25
2021	1.17	2.10
2022	0.79	2.09

From 2019Q1 to 2020Q1, there was one biosimilar, while from 2020Q3 to 2021Q1, there were four biosimilars. From 2021Q3 to 2022Q3, there were 12 biosimilars. Finally, 2022 is the year that average prices for both the originator and the biosimilars were the lowest. We notice that when demand for the biosimilars peaked (2022), shortages for the biosimilars were faced. An explanation for the shortages in Spain and Italy is probably caused due to the high demand in the EU.

Year	AVAS TIN - ROCH E	MVASI - AMGE N	ZIRAB EV - PFIZ R	AYBIN TIO - ORGA NON	OYAV AS - STAD A	ALYMS YS - ZENTIV A	ABEVM Y - VIATRI S	BEVACIZU MAB L.U. - LAB UNKNOW N	SYNDY MA - CIPLA	BEVACI ZUMAB TEVA - TEVA	VEGZELMA - CELLTRION	ALYMS YS - MABXI ENCE	ALYMS YS - G.L. PHAR MA	ALY MSY S - SERV IER
2019	463,994	-	-	-	-	-	-	1,174	-	-	-	-	-	-
2020	371,527	32,923	39,357	4,354	-	-	-	2,925	-	-	-	-	-	-
2021	178,573	152,713	105,154	56,968	5,975	3,978	609	3,781	274	65	-	1,802	107	300
2022	97,101	185,905	99,758	79,469	38,232	17,738	5,422	5,162	2,784	525	121	12,056	1,171	1,092

TABLE A8: Demand: Average number of standard units (Bevacizumab).

Note: This table includes the average number of standard units based on Bulgaria, Denmark, Greece, Italy, Poland, Portugal, Romania, Serbia, Slovenia, Spain and the US.

The market concentration in the year or the previous year of the shortage/discontinuation, was the following:

TABLE A9: Market concentration (Beverizumab).

Year of or before the shortage	Herfindahl–Hirschman index (HHI)	Market concentration (Denmark, Greece, Italy, Poland, Portugal, Romania, Serbia, Slovenia, and Spain)
2019	9,940	Concentrated
2020	6,920	Concentrated
2021	2,672	Concentrated
2022	2,084	Concentrated

Notes: Based on average calculations for all of the examined countries



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