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UNDERSTANDING THE IMPACT ON PATIENTS AND HEALTH SYSTEMS

The Cost of Drug Shortages

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Executive Summary

Across the globe, drug shortages are becoming increasingly common. Shortages have been observed across a range of therapeutic areas, particularly in the off-patent generic and biosimilar markets. Optimal policy design and decision-making require an understanding of the root causes of drug shortages, as well as their impact.

Very low prices in some generic and biosimilar markets are a key driver of drug shortages.

In previous research, we demonstrated that price erosion – caused mostly by cost-containment policies – is a key underlying driver of drug shortages. Commercially unattractive markets with low profit margins result in markets with few producers. This limits the bandwidth and resilience to deal with demand shocks or supply issues, resulting in a higher likelihood of a drug shortage occurring. Healthy generic/biosimilar markets should therefore be a key focus for policies addressing drug shortages, which may mean easing cost-containment policies in order to promote better investment in more resilient supply chains. This could mean higher prices and spending in the short-term, to *reduce the risk* and costly impact of drug shortages in the longer term.

For decision-makers to understand this trade-off, it is important to know more about the cost of drug shortages: their potential scale, how they manifest, and who bears those costs. This can then promote better-informed decisions around the design and scale of policies to mitigate drug shortages.

The disruptions caused by drug shortages impact health systems and patients via three key routes: price increases, additional healthcare resource use, and patient health impact.

To design a framework to estimate the cost of a drug shortage, we examined the literature over the last 10 years to identify the key themes and contributing elements to the impact and cost of drug shortages. Price increases were identified to be a key feature of drug shortage impact, encompassing both the cost of switching to higher-cost alternatives, as well as an upward trend in the price of the drug itself in shortage. Additional healthcare resource use captures the time and labour costs associated with managing the shortage, particularly for pharmacists, e.g. adjusting inventories, identifying alternatives and substitution protocols, and altering purchasing practices. Finally, the patient's health and quality of life impact must be considered as the most serious risk and consequence of a drug shortage, in cases where the shortage leads to delays in treatment or sub-optimal care.

We combine these three factors to generate a framework for estimating the cost of a drug shortage, which we then applied to three hypothetical case studies selected to represent a breadth of drug shortage impact scenarios across treatments with very different characteristics (biosimilar, small molecule generic, generic injectable), applications, patient populations, and market dynamics: trastuzumab, statins and saline.

The potential cost impact of drug shortages is huge. Relative stakeholder impact varies greatly depending on the type of drug in shortage. Effects differ by setting, with marked differences between the US and Europe.

Trastuzumab is a highly effective targeted biological therapy for the treatment of early-stage HER2-positive breast cancer. No large-scale shortages of trastuzumab have yet been reported. We found that the cost to the health system and patients of a trastuzumab shortage could be $519 million in the US and €16.6 million in the EU. The greatest impact of a shortage of trastuzumab is likely to be the health losses suffered by patients who either are denied or face a delay in access to treatment. The likely scale of the health system and patient disruption, as well as subsequent costs, is highly sensitive to the proportion of patients that we (assume) cannot switch treatments because of the limited total supply of trastuzumab resulting from the shortage.

Statins are a widely prescribed small-molecule therapy used to lower cholesterol and reduce the risk of heart and blood vessel disease. No large-scale shortages of statins have yet been reported. We predict that the cost of a statin shortage would be driven by additional healthcare resource use (EU) and price increases (US). Although patient disruption is likely to be small (given many alternative products that patients can switch to), the health system costs of managing a shortage and switching patients to alternative therapies are likely to be significant given the huge scale of statin use. For this reason, healthcare resource use represented the biggest proportion of costs for the EU. In the US, the cost of purchasing alternative statins is likely to be significant, particularly considering price increases that could occur. Total costs using our base case assumptions reached $1.45 billion in the US and €63 million in the EU. The large difference is explained by the inclusion (for US) or not (for EU) of costs associated with price increases of the drug in shortage and its alternatives. This is because for the EU case, we assume that the cost of purchasing substitute drugs is covered by the manufacturer.

Saline has multiple uses and is a key medical supply for hospital-based care. Disruption in saline production has become more commonplace over recent years. The market concentration of saline production is high, meaning that there is a high risk that any disruption will lead to a critical supply shortage, causing prices to rise and hospitals to ration. We anticipate the impact of a saline shortage to have the greatest impact on staff time and the health care system. The health system and patient costs of a saline shortage are very difficult to quantify given the broad use of saline across all elements of hospital care but are likely to be extremely high.

Policymakers should weigh shortage costs against expenditure control benefits to foster sustainable drug markets and resilient supply chains.

The literature review and illustrative case studies highlight the broad spectrum and heterogeneity of drug shortage impacts, in terms of the stakeholders they most impact, the degree of impact, and how they differ across settings. They also demonstrate the potentially huge magnitude of those costs.

While precise estimates are impossible, and results are highly sensitive to changes in the assumptions made, there is no doubt of the critical impact of drug shortages on patients and health systems. Although databases tracking the number of shortages exist, further research is needed to track their impact. We contribute a general framework for the cost estimation of a drug shortage, applied to some hypothetical case studies. These estimates need to be refined and generalised with further research.

We find that the costs to society of key medicinal products running into shortage could be huge. Existing policies that emphasize cost-containment and expenditure control, particularly for off-patent medicines, overlook the risks of drug shortages that those policies may cause, and their potential catastrophic costs. Policymakers should consider this trade-off, in order to promote sustainable drug markets and resilient supply chains in the long-term.

1. Introduction

Drug shortages are becoming commonplace, occurring across a broad range of therapeutic areas, and affecting low-, middle- and high-income countries. Drug shortages are generally defined as periods of time when the supply of a medicine does not meet the demand for that medicine (FDA, 2024; European Commission, 2023). In the US, the number of ongoing and active shortages by the first quarter of 2024 totals 323, *"[…] the highest since we began tracking data in 2001"* (ASHP, 2024). European countries and Canada have also reported significant drug shortages in recent years (Videau et al., 2019; Videau, Lebel and Bussières, 2019), which is consistent with rising reports of shortages across South America (Acosta et al., 2019), Africa (Yenet, Nibret and Tegegne, 2023), Asia (Yang et al., 2018; Koizumi et al., 2021; Chebolu-Subramanian and Sundarraj, 2021) and Australia, among others, in Oceania (Tan, Moles and Chaar, 2016).

A report by the OECD found medicine shortage notifications totalling more than 46,000 for the period of 2017-2019 across the 14 OECD countries included in the study. Notifications per country ranged from 195 in Germany to 8,863 in Iceland (Chapman, Dedet and Lopert, 2022). Even more concerning than the widespread nature of drug shortages is the fact that the trend is rising. Over the study period, the number of shortage notifications in a sample of 14 OECD countries increased by 60%, from 11,000 to more than 17,500 (Chapman, Dedet and Lopert, 2022). In the US, the number of active, shortages increased by 46%, from 220 in Q3 2021 to 323 in Q1 2024 (ASHP, 2024). In the EU, shortage notifications have increased steadily since 2010, de Jongh et al. (2021) show in Figure 2 of the report *Future-proofing pharmaceutical legislation study on medicine shortages*. To add to the issue, the COVID-19 pandemic exacerbated existing medicine supply issues and demonstrated concerning global medicine supply vulnerabilities (Callaway Kim et al., 2024; Sen-Crowe, McKenney and Elkbuli, 2021; Lau et al., 2022; Dapke et al., 2021). The continuous global increase of drug shortages over the last 20 years therefore represents a general dynamic with no visible ceiling in the short term.

The impact of drug shortages is far-reaching and compounding. Drug shortages predominantly affect off-patent medicines (Napier et al., 2024) which represent 60%-80% of total sales volumes in key markets globally (KPMG, 2020; IGBA, 2021). Drug shortages lead to poorer patient outcomes (Phuong et al., 2019) due to the associated treatment delays or impact of switching to an alternative treatment, if there is one. Even where alternatives exist, they may be less effective or have different adverse event profiles and/or lower adherence rates. Health systems face significantly increased labour costs and staff time utilisation to manage drug shortages, particularly for pharmacists (Kaakeh et al., 2011a). Managing drug shortages can lead to an unsafe environment for healthcare professionals and patients, with medication errors more likely and inefficiencies in healthcare delivery (Truong, Rothe and Bochenek, 2019; Caulder et al., 2015).

Policymakers are increasingly aware of the magnitude of the problem. Recently, the US Department of Health and Human Services (HHS) released the white paper *Policy Considerations to Prevent Drug Shortages and Mitigate Supply Chain Vulnerabilities in the United States* (HHS, 2024). The European Commission has also introduced policy proposals and measures to address drug shortages and mitigate their effects in the proposed Reform of EU Pharmaceutical Legislation (European Commission, 2024).

Optimal policy design and decision-making require a good understanding of the roots of the problem. In our previous report, we examined the drivers of drug shortages and policies to tackle them (Napier et al., 2024). The main drivers of drug shortages identified were price erosion, supply issues (including quality issues), generic markets characteristics, parallel trade, demand issues (including

shocks and fluctuations), inflexible tendering and regulatory issues. The common overarching factor that can be seen to crosscut all seven drivers identified is price erosion in drug markets. Healthy markets with competitive prices provide incentives for multiple manufacturers to invest and compete. Excessive price erosion, often as a consequence of cost-containment and expenditure-control policies, reduces the attractiveness for manufacturers to invest and supply in some markets, reducing the number of competitors, and as a result, increasing the risk of shortages (Napier et al., 2024).

Given the impact on patients and public health, policymaking must aim to address the drivers of shortages. These drivers are well-known targets as evidenced in the literature. But, to motivate and better inform policy changes, it is necessary to understand the potential costs and benefits of doing so. We have already suggested that promoting a healthy generic/biosimilar market is required to address the root cause of drug shortages, which may entail removing some of the aggressive cost-containment policies in place, thereby providing better incentives for manufacturers to invest, compete and build the required redundancies (e.g. surplus capacity and back-up systems) at each stage of the supply chain to make it more resilient and resolve shortages. In the short term, such a policy shift may drive prices up, increasing costs for health systems but leading to a reduced risk of shortage in the long term. It is important to understand this economic trade-off between the benefit of very low drug prices and the cost of drug shortages that low prices make more likely (Pauwels et al., 2014). To support this aim, we investigate the potential cost of no action: what is the potential scale of drug shortage costs, and who bears those costs?

Few attempts have been made to quantify the costs of drug shortages. This report provides indicative evidence of the potential magnitude of those costs based on three hypothetical drug shortage case studies. The results of the study thereby contribute to (i) methods development for the estimation of drug shortages costs, and (ii) better information and evidence on those costs, to inform policymaking.

In this report, we first outline our literature review (section 2) which informed our framework for cost estimation, described in section 3. In section 4, we outline the results of our three hypothetical case studies, demonstrating the potential scale of drug shortage costs and the variability in stakeholder impact. In section 5, we discuss the results, and potential policy implications. In section 6, we conclude the report emphasising the urgency for action required, as well as the need for further research.

2.Literature Review

In this section, we present the methods and results of the targeted literature review, the aim of which was to better understand and characterise the wide-reaching impacts of drug shortages.

2.1 Methods

Scope

The main objectives of the literature review were to:

1. Document and review the literature on the cost of drug shortages, identifying their impact in terms of monetary, patient, and health system costs.

2. Identify factors indicating disruption caused by a drug shortage in the health system.

3. Create a cost of drug shortage framework to provide a starting point for estimating the cost of a drug shortage.

Search Strategy and Databases

Table 1 below details the search strategy, which we performed in Google Scholar. We considered articles published between January 2013 and December 2023. We aimed to capture literature and analysis from different research perspectives (including economic, public policy and medical). In addition, we conduct a targeted review of data sources, key websites (news, grey literature), and expert authors.

TABLE 1 SEARCH STRATEGY

Domain	Search commands	Database information	Search Criteria
Cost of Drug shortages	(drug shortages (AND (cost of drug shortages OR health costs OR monetary costs OR system costs health care system disruption OR patient impact OR small-molecule OR branded medicines OR generics OR biosimilars)) AND (shortage management OR drug shortage cost OR hospital OR procurement OR sub-optimal treatment OR medicines replacement OR hospital pharmacies OR hospital staff OR stock availability OR administrative efforts OR trade-offs OR health system disruption indicators OR drug shortage factor OR shortages management time OR drug type OR price increase OR 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)	Google Scholar hits: 17,900 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: 08 November 2023

Inclusion and Exclusion Criteria

We reviewed titles and abstracts and included and excluded papers by assessing their relevance against our literature review objectives. Papers from a US and European perspective were prioritised, but papers from a wider international perspective were included when they were particularly relevant.

Evidence Assessment

After applying the search criteria, we screened the first 100 hits. To ensure our literature review was informed by studies of the highest quality and relevance, we performed an evidence assessment using a green, amber, and red colour coding system to consider publication quality and publication relevance (based on the objectives and setting), as summarised in Table 2. This process is designed to provide an objective assessment, inform our decision-making and provide transparency regarding the basis for our decisions.

From the 100 examined papers, we classified 18 as red and 40 as amber for either publication quality or relevance, or both. Forty-two were classified as green for both quality and relevance. We disregarded the 18 studies classified as red, and after a full-text review, a total of 22 papers were included. An additional seven sources were identified from a targeted review of the grey literature

.

TABLE 2 EVIDENCE ASSESSMENT

	Green	Amber	Red
Publication quality	Peer-reviewed papers in top journals, journals with an impact factor of more than one, highly cited and field expert authors.	Mostly 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	Cost of shortages and healthcare system disruption (price increase, cost of distribution to operations, patient impact), and indicators of disruption in the healthcare system.	General analysis on the cost of shortages.	Mainly journalism, media news, blogs, etc. on drug shortages.

2.2 Results

From our analysis of the literature, the impact of drug shortages can be grouped into three categories:

- The impact of drug shortages on prices;
- Additional healthcare resource use to prevent and manage drug shortages;
- The patient impact of drug shortages.

2.2.1 Price Impact of Drug Shortages

Many studies found that drug shortages can impact the prices of the drugs themselves in shortage, as well as substitute drugs. In the US alone, a study from 2018 estimated that this effect is responsible for $230 million per year in additional costs (Hernandez et al., 2018).

Similarly, a report from the ASPE (the Office of the Assistant Secretary for Planning and Evaluation) found that drug shortages lead to higher drug prices (ASPE, 2023). Their analysis of US data found that there was a 16.6% increase in the price of drugs in shortage. They also observed an effect on the price of substitute drugs. In some cases, the price increase of substitutes was three times greater than the price increase of the drug in shortage (ASPE, 2023).

An analysis of prescription claims data from commercial health plans in the US was undertaken between 2008 and 2014 (Dave et al., 2018). The results showed that periods of drug shortages were associated with increases in the price of drugs that faced shortages, with longer duration of shortages leading to greater price increases (Dave et al., 2018).

Furthermore, a survey of healthcare system pharmacists in Southeastern US reported mark-ups of up to 300%-500% on medicines in shortage (Caulder et al., 2015), representing a significant cost impact. The price of medicines used in intensive care units have been found to be increasing, with drug shortages being one of the key drivers of the increase (Flannery et al., 2017).

Evidence of increased prices of drugs in shortage was only identified in the US setting, with no evidence found of this effect in Europe. However, a survey of European hospital pharmacists reported that over half of the respondents had to pay a higher price to procure from alternative sources 'either most of the time or always' when there was a drug shortage (Miljković et al., 2019).

2.2.2 Additional Healthcare Resource Use to Prevent and Manage Drug Shortages

Drug shortages have a significant impact on health systems, due to the additional labour costs both when managing and preventing them, and the opportunity cost of this time.

The most direct impact is the additional time spent by pharmacists in managing drug shortages. From both a US and European perspective, these activities involve increasing the inventories of certain drugs, identifying alternatives and substitution protocols, and altering purchasing practices; all of which have led to cost increases and adverse budgetary impacts (Goldsack et al., 2014; Wiggins et al., 2014; Miljković et al., 2019).

Three studies were identified that reported the time spent by hospital pharmacists in Europe to resolve drug shortages. In Belgium, hospital pharmacists spent a median of 109 minutes per week to a maximum of 216 minutes per week (De Weerdt et al., 2017a), with hospital pharmacists spending the most time dealing with shortages. In France, a survey of hospital pharmacists reported that over 50% spend more than four hours (240 minutes) a week managing drug shortages, with approximately 35% spending over six hours (360 minutes) per week (APM news, 2023). Taking a wider European perspective, the Pharmaceutical Group of the European Union (PGEU) in a 2022 survey, found that pharmacy staff were spending six hours and 40 minutes on average dealing with medicine shortages (PGEU, 2023). All these estimates represent a significant time cost associated with drug shortages.

Similarly, in the US, pharmacists and pharmacy technicians spend a significant amount of time responding to and mitigating the impact of medicine shortages (Costantino, 2021). Indeed, a 2011 study found that the total labour costs associated with managing drug shortages were $216 million annually, estimated from a survey of directors of pharmacies (Kaakeh et al., 2011b). A more recent 2019 estimate found that at least $359 million was spent a year on labour resources to manage shortages (ASPE, 2023). With an increasing incidence of drug shortages in recent years (Napier et al., 2024), the current figure is likely much higher.

Furthermore, shortages of certain pharmaceuticals, like vaccines and anti-microbials, can have external impacts, where the shortages could impact antimicrobial stewardship efforts (Beraud, 2021; Honda et al., 2020). This was seen in Japan, where a shortage of an anti-microbial led to increased consumption of alternatives, hence impacting stewardship efforts and potentially promoting antimicrobial resistance (Honda et al., 2020).

2.2.3 Patient Impact of Drug Shortages

When a drug cannot be delivered to meet patient demand in a timely way, all stakeholders are affected, whether this is economically, humanistically, or clinically. Impact on patients' health and quality of life should be considered most seriously. A survey of European hospital pharmacists found that 90% agreed that drug shortages were a current problem in delivering the best care to patients (Miljković et al., 2019). Similarly, in the US, the results of a survey found that a majority of hospitals have experienced drug shortages and that these have adversely impacted patients (Li et al., 2015b).

During times of shortages, out-of-pocket costs, rates of drug errors, adverse events, and mortality have been found to increase (Phuong et al., 2019). In addition, patients have experienced side effects, needed to postpone treatments, or have experienced suboptimal care (De Weerdt et al., 2017b; McKeever, Bloch and Bratic, 2013). Furthermore, both safety and clinical outcomes have been impacted due to delays or changes in treatment regime (Li et al., 2015a). All of these have a significant and direct impact on patients.

The impacts of substituting drugs are particularly observable in oncological drug shortages. Substitution often involves less effective and more toxic alternatives, and in some cases no suitable alternative is available (Nonzee and Luu, 2019). In a survey of hospital pharmacists, 45% reported that drug shortages have occurred in drugs that are life-sustaining or life-preserving, such as oncology drugs (Pauwels et al., 2015). Furthermore, shortages have been observed in multi-agent combination chemotherapy and supportive care agents, which make up the core of paediatric oncology treatment regimens (Unguru et al., 2019). Few alternatives exist to treat these very serious childhood cancers, with shortages resulting in medication errors, delayed administration, inferior outcomes, and patient deaths (Unguru et al., 2019).

2.2.4 Additional Impacts of Drug Shortages

Almost every stakeholder in the health system will be affected by drug shortages in some way (Pauwels et al., 2015), including patients, caregivers, healthcare providers, third-party payers, the pharmaceutical industry, and regulators (McKeever, Bloch and Bratic, 2013).

Manufacturers will likely see reduced profits when a drug is in shortage, patients or health systems pay more for alternative treatments, and society pays for the additional healthcare costs (De Weerdt et al., 2017b). In addition, a study found that lower-priced generic drugs were associated with an increased risk of shortage in comparison to medium- and higher-priced generics (Dave et al., 2018). Governments have to spend more on drugs in shortage, and substitutes (Donelle et al., 2018).

3. Framework for the Estimation of Cost

Drawing on the key themes in the literature, we developed an overarching framework for cost estimations, which we then apply to case studies of specific drugs. Each component of the framework will not necessarily apply to all types of drugs in shortage, with different shortages impacting the components to varying degrees. Furthermore, the geographical setting will impact the relative weight of each component, even for the same drug. For example, in the literature, there was scant evidence of price increases of drugs in shortage from a European perspective, whereas for the US this appeared to be an important feature of drug shortage costs.

Figure 1 below sets out the framework we have developed, informed by the literature review. It is composed of three elements:

1. The price increase of drugs
2. Additional healthcare resource use
3. Health impact to patients

FIGURE 1. FRAMEWORK FOR ESTIMATING THE COST OF A DRUG SHORTAGE

Note: Each element of the framework won't apply to all types of drug shortages, with different shortages impacting the elements to different degrees. Geographical setting also impacts the relative weight of each element, even for the same case study.

'**The price increase of drugs'** component accounts for both the switching to higher cost alternatives and the increase in the price of the drug in shortage. As mentioned above, there are multiple sources of evidence in the literature of this effect seen in the US (ASPE, 2023; Dave et al., 2018; Caulder et al., 2015; Hernandez et al., 2018). However, there is no evidence of prices of drugs increasing in Europe

as a result of drug shortages, although pharmacists have reported switching to more expensive alternatives (Miljković et al., 2019).

The **'additional healthcare resource use'** accounts for the time cost associated with managing and preventing drug shortages in the healthcare system. As the literature has evidenced from both a US and European perspective, this represents a significant amount of labour time (Goldsack et al., 2014; Wiggins et al., 2014; Miljković et al., 2019; De Weerdt et al., 2017b; PGEU, 2023; ASPE, 2023; Kaakeh et al., 2011b; Costantino, 2021).

The **'health impacts to patients'** captures the health losses patients suffer due to a drug shortage. In the literature, this can include drug errors, adverse events, side effects, delaying of treatment, and switching to less effective substitute drugs (Phuong et al., 2019; Li et al., 2015b; Nonzee and Luu, 2019; Unguru et al., 2019; De Weerdt et al., 2017b; McKeever, Bloch and Bratic, 2013). In order to convert to a scale in line with the other cost elements, these are monetised using the appropriate value of a QALY in the corresponding setting i.e. estimates prevailing cost-effectiveness threshold used (implicitly or explicitly) to support reimbursement decisions in those countries.

4. Case Studies

Leaning on the framework outlined in section 3, we have developed cost estimation models to provide illustrative estimates of hypothetical drug shortage costs. The aim is to show the potential scale and source of these costs, as well as highlight the heterogeneity in the impact of different shortages.

We selected three hypothetical case studies, chosen to represent examples that illustrate a breadth of shortages impact scenarios in treatments with very different applications, patient populations, and market dynamics. The case studies were also selected to represent different categories of drug for which a shortage may lead to a significant impact, namely

- *biologics - case study 1 trastuzumab* – a biologic for the treatment of patients with early-stage HER2-positive breast cancer. On top of the originator biologic there are six biosimilars available in the US (American Journal of Managed Care, 2024) and seven in Europe (Generics and Biosimilars Initiative, 2023). No shortages of trastuzumab have yet been reported in practice.
- *small molecule generics - case study 2 statins* – small molecule therapy used to lower cholesterol and reduce the risk of heart and blood vessel disease. There are many generic manufacturers of statins. No shortages of statins have yet been reported in practice (in the FDA or EMA databases).
- *generic injectables - case study 3 saline* – a crystalloid fluid i.e. an aqueous solution of electrolytes and other hydrophilic molecules, representing an essential part of hospital care, with diverse uses including fluid resuscitation, intravenous therapy, dilution of medication and wound irrigation. Manufacturing of saline is concentrated among just a few manufacturers and frequent shortages in supply have been observed.

While the examples are largely hypothetical and the quantification of shortage costs illustrative, we demonstrate:

1. the wide-reaching impact of drug shortages on patients, spending, and health system resources

2. that the impact on the health system and stakeholders varies greatly depending on the type of drug shortage.

3. that the cost impact of drug shortages in all cases is significant, but differs vastly depending on the setting, with marked differences between the US and Europe.

For each case study, the analysis was conducted in several steps. Firstly, the patient population is defined, and the key inputs for the analysis are set out. Following this, each component of the cost of a drug shortage framework is considered for cost calculations. The evidence to inform the estimates comes either from the results of the literature review or additional targeted searches in the academic or grey literature as relevant to the particular case study. Cost estimates for healthcare resource use are inflated to 2024 prices. In addition, we use market share data from IQVIA and data on spending on medicines from Medicare Part D. We present the results at the beginning of each case study, providing a discussion of the results in section 5 with additional sensitivity analyses in the Appendix.

4.1 Case Study 1: Trastuzumab

In the US, we estimate a shortage of trastuzumab would lead to health system costs and (monetised) patient health losses totalling approximately $519 million, while in the EU our estimate is $16.6 million. In the US, the monetised health impact, at $450 million, is the main contributor to the total cost of a trastuzumab shortage, representing 86% of the total cost of the shortage. In the EU, the dominance of patient health loss as a proportion of the total shortage cost is even greater, at $16.2 million (98% of the total cost). This is driven by the health losses resulting from lack of access to treatment, monetised by the appropriate cost-effectiveness threshold, for those patients that we assume are unable to switch either to the branded product or to another biosimilar. These results are summarised in Figure 2.

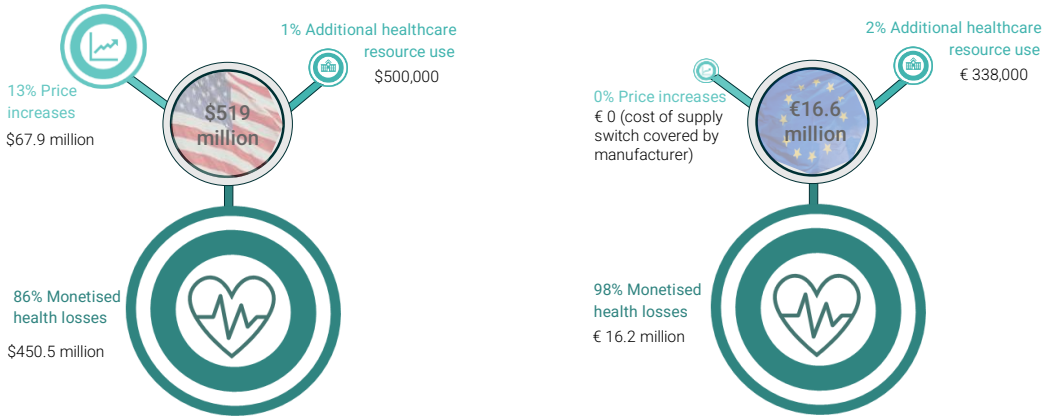

FIGURE 2. THE POTENTIAL COST OF A TRASTUZUMAB SHORTAGE: BASE CASE

Table 3 and Table 4 show the range of results based on alternative, more or less conservative parameter values, with those alternative parameter values outlined in the table below.

TABLE 3 TRASTUZUMAB US CASE STUDY RESULTS RANGE

Key Input	Base Case	Lower Bound	Upper Bound
Shortage duration (days)	548	418	548
QALY losses (per patient)	0.84	0.64	1.04
The proportion of patients able to switch to alternative products	93.25%	93.25%	88%
Overall cost	$519 million	$267 million	$747 million
Range: $267 Million - $747 Million			

TABLE 4 TRASTUZUMAB EU CASE STUDY RESULTS RANGE

Key Input	Base Case	Lower Bound	Upper Bound
Shortage duration (days)	137	137	183
QALY losses (per patient)	0.84	0.64	1.04
Value of QALYs lost (/QALY)	€50,000	€20,000	€80,000
The proportion of patients able to switch to alternative products	98%	98%	92%
Overall cost	€5.2 million	€16.6 million	€172 million
Range: €5.2 Million - €172 Million			

4.1.1 Population and Key Inputs

Trastuzumab is a highly effective targeted biological therapy for the treatment of cancers including advanced stomach cancer, cancer of the gastro-oesophageal junction, and breast cancer (Cancer Research UK, 2024). No shortages of trastuzumab or any of its biosimilars have yet been reported in the FDA or EMA databases, so this case study is hypothetical. Using the cost of shortage framework outlined in section 3, we estimate the cost of a hypothesised trastuzumab shortage.

The population of interest for the trastuzumab case study is those with early-stage HER2-positive breast cancer. In the US, we have estimated 38,338 new cases per year based on the most recent CDC data, and apply an estimate of the proportion of cases that are early-stage HER2-positive (CDC, 2023b; Cronin et al., 2010). In the EU, we have estimated 51,541 new cases per year based on the most recent data from the European Cancer Information System, and apply an estimate of the proportion of cases that are early-stage HER2-positive (European Cancer Information System, 2020; Rakha et al., 2015).

As no drug shortages have been observed in the EMA or FDA databases, we assume that the shortages will last the average length of a drug shortage in each setting. In the US, this is 548 days according to a US Senate report on drug shortages (HSGAC Majority Staff Report, 2023). In the EU, this is 137 days according to a report from the Publications Office of the European Union (Publications Office of the European Union, 2021).

The average time on therapy for trastuzumab falls between the average shortage durations in the US and EU. A meta-analysis of 13,864 women from seven randomised trials, reported the mean scheduled treatment duration for trastuzumab for HER2-positive breast cancer was 14.4 months (438 days) (Bradley et al., 2021).

For the US perspective, using IQVIA data on the market share of the trastuzumab originator (Herceptin) and its biosimilars, we have assumed the drug shortage occurs in the biosimilar with the greatest market share to model a shortage causing a significant impact as the three main competitors (branded originator and two biosimilars) represent an 84% of the market ranging between 24% and 31% (propriety IQVIA data, 2023 Q3).

A key assumption in the trastuzumab case study is that some patients will be unable to switch to other trastuzumab products when a drug shortage occurs, resulting in them receiving the previous standard of care. The proportion of patients this applies to is informed by a US Department of Health and Human Services report (ASPE, 2023) and a report from the Publications Office of the European Union (Publications Office of the European Union, 2021). They report falls in sales volumes of drugs following a shortage in each setting.

In the US, the fall in sales volume was between 28%-35% compared to the year before a drug entered a shortage (ASPE, 2023). This is applied to patients who were receiving the biosimilar product in shortage, representing 31% of the market share before the shortage. Therefore, as a percentage of the whole patient population, approximately 93% of patients can switch. Whereas, from the EU perspective, the fall in sales volume is only 2%, taken from a median of values in the EU report (Publications Office of the European Union, 2021). This is applied to the entire patient population in the EU case study as we did not have the required market share data, hence we are not looking at any specific product in shortage in the EU case study. The key inputs are shown below in Table 5.

TABLE 5 SUMMARY OF KEY INPUTS TRASTUZUMAB

Key Input	Value (US Perspective)	Value (EU perspective)
Shortage duration (days)	548	137
Population size	38,338	51,541
The proportion of patients able to switch to alternative products	93.25%	98%

4.1.2 Price Increase of Drugs

Using proprietary IQVIA market share data, the average spend per beneficiary from Medicare PtD data (Centres for Medicare & Medicaid Services, 2023), and the estimated population size of those with early-stage HER2-positive breast cancer, we calculated the current spending on trastuzumab over 548 days (the shortage period). We assumed that all trastuzumab biosimilars cost the same, based on a lower average sales price of 43% in comparison to Herceptin (Jeremias, 2023). This was applied since there was missing data regarding the average spend per beneficiary on trastuzumab biosimilars in the Medicare PtD data.

Then, assuming a shortage in a trastuzumab biosimilar, we redistribute the market share to the branded product and the biosimilars, proportional to their current market share. As observed in the literature, we assume an increase in the price of trastuzumab products. As per a US Department of Health and Human Services report, we apply a 14.6% increase in the price in the US of the trastuzumab biosimilars, while assuming the price of the branded product is constant (ASPE, 2023). We also apply the fall in sales volume of 93.25%.

4.1.3 Additional Healthcare Resource Use

In the US and EU case studies, we take different approaches to estimating the additional healthcare resource use, due to the availability of data.

For the US perspective, we use a top-down approach to estimating the additional healthcare resource use. The value used is based on a figure reported in a US Department of Health and Human Services report (ASPE, 2023). The estimate gives an aggregate amount spent per year on managing and mitigating drug shortages of $359 million. The value is in 2019 prices, which we inflate to January 2024 prices using an inflation index of Medical Care in the US (U.S. Bureau of Labor Statistics, 2024).

For this estimate to be appropriate to the trastuzumab case study, three additional adjustments were made to the value. Firstly, the aggregate figure was adjusted to a per-shortage value based on the number of shortages in 2019 reported in the FDA database (Napier et al., 2024). Secondly, the figure was weighted upwards to the shortage duration of 517 days, as the original estimate was a per-year value. Finally, the figure was adjusted to the size of the patient population, assuming that the size of the patient population is proportional to the disruption caused by the drug shortage. The average drug shortage affects an average of 652,100 consumers (ASPE, 2023), therefore the cost estimate is adjusted based on the population size affected by the trastuzumab shortage.

For the EU perspective, we take a bottom-up approach. We used an estimate of the number of hours spent on average managing drug shortages per week by pharmacists in a survey from the PGEU, as this estimate is taken from multiple EU countries. To calculate the cost of this time, the average salary of all EU workers was applied (Eurostat, 2023), as more specific salary information of pharmacists across the whole EU could not be obtained. Then, to aggregate this value, the cost of the time was applied to the number of pharmacists in the EU (Eurostat, 2024). In the same way as before, the aggregate figure was adjusted to a per-shortage value, based on the number of shortages reported in Germany (Publications Office of the European Union, 2021), as this is the largest country and economy in the EU. Furthermore, the figure was weighted downward by the size of the population affected by the drug shortage. No EU figure on the average number of people a drug shortage affects was found, so we applied the same weighting as in the US case study.

4.1.4 Patient Impact

The health losses estimated for patients are due to patients not being able to switch to alternative, equivalent products. For the trastuzumab case study, we assume that a proportion of patients are unable to switch to Herceptin or other biosimilars. The health losses are informed by the health outcomes achieved from the use of the previous standard of care, which is less clinically effective than trastuzumab. The most case-specific evidence on the QALY gains/losses in comparison to the standard of care were selected.

For both the EU and US case studies, the QALY losses are informed by a product lifecycle value assessment of trastuzumab, based on registry data in Sweden (Justo, Wilking and Jönsson, 2023). For the HER2-positive early breast cancer indication, the study reports the projected QALYs gained per treated patient, in comparison to the standard of care. This standard of care has remained stable in the period of the study analysis (2000-2021), which includes 'combinations with chemotherapy such as taxanes (docetaxel or paclitaxel), capecitabine or platinum compounds (cis- or carboplatin) and/or hormonal therapies such as tamoxifen and aromatase inhibitors' (Justo, Wilking and Jönsson, 2023).

We assume that a proportion of patients cannot switch to another trastuzumab alternative and will therefore lose out on the QALY gains. The proportion of patients who cannot switch is informed by the observed fall in sales volumes of drugs that have experienced shortages. In the US case study, this is from a figure reported in a US Department of Health and Human Services report (ASPE, 2023). In the EU case study, this is informed by the observed fall in sales volume reported in an EU report (Publications Office of the European Union, 2021).

Finally, the health losses are monetised using a per QALY value for each setting. In the US, this is the lower bound ICER threshold of $100,000/QALY (ICER, 2019), which also aligns with an estimate of the health opportunity cost threshold in the US (Vanness, Lomas and Ahn, 2020). In the EU case study, QALYs are valued at €50,000/QALY (European Commission, 2024), based on the midpoint of an estimate of the (implied) monetary value of a QALY in Germany (€20,000-€80,000/QALY).

4.2 Case Study 2: Statins

In order to model the potential impact of a statin shortage, we assume for illustrative purposes a shortage in the availability of the statin with the greatest market share in the US: atorvastatin. In the US, we estimate that a shortage of atorvastatin could cause $1.45 billion in costs while in the EU our estimate is $63 million. The price increase of drugs in shortage – equivalent to $1.4 billion – is the main contributor to the total cost of an atorvastatin shortage representing 96% of the total cost of the shortage. In the EU, the additional healthcare resource use represents the full cost estimate of a statin shortage at $63 million.

The significant cost difference between the two settings is driven by the fact we did not identify and incorporate the effect of price increases (for the drug in shortage and its competitors) as a result of drug shortages in the EU setting, as this element is not well reported in the literature. These results are summarised in Figure 3.

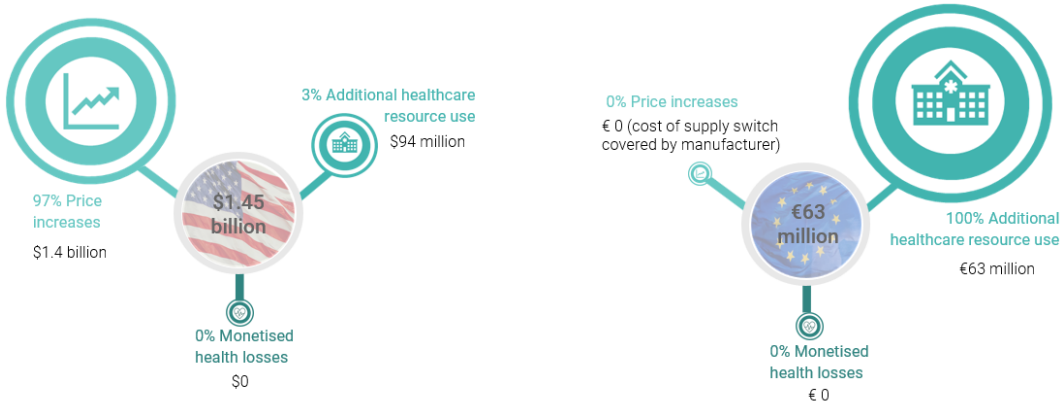

FIGURE 3 THE POTENTIAL COST OF A STATIN SHORTAGE: BASE CASE

Table 6 and Table 7 show the range of results based on alternative, more or less conservative parameter values, with those alternative parameter values outlined in the tables.

TABLE 6 STATIN US CASE STUDY RESULTS RANGE

Key Input	Base Case	Lower Bound	Upper Bound
Shortage duration (days)	548	418	548
Price increase of atorvastatin and substitutes	14.6%	0%	14.6%
The proportion of atorvastatin/statin in shortage	25%	30%	50%
Overall cost	$1.45 billion	$347 million	$1.84 billion
Range: $347 million – $1.84 billion			

TABLE 7 STATIN EU CASE STUDY RESULTS

Key Input	Base Case	Lower Bound	Upper Bound
Shortage duration (days)	137	137	183
The proportion of atorvastatin/statin in shortage	25%	30%	50%
Overall cost	€63 million	€50.8 million	€135 million
Range: €50.8 million-€135 million			

4.2.1 Population and Key Inputs

Statins are a widely prescribed small-molecule therapy, used to lower cholesterol and reduce the risk of heart and blood vessel disease. There are many different statins on the market, for example, atorvastatin, simvastatin, and rosuvastatin, to name the three most widely used. No shortages of statins have been reported in the FDA or EMA databases, so this case study is also purely hypothetical.

The population of interest for the statins case study is those with high cholesterol. In the US, there are approximately 47 million people taking statins per year based on the most recent CDC data (CDC, 2023a). In the EU approximately 50 million people take statins, based on statin usage in the UK applied to the EU adult population (Kulkarni, Watts and Kostapanos, 2024; Statista, 2024).

As no drug shortages have been observed in the EMA or FDA databases, we will assume that the shortages will last the average length of a drug shortage in each setting. In the US, this is 548 days according to a US Senate report on drug shortages (HSGAC Majority Staff Report, 2023). In the EU, this is 137 days according to a report from the Publications Office of the European Union (Publications Office of the European Union, 2021).

From the US perspective, using IQVIA data on the market share of the different statin products (propriety IQVIA data), we assume the drug shortage occurs in the statin with the greatest market share (2023 Q3): atorvastatin. From the EU perspective, the shortage is not specific to any Statin product, as we do not have market share or pricing data for the EU. We assume that proportion of the statin in shortage is the same as in the US perspective.

In contrast to the trastuzumab case study, in the case of statins, all patients are assumed to be able to switch to an alternative statin or atorvastatin supplier, as there are many different alternative products and many generic manufacturers for each product. Since there are no significant differences in the efficacy of statin products (Zhou et al., 2022; Jacobson et al., 2013), no health losses are assumed to occur from those patients switching from atorvastatin to an alternative product.

For the US estimate, an important assumption was regarding the proportion of atorvastatin in shortage. Whereas for the trastuzumab case study, we considered a shortage of a biosimilar product with just one manufacturer (and therefore assume 100% of one biosimilar is in shortage), there are in practice many manufacturers of atorvastatin, making it unrealistic to assume all atorvastatin would become unavailable. The fall in sales volume observed in the US Senate report on drugs shortages (HSGAC Majority Staff Report, 2023) is therefore applied, corresponding to approximately a 30% decline in the volume of atorvastatin, representing approximately one manufacturer facing a

complete shortage. However, we will present the impact of changing this assumption upwards and downwards on the results in the Appendix.

TABLE 8 KEY INPUTS STATINS

Key Input	Value (US Perspective)	Value (EU perspective)
Shortage duration	548	137
Population size	47 million	50 million
The proportion of patients able to switch to alternative products	100%	100%
The proportion of atorvastatin/statin in shortage	30%	30%

4.2.2 Price Increase of Drugs

Using IQVIA market share data, the average spend per beneficiary from Medicare PtD data (Centres for Medicare & Medicaid Services, 2023), and the estimated population size of those taking statins, we calculated the current spending on all statin products over 548 days (the shortage period).

Then, assuming a shortage in atorvastatin, we redistribute the market share to the alternative statins, proportional to their current market share, and the proportion of atorvastatin in shortage (30%). As observed in the literature, we assume an increase in the price of the statin products, by 14.6% in the US (ASPE, 2023).

4.2.3 Additional Healthcare Resource Use

For the statin case studies, the same approach as in the trastuzumab case study in estimating the additional healthcare resource, from both the EU and US perspectives, was taken (see section 4.1.3).

Figures were adjusted to the size of the patient population, assuming that the size of the patient population is proportional to the disruption caused by the drug shortage. The average drug shortage affects an average of 652,100 consumers (ASPE, 2023). Therefore, the cost estimate is adjusted based on the population size affected by the atorvastatin shortage. No EU figure on the average number of people a drug shortage affects was found, so we applied the same weighting as in the US case study.

4.2.4 Patient Impact

As outlined in section 4.2.1, no health losses are assumed to occur in this case study. All patients are assumed to be able to switch to an alternative statin or atorvastatin supplier, as there are many alternative products and many manufacturers. Therefore, we assume there to be no health losses, since there are no significant differences in the efficacy of statin products (Zhou et al., 2022; Jacobson et al., 2013).

However, there may be issues around adherence when switching patients to different products, in addition to a delay in being switched to an alternative product. These effects are not captured in this case study but may have a detrimental impact on patient health.

4.3 Case Study 3: Saline

Saline is an essential part of hospital care, and shortages have been seen to cause severe disruption. Its uses include fluid resuscitation, intravenous therapy, dilution of medications and wound irrigation (DoveMed, 2023).

IV saline, as well as other injectable products, are more than twice as likely to experience drug shortages compared to other dosage forms (HSGAC Majority Staff Report, 2023). It has a vulnerability score, the assigned risk of future shortages based on historical trends, of 95% according to US Pharmacopeia (USP) (HSGAC Majority Staff Report, 2023), a very high risk due to low profitability and complex manufacturing. This is highlighted by the multiple saline shortages over the last 15-20 years, which have been due to both supply/manufacturing issues (Mazer-Amirshahi and Fox, 2018), and increased demand, particularly in flu seasons and the Omicron wave of the Covid-19 pandemic (Edney, 2022).

The production demands for saline are very challenging, as such vast quantities are needed, and the production processes are complex. This is compounded by the insufficient capacity of other suppliers to make up the difference when a shortage occurs (Mazer-Amirshahi and Fox, 2018).

Furthermore, manufacturing challenges have been seen in recent years with IV saline. The historical fill rate, the percentage of orders that are able to be fulfilled from available stock, of IV saline is above 98%. However, in October-November 2021, this dropped to a low of 22% and never went above 51% (HSGAC Majority Staff Report, 2023). IV saline has been in shortage since 2021 and has experienced shortages for over a decade, due to low profitability, manufacturing complexities, and quality issues (HSGAC Majority Staff Report, 2023).

In previous saline shortages, the FDA has approved imports from other countries such as Spain and Norway (Dembosky, 2014) and from Ireland, Australia, Mexico, Canada and Germany (Nadeau, 2022), to mitigate shortages. However, this has the potential spillover effect of causing drug shortages in those countries, since they still need to supply their own hospitals (KQED, 2014). Furthermore, prices of imported saline can be up to 10 times higher than US-produced saline (Weiner, 2014).

The supply of saline is highly vulnerable, and we expect the impact of a saline shortage to be large and wide-reaching. Due to the huge spectrum of saline uses, the inability to define a specific patient population in the same way as case studies 1 and 2, and a lack of evidence, it was not possible to quantify the cost of a saline shortage. Instead, in the following sub-sections we will describe some of the literature and grey literature on the expected impact of a saline shortage.

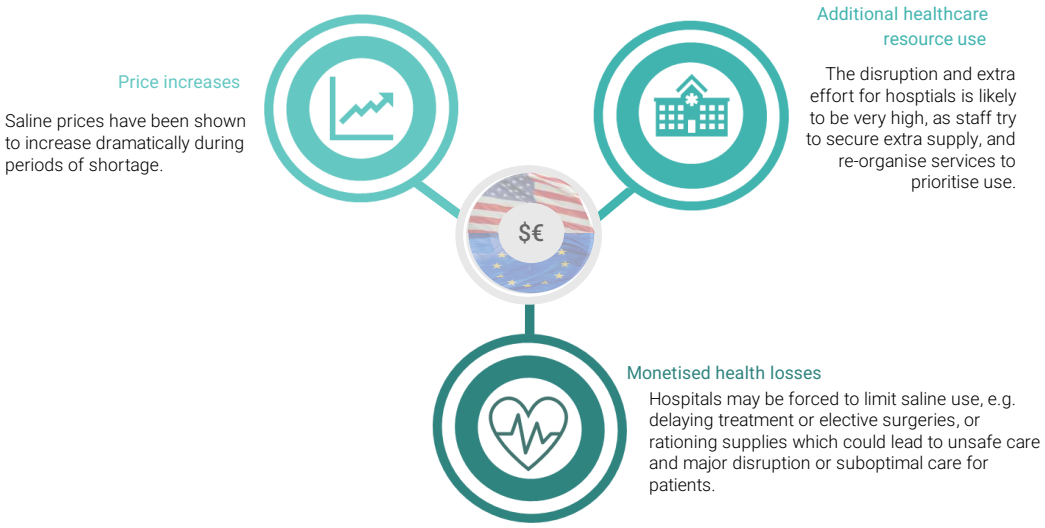

FIGURE 4 SUMMARY OF UNQUANTIFIED COST OF A SALINE SHORTAGE

4.3.1 Price Increase of Drugs

There is some evidence that shortages of saline may have impacted the price of saline. Between 2014 and 2018, the wholesale price of saline more than doubled, which has been partly attributed to the instances of shortages in this period (Crow, 2018). However, some price increases may be driven by the markup charged by hospitals, rather than the manufacturer's price. An investigation found that some hospitals were charging a mark-up of 100-200 times (Bernstein, 2013).

Similarly to the impact on the labour time cost, the quantification of the patient impact and increase in the price of saline is not possible. However, as we have shown, the disruptive effect of saline shortages is likely to be enormous, and of huge cost to health systems and the patients that they serve.

4.3.2 Additional Healthcare Resource Use

Past shortages of saline have significantly impacted the health system due to its multiple uses and therefore the vast numbers of hospitals and people affected.

In times of shortage, temporary measures must be devised which can be extremely resource intensive. For example, “technicians worked through the night to mix saline by hand, while nurses injected the solution of salt in the water into patients using syringes” (Crow, 2018). In addition, “at the peak of the crisis, the hospital had the equivalent of eight full-time pharmacy employees battling the shortage” (Crow, 2018).

Furthermore, significant additional time spent sourcing alternative supplies has been described in the literature. For example, “Nurses have been spending several hours tracking down suppliers who can provide the intravenous (IV) solutions necessary for patients scheduled to receive chemotherapy” (Kuehn, 2014).

This approach of ‘muddling through’ a shortage of saline, as described in the examples above, will have significant consequences on staff time and ultimately the ability of the health system to

function efficiently. Using the figures used in case studies 1 and 2 for the labour time cost of drug shortages is inappropriate, as the population size of saline usage is very challenging to define, and the impact is expected to be much larger for saline. In addition, quantifying estimates from the narrative examples shown here is not possible.

4.3.3 Patient Impact

Saline has many uses and is a key medical supply for hospital-based care. Therefore, patient care will very likely be greatly impacted when faced with a shortage in saline supply.

Saline shortages have been described to impact patient care in the following ways: increased medication errors and adverse events, dilution errors and microbial contamination, and delays in patients receiving treatments (Mazer-Amirshahi and Fox, 2018; Kuehn, 2014).

An American Society of Health System Pharmacists (ASHP) survey was undertaken to assess the severity of sterile injectable drug shortages (ASHP, 2022). Normal saline syringes or vials ranked 3rd out of 23 drugs, in terms of how severe a shortage is, with over 50% of respondents categorising the shortage as severely impactful (ASHP, 2022).

5. Discussion of results

In this report, through the use of case studies, we have provided illustrative estimates of the cost of a drug shortage. The case studies highlight the broad spectrum and heterogeneity of drug shortage impact, in terms of the stakeholders they most impact, the degree of impact, and how they differ across settings. In the Appendix, we present further details and sensitivity analyses for our modelling. Given the large divergence between EU and US cost estimates, in section 1.3 of the Appendix, we demonstrate the impact on total costs of holding more of the underlying assumptions constant between the two (EU and US) settings.

5.1 Case Studies

Trastuzumab

For the trastuzumab case study, in both the US and EU settings, we predict that the greatest impact of the shortage would be the monetised health losses to patients. This is mainly driven by the inability to switch all patients to an equally effective treatment alternative. Trastuzumab was developed for the treatment of HER2 positive breast cancer patients, a relatively small patient subpopulation representing around 20% of the total breast cancer population. Before trastuzumab, HER2 positive patients had worse overall survival than HER2-negative patients. Trastuzumab has reversed this. Not having access to trastuzumab therefore would involve huge health loss for these patients as the results from our case study highlight. Furthermore, this does not consider some of the additional health losses patients may suffer because of a drug shortage including adverse events, medication errors, and side effects. Overall, patients are the stakeholder group who would be most affected by a shortage of this type.

The quantitative results are highly sensitive to the assumptions surrounding the monetisation of the health losses, including the magnitude of QALY losses, the threshold used to ascribe a monetary value to them, and how many patients we assume can switch to alternative drug products. However, we believe that the base case assumptions are conservative, particularly in the case of the switching assumption for the EU. In the Appendix, we demonstrate the impact of varying these assumptions on the results.

If the proportion of patients who could switch to alternative trastuzumab biosimilars (or the originator) fell to 90% from 98%, the cost impact would increase to €81.5 million from €16.6 Million, holding all else constant. Similarly, in the US case study, if the proportion of patients who could switch fell from 91% to 88%, the cost of the shortage would increase to $606 million, from $519 million.

The impact on the health system is relatively small in comparison to the other elements of the drug shortage cost, as the patient population is relatively small. Therefore, the aggregate health system impact is not expected to be as large, in contrast to larger volume indications. This is underlined by the assumption that the labour spent managing drug shortages is proportional to the size of the affected population.

There are differences in the estimated cost of a shortage for the US and the EU, explained by a threefold reason:

- The higher proportion of patients unable to switch to an equally effective alternative of treatment in the US (6.75%) compared to the EU (2%)
- The higher cost-effectiveness threshold used in the US ($100k/QALY) to monetise the health impact, compared to the EU ($50k/QALY)
- The price increase of the trastuzumab biosimilar in shortage and its competitors in the US (14.6%), an impact not taking place in our model for the EU.

On the latter, we have modelled no price increase impact of shortages in the EU based on the differences in the regulatory and legal framework characterising the EU and US, as well as on the lack of existing literature reporting price increases of drugs in shortage and its alternatives in the EU. The standard procurement and contracting in the EU are such that the cost of purchasing substitute drugs is often contractually covered by the manufacturer, and so does not represent a cost for the health system. However – even if the cost of substitute drugs is covered by the manufacturer – this represents a real cost to the system that is associated with increased risk for manufacturers, which can negatively impact market entry and resulting competition. We believe that modelling no price impact for the EU is a very conservative assumption that, if anything, underestimates the cost of the shortage, as there is evidence of pharmacists reporting switching patients to more expensive alternatives (Miljković et al., 2019).

Statins

For the statin case study, in the US, the greatest impact of the shortage is the increased price of drugs and the cost of switching to alternatives, with payers and/or consumers being the stakeholders most affected by this shortage. This is driven by the high volume of drugs serving a large patient population, the switching to more expensive statins and the increased price of atorvastatin and alternative statins in response to the shortage and pressuring demand.

A key underlying assumption informing this estimate is the proportion of the total volume of atorvastatin in shortage. As this increases, the shortage affects a larger population, therefore more patients are switching to more costly alternatives. This impacts both the price impact of the shortage, as well as the additional healthcare resource use. The range presented in the results as well as in the Appendix presents the impact of varying these assumptions on the overall results.

If 75% of the total volume of atorvastatin is in shortage, compared to 30% in the base case, the overall cost of the shortage would increase to $2.36 billion from $1.45 billion in the base case. Similarly, in the EU case study, the same increase in the total volume would result in a cost of shortage of €152 million compared to €63 million in the base case.

The patient population for statins is much larger than that of trastuzumab, and therefore the impact on the health system of a statin shortage is relatively larger. This is underlined by the assumption that the labour time spent managing drug shortages is proportional to the size of the affected population, an assumption we made in the absence of precise information about the impact a statin shortage would have on the health system.

In the EU, the additional healthcare resource use is the only component of the framework applicable to a statin shortage. Patients are all switched to alternatives and price increases in the EU are assumed to be internalised by manufacturers, as previously discussed. However, given the volume of drugs likely affected, this represents significant costs associated with paying for substitute statins for millions of patients.

The inclusion or not of costs associated with price increases of the drug in shortage (and its alternatives) explains the big difference in the cost estimate of a statin shortage between the US and the EU, accounting for $1.4bn in the US, and being absent in our EU modelling. For the EU case, we assume that the cost of purchasing substitute drugs is covered by the manufacturer so does not form part of the overall cost estimates for the health system. However, this represents a real and significant cost of shortages, whether absorbed by the health system or the industry. High costs for industry as a result of a product shortage means a significant risk for manufacturers, which can negatively impact market entry and resulting competition, and therefore greater risk of future shortages.

Saline

The saline case study exemplifies the broad disruption to health systems and patients that a shortage can cause, particularly for a product with so many uses for a variety of healthcare services and in multiple different sizes and dosages. For this very same reason, we have been unable to define a patient population that is impacted by the shortage to apply the same methodology used for trastuzumab and statins to produce cost estimates. Without a set of further assumptions or further research, we are unable to generate the required input data. However, as reported, the reviewed literature indicates that saline products are subject to high vulnerability and risk of shortage due to supply issues, peaks in demand and associated manufacturing complexity and costs. The impact of a saline shortage has been evidenced to be intensively costly for healthcare staff and systems. The observed price increases as a result of demand outweighing supply have been significant. Finally, the impact on patients is likely to be significant due to the potential deleterious effects of any necessary rationing of saline, and the delays in treatment procedures or higher risk of errors and adverse events that are likely to result.

5.2 Policy Implications

Using three case studies we have provided illustrative estimates of the cost of a shortage. The case studies together also illustrate the skewed distribution of those shortage costs, with some drug shortages potentially resulting in modest system costs but a proportion of them leading to massive costs. Shortages are rising in scope and number affecting developed and developing countries globally. Chapman et al. estimated that the number of shortages increased from around 11,000 in 2017 to more than 17,500 in 2019 in a sample of 14 OECD countries (Chapman, Dedet and Lopert, 2022).

Our illustrative estimates of the cost of a shortage range from €63 million to $1.6 billion. Case studies are individual but in real-life costs of shortages are likely to be compounded if multiple molecules are in shortage at the same time. Together, the increasing number of shortages now arising and the potential costs of a shortage that we have illustrated in this report provide policymakers with a more comprehensive picture of the magnitude of shortages' costs to society.

In a previous report, *The Dynamics of Drug Shortages*, we discussed the causes of drug shortages and concluded that price erosion in the generic and biosimilar markets appears to be a key driver of drug shortages (Mouret et al., 2022; Dubois, Majewska and Reig, 2023; Chapman, Dedet and Lopert, 2022; Kent, 2021; Dranitsaris et al., 2017). This price erosion in the generic and biosimilar markets does not seem to be driven by market competition (with markets often being highly concentrated), but rather rooted in other causes such as cost-containment policies (Napier et al., 2024). Paradoxically, policies to control expenditure and cost may end up causing additional costs by increasing the risk and number of shortages. For example, in the trastuzumab case study for the US,

we have estimated a shortage cost to be $519 million, with up to $67.9 million of them being due to the price increase of the alternatives used to switch patients and $451 million due to monetised health losses (QALY losses). Our results in this report highlight that the large cost impact of shortages must be taken into account given the increased risk of shortages that some of the cost-containment and expenditure-control policies may cause. This is especially so given the context that pharmaceutical spending has grown at a lower rate than health spending in the last decades, demonstrated by the decline in the share of pharmaceutical spend over the total health spending (IQVIA, 2024). Furthermore, the savings from the use of off-patent medicines are offset by the increased spending on branded medicines (IQVIA, 2024), hence resolving drug shortages and mitigating their cost could serve to improve health system efficiency and sustainability.

Quality issues and quality regulation of supply chains along with highly concentrated markets for inputs, active pharmaceutical ingredients, and final medicinal products seem to be another risk-increasing factor contributing to supply issues and drug shortages (Napier et al., 2024). Price erosion and low margins make investments in maintaining and upgrading manufacturing capacity unattractive, leading to high concentration in supply chains and increased quality issues causing costly shortages. Policies to promote healthier and more sustainable biosimilar and generic markets that incentivise investments in resilient high-quality supply chains, grounded in building in redundancies at each of its steps, are needed to reverse current drug shortage trends. In recognition of this challenge and its causes, several stakeholders are calling for enhanced incentives in the form of higher prices for some drugs, in order to allow manufacturers to invest in more resilient supply chains and thereby avoid costly drug shortages (Hernandez et al., 2024) The framework for estimating the cost of a shortage and the case study results in this report contribute to making policymakers aware of this policy need.

Policy proposals have emerged, showing policymakers' rising concerns about the growing seriousness of the issue of drug shortages. To mention two of the most relevant, the EU has introduced proposals to address drug shortages in its EU pharmaceutical legislation reform (European Commission, 2024), and the Department of Health and Human Services (HHS) in the US, has recently published a white paper on *Policy Considerations to Prevent and Mitigate Supply Chain vulnerabilities in the United States* (ASPE, 2024). The focus of the EU proposals is to strengthen information systems and distribute obligations between manufacturers and the EMA to generate shortage prevention, mitigation and management plans. These plans will potentially increase the costs to manufacturers and likely worsen the problem if they are not complemented with the right incentives. Issues like price erosion, concentrated supply, and quality issues previously mentioned in this report that increase the risk of shortages are neither discussed nor considered targets for the policy reforms to address. The HHS white paper for the US recognises that low prices and profit margins are leading to concentrated markets and supply chains, and overreliance on few suppliers or manufacturers, frequently located overseas. The proposal's focus includes more transparency to improve information systems needed to prevent or anticipate shortages, aligning incentives by rewarding resilience, and the implementation of the *Manufacturer Resilience Program (MRAP)*. Although MRAP has merits and the HHS recognises that incentives need to be aligned for promoting market sustainability, MRAP proposals may increase the cost of manufacturing if implemented at the company level, therefore increasing the risk of shortages if some of them deter market entry.

6. Conclusion and Recommendations

The literature review and illustrative case studies highlight the broad spectrum and heterogeneity of drug shortage impact, in terms of the stakeholders they most impact, the degree of impact, and how they differ across settings. They also demonstrate the potentially huge magnitude of those costs, as well as their highly skewed distribution.

In markets where many alternative substitutes exist, such as the statin case study, most of the cost of a shortage is driven by the health system and administrative disruption, as well as (in some healthcare settings) the expected price increases that result from increased demand for competitor/substitute medicines of the same class.

In markets with fewer alternative medicine options to switch unserved patients and lower volumes such as the (biosimilar) market for trastuzumab, shortages impact patients the most, causing health losses (QALY losses) which might reach hundreds of millions per shortage once monetised.

For medicinal products like saline that are used in multiple health services and treatments, we would expect the greatest impact to be on the additional healthcare resources contributing to "muddling through" and managing the drug shortage.

Policymakers need to be informed not only about the number and the duration of existing drug shortages but also about their potential impact on society and health systems. Only the combination of these two elements will provide an accurate magnitude of the issue to address. Although high-quality databases recording number shortages exist, further research is needed to estimate the costs of a shortage. In this report, we have contributed to this end with a general framework for the cost estimation and estimates for two representative case studies. These estimates need to be refined and generalised with further research.

A general lesson from our research is that if key medicinal products run into shortage the costs to society could be huge. Current policies focusing on cost containment and expenditure control neglect these potential costs. Policymakers should consider the magnitude of shortage costs and balance them with the expected benefits of expenditure control measures if they aim to promote sustainable drug markets and resilient supply chains in the long term that generate mutual gains for all stakeholders.

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A.1. Appendix 1: Assumptions and sensitivity analyses

1.1 Trastuzumab Case Study Sensitivity Analyses

1.1.1 Duration of Shortage

In the baseline estimates, we applied the average length of drug shortages in each setting, as no shortages of trastuzumab have occurred. This was 548 days in the US and 148 in the EU case studies (HSGAC Majority Staff Report, 2023; Publications Office of the European Union, 2021). However, this parameter has a large impact on all components of the cost of shortage framework. In the **tables** below, we present the impact of varying the duration of the shortage on the overall cost of shortage value.

TABLE 9 US TRASTUZUMAB CASE STUDY – IMPACT OF THE DURATION OF SHORTAGE

Duration of shortage	Estimate
548 days (base case)	**$518 million**
418 days*	**$396 million**
1 year	**$346 million**
6 months	**$172 million**

***Alternative estimate of the average duration of a drug shortage in US (Gupta et al., 2019)**

TABLE 10 EU TRASTUZUMAB CASE STUDY – IMPACT OF THE DURATION OF SHORTAGE

Duration of shortage	Estimate
1 year	**€44.2 million**
5 months*	**€18.3 million**
137 days (base case)	**€16.5 million**

***Alternative estimate of the average duration of a drug shortage in the EU (Napier et al., 2024)**

In the US case study, increasing the shortage duration from 6 months to 548 days (1.5 years) increases the overall cost of shortage by $346 million. This is largely driven by more health losses suffered by patients due to the longer shortage duration.

In the EU case study, increasing the shortage duration from 137 days (~2.5 months) to a year increases the overall cost of shortage by €27.7 million. This is mainly driven by the increased health losses suffered by patients due to a longer shortage duration.

1.1.2 Switching to Alternative Trastuzumab Products.

An important assumption in the trastuzumab case study is the proportion of patients able to switch to alternative products. This is because those who cannot are assumed to receive the previous standard of care and therefore have worse health outcomes in terms of QALYs (Justo, Wilking and Jönsson, 2023). The impact of varying this assumption is presented in the Tables below.

TABLE 11 US TRASTUZUMAB CASE STUDY – IMPACT OF VARYING THE SWITCHING ASSUMPTION

The proportion of patients able to switch to alternative products	Estimate
88%	**$606 million**
91% (base case)	**$519 million**
94%	**$424 million**
97%	**$333 million**

TABLE 12 EU TRASTUZUMAB CASE STUDY – IMPACT OF VARYING THE SWITCHING ASSUMPTION

The proportion of patients able to switch to alternative products	Estimate
90%	**€ 81.5 million**
92%	**€ 65.2 million**
94%	**€ 49.0 million**
96%	**€ 32.8 million**
98% (base case)	**€ 16.5 million**

In the US case study, increasing the proportion of patients who can switch to an alternative product from 88% to 97%, has a difference in cost of $273 million. When fewer patients can switch to alternative trastuzumab products, greater health losses are suffered, increasing the overall cost of shortage.

In the EU case study, increasing the proportion of patients who can switch to an alternative product from 90% to 98%, has a difference in cost of $65 million. Again, driven by more patients suffering QALY losses.

1.2 Statin Case Study Sensitivity Analyses

1.2.1 Duration of Shortage

In the baseline estimates, we applied the average length of drug shortages in each setting, as no shortages of statins have occurred. This was 548 days in the US and 148 in the EU case studies (HSGAC Majority Staff Report, 2023; Publications Office of the European Union, 2021). However, this parameter has a large impact on the estimated cost of shortage. In the **tables** below, we present the impact of varying the duration of the shortage on the overall cost of shortage value.

TABLE 13 US STATIN CASE STUDY – IMPACT OF THE DURATION OF SHORTAGE

Duration of shortage	Estimate
548 days (base case)	**$1.45 billion**
418 days*	**$1.11 billion**
1 year	**$968 million**
6 months	**$483 million**

*Alternative estimate of the average duration of a drug shortage in US (Gupta et al., 2019)

TABLE 14 EU STATIN CASE STUDY – IMPACT OF THE DURATION OF SHORTAGE

Duration of shortage	Estimate
1 year	**€169 million**
5 months*	**€70.2 million**
137 days (base case)	**€63.3 million**

*Alternative estimate of the average duration of a drug shortage in the EU (Napier et al., 2024)

In the US case study, increasing the shortage duration from 6 months to 548 days (1.5 years) increases the overall cost of shortage by $967 million. This is driven mainly by having to purchase more expensive alternative statins over a longer period of time.

In the EU case study, increasing the shortage duration from 137 days (~2.5 months) to a year increases the overall cost of shortage by €105.7 million. This is driven by greater healthcare resource use due to a longer shortage duration.

1.2.2 Volume of Atorvastatin in Shortage

A key assumption in the statin case study is the percentage of atorvastatin/statins in shortage. In comparison to the trastuzumab case study, where there is a shortage of a biosimilar product with one manufacturer. We implicitly assume 100% of the product is in shortage.

Whereas with atorvastatin/statins, there are many different manufacturers, and it's unrealistic to assume all atorvastatin is unavailable. The fall in sales volume observed in the US Senate report on drugs shortages will be applied in the base case (HSGAC Majority Staff Report, 2023), corresponding to approximately a 30% decline in the volume of atorvastatin/statins. The impact of varying this assumption is presented in the Tables below.

TABLE 15 US STATIN CASE STUDY – IMPACT OF DIFFERENT FALLS IN VOLUME

Percentage of Atorvastatin in shortage	Estimate
75%	**$2.36 billion**
50%	**$1.84 billion**
30% (base case)	**$1.45 billion**
25%	**$1.33 billion**

TABLE 16 EU STATIN CASE STUDY – IMPACT OF DIFFERENT FALLS IN VOLUME

Percentage of Statins in shortage*	Estimate
38.2%	**€ 152 million**
25.5%	**€ 101 million**
15.3% (base case)	**€ 63.2 million**
12.73%	**€ 50.8 million**

*The percentages here correspond to the percentages of atorvastatin in shortage in the US case study, applied to the overall statin volume.

In the US case study, increasing the percentage of atorvastatin in shortage from 25% to 75% increases the overall cost of shortage by $1.33 billion. This is driven mainly by a much larger population being affected by the shortage, leading to more patients switching to more costly alternatives.

In the EU case study, increasing the percentage of atorvastatin in shortage from 12.73% to 38.2% increases the overall cost of shortage by €101.2 million. This is driven by greater healthcare resource use due to a larger population being affected by the drug shortage.

1.3 Holding Assumptions Constant Across Settings.

As an additional comparison of the EU and US case studies results, we performed a scenario analysis in which we held constant some of the key assumptions and input values across EU and US settings. Shown in Table 17 are the input values we held constant for the trastuzumab case study, namely the shortage duration and the proportion of patients able to switch to alternative treatments. These parameters were chosen as they impacted the results significantly and the assumed values applied were different between the EU and US settings. The results of this scenario analysis are presented in Table 18.

TABLE 17 – TRASTUZUMAB INPUT VALUES HELD CONSTANT

Input value/Assumption	Value
Shortage duration	**1 Year**
The proportion of patients able to switch to alternative products	**90%**

TABLE 18 – TRASTUZUMAB SCENARIO RESULTS

Setting	Total cost
US	**$358 Million**
EU	**€217 Million**

Setting these input values equal results in total shortage costs being much closer in absolute value between the US and EU compared to the base case results. The remaining parameters driving the difference are the value of the monetised QALY losses, the size of the populations, the different estimates of additional healthcare resource use, and the consideration of the price increase of drugs in shortage.

A similar analysis was performed for the statin case study. Table 19 shows the input values we held constant, namely the shortage duration and the proportion of the statin in shortage. In the same way as the trastuzumab setting, these parameters were chosen as they impacted the results significantly. The results of the scenario analysis are presented in Table 20.

TABLE 19 – STATIN INPUT VALUES HELD CONSTANT

Input value/Assumption	Value
Shortage duration	**1 Year**
Proportion of statin/atorvastatin in shortage	**50%**

TABLE 20 – STATIN SCENARIO RESULTS

Setting	Total cost
US	**$1.2 Billion**
EU	**€0.27 Billion**

Setting these input values equal means that the total costs are closer in terms of absolute value compared to the base case results. The remaining parameters driving the difference are the different estimates of additional healthcare resource use and the consideration of the price increase of drugs in shortage.

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