Medicines for Europe's views on the Economist Intelligence Unit report on medicine shortages

Medicines for Europe asked the Economist Intelligence Unit to investigate the causes of medicine shortages out of concern that the current policy framework is failing to address this serious health risk. The generic, biosimilar and value-added medicines industries represented by Medicines for Europe are afraid that the EU regulatory and market framework is leading to a business environment that is unsustainable for multiple manufacturers to compete in the supply of essential medicines for public health. Recent experience, acknowledged in this report, has shown that the root cause of shortages is multifaceted and includes payer procurement policies, manufacturing risks and regulatory factors. We are therefore keen to engage with payers and regulators to address the measures that are leading to an increased risk of supply disruptions. Fostering a healthy competitive environment with multiple companies supplying the market is essential to guarantee supplies for patients.

While we acknowledge the effort of the Economist Intelligence Unit to identify and address the root causes of shortages, we would like to further reflect on three specific recommendations in the report which could have an opposite effect when implemented incorrectly:

- "*Agree on a common definition of medicine shortages*": The emphasis is on finding a common definition of shortages instead of addressing common understanding of the different root causes of the shortages;
- "*Implement EU early-notification requirements for manufacturers at national level for situations in which medicine shortages are expected*": a national early notification system that does not address the lack of coherent communication in the EU Internal Market and the need for an EU-led solution;
- "*Enhance the efficiency of regulatory procedures and implement fast-track processes to mitigate acute medicine shortages*": While regulatory efficiency is key to reacting more flexibly when the risk of shortages increases, creating high cost regulatory requirements such as requiring multiple API suppliers when manufacturers have no possibility in most EU markets of recovering the cost of this additional investment can only result in more companies withdrawing medicines from the market.

The sustainability of healthcare budgets in Europe has been intensely pressured by multiple factors, such as a growing and ageing population, an increased disease burden, the introduction and increased cost of new innovative medicines[1,2,3]. To overcome these challenges, several national authorities have adopted austerity measures and applied short-term cost-containment measures to pharmaceuticals, including to generic medicines despite their low cost (around 4% of total healthcare expenditure in Europe) and their relevance for

[1] The Parliament Magazine. 2015. Available at: https://www.theparliamentmagazine.eu/articles/opinion/many-patients-europe-have-limited-or-no-access-treatment
[2] Eurostat Population Statistics
[3] OECD, Fiscal Sustainability of Health Systems: Bridging Health and Finance Perspectives. 2015.

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care (62% of medicines dispensed today in Europe are generics). Short-term cost-cutting measures, such as ad-hoc price cuts, external reference pricing, payback, tendering, etc., have driven the prices of some off-patent medicines to unsustainably low levels. This causes manufacturers of generic medicines to withdraw from the market, resulting in the increased risk of medicine shortages[4,5,6]. The evidence is now compelling that many national markets across Europe are relying on too few suppliers for essential life-saving medicines in both the hospital and ambulatory sectors, as was recently acknowledged at the WHO Fair Pricing Forum in Amsterdam in May 2017.

Addressing the root causes to prevent and mitigate medicine shortages requires a healthy, predictable and pro-competitive market as well as regulatory efficiency[7] and transparency in the supply chain from manufacturer to patient. The debate on finding a common definition of medicine shortages has already taken many years with no result due to the inherently different perspectives among stakeholders stemming from their positions within the medicines system. In essence, a patient should have access to medicines and be able to be treated. Any further quest to find a common definition of medicine shortages runs the risk of detracting from the real issue of addressing the cause of the shortage, which is the more critical aspect to finding a solution to the problem.

In addition, national notification systems have proven to be counter-productive when applied indiscriminately as in Canada or the Netherlands where, despite the existence of an early notification system, the frequency of shortages has gone up over the last years. Notification can be effective if it results in a collaborative safe-haven approach for authorities, payers and supply chain actors. The period of notification should be flexible to the circumstances of medicine shortages and coercive measures should not be applied to the manufacturer. Notification also needs to fit into the EU Internal Market as medicines can be traded across national borders. Regrettably the industry proposal for a common European communication plan in 2014 has had no response from the European Commission and European Medicines Agency[8].

Finally, the report suggests that a requirement for manufacturers to have multiple API suppliers would decrease the risk of medicine shortages. Unfortunately, the report does not explain that the driver of consolidation in the manufacturing industry, including consolidation in the API sector, is grounded in procurement policies that are based on short-term cost containment. Studies have shown the direct link between procurement policies in Germany and the reduction of the number of EU API suppliers for antibiotic production in Europe[9], for example. The introduction of a requirement to have multiple API suppliers would significantly increase the regulatory burden in the EU (for manufacturers and regulators), where most markets do not allow generic manufacturers to increase government-established prices to cover the additional cost of using multiple API suppliers. This measure could again lead to manufacturers withdrawing medicines from the market, thus increasing the risk of shortages.

[4] SFK (Foundation for Pharmaceutical Statistics), Pharmaceutisch Weekblad. 2014.
[5] APM Health 2015. Available at: http://www.apmhealtheurope.com/home.php.
[6] QuintilesIMS Health. An International Comparison of Best Practice Approaches to Drug Shortages. 2015.
[7] Medicines for Europe. Regulatory Efficiency report. 2015. Available at: http://www.medicinesforeurope.com/wp-content/uploads/2016/03/EGA_Regulatory_Efficiency_Report_2015_low.pdf
[8] Industry Communication Principles to Authorities. 2014. Available at: https://connect.dcat.org/blogs/regulatory-news/2015/01/23/eu-associations-issue-joint-principles-on-communicating-drug-shortages#.WTpyWBxPpPY
[9] IMS Health (2015) - Best Practice Ansätze bei Arzneimittelengpässen im internationalen Vergleich

The Economist Intelligence Unit

Healthcare

Addressing medicine shortages in Europe

Taking a concerted approach to drive action on economic, manufacturing and regulatory factors

A report by The Economist Intelligence Unit

Commissioned by

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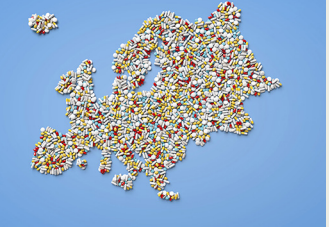
Contents



About this report

Addressing medicine shortages in Europe: Taking a concerted approach to drive action on economic, manufacturing and regulatory factors is an Economist Intelligence Unit (EIU) Healthcare study that was supported by Medicines for Europe; nevertheless Medicines for Europe does not necessarily agree with all the statements mentioned. This report discusses the causes contributing to shortages of medicines and articulates calls to action to address them.

Aditi Karnad, Health Research Analyst, was the main project researcher, supported by Anelia Boshnakova, Senior Information Specialist. Annie Pannelay, Principal for EIU Healthcare, served as senior adviser.

We wish to thank the experts listed in the *Expert interviews* section for their time and insights. The Economist Intelligence Unit bears sole responsibility for the content of this report. The findings of the report and the views expressed in it do not necessarily reflect the views of the experts involved.

Executive summary

In recent years, the prevalence of medicine shortages has increased in Europe. Medicine shortages affect patient outcomes, pharmacists' time and budgets, and clinicians, as well as manufacturers, in many ways. The causes of shortages are multifactorial and fall within three main categories, namely economic, manufacturing and regulatory causes. In this report, shortages are considered to be an interruption to the supply of medicines, and a distinction needs to be made in order to aid understanding of the focus of this document:

- Medicine shortages due to economic, manufacturing or quality issues.
- Non-availability of medicines, which is a separate topic not covered in this report; this refers to the lack of, or lag in, the introduction of new medicines, and is most frequently associated with high-priced medicines.

It is beneficial to acknowledge that although the causes of shortages can be seen as complex, the key to addressing medicine shortages is the maintenance of fair economic conditions for essential medicines. Policies need to be developed in order to achieve this objective in Europe, and require implementation at national level. Achieving this goal would support the sustainability of an active, multi-source manufacturing environment associated with a lower risk of shortages.

The procurement processes and supply chain for medicines involve a large number of stakeholders, including national and supranational competent authorities, manufacturers, wholesalers, parallel distributors, pharmacists, clinicians and patients. It is imperative to create a shared vision of what actions can be taken to address the issue of medicine shortages.

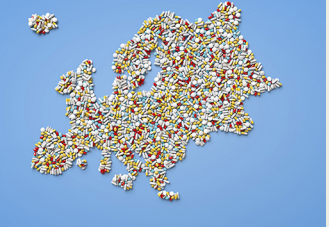
A concerted approach needs to involve both initiatives to prevent shortages and also actions to mitigate their impact. Among the long list of actions considered, this report highlights the most promising ones, which are those that have demonstrated the most traction across different stakeholder groups.

The following calls to action are recommended in order to address medicine shortages:

- Improve tendering practices to introduce appropriate tender criteria, taking into account other aspects in addition to price
- Consider specific measures to maintain healthy multi-supplier markets

Actions to facilitate management of shortages involve:

- Agree on a common definition of medicine shortages
- Implement EU early-notification requirements for manufacturers at national level for situations in which medicine shortages are expected
- Develop a system that ensures transparency around medicine shortages at national level



- Enhance the efficiency of regulatory procedures and implement fast-track processes to mitigate acute medicine shortages
- Allow greater flexibility on delivery of medicines and the movement of packs across borders during medicine shortages

In recent years, the issue of medicine shortages has been researched and addressed in several policy papers by various organisations, and has been raised as part of discussions in many European countries. Alongside the above recommendations, action and implementation is required to ensure that patients have access to the medicines they need.

Objectives and methodology

A report published by the European Association of Hospital Pharmacists in November 2014 showed that 86% of the 607 responding pharmacists in 36 European countries had experienced problems sourcing medicines.[1] Over the past two decades, a number of stakeholders have taken steps to develop a better understanding of the root causes of medicine shortages and to address these issues.

The Economist Intelligence Unit (EIU) has adopted a 360-degree approach, taking into account perspectives from patients, pharmacists, policymakers, academics and representatives of industry (both innovative and generic manufacturers).

In the interests of taking a comprehensive standpoint to understand medicine shortages, the EIU used a three-step approach:

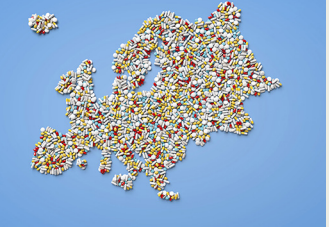
- Identifying initiatives that have emerged, and evaluating how they have developed new policies that can lead to improvements around maintaining access to treatment for patients.
- Collecting perspectives from various stakeholders to evaluate which barriers need to be removed in order to minimise supply issues.
- Providing recommendations for actions to address medicine shortages.

As part of its research, the EIU spoke to experts from European countries and the EU.* Interviews took place in February and March 2017 with:

- Patient group representatives
- Generic pharmaceutical industry representatives
- Innovative pharmaceutical industry representatives
- Academics
- Representatives from European regulatory bodies
- Representatives from national medicines agencies
- Hospital pharmacists

Medicines for Europe (formerly the European Generic and Biosimilar Medicines Association) commissioned this research to understand and highlight the issues identified by existing endeavours, in order to generate suggestions for realistic and practical initiatives for concerted action.

* A full list of experts is provided in the *Expert interviews* section.



Background

The first challenge—defining medicine shortages

Definition of medicine shortages

There are several definitions of medicine shortages in the literature. A 2015 paper by De Weerdt and Simoens outlined four possible situations that qualify as medicine shortages: (i) supply is unable to meet demand, (ii) supply is interrupted, (iii) the medicine is not able to be delivered, and (iv) the medicine is unavailable to patients.[2] Most definitions encompass these four situations in their definitions of medicine shortages. However, it has been suggested by some researchers that the term "medicine shortages" is misleading and that there is a need for a commonly accepted definition that is broad enough to cover all aspects.[3]

For the purposes of this report, the following definition will be used: medicine shortages occur when the supply of medicines identified as essential by the health system is insufficient to meet public health and patient needs. This definition describes situations in which patients are unable to receive their prescribed treatment or a direct alternative for a period of time during which their health outcomes may be impacted. "Direct alternative" is defined by substitution due to medical need to the same chemical molecule produced by a different manufacturer. This understanding of the concept of medicine shortages is based on the draft definition discussed at an expert meeting convened by the World Health Organisation.[4]

Medicine shortages have been a global issue in healthcare for some time, and more recently have increasingly been affecting European countries. As a result, medicine agencies have expressed concerns about the long-term supply of medicines.[5] There is general agreement that every health system should be able to receive a continuous supply of high-quality and affordable essential medicines.†

The duration of medicine shortages can range from a few days to several months. Acute and chronic medicine shortages have the potential to compromise patient outcomes, and in addition they are expensive and impose a time burden on health systems.

The issue has sparked the interest and involvement of major organisations; the European Medicines Agency (EMA, responsible for scientifically assessing and monitoring the safety of pharmaceutical medicines) held a meeting in October 2013 to develop a proactive approach to addressing medicine shortages.[6] The meeting, which involved various stakeholders (representatives of national competent authorities, healthcare professionals, pharmaceutical manufacturers and patients), resulted in the establishment of a working task force with the remit of developing tools that could support the supply chain and prevent future disruptions to it. Additionally, it was agreed that there was a need for a harmonised definition of "medicine shortages" in order to deal with the problem effectively.

Following this, in December 2015 the World Health Organisation (WHO) convened a meeting to discuss the underlying reasons behind medicine shortages, as well as the challenges that needed to be overcome. The discussion also delved into existing local initiatives, in the hope of identifying novel

† As defined by the WHO.

solutions that might be effective in solving the problem globally.[5]

The frequency and duration of medicine shortages have reached a point where it is now imperative that shortages are resolved, with the help of both healthcare professionals and manufacturers. As part of this effort, appropriate risk-management strategies are required. The key aim is to ensure that patients receive the care that they need.

Medicines affected

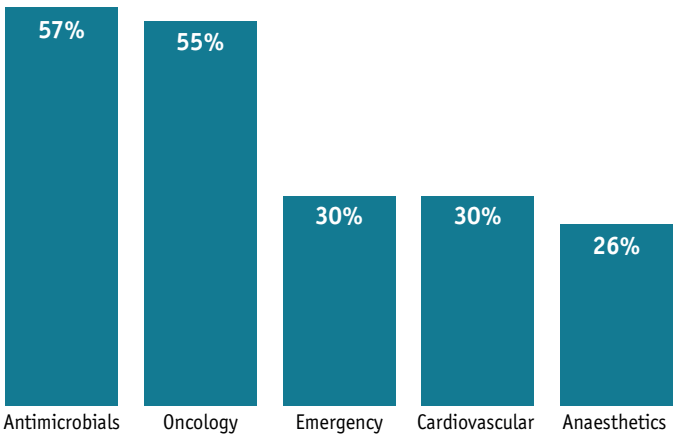
Generic medicines (off-patent medicines)

The European Medicines Agency (EMA) defines a generic medicine as "a medicine that is developed to be the same as a medicine that has already been authorised—the reference medicine". A generic medicine contains the same active substances as the reference medicine and is used at the same dose. When generic versions of a reference medicine are on the market, the market is referred to as multi-source market—in contrast to the situation where only one manufacturer is supplying a specific medicine.[7]

Innovative medicines (on-patent medicines)

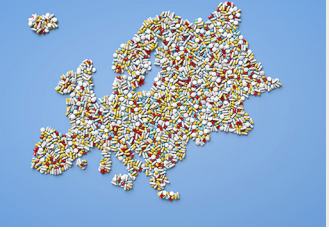
As pharmaceutical companies develop innovative compounds to treat or prevent diseases, they are granted market exclusivity for the medicines approved for market use for a number of years. This allows a manufacturer to enjoy a period during which no other supplier can market its innovative medicine. During the period of market exclusivity granted to the original medicine supplier, the market is referred to as single-source market. Innovative medicines are marketed under a name assigned to them by their manufacturers. The proprietary name is trademark-protected, and remains in use even after market exclusivity has ended (when suppliers operate in a multi-source market). The active ingredients are the same as in the medicine's generic counterparts; inactive ingredients may be different.[8]

Figure 1: The areas in which medicine shortages are most commonly reported: the percentage of 607 respondents who reported shortages for antimicrobial agents, oncology medicines, emergency medicines, cardiovascular medicines and anaesthetics



Source: EAHP 2014.

The European Association of Hospital Pharmacists (EAHP) conducted a survey of medicine shortages in 2014 and found that the most commonly affected medicines were antimicrobials, oncology medicines, emergency medicines, cardiovascular medications and anaesthetics, with the impact being felt among both generic and innovative medicines. The same survey reported that, among the 36 countries in Europe surveyed, Denmark, the Netherlands, Portugal and Croatia experienced the highest recorded prevalence levels of



medicine shortages (including generics and branded generics).[1]

A 2014 study by Pauwels *et al* on medicines shortages in European countries found that 52% of essential medicines shortages were associated with injectables; 40% oral; and 8% topical or dermatological. The same study found that seven European countries— Belgium, England, France, Germany, Italy, the Netherlands and Spain—have national reporting systems for medicine shortages.[9] Concern has also been expressed more generally around shortages of preventive medicines such as vaccines, as well as pain medications, psychiatric medicines and gynaecological products, to name only a few.[1]

Examples of medicine shortages include:[1]

- Amoxicillin (oral)—a broad specific antibiotic
- Ibuprofen IV—a non-steroidal medicine used to provide relief from pain and inflammation
- Labetalol IV—a beta-blocker used in patients with heart conditions
- Levothyroxine—a thyroid hormone

The impact of medicine shortages

The impact of medicine shortages is felt by several groups of people—primarily patients, but also pharmacists and physicians—who are personally impacted in their health or their day-to-day work.[10] The pharmaceutical industry and wholesalers also see shortages as a significant issue: for them, it matters more from a business and mission standpoint.

Patients:

In the event of a medicine shortage, it is often the case that patients are not well informed about the medicines that they are prescribed and any potential substitutions made. The Common Position paper of the European Organisation for Rare Diseases (EURORDIS) calls for patients to be given information about any ongoing medicine shortages and how these could affect their care.[10]

- Patient outcomes are at the forefront of the impact felt as a result of medicine shortages. For medicines with no therapeutic alternative, shortages can result in prolonged hospital stays, delays and cancellations of medical procedures, ineffective treatment and increases in the incidence of adverse events.
- The use of unfamiliar alternative treatments sometimes leads to an increased risk of medication errors and poor patient outcomes.
- Additionally, medicine shortages can mean that patients have to make otherwise unnecessary out-of-pocket payments.

Pharmacists:

The 2014 EAHP report on hospital medicine shortages surveyed 607 hospital pharmacists in over 30 countries:

- 86% of hospital pharmacists reported having an existing medicine shortage in the hospital that

they worked in and said that this negatively affected the care provided to patients and the operation of the pharmacy.

- 66% of the same respondents said that medicine shortages occurred on a weekly or even daily basis.[1]

For pharmacists, medicine shortages mean increased time spent sourcing alternative therapies and taking inventory of the medicines required. According to a 2013 survey of medicine shortages by the Pharmaceutical Group of the European Union (PGEU), community pharmacists spend between 2.5 and 5 hours a week looking for alternative treatments.[10] Additionally, in a small number of cases pharmacists are not able to find an alternative.[10]

Pharmacies obtain their medicines from a range of sources, including pharmaceutical manufacturers, wholesalers, parallel traders and other pharmacies or hospitals, and sometimes even have resort to producing medicines themselves.[1] This can reduce the amount of time that they can spend giving patients advice. There can also be a financial burden on pharmacies as a result of medicine shortages, due to the fact that pharmacists have to stock more expensive medicines.

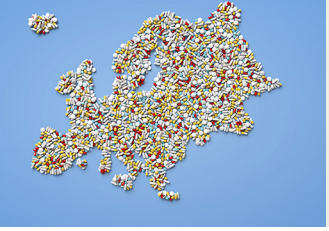
Physicians and nurses:

Physicians have to manage medicine shortages, and may have to switch to a substitute treatment when the medicine originally prescribed is unavailable or in limited supply which may impact the patient outcomes. This increases the burden of risk management and the liability to physicians' practices. Additionally, ethical challenges may arise when physicians have to decide which patients to prioritise depending on the severity of their conditions.

Like pharmacists, physicians have to spend increased time during their shifts familiarising themselves with new prescribing parameters and patient-monitoring practices when there are medicine shortages. This takes away from time spent on direct patient care.

Manufacturers:

The impact on the pharmaceutical industry during medicine shortages also needs to be taken into consideration, as manufacturers too have an interest in addressing this issue. The industry has an incentive to resolve medicine shortages, firstly because medicine shortages conflict with the mission of private manufacturers of generic medicines (making medicines available to patients), and secondly because the current tender-based supply system involves penalties for manufacturers that fail to supply the quantities of medicines agreed in tender contracts.



Causes and drivers of medicine shortages

In order to address the issue of medicine shortages, the underlying causes must be well understood.

The causes and drivers of medicine shortages are multifactorial. They comprise a combination of economic causes, disruptions to the supply chain, manufacturing problems and quality compliance issues, along with other aggravating factors such as regulatory time lags, which result in situations where demand for certain medicines cannot be met by supply.

Medicine shortages can affect both innovative and generic medicines. The 2014 EAHP survey showed that 51.8% of the EU respondents reported shortages of innovative medicines, while 36.5% experienced generic-medicine shortages.[1]

The 2014 study by Pauwels *et al.* found that, of all reported medicine shortages, 63% were of innovative medicines and 37% were of generics. For essential medicines, 55% of reported shortages were for on-patent products.[9] The highest prevalence levels of innovative-medicine shortages as reported in the Pauwels study were in Belgium, Spain, Austria and Slovakia. The Bulgarian, Irish, Swiss, Italian, Norwegian, French and Polish pharmaceutical markets were also the subject of concerns regarding shortages of innovative medicines.[9]

As described in a report published by Birgli, a management consulting platform, in 2013, shortages of medicines can be categorised as having three possible root causes: economic, supply-chain or regulatory.[3]

Economic causes

The economic climate has been fragile across the globe for the past few years, with the result that governments have faced significant challenges. In such financially difficult times, in order to address budget constraints there are several mechanisms in place to set the prices of medicines, and this can create an unattractive business environment for manufacturers. Pricing approaches vary between different European countries and can contribute to medicine shortages.[1]

1. ***Price/volume ratio in a market:*** The combination of low volume use of medicines and the cutting of prices for medicines can reduce the attractiveness of a market to manufacturers.

1.1. ***Low volumes –*** When combined with low prices, low demand for certain medicines contributes to the shrinking supply-sustainability of certain markets.

1.2. ***Low prices –*** Low prices as a result of price cuts may lead to making medicines markets less attractive for suppliers to continue to produce and supply medicines below a certain price threshold.

2. ***Pricing mechanisms (net and gross):***

2.1. ***Reference pricing –*** Reference pricing is a mechanism used as a benchmark to set the list price (or gross price) of a medicine through comparison of prices of equivalent or

similar medicines, either in the same country (internal reference pricing) or in other countries (external reference pricing).

2.2. Tendering/procurement – Tendering applies to multi-source markets for which healthcare institutions or health insurance funds procure medicines and award contracts to suppliers based almost exclusively on price. Tenders are awarded at a specific price, but there is the possibility that the volume of demand for a medicine may change during the duration of the tender agreement. Variations in demand for medicines, in combination with cost-containment measures such as payback policies (see "payback policies" below), can lead to medicine shortages. As part of the tendering process, the definition of timelines can impact manufacturers (see "short lead times" in the *Manufacturing and supply-chain causes* section, below). Tendering is a public-procurement mechanism often applied in a hospital market. Only certain countries, such as Germany and the Netherlands, apply tendering in the retail medicines distribution channel.

2.3. Payback policies – Payback policies aim to control excessive spending. The European Commission defines payback policies as a process that "requires manufacturers to pay back a share of their revenue if a pre-specified budget ceiling for public pharmaceutical expenditure is exceeded".[11]

3. Parallel trade – EU trade laws allow for the free movement of goods across countries. This means that parallel traders are able to purchase medicines in low-price countries and sell them in high-price countries, which can lead to depletion of stocks in the lower-priced markets.

Manufacturing and supply-chain causes

Issues in this category are related to the streamlining of production facilities and processes.

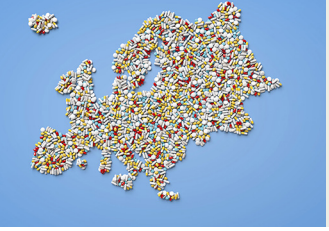
1. Small number of medicine manufacturing sites – The existence of only a few production facilities could increase the risk of a medicine shortage in the case of a manufacturing problem.

2. Just-in-time supply chain – "Just in time" is an inventory strategy that companies employ to increase efficiency and reduce waste by delivering goods only as they are needed in the supply chain. This means that companies are less able to adapt to variations in the volume of demand.

2.1. Short lead times – Short lead times specified in tenders from payers mean that manufacturers have to supply medicines in a timeframe that may not match their production planning needs. For example, when the demand for the medicines exceeds the agreed amount in the tender contract.

3. Active pharmaceutical ingredient (API) sources/regulation – Manufacturers of medicines are dependent on APIs, and so changes in supply, quality and regulation of APIs could cause disruptions in the supply of medicines.

4. Quality-related problems (good manufacturing practice) – This refers to situations in which quality issues arise with regard to medicines—that is, they no longer comply with good manufacturing practice.



5. ***Natural disasters and accidents*** – Sudden shocks to the supply chain can cause disruptions to supply.

Regulatory aggravating factor

In Europe, pharmaceutical legislation and guidelines regulate the entire life-cycle of medicines, from their development and approval to their entry to the market and availability to patients.

> ***Regulatory time lag*** – Regulatory requirements are in place to ensure safe and well-regulated markets for medicines. During a medicine shortage, when a manufacturer needs to adapt its production to changes in demand or supply, the time taken to meet these regulatory requirements and gain approval can delay the mitigation of the shortage.

Table 1: Causes of medicine shortages in multi-source and single-source markets

Cause	Generics (multi-source)	On-patent (single-source)
Economic		
Price/volume ratio in a market	✓	*
Low volumes	✓	*
Low prices	✓	*
Pricing mechanisms (net and gross)	✓	*
Reference pricing	✓	*
Tendering/procurement	✓	-
Payback policies	✓	-
Constrained healthcare budgets	✓	*
Parallel trade	✓	✓
Manufacturing		
Small number of manufacturing sites	✓	✓
Just-in-time supply chain	✓	✓
Short lead times	✓	✓
API sources/regulation	✓	✓
Quality-related problems (good manufacturing practice)	✓	✓
Natural disasters and accidents	✓	✓
Regulatory aggravating factor		
Regulatory time lag	✓	*

✓ May contribute to medicine shortages

* Non-availability

Table 1 shows the way in which economic, supply-chain and regulatory drivers affect single-source and multi-source markets. There is significant overlap in how these three sets of conditions affect shortages of both on-patent and generic medicines.

Shortages can occur in the case of both generic and innovative medicines, but, as shown in Table 1, some causes only apply in single-source or multi-source markets. Although both economic

and manufacturing causes affect generic medicines, on-patent medicines are mainly affected by manufacturing issues.

The various drivers listed in Table 1 can be categorised as either causes of medicine shortages or as non-availability of medicines.

Medicine non-availability can be defined as not introducing new, innovative medicines to market: non-availability occurs prior to the launch of a medicine. For example, new innovative medicines may not be available because of pricing and reimbursement decisions made by payers. In other instances, both innovative and generic medicines can be non-available when they are not purchased by payers or hospitals.

A medicine shortage, on the other hand, is best described as a temporary disruption to the supply of a medicine. Medicine shortages occur after the launch of a medicine.

The causes, implications and solutions differ between single-source (on-patent) and multi-source (generic) products. However, the priority continues to be that patients should receive the medicines that they need.

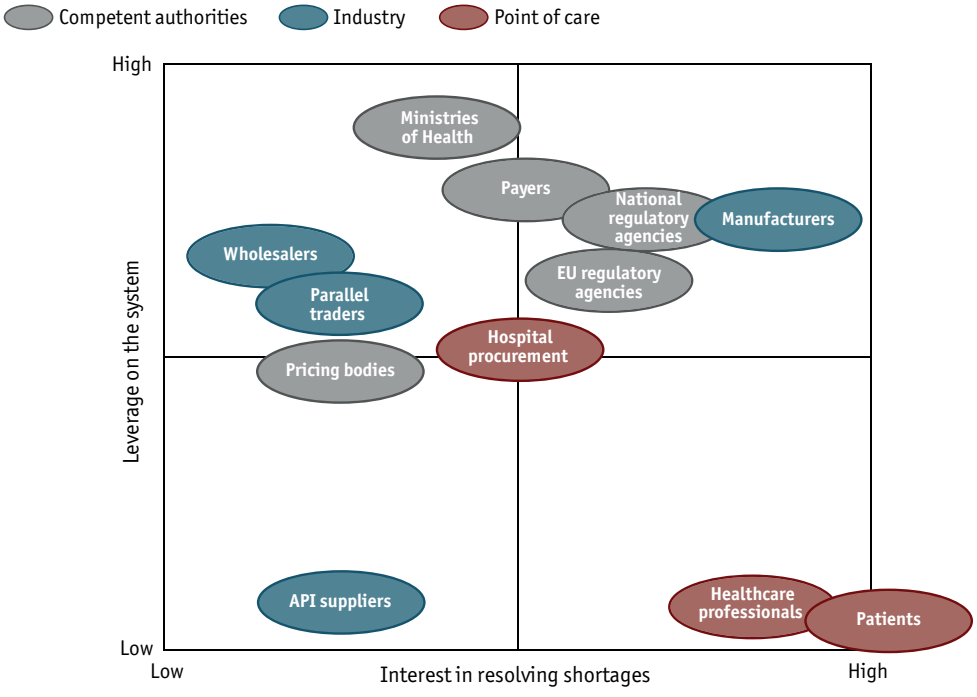
Capturing stakeholder views

Mapping of stakeholders

Medicine shortages are recognised by all stakeholders to be a complex problem, embedded within a multi stakeholder system. This makes the issue difficult to understand, and even more challenging to solve. Different stakeholder groups have different degrees of interest in resolving medicine shortages, and also have varying levels of ability and leverage to influence the current system. Figure 3 offers a graphical representation of this, showing four quadrants pertaining to stakeholders' levels of interest in resolving shortages and their leverage within the current system.

For example, patients are placed at the bottom right of the lower-right quadrant, as they are heavily impacted by medicine shortages but have little or no power to influence the system. Meanwhile, healthcare professionals deal with medicine shortages on a day-to-day basis, but even so there are cases where they are unaware of an ongoing medicine shortage and have little power to change the situation.

A graphical representation of stakeholders, pertaining to interest in addressing medicine shortages and leverage on the system to do so



Although other stakeholders may have a high degree of interest in addressing medicine shortages, the issue is not as critical for them as it is for patients and healthcare professionals. Some of those stakeholders, such as health authorities and regulatory agencies, have a high level of ability to change

the system but do not always have a high degree of interest in doing so, as they do not always know when there are medicine shortages, nor do they always have access to the relevant data.

Key insights from interviews

The interviews were conducted with the aim of gaining a comprehensive view of the issue of medicine shortages and representing all the stakeholders involved with it. There appear to be several different causes of medicine shortages, as highlighted in the previous chapter, and all stakeholders agree that both the prevention and the management of medicine shortages are of paramount importance.

This section presents the key points raised in the interviews. As expected, on some topics all stakeholders were in agreement whereas stakeholder views differed on others. This section aims to highlight the main takeaway messages, while still representing all stakeholder views.

Key points:

- Patients should be the top priority
- Stakeholders need to agree on a consistent definition of a medicine shortage
- Effective communication is needed between stakeholders
- Better tendering practices are required
- Management of medicine shortages needs to be facilitated
- Parallel trade needs to be addressed

Patients should be the top priority

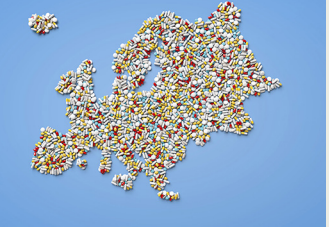
The patient perspective and the corporate perspective are not always fully aligned.

Over recent years the frequency of medicines shortages has been on the rise for various therapies. Despite this, recent progress has been encouraging; more and more stakeholders are actively working to address the issues.

All stakeholders are aware of the impact of medicine shortages on patients and of their responsibilities in terms of public health. However, there remains a disconnect between patients and other stakeholders. One stakeholder said that the patient perspective and the corporate perspective are not always fully aligned.

Patient-group representatives added that a lack of information around medicine shortages remains one of the most problematic issues for patients. Patients are often the last group to be informed about a medicine shortage, if they are told at all. It is imperative that they are made aware of supply disruptions if these are going to have a direct impact on their treatment. For example, the duration of medicine shortages and the way in which patients can monitor the status of shortages need to be prioritised. This issue is also experienced in in-patient hospital settings, where patients are not told when they are not receiving the preferred treatment and are instead being given an alternative. It is essential to convey this information to patients when there is the potential for adverse effects and the possibility of prolonged hospitalisation.

Patients would like to have greater representation and more input into the decision-making process around addressing potential supply issues affecting their medicines. They feel that patient



empowerment and a patient-centred approach are necessary. The Common Position Paper described in Box 1 shows that patient organisations are in fact aware of, and are getting involved with initiatives to mitigate medicine shortages, and this needs to continue.[10]

Box 1. Common position between patient, consumer and healthcare professional organisations involved in the activities of the European Medicines Agency (EMA) on supply shortages of medicines[10]

The Common Position paper has been signed by 45 patient and healthcare professional stakeholder organisations. It explains the consequences of medicine shortages for patients, healthcare professionals and healthcare providers, before looking into the possible causes of medicine shortages. These are categorised as medical or regulatory, economic, and manufacturing causes, as well as causes related to the organisation of the pharmaceutical market. The paper calls for the prioritisation of supply of medically necessary medicines, and proposes recommendations to the EMA regarding the regulatory framework, public authorities and pharmaceutical manufacturing industry (both before and during medicine shortages).

Stakeholders need to agree on a single definition of a medicine shortage

We need a harmonised definition of medicine shortages.

Currently, there are several definitions of medicine shortages in use, which vary between countries. Different organisations refer to and use several different definitions of medicine shortages. A qualitative study in 2015 by De Weerdt *et al.* identified 26 definitions; some of these provide a broad definition, while others specify when to report a medicine shortage.[2] This fragmentation poses several problems for stakeholders, including when to report a medicine shortage and when to respond to a shortage. The lack of a universally accepted definition also serves as an obstacle to developing a harmonised approach and finding solutions Europe-wide. There was a strong shared sense among interviewees for this report that a common definition needs to be adopted.

Industry representatives highlighted the fact that a unified definition of a medicine shortage is critical. They recognise that, when dealing with a complex situation like medicine shortages, it is necessary to start addressing and remedying the basic elements before targeting the more difficult and intractable issues. Additionally, they emphasised that there needs to be greater clarity between the definitions of a medicine shortage, non-availability and lack of access to a medicine. At the same time, manufacturers suggested that, because there are several reasons behind why a medicine may not be available on the market, any definition of medicine shortages should identify the reasons why a medicine is not able to reach patients.

The existing definitions of medicine shortages vary between countries in terms of the timelines mentioned (if they are specified at all), and encompass both supply and demand aspects; this can become confusing. The World Health Organisation (WHO) convened an expert meeting in October 2016 with the intention of developing technical definitions of medicine shortages.[4] This was a follow-up

action to a resolution passed at the 69th World Health Assembly in May 2016: during the assembly, it was decided that a technical definition of medicine shortages was needed which was to be written in consultation with experts from WHO member states, taking into account access and affordability of medicines for patients. During the October 2016 expert meeting, a medicine shortage was described in a draft definition as a situation in which "the supply of medicines, health products and vaccines identified as essential by the health system is considered to be insufficient to meet public health and patient needs".[4]

The view of patient group representatives was that a different definition of medicine shortages could be tailored for each stakeholder. As such, each definition would encompass a time element—so, for example, for pharmacists a medicine shortage would exist if a medicine had not been supplied for 72 hours.

Communication is key

Good communication is needed in order to build confidence in the system.

There was widespread consensus among interviewees that communication between the various stakeholders during a medicine shortage is often disjointed, with several parallel discussions taking place at the same time.

Several task forces currently operate at EU level with the remit of finding ways to prevent and mitigate shortages. The objective of the EMA taskforce is to more specifically address medicine shortages associated with "manufacturing disruptions linked to problems such as quality defects or Good Manufacturing Practice compliance issues". This objective is in line with the mission of the EMA, which includes enabling timely patient access to medicines, yet is not in itself sufficient to address medicine shortages when other causes are involved.

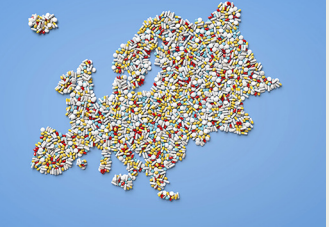
Academics and policymakers commented that a task force needs to involve the right people, and have a clear mandate and a set end point. One active network is the European Medicines Shortages

Box 2. COST Action CA15105: European Medicines Shortages Research Network – Addressing supply problems to patients (medicine shortages)[12]

The European Cooperation in Science and Technology (COST) understands that medicine shortages have a significant negative impact on patients and healthcare systems. Its action CA15105 creates a research network to be implemented over a four-year period, with the main aim of understanding the steps needed to mitigate the problem of medicine shortages.

The European Medicines Shortages Research Network has specific objectives:

1. To agree on a set of definitions around medicine shortages
2. To understand the prevalence of medicine shortages in European countries
3. To assess the direct impact of medicine shortages on patients and healthcare systems
4. To review the socioeconomic impact on healthcare systems
5. To understand the primary causes of medicine shortages and to provide an overview of medicine shortages to policymakers, regulatory agencies and other stakeholders
6. To develop a statement identifying long-term solutions



Research Network, created by the European Cooperation in Science and Technology (COST) (see Box 2), which is in the process of creating a platform to bring together all stakeholders to agree on solutions to mitigate medicine shortages in Europe.[12]

Increased collaboration between national- and European-level authorities will be beneficial. This need for bodies at the two levels to work together more closely was emphasised by all stakeholders. For example, the EMA operates a public medicine-shortages catalogue. This shows a medicine's name, its medicine shortage status (for example, "ongoing") and the date when the shortage entry was first published in the catalogue, and is updated on a regular basis.[13]

The catalogue has the objective of providing information on medicine shortages affecting more than one EU member state, and therefore does not provide a full overview of all medicine shortages occurring in the EU, as the majority of medicine shortages are dealt with by national medicines authorities. Our research confirms that it would be valuable for each EU state to have a national medicine-shortage catalogue, as this would give pharmacists and other stakeholders access to information about medicine shortages, helping them to address issues quickly and efficiently. Although most EU states have a process in place for reporting shortages, in 2014 only seven countries out of 28 had national medicine-shortage catalogues.[6] EIU research conducted in 2017 shows that this number has since increased to 12. Examples of operational catalogues include: the Federal Agency for Medicines and Health (FAGG-AFMPS) in Belgium, the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) in Spain and Farmanco in the Netherlands. Farmanco's database displays medicine shortages by showing the active ingredient, the proprietary name of the medicine, its administration route, its revision date and the impact of the shortage. Various aspects of shortages can be reported, including "alternatives available; import possible; limited availability; and impending medicine shortage". These catalogues could be used as models by other EU states wishing to implement their own catalogues.[14]

Patient group representatives shared their views on their desire for a system in which patients are able to report shortages of medicines themselves. In Romania, a website and reporting system has been created that allows patients, patient groups and medical staff to notify the Ministry of Health if they are unable to obtain a certain medication. For each notification of a medicine shortage, the ministry has four days to assess the situation, seven days to look into any measures the state authorities have taken to address the issue, and a year to compile a summary of the measures taken by the authorities to help patients cope with the medicine shortage. The website also publicly displays each medicine-shortage notification with a countdown to the four-day deadline by which the ministry must assess the situation.[15]

There was some variety of opinion among stakeholders about notification of medicine shortages by suppliers. There was consensus across medicine manufacturers that notifications were sent to the relevant authorities immediately by manufacturers when supply disruptions were predicted. However, policymakers and pharmacists suggested that this was not necessarily common practice, and they agreed that early-notification procedures needed to be enforced.

At present, EU legislation (Article 23a, Directive 2001/83/EC) states that pharmaceutical manufacturers are obliged to submit a pre-notification to the relevant health authorities if a product's

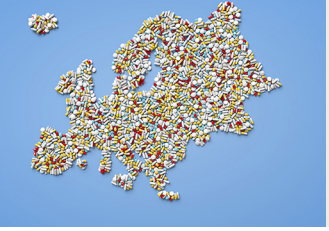
supply will be disrupted either temporarily or permanently. The directive states that authorities must be notified no less than two months prior to interruption of supply to the market.[16] An EMA survey showed that although the directive operates at EU level, only 21 of the bloc's 28 member states had transposed the measure into national-level legislation. Some countries that have made national laws on supply interruptions have different timeframes within which the authorities have to be notified of medicine shortages—for example, six months in Belgium.[6]

In the US, under Section 506C(f) of the Federal Food, Drug, and CosmeticFood and Drug Administration Safety and Innovation Act, manufacturers are required to notify the Food and Drug Administration (FDA) at least six months prior to the date of interruption or discontinuation of a medicine, or "if that is not possible, as soon as practicable thereafter, but in no case later than five business days after the discontinuation of interruption in manufacturing".[17, 18] Failure to comply results in the FDA issuing a letter to the manufacturer, after which the company has 30 days to submit a written response giving the reasons for non-compliance and for the interruption to supply. If this response has not been received by the authorities 45 days after issue of the FDA letter, the FDA makes its letter and the manufacturer's response publicly available on the FDA Drug Shortages website.

Industry representatives pointed out that in some cases manufacturers do not report medicine shortages if they know that they will be able to resolve disruptions within a few days or weeks. Additionally, representatives raised the issue that it can be challenging to predict the occurrence of a shortage, as in the majority of cases supply disruptions occur suddenly. However, pharmacists and policymakers responded that the more information is made available, the better (even if there is the possibility of raising false alarms), as this allows them to prepare for a medicine shortage and put a plan in place. Although industry representatives stated that they did not feel that notifications of medicine shortages should be made mandatory in national legislation, other stakeholders agreed that doing so would ensure that notifications are submitted. Manufacturers also said that the early-notification system should be treated as an opportunity for stakeholders to work together to address shortages.

Representatives from regulatory bodies voiced the opinion that there should be a "safe haven" where manufacturers can communicate with competent authorities and regulators. Based on their own experiences, they mentioned the fact that manufacturers may worry that regulators respond too harshly to notifications of medicine shortages, for example by imposing penalties. Their view is that this is generally not the case as long as discussions can be held on any vulnerabilities in the supply chain and solutions suggested. Another issue raised by manufacturers was the lack of a harmonised system to report medicine shortages. Industry representatives explained that manufacturers currently have to file a different report for each country in the EU, which requires them to use 28 different ways of reporting a shortage. They argued that there needs to be a standardised method of reporting, as well as greater clarity on whom they must report to.

Pharmacists suggested that when a shortage of a medicine is announced by the national competent authority, information on alternative therapies should also be provided. They added that knowledge is power and pharmacists have to put in a huge amount of work during a medicine shortage, which has a negative impact on immediate patient care.



Better tendering and procurement practices are needed

Tender criteria should be structured around the type of medicine, the volume of demand and the size of the market.

Once a medicine has entered the public domain, its original manufacturer loses market exclusivity and it becomes part of a multi-source market. The tendering process is used when payers, such as governments or hospitals, procure medicines from the multi-source market. The practice of procurement involves bidding on the price to be paid for a medicine. As things stand, except in a few cases, tenders for medicines in Europe are most often issued based on price.

This leads to low price ceilings, which in turn may cause manufacturers to exit an unattractive market. Policymakers interviewed suggested, however, that low price ceilings and margins may not be the key reason for medicine shortages. For example, in the Dutch market the number of recorded shortages of generic and on-patent medicines is similar, yet manufacturers of on-patent medicines tend to have higher margins relative to their production costs. The policymakers therefore suggested that the main reason behind medicine shortages could be deficiencies in the planning of production.

The risk of a shortage of a medicine is higher when there is only one or a small number of manufacturers, as production risks are concentrated on fewer production lines. All stakeholders interviewed recognised that a tendering system needs to be developed that takes into account other factors than just price. A 2009 report by researchers from the London School of Economics described an ideal tendering process as follows: "An effective tendering process takes into account several criteria, rather than focusing on a single criterion, in order to ensure the availability of the needed pharmaceuticals in the required quantities, at reasonable prices and at a recognized quality standard."[19]

One approach suggested by representatives of generic manufacturers to address this issue is the adoption of multi-winner tendering practices, which have been implemented for hospitals in some European countries—such as Italy and the Netherlands—with varying degrees of success. A multi-winner tender exists when a procurer awards the tender to more than one manufacturer and there are therefore multiple suppliers to meet demand for the same medicine. Often, the multi-winner tender is structured around a tiered pricing system whereby each manufacturer supplies at a different price. Another option suggested by industry representatives is multi-lot tenders, in which the volume of medicine needed is split into several lots, with a separate tender for each lot.

Industry representatives made the case that having multiple winners of a tender would guarantee the supply of a medicine, and also that it would result in reduced volatility and increased predictability and stability of supply. Manufacturers suggested that the ideal situation is to have three winners of a tender. However, pharmacists stated that the number of tender winners should not be fixed, but instead should be based on the volume of demand, the size of the market and the type of medicine.

Other stakeholders agreed that although the multi-winner tendering system is a good idea in principle, it may not work so well in practice. Regulators' representatives noted that it might be more realistic to expect multiple bids to enhance supply rather than to guarantee it. Even then, they suggested that if one manufacturer were to experience a supply issue, the others might not have the

capacity to step in and supply at levels above their agreed volumes. Hospital pharmacists said that, based on their experiences, in the case of multi-hospital tenders, managing a multi-winner tendering system involves challenges, such as the need to have a process in place to decide which hospital pays the higher price for a medicine as set by the differential pricing system. Likewise, stock management for in-house hospital pharmacists requires changes to their usual practices, and this takes time away from patient care. Industry representatives recognised that changing tendering practice to a multi-winner design would require a change in thinking.

The need for change in tender design was agreed by all. All stakeholders acknowledged that single-supplier tender systems create low price ceilings for manufacturers and that fairer economic conditions need to be created.

The idea that tenders should be based on more than just price also received unanimous approval: manufacturers should provide information on their capacity to supply and their history of medicine shortages, in order to enable procurers to have greater trust in their supply security. From their side, manufacturers need to be given information on the volume of demand from the payer when the tender is issued, to enable them to predict the volume that they will need to supply. Pharmacists and policymakers suggested including a two-way pro rata penalty for failure by either party in honouring the terms of the contract. The introduction of longer timeframes and lead times into tenders was also suggested, to allow all parties time to plan ahead, but in this area views differed, and there was a lack of consensus on the optimal time lines across supply and demand.

Management of medicine shortages

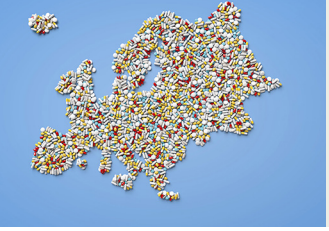
Enhanced co-operation is needed between regulators and manufacturers where they can discuss and prioritise regulation during a medicine shortage.

Prevention of medicine shortages is critical, but there will always be situations that cannot be predicted in advance, and in such cases management is essential to minimise the harmful impact on patients.

Manufacturers, regulators and policymakers identified the problem that, during a medicine shortage, current regulatory procedures take too long to get a new substitute medicine into the market when a small number of suppliers or a single supplier is struggling to meet demand. As things stand, from the viewpoint of manufacturers the regulatory procedure—for example, the selection of a new API supplier—is seen as a lengthy process that can hinder the rapid release of medicines to facilitate timely supply. Manufacturers suggested that one way to address this issue could be to fast-track regulatory procedures.

Academics confirmed that during a medicine shortage the existing inefficient regulatory procedures are an inconvenience and are unacceptable.

Representatives from regulatory bodies proposed that having the right to fast-track regulatory procedures could be linked to a manufacturer's track record, for example their good manufacturing practice (GMP) compliance history. As regulators are generally aware of a manufacturer's compliance history through inspections, a "trusted supplier" model could be established. One suggestion was that, as part of such a model, manufacturers be asked to produce a medicine shortage prevention



plan to show that they are aware of any vulnerabilities and risks to their supply chain (for example, having only one supplier of an API). Policymakers added that manufacturers should accept the moral obligation as providers of medicines to keep their products on the market. They suggested that to reduce the risk of supply issues caused by problems with APIs, and as part of good practice, manufacturers should have more than one API supplier when obtaining market authorisation for their medicines.

Manufacturers stressed that the issue of regulatory fees in the event of medicine shortages needs to be addressed, as sometimes manufacturers are asked to step in and produce medicines but no specific consideration has been given to the fees to be paid by manufacturers to regulatory bodies. It was suggested that reducing regulatory fees e.g. variation fees in such cases would be desirable. This idea was also well received by other stakeholders.

There is an increased need for pharmacists to be able to substitute a medicine in the event of a medicine shortage, but this should be done with guidance from clinicians.

In the midst of a medicine shortage, pharmacists are sometimes required to substitute the unavailable medicine with a therapeutic alternative. Pharmacists are knowledgeable enough to do this. However, in some countries there is legislation in place that restricts pharmacists' ability to substitute one medicine for another. This can cause problems, as pharmacists need to gain approval from clinicians regarding alternative medicines and are under immense time pressures to provide patients with a suitable form of treatment. Manufacturers commented that when pharmacists are required to substitute a medicine in case of medical need they need to be protected from legal liability.

There was general consensus among stakeholders that pharmacists ought to be granted greater flexibility to make substitutions during medicine shortages in cases of medical need. However, it was agreed that this needs to involve a co-ordinated approach whereby clinicians provide pharmacists with guidance. Academics recognised that although this was a good solution, pharmacists have to be careful with regard to which medicines qualify to have their cost reimbursed under health insurance programmes, as in some cases insurance may not cover the cost of a substituted medicine. They added that substitute medicines should be made available regardless of insurance cover. Hospital pharmacists mentioned that one issue is that clinicians are often not aware of a medicine shortage. This problem needs to be addressed so that clinicians can immediately prescribe an alternative medicine for their patients.

Harmonised pack sizes and e-leaflets are a cost-effective and logical solution to make movement of medicines across borders feasible during a medicine shortage.

During a medicine shortage, when stocks of a certain medicine are low in some countries, medicine could be moved by the manufacturer across borders from countries where stocks are high. However, manufacturers claim that the difference in pack sizes between countries can prevent this from being feasible. In addition, the languages used in patient leaflets may not be the same as in the country receiving the medicine. Manufacturers suggest that one way to get around this difficulty is to standardise pack sizes across Europe and to implement the use of "e-leaflets". E-leaflets could be available online, with the option to print them in the appropriate language at the point of

dispensation of the medicine, given that pharmacists always have access to the internet. Academics emphasised that in e-leaflets the core language must be English, with the option to include any other languages. The idea of e-leaflets was welcomed by all stakeholders.

Parallel trade

Management of parallel trade in emergency situations is important, but often faces political opposition.

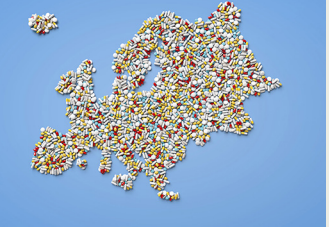
Parallel trade can contribute significantly to medicine shortages. As mentioned previously, EU trade laws permit the free movement of goods between countries, which means that parallel traders are legally able to purchase medicines in low-price countries (such as Bulgaria, Greece, Portugal, Romania, Slovakia and the UK) and sell them in high-price countries. This can lead to depleted stocks in the lower-priced markets.[20]

At present, measures to prevent parallel trading of medicines during a shortage are the prerogative of individual EU member states. Some countries, including Greece, Bulgaria and Slovakia, have put in place measures such as parallel-export bans in the event of shortages to protect domestic medicine stocks. In Slovakia, parallel traders are required to notify the authorities of their intention to export any medicines 30 days prior to the date of export; this allows the authorities to check the availability of the medicines and, if stocks are low, to block the export. However, such measures have not always been well received by EU level authorities, and they have often face legal opposition, with some having being repealed.[21]

Experts from EU regulatory bodies made the case that because parallel trade is legal under EU competition law, any measures implemented at national level must be justified on public health grounds. Articles 34-36 of the Treaty on the Functioning of the European Union state that the movement of goods can be challenged on the basis of public mortality, public policy or public security.[22] This raises the question: How is public health need justified, and at what point does restriction of trade become unreasonable?

Policymakers made the point that further research is needed in order to be able to justify public health benefit or a negative impact on public health: there needs to be a harmonised definition and clarity on the point at which public health need is considered to be significant enough to justify implementing a ban on parallel exports as an emergency measure during medicine shortages.

The idea of introducing transparency regarding stock levels of medicines in each country was also raised by some stakeholders. The establishment of the European Medicines Verification System could facilitate transparency in the supply chain. If manufacturers have insight into the level of their remaining stocks in a market, they can improve the management of their supply. Additionally, trade in medicines does not necessarily always have a negative impact: it has the potential be used to make agreements with other countries to move medicines across borders when supplies of essential medicines are low.



Where to next?

As we have seen, issues have been flagged up at various stages of the supply chain, from pre-production (with the quality of APIs) to GMP compliance problems; regulatory time lags; procurement policies; and distribution of medicines by methods such as parallel trade.

In recent years, the issue of medicine shortages has been researched and addressed in a number of policy papers by various organisations, and has been raised as part of discussions in many European countries. However, alongside the recommendations highlighted in this report, action and implementation is required to ensure that patients have access to the medicines that they need.

Similarly, although several definitions of medicine shortages have been developed and further definitions continue to be drafted, no single one of these has yet been chosen and adopted by all stakeholders in Europe or internationally.

It is also important to acknowledge that although medicine shortages can have a number of different causes, one important key to addressing them is to maintain fair economic conditions, especially for medicines deemed medically essential. Markets where only a small numbers or suppliers are present or are bidding to supply medicines are a sign that market conditions are not attractive for suppliers. A shrinking number of suppliers is also recognised by the EMA as posing a risk of medicine shortages. Individual countries need to take responsibility for devising policies and taking action to ensure that the risks are managed and that medicine shortages are prevented.[23]

All systems need to be made more transparent in order for the issue of medicine shortages to be better managed. In the following section, containing calls to action, we look at recommendations for numerous aspects of medicine shortages, from prevention to management. From the long list of actions that were considered, we have included the most promising ones—those that have the most traction across the various different stakeholders.

Calls to action

Prevention of medicine shortages

Action I.

Improve tendering practices to introduce appropriate tender criteria, taking into account other aspects in addition to price

Appropriate timelines for tenders are recommended, in particular to balance lead times, so that procurers provide optimal visibility regarding expected volumes and so that tenders can accommodate pharmaceutical manufacturers' capacity to meet demand.

Tendering practices should adopt a holistic approach by introducing tender criteria other than price. Additionally, tender models may consider a multiple-winners design.

In order to build a system that fosters predictability, any penalties should be pro rata and proportionate for either party if it is not able to honour the terms of the tender contract.

Procurers:

The procurer should make the level of demand for medicines clear on the tender, and should commit to receiving the agreed volume of medicines from the manufacturers.

The procurer can decide the number of suppliers needed to provide the volume of medicine required, based on the type of medicine and manufacturers' capacities to supply them.

Procurers can include supplier reliability as a tender criterion, to be reviewed on an annual basis.

Manufacturers:

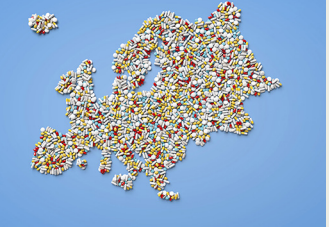
Manufacturers should make their capacity to supply clear on the tender, and should commit to delivering the agreed volume of medicines to the procurers.

Manufacturers should be transparent with regard to their past supply disruptions and should make clear any risks to their supply chain (for example, only one API supplier) when bidding for a tender.

Action II.

Consider specific measures to maintain healthy multi-supplier markets

Examples of how to prevent medicine shortages include having fair economic options to ensure a predictable multiplayer market. For example, by providing incentives to improve manufacturing facilities or rewarding manufacturers for compliance to good manufacturing practice (GMP).



Management of medicine shortages

Action I.

Agree on a common definition of medicine shortages

As mentioned earlier in this report, there are several different definitions of medicine shortages, as defined by various organisations.

All stakeholders need to agree to refer to and use one definition of medicine shortages that makes clear the trigger point and the timeframe within which to report a medicine shortage.

Every EU member state should have in place a transparent process to trigger action during a medicine shortage and to determine whether a medicine is essential. One way of doing this could be to adopt a list of essential medicines.

Action II.

Implement EU early-notification requirements for manufacturers at national level for situations in which medicine shortages are expected

A mandatory early-notification requirement should be implemented to ensure that manufacturers notify the national competent authorities as soon as possible if they foresee a future medicine shortage. As mentioned previously, EU legislation (Article 23a, Directive 2001/83/EC) states that pharmaceutical manufacturers are obliged to submit a pre-notification to the relevant health authorities two months before a product's supply will be temporarily or permanently disrupted.19 However, there has been resistance to implementation of this requirement at national level, and this issue needs to be addressed. There is a clear need for EU-led initiatives to be implemented in every member state.

The early-notification system should be used in a constructive way, as an opportunity for stakeholders to work together to tackle medicine shortages.

Priority should be given to medicine-shortage reports relating to essential medicines for which no alternatives are available on the market.

All EU member states should enforce the early-notification requirement as specified in the relevant EU directive by incorporating it into national law.

Notification should use a standardised template to enable harmonised reporting.

As part of early notification, manufacturers need to include the reasons for supply disruptions and their short-term plans for addressing them. This will allow authorities to develop strategies for the prevention and management of future medicine shortages.

The consequences for manufacturers of failure to adhere to national legislation around mandatory early-notification requirements are the responsibility of the member states.

Action III.

Develop a system that ensures transparency around medicine shortages at national level

Each EU member state should develop a national medicine-shortages catalogue website that is available for viewing by all stakeholders. Each entry should state the product's name, the marketing authorisation holder, the status of the medicine shortage, the start and end dates of the shortage and the cause of the shortage.

National shortages catalogues can be real-time platforms/databases that are able to feed harmoniously into the EU-level medicine-shortages catalogue.

National authorities should use information from early-notification reports, as well as reports from pharmacists unable to source medicines, to update national medicine-shortage catalogues.

Additionally, if possible authorities should analyse the occurrence of medicine shortages and provide recommendations on therapeutic alternatives to patients and healthcare professionals. This responsibility could lie with the body issuing guidelines or determining care pathways.

Action IV.

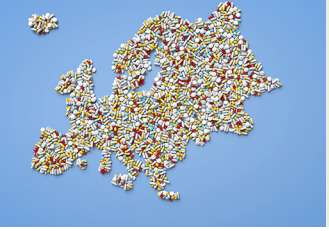
Enhance the efficiency of regulatory procedures and implement fast-track processes to mitigate acute medicine shortages

Manufacturers should ensure that they have a medicine-shortage prevention plan in place that outlines any vulnerabilities in their supply chains (for example, risk due to the use of only one API supplier). This, along with manufacturers' track records on GMP compliance, can be used by regulators to build a '"trusted supplier" model.

Regulators should review and update the trusted supplier model on a yearly basis.

Regulators should use the trusted supplier model when allowing particular manufacturers to use fast-tracked regulatory procedures in order to prevent or resolve medicine shortages.

Regulators should consider reducing regulatory fees when asking a manufacturer to step in to supply a market during a medicine shortage.



Action V.

Allow greater flexibility on delivery of medicines and the movement of packs across borders during medicine shortages

Pharmacists should be able to substitute medicines in cases of medical need. When such substitutions are made, it is crucial that patients are made aware of the substitution and are provided with information about it by pharmacists.

Pharmacists should be able to switch medicines with different administration routes of the same medicine. However, this should only be done when the medicine is suitable for the patient and with the agreement of the prescribing physician.

The implementation of the EU Falsified Medicines Directive (FMD) in February 2019 and increased use of tracking tools should be seen as enabling the adoption of standardised medicine packs across Europe, and allowing improvements in transparency around the movement of packs across borders during medicine shortages.

Medication-information leaflets should be made available and accessible to patients electronically as e-leaflets. E-leaflets should be made available in various different languages (with English remaining as a common language) so that they can be adapted to all European countries.

Expert interviews

To support the research that was conducted and analysed for this report, The Economist Intelligence Unit interviewed experts involved in initiatives tackling medicine shortages in Europe. We wish to thank these experts for their time and insights. Participants are listed below:

- John Berridge, International Society for Pharmaceutical Engineering (ISPE)
- Frank Bouisset, Sandoz
- François Bouvy, European Federation of Pharmaceutical Industries and Associations (EFPIA)
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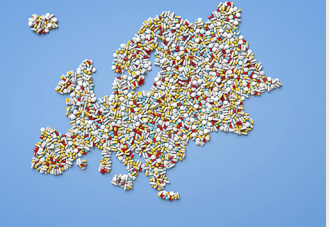
- Joan Peppard, European Association of Hospital Pharmacists (EAHP)
- Adrian van den Hoven, Medicines for Europe
- Paul van Hoof, GlaxoSmithKline
- Marcel van Raaij, Ministry of Health, the Netherlands



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