The Economist Intelligence Unit Healthcare

About this report

Cancer medicines shortages in Europe, Policy recommendations to prevent and manage shortages is an Economist Intelligence Unit (EIU) Healthcare study which was supported by the European Society for Medical Oncology (ESMO). This report discusses the causes contributing to shortages of oncology medicines and articulates recommendations to address them.

Anelia Boshnakova, Senior Information Specialist was the main project researcher, supported by Aditi Karnad, Health Research Analyst. Annie Pannelay, Principal for EIU Healthcare served as senior advisor and Daljeet Singh was responsible for layout and design. We wish to thank the experts listed in the Objective and methods section for their time and insights.

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Executive summary

Access to medicines for cancer patients is crucial for providing high quality care. However, cancer medicines shortages are a problem affecting countries across Europe. These shortages occur when the supply of medicines, identified as essential by the health system, is insufficient to meet public health and patient needs.[1] Why do these shortages exist, and how can we prevent them? The Economist Intelligence Unit were commissioned by the European Society for Medical Oncology (ESMO) to investigate medicines shortages in Europe, what can be done to prevent medicines shortages, explore their impact on the provision of care and how to mitigate the impact on patients, clinicians and pharmacists.

The research team performed a review of the academic and grey literature, and convened a panel of experts, with the goal of developing policy recommendations to improve the management of medicines shortages in Europe.

The World Health Organization (WHO) has led on tackling the issue of medicines shortages globally. The WHO emphasises the need for coordinated action between multiple stakeholders to prevent and manage shortages, in order to meet targets in the United Nations' 2030 Agenda for Sustainable Development.[2] However, the system for regulating medicines in the 31 countries of the European Economic Area (EEA) – which includes the 28 European Union (EU) countries plus Iceland, Liechtenstein and Norway – is unique in the world.[3] It is based on a regulatory network of about 50 national competent authorities in the EEA Member States working together with the European Medicines Agency (EMA) and the European Commission.[4] The EMA has a key role in coordinating initiatives to develop long-term strategies for the prevention and mitigation of the impact of medicines shortages in Europe. The EMA has primarily had to deal with shortages caused by quality and manufacturing issues.

A range of stakeholders, including international health organisations, manufacturers, wholesalers, pharmacists, clinicians and other healthcare professionals, have suggested finding global or European solutions to the issue of medicines shortages. However, healthcare remains a national responsibility in EU Member States. Therefore, medicines shortages cannot be resolved by supranational institutions alone. EU countries' governments and health authorities need to focus on policy measures at a national level. When national policies addressing the issues of medicines shortages are in place, cross-country collaboration will be more impactful in finding solutions that could be implemented across Europe.

Informed by findings from our literature review and following consultation with experts representing all key stakeholders, we present six policy recommendations for countries across Europe.

Six policy recommendations to address cancer medicines shortages in Europe

Recommendation 1

Introduce legislation for early notification requirements for medicines shortages

- National legislation for early notification from manufacturers should be implemented in all European countries, as stipulated in Directive 2001/83/EC.
- The legislation should include a requirement for manufacturers to provide information about the reasons for discontinuation of supply.

Recommendation 2

Establish strategic plans for medicines shortages

- Countries should establish a task force to develop a national strategic plan for medicines shortages, underpinned by national legislation and funding.
- This initiative could be proposed at a European level, with countries having an option to implement it on a national level.

Recommendation 3

Develop catalogues of shortages

- All European countries should develop a national system for reporting medicines shortages based on a minimum set of data requirements.
- European regulatory authorities (Heads of Medicines Agency (HMA)/EMA) could 1) coordinate the development of a harmonised procedure for reporting of shortages, based on a shared definition, and 2) develop a platform/database to collate the reports from the national systems.
- All stakeholders, including patients and physicians, should have access to a user-friendly, web-based system to report shortages.

Recommendation 4

Develop essential medicines lists and assess the risk for shortages

- Countries should develop national essential medicines lists based on the WHO Model List of Essential Medicines (EML).
- The EMA Risk Indicators for Shortages (manufacturing and quality) should be used to identify high-risk products.

Recommendation 5

Introduce incentives for production infrastructure improvements

- Health systems/payers in European countries should consider financial incentives for production infrastructure improvements to address economic causes of manufacturing issues.
- Incentives for suppliers to enter and remain in a national market could also be considered.

Recommendation 6

Establish procurement models designed to prevent medicines shortages

- Good procurement practices that address predictability and profitability for medicines manufacturers should be identified. These could include using tender criteria that include price as well as other factors, e.g. quality track record of manufacturers.
- Tender cycle harmonisation could be considered within and across countries.
- National procurement for medicines experiencing shortages could be considered.

Objectives and methods

The focus of this research is medicines shortages rather than medicines unavailability, which is a broader concept and includes, among other reasons, lack of access to medicines due to high cost (unaffordability). Medicines shortages occur when the supply of medicines "identified as essential by the health system" is "insufficient to meet public health and patient needs."[1] This understanding of the concept of medicines shortages is based on the draft definition that was discussed at an expert meeting convened by the WHO.[1]

This study investigates how and why medicines shortages in Europe are affecting essential cancer medicines and what can be done to prevent and mitigate the impact on patients, clinicians, pharmacists and other stakeholders. The study was commissioned by ESMO in keeping with its mission to promote equal access to optimal cancer care for all cancer patients. In the last decade ESMO has conducted a series of studies on the availability, out-of-pocket costs and accessibility of opioids and antineoplastic medicines in Europe.[5, 6]

The aim of this research is to recommend policy measures that could be successful in addressing the issue of cancer medicines shortages in the European context. Parts of the discussion are more pertinent to the countries of the European Union and the European Economic Area – the 28 EU countries plus Iceland, Liechtenstein and Norway. Where relevant, we have included examples from other geographies, most notably the United States of America (USA). The policy measures discussed here are, nevertheless, applicable to the 53 countries in the WHO European Region and across the world.

This research project included a literature review to investigate the magnitude and causes of cancer medicines shortages and their impact on patient care. The systematic and structured search included the following steps:

- Focused searching of the biomedical database MEDLINE/PubMed
- Search of specialist sources for non-journal literature (using Google advanced search techniques and targeted searches of relevant organisations' websites)
- Supplementary search techniques e.g. citation tracking, reference list scanning, and related articles searches (using PubMed and Google Scholar related search algorithms)

Existing policy initiatives addressing the issue of medicines shortages were reviewed and analysed, and key themes identified. Selected policy initiatives were discussed with a panel of experts at an advisory editorial board meeting, and one-to-one interviews. The expert panel included representatives of health authorities, professional associations of pharmacists, oncologists, and the pharmaceutical industry, as well as patient advocacy groups:

- Brendan Cuddy, European Medicines Agency (EMA), Observer
- Alexandru Eniu, European Society for Medical Oncology (ESMO)

- Richard Freudenberg, European Association of Euro-Pharmaceutical Companies (EAEPC)
- Roberto Frontini, European Association of Hospital Pharmacists (EAHP)
- Klaus Meier, European Society of Oncology Pharmacy (ESOP)
- Koen Nauwelaerts, Medicines for Europe
- Vlad Voiculescu, Former Minister of Health, Romania
- Malvika Vyas, European Society for Medical Oncology (ESMO)
- Andrew Winterbottom, Fight Bladder Cancer

After the advisory meeting we conducted additional interviews with Klaus Meier, President of the European Society of Oncology Pharmacy; Vlad Voiculescu, Former Minister of Health in Romania; and Dr Fatima Cardoso, Director Breast Cancer unit, Champalimaud Clinical Centre, Portugal and Member of ESMO's Executive Board.

The Economist Intelligence Unit bears sole responsibility for the content of this report. The findings and the views expressed in the report do not necessarily reflect the views of the experts involved.

We thank the ESMO Public Policy Steering Committee for their input.

Magnitude, causes and impact on patient care

What are medicines shortages?

Various definitions of medicines shortages are used by different organisations. A recent review identified twenty-six definitions of medicines shortages, whereas a WHO commissioned systematic review found an even larger number of definitions – fifty-six.[1, 7]

Others attempts at definitions state that even the term "shortages" is not broad enough to fully describe the issue.[7-10] Significant work towards the development of a harmonised definition of medicines shortages has been carried out in the last few years under the coordination of the WHO and the EMA.[1, 11, 12]

Medicines shortages are common and mostly affect cheap, generic medicines

Medicines shortages are a global problem, affecting countries at all levels of development.[13, 14] The WHO emphasises the coordinated action of multiple stakeholders to prevent and manage shortages to enable member countries to meet the targets related to access to medicines of the United Nations' 2030 Agenda for Sustainable Development.[13]

In the period leading up to 2012 the USA experienced frequent medicines shortages, with an estimated 500,000 cancer patients affected by oncology medicines shortages annually.[15] The situation with escalating medicines shortages in the country was addressed by creating a legal mandate for action, through a Presidential Executive Order and new legislation.[16] As a result the US Food and Drug Administration (FDA) developed a strategic plan for the prevention and mitigation of drug shortages for a range of medical conditions including cancer.[17]

Europe is no exception, medicines shortages have also become more commonplace in the last decade. Several recent surveys of hospital pharmacists, community pharmacists and clinicians found that in the last ten years most European countries have experienced medicines shortages with increasing frequency.[5, 9, 18, 19] About two-thirds of the respondents in the 2014 European Association of Hospital Pharmacists (EAHP) survey reported that shortages occur on a daily or weekly basis.[18]

These surveys all found that cancer medicines are one of the classes of medicines most commonly affected by shortages. The 2014 EAHP survey conducted in 36 countries reported that over half of the respondents (55%) have experienced shortages of cancer medicines.[18] After antimicrobial agents, oncology medicines were the class of medicines most frequently affected by shortages. The cancer medicines most commonly affected were: 5-flouroucil, carboplatin, cisplatin, doxorubicin (liposomal), etoposide, melphalan, methotrexate, oxaliplatin, and vincristine.[18]

A 2015 survey of 161 hospital pharmacists conducted by Pauwels et al. in 26 EU and non-EU countries in Europe also found that a large proportion of respondents (51%) reported shortages of cancer medicines.[9] Most of the affected medicines were inexpensive, generic, injectable medicines. Similar findings were reported in a survey of 48 European countries published in 2016 by ESMO in collaboration with medical oncology societies worldwide, international organisations and oncology pharmacists. This study found that common, inexpensive anticancer medicines included in the WHO

Model List of Essential Medicines, e.g. tamoxifen or cisplatin, were affected by shortages "largely due to manufacturing and distribution issues".[5]

A 2014 study by Pauwels and colleagues, focused on seven countries (Belgium, England, France, Germany, Italy, the Netherlands and Spain) that have a medicines shortages reporting system.[20] It found that shortages of "antineoplastic and immunomodulating agents", medicines used for the treatment of cancer, represented 12% of all reported medicines shortages. The cancer medicines in short supply involved mostly generic medicines (54%) and injectable medicines (79%). Cancer medicines shortages are particularly challenging due to the impact on individual cancer patients' outcomes and the potential for a shortage of a single medicine to impact many patients as the same products are used – albeit through different protocols – to treat a wide range of cancers.[20]

Although several recent surveys present some data about oncology medicines shortages in Europe, a number of studies emphasise the scarcity of quantitative data, which makes it very difficult to assess the actual severity of the situation in Europe and estimate which countries are most affected.[8, 20]

Medicines shortages harm patients and push up costs

Surveys conducted by the EMA, EAHP, the Institute for Safe Medication Practices (ISMP) and others in Europe and the USA report that medicines shortages have a significant impact on patient care.[9, 18, 21, 22] Shortages can lead to failure to treat, delayed treatment, the use of less desirable – often expensive – alternative products, an increased potential for errors or adverse events related to using alternative medicines or dosages, and exclusion from treatment, to list just a few of the reported outcomes.[9, 23-28] Inability to provide curative treatment or delaying chemotherapy as a result of shortages can have significant consequences for patient outcomes, including survival rates.[15]

For paediatric cancers the situation can be particularly serious, as the medicines affected by shortages are curative and with few proven effective alternatives.[29] To minimise the impact on the care for this particularly vulnerable patient group, a number of ethical protocols and frameworks have been developed in the US for prioritising or rationing limited supplies of chemotherapy or adjuvant therapy medicines.[29-31] This work required the efforts of multidisciplinary groups of experts including paediatric oncologists, pharmacists and hospital administrators.

However, published academic literature on the impact of medicines shortages on cancer patients' outcomes is scarce. With few exceptions[32] the vast majority of clinical studies on the impact of cancer medicines shortages on patient care are based in the USA.[33-41] In a 2015 recent study Pauwels and colleagues found that medicines shortages in European countries have not been empirically investigated as much as in the USA.[9]

The economic impact of oncology medicines shortages on healthcare payers, providers and cancer patients has been the focus of several studies.[42-44] Increased costs for the healthcare system result from staff time diverted to dealing with shortages and the higher costs of alternative treatments for payers/insurers.[18, 23, 44] A survey by the European Society of Oncology Pharmacy (ESOP) found that around two-third of cases (67.3%) of medicines shortages were managed by pharmacists without disrupting the treatment of patients. However, this comes at the cost of the extra time spent on managing shortages and the higher costs for alternative medicines.

Higher costs of alternative cancer treatments have also led to significant increases of patient out-of-pocket payments in the US.[44] Pauwels and colleagues' survey of medicines shortages in general (not focused on oncology medicines) in 26 European countries found that shortages had a significant impact on healthcare providers' costs, but "rarely or never" had a direct cost impact on patients.[9] However, the financial implications for patients could be more serious than thought, as most of the respondents were from countries with strong public health systems.

Interviews conducted for this research highlighted the lack of awareness about the issue of medicines shortages among patients and the general public, and even policymakers in many European countries. For example, Klaus Meier described in our interview how about 170,000 patients with colon cancer in Germany could not be treated properly as a result of shortages of fluorouracil (5FU) five years ago. This seemingly came as a great surprise to the general public and healthcare policymakers. [Interview with Klaus Meier, 20th February 2017] Another interviewee, Fatima Cardoso, noted that news media usually cover issues with access to new, expensive medicines, while shortages of inexpensive medicines rarely register in the public interest. [Interview with Fatima Cardoso, 20th March 2017]

Awareness about medicines shortages among all stakeholders is crucial to "stimulate collaboration and introduce specific measures against shortages".[8] The lack of awareness among patients and the general public might explain why not much has been done to address the issue of shortages in some countries.

Although there is general agreement about the significant impact of cancer medicines shortages on patient care, there is a need for robust data about the impact of shortages on patient outcomes and the out-of-pocket costs for cancer patients and their families.

Shortages are the result of the interplay of many issues

The causes for medicines shortages are complex and multifactorial.[10, 45, 46] A 2016 report by the FDA identified the following reasons for these shortages: [47]

- Quality: manufacturing issues – 37%
- Quality: delays/capacity – 27%
- Raw materials – 27%
- Increased demand – 5%
- Discontinuation – 2%
- Loss of manufacturing site – 2%

In 2013 the consultant group Birgli published a report on medicines shortages in Europe that aimed to investigate the causes behind shortages, the current action to reduce shortages, and to propose a number of solutions for a range of stakeholders.[10] The Birgli report identified 19 different reasons for medicines shortages – categorised as either unpredictable or predictable shortages. Their research concluded that there are three main areas of underlying causes: economic, business, and supply chain root causes.[10]

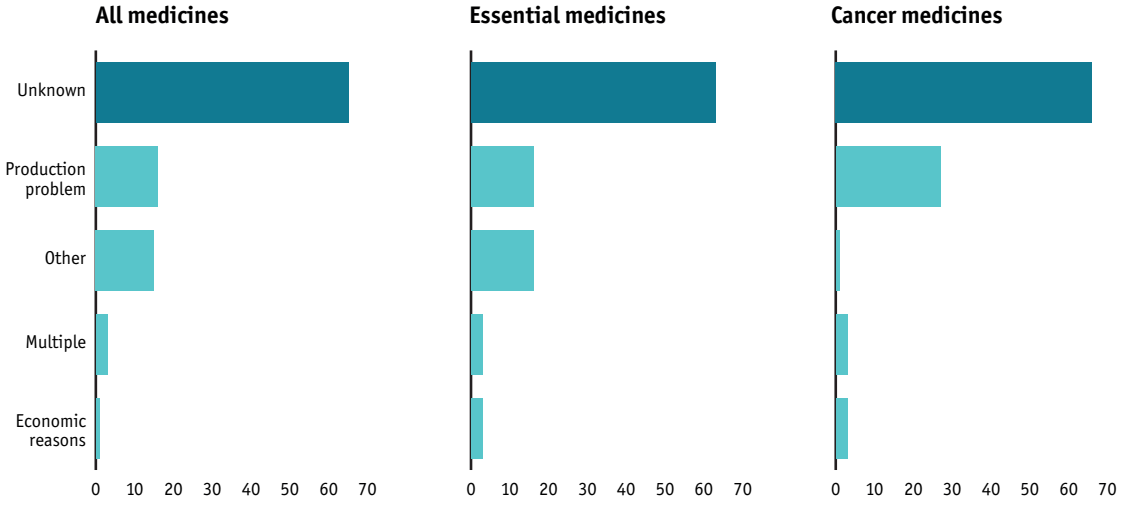
To ensure access to healthcare, payers and policymakers often attempt to reduce healthcare spending through reductions of pharmaceutical prices via a tendering process based exclusively on price. Such cost-cutting measures can lead to medicines shortages as manufacturers may decide to withdraw from the market in a certain country – as happened in Greece in 2012 – or cease production of products that are no longer profitable.[10, 46]

National medicines reimbursement and pricing policies vary between countries in Europe. Prices of medicines are regulated on a national or even on a regional level within countries, based on multiple criteria for negotiations with manufacturers/distributors.[46] Differences in the prices of medicines between countries can result in parallel trade within the common internal EU market, and thus cause or exacerbate medicines shortages in some "lower price" countries.[46] This is a leading cause for medicines shortages affecting a number of Eastern and Central European countries, as well as Portugal and the UK.

De Weerdt and colleagues conducted a review in 2015 to investigate the legal and regulatory measures in the European pharmaceutical framework as a potential cause for medicines shortages.[46] They found that price and quality regulations are both important causes of medicines shortages or medicines unavailability.

Using the list of shortages presented in the Birgli report, almost half of the 161 respondents (41%) of a 2015 survey of hospital pharmacists by Pauwels et al. identified "manufacturing problems" as the most common cause of shortages.[9, 10] However, about a third of the pharmacists did not provide a reason for the shortages.[9] Similarly, a 2014 study by Pauwels and colleagues conducted in seven countries that had a reporting system for medicines shortages reported that in 64% of cases (435 of 671 medicines) the reasons for shortages were unknown.[20] Production problems were identified as the leading cause for oncology medicines shortages (27%), and again, the causes for shortages for the vast majority (66%) of cancer medicines in short supply were unknown (see Figure 1).[20]

Figure 1. Causes of shortages reported by hospital pharmacists



Source: Pauwels et al. 2014[20]

Different stakeholders have different perspectives and insights into the causes of shortages. However comprehensive, reliable information about the causes of medicines shortages in Europe is not available. Even in countries that have implemented national reporting systems the causes for shortages are "widely underreported".[20]

Current policy frameworks for medicines supply

The system for regulating medicines in the 31 countries of the EEA is unique in the world.[3] The system is based on a regulatory network of about 50 national competent authorities in the EEA Member States working together with the EMA and the European Commission.[4] The European Commission provides guidelines for Good Manufacturing Practice (Directive 2003/94/EC) and Good Distribution Practice (Guidelines of 5 November, 2013/C 343/01). EU legislation requires that each country "operates to the same rules and requirements" for the authorisation and monitoring of medicines.[4] Once medicines have been granted marketing authorisation they can be distributed and traded within the territory covered by the relevant regulatory authority.

Box 1. The European regulatory framework for medicines

Marketing authorisation for medicinal products

The EEA system has three different routes for medicines authorisation – centralised, decentralised, and mutual recognition route. The centralised procedure is compulsory for new medicines for the following conditions: human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS); cancer; diabetes; neurodegenerative diseases; auto-immune and other immune dysfunctions; and viral diseases.[3] The EMA is responsible for the scientific assessment and monitoring of the safety of medicines developed by pharmaceutical companies.[3] Based on this assessment the European Commission grants or refuses marketing authorisation for medicines.[4]

The decentralised procedure is used when manufacturers apply simultaneously for marketing authorisation from the national competent authorities in more than one country if the medicine has not yet been authorised in the EU.

The mutual recognition procedure is used when a company has a medicine authorised in one country and submits an application for this authorisation to be recognised in other EU countries.

Licensing of manufacturers, importers and distributors

The national regulatory authorities of each EU Member State are responsible for the licensing and supervision of manufacturers and distributors in their respective jurisdictions.

EU directives and national laws regarding the supply of medicines

EU directives are one of the legal instruments available to the European institutions for implementing EU policies. For a directive to take effect at national level, EU countries must adopt a law to transpose it. While the transposition of the directives is mandatory, countries have some flexibility in the process which allows them to take into account specific national characteristics. There are a number of EU directives regarding the supply of medicines in EU Member States.[46] Article 81 (Directive 2001/83/EC) states that after entering the market, marketing authorisation holders and distributors are responsible for the "appropriate and continuous supply" of medicines to meet the needs of patients.[46] Article 23a of the same directive stipulates that manufacturers should provide at least two months' notice in advance of a temporary or permanent discontinuation of supply to the market.[46]

Box 1. The European regulatory framework for medicines (continued)

Heads of Medicines Agencies (HMA) forum
The HMA is a network of the heads of the national competent authorities responsible for the regulation of medicinal products in the EEA. The HMA co-operates with the EMA and the European Commission in the operation of the European medicines regulatory network which is a "unique model for cooperation and work sharing on statutory as well as voluntary regulatory activities".[4]

Procurement practices can affect the security of medicines supply

Procurement practices are different for single and multi-source products. Moreover, most of the time oncology treatments are based on the combined use of multiple products - generics or branded medicines, the latter still in a period of market exclusivity.

A 2016 report by the WHO Regional Office for Europe investigated how different public procurement practices could influence prices and ensure the security of the supply of medicines.[48] Although this report focuses on access to new, high-cost medicines in Europe, it provides an overview of the current public procurement practices that also influence the supply of generic, or inexpensive medicines.

Certain procurement practices for generic medicines could result in medicines shortages. One example is when competition among manufacturers to win tenders leads to market exit of some companies because the overall business attractiveness decreases. This in effect creates a supply risk as a result of a "de facto monopoly" of the winning manufacturer.[48]

Different national or regional institutions are responsible for the procurement of medicines within European countries. These can be government agencies or autonomous organisations, such as hospitals. Although aligned with EU rules regarding procurement, national legal frameworks may differ substantially. For example, the use of multi-year tenders and agreements may be limited in some countries due to annual budget planning.[48]

Developing procurement practices that support a sustainable and healthy market for medicines should be a strategic priority for all stakeholders including healthcare policymakers, payers and providers, as well as medicines manufacturers and distributors. There have been a number of calls to find a Europe-wide solution for the problem of medicines shortages. However there are multiple barriers and challenges for finding a common solution for the 31 markets comprising the EEA – a number that increases if we consider that healthcare is provided at regional level in many countries. These barriers include the diverse health systems and funding mechanisms across Europe, the differences in the national legal frameworks, reimbursement and pricing policies, and medicines procurement models. The lack of a common definition of shortages is also an obstacle for developing a common approach.[11]

Existing policy initiatives addressing medicines shortages

The EMA has played an important role in addressing the issue of medicines shortages and coordinating initiatives to develop long-term strategies for the prevention and mitigation of their impact in Europe and globally. In 2013 the EMA organised a workshop on shortages with different stakeholder representatives. Following the workshop, an inter-industry task force was set up with the objective of proposing solutions to prevent the root causes of shortages related to manufacturing and quality problems.[11, 21, 49] An implementation plan was developed which focused on the assessment of shortages related to the supply chain, developing risk-minimisation measures, alleviating the impact on patients, and communicating within the EU regulatory framework.[50]

The HMA network is also involved in setting policy measures for medicines shortages. Availability of appropriately authorised medicines (including the issue of shortages), is one of eleven key priorities in the HMA's a multi-year work plan to 2020.[51]

The EMA is mainly involved with shortages due to "manufacturing disruptions linked to problems such as quality defects or Good-manufacturing-practice (GMP) compliance issues."[11, 50] Shortages related to economic or business causes – such as pricing and reimbursement policies, procurement practices, or parallel trade – are not within the remit of the EMA.

Below we discuss several specific policy initiatives for the prevention and mitigation of medicines shortages. It is important to note that most of these initiatives were designed to address medicines shortages for all therapeutic areas; however, they are applicable to oncology medicines shortages.

National strategic plans to prevent medicines shortages

In Europe, medicines shortages are often dealt with on a case-by-case basis, or at the level of a single hospital, especially in countries that have not implemented national reporting systems for shortages that are accessible to all stakeholders. This could explain the scarcity of comprehensive and reliable data about the magnitude of the problem and the lack of awareness among policymakers and the general public in some countries.

The only country with a national strategic plan for medicines shortages is the USA. The 2012 FDA Safety and Innovation Act directed the FDA to establish a task force on drug shortages with the remit of developing a strategic plan for preventing and mitigating shortages. The FDA strategic plan, published in 2013, has two main goals.[17] The first is to strengthen the mitigation response to shortages by improving and streamlining the FDA's activities once it receives a notification of a supply disruption. The second goal is to develop long-term prevention strategies to address the underlying causes of supply disruptions and prevent shortages.[17]

The national medicines agencies in several EEA countries have developed long-term national pharmaceutical strategies, e.g. Denmark, Ireland and Sweden. These strategic documents address the

issue of medicines shortages, but only briefly. It should not be difficult to expand these strategies, or develop stand-alone plans for a coordinated national response to addressing the issue of medicines shortages.

Early notification requirement

According to Article 23a (Directive 2001/83/EC) pharmaceutical manufacturers authorised to supply medicines in the EU are obliged to notify the relevant regulatory authorities at least two months in advance of a temporary or permanent discontinuation of supply to the market.[13, 46, 50] As most cases of medicines shortages are dealt with at the national level the advance notice would allow all stakeholders, including pharmacists and clinicians, time to plan for alternatives.[46]

EU directives require Member States to achieve specific goals, and to this end appropriate rules need to be introduced in national laws. A 2015 survey conducted by the EMA found that mandatory notification for shortages is required by law in most EU Member States (21 of 28 countries) however seven countries had not introduced this requirement into national legislation.[11] However the lack of a common definition (or a definition at all in 18 of 28 countries) and the consequent different conditions of reporting of shortages, make comparisons across countries very difficult.[11]

As EU directives are not transposed directly, EU countries have some flexibility in the interpretation of the requirements. Due to this flexibility, national laws related to shortages can sometimes vary significantly, for example, under French law the timeframe for notification is one year, while Belgian law requires at least 6 months' notice of permanent cessation of the supply of a reimbursable medicine.[46]

Although the EU directive does not require manufacturers to provide reasons for the disruptions in supply, some countries have passed national laws that require this information (e.g. Italy and the Netherlands).[46]

In the USA, the 2012 FDA Safety and Innovation Act required manufacturers to provide early notification of potential shortages six months in advance. The FDA prioritises medicines that are medically necessary, i.e. medicines used to treat or prevent a serious medical condition for which there is no alternative treatment that healthcare providers have determined to be an acceptable substitute.[17, 47, 52] Regulatory measures for prevention and mitigation of shortages in response to early notifications could include: regulatory discretion to "allow release of products with quality issues, if not presenting a risk to public health", working with other manufacturers to increase production, expedited review of production changes and upgrades, and temporary imports.[52] The FDA recently reported that progress has been made in the last few years to reduce the number of shortages, both those reported and those averted. As seen in Table 1 below, the majority of shortages affected injectable medicines "including chemotherapy, anaesthesia and other acute drugs".[47]

One of the reasons for the success of the early notification approach is that it has been applied at a national level where roles and responsibilities of stakeholders are more clearly defined. In the US it is mainly manufacturers and inspectors who provide early notification of shortages.

In Europe, it seems that not all stakeholders have a clear understanding of how responsibilities are allocated and who should lead this initiative. A 2015 qualitative study by Bogaert and colleagues, with

Table 1. Number of shortages that were reported or prevented in the US in 2011 – 2015.

		Shortages reported	Shortages averted
2011	All forms	251	191
	Injectables	183	165
2012	All forms	117	281
	Injectables	84	213
2013	All forms	44	170
	Injectables	35	145
2014	All forms	44	101
	Injectables	30	62
2015	All forms	26	142
	Injectables	15	92

Source: FDA, 2016.[47]

a focus on France and Belgium, cited the opinion of a representative of wholesalers according to whom the European institutions (no specific institutions were mentioned) should monitor manufacturing issues and provide an "early warning with regard to any centrally registered drug shortages".[8]

Catalogues of shortages

The EMA has developed a catalogue of medicines shortages that is publicly available on its website. The catalogue includes only shortages that affect more than one EU Member State.[50] As previously mentioned, in Europe most medicines shortages are dealt with at national level. The EMA is only involved when a shortage is linked to a safety problems or when it affects several Member States.[3, 50] The catalogue includes potential, ongoing and resolved shortages. In addition to the catalogue, the EMA provides support to national regulators in Europe in a number of areas, including, for example, instructions for escalation of shortages from national to European level and resources for issuing treatment recommendations during shortages of certain products.[50]

In the USA, the FDA and the American Society of Health-System Pharmacists (ASHP) provide dedicated websites for information of medicines shortages.[53, 54] At the time of the writing of this report, there were 15 oncology medicines listed on the FDA Drug Shortages Database, 12 of which were not resolved. It should be mentioned here that although the number of new shortages has been reduced significantly, some old shortages still persist.

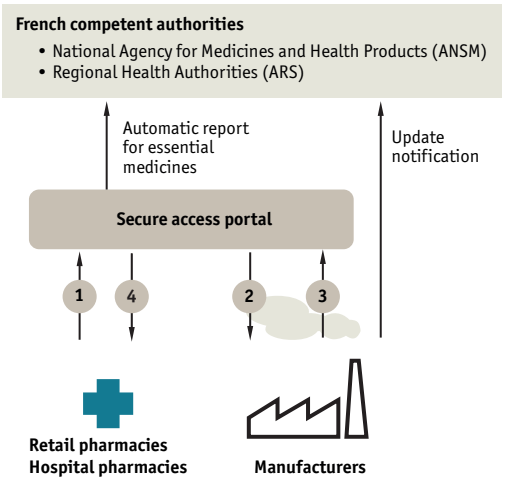
Although shortages are a national responsibility, not all EU Member States provide publicly available information on medicines shortages, and when they do the information shared varies.[49] A 2015 study by Pauwels and colleagues found that only seven countries in Europe have reporting systems for medicines shortages: Belgium, England, France, Germany, Italy, the Netherlands and Spain.[20] Different stakeholders reported the shortages recorded in these systems: marketing authorisation holders, pharmacists, wholesalers, healthcare providers, health departments, patients or associations. The type of medicines shortages that were reported also varied from medicines without therapeutic alternatives, or where shortages pose a risk for public health (Belgium, France and Germany), to all medicines (Italy, Spain, and the Netherlands), or only medicines provided by community pharmacies (England).[20]

In 2013, a reporting system for medicines shortages was launched in France to enable visibility on supply issues and improve communication among stakeholders (see Figure 2).

Figure 2. Unique reporting system in France using pharmaceutical dossier (PD)

The system provides a platform to automatically report missing medicines from pharmacists stocks, through a secure access to manufacturers. Manufacturers have to maintain a hotline for pharmacists to call in, which is used as an alternative to the automated reporting. When a product is reported missing on a site, the manufacturer has to respond in a timely manner and inform the pharmacist when the medicine will be made available again. The system enables pharmacists to adjust – or not – the prescription and have accurate information on when the issue will be resolved.
The software was integrated with community pharmacies systems in 2014 and most suppliers as of 2016 (90%) have implemented it.
The system aims at managing shortages rather than preventing them, yet has proven useful in improving transparency about disruptions in supply as the information is publicly available online. Costs involved at national level are around half a million euros per year.

Simplified representation of French reporting system



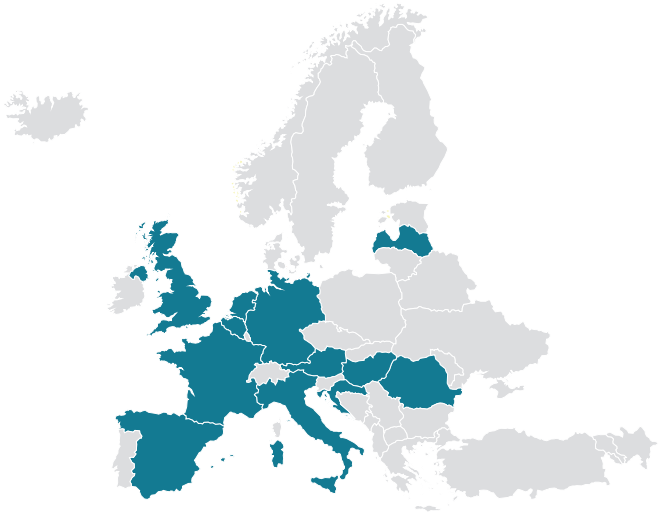
EIU research conducted via a search of the websites of the national medicines agencies in the EEA member countries found that five more countries (Austria, Croatia, Hungary, Latvia, and Romania) have created catalogues or lists of shortages that are updated on a regular basis (see Figure 3 below).

A 2013 workshop convened by the EMA recommended that all stakeholders should be involved in the notification of shortages.[11] These include manufacturers, wholesalers, distributors, pharmacies and other health care providers, as well as patients. The 2016 HMA stakeholder meeting discussed the need to harmonise the reporting procedures for medicines shortages across EEA Member States and called on the national competent authorities to use a template that provides the same content, using the same format and the same trigger points.[20, 56] A 2016 report by the EMA suggests that there seems to be some reluctance among regulators to use a harmonised reporting template, who preferred to "agree on a common trigger point, and harmonised data requirements across the EU".[11] Coordinated activities to address the issue of shortages would require a harmonised definition of shortages and standardisation of shortage notification systems and reporting mechanisms.

EMA critical medicines classification and the WHO Model List of Essential Medicines

Addressing the issue of shortages of medicines worldwide, the WHO highlighted the need to develop a consolidated global list of medicines in short supply or at risk of shortages. This list should be based on the WHO Essential Medicines List (EML).[12, 13] The current version of the EML, which was revised in 2015 with contributions from a number of organisations including ESMO, includes 46 essential cancer medicines.[57]

Figure 3. Countries in Europe where there was a list of medicines shortages as of 2017



Source: EIU research; Pauwels et al. 2014[20]

The WHO EML is not used in many European countries, as it is generally considered that health systems in Europe provide access to more than just "the minimum medicine needs for a basic health-care system".[58] However the ESMO European Consortium Study on the Availability, Out-of-pocket Costs and Accessibility of Antineoplastic Medicines found that many of the oncology medicines on the WHO EML list have been affected by shortages.[5]

The EMA has suggested a similar concept to prioritise the shortages of medicines categorised as critical based on two criteria: therapeutic use, and availability of alternatives.[59] Medicines intended for the treatment of life-threatening or serious diseases, for which there are no alternative treatments are considered critical. Using these criteria, oncology medicines would fall into the category of critical medicines.

Risk assessment approach for preventing of medicine shortages

The EMA has developed a list of risk indicators for shortages related to manufacturing and quality issues that can be useful to identify situations that can lead to shortages for critical medicines.[60] The 11 risk indicators focus on factors such as: the number and locations of registered manufacturers of Active Pharmaceutical Ingredients (API) or of Finished Pharmaceutical Products, GMP compliance records of manufacturers, factors related to manufacturing process complexity, need for long lead times, previous problems with the supply, and whether product features could potentially prohibit switching patients to an alternative medicine. This tool could be used as a model for developing risk assessment strategies for shortages related to other causes.

Export bans and other measures to minimise the effect of parallel trade

Parallel trade is an important cause of medicines shortages in Europe, affecting a number of countries with relatively low prices of medicines, for example, Bulgaria, Estonia, Greece, Poland, Portugal, Romania, Slovakia, and the UK. Some of these countries have implemented legislative measures to make

medicines exports more difficult.[46] In the case with Estonia, these measures have been challenged by a pharmaceutical association which has submitted a complaint to the European Commission.[46]

In May 2016 the Commission called on Portugal and Slovakia to remove "unjustified restrictions" on the export of medicines citing Articles 34–36 of TFEU. The countries were given the chance to respond, before being referred to the Court of Justice of the EU.[61]

In January 2014 the Bulgarian Parliament passed amendments to the Medicinal Products in Human Medicines Act, which aimed to restrict parallel export from the country. However in January 2015 the Bulgarian Constitutional Court repealed these amendments, as the criteria for restrictions were not considered sufficiently clear. [62]

In 2013 the UK Department of Health issued guidance for the trade of medicines that were developed jointly with 11 organisations.[63] The guidance sets out key legal and ethical obligations that manufacturers, wholesalers, NHS Trusts, registered pharmacies and dispensing doctors have in the supply and trading of medicines. The guidance warns that if wholesalers choose to export medicines that are in short supply in the UK and as a consequence the needs of patients in the UK are not met, the holder of a wholesale dealer's licence could be in breach of the 2012 Regulations and could face regulatory action against his licence, and/or criminal prosecution."[63]

Further research is required into the issue of parallel trade to explore and define measures that could minimise its effect on medicines shortages. [Interview with Vlad Voiculescu, 9th March 2017]

Joint procurement of medicines as a measure to prevent and mitigate shortages

A 2016 report of the WHO Regional Office for Europe, with a focus on public procurement practices for high cost medicines, found that there is some interest in joint procurement among European countries.[48] Joint procurement refers to a situation where "several buyers come together in a single process to get better prices or access." [64] A WHO Regional Office for Europe policy brief published in February 2017 found that the increased voluntary cross-country collaboration in procurement of medical technologies is driven by the desire to enhance transparency, share experiences, strengthen negotiating power and ensure sustainable access to health technologies.[64]

It has been suggested that joint procurement of medicines at a European level could be a solution to the problem of shortages of inexpensive, essential medicines. WHO has also proposed that an international agreement should be investigated and suggested that multiyear advance purchase commitments could be one solution for the problem with shortages.[13]

There have been only a few examples of joint procurement initiatives in Europe and they were not aimed at addressing the issue of medicines shortages. These include the BeNeLuxA collaboration between Belgium, the Netherlands and Luxembourg on procurement of medicines for rare diseases (orphan medicines) and the EU Joint Procurement Agreement to Procure Medical Countermeasures signed by 24 EU countries.[64]

The 2015 collaboration between Romania and Bulgaria is one example of a joint procurement agreement that aims to achieve better bargaining power and also facilitate exchange of medicines in short supply.[64] Another example is the Baltic Partnership Agreement – including Estonia, Latvia and Lithuania – that was set up for joint procurement of vaccines.[64] One of the goals of this agreement is to

address medicines shortages through the lending of centrally procured medicines from one country to another. There have been several lending processes in the last few years, which have "helped countries to solve serious shortage problems."[64]

However, the 2017 WHO policy brief concluded that there are many challenges for the successful cross-border collaborations in medicines procurement. It found limited evidence to be able to draw any conclusions about the effectiveness of joint procurement.[64]

While in theory joint procurement seems a promising solution, its main advantage is increased transparency and stronger negotiating position for the participating countries. As it does not address the causes for medicines shortages, it could be a temporary mitigation measure but not a prevention measure. Regional or bilateral collaboration agreements for exchanging or "lending" of medicines in short supply need to be explored further as a potential solution.

Policy recommendations

In this section we present a set of policy recommendations to address the cancer medicines shortages problem in Europe. These recommendations reflect the findings from the literature review and the consultation with an expert panel of representatives of the main stakeholders.

Healthcare is a national responsibility in EU Member States. Therefore governments and the health ministries have a responsibility for addressing the problem of shortages and establishing "effective supply mechanisms" for essential cancer medicines.[5] European-level organisations could take a coordination role, and could provide guidance and support, as demonstrated by the work carried out by the EMA and the HMA over the last decade, but supranational organisations alone cannot resolve the problem of medicines shortages. A concerted effort of all stakeholders at the national and supranational level is required to address this complex and multifaceted issue.

Recommendation 1
Introduce legislation for early notification requirements for medicines shortages

Not all EU countries have national laws transposing the EU requirement (Directive 2001/83/EC) for pharmaceutical manufacturers to provide notice at least two months in advance of a temporary or permanent discontinuation of supply to the market. National legislation for early notification from manufacturers should be implemented in all European countries. Moreover, greater harmonisation of national legislation including a common definition and trigger points across EU Member States will ensure better compliance from manufacturers and will facilitate developing strategies for managing shortages and preventing future shortages.

- National legislation for early notification from manufacturers should be implemented in all European countries, as stipulated in Directive 2001/83/EC.
- The legislation should include a requirement for manufacturers to provide information about the reasons for discontinuation of supply.

Recommendation 2
Establish strategic plans for medicines shortages

The existence of a national strategic plan for medicines shortages will allow for a coordinated response at a national level with a clear allocation of responsibilities for specific actions. This will ensure that the issue is addressed in a coordinated manner, with the collaboration of all stakeholders, including national competent authorities, industry, distributors, pharmacists, clinicians and other healthcare providers, as well as patients and patient organisations. Moreover, it will engage the attention of policymakers and health authorities and will raise awareness of the issue as a national problem. By assessing the causes for shortages and existing policies and practices for medicines procurement, it can provide a clearer picture of the situation in a given country. The plan can identify national priorities and describe the roles of different stakeholders, as their participation and collaboration is critical to ensure that patients have access to the medicines they need.

- Countries should establish a task force to develop a national strategic plan for medicines shortages, underpinned by national legislation and funding.
- This initiative could be proposed at a European level, with countries having an option to implement it on a national level.

Recommendation 3
Develop catalogues of shortages

It is essential to have comprehensive, reliable data about medicines shortages in every member country of the EU/EEA. A catalogue or database of shortages that is easily accessible for all stakeholders, including patients, can provide the missing data and ensure visibility of the problem. Awareness about medicines shortages will facilitate collaboration among stakeholders to resolve the issue. Having reliable information will also help pharmacists and prescribers identify alternative treatments or suppliers, and ultimately help clinicians provide appropriate care to cancer patients. To maximise the impact of these systems. countries should strive towards a standard minimum set of data elements. The catalogues should also be searchable by medicine name and therapeutic area to make it easier for all stakeholders to identify the information they need.

- All European countries should develop a national system for reporting medicines shortages based on a minimum set of data requirements.
- European regulatory authorities (HMA/EMA) could 1) coordinate the development of a harmonised procedure for reporting of shortages, based on a shared definition, and 2) develop a platform/database to collate the reports from the national systems.
- All stakeholders, including patients and physicians, should have access to a user-friendly, web-based system to report shortages.

Recommendation 4
Develop essential medicines lists and assess the risk for shortages

The advisory board suggested that a list of essential medicines based on the WHO EML should be used in all countries. A risk assessment approach should be used to understand the underlying causes for medicines shortages on this list and flag high-risk situations, for example identify products with a single manufacturer, and implement measures to address potential shortages. This could require a coordinated international action such as developing a European catalogue of shortages.

- Countries should develop national essential medicines lists based on the WHO Model List of Essential Medicines.
- The EMA Risk Indicators for Shortages (manufacturing and quality) should be used to identify high-risk products.

Recommendation 5
Introduce incentives for production infrastructure improvements

The initiative to incentivise manufacturers of vulnerable medicines has been suggested in the literature in the US context. A number of mechanisms to encourage manufacturers to stay in a market

or to enter a market threatened by shortages have been mentioned including tax credits or rebates, and an expedited approval process for new suppliers.[65]

As part of the long-term prevention strategies that aim to address the underlying causes of supply disruptions, the FDA strategic plan has highlighted the need to develop methods to incentivise and prioritise manufacturing quality. The plan suggests that payers should explore economic incentives to encourage high quality manufacturing that could help reduce the occurrence of shortages.

- Health systems/payers in European countries should consider financial incentives for production infrastructure improvements to address economic causes of manufacturing issues.
- Incentives for suppliers to enter, and remain in, a national market could also be considered.

Recommendation 6
Establish procurement models designed to prevent medicines shortages

Certain procurement practices for generic medicines could result in medicines shortages. The choice of procurement method and type of award should be based on a comprehensive analysis of the market conditions, for example, the number of suppliers in the market, the market capacity, demand for the product, its cost, plans for future use, etc. When risks to supply security are identified in this analysis, the tender criteria and agreements should be adjusted to mitigate this risk. For example, extended contract periods could be used, or agreements that ensure supply guarantee.[48]

- Good procurement practices that address predictability and profitability for medicines manufacturers should be identified. These could include using tender criteria that include price as well as other factors, e.g. quality track record of manufacturers.
- Tender cycle harmonisation could be considered within and across countries.
- National procurement for medicines experiencing shortages could be considered.

Conclusion

The recommendations proposed in this report are based on secondary research and conversations with experts representing the main stakeholder groups: patients, clinicians, pharmacists, manufacturers, and policymakers. We have prioritised policy measures that have been discussed in the past few years by a number of stakeholders who are largely in agreement about the need for such measures. A strong consensus among stakeholders would facilitate the implementation of these key policy measures across Europe and help to prevent medicines shortages and minimise their impact on cancer patient care.

However, much of this research has been challenging because there has been a widespread lack of data, awareness and accountability around the issue of medicines shortages. Therefore, in addition to the recommendations, we would like to draw the reader to some of the key information gaps faced by individuals and organisations trying to effect change. They are:

A lack of data on shortages

There is a scarcity of quantitative data about cancer medicines shortages in Europe, which makes it very difficult to assess the actual severity of shortages or which countries are the most affected.

A lack of data on patient impact

Although there is general agreement about the significant impact of cancer medicines shortages on patient care, there is a need for robust data on the impact of shortages on 1) patient outcomes and 2) out-of-pocket costs for cancer patients and their families.

A lack of data on the causes of shortages

Different stakeholders have different perspectives and insights into the causes of shortages. However comprehensive, reliable information about the causes of medicines shortages in Europe remains unavailable.

A lack of awareness about shortages

The lack of awareness among patients, the general public, and even policymakers, might explain why not much has been done to address the issue of shortages in many countries.

A lack of accountability

There is a lack of clarity about who should take responsibility for and lead efforts to resolve the complex issue of medicines shortages. The research conducted for this project highlighted the need for a strong national response and the importance of collaboration between national and supranational regulatory authorities and other stakeholders.

A lack of understanding about the unique regulatory framework in Europe

There have been a number of calls to find a Europe-wide solution for the problem of medicines shortages. The EMA is a part of a regulatory network along with national competent authorities and the European Commission. The EMA is mainly involved with shortages that arise due to manufacturing and quality issues. Shortages related to economic or business causes – such as pricing and reimbursement policies, procurement practices, or parallel trade – are not within the remit of the EMA.

As this report was being edited, in March 2017 the European Parliament published a resolution on EU options for improving access to medicines (2016/2057(INI)).[66] Not surprisingly, the resolution highlights many of the issues outlined above, for example, that the EU has not implemented a "transparent reporting mechanism on the causes of medicines shortages" and lags behind the USA in this respect.[66] The policy recommendations proposed in this report resonate with the calls for actions in the resolution. More importantly, the European Parliament resolution calls for the European Commission and Council to enhance the remit of the EMA to coordinate the Europe-wide activities for dealing with medicines shortages.[66]

Until there has been improvement in the above issues, effecting and measuring change will remain challenging. Medicines shortages in cancer care in Europe is too important an issue to be ignored. We call on national governments and health authorities to work on improving standards and processes to prevent and manage shortages across the region.

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