Future-proofing pharmaceutical legislation — study on medicine shortages

Final report

Technopolis Group, Ecorys BV, Milieu Law & Policy Consulting
November 2021

Authors: Thyra de Jongh, Dominik Becker, Mathieu Boulestreau, Anoushka Davé, Felix Dijkstal, Robert King, Liana Petrosova, Peter Varnai, Christiaan Vis, Wim Spit, Maxime Moulac, Florent Pelsy

November 2021. Technopolis Group, Ecorys B.V., Milieu Law & Policy Consulting

The authors gratefully acknowledge professor Brian Godman, professor Aukje Mantel-Teeuwisse and Bruno Bonnemain for their expert guidance and feedback at various stages of this study. Thanks goes out also to all individuals and organisations who facilitated access to data and who shared their experiences and perspectives with the study team.

ABSTRACT

English

Medicine shortages present a growing problem for many EU/EEA countries. Consequences of shortages include a decreased quality of treatment received by patients and an increased burden on healthcare professionals, who need to identify and provide alternative treatments, and on health systems. In recognition of the problem and of the need for concerted action at the European level, the European Commission requested an analysis of medicines in shortage in the EU and their root causes, as well as an assessment of the current regulatory framework, to devise potential legislative and non-legislative solutions. This study involved analysis of data from sources including national shortage registers, extensive consultations with key stakeholders and published literature. It highlights that comprehensive comparative analysis is severely hampered by a lack of high-quality, standardised information about shortage monitoring at national level. Notwithstanding data limitations, the study confirms that medicine shortages occur frequently across the region, most often involving older, off-patent and generic medicines. The causes are multifactorial with bottlenecks identified along the entire pharmaceutical value chain, from manufacturing of raw materials to national pricing and procurement practices. A series of 16 policy measures are presented for action at EU and national level.

German

Der Mangel an Arzneimitteln stellt für viele EU/EWR-Länder ein wachsendes Problem dar. Engpässe gefährden die Qualität der Behandlung von Patienten und belasten die Angehörigen der Gesundheitsberufe, die regelmäßig alternative Behandlungen ermitteln und anbieten müssen. Die Europäische Kommission hat das Problem und die Notwendigkeit einer konzertierten Aktion auf europäischer Ebene erkannt und eine Analyse der Arzneimittelknappheit in der EU und ihrer Ursachen in Auftrag gegeben, um mögliche Lösungen zu entwickeln. Diese Studie umfasste die Analyse von Daten aus den nationalen Verzeichnissen über Arzneimittelknappheit, umfassende Konsultationen mit den wichtigsten Interessengruppen und die Durchsicht von Dokumenten. Sie zeigt, dass eine umfassende vergleichende Analyse durch einen Mangel an qualitativ hochwertigen, standardisierten Informationen über nationale Mangelsituationen stark behindert wird. Ungeachtet der Datenbeschränkungen bestätigt die Studie, dass es in der gesamten Region häufig zu Arzneimittelknappheit kommt, wobei meist ältere, patentfreie und generische Arzneimittel betroffen sind. Die Ursachen sind vielschichtig, und es wurden Engpässe entlang der gesamten pharmazeutischen Wertschöpfungskette festgestellt, von der Herstellung von Rohstoffen bis hin zur nationalen Preisgestaltung und Beschaffungspraxis. Es wird eine Reihe von 16 Empfehlungen für Maßnahmen der EG, der Mitgliedstaaten und anderer wichtiger Interessengruppen ausgesprochen.

French

Les pénuries de médicaments constituent un problème croissant pour de nombreux pays de l'UE/EEE. Les pénuries compromettent la qualité du traitement que reçoivent les patients et constituent une charge pour les professionnels de la santé qui doivent régulièrement identifier et fournir des traitements alternatifs. Consciente du problème et de la nécessité d'une action concertée au niveau européen, la Commission européenne a demandé une analyse des médicaments en pénurie dans l'UE et de leurs causes profondes, afin de trouver des solutions potentielles. Cette étude a comporté une analyse des données des registres nationaux de pénurie, des consultations approfondies avec les principales parties prenantes et un examen des documents. Elle met en évidence le fait qu'une analyse comparative complète est fortement entravée par le manque d'informations standardisées de haute qualité sur les situations de pénurie nationales. Malgré les limites des données, l'étude confirme que les pénuries de médicaments sont fréquentes dans la région et qu'elles concernent le plus souvent des médicaments anciens, hors brevet et génériques. Les causes sont multifactorielles et des goulets d'étranglement ont été identifiés tout au long de la chaîne de valeur pharmaceutique, de la fabrication des matières premières aux pratiques nationales de tarification et d'approvisionnement. Une série de 16 recommandations est proposée pour une action impliquant la CE, les États membres et d'autres acteurs clés.

TABLE OF CONTENTS

ABBREVIATIONS

Abbreviation	Explanation
API	Active Pharmaceutical Ingredient
ATC	Anatomical Therapeutic Chemical code
CMC	Chemistry, Manufacturing and Control
CMO	Contract Manufacturing Organisations
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
EML	Essential Medicines List
EMVS	European Medicines Verification System
EphMRA	European Pharmaceutical Market Research Association
EU	European Union
FDA	United States Food and Drug Administration
FMD	Falsified Medicines Directive
GDP	Good Distribution Practices
GMP	Good Manufacturing Practices
HMA	Heads of Medicines Agencies
INN	International Non-proprietary Name
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MS	Member States
NCA	National Competent Authority
NIP	National Immunisation Programme
OECD	Organisation for Economic Co-operation and Development
PGEU	Pharmaceutical Group of the European Union
PPD	Public Procurement Directive
PSO	Public Service Obligation
SPOC	Single Points of Contact
SU	Standard Unit
TFEU	Treaty on the Functioning of the European Union
WHO	World Health Organization

COUNTRY CODES

2-letter code	Country	2-letter code	Country
AT	Austria	IE	Ireland
BE	Belgium	IT	Italy
BG	Bulgaria	LT	Lithuania
CY	Cyprus	LU	Luxembourg
CZ	Czechia	LV	Latvia
DE	Germany	MT	Malta
DK	Denmark	NL	Netherlands
EE	Estonia	PL	Poland
EL	Greece	PT	Portugal
ES	Spain	RO	Romania
FI	Finland	SE	Sweden
FR	France	SI	Slovenia
HR	Croatia	SK	Slovakia
HU	Hungary		

EPHMRA ANATOMICAL CLASSIFICATION

Code	Description
A	Alimentary tract and metabolism
B	Blood and blood forming organs
C	Cardiovascular system
D	Dermatologicals
G	Genito-urinary system and sex hormones
H	Systemic hormonal preparations (excluding sex hormones)
J	General anti-infectives systemic
L	Antineoplastic and immunomodulating agents
M	Musculo-skeletal system
N	Central nervous system
P	Parasitology
R	Respiratory system
S	Sensory organs
T	Diagnostic agents
V	Various

EXECUTIVE SUMMARY

Introduction

Member States and many stakeholders, including pharmacy organisations, have signalled a rise in shortages of medicinal products in the European Union (EU). Shortages present a major problem for the quality and continuity of patient care. At best, patients can be provided with an equivalent medicine, but if no such equivalent is available, pharmacists may have to resort to therapeutic substitution. This can increase the risk of reduced treatment compliance or incorrect use of the medicine, leading to lower treatment effectiveness and disease progression.[1,2,3] Substitutes may also pose an increased risk or incidence of adverse events. In the worst case, there may be no suitable alternatives. Medicine shortages also have important economic consequences.[4,5,6] Many pharmacists spend several hours per week on conferring with prescribers about suitable alternatives and on sourcing these. Patients may face higher costs when prescribed alternatives are more expensive or if they must pay for additional visits with their healthcare provider to discuss alternatives.[7]

The problem of shortages has received significant public and political attention in the EU. The European Parliament and Council have both identified shortages as a major public health concern. They have called on the European Commission, Member States and other relevant stakeholders to take action.[8,9,10] In December 2016, the European Medicines Agency (EMA) and Heads of Medicines Agencies (HMA) created a Task Force on the Availability of Authorised Medicines for Human and Veterinary Use. Since 2019, this Task Force has been running a pilot programme on establishing a single point of contact (SPOC) network on shortages to improve information sharing between Member States, the EMA and the Commission and to coordinate actions to help prevent and manage shortages. Actions to secure the supply of medicines across the EU and avoid shortages are also included under the EU Pharmaceutical Strategy for Europe, adopted in November 2020.[11] Another step is the launch of a structured dialogue with and between actors in the pharmaceutical manufacturing value chain and public authorities, which aims to identify policy tools and propose actions to strengthen the continuity and security of supply in the EU.[12]

The COVID-19 pandemic has further spotlighted problems with availability of medicines and vulnerabilities in pharmaceutical supply chains. In response, in March 2020 the Commission, together with the EMA and Member States set up an *EU Executive Steering Group on Shortages of Medicines Caused by Major Events* to effectively respond to and prevent the escalation of shortages.[13]

---

[1] McBride A, Holle LM, Westendorf C, Sidebottom M, Griffith N, Muller RJ, Hoffman JM: National survey on the effect of oncology drug shortages on cancer care. Am J Health Syst Pharm 2013, 70:609–617

[2] Rider AE, Templet DJ, Daley MJ, Shuman C, Smith LV: Clinical dilemmas and a review of strategies to manage drug shortages. J Pharm Pract 2013, 26:183–191.

[3] Phuongid, J. M., Penm, J., Chaar, B., Oldfield, D., & Moles, R. (2019). The impacts of medication shortages on patient outcomes: A scoping review. https://doi.org/10.1371/journal.pone.0215837

[4] Shaban, H., Maurer, C., & Willborn, R. J. (2018). Impact of Drug Shortages on Patient Safety and Pharmacy Operation Costs. Retrieved from www.fedprac.com

[5] WHO. (2016). Global approaches to addressing shortages of essential medicines in health systems. WHO Drug Information, Vol. 30, pp. 180–185.

[6] de Weerdt, E., Simoens, S., Casteels, M., and Huys, I. (2017). Clinical, economic and policy implications of drug shortages in the European Union. Appl. Health Econ. Health Policy, 15 (4), 441–445. doi: 10.1007/s40258-016-0264-z

[7] Hyde, R. (2020). Europe faces worsening medicine shortages. Lancet (London, England), 395(10223), 481–482. https://doi.org/10.1016/S0140-6736(20)30354-8

[8] European Parliament resolution of 2 March 2017 on EU options for improving access to medicine (2016/2057(INI)) https://www.europarl.europa.eu/doceo/document/TA-8-2017-0061_EN.html. Accessed 21 May 2021.

[9] Resolution of 17 September 2020 on the shortage of medicines – how to address an emerging problem. https://www.europarl.europa.eu/doceo/document/TA-9-2020-0228_EN.html.

[10] Council of the European Union. (10 June 2021) Draft Council Conclusions on access to medicines and medical devices for a stronger and resilient EU. Available at: https://data.consilium.europa.eu/doc/document/ST-8786-2021-INIT/en/pdf.

[11] European Commission. A pharmaceutical strategy for Europe. Available at: https://ec.europa.eu/health/human-use/strategy_en.

[12] Structured dialogue on security of medicines supply | Public Health (europa.eu)

[13] European Medicines Agency (Press release 10 April 2020) Update on EU actions to support availability of medicines during COVID-19 pandemic. Available at https://www.ema.europa.eu/en/news/update-eu-actions-support-availability-medicines-during-covid-19-pandemic. Accessed 13 June 2021.

The EU pharmaceutical legislation, specifically Directive 2001/83/EC, contains two provisions to address the supply of medicinal products in the EU.[14] Article 23a requires the marketing authorisation holder (MAH) to submit a pre-notification to the relevant national competent authorities (NCAs) "if a product ceases to be placed on the market of a Member States, either temporarily or permanently". Authorities must be notified, other than in exceptional circumstances, no less than two months before the interruption. Additionally, Article 81 of the same directive requires MAHs and wholesale distributors of a medicine that is placed on the market to "ensure appropriate and continued supplies", within the limits of their responsibilities, to cover the needs of patients. Member States should transpose these articles into their national legislative frameworks and are expected to put in place systems to monitor and enforce compliance.

Study objectives

In March 2020, the European Commission Directorate-General for Health and Food Safety (DG SANTE) commissioned a consortium consisting of Technopolis Group, Milieu Law & Policy Consulting and Ecorys to conduct a study on medicine shortages. The study was to provide:

- an overview of medicines in shortage in the EU, including their specific characteristics, as well as an analysis of the root causes of the shortages
- an evidence-based assessment of whether the current framework (at EU and national level) to address the issue of shortages is fit for purpose
- an overview of potential solutions to address shortages, taking into account their root causes and the shortcomings of the current system

This report contains the results of that study. It focused on the situation in the EU/EEA in the period 2004-2020. With regards to data from national shortages registries, the period that could be covered is limited to the years 2007-2020, because no country was able to share data from before 2007. The scope of the study was limited to medicines for human use, thus excluding veterinary medicines.

A variety of data sources was used. Information on notified shortages was obtained from the registers kept by NCAs of the EU/EEA countries. In total, data were obtained from 22 countries. The data from the registers was linked to a commercial data set from IQVIA MIDAS containing information on pharmaceutical sales. Stakeholders were extensively consulted via key informant interviews, targeted online surveys, focus group discussions and an invitational final consultation event. The obtained primary data was used alongside information obtained from review of grey and academic literature.

Key findings

The present study adds to a fast-growing body of work in various ways:

- It has compiled and analysed the thus-far largest set of data from across the EEA, using data from the national shortage registries of 22 EEA countries
- It includes a comprehensive analysis of these data sets on key product characteristics, comparing findings against a matched set of medicines not in shortage to determine whether certain characteristics predispose products for greater risk of shortage
- It has applied guidance developed at the EU-level to standardise information of reported root causes of shortages and allow for an aggregated analysis across national data sets
- It considered how the current EU legal framework, specifically Articles 23a and 81 of Directive 2001/83/EC, has contributed to preventing and mitigating shortages, whilst assessing how this framework is consistent with and has been complemented by actions taken nationally by the Member States
- It included a broad-based consultation with stakeholders to discuss the underlying issues and derive a set of recommended solutions

Defining and reporting of medicine shortages

There are significant variations within the EU in how countries define a shortage with further differences in how and when these definitions are used. In response to this problem, in 2019, the EMA and HMA released an agreed "shortage" definition.[15] Stakeholders widely view this as a useful

[14] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Available at https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf.EUR-Lex - 02001L0083-20210526 - EN - EUR-Lex (europa.eu). Accessed 13 June 2021.

15 HMA/EMA (2019) Good practice guidance for communication to the public on medicines' availability issues.

step, though some feel the definition does not adequately differentiate between critical and non-critical shortages. Member States also are far from uniform in their standards and systems for notification of shortages and in the information they request. The lack of standardisation and harmonisation is hampering information sharing and comparative analysis between countries. It also creates inefficiencies for parties tasked with notification of shortages. Improved harmonisation is widely viewed as a prerequisite for the development of effective and appropriately tailored actions to prevent and mitigate shortages.

Trends and characteristics of medicine shortages

Notified shortages have strongly increased over the last five to ten years. Although this increase can be partially explained by more widespread and better notification, it also reflects a real increase in the number of times a pharmacist is not able to offer a patient their preferred medicine and the impact of this is felt in several ways. It creates a significant burden on pharmacists and physicians tasked with providing the best possible treatment alternative. Even more crucially, it puts patients at risk from worse health outcomes and causes distress. However, most shortages are localised and impact some countries but not others, pointing towards issues with inequitable distribution and access rather than with global supply issues for those shortages.

Shortages can arise for any type of medicine, but those at highest risk include pain relief medication, antihypertensives, anti-infectives and oncology medicines. Most shortages involve older, off-patent and generic medicines, which has been widely attributed to the low profit margins associated with these products. Although for most products in shortage an alternative may be found through, for instance, generic substitution or importation, for approximately a quarter of cases the product in shortage may represent the only available version. The national shortage registries, however, offer very limited insight into the criticality of product shortages and their impact on the quality and continuity of treatment to patients.

Root causes of shortages

Proper understanding of the root causes of shortages remains substantially challenged by inconsistent and limited reporting. Moreover, reporting of root causes is generally reductionist, singling out the most acute cause (e.g. a problem at the production site) but without considering the underlying more systemic issues (e.g. consolidation of manufacturing, resulting in a very limited number of production sites) and market-related factors (e.g. single-winner procurement practices). Reporting of root causes of shortages suggests that around half of all cases can be traced back to issues with quality and manufacturing. Commercial reasons, including market withdrawals, and unexpected increases in demand are other common causes of shortages. For example, the COVID-19 pandemic posed a major challenge to the continued availability of critical medicines used in the treatment of COVID-19 patients due to surge demand.

The available information is, at present, insufficient to quantify the importance of outsourcing of pharmaceutical production (including the production of APIs) and of parallel distribution as potential risk factors for shortages. More generally, austere pricing policies and industry consolidation are viewed by stakeholders as systematic factors that contribute to or aggravate shortages. Market factors play an especially important role in product withdrawals for commercial reasons, which have been happening with increasing frequency in recent years. The large majority of medicines that are permanently withdrawn from a particular market involve products with low sales revenues in those markets, for which the MAH has decided that the generated revenue on the product no longer justifies the costs of maintaining the product on that market. This may be the case if the demand for the product has declined, for instance because better products have become available, but also if the market conditions no longer enable the MAH to earn a sufficient profit margin on the product.

Evaluation of the EU legal framework

The current EU legal framework, through the Community Code relating to medicinal products for human use (Directive 2001/83/EC), contains two provisions that may help prevent and mitigate shortages. Article 23a requires MAHs to notify the NCA at least two months in advance of their intent to suspend the marketing of a product it has placed on that market, whilst Article 81 mandates MAHs and wholesalers to ensure, within the limits of their responsibility, the continued and appropriate supply of medicines placed on the market. This study shows that all Member States have transposed these provisions into national legislation but have operationalised them in different ways.

Because in most countries the transposition took place years before the introduction of a shortage notification registration system, the data to substantiate where these provisions have enabled Member States to effectively slow down the incidence of shortages is largely lacking. The notification obligation imposed by Article 23a has generally been helpful to authorities in preparing for product withdrawals and mitigating the impact thereof. The supply obligation dictated by Article 81 is, by

itself, very generally formulated and many Member States have introduced a variety of measures to impose more specific obligations on MAHs and, in some cases, other parties. These vary from stock keeping obligations, to mandatory reporting on stock levels and export restrictions. Based on the limited availability of data and the concurrent presence of different preventative or mitigating measures, only the effects of stock keeping obligations on the growth in notified shortages could be isolated. However, no firm conclusions could be drawn about the impact of stock obligations on the level of (notified) shortages in the countries where they were introduced.

The costs that could be attributed directly to the obligations under the EU legal framework are difficult to quantify as, to a significant degree, these are absorbed by the normal operational costs of the parties on whom the obligations fall. On the other hand, there are important benefits to patients and health systems, in the form of costs avoided and continuity of care, from avoided shortages or from shortages that are resolved more quickly or mitigated better. These benefits may be viewed as adequate justification for the costs. Articles 23a and 81 are, for the most part, internally coherent with the objectives and provisions of the broader EU legal framework.

EU-level coordination has already resulted in the development of useful new guidance and structures for dialogue and cooperation to tackle medicine shortages. However, there remains considerable scope for improvement through greater adoption of harmonised definitions and criteria and uniform implementation of guidelines.

Recommendations

Following extensive consultation with stakeholders, a series of 16 solutions has been identified which could address different aspects of the issue of shortages. These solutions collectively cover areas related to the collection and sharing of data and information between parties, supply chain issues, market issues and mitigation strategies. Specifically, the following recommendations could be considered by the European Commission, EMA and/or Member States:

- Establish and follow a centralised and harmonised EU-wide definition of medicine shortages
- Establish and mainstream harmonised reporting criteria for shortages, collecting sufficiently detailed information on key parameters (e.g. product details, MAH, details on the shortage and impact)
- Develop an EU-wide list of medicines for which shortages are the most critical and develop policies and/or regulations to improve their availability
- Set up stakeholder dialogue platforms for/between supply chain stakeholders, patients, and healthcare providers, respectively at Member States level
- Develop EU-wide and uniform legislation allowing for imposing financial sanctions if notification requirements and/or supply responsibilities are not met
- Require greater transparency of industry supply quotas as well as parallel traders' and wholesalers' transactions
- Require suppliers to have adequate shortage prevention and mitigation plans in place
- Introduce legal obligations for MAHs and wholesalers to maintain a safety stock of (unfinished) products for medicines of major therapeutic interest at EU-level
- Adopt common principles for the introduction of national restrictions on intra-EU trade
- Allow for greater flexibilities for emergency imports of specific products in case of market withdrawals and other critical shortages
- Incorporate requirements for having more diversified, multiple tenderers and thereby supply sources in public procurement tenders
- For EU authorities to reduce the administrative and cost burden submission of post-approval changes
- Enable an accelerated mutual recognition procedure (MRP) within the EU
- Enable a (more) efficient Repeat Use Procedure
- Develop an EU-wide medicines packaging and labelling regulation that included flexibilities for digital leaflets and multi-country/multi-language packaging and labelling
- Include information about available alternative medicines in shortage databases

Implementation of these recommendations will require action by different sets of stakeholders, with some requiring coordination at the level of the European Commission or the EMA whilst others will need to be supported and coordinated by competent authorities or similarly responsible bodies in the

Member States. The recommended solutions still lack operational detailing. The development of this will require further consultation and reflection by policy makers.

Importantly, the recommendations offered were selected based on inputs collected from stakeholders with sometimes opposing interests. The scoring framework used allowed for the interests of different groups of stakeholders to be given equal weight. This was done to arrive at a set of recommendations for which there could be deemed to be sufficient support for the solutions to be actionable. However, it also allowed for solutions to be rejected from the list of recommendations even if they could offer substantial benefit but were strongly opposed by certain groups of stakeholders. Ultimately, it will be up to national and European authorities to decide if such solutions should still be pursued in the face of potentially strong opposition.

Final reflections

Despite persisting data limitations, it is evident that medicine shortages are an important problem. There is no reason to believe this problem is temporary or that it will go away on its own. It is thus safe to say that action is needed: action by those working in the different parts of the pharmaceutical value chain but also action by policymakers, at both the national and European levels. Crucially, any policy actions should aim to maximise the potential for achievement of its objectives while minimising the risk of unwanted consequences.

In recent years, many countries have put systems in place to collect important data on shortages and their causes. That is a step in the right direction. However, this study, as others before it, has shown that the data can be further improved. Continuous effort will thus be needed to optimise the data and keep feeding into the evidence base.

This study has confirmed that shortages are often not so much a problem of whether a medicine is available but one of where it is available. Even in the context of the European Union, founded on principles of solidarity, some countries face challenges of medicines shortages daily whereas others rarely experience them. This points towards some fundamental issues that have little to do with sourcing and manufacturing and much more with commercial decisions by suppliers on the one hand and national policies on the other. Here, many parties share responsibility. Suppliers take decisions based on considerations of profitability, selecting markets to supply based on willingness and ability to pay and ignoring others. Governments have also put pressure on prices that has led to supply chains that are lean to the point of vulnerability. This requires critical reflection on the part of all stakeholders not only of the roles of others but also of their own responsibilities.

The solutions recommended combine fairly obvious and easily implemented actions with proposals for more radical and systemic changes to the pharmaceutical value chains. These systemic changes may be more challenging to implement and they carry an associated cost but may ultimately prove to be the most essential and beneficial to patients, healthcare professional and health systems.

1. INTRODUCTION

1.1. Medicine shortages in the European Union

Medicine shortages are a growing problem in the European Union (EU). Member States and many stakeholders, including pharmacy organisations, have signalled a rise in shortages of medicinal products in recent years.[16] A 2020 survey conducted by the Pharmaceutical Group of the European Union (PGEU) among its member organisations found that all 26 responding countries had experienced medicine shortages in the past 12 months and most countries (n=17, 65%)[17] indicated that the situation had gotten worse compared to the year prior.[18] In nearly one third of responding countries (n=8, 31%), over 400 medicines were reported as short in supply. These shortages exist across therapeutic areas, including vaccines and life-saving medicines. A similar survey in 2019 across 39 European countries (27 EU and 12 non-EU) on behalf of the European Association of Hospital Pharmacists (EAHP) showed similar results, with 95% of respondents citing medicines shortages as a current problem in delivering the best care to patients.[19]

The COVID-19 pandemic has further spotlighted problems with availability of medicines and vulnerabilities in pharmaceutical supply chains.[20] Increased demand for products used in the treatment of COVID-19 patients, disruptions to global production and distribution channels and export restrictions on raw materials and finished products, all contributed to an increase in the risk of medicine shortages as a direct result of the pandemic.

To patients, medicine shortages present a major problem. At best, patients can be provided with an equivalent medicine, such as a generic substitute or different formulation of the same medicine. If no such equivalent is available, pharmacists (after consultation with a prescriber or based on recommendations by a medicines agency) may have to resort to therapeutic substitution, dispensing a different medicine from the same class of medicines with a similar therapeutic profile, or have to offer an alternative treatment regimen. In both situations, there can be an increased risk of reduced treatment compliance or incorrect use of the medicine, if pharmacists or physicians do not have sufficient time to properly explain the substitution to patients. This in turn may contribute to lower treatment effectiveness and disease progression.[21,22,23] Substitutes may also have different pharmacokinetic profiles from the preferred medicines and could pose an increased risk or incidence of adverse events. In the worst case, there may be no suitable alternatives at all.

[16] In this report, the terms 'medicinal products' and 'medicines' are used interchangeably and denote medicines as well as vaccines. The focus of this report is exclusively on medicines for human use, thus excluding medicines for veterinary use. Whilst the primary focus is on prescription medicines, data from national shortage registries may include both prescription and non-prescription medicines. Thus, some observations may be based on both.

[17] Throughout this report, when reporting survey data, the symbol 'n' represents the number of respondents that provided the indicated response. The total number of responses to a particular question, when indicated, is denoted by 'N'.

[18] PGEU (2021). PGEU Medicine Shortages Survey 2020 Results. Available at https://www.pgeu.eu/wp-content/uploads/2019/03/2020-PGEU-Medicine-Shortages-Survey-Results-v2.pdf. Accessed 27 July 2021. PGEU member organisations are national associations of community pharmacists.

[19] EAHP (2020). 2019 EAHP Medicines Shortages Report: Medicines shortages in European hospitals. Available at: https://www.eahp.eu/sites/default/files/eahp_2019_medicines_shortages_report.pdf.

[20] For instance: European Medicines Agency. Availability of medicines during COVID-19 pandemic. Available at: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/availability-medicines-during-covid-19-pandemic; Balfour H. (19 November 2020) Pharma supply chain still highly vulnerable to COIVD-19 pandemic, says research. European Pharmaceutical Review. Available at: https://www.europeanpharmaceuticalreview.com/news/133953/pharma-supply-chain-still-highly-vulnerable-to-covid-19-pandemic-says-research/.

[21] McBride A, Holle LM, Westendorf C, Sidebottom M, Griffith N, Muller RJ, Hoffman JM: National survey on the effect of oncology drug shortages on cancer care. Am J Health Syst Pharm 2013, 70:609–617

[22] Rider AE, Templet DJ, Daley MJ, Shuman C, Smith LV: Clinical dilemmas and a review of strategies to manage drug shortages. J Pharm Pract 2013, 26:183–191.

[23] Phuongid, J. M., Penm, J., Chaar, B., Oldfield, D., & Moles, R. (2019). The impacts of medication shortages on patient outcomes: A scoping review. https://doi.org/10.1371/journal.pone.0215837

Medicine shortages also represent a serious problem to the efficiency of health systems.[24,25,26] For instance, the PGEU survey indicates that community pharmacy staff spend on average 6.3 hours per week dealing with medicine shortages.[18] When pharmacists are not permitted to offer alternative medicines to patients directly, patients must make additional appointments at their prescribing physician for alternative prescriptions.[27] This poses both an administrative and financial burden on the entire health system. Shortages can also financially impact patients when their prescribed alternatives are associated with higher co-payments.

The problem of medicines shortages is by no means limited to the European Union. For instance, in the United States, the US Food & Drug Agency (FDA) recorded a fivefold increase in reported medicine shortages from 61 in 2005 to over 250 in 2011.[28] After this peak, the number of new shortages per calendar year has declined again. As of July 2021, the FDA shortages database listed 109 medicines as 'currently in shortage'.[29] In Canada, a study of prescription medicines available on the market between 2017 and 2018 found that 461 (13%) out of analysed 3,470 'markets'[30] were reported as being in shortage in the Drug Canada Shortages Database.[31] The Therapeutic Goods Administration of Australia meanwhile lists nearly 300 current shortages in its medicine shortage reports database.[32] It should be noted that, because shortage definitions and notification criteria differ between territories, the number of notifications in each of these territories is not directly comparable to each other.

1.2. EU level action on medicine shortages

The problem of shortages has received significant public and political attention in the EU. Shortages have been a priority for Member States and European Parliament for many years. Addressing shortages of medicines has been raised by the recent Bulgarian, Dutch, Slovak, Romanian and Portuguese Presidencies of the Council. In 2017, the European Parliament (EP) adopted a resolution on access to medicinal products.[33] In this resolution, medicine shortages were flagged as a major concern. The European Commission was called on to further analyse the causes of shortages, establish a list of essential medicines that are in short supply and develop a mechanism whereby medicine shortages across the EU are reported on an annual basis. Since then, concerns about shortages of medicines have intensified. In September 2020, the EP adopted a separate resolution 'on the shortage of medicines – how to address an emerging problem'.[34] Following on its previous recommendations, in this resolution the EP called on the Commission, Member States and other relevant stakeholders to work together to address the issues through a variety legislative and non-legislative actions. Most recently, the *Council Conclusions on Access to medicines and medical devices*

[24] Shaban, H., Maurer, C., & Willborn, R. J. (2018). Impact of Drug Shortages on Patient Safety and Pharmacy Operation Costs. Retrieved from www.fedprac.com

[25] WHO. (2016). Global approaches to addressing shortages of essential medicines in health systems. WHO Drug Information, Vol. 30, pp. 180–185.

[26] de Weerdt, E., Simoens, S., Casteels, M., and Huys, I. (2017). Clinical, economic and policy implications of drug shortages in the European Union. Appl. Health Econ. Health Policy, 15 (4), 441–445. doi: 10.1007/s40258-016-0264-z

[27] Hyde, R. (2020). Europe faces worsening medicine shortages. Lancet (London, England), 395(10223), 481–482. https://doi.org/10.1016/S0140-6736(20)30354-8

[28] Drug Shortages for Calendar Year 2020: Report to Congress (2021). U.S. Food & Drug Administration. Available at: https://www.fda.gov/media/150409/download. Accessed 27 July 2021.

[29] Current and Resolved Drug Shortages and Discontinuations Reported to FDA. (2021) U.S. Food & Drug Administration. Accessible at https://www.accessdata.fda.gov/scripts/drugshortages/. The FDA defines a current shortage as "a situation in which the total supply of all clinically interchangeable versions of an FDA-regulated drug is inadequate to meet the current or projected demand at the user level. In general, the FDA's Drug Shortage Program focuses on shortages of medically necessary products that have a significant effect on public health".

[30] A market is hereto defined as "all medicines of the same active ingredient, dosage form, route of administration and strength".

[31] Zhang W, Guh DP, Sun H et al. (2020). Factors associated with drug shortages in Canada: a retrospective cohort study. CMAJ Open 31;8(3) doi: 10.9778/cmajo.20200036.

[32] Medicine shortage reports database. Australian Government Department of Health, Therapeutic Goods Administration. Available at: https://apps.tga.gov.au/Prod/msi/search?shortagetype=All. Accessed 13 August 2021.

[33] European Parliament resolution of 2 March 2017 on EU options for improving access to medicine (2016/2057(INI)) https://www.europarl.europa.eu/doceo/document/TA-8-2017-0061_EN.html. Accessed 21 May 2021.

[34] Resolution of 17 September 2020 on the shortage of medicines – how to address an emerging problem. https://www.europarl.europa.eu/doceo/document/TA-9-2020-0228_EN.html.

for a Stronger and Resilient EU invite the Commission and Member States to closely collaborate to facilitate timely solutions, in particular regarding shortages of critical medicines.[35]

The need to secure the supply of medicines across the EU and avoid shortages is explicitly part of the EU Pharmaceutical Strategy for Europe, adopted in November 2020.[36] Under the Strategy, the Commission proposes a revision to the pharmaceutical legislation that would include introduction of stronger obligations for supply and transparency, earlier notification of shortages and withdrawals, enhanced transparency of stocks and stronger EU coordination to monitor, manage and avoid shortages.[37] Another action is the launch of a structured dialogue with and between actors in the pharmaceutical manufacturing value chain and public authorities. The aim of the *Structured dialogue on security of medicines supply*[38] is to formulate policy options and propose actions to strengthen the continuity and security of supply in the EU.

As a European agency responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU, the European Medicines Agency (EMA) is involved in dealing with shortages in various ways. In December 2016, the Agency and Heads of Medicines Agencies (HMA) created a Task Force on the Availability of Authorised Medicines for Human and Veterinary Use'. Since 2019, the Task Force has been running a pilot programme on establishing a single point of contact (SPOC) network on shortages to improve information sharing between Member States, the EMA and the Commission and to coordinate actions to help prevent and manage shortages.[39] In 2019, the Task Force also published a 'Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA)'. On 11 November 2020, the Commission adopted a proposal to extend the mandate of the EMA to facilitate a coordinated EU-level response to health threats and to reinforce the systems and processes established in response to the pandemic. This includes monitoring and mitigating the risk of shortages of critical medicines and medical devices.40,41 It also provides for electronic monitoring and reporting systems for reporting information provided by national agencies and marketing authorisation holders regarding shortages of a specific list of medicines in times of crisis.

In response to the COVID-19 pandemic and its impact on availability of medicines, in March 2020 the Commission, together with EMA and Member States set up an *EU Executive Steering Group on Shortages of Medicines Caused by Major Events* to effectively respond to and prevent the escalation of shortages.[42] Jointly with the pharmaceutical industry, the Steering Group has also set up an early-warning shortage notification system (i-SPOC) through which pharmaceutical companies report directly to the EMA any issues related to the availability of crucial medicines being used in the context of COVID-19. In June 2021, the group furthermore adopted a reflection paper on forecasting demand for medicinal products in the EU/EEA.[43]

---

[35] Council of the European Union. (10 June 2021) Draft Council Conclusions on access to medicines and medical devices for a stronger and resilient EU. Available at: https://data.consilium.europa.eu/doc/document/ST-8786-2021-INIT/en/pdf.

[36] European Commission. A pharmaceutical strategy for Europe. Available at: https://ec.europa.eu/health/human-use/strategy_en.

[37] European Commission. (2020) Pharmaceutical Strategy for Europe: reader-friendly version. Available at: https://ec.europa.eu/health/sites/default/files/human-use/docs/pharma-strategy_report_en.pdf.

[38] Structured dialogue on security of medicines supply | Public Health (europa.eu)

[39] Availability of medicines, EMA website. https://www.ema.europa.eu/en/human-regulatory/post-authorisation/availability-medicines.

[40] European Parliament. (April 2021) Extension of the Mandate of the European Medicines Agency (EMA) / 2020-11. Available at https://www.europarl.europa.eu/legislative-train/theme-promoting-our-european-way-of-life/file-ema-mandate-extension#:~:text=On%2011%20November%202020%2C%20the,State%20of%20the%20Union%20address. Accessed 13 June 2021.

[41] European Commission. (November 2020) Proposal for a Regulation of the European Parliament and of the Council on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices COM(2020) 725 final. Available at: https://ec.europa.eu/info/sites/default/files/proposal-mandate-european-medicines-agency_en.pdf.

[42] European Medicines Agency (Press release 10 April 2020) Update on EU actions to support availability of medicines during COVID-19 pandemic. Available at https://www.ema.europa.eu/en/news/update-eu-actions-support-availability-medicines-during-covid-19-pandemic. Accessed 13 June 2021.

[43] HMA/EMA. (3 June 2021) Reflection paper on forecasting demand for medicinal products in the EU/EEA EMA/162549/2021. Available at: https://www.ema.europa.eu/en/documents/other/reflection-paper-forecasting-demand-medicinal-products-eu/eea_en.pdf.

1.3. EU legal framework for preventing and mitigating shortages

The EU pharmaceutical legislation, specifically Directive 2001/83/EC, contains two provisions to address the supply of medicinal products in the Union.[44] Article 23a requires the marketing authorisation holder (MAH) to submit a pre-notification to the relevant national competent authorities (NCAs) "if a product ceases to be placed on the market of a Member States, either temporarily or permanently". Authorities must be notified, other than in exceptional circumstances, no less than two months before to the interruption. Member States should transpose this into their national legislative frameworks.

Additionally, Article 81 of the same directive requires MAHs and wholesale distributors of a medicine that is placed on the market to "ensure appropriate and continued supplies", within the limits of their responsibilities, to cover the needs of patients. Application of this provision similarly requires Member States to put in place systems to monitor compliance with the requirement and to enforce this, for instance by imposing penalties in case of failure to do so.

1.4. Study objectives

In recognition of the growing problem of medicine shortages in the EU and of the need for concerted action at the European level, in March 2020, the European Commission Directorate-General for Health and Food Safety (DG SANTE) issued a request for services for a study on medicine shortages. The study was to provide:

- an overview of medicines in shortage in the EU, including their specific characteristics, as well as an analysis of the root causes of the shortages
- an evidence-based assessment of whether the current framework (at EU and national level) to address the issue of shortages is fit for purpose, in line with the Better Regulation guidelines
- an overview of potential solutions to address shortages, taking into account their root causes and the shortcomings of the current system, as identified by this study

This report contains the results of this study.

[44] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Available at https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf.EUR-Lex - 02001L0083-20210526 - EN - EUR-Lex (europa.eu). Accessed 13 June 2021.

2. METHODOLOGY

2.1. Study questions and scope

The study questions and scope were refined and agreed with the Commission in the inception phase of the study, as specified in Annex A. The study focused on the situation in the EU/EEA in the period 2004-2020. However, with regards to data from national shortages registries, the period that could be covered is limited to the years 2007-2020, because no country was able to share data from before 2007.

The scope of the study was limited to medicines for human use, thereby excluding veterinary medicines. Although the focus was on prescription medicines, the available data on notified shortages and non-shortage medicines did not provide information on whether these concerned prescription-only medicines or also medicines that are available without prescription ('over-the-counter' medicines). Consequently, the quantitative analyses presented in this report are based on a combination of prescription and non-prescription medicines. A clear separation between the two would, at any rate, not have been possible as some medicines can be obtained over-the counter in some countries but require a prescription in others. The stakeholder consultation, however, primarily focused on actors involved in the manufacturing and dispensing of prescription medicines. No organisations or individuals were involved that exclusively represent the interests of the non-prescription medicine sector.

The following methods and data sources were consulted:

Method	Data sources
Literature review	Systematic review of academic, peer-reviewed articles; Review of publications by key stakeholder organisations ('grey literature')
Key informant interviews	Representatives of EU national competent authorities, pharmaceutical manufacturers[45], wholesalers and parallel distributors, and pharmacy organisations
Surveys	Three parallel online surveys of 1) EU national competent authorities; 2) supply chain actors (manufacturers, wholesalers and parallel distributors); 3) pharmacy organisations.
Focus group	Invitational focus group attended by representatives of EU national competent authorities, trade associations for the distribution and wholesale industry, pharmacists and physicians, patient and consumer organisations
Quantitative analysis of shortage notifications	National shortages registries (shared or public) of EU Member States, EMA/SPOC register; Data from IQVIA MIDAS
Solutions consultation	Two consecutive online surveys and panel discussion with key stakeholders from national competent authorities; supply chain actors (manufacturers, wholesalers and parallel distributors); pharmacy organisations; medical associations; patient and consumer organisations.
Assessment of legal framework	Interviews with representatives of national authorities; desk research

Separate stakeholder groups have been involved in different ways and at different times throughout the study. Overall, all major stakeholder groups have had opportunity to provide input and feedback to the study team. In all cases, adequate representation of these stakeholder groups was reached to provide a balanced representation of perspectives in this report. Preliminary findings were presented to a wide range of invited stakeholders during a final consultation workshop on 1 July 2021. Groups that were not involved in this study, but which could have provided additional perspectives, include representatives of national healthcare systems and health insurance organisations, procurement agencies, and Contract Manufacturing Organisations.

The following paragraphs provide a summary description of the tasks performed for this study, the methods used and their main limitations. A more detailed methodology description is provided in the Annexes to this report.

[45] In this report the term (pharmaceutical) manufacturer refers to the party that is responsible for the production and placing on the market of a medicine and is used interchangeably with the term Marketing Authorisation Holder, even though it is recognised that many MAHs use Contract Manufacturing Organisations (CMO) for production. No CMOs were included in the consultation activities for this study.

2.2. Literature review

A systematic key word-based search was performed of academic (peer-reviewed) and grey literature. Peer-reviewed literature was identified from the PubMed/Medline, Scopus, and the Cochrane Library databases, while grey literature was identified from Google, Google Scholar, and EC, EMA, OECD and WHO websites (Annex B). In addition to structured searches, literature was identified from reference lists in included publications and individual (unstructured) searches. In total, 50 publications/documents were included in the main literature review (Figure 17, Annex B). Relevant information was extracted and has been reported in the corresponding sections of this report.

2.3. Interviews and focus group

Interviews were conducted with representatives of national competent authorities dealing with shortages in the Member States, representatives of supply chain actors (innovator and generic pharmaceutical companies, manufacturers of active pharmaceutical ingredients (APIs), wholesale distributors and parallel traders) and representatives of pharmacy associations (hospital and community). In total, 21 individual or group interviews were conducted (Annex C, Table 24). The interviews were conducted in a semi-structured fashion, using tailored interview guides as a basis. Data from the interviews were analysed through review of notes and discussion within the study team. Findings from these interviews have been incorporated, in anonymised form, in the relevant sections of this report.

Separately, an online focus group was held on 7 May 2021 with around 50 invited representatives of national competent authorities, pharmacists (community and hospital), physicians, patient and civil society organisations, and representatives of the European associations for the pharmaceutical wholesaling-distribution and parallel distribution industries (Annex C, Table 25). Purpose of this event was to discuss preliminary findings to identify points for further analysis, provide context to observations and collect additional perspectives. The event consisted of an introductory presentation of findings by the study team, followed by moderated parallel discussions. The collected feedback was used to refine analyses and findings.

2.4. Surveys

Three individual online administered **surveys** were conducted, with representatives of respectively 1) national competent authorities of the Member States, 2) supply chain actors (innovative and generic pharmaceutical companies, wholesale distributors, and parallel distributors), and 3) pharmacy organisations. Invitations to participate in the surveys were disseminated by the relevant European sector associations. Survey questions are provided in Annex D. In total, 375 unique responses were received that were distributed across stakeholder groups as indicated in Table 1. Responses to closed questions were analysed by tabulation and, where relevant, disaggregated by specific stakeholder groups. A full overview of the analysis per question is included in Annex H. Information derived from these analyses has been integrated in the relevant sections of this report.

Table 1 Survey respondents

Respondent group	Responses
Version 1: National competent authorities	
National authorities	18 (14 countries)
Version 2: Supply chain actors	
Manufacturers of APIs or intermediates	55
Manufacturers of innovative medicines	47
Manufacturers of generic medicines	44
Wholesale distributors	76
Parallel distributors	24
Other (not specified)	10
Version 3: health professionals	
Community / retail pharmacists	23
Hospital pharmacists	78

For the collection of cost estimates associated with the implementation, monitoring and enforcement of the obligations laid down in Articles 23a and 81 of Directive 2001/83/E, a separate Excel-based

template was shared with NCA representatives as part of the survey. A similar template was shared with supply chain actors to collect information on their costs for compliance with the obligations.

2.5. Analysis of shortage registries

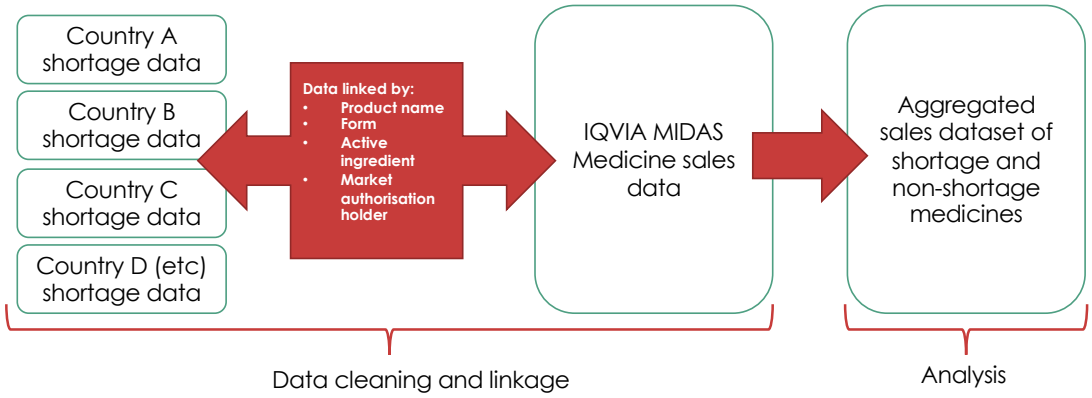
Data collection and processing

The study team requested data from the national shortage registries for all 30 EU/EEA countries through the members of the SPOC network. Of these, 17 provided data sets directly and for a further five were obtained from online public registries. Thus, shortage data were obtained for 22 countries (for more details on the methodology used for analysis of data from the national shortage registries, see Annex E).[46] These data were merged and then linked to data from the IQVIA MIDAS pharmaceutical sales database to create a single dataset with information on both shortages and sales, that could be used for detailed analyses. Linkage was done based on international proprietary name, name of the manufacturer, pharmaceutical formulation and active ingredient(s). Pharmaceutical formulation was re-coded manually to achieve a higher level of aggregation (Annex E, Table 28). Active ingredients and manufacturer names were cross-checked and matched to the format/order used in the sales dataset.

Although Denmark and Iceland provided national level data, these countries had not been included in the IQVIA MIDAS database and thus could not be included for further analysis. The national data sets provided by EU/EEA countries were complemented by shortage notifications recorded in the SPOC registry. In total, the compiled data set contained 22,487 reported medicines in shortage (Annex E, Table 30).

Differences in how data are collected from country to country necessitated extensive data cleaning and restructuring to enable sufficiently accurate data linkage.

Figure 1. Quantitative methodology schematic



The exact information (variables) included in country level data sets and how these were reported differed greatly (Annex E, Table 26 and Table 27). Where possible and necessary, information was thus manually standardised. Some, but not all, Member States included information on reported root causes in their registries. Like with other variables, there are very significant variations in how such information is reported. To further standardise this, any reported root causes were reclassified using the EU SPOC Network classification of root causes (Annex E, Table 29). Where more granular information was available, this was included as a separate variable.

In the medicine sales dataset from IQVIA MIDAS sales data (volume and revenue) were summed across all pack sizes of a medicine. Last, the data set was expanded with information on the manufacturer's history of (non-)compliance with EMA Good Manufacturing Practice (GMP)[47], as well as whether a product was included in the WHO's Essential Medicines List (EML)[48] (both binary variables). A variable on inclusion in the WHO EML was added to help assess therapeutic criticality of medicines in shortage. The unit of analysis was used was medicines that have been in shortage

[46] Austria, Belgium, Croatia, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Netherlands, Norway, Portugal, Romania, Slovakia, Slovenia, Spain, and Sweden.

[47] See: https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice

[48] See: https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/essential-medicines-lists

where each medicine was defined by the linking variables of international proprietary name, MAH, formulation and active ingredients.

Data analysis

Analysis was conducted using an aggregated dataset of shortage and non-shortage medicines. This allowed for the comparison of characteristics between shortage and non-shortage medicines. For summary characteristics of medicines in shortage basic frequencies were calculated (e.g. pharmaceutical formulation and anatomical classification code[49]). Shortage duration was calculated first by finding the average duration per medicine that had been in shortage (some medicines had multiple shortage events), and then averaging the duration across medicines. Various statistical tests were applied to assess the differences of key characteristics between shortage and non-shortage medicines and the association between statistically significant results.

A comparison of market trends and relative importance of a medicine to its manufacturer between shortage and non-shortage medicines was also conducted. Here each shortage medicine was matched to five 'nearest neighbour' non-shortage medicines based upon a set of variables (ATC2[50], pharmaceutical formulation, and time on the market). The comparison considered revenue, volume sold and list price. Relative importance of a medicine to its manufacturer was calculated as a percentage of the total revenue sold for a medicine out of the total revenue sold for the relevant manufacturer, as taken from the IQVIA MIDAS sales data.

Limitations

There are significant limitations in the available data which, in turn, impact the robustness of the findings derived from their analysis. Most countries have only relatively recently begun collecting standardised information on medicine shortages. No country provided information from before 2007. Consequently, the robustness of the presented analyses rapidly decreases for older shortages.

The identification of 'products' – based on matching of information on product name, active ingredient, form and manufacturer and summed over all pack sizes – was done on the national data sets before these were aggregated. However, countries may use different names for the same product, or the name of the manufacturer may differ because it is provided in the local language or is listed as a local subsidiary. In the aggregated data set, these entries were still treated as separate products. This leads to an overestimation of the number of products in shortage and an underestimation of how often multiple countries are affected by the same product shortage. Whilst this impacts the accuracy of numbers reported as absolute values or frequencies, it is not expected to have a significant impact on reporting of relative numbers or trends as there is no reason to assume the issue applies differently for different types of products.

Estimations of the duration of shortages are severely limited by gaps and inconsistencies in the information included in the registries. Many data entries did not provide an (estimated) end date for the shortage. It could not be determined if the lack of information was indicative of a still current shortage or was simply the result of an omission to enter an end date into the system. It was assumed that entries for which no end date was specified signified a current shortage. Second, whilst some countries require notification of any medicine shortage, regardless of the expected duration, others (e.g. Sweden) only require notification if the shortage is expected to last longer than three weeks. This may lead to an overestimation of the average shortage duration as briefer shortages remain unreported. Conversely, underestimation can also occur because of brief but rapidly recurring shortages. It was observed that, in some data sets, the same medicine was notified as being in shortage repeatedly with only a few days between consecutive reporting periods. These instances were treated as separate shortages, with the duration as specified by the time between the reported start and end date. However, these data do not offer any insight into whether in the intervening days the medicine was supplied again or whether the separate entries should really be viewed as one longer shortage.

[49] All products have been classified according to the Anatomical Classification of Pharmaceutical Products, a classification system developed and maintained by the European Pharmaceutical Market Research Association (EphMRA). The classification system is similar to the WHO Anatomical Therapeutic Chemical Classification system, but whereas the WHO system classifies substances according to the therapeutic or pharmaceutical aspects and in one class only, the EphMRA system classifies products mainly according to their indications and use. Anywhere in this report the abbreviation ATC is used, it refers to the EphMRA classification. See also: EphMRA Intellus WorldWise. (November 2020). Comparison of the WHO ATC Classification & EphMRA/Intellus Worldwide Anatomical Classification. Available at: https://www.ephmra.org/media/4974/ephmra-who-comparison-booklet-2020.pdf.

[50] As based on EphMRA classification level 2.

The data sources upon which the information collected in the national shortage registries is based vary between countries: some registries contain only reports by manufacturers and wholesalers, who are obliged to notify authorities in case of supply problems. However, in a few countries (e.g. Spain and Ireland) also other parties, such as pharmacies or patient associations, can report shortages into the system. Countries furthermore differ in what shortages they require MAH and wholesalers to report (e.g. only critical medicines or all medicines) and when they are expected to do so.

Strength of medicines in shortage was reported in an inconsistent manner from country to country, such that linking national level shortage data to shortage data using this variable was not possible. Thus, sales data was summed across all dosages of a given medicine.

Overall, it should be concluded that, even though this study builds on the most comprehensive set of shortage notifications collected for the EU to date, the significant differences in how and when shortages are notified, what variables are included and how these are reported introduce uncertainties into the study findings that are based on analysis of these data sets. These findings should thus be interpreted with due consideration of these limitations and be understood alongside the more qualitative findings.

2.6. Assessment of the EU regulatory framework

The transposition of Articles 23a and 81 in their respective Member States and any additional measures adopted for the prevention and mitigation of shortages, including via public procurement rules, was mapped via review of national policy documents and legal texts. Relevant documentation was hereto identified and reviewed by national legal experts designated by the study team. This analysis was further supported, wherever possible, through interviews with the national competent authorities. These interviews were in addition to those previously discussed in Section 2.3 and were conducted by the national legal experts. The interviews served to collect views from the national authorities specifically in relation to the assessment of the legal framework, focusing on the evaluation criteria of effectiveness, efficiency, coherence, relevance and EU added value.

Analyses performed based on data from the national shortage registries (Section 2.5) and information collected from stakeholders via interviews (Section 2.3) and surveys (Section 2.4) further informed the assessment. For the assessment of internal coherence within the broader EU legal framework, applicable Directives and guidance documents were reviewed. No further relevant information was identified in academic literature.

A particular challenge for the evaluation of the EU legal framework, particular regarding its effectiveness and efficiency, is the absence of suitable comparators. In nearly all Member States, both Articles were transposed into national legislation no later than 2007 (six years after the Directive‘s adoption in 2001), whilst the data collected from national shortage registries does not date further back than 2007 in any country. In most cases, there is even no data available from before 2011. Thus, NCAs could not provide any (quantitative) evidence on which to judge the shortage situation in their countries prior to the transposition of these Articles. Additionally, the fact that transposition has taken in place in all countries before the start of data collection means that comparisons between countries with and without transposition are not possible. Consequently, the evaluation rests primarily on qualitative information collected through consultations with key stakeholders.

A separate cost-benefit analysis supported the assessment of the effectiveness and efficiency of the legal framework. Input parameters for the analysis were obtained through survey responses. However, very few stakeholders provided any of the requested information that was hereto required and the collected responses vary substantially. Consequently, the cost-benefit analysis is strongly based on assumptions and data with a high uncertainty. The cost-benefit assessment methodology is further detailed in Annex F.

2.7. Product case studies

A series of five illustrative product case studies has been performed. Their purpose is to illustrate the different causes and consequences of shortages. Selection of products was based, in consultation with experts, on the following criteria:

- Diversity in therapeutic use and criticality
- Diversity in root causes of shortages
- Relation to COVID-19

Availability of publicly accessible information and inclusion in the national shortage registries analysed for this study were also factored in. All case studies were based on review of documentation

and analysis of shortage notifications in the national registries. No primary data specific to these products was collected.

The product case studies are limited by a reliance on public information published and retrievable in English, French, German or Dutch. Manufacturers of the selected products were not consulted on these product case studies, nor were they given opportunity to review the cases.

2.8. Analysis of potential solutions

The assessment of potential solutions to medicines shortages was implemented through five steps (a detailed description of the process is provided in Annex J). First, 169 potential solutions were identified from various data sources, including literature and stakeholder consultations. These solutions were filtered and clustered according to their relevance and corresponding root causes (or related issues) identified in the preceding parts of the study. The remaining solutions were then further developed to arrive at a list of 38 solutions. For these 38 solutions, a set of 'solution fiches' was developed as the starting point for the consultation process.

An invitation to an online invitation-only survey platform, containing the fiches, along with an introduction to the process and a set of assessment criteria, was shared with a group of 100 select stakeholders (fiches included in Annex J.7). These stakeholders were drawn from the various stakeholder groups with whom the study team had interacted throughout the process and selected to ensure a sufficient balance between different interests and perspectives.

The first round of assessment criteria related to effectiveness, efficiency, relevance, and feasibility. Each solution was scored on a 5-point scale and respondents could provide further comments. In total, 69 responses (69%) were received and processed. Scores were converted into numeric values, from which total assessment scores were calculated. Scores were also calculated that reflect the degree of consensus within and between stakeholder groups. A more detailed methodological explanation is provided in Table 47. The calculated scores and open comments informed the selection of a short-list of 22 solutions. In the selection, due consideration was given to the need to offer solutions for various types of identified root causes.

Short-listed solutions were submitted for a second round of assessment by the 69 stakeholders who had contributed to the first round. Where necessary, the solution fiches were refined to address issues raised by participants. Solutions were now scored on a new set of scoring criteria: EU-added value, coherence, risk of unintended consequences, ease of implementation and urgency of implementation. A more detailed description of all assessment criteria can be retrieved from Table 48. In total, 56 responses (81%) were received.

For both rounds of analysis, four separate stakeholder groups were formed: 1) patient organisations, pharmacists and health professionals; 2) pharmaceutical manufacturers (innovative, generic and API); 3) wholesalers and parallel distributors and 4) national competent authorities in the EU/EEA countries. This grouping was informed by a sense of common interests within these groups, although the study team is aware that none of these groups are homogeneous. Whilst further division of the groups could have deepened the understanding of why consensus on some solutions was lower within some groups, the resulting low number of responses per group would have reduced the robustness of results.

Once all survey results were obtained, the results of these were discussed with a panel of stakeholders drawn from the respondents. The discussion focussed on the views on the remaining solutions, reasons for (lack of) support, conditions for implementation and consideration of external factors. From the survey results and panel discussion, a final set of 16 solutions was drawn up, as presented in Chapter 8 of this report.

2.9. Triangulation approach

Throughout this report, findings were triangulated wherever possible (Table 2). By this, we mean that supporting or refuting evidence was sought for any presented statements from multiple independent data sources. In line with the Commission's indicated emphasis on objective and quantitative data, the presentation of findings is structured foremost around the observations derived from analysis of the national shortage registries. Information from stakeholder consultations (interviews, focus groups, surveys) and from literature are used primarily to further place these observations in context. However, the significant data limitations discussed previously with regards to the data from the national shortage registries mean that the quantitative results cannot necessarily be taken as the complete and objective truth and that more qualitative observations deserve sufficient weight in drawing conclusions as well.

Table 2 Data sources, data limitations and strength of evidence

Area of findings (Chapter)	1. Data source(s)	Limitations
Defining and reporting of shortages (Chapter 3)	1. Peer-reviewed and grey literature (e.g. official NCA websites or documents) 2. Stakeholder survey responses. Data obtained from NCA representatives was taken as having most authority in regard to national criteria and systems. 3. Stakeholder interviews and focus group	Information from literature was not always up-to-date and may not yet capture changes made after establishment of the SPOC Network (in April 2019). In some countries, there are apparent inconsistencies in responses provided by different representatives of the NCA or with information from literature. Where these were identified, they have been explicitly indicated in the report.
Characteristics and trends of shortages (Chapter 4); Root causes of shortages (Chapter 5)	1. National shortage registries (shared or public) in the EU Member States, SPOC register and linked with IQVIA MIDAS data set. 2. Peer-reviewed and grey literature (e.g. member surveys and white papers by stakeholder associations) 3. Stakeholder responses from surveys and interviews	Highly inconsistent and incomplete reporting within and between national shortage registries results in significant uncertainties (and possibly bias) in findings derived from these data sets. Uncertainties are greatest for older data. To mitigate this and facilitate the greatest possible extent of comparative analysis, data sets were manually cleaned, restructured and standardised. Available literature relies largely on similar data sets and thus shares the same biases and limitations. Many consulted stakeholders represented clear sectoral interests, particularly regarding identification of root causes. Their perspectives are thus heavily informed by these interests. The limitations introduced by possible bias of stakeholders have been mitigated by, where possible, juxtaposing different perspectives and clearly identifying the stakeholder group whose perspectives are presented.
Evaluation of the EU legal framework (Chapter 6)	1. NCA documentation on transposition and implementation of legal frameworks 2. EU Directives and guidelines 3. National shortage registries (shared or public) in the EU Member States, SPOC register and linked with IQVIA MIDAS data set (outcomes captured in Chapters 4 and 5) 4. Interviews with NCA representatives by country correspondents 5. Stakeholder responses from surveys and interviews	Official documentation explicitly indicating how the EU legal framework has been transposed and implemented differs per country and, in some countries, availability of information was limited. Interviewed and surveyed stakeholders did not always have a comprehensive overview of the relevant issues or, in particular, their impact on the occurrence and impact of shortages. Cost-benefit analysis (CBA) is severely limited by a lack of robust quantitative data on both costs and benefits. Where quantitative data was absent, a qualitative description of possible costs and benefits has been presented. Although such data have not been incorporated into the CBA itself, it is used for contextualisation of the available analysis.
Product case studies (Chapter 7)	1. Peer-reviewed and grey literature (e.g. news media, NCA reports) 2. National shortage registries (shared or public) in the EU Member States, SPOC register and linked with IQVIA MIDAS data set.	Extent and depth of information available differs per product and has a bias towards literature available in English and captured in mainstream media. No product-specific information was sought from manufacturers, national authorities or patient organisations.

Potential solutions (Chapter 8)	1. Peer-reviewed and grey literature (e.g. white papers and reports by stakeholder associations) 2. Solutions consultation with selected stakeholders 3. Stakeholder responses from surveys and interviews 4. Final validation workshop	The recommended solutions are based primarily on the perspectives of different groups of key stakeholders. For most solutions, there is at present insufficient (quantitative) evidence to support a full impact assessment or to estimate the cost of implementation. The solutions also lack sufficient operational detailing for such assessment and rather should be viewed as preliminary proposals in need of further development. In the selection of solutions for recommendations a scoring system of weighted average ranking by various stakeholder groups was used. The groups were formed on the basis of similar interests but nonetheless are internally heterogeneous. All stakeholder groups were given equal weighting, regardless of the number of participants in each group. Whilst useful for showing overall strength of support for each solution, in the further development of solutions a different decision-making system may be preferable.

3. DEFINING AND REPORTING SHORTAGES IN THE EU

For a good analysis of the issue of medicines shortages, it is necessary to understand what different sets of stakeholders mean by this and how they measure it. Many Member States and other parties have formulated shortage definitions and have operationalised their definitions for use in the context of notification requirements and systems. For a proper overview of how this is done and how it impacts on our understanding of the issues, this chapter sets out to address the following study questions:

- How do stakeholders define a shortage (essential elements of the definition)?
- How do stakeholders feel shortages should be measured?
- What are the national definitions of a shortage in the EEA? What are their advantages and disadvantages?
- What are the national criteria for notifying a shortage in the EEA? What are their dvantages and disadvantages?

3.1. Defining medicines shortages

There is no single universally accepted definition of what constitutes a medicine shortage. Table 41 and Table 42 (Annex G) present some internationally proposed definitions. All refer to shortages in the context of authorised medicinal products and exclude non-availability of new products before their launch on the market. Most define a shortage as a disruption of supply and/or an inability to meet demand. There are also significant variations within the EU in how countries define a shortage. Table 42 illustrates some of these definitions and illustrates how countries differ in which products are considered within the scope of a definition, and when they consider a product to be in shortage. Whilst some countries limit their definition to essential[51] or critical[52] medicines, others include any authorised medicinal product. This lack of an agreed upon definition, even within the EU, has long been considered a barrier to a better understanding of the extent of medicine shortages, their causes and consequences and consequently efforts to address the problem.

In response to this problem, in 2019, the EMA and HMA released the first harmonised "shortage" definition.[53] It is intended as a first step to promote communication and coordination among European pharmaceutical stakeholders, regulators and professionals working in different national healthcare systems to improve their resilience to shortages. Among the competent authorities of Member States that responded to our survey[54], nine countries (60%) indicated that they are currently using the EMA definition whereas six (40%) countries use their own national definitions. The EMA definition is also widely used by supply chain actors[55], with 136 out of 199 respondents (68%) confirming its use within their organisations. Among responding pharmacists, 37 out of 67 (55%) use the EMA definition.

The introduction of the EMA definition is widely seen by stakeholders as a useful step. Most survey respondents (185 (93%) supply chain actors, 54 (81%) pharmacists) indicate this definition is adequate to identify medicine shortages. Nonetheless, there are some critical stakeholders as well, primarily representatives of the pharmaceutical industry in both survey and interview responses. These stakeholders suggest that the EMA definition does not properly define demand and does not consider other factors such as patient need, the criticality of a medicine or the duration of a shortage. They argue that demand should be measured nationally against patient needs (prescription-based demand) rather than against order volumes, as the latter may, in some countries, significantly

[51] According to the World Health Organization (WHO), essential medicines are medicines that "satisfy the priority health care needs of the population" and to which people should have access at all times in sufficient amounts. https://www.who.int/rhem/signpost/essential_medicines/en/ Accessed 13 July 2021.

[52] Critical medicines are medicines that must not be omitted, or their administration delayed as this has the potential to cause harm. In determining what medicines are critical, the EMA considers two criteria of importance: therapeutic use and availability of alternatives. https://www.ema.europa.eu/en/documents/other/criteria-classification-critical-medicinal-products_en.pdf Accessed 13 July 2021.

[53] HMA/EMA (2019) Good practice guidance for communication to the public on medicines' availability issues.

[54] Austria, Belgium, Denmark, Estonia, Finland, Germany, Iceland, Ireland, Latvia, the Netherlands, Portugal, Slovenia, Spain and Sweden. As the survey could be completed by more than one representative of a national competent authority, some countries submitted multiple responses. In total, 18 responses were submitted from 15 separate countries. For Germany, 3 responses were received of which 1 indicated use of the EMA definition and 2 of a national definition. It is possible that EMA and national definitions are used in parallel.

[55] Throughout this report, the term 'supply chain actors' is used to describe the collective of manufacturers of innovative medicines, generic medicines and APIs, wholesalers-distributors and parallel distributors. As this group is rather heterogeneous and their interests and positions on many issues will differ, where considered relevant, responses have been further disaggregated by stakeholder subgroups.

exceed the former. It is argued that at times demand is deliberately overstated or is distorted by distribution chain dynamics. This claim could not be independently substantiated as data on order volumes in relation to patient need (based on prescriptions issued or on the size of the treatment population and treatment regimen) are not publicly available. Manufacturers of innovative and generic medicines expressed concerns that the EMA's definition (and similar national definitions) may place unreasonable supply expectations on them. The industry's position on this has been discussed by the HMA/EMA Task Force on the availability of authorised medicines who agreed there was no evidence to support updating of the EMA definition.

Both supply chain actors and health professionals, in survey responses and interviews, emphasise that not all shortages are alike and that many definitions, including the EMA definition, do not consider the criticality of a medicine. Whilst all shortages have some measure of impact on patients and health systems, many shortages can be mitigated at the hospital or pharmacy level by dispensing a generic or therapeutic substitute or by sourcing the medicine from elsewhere (e.g. through parallel import). By not distinguishing between critical and non-critical shortages, the problem of shortages may be overstated and misunderstood. Additionally, manufacturers and wholesalers argue that many shortages are resolved within a matter of days and that their mandatory notification creates an unnecessary administrative burden. By contrast, pharmacy organisations and patient organisations take the view that a shortage should be defined as any occasion whereby a patient is unable to receive a prescribed medicine, regardless of the nature of the medicine or the duration of the shortage. Mitigating the impact of even relatively inconsequential shortages may furthermore take considerable time and effort on the part of pharmacists and physicians and thus have clear impacts on the efficiency of the health system overall, even if the quality of care can be largely maintained.

3.2. Notification of medicines shortages

Given the variations between definitions, it is unsurprising that multiple studies have confirmed that there is no uniformity in the requirements and systems for notification of shortages between EU Member States (Table 43).[56,57,58] As further described in Section 6.1, all countries have transposed Article 23a into national legislation, requiring MAHs and wholesalers to notify national competent authorities of any shortages (including anticipated and impending shortages). Consulted representatives of MAHs and wholesalers observe that the systems through which they must notify shortages to national authorities are not uniform. Whilst some countries have electronic systems into which these parties can directly report shortages in a standardised format, in other countries shortages must be reported by email. In some countries, reporting by MAHs and wholesalers can be complemented by notification, usually on a voluntary basis, by pharmacists, physicians or even patients (Table 43).[57] For example, in the Netherlands, the Dutch pharmacists association KNMP provides pharmacist-gathered data and supply chain updates on its Farmanco website to inform its members and the public at large on the existence of a shortage, its duration, probable cause and potential alternatives.

There are also notable differences in the exact notification requirements between countries. For instance, in Denmark, only "serious" shortages need to be reported, whilst in Sweden only shortages with an expected duration exceeding three weeks require notification. Additionally, the type of information MAHs and wholesalers must provide differs. Typically, a shortage notification should include at a minimum information about product characteristics (name, dosage, formulation), the nature and time of the shortage. In July 2019, the HMA/EMA issued guidance to MAHs for reporting of shortages, based on the common EU (EMA) definition.[59] The guidance includes a template detailing what information should be included, covering basic product details (e.g. name, active substance, ATC, form, strength, pack size), details on the shortage (e.g. start and expected end date, reason, impacted countries, risk assessment) and impact assessment (e.g. potential alternatives, estimated

[56] Pauwels, K. et al. (2014) 'Drug shortages in European countries: A trade-off between market attractiveness and cost containment?', BMC Health Services Research, 14(1). doi: 10.1186/1472-6963-14-438.

[57] Vogler, S. and Fischer, S. (2020) 'How to address medicines shortages: Findings from a cross-sectional study of 24 countries', Health Policy. Elsevier Ireland Ltd, 124(12), pp. 1287–1296. doi: 10.1016/j.healthpol.2020.09.001.

[58] WHO Regional Office for Europe (2020) Assessing the magnitude and nature of shortages of essential medicines and vaccines and nature of shortages. Copenhagen.

[59] HMA/EMA. (1 July 2019). Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA) EMA/674304/2018. Available at: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-detection-notification-shortages-medicinal-products-marketing-authorisation-holders-mahs_en.pdf.

population size affected). However, many elements are not mandatory and, thus far, are not required by NCAs.

Authorities may additionally request information on the availability of alternative medicinal products, the population affected by shortage and the risk for patient safety or a reduction in treatment access. Although the analysis of national shortage registries indicates this type of data is frequently not included in public registries, it may be available in some form in more detailed shortage dossiers held by national competent authorities. Only a few registries publish information on possible solutions for managing a shortage (e.g. existence of alternative medicines).[57] Most European reporting systems do not include information on possible substitutes and clinical guidance for healthcare professionals, unlike systems in Australia, Canada, and the United States.

After the national authority charged with maintaining the register verifies the accuracy of the information provided, information on shortages is kept in national registries, most of which are publicly accessible. A 2019 report by the EMA and HMA indicated that in the large majority (87%) of Member States authorities publish shortage data.[60] Most do so in web-based listings. Other reported tools include press releases, newsletters, and social media. However, most countries set no criteria for publication of shortage notices. For instance, even though in Denmark, Finland, Greece, Hungary, Portugal and Romania reporting is mandatory, these countries do not publish data on shortages.[61]

3.3. Standardisation and harmonisation of definitions and notifications of medicine shortages

The different, sometimes conflicting, perceptions on how medicines shortages should be defined clearly illustrate the difficulty of arriving at a common definition across countries and stakeholders. Moreover, some representatives of NCAs have suggested that different definitions may serve different purposes and thus can co-exist if there is clarity about their use. For instance, distinguishing between critical and non-critical medicines can aid in prioritising actions to prevent and mitigate shortages of critical products. Conversely, a more inclusive definition and associated notification system can offer a more comprehensive overview of the causes and consequences of shortages. Thus, it is conceivable that countries use separate definitions for critical and non-critical medicines in parallel, each with their own notification requirements.

The wide variety of notification requirements and systems pose significant challenges. Consulted MAHs and wholesalers indicate that, to them, these variations mean that reporting of shortages cannot easily be centrally coordinated or automated. Instead, notification is typically done manually by national or regional offices. In cases where shortages affect more than one country, having to report this information in different formats and reporting systems simultaneously creates significant duplication of efforts. Moreover, as illustrated by the previously discussed methodological limitations to this study, the lack of standardisation means that shortage data cannot easily be compared between countries. This makes it harder for competent authorities, pharmacists, physicians and patients to understand what caused the shortage, what is the full extent of the shortage or where supplies may still be available. Knowing whether and where any stock remains available would aid authorities or pharmacists in devising the most appropriate mitigation strategies (e.g. by redistributing remaining supplies or by importing the medicine from another Member State).

Consulted stakeholders all recognise the importance of a proper notification and monitoring system for medicine shortages. Across stakeholder groups, nearly all survey respondents agree that a shortage notification should include, at a minimum, the product name, expected start and end date of the shortage and the shortage status (expected, ongoing, etc).[62] Most also see need for inclusion of the MAH name and the reason for the supply disruption.[63] Opinions are more divided on the relevance of including information about product composition, market size, country where the product is authorised, where in the supply chain the disruption has occurred or a shortage mitigation

[60] EMA and HMA (4 July 2019) Good practice guidance for communication to the public on medicines' availability issues. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/good-practice-guidance-communication-public-medicines-availability-issues_en.pdf Accessed 13 July 2021.

[61] WHO Regional Office for Europe (2020) Assessing the magnitude and nature of shortages of essential medicines and vaccines and nature of shortages. Copenhagen.

[62] Among NCA representatives 94% of respondents consider these elements to be necessary in the reporting of a medicine shortage, compared to 85% of supply chain actors and 85% of pharmacists.

[63] Among survey respondents, 94% of NCA representatives, 79% of supply chain actors and 65% of pharmacists consider the MAH name to be necessary to report. Reason for the supply disruption is deemed necessary information by 94% of NCA representatives, 75% of supply chain actors and 67% of pharmacists.

plan.[64] Some stakeholders emphasise that, even with all of these elements included, a shortage notification in itself may not offer sufficient information to effectively understand the extent of a shortage or mitigate its impact. To support pharmacists with mitigating the effects of a shortage, they advocate for the inclusion of information on potential alternatives.

Summary

There are significant variations within the EU in how countries define a shortage, with further differences in how and when these definitions are used. At its most basic, definitions focus solely on lack of (sufficient) availability of the product whilst more sophisticated definitions include elements such as a minimum timeframe for unavailability or the criticality of the product or shortage situation. The lack of standardisation and harmonisation between Member States severely hinders comparative analysis. It also creates inefficiencies from the perspective of stakeholders that are under a notification obligation (MAHs, wholesale distributors) and limits effective information sharing.

The introduction and growing adoption of an agreed definition developed by the EMA/HMA has the potential to improve harmonisation. Nonetheless, other definitions may continue to be used in parallel depending on the national context and specific purpose. It is widely considered important to allow for a distinction to be made between critical and non-critical shortages (distinguished by their impact on the quality and continuity of patient care), and devise particular strategies to prevent and mitigate such shortages.

[64] While 83% of responding NCA representatives consider it necessary to include a mitigation plan in the reporting, this is the case for only 60% of supply chain actors and 63% of pharmacists. Similarly, while 67% of NCA representatives find market size a necessary element of a shortage notification, only 51% of supply chain actors and 22% of pharmacists agree.

4. CHARACTERISTICS AND TRENDS OF MEDICINES SHORTAGES

Whilst shortages have been studied extensively, to date there has been no comprehensive analysis of all notified shortages in the European Union. This study addresses this data gap through compilation and comprehensive analysis of data from 20 national shortage registries from EEA countries and by triangulating these results with observations and opinions of key stakeholders. The chapter address the following study questions:

- How many and which medicines are currently in shortage in the EEA?
- What (groups of) medicines are at highest risk of being in shortage in the EU?
- Has the profile of medicines in shortage changed over time? If so, in what ways?

4.1. Shortage notifications over time

Overall, notifications of shortages of medicines have steadily increased across the EU since 2007 (Figure 2, blue bars).[65] Since during this period the number of countries reporting also increased, a correction was made by dividing the total number of notifications by the number of countries reporting (red bars). Although around 70% of the increase over 2008-2020 can be attributed to the increase in the number of Member States reporting shortages, even after this adjustment, there is still a notable increase in notifications.

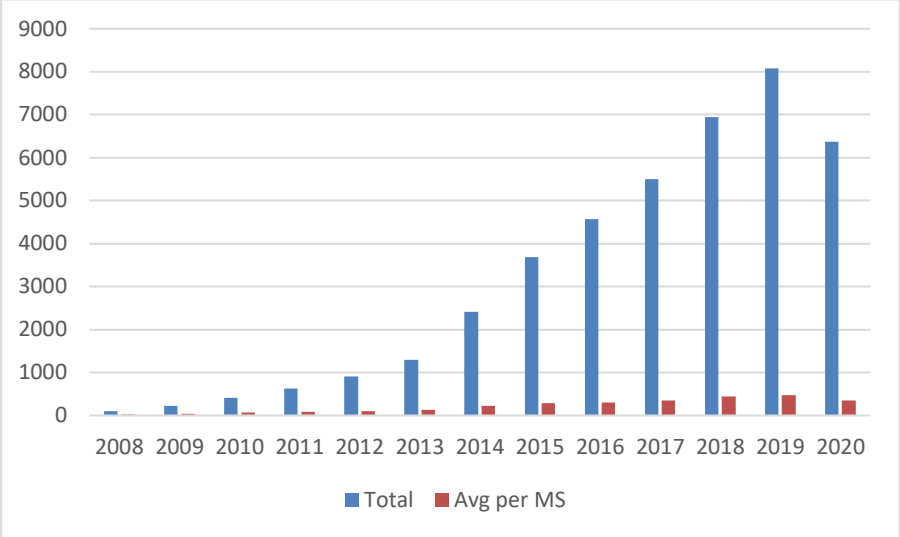
The observed increase can be interpreted in multiple ways. For one, it may reflect an actual increase in the occurrence of shortages. However, during this time many Member States have put in place new systems and requirements for notification of shortages that may have contributed to improved reporting and thus to an increase in the number of notifications. Additionally, increasing numbers of authorised medicines and changes to a country's list of approved medicines may have influenced the total number of notifications. Based on information from stakeholders, the most likely scenario is a combination of these factors.

Most surveyed representatives of NCAs (n=14, 71%) and pharmacists (n=44, 89%) have observed an increase in shortages over the past two to five years. Data collected by the EAHP and PGEU[18,19] among hospital and community pharmacists also clearly suggests that shortages are becoming more common and that improved reporting alone cannot account for the observed trend. Surveyed and interviewed manufacturers, however, emphasise that changes in definitions and reporting of shortages, as well as heightened attention to the issue, have driven increased reporting. They suggest that a lack of proper historic data prevents a proper assessment of the evolution of the issue.

The data set compiled for this study confirms the difficulties of performing a trend analysis purely based on notifications to the national competent authorities. However, the narrated experiences shared by those most directly affected by shortages (patients, pharmacists, and health professionals) and by authorities dealing with shortages on a regular basis offer compelling evidence that shortages are indeed on the rise.

[65] Data collection for this study began in October 2020. Consequently, for some countries data for the months October, November and December of 2020 is missing. Some countries also had not updated all shortages reported in 2020.

Figure 2 Total shortages reported and average[66] shortages per Member State

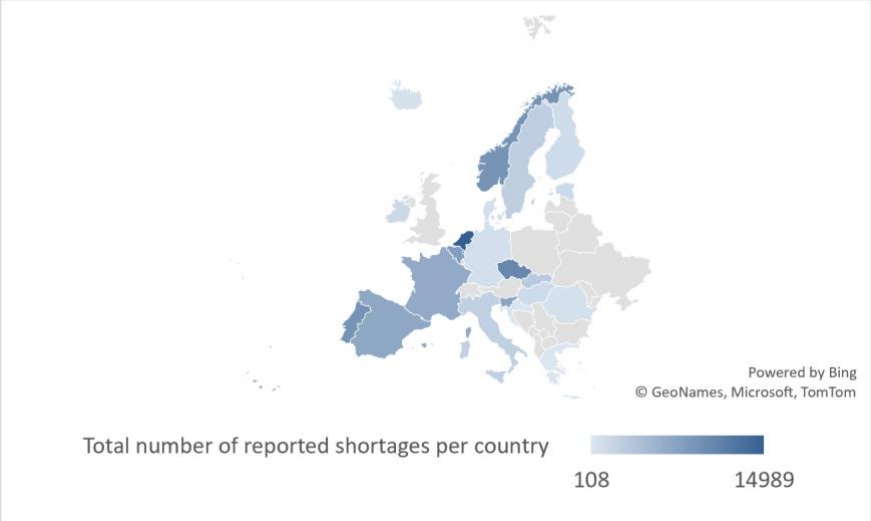


Source: Technopolis Group, based on data provided by NCAs or publicly available. AVG per Member State= Total shortages reported divided by the number of Member States reporting. Data for 2020 are lower due to incomplete reporting.

4.2. Shortage notifications by country

Analysis of data from the national shortage registries reveals significant differences in the total number of reported shortages between countries (Figure 3). As many as 14,989 instances of shortages were notified in the Netherlands, whilst Greece only recorded 108 instances. Although such differences may reflect, at least in part, real variation in the extent to which countries experience shortages, it is also heavily influenced by when notification began. For example, data included for Hungary, Slovenia and Spain dates back to 2007, whilst for Greece data collection began only in 2019. As indicated in Section 3.2., the number of shortage notifications, 109,757 in total, is further influenced by national definitions and notification requirements. Consequently, country-by-country comparisons of overall shortage notifications are difficult in light of differences in the time-period covered by the reporting as well as by the lack of standardised reporting.

Figure 3 Total number of shortages reported since 2007, by country



Source: Technopolis Group, based on data provided by NCAs or publicly available. Darker shades of blue indicate higher numbers of reported shortages. A total of 109,757 shortage notifications were reported.

[66] The 'average' number of shortages presented here is calculated by dividing the total number of shortages reported by the number of countries reporting. This is done to correct for an increasing number of countries reporting. It should, however, not be interpreted as a direct reflection of the average number of shortages increased by countries, as the number of shortages reported per country is not normally distributed and numbers cannot readily be compared between countries.

To provide a more nuanced view of the reporting of shortages across countries, shortage notifications were compared across countries for 2019, the most recent year for which reporting was complete (Table 3). In this year, the Netherlands and Portugal recorded considerably more shortage notifications than any other country. These notifications concerned more than 1,600 individual medicines. By contrast, Austria, Croatia, Iceland and Greece that year recorded fewer than 100 shortages, affecting 60 or fewer different medicines.

Table 3 Overview of shortage notifications per country in 2019

Country	# Notifications	#Products	Country	# Notifications	#Products
Portugal	6,633	2,991	Estonia	289	221
Netherlands	4,816	1,631	Germany	181	137
Belgium	2,123	996	Romania	162	119
Norway	1,474	736	Hungary	160	113
France	1,470	951	Slovakia	154	118
Spain	1,376	884	Austria	76	61
Slovenia	1,080	475	Croatia	41	30
Sweden	963	612	Iceland	26	21
Ireland	764	484	Greece	13	9
Italy	454	329			

Source: Technopolis Group, based on data provided by NCAs or publicly available. The reported numbers of products associated with notifications are an approximation, as not all countries provided information on the full set of variables used to define a medicinal product.

Out of the 22,487 shortages in the comprehensive data set, nearly one fifth (18%, 4,038) were listed as 'current' at the time the data was shared.[67] For each medicine, there were on average two separate notifications.[68] On average, 1.25 countries[69] were affected. The range of occurrences is, however, very wide. In the case of tablets of the tranquilizer Xanax (alprazolam), 207 separate notifications were recorded, originating from 11 different countries at various points in time. The most wide-spread case of a product shortage involved Celebrex (celecoxib), a nonsteroidal anti-inflammatory medicine, for which a shortage was recorded in 14 countries at various times. These findings support observations made by stakeholders that shortages often tend to be limited to one or a few countries at any time. This points towards issues in the downstream distribution chain under the influence of national policies and practices. Thus, whilst even for shortages that are highly localised, there can be underlying issues (e.g. manufacturing or quality problems) that affect the global supply levels, the extent to which these issues translate into shortages differs from country to country. This is further discussed in Section 0.

4.3. Product characteristics of medicines shortages

Prevention and mitigation of medicines shortages benefits from a good understanding of what type of products are most at risk. Variables to consider are, for instance, therapeutic class, product formulation, patent status or whether a medicine is a generic, multi-source product. Other potentially relevant factors relate more to the production and distribution of a product, such as the location and number of producers for raw and unfinished materials or the production technique.

To further understand what factors are most closely associated with shortages, a comparison was made between shortage and non-shortage medicines on several variables of interest. These variables were derived from the data included in the national shortage registries. In total, nine individual variables were considered. Although all nine variables (see Annex E, Table 33 for full details) show a small but statistically significant difference between shortage and non-shortage medicines, this

[67] As explained in Section 2.5, this includes any shortage for which no (expected) end date was recorded. It is, however, likely that this data treatment overestimates the true extent of current shortages.

[68] Median of 2 and mean of 4.5 instances of shortage per medicine reported in shortage. As discussed in Section 2.5, the analysis likely underestimates the number of countries affected because of how individual products were identified.

[69] Median of 1 and mean of 1.25 countries affected per medicine in shortage.

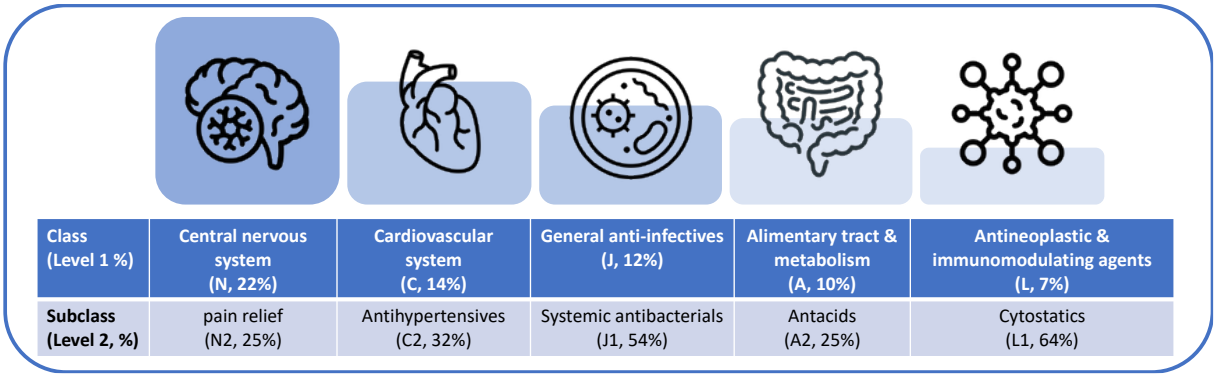
may be in part due to the large sample size used.[70] Further statistical analysis suggests the strongest, yet still only modest, association occurs between the generic status and the likelihood of a shortage. The following paragraphs provide further insight into the analysed variables.

4.4. Association with therapeutic area and formulation

To test for association between risk of shortage and the therapeutic area targeted, the Anatomical Classification code (ATC1) of a medicine was used. Notified shortages most frequently concerned medicines used to treat conditions of the nervous system (ATC N, 22%) (Figure 4). These medicines had a 55% increased probability of going in shortage.[71] Other classes of medicines frequently notified as being in shortage are cardiovascular medicines (ATC C, 14%), anti-infectives (ATC J, 11%), medicines to treat conditions of the alimentary tract and metabolism (ATC A, 10%) and oncology medicines (ATC L, 7%). The first two had respectively 32% and 48% increased probability of being in shortage than expected based on the distribution of non-shortage medicines across therapeutic areas. Oncology medicines had a 39% increased probability of being in shortage. By contrast, although they form the fourth largest group of products in shortage, medicines acting on the alimentary tract and metabolism had a 40% reduced probability of a shortage.

Within these broad groups of medicines, the respective subclasses of products most frequently in shortage included pain relief medication (ATC N2), antihypertensives (ATC C2), anti-bacterial products (ATC J1), antacids (ATC A2) and chemotherapy medicines (ATC L1). Comparison with non-shortage medicines at ATC1 level indicates that, while there is a statistically significant difference in the distribution pattern across therapeutic areas, the association between anatomical classification and shortages is relatively weak.

Figure 4 Top-5 of shortage notifications by therapeutic area



Class (Level 1 %)	Central nervous system (N, 22%)	Cardiovascular system (C, 14%)	General anti-infectives (J, 12%)	Alimentary tract & metabolism (A, 10%)	Antineoplastic & immunomodulating agents (L, 7%)
Subclass (Level 2, %)	pain relief (N2, 25%)	Antihypertensives (C2, 32%)	Systemic antibacterials (J1, 54%)	Antacids (A2, 25%)	Cytostatics (L1, 64%)

Source: Technopolis Group, based on information from the national shortage registers. Note that percentages shown at the subclass (level 2) are relative to the corresponding class (for instance, pain relief medicines (N2) represent 25% of all central nervous system medicines (N) that are listed in shortage.)

These findings are largely consistent with those made previously by others. The surveys conducted by the PGEU and EAHP indicate that, although supply problems have been observed across all conditions and product types, they particularly affect cardiovascular, oncology and preventative medicines, antimicrobials and anaesthetics.[72,73] Hospital and community pharmacies were similarly impacted by these shortages. This suggests that the shortage notifications to NCAs reflect the real life experiences of pharmacists. Studies of shortages in the United States report greatest supply problems with sterile solutions, emergency medicines, antibacterial medicines, vaccines and immunoglobulin products. This suggests that, although there is some overlap between the situations in the EU and in the US, there are also some notable differences. This may potentially be explained by very substantial differences in market characteristics between these regions, such as pricing and

[70] Chi Squared test is sensitive to large sample sizes, whereby results may show statistical significance but not be substantively significant. Further testing has been done (Cramer's V) to assess the strength of a relationship.

[71] Probability is herein defined as the relative frequency of shortage notifications in this class of products compared to the relative frequency of medicines in this class for all non-shortage medicines. A positive value thus means the product shows a higher than 'normal' probability of shortage.

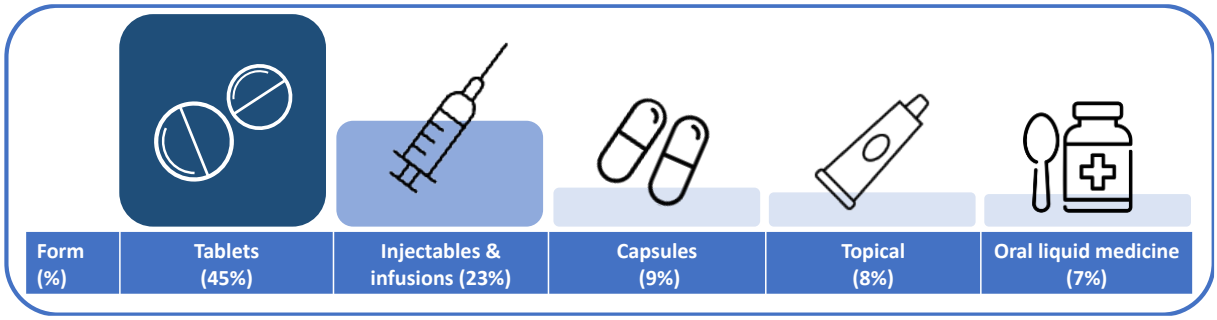
[72] 2019 EAHP Medicines Shortages Report. Medicine Shortages in European Hospitals. Available at https://www.eahp.eu/sites/default/files/eahp_2019_medicines_shortages_report.pdf Accessed 15/06/2021.

[73] PGEU Medicine Shortages Survey 2020 Results. Available at https://www.pgeu.eu/wp-content/uploads/2019/03/2020-PGEU-Medicine-Shortages-Survey-Results-v2.pdf. Accessed 15/06/2021.

procurement policies or the greater fragmentation of the European market, or by differences in the structure of the pharmaceutical supply chain (e.g. production location of APIs and finished products). However, as the collection and analysis of primary data (including shortage notifications) was outside the scope of this study, it is not possible to further test this hypothesis.

Nearly half (45%) of all reported shortages concern medicines in tablet form, whilst around a quarter (23%) concern medicines that are administered as injectables or infusions (Figure 5). The latter, however, had a somewhat higher probability of being in shortage (+32%) than tablets (+26%).[74] Other formulations make up relatively small volumes of overall notifications. Statistical analysis shows that the overall association between probability of shortage and formulation is weak but that the association is significant for injectables/infusions and tablets. (Annex E, Table 33).

Figure 5 Top-5 of shortage notifications by form



Because many shortages are caused by problems with manufacturing (discussed in more detail in Section 5.2), an important question is to what degree specific production techniques pose increased risks of shortages. However, the shortage registries do not contain information about the medicine's underlying production techniques, even though for some types of products there is a connection between formulation and production method. For instance, biological medicines[75] (including vaccines) are typically administered via injection. However, also small-molecule medicines produced through chemical synthesis can be administered this way and thus the connection between production technique and form, or any other reported variable, is not sufficiently strong to inform further analysis.

Instead, stakeholders were surveyed about the possible relation between shortages and specific production techniques. Manufacturers of both innovative and generic medicines consider products that are produced as powder for injection through lyophilisation[76] at increased risk of shortage (further discussed in Section 5.2). They also singled out products that are produced in small batches or pack sizes as most associated with shortages (Figure 82). The second observation is further confirmed by interviewed manufacturers, in particular those involved in the marketing of vaccines. They indicated that these products need to be produced in small batches because countries demand different product presentations. For instance, whilst some countries require single dose presentations because the product is administered infrequently to patients, others require the same product in a multi-dose presentation because it is given to multiple patients within a short space of time.[77] Other differences may pertain to dosage, needle gauge or length, or combinations of vaccines into a single product (multivalent vaccines). Further differentiation is introduced by national packaging and labelling requirements. All these variations are said to create inefficiencies in the production. Moreover, if products for specific markets experience any disruption in the supply, this cannot easily be absorbed by redistribution of products destined for other markets that use different presentations.

4.5. Relation to patent status, generic status and product age

For nearly all (97%)[78] of the shortage medicines the patent had expired before 1 January 2021, with an average time since patent expiry of over 19 years (7,001 days). This is similar to the situation for non-shortage medicines (18.5 years or 6,759 days), where the patent had expired before 1 January

[74] Probability is herein defined as the relative frequency of shortage notifications for medicines in this formulation compared to the relative frequency of medicines in this formulation for all non-shortage medicines. A positive value thus means the product shows a higher than 'normal' probability of shortage.

[75] A biological medicine is a medicine that contains one or more active substances made by or derived from a biological source. EUPATI. Biologic medicines. Available at: https://toolbox.eupati.eu/resources/biologic-medicines/. Accessed 30 July 2021.

[76] Lyophilisation is a technique whereby a liquid medicine is converted into powder form by freeze-drying. The medicine is rehydrated shortly before injection.

[77] For instance, in the context of mass vaccinations administered by public health services or at travel clinics

[78] The analysis excludes all medicines with a patent expiry date listed as "01-01-1900", which is a default entry in the IQVIA database, and therefore only applies to 7,507 out of the total of 22,487 medicines in shortage.

2021 for 95% of medicines. Statistical analysis indicates that neither patent status nor time since launch are significantly associated with a medicine being in shortage or not. It should be noted that medicines can benefit from market protection through other intellectual property rights besides patents, which may extend the effective protection time substantially beyond the expiry of the patent.[79] The data set used for this analysis, however, does not contain information about the extent of protection by these other forms of intellectual property. On average, shortage medicines were around 24 years[80] (8,797 days) old, rendering them somewhat older than the average non-shortage medicine (22 years).

Just over half of all reported shortages (52%) involve generic medicines[81], compared to 36% of non-shortage products. Non-generic medicines account for 37% of reported shortages, with non-generic medicines including both still-patented medicines and original medicines that are not (or no longer) protected. Statistical analysis points towards a modest association between the status of a medicine as a generic and the likelihood of shortage. Potentially an even more relevant distinction than that between generic and non-generic medicines is that between multisource and single source products. A multisource product can hereto be defined as a product for which there are multiple providers in a market offering an interchangeable product (based on equivalent active ingredient(s), strength and form). A recent White Paper by IQVIA finds that 52%-79% of shortages[82] involve generic products, which it assumes to be mainly 'multisource products'.[83] Additionally, it is estimated that 3.5% to 28%[84] of shortages involve 'no longer protected, original products' for which there are alternative generics or parallel import products available and that thus can be considered multisource products.

A similar analysis in the context of this study is challenged by inconsistent reporting of strength in the national shortage registries, which means that equivalency cannot easily be established. However, as the distribution of shortages in the data set included in the present analysis for both the share of generic versus non-generic medicines and for patent protected medicines, are within the ranges observed by IQVIA across a somewhat smaller data set[85], the IQVIA findings can be used as input variables. Based on these, it is estimated that around 76% of all shortages involve multisource products for which alternatives exist, in the form of generic alternatives or via parallel import.[86] For the remaining 24% of shortages, the product in shortage likely represents the only available version.

Consulted stakeholders widely confirm that off-patent, generic and older medicines are far more often in shortage than still-patented medicines. This view is shared across supply chain actors, NCAs and health professionals involved in dealing with shortages, who all indicate that generic medicines are more likely to be in shortage because of their limited profitability. Price pressures force generic manufacturers to focus on cheap and efficient production to maximise profit margins, such as by reliance on single source, lowest-cost suppliers of APIs and raw materials. Whilst this has successfully pushed down prices for generic medicines and allowed health systems to reduce its expenditure on pharmaceutical products, it has resulted in less diversified and consequently more fragile supply chains, as well as less emphasis on supply chain management.

[79] This includes supplementary protection certificates (SPCs) and the paediatric extension of the SPC, data exclusivity and market protection and orphan market exclusivity. Some forms of protection are mutually exclusive (e.g. paediatric extension of the SPC and orphan market exclusivity), others exist in parallel. The scope and duration of protection varies, depending on the product and its application.

[80] As measured by the time since the marketing authorization was issued.

[81] Indicated in the IQVIA MIDAS data set as: generic product, early entry generic product or biocomparable product (definitions provided in Annex E). Other categories not shown here are 'non categorized' and 'other' products.

[82] The unit of analysis used by IQVIA is the 'stock keeping unit' (SKU), used to normalize data across countries.

[83] Troein P, Newton M, Wasik AM, Coucoravas C, Scott K. (2020). Reporting of medicine shortages in Europe: white paper. IQVIA.

[84] The paper indicates that 5% to 40% of reported SKUs are 'no longer protected' original products and goes on to state that 70% of these have alternative generics or parallel import products. Thus, it can be said that 70% x (5% to 40%) = 3.5% to 28% of this group of products are multisource products.

[85] The analysis performed by IQVIA was limited to data from Austria, Belgium, Denmark, Germany, Hungary, Ireland, Italy, Lithuania, Norway, Sweden and Spain.

[86] The approach assumes that the 3% of still patent-protected products are all included in the 37% of non-generic medicines. No longer protected, non-generic medicines thus account for 34% of all shortages. IQVIA furthermore estimates that 70% of these can be substituted with generic or parallel imported products. Consequently, 52% (all generic medicines) + (70% * 34% no-longer protected, non-generic medicines) = 76% of shortages are estimated to be interchangeable.

4.6. Manufacturer characteristics

Possible sources of shortages, particularly when shortages are reported as having been caused by underlying quality or manufacturing issues, include inexperience or deliberate negligence on the part of the manufacturer. To further test the importance of characteristics associated with the manufacturer in the likelihood of shortages occurring, statistical tests were performed against the company size of the manufacturer (as approximated by its number of authorised products in the overall IQVIA MIDAS data set) and the manufacturer's history of compliance with Good Manufacturing Practice.

Manufacturers with a documented history of GMP non-compliance are found to be somewhat more likely to be associated with product shortages but the observed association is weak (Annex E, Table 33). It should nonetheless be noted that very few companies (n=58, 0.6% of all 9,461 listed manufacturers) have a history of GMP non-compliance and that, by far, most shortages occur with products that are marketed by companies without known GMP compliance violations (Table 31).

Table 4 Manufacturers of shortage products with history of GMP non-compliance

History of GMP compliance	# Manufacturers with medicines in shortage	% of manufacturers listed in IQVIA MIDAS (N = 9,461)
No history of GMP non-compliance	1,687	18%
History of GMP non-compliance	58	0.6%

The top-10 largest manufacturers, including both innovative and generics companies, are somewhat more likely to be the MAH for products in shortage than other manufacturers but here too the association is weak (Annex E, Table 33). The direction of the association suggests that having substantial experience with the manufacturing and marketing of medicines does not help to protect against the risk of shortages.

4.7. Criticality of medicines shortages

Even though any shortage will have some measure of impact on patients and health care providers, not all shortages are equally severe. The impact (severity) of a shortage depends on multiple factors. First, it depends on the extent of the supply problems; is a product completely unavailable anywhere or are supply levels below demand but the product remains available albeit in reduced quantities? In the latter case, the impact of the shortage may be mitigated by moving around stock and by rational dispensing of the medicine to those most in need. The impact of a shortage furthermore depends on the duration of a shortage. Shortages that are resolved within days will typically have less impact than those that are sustained over weeks or months.

A further consideration is the criticality of the product itself. Shortages of potentially life-saving medicines will have far greater impact than those for relatively minor ailments. For instance, consulted stakeholders commonly highlighted problems stemming from shortages of oncology medicines even though these medicines make up a relatively small share (7%) of all reported shortages. Some authors have suggested that shortages of oncology medicines pose a special challenge because cancer affects many people and because many oncology medicines have a narrow therapeutic window, meaning that these products cannot easily be substituted.[56] It is often deemed impossible to make changes to the therapy when a patient is already on an approved treatment protocol.

In the following paragraph, the criticality of medicines shortages will be assessed using various metrics:

- Availability
  - Remaining volumes at EU and national level
  - Duration of shortage
- Product criticality
  - Inclusion on WHO Essential Medicines List
  - Therapeutic use and availability of substitutes

4.7.1. Extent of shortages by remaining volume

Most countries define a shortage simply as any situation whereby supply does not meet demand, but do not define how wide the gap between the two must be before a notification must be made. Consequently, some notifications will involve products for which the supply disruption is relatively

small, whereas in the most extreme cases the supply issues are so substantial that all stock is depleted. To better understand the extent of product shortages and their impact on overall product availability, an analysis was performed of the total remaining sales volume during a reported shortage compared to the sales volume for that same product a year earlier (reference period). This approach is based on several assumptions:

- The recorded sales in the first quarter where the shortage was reported represent all remaining supply (i.e. all product sold is made available in the market and not held in stock, no safety stocks were used to mitigate the shortage)
- Demand can be approximated by the recorded sales in the same quarter exactly one year before the shortage was first reported (reference period). This further assumes that:
  - Demand is stable in the period between the start of the shortage and the reference period
  - All product sold in the reference period was made available in the market (not held in stock or traded) and was sufficient to meet demand

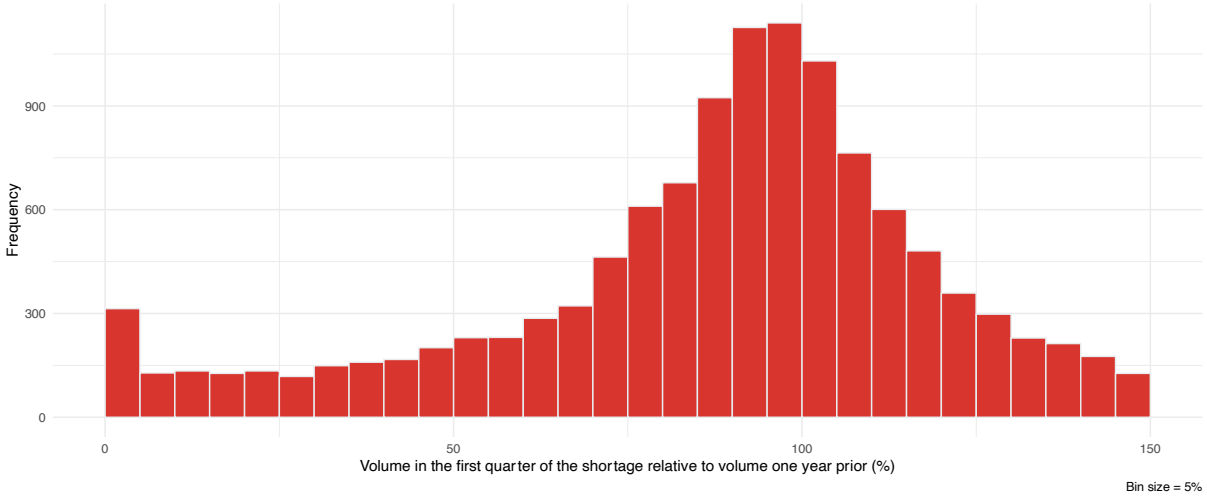
It may be possible to mitigate a product shortage by temporarily dispensing a different dosage of the medicine and adjusting the frequency with which the medicine must be taken to this. For this analysis, all different dosages (but not different formulations) of a product were thus aggregated to account for possible dosage substitution effects. Shortages for products for which the NCA had indicated these were linked to temporary or permanent withdrawals were excluded from the analysis, because here the intent of the MAH was to remove the product from a market completely.[87] This is distinct from a situation in which the MAH strives to ensure continued supply to a market but is unable to do so. The analysis was consequently limited to the 14 countries that supplied information about product withdrawals (Table 5).

It is found that, for most shortage medicines, the total sales volume[88] across affected countries during a shortage remained above 20% of the previously recorded volume (Figure 6). Only 6% of shortage medicines saw a drop in volume to below this level. This suggests that, for most shortage medicines, there remained a relatively high level of product availability across the affected countries even though, at the country level, available supplies were insufficient to meet demand. It cannot easily be determined to what extent dosage substitution allowed for this. Additionally, as this analysis aggregates across all countries where the product (in any dosage) was reported as being in shortage at any point in time, it does not offer insight into the impact on individual countries. Because shortages could have occurred at different points in time in different countries, it is possible that a reduction in volume in one country was offset by still normal supply levels in another country. Even when shortages affected multiple countries simultaneously, some countries may have experienced a greater volume reduction than others, as manufacturers or wholesales prioritise supply of some markets over others. Representatives of NCAs that were interviewed or participated in focus groups have suggested this is not uncommon.

[87] A separate methodological limitation was the inclusion of negative sales volumes in the IQVIA MIDAS data set. These were most typically recorded after the withdrawal of a product when unsold products were returned to the manufacturer. Negative values severely skewed the calculation of median volume changes. By excluding withdrawn products from the analysis, a more accurate analysis could be performed.

[88] Summed over the countries where the product was reported in shortage, thus excluding countries where there was no report of a shortage for the product. The total sales volume across the EU would thus have been significantly higher still.

Figure 6 Change in volume sold in first quarter of a shortage compared to 1 year prior*



Source: Technopolis Group, based on sales data from the IQVIA MIDAS database and shortage notifications by NCAs. Volumes sold are displayed only up to 150%. Frequency refers to the number of notifications for which the volume change falls within the limits of the 'bin' indicated by the vertical bar.

To get a better understanding of the extent of shortages in individual countries, the volume effect analysis was repeated at the country level (Figure 7). The resulting observed volume changes at the individual product level were then averaged across all notifications in the country to provide an estimate of the severity of national shortage situations. The findings suggest that countries typically experience a volume reduction of less than 10% during a shortage (Table 5).[89] However, these results obscure very large variations in volume changes between individual products that significantly reduce the relevance of these findings. Some countries even report a net increase in volumes sold across all shortages, despite the data being average over a large number of notifications (Belgium, Portugal). This suggests that the assumptions underlying the analysis do not always hold valid at the product level. A net increase could, for instance, occur when demand rapidly increases, and this increased demand can only partially be met by an increase in supply.

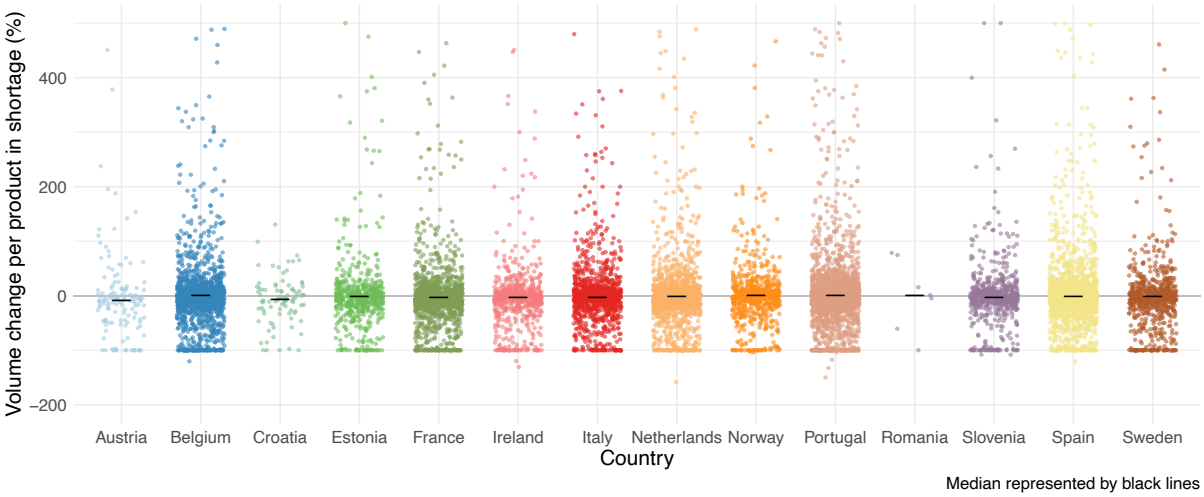
As an alternative measure for how often countries experience very severe shortages, the proportion of products for which the volume decreased to 20% or less of that in the reference period was calculated (Table 5).[90] Such severe shortages were most commonly recorded in Romania and Austria. As with the median volume change, however, the observed pattern cannot readily be accounted for with data from stakeholder observations or other sources.

This analysis assumes all product sold is used to meet patient demand in the national market. However, as indicated previously, some interviewed manufacturers have suggested that in some countries demand is deliberately overstated to create supply surplus that can be parallel traded. It is thus possible that the sales volume in the reference period overstates the true demand and that the gap between supply and true demand during the shortage is less severe than suggested by this analysis. The lack of information about real demand, both in the shortage situation and during the reference period, means that the volume effect analyses may both under- and overestimate the severity of any shortage. Whilst the volume effect analyses findings should thus be interpreted with great reserve, they suggest that even at the country level most shortages do not reach the point of complete product unavailability.

[89] Due to high variability in the data, the median percentage change provides a more accurate representation of the severity of shortages in different countries than the average.

[90] In cases where the same product was reporting in shortage within a country at multiple points in time, the average volume drop-off was used.

Figure 7 Volume change per product in shortage, per country



Source: Technopolis Group, based on sales data from the IQVIA MIDAS database and shortage notifications by NCAs. Volume change calculated as the percentage change in between volume sold in first quarter of a shortage and volume 1 year prior

Table 5 Summary statistics on change in sales volumes for medicines in shortage, per country

Country	# Products	Median volume change (%)	Shortages with volume change to ≤ 20% (%)
Austria	144	-8%	13%
Croatia	88	-6%	8%
France	1,256	-3%	8%
Sweden	734	-2%	11%
Ireland	653	-2%	10%
Slovenia	674	-2%	9%
Estonia	566	-2%	8%
Italy	1,009	-2%	7%
Netherlands	1,417	-1%	8%
Spain	2,056	-1%	7%
Romania	7	1%	14%
Belgium	1,646	1%	9%
Norway	705	1%	8%
Portugal	2,823	1%	7%

An additional dimension to the distribution of shortages is concurrency, i.e. the extent to which a product shortage affects multiple countries at the same time. To account for some differences in the exact time at which a shortage was notified, a concurrent shortage is hereto defined as a situation whereby a product was notified as being in shortage in four or more countries within the same quarter. By this definition, concurrent shortages happened in 46 instances and affected, on average, 4.7 separate countries at a time.[91] In 17 instances, the shortage even affected five or more countries, showing that such wide-spread shortages, whilst relatively rare, do occur. One of the most wide-spread shortages concerned Desmopressin (deamino D-arginine vasopressin, DDAVP), an anti-diuretic hormone: in Q3 2020 this product was reported as being in short supply in seven different countries. Similarly wide-scale shortages were observed for the antibiotic Dalacin (clindamycine), the anti-inflammatory agent Medrol (methylprednisolon), growth hormone Genotropin (somatropin), the antifungal Diflucan (fluconazole) and the antidepressant Zoloft (sertraline), which likewise

[91] As indicated in Section 2.5, the way in which separate products have been identified in the aggregated data set likely underestimates concurrency.

affected 14 countries with repeated supply disruptions in multiple quarters per product between 2017 and 2020. The majority of concurrent shortages were observed in the first quarter of 2020.

The countries that were most often affected by concurrent shortages are Belgium (30 products), Portugal (28 products), and Sweden (24 products). This indicates that when a shortage situation arises due to problems that affect the global supply levels, these countries are most likely to be affected. The most common concurrent shortages are those simultaneously affecting Belgium and Portugal (n=28), followed by shortages in Sweden on the one hand and Portugal (n=20), Ireland (n=19), Norway (n=18) or Belgium (n=17) on the other (Annex E, Table 35). Beyond this, the number of concurrent shortages is too low for identification of clear clusters of countries. Whilst the analysis of concurrency shows that shortages do, on occasion, affect a significant number of countries, it also shows that this situation is relatively rare: concurrent shortages represent just 0.2% of all products reported in shortage (22.5K).

Jointly, the analyses of impact on sales volume and concurrency of shortages indicate that it is very rare for any medicine to be completely or even largely unavailable everywhere in the EU. Rather, there is a significant inequity in how shortages and their impact are distributed. This is consistent with the observations made by NCA representatives and healthcare professionals that, even when the supply disruption itself is caused by issues that happen outside of the country, the severity and duration of shortages are influenced by local factors, such as national pricing and tendering policies, causingsome countries to be preferentially supplied over others. The role of national policies and economic factors as a cause of shortages is further discussed in Section 5.3.

4.7.2. Duration of shortages

It is useful to distinguish between short and more sustained shortages as they may differ in their root causes. Longer shortages may be more likely to be caused by manufacturing and quality issues, as these sorts of issues can take weeks or even months to be resolved. By contrast, shortages that are caused by, for instance, supply quotas or incorrect forecasting may be resolved more quickly as they reflect problems with local availability rather than with overall supply. Indeed, various stakeholders have argued that many shortages can be rapidly resolved by redistributing available supplies, either locally or between countries. Representatives of MAHs even suggest that these situations should not be considered real shortages and that their mandatory notification creates an unnecessary burden on the suppliers as well as on the national authorities tasked with recording and management of shortages.

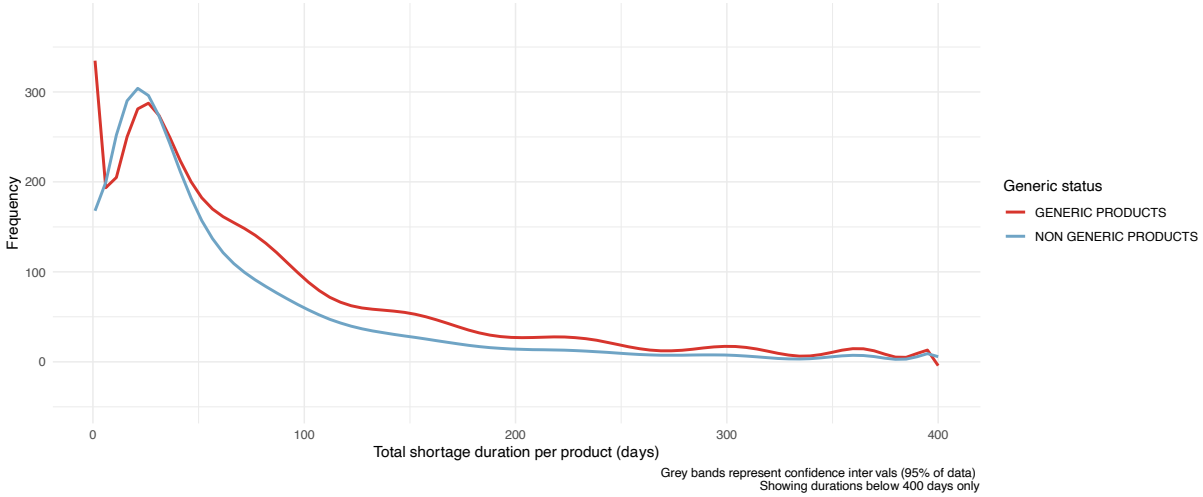
To fully understand the typical duration of a shortage and the possible association between shortage duration and root cause, shortage duration was analysed based on information provided in the national shortage registries regarding start and end dates. It is found that the average duration across all notifications was 137 days (Figure 8) and that 66% of all notifications were resolved within the first three months. The minimum length of shortage was one day, the maximum duration was approximately 13.5 years and is associated with Amoxicillin which went into shortage in Spain in September 2005 and was in shortage until March 2019.[92] While a shortage of this duration is likely to be associated with a withdrawal, Spain did not report this particular shortage as such.

As discussed in the limitations to this study, these observations should be interpreted with some caution as the analysis does not account for multiple shortages of the same product recurring within days of each other (intermittent shortages). There is also possible bias caused by underreporting of shortages with short duration, as well as different thresholds on minimal duration for mandatory notification between Member States. In practice, patients and pharmacists may experience much longer periods of product unavailability than these data suggest. Nonetheless, the quantitative information is consistent with the results from the online surveys: 57% of NCA respondents indicated that most shortages are resolved within days.

Generic medicines remain in shortage on average for 20 days longer than non-generic medicines (125 days vs 104 days) (Figure 8). Shortages of non-generic medicines are slightly more often resolved within the first 30 days (35% of notifications vs 27% of notifications). Whilst the differences are relatively small, they suggest underlying differences in the causes for the shortage. For instance, non-generic medicines include patent-protected (single source) medicines, which are more typically the subject of industry-imposed supply quota than generic medicines. Shortages due to quotas are normally quickly resolved once a new supply period begins. However, as supply quotas are not identifiable in the collected data as a root cause of shortages, it is not possible to further test this hypothesis.

[92] Shortage notifications linked to temporary or permanent market withdrawals were excluded from shortage duration calculations.

Figure 8. Distribution of shortage duration in days for generic and non-generic medicines



Shortages that were reported as having been caused by an 'unpredicted major event or natural disaster' were typically resolved fastest (66 days) (Table 6).[93] It is worth noting that many of the notifications in this category represent shortages that were linked with the COVID-19 outbreak (which is considered an unpredicted major event) and that could equally be considered a form of unexpected increased demand.

Shortages linked to unexpected demand increases, distribution issues or regulatory issues were, on average, resolved within two to four months. Supply problems resulting from issues with quality or manufacturing generally lasted around 3.5 months). Even after excluding product withdrawals, shortages attributed to commercial reasons took longest, lasting over 6 months on average. This is not entirely surprising as commercial and market factors typically do not often drastically change.

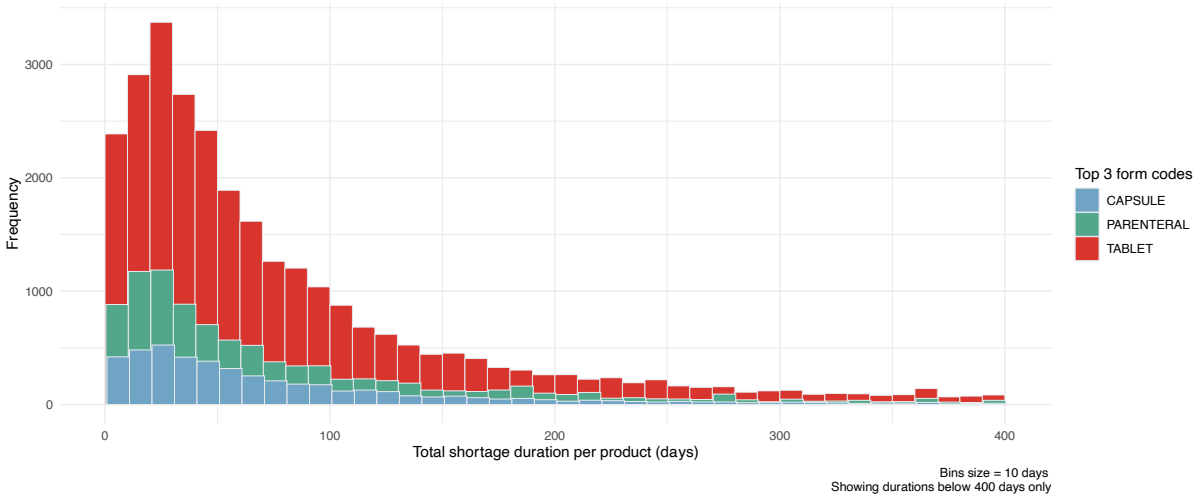
Table 6 Average shortage duration (days) by reported root causes

SPOC Root Cause	Average shortage duration (days)	Number of shortages notifications
Commercial reasons	186	1,678
Regulatory issue	119	987
Quality or manufacturing issues	106	20,500
Distribution issue	89	13,492
Unexpected increased demand	68	4,207
Unpredicted major event or natural disaster	66	392

Product characteristics themselves could also be associated with shortage duration because of underlying differences in, among others, manufacturing processes, stock levels or storage requirements. For instance, injectable medicines more often require refrigeration and have a shorter shelf-life than tablets. To avoid the risk of wastage, overall stock levels of more perishable products may be lower, resulting in reduced ability to use stock to absorb demand shocks or supply disruptions. These shortages could thus be more sustained. However, analysis of shortage duration by the three most common formulations (tablets, injectables/infusions, capsules) shows no such association (Figure 9). In fact, shortages of injectables/infusions are somewhat more often resolved within the first 20 days than those of capsules or tablets.

[93] Products that were listed by the NCA as having been temporarily or permanently withdrawn were excluded from this analysis as in these situations the manufacturer is not actively working to resolve the shortage.

Figure 9 Shortage duration in days, by 3 most common forms



4.7.3. Product criticality

Improved understanding of the impact of product shortages on patients, and thus of how to devise appropriate strategies to prevent them or mitigate their impact, benefits from being able to distinguish between critical and non-critical medicines. In 2016, the EMA issued guidance to Member States on how to classify medicinal products as 'critical' in the context of shortages due to GMP non-compliance or quality defects.[94] It states that criticality of a product depends on therapeutic use and the availability of alternatives. A medicinal product for human use can be considered critical if it is "an integral part of the treatment for or prevention of a disease, which is life-threatening or irreversibly progressive, or without which the public health could be severely harmed" and in case no appropriate alternatives are available. Following this guidance, among the 112 ongoing notifications[95] on the SPOC register as of October 2020 14 (13%) were considered "non-critical, but [having] an impact on public health", whereas 98 (88%) were said to have the "potential to be considered critical". Unfortunately, just a few national shortage registries contain such information about product criticality. In France, all shortage notifications are collected for medicines considered to be of 'Major Therapeutic Interest" and, since December 2019, the Belgian shortages registry classifies all products by criticality. However, most national registers do not yet contain any information about criticality, therapeutic importance or the availability of alternatives.[96] The accessible variables most closely associated with product criticality are: 1) inclusion on the WHO Model List of Essential Medicines (EML), and 2) therapeutic area (by anatomical classification). Neither variable is without limitations.

Products are placed on the WHO EML not only because of their therapeutic importance but also because of their affordability and potential for use in low-resource settings. This excludes many innovative medicines that are often priced at a premium, despite their potentially high importance to patients. Alternatively, the use of therapeutic area as a proxy for product criticality implies that a medicine's importance is directly associated with the disease area targeted. Whilst it can be argued that some groups of diseases have a more severe impact on the quality of life of a patient than others and that medicines against these diseases are thus of greater therapeutic importance, the relationship between these elements is complex. Potentially life-saving medicines can be found in all or most therapeutic areas. Conversely, not all products within a therapeutic area have the same therapeutic importance. Thus, neither variable on its own should be seen as a true measure of criticality. Moreover, these variables do not consider whether appropriate substitutes are available.

[94] European medicines Agency, Inspections and Human Medicines Pharmacovigilance. (17 March 2016) Criteria for classification of critical medicinal products for human and veterinary use. EMA/24304/2016. Available at: https://www.ema.europa.eu/en/documents/other/criteria-classification-critical-medicinal-products_en.pdf. Accessed 3 August 2021.

[95] The register contains 134 records. Active notifications exclude those that are categorized as "expected to or has been withdrawn".

[96] According to the EMA guidance, the assessment of therapeutic importance or the availability of appropriate alternatives should be "supported by literature and EU treatment guidelines and/or recommendations of physicians' / other healthcare professionals' organisations, if available" and should consider several caveats. This assessment should thus be done on a product-by-product and country-by-country basis by hereto qualified professionals and is beyond the scope of this study.

Out of all reported medicines in shortages, 33% have been included on the WHO EML compared to 23% of non-shortage products (

Table 7). One of the most frequently reported shortages of medicines on the EML includes the common non-prescription pain reliever aspirin. A contributing factor to this may have been the COVID-19 outbreak. Soon after the outbreak reached Europe, countries began reporting surge demand for over-the-counter pain relief and anti-inflammatory medicines resulting in supply problems.[97] Within the analysed data set shortages of aspirin have occurred at various points in time, including but not limited to that around the onset of COVID-19.

Notwithstanding their obvious importance to patients seeking to relief the symptoms of an infection or other ailment, shortage of over-the-counter medicines are typically not life-threatening. As such, this observation underlines that the criticality of a medicine is best defined by other criteria. Consulted stakeholders have indicated that many Member States have begun compiling their own national lists of critical medicines, or are considering doing so, to put in place measures aimed specifically at safeguarding their supply. In survey responses, representatives for the national authorities of Germany, Slovakia and Spain mentioned having implemented a national list of essential medicines and medicines at high risk of shortage. Eight other countries reported that they are considering this.[98]

Table 7 Distribution of products in IQVIA by shortage status and EML inclusion

Type of product	Included on the EML
Shortage products	33% (7,508 out of 22,487)
Non-shortage products	23% (38,575 out of 169,851)

Information was also requested from the national competent authorities about the existence of appropriate substitutes for medicines in shortage. However, only Belgium, Austria and Italy were able to provide such information, reporting alternatives were available for 7%, 59% and 77% of notifications respectively. Consequently, comprehensive analysis of product criticality based on potential substitution with appropriate alternatives was not possible.

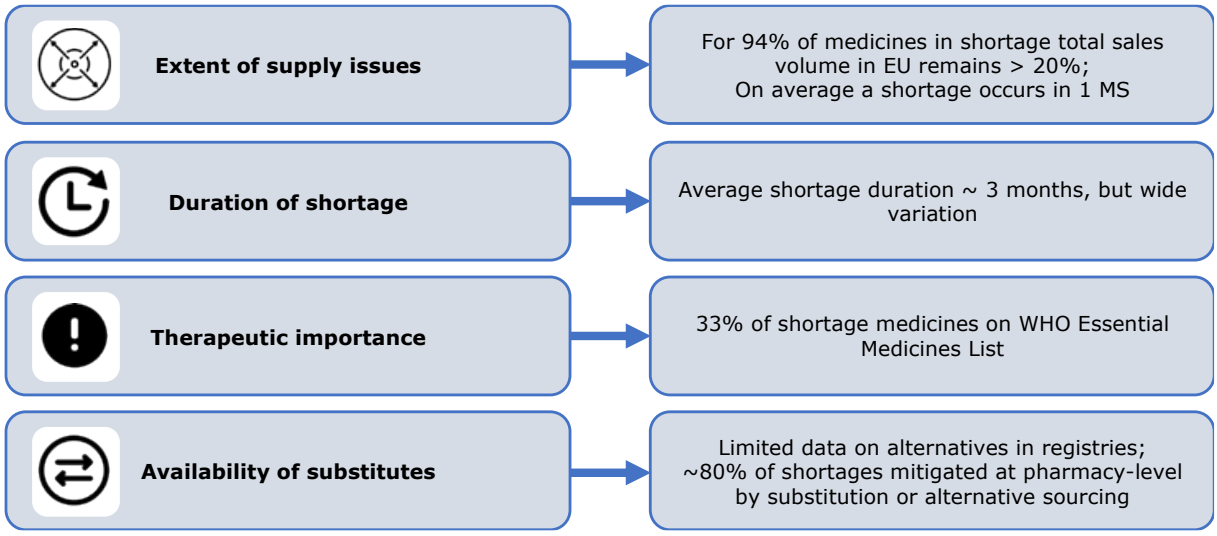
Interviewed and surveyed pharmacists have suggested that approximately 80% of all shortages do not pose a critical problem to patients as they can be either resolved quickly because the product can be sourced from elsewhere or because their impacts can be mitigated by dispensing an appropriate alternative. At the same time, they indicate that criticality criteria are important in the assessment of a shortage notification and thus should be better defined and reported to allow early identification of critical shortages that can have a detrimental effect on the patients.

Overall, the shortage registries offer very limited insight into the criticality of product shortages and their impact on the quality and continuity of treatment to patients (Figure 10). Whilst in some countries there are initiatives to integrate relevant information into the national shortage registries, this is not yet done on a wide scale. Available data on the extent of shortages (in terms of availability and duration) and anecdotal information from pharmacists suggests that most shortage situations can be addressed without serious harm to the patient, even if they cause significant inconvenience to both the patient and the health professionals involved. Nonetheless, shortages do also regularly affect products for which there may not be any appropriate alternatives. At present, most national registries do not identify these most critical products.

[97] For instance: Wood Z, Butler S. (12 March 2020) Coronavirus triggers sharp rise in price of pain relief medication. The Guardian. https://www.theguardian.com/world/2020/mar/12/coronavirus-triggers-sharp-rise-in-price-of-pain-relief-medication. Accessed 16 June 2021.

[98] Austria, Belgium, Estonia, Finland, Iceland, Latvia, Poland and Sweden.

Figure 10 Summary of outcomes on criticality of shortages



Summary

Notified shortages have strongly increased over the last five to ten years. Although this increase can be partially explained by more widespread and better notification, it also reflects a real increase in the number of times a pharmacist is not able to offer a patient their preferred medicine. However, most shortages are localised and some countries are more often and more severely impacted than others, pointing towards issues with inequitable distribution and access.

Shortages can arise for any type of medicine, but those at highest risk include pain relief medication, antihypertensives, anti-infectives and oncology medicines. Most shortages involve older, off-patent and generic medicines, which has been widely attributed to the low profit margins associated with these products. Although for most products in shortage an alternative may be found through, for instance, generic substitution or importation, for approximately a quarter of cases the product in shortage may represent the only available version. The national shortage registries, however, offer very limited insight into the criticality of product shortages and their impact on the quality and continuity of treatment to patients.

5. ROOT CAUSES OF SHORTAGES

Key to the prevention of shortages and mitigation of their impacts is a proper understanding of their root causes. This chapter therefore explores answers to the following study questions:

- According to stakeholders, what are the main reasons for shortages?
- What are the root causes of shortages in the EEA?
- Are the root causes different depending on the type of medicine in shortage?

Various analyses of the causes of shortages already exist. For instance, in October 2019, the FDA published an analysis that identified three main root causes of shortages: 1) a lack of incentives for manufacturers to produce less profitable medicines; 2) failure by the market to recognise and reward manufacturers for having mature quality systems; and 3) logistical and regulatory challenges that make it difficult for the market to recover from a disruption.[99] That same year, the French Prime Minister received a report on the situation in France that included its own analysis of root causes. It signals problems with the production of active ingredients and raw materials, as well as with manufacturing of finished products. Similar to the FDA report, economic reasons are also identified as another main driver of shortages.[100] Numerous industry groups[101] and professional pharmacy organisations[102,103] have offered their own position papers and reports on the root causes of shortages. Collectively, such reports paint a varied picture of factors along the entire pharmaceutical supply chain that can lead to shortages.

To better understand the circumstances that contribute to product shortages in their countries, NCAs may ask MAHs and wholesalers to submit information about the causes of the shortages along with the notification, and to indicate what steps are being taken to solve the issues. Out of the 14 countries for which NCA representatives completed the study survey, eight indicate recording root causes in their reporting system (six according to their own definitions of root causes and two in line with SPOC definitions).[104] In the data at our disposal, 15 out the 22 countries who reported shortage data have begun systematically collecting information on the causes of specific shortages.[105] Some request this information using predefined categories of root causes. However, this has at times posed challenges when these categories are not sufficiently granular. For instance, in Sweden it was reported that, in a previous iteration of the reporting system, nearly all respondents selected 'other' as the root cause. Consequently, it was decided to expand the list of options, remove the 'other' category, and offer the possibility to add information in free form. Even when root causes are reported using a categorisation scheme, these schemes are not standardised between Member States, complicating sharing of information and comparative research. To improve this situation, in 2019 the SPOC

[99] U.S. Food and Drug Administration (2019). Drug Shortages: root causes and potential solutions. Available at: https://www.fda.gov/drugs/drug-shortages/report-drug-shortages-root-causes-and-potential-solutions.

[100] Biot J, Benhabib A, Ploquin X. (2019) Rapport au Premier Ministre: mission stratégique visant à reduire les pénuries de medicaments essentiels. Available at: https://www.vie-publique.fr/sites/default/files/rapport/pdf/274702.pdf.

[101] In 2019, the Association of the European Self-Medication Industry (AESGP, manufacturers of non-prescription medicines, food supplements and self-care medical devices), Affordable Medicines Europe (formerly the European Association of Euro-Pharmaceutical Companies, licensed parallel distribution industry), the European Industrial Pharmacists Group (EIPG, pharmacists employed in the pharmaceutical or allied industries), the European Federation of Pharmaceutical Industry associations (EFPIA, R&D based pharmaceutical industry), the European Healthcare Distribution Association (GIRP, wholesalers-distributors), Medicines for Europe (generic medicines industry) and Vaccines Europe (vaccine producing industry) have jointly published a position paper *medicines shortages: root causes and potential solutions*. Available at: https://www.efpia.eu/media/413378/addressing-the-root-causes-of-medicines-shortages-final-051219.pdf.; In January 2021 the European Fine Chemicals Group offered the European Commission its report on a study on the risk of (future) shortages associated with factors in the upstream pharmaceutical value chain. The executive summary of this study is publicly available at: https://efcg.cefic.org/mediaroom/iqvia-for-efcg-executive-summary/.

[102] European Association of Hospital Pharmacists (revised version adopted in June 2019). EAHP Position Paper on Medicines Shortages. Available at: https://eahp.eu/sites/default/files/eahp_position_paper_on_medicines_shortages_june_2019.pdf.

[103] Académie nationale de Pharmacie. (2018) Rapport de l'Académie nationale de Pharmacie: Indisponibilité des medicaments. Available at: https://www.acadpharm.org/dos_public/2018_06_20_AnP_RAPPORT_INDISPONIBILITE_MED_VF1.pdf

[104] Belgium, Denmark, Germany, Ireland, the Netherlands and Portugal classify causes using their own definitions; Finland, Germany and Spain use classifications based on the SPOC definitions; Austria, Estonia, Latvia, Slovenia and Sweden do not record root causes.

[105] These countries are Austria, Belgium, Croatia, Estonia, France, Hungary, Iceland, Ireland, Italy, Netherlands, Norway, Portugal, Romania, Spain and Sweden.

network introduced a root causes classification scheme, comprising eight categories.[106] For this study, available data on root causes from the national shortage registries conducted were recoded against the SPOC classification (Table 8) to facilitate analysis across all included countries.

Table 8 SPOC Network definitions and classification of different shortage root causes

SPOC classification	Definition
Quality issues	Unforeseen disruptions within the manufacturing process leading to quality defects (API or finished product), including recalls.
Manufacturing issues	Unforeseen disruptions within the manufacturing process caused by GMP compliance problems (API or finished product). Manufacturing issues also include capacity issues.
Regulatory issues	When requirements or obligations relating to the grant of the authorisation have not been fulfilled after authorisation and 'placing on the market', e.g. Brexit. Failure to implement safety features, i.e. MAH failure to implement the unique identifier and the tamper evident features on the pack are also considered regulatory issues.
Safety and efficacy issues	If the medicinal product lacks therapeutic efficacy (or decrease efficacy), there are new safety risks identified requiring precautionary action, or the risk-benefit balance of the medicine is no longer favourable.
Unpredicted major events or natural disasters	May indirectly lead to shortages of medical products, e.g. the ongoing swine fever in China or the earthquake in Japan in 2011
Unexpected increased demand	Due to previous defects, due to market cessation/shortage of alternative products (e.g. generics), due to great awareness about a specific disease prevention or new treatment guidelines and/or recommendations of physicians'/veterinarians'/other healthcare professionals' organisations, change in reimbursement conditions, change in epidemiology
Distribution issues	Distribution channel structures, parallel trade or export to outside of the EU, quotas, supply chain policy (e.g. DTO), logistic issues
Commercial reasons	Company-driven decisions linked to business aspects such as pricing negotiations; discontinuation; change in reimbursement status; low sales (i.e. low number of patients); business strategies prioritising other markets.

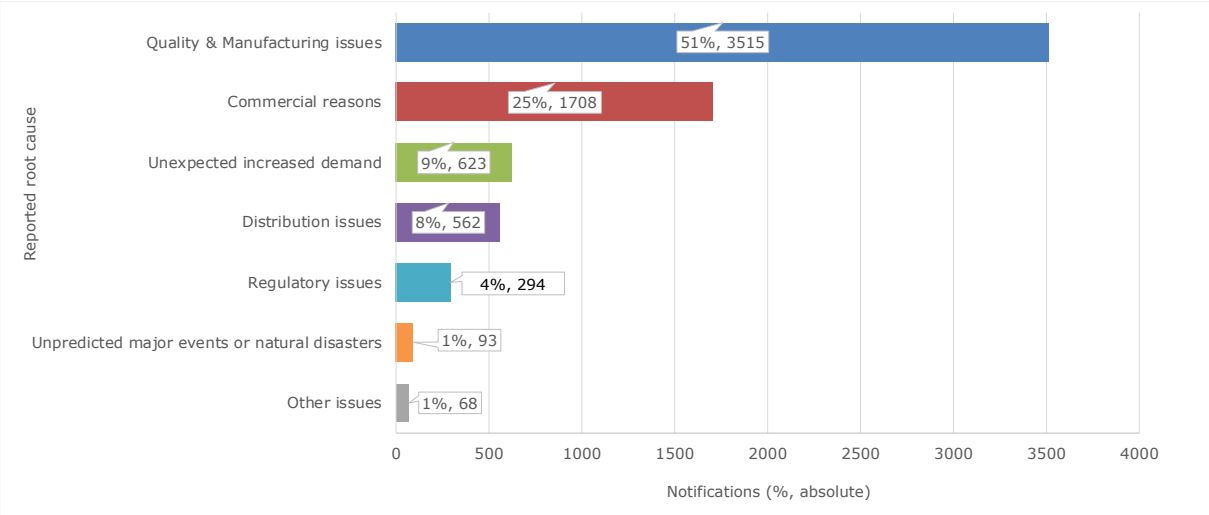
Source: List of definitions and classification of different shortage root causes provided by the SPOC network (HMA/EMA (22 January 2020). Annex 1 – List of definitions and classification of different shortage root causes. EMA/912132/2019 Rev.3.).

[106] HMA/EMA (22 January 2020). Annex 1 – List of definitions and classification of different shortage root causes. EMA/912132/2019 Rev.3.

5.1. Reporting of root causes

In total, information on the root cause of the shortage was provided for 6,863 shortages. By far the most often recorded cause relates to quality and manufacturing issues (51%)[107] (Figure 11). Commercial reasons, which have previously been noted as a prevalent root cause of shortages in Europe[108], were the second most common reported root cause (25%). Both observations are discussed in more detail later in this section.

Figure 11 Reported root causes of medicine shortages (SPOC categorisation)



Source: Technopolis group, based on data from national shortage registries for Austria, Belgium, Croatia, Denmark, Estonia, France, Iceland, Hungary, Ireland, Italy, Netherlands, Norway, Portugal, Romania, Spain, and Sweden.

A further trend analysis of reported root causes by start year of notification shows that, between 2014 and 2020, (Figure 12):

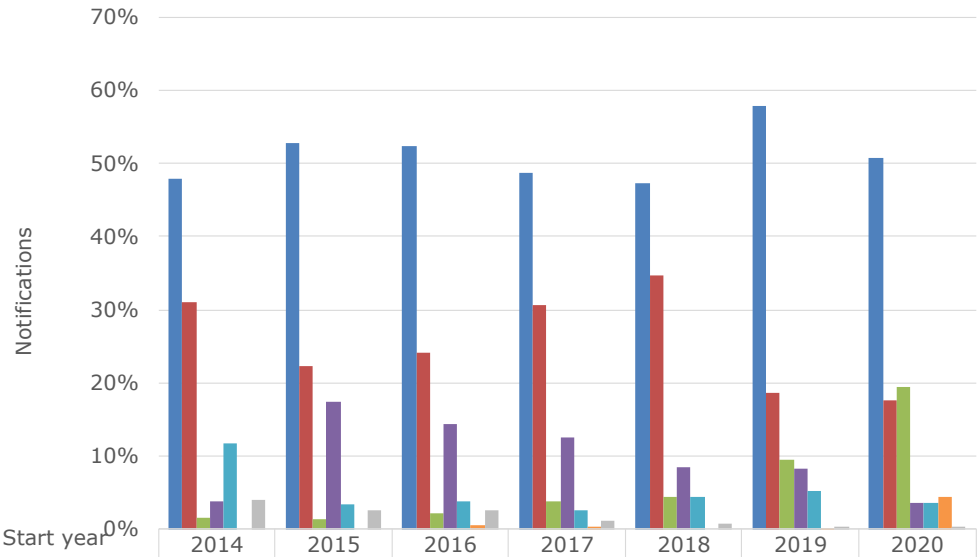
- **Quality & Manufacturing issues** were consistently the main root cause of shortages, accounting for around half of all notifications; the relative contribution remained between 48% and 58% of all notifications.[109]
- **Commercial reasons** as a reported cause of shortages strongly increased between 2015 and 2018 up to a third (31%) of all notifications; this has since declined again to around a fifth (18-19%) of notifications.
- **Unexpected increased demand** strongly increased as a reported root cause in 2019 and 2020, becoming the second most reported reason (19%). For 2020, this includes the effects of COVID-19 (see also Section 5.8)
- **Distribution issues** have steadily declined as a reported root cause of shortages since 2015.
- **Regulatory issues** have never been responsible for more than 5% of notifications (with a reported root cause) since 2015.
- Until 2019, **unpredicted major events or natural disasters** had been reported only sporadically as a root cause of shortages; however, 2020 saw a noticeable increase in reporting of this cause following the COVID-19 outbreak (see also Section 5.8)

[107] The current SPOC classification of root causes differentiates between quality and manufacturing issues. However, this distinction was not made in the same way before November 2019 and thus some entries had been classified as 'quality/manufacturing issues'. Moreover, in some of the NCA reporting, the information provided on the cause of the shortage is not always sufficiently detailed to establish whether the issue is one of quality or of manufacturing. Therefore, these have here been grouped. In future, however, the SPOC classification encourages countries to report the issues separately.

[108] Scholz N. European Parliamentary Research Service (April 2020) Addressing shortages of medicines. Available from: https://www.europarl.europa.eu/RegData/etudes/BRIE/2020/649402/EPRS_BRI(2020)649402_EN.pdf.

[109] All percentages reported as a share of all notifications for which a root cause was included in the reporting.

Figure 12 Time trends in reported root causes of shortages (2014-2020)



	2014	2015	2016	2017	2018	2019	2020
Quality & Manufacturing issues	48%	53%	52%	49%	47%	58%	51%
Commercial reasons	31%	22%	24%	31%	35%	19%	18%
Unexpected increased demand	2%	1%	2%	4%	4%	10%	19%
Distribution issues	4%	17%	14%	13%	9%	8%	4%
Regulatory issues	12%	3%	4%	3%	4%	5%	4%
Unpredicted major events or natural disasters	0%	0%	1%	0%	0%	0%	4%
Other issues	4%	3%	3%	1%	1%	0%	0%

Source: Technopolis Group, based on notifications in national shortage registries. Share expressed as the number of shortages reporting a particular root cause relative to all shortages with a reported root cause that year. The period 2014-2020 was chosen as prior to this, information on root causes was too sporadic for proper trend analysis.

A more detailed analysis of root causes was possible only for notifications from Ireland and Portugal as other countries did not provide sufficiently granular data.[110] Here, the two most frequently detailed causes involved changes of manufacturers or manufacturing sites (n=40) and increased demand for a product in other countries (n=35) (Table 9). Whilst these findings cannot directly be extrapolated to other Member States, they offer a somewhat more fine-grained understanding of what issues can contribute to shortages. They suggest, for instance, that there is an increased risk of manufacturing issues when a new manufacturing site is used and that the effects of increased demand in one country can have a knock-on effect in another.

Table 9 Top-10 Detailed root causes of shortages, as reported in Portugal and Ireland

Detailed root cause	SPOC classification	Reports
Change of manufacturer/manufacturing site	Quality/Manufacturing issue	40
Increased demand in another country	Increased demand	35
Shipping delay	Distribution issue	24
Batch rejected	Quality/Manufacturing issue	18
API unavailable or in shortage	Quality/Manufacturing issue	17
Discontinued	Commercial reasons	16
Low market potential/demand	Commercial reasons	15
Incorrect forecasting/sales planning	Commercial reasons	10
Manufacturing delay	Quality/Manufacturing issue	5
Receiving API delayed	Quality/Manufacturing issue	4

Source: Technopolis Group, based on data provided by the NCAs of Portugal and Ireland. Notifications have been indicated only as absolutes as, even within these data sets, most notifications did not contain this level of detail. It thus cannot be

[110] Some other countries also included additional (free form) information, but this was done only very sporadically.

ruled out that other notifications have similar causes, meaning that it is not known if these individual reports are an accurate representation of all notifications in the included data sets.

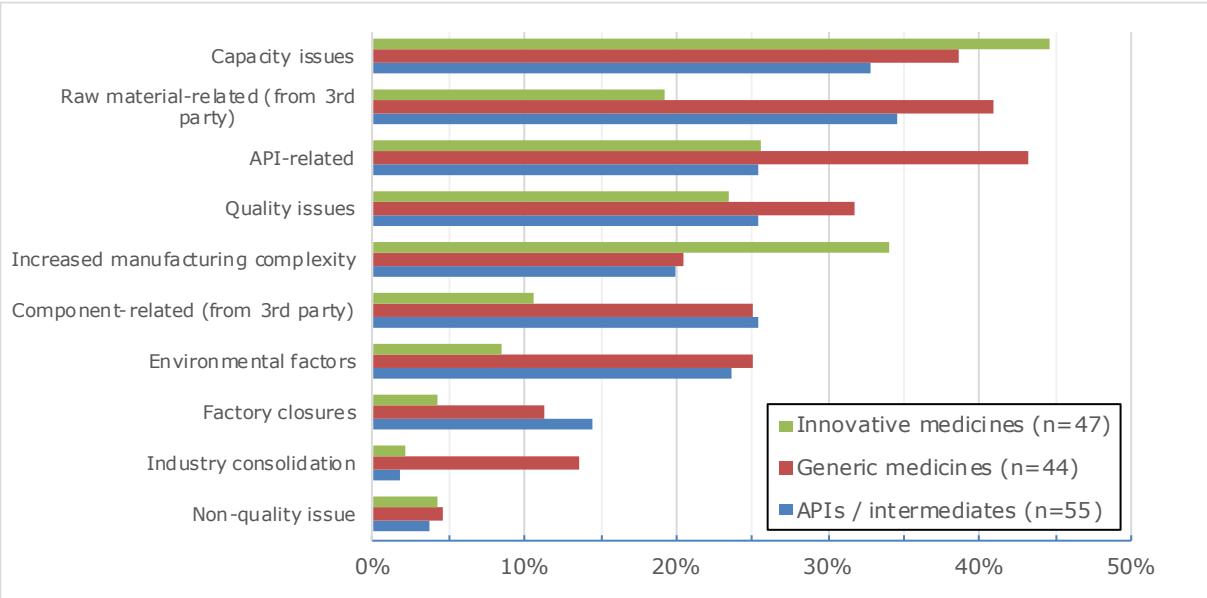
5.2. Quality and manufacturing issues

The observation, based on data from the national shortage registries, that quality and manufacturing issues are among the leading causes of shortages is supported by information obtained from stakeholders via interviews and surveys. Nearly all (90%) survey respondents from NCAs, as well as pharmaceutical wholesalers or distributors (96%) report manufacturing issues as one of the three main reasons for product shortages (Figure 29, Figure 79). Their views are shared, albeit to a somewhat lesser extent, by many (60%) pharmaceutical manufacturers.

Many pharmaceutical manufacturers report having experienced problems with manufacturing capacity as well as with sourcing of APIs, raw materials, and other components (Figure 13). These latter problems are reported more with the production of generic medicines than of innovative medicines, indicative of different structures of the respective supply chains. A recent analysis performed for the European Fine Chemicals Group indicates that most of the innovative APIs are still manufactured in Europe but that price pressures on generic manufacturers have pushed these companies towards lowest price API suppliers, most of which are based outside of Europe.[111] Most countries did not provide data on where APIs for products in shortage were sourced; consequently, this study could not independently assess the association between location of API production and shortages.

Producers of innovative medicines more often reported supply problems due to increased manufacturing complexity. Significant supply disruptions due to non-quality related issues (e.g. mechanical or software failure during manufacturing) or factory closures appear to be relatively uncommon.

Figure 13 Manufacturing-related factors that have affected the ability of manufacturers to ensure appropriate and continued supply



Source: Technopolis Group, based on survey responses by manufacturers (and industry associations representing manufacturers) of APIs/intermediates, generic medicines and innovative medicines. Respondents were asked to select up to five factors (not limited to manufacturing) that had most affected their ability to ensure appropriate and continued supply.

Most (70%) NCA representatives have linked shortages also to quality issues and batch recalls. This view is shared by a significant number of manufacturers (40% of API/finished products manufacturers, 45% of generics manufacturers, 37% of innovative manufacturers). Some note in their open comments that quality issues should be distinguished from batch recalls. They furthermore

[111] EFCG. (December 2020). EU Fine Chemical Commercial KPI: Executive Summary. Available at: https://efcg.cefic.org/wp-content/uploads/2021/06/20201211_IQVIA-for-EFCG_Executive-summary.pdf.

highlight that delays in the quality control process – rather than actual quality problems – can be a cause of shortages.

The pronounced role of manufacturing issues as a cause of shortages raises the question of whether there is a relation between specific types of products and the cause of their shortage. A proper understanding of such a relationship could inform the design of more targeted solutions. If, for instance, manufacturing issues are most closely associated with shortages of injectable medicines, this could argue in favour of additional scrutiny of the manufacturing of these types of products. Alternatively, if shortages of anti-infective medicines show a clear link to problems with sourcing of APIs, there is a case for diversifying sourcing of APIs for this group of medicines.

To determine the association between the causes of shortages and product characteristics, the reporting of each root cause in a specific therapeutic class (Level 1) relative to the reporting of this cause across all notifications was determined (Table 10).[112] Reporting of quality/manufacturing issues was somewhat more often associated with cardiovascular medicines (ATC C), systemic hormonal preparations (ATC H) and dermatologicals (ATC D). However, these associations are weak and, overall, there is no apparent association between quality/manufacturing issues and therapeutic area. This may, in part, be caused by the high level of aggregation used in this analysis, which does not distinguish between quality issues and manufacturing issues and does not differentiate between various types of manufacturing issues. This renders the category of a 'catch-all', possibly underlying patterns. A better separation between quality issues on the one hand and manufacturing issues on the other in the data reported by NCAs (as suggested by the current SPOC classification of root causes) may allow identification of clearer patterns.

Table 10 Association between quality/manufacturing issues as root cause of shortages and therapeutic area

ATC1	Relative frequency	# shortages	ATC1	Relative frequency	# shortages
C	1.17	936	**S**	0.99	227
H	1.08	125	**G**	0.98	442
D	1.07	365	**M**	0.97	447
P	1.03	34	**B**	0.96	197
N	1.01	1,393	**J**	0.89	819
L	1.00	415	**K**	0.89	110
T	1.00	49	**R**	0.87	523
A	0.99	711	**V**	0.81	70
Total					**3,515**

Source: Technopolis Group, based on data from national shortage registries. A relative frequency > 1.0 indicates a higher reporting of the root cause within the specific therapeutic relative to representation of the therapeutic class in the data set; < 1.0 indicates lower relative reporting.

Within the data provided by the NCAs, there are 571 shortages that have listed more detailed information that allows quality/manufacturing issues to be linked more specifically to issues with production or sourcing of APIs. These issues are most strongly associated with antiparasitic products (ATC P, relative frequency 2.12)[113], medicines to treat diseases of the sensory organs (ATC S, relative frequency 1.32), cardiovascular medicines (ATC C, relative frequency 1.18) and dermatologicals (ATC D, relative frequency 1.12). It should, however, be recognised that the number of shortages listing any information about underlying quality or manufacturing issues is relatively small (8% of all shortages for which information on root causes has been provided) overall and never more than 112 shortages within any therapeutic area. As a result, small numbers of notified shortages can have a strong effect on the observed relative frequency and associations should be treated with considerable caution. Only a very small number of notified shortages (n=75) contain information whereby it is explicitly stated that the quality/manufacturing issue pertains to the finished product. Overall, however, the available data from national shortage registries are insufficiently granular to draw

[112] Analysis was done by: 1) calculating the proportion (%) of notifications per root cause within each therapeutic area relative to all notifications for which at least one root cause was listed (variable A); 2) calculating the proportion (%) of all root cause notifications within a therapeutic area relative to all notifications for which at least one root cause was listed (variable B); and 3) calculating the ratio of variable A to variable B. A ratio higher than 1.0 indicates a positive association between therapeutic area and root cause.

[113] Relative frequency calculated as previous.

unambiguous conclusions about whether therapeutic areas are differently affected by quality or manufacturing issues with either APIs or finished products. The classification of root causes proposed by the SPOC network also does not foresee in separate reporting of issues related to APIs or finished products.

Similar analysis for the association between quality/manufacturing issues and product formulation shows that such issues are, in relative terms, somewhat more common for tablets than for other formulations, but differences are small (Table 11). As with the analysis for association between reported root cause and therapeutic area, it is possible that the high level of aggregation used conceals some patterns. For a more fine-grained understanding of quality and manufacturing issues, a further distinction between the different types of issues, as well as more detailed information on where in the manufacturing process (e.g. production of intermediates, filtration & drying, filling and packaging process) issues have occurred could be helpful. At present, such information is collected by some NCAs, typically as free form information, but the information is not standardised and highly incomplete. Some stakeholders in interviews and survey responses have suggested that manufacturing of, in particular, lyophilised (freeze-dried) products for injection is relatively more prone to problems. The lyophilisation process itself is considered complex and challenging.[114] The lack of more detailed data on quality and manufacturing issues, however, does not allow this finding to be corroborated with information from national shortage registries.

Table 11 Association between quality/ manufacturing issues as root cause of shortages and formulation

Form	Relative frequency	# Shortages
Tablet	1.05	1,558
Topical	1.00	304
Injectable/infusion	1.00	804
Capsule	0.97	291
Lung	0.96	54
Ophthalmic	0.96	103
Oral liquid	0.88	273
Rectal systemic	0.79	39
Total		**3,426**

Source: Technopolis Group, based on data from national shortage registries. Only the eight most common formulations (n=3,426) are included as for others the occurrence is too low for meaningful interpretation of the results.

5.3. Commercial reasons

A substantial number of notified shortages (25%, n=1,708) have been attributed to 'commercial reasons', including product discontinuations. Most of these involve nervous system medicines (ATC N, n=301), anti-infectives (ATC J, n=215) and oncology medicines (ATC L, n=197). However, this is largely in line with their expected relative frequency and does not signal greater issues with the commercial viability of these product classes than with others (Table 12). Some consulted stakeholders, in interviews and survey responses, have nonetheless suggested that cheap, older oncology medicines are at increased risk of shortage because of economic reasons. This view is also supported by a 2014 study comparing the causes of shortages between oncology medicines and all medicines, as reported by surveyed hospital pharmacists.[56,115]

[114] Mirasol F. (1 January 2020) Lyophilization presents complex challenges. BioPharm International 33(1): 22-24. Available at: https://www.biopharminternational.com/view/lyophilization-presents-complex-challenges. Accessed 6 August 2021.

[115] Boshnakova A, Karnad A. (2017) Cancer medicines shortages in Europe: policy recommendations to prevent and manage shortages. The Economist Intelligence Unit. Available at: https://www.eiu.com/graphics/marketing/pdf/ESMO-Cancer-medicines-shortages.pdf.

Table 12 Association between commercial reasons as root cause of shortages and therapeutic area

ATC1	Relative frequency	# Notifications	ATC1	Relative frequency	# Notifications
R	1.39	181	**J**	1.05	215
K	1.24	34	**L**	0.97	100
T	1.23	15	**S**	0.96	54
M	1.20	133	**H**	0.90	28
B	1.16	57	**N**	0.87	301
D	1.13	103	**G**	0.81	89
A	1.11	197	**C**	0.76	177
V	1.09	19	**P**	0.59	5
Total					**1,708**

Source: Technopolis Group, based on data from national shortage registries.

Given the high-level nature of most of the reporting of root causes, the data from the national shortage registries offer very little insight into the precise underlying issues that influence a product's commercial viability or the MAH's decision to discontinue a product in a particular market. The somewhat more detailed data for Portugal and Ireland include notifications linked to product discontinuation (n=16), low market potential/demand (n=15), incorrect forecasting or sales planning (n=10) and being unable to market (n=2).

It should be noted that reliance on reporting to NCAs of 'commercial causes' as a root cause for notified shortages may underestimate the true role of economic factors. This is because even when the stated root cause of a shortage is an issue 'upstream' in the pharmaceutical value chain, such as the unavailability of APIs for manufacturing, the consequences of this issue may be felt differently across countries depending on national economic and market structure factors. For instance, **national procurement practices** can have a major impact on product availability and resilience against supply disruptions. Procurement practices whereby tenders are primarily evaluated on price, without consideration for other issues such as multi-sourcing, may force prices down to the level where it is no longer attractive for potential bidders to remain in a market. This reduces the competition and leaves markets vulnerable when remaining suppliers experience disruptions. A similar effect can be seen with "winner-takes-all" tenders, whereby the winning bidder becomes the sole supplier to a market for a given period for a specific product. Losing tenderers may decide to stop production (and potentially not renew the marketing authorisation) for that medicine all together as their market share has become too small to be economically attractive. This again has the effect of thinning out competition, leaving the market dependent on a single or only a few suppliers and reduces the absorptive capacity in case of demand shocks or production problems.

Differing practices between countries can also have distorting consequences as efforts to prevent or respond to shortages in one country may have the unwanted by-effect of increasing (the risk of) shortages in another. For instance, tenders that include **financial penalties** to suppliers for failure to meet their supply obligations can result in suppliers preferentially serving those markets at the expense of markets that impose no or lower penalties. Among surveyed generics manufacturers, 23% (10 out of 44) responded that penalties due to non-compliance with delivery agreements had affected their ability to supply, even though they indicated that the impact of this on their operations had been relatively low. Manufacturers of innovative medicines did not find that these penalties had any impact on their ability to supply. Although penalties can, in principle, be applied also on wholesalers if they fail to meet their contractual supply obligations, surveyed organisations did not find this to have been the case.

Alongside procurement practices, the **profitability** of a particular product may also affect the likelihood that an MAH will continue to supply a specific market. Many surveyed pharmaceutical manufacturers indicated that insufficient product profitability had affected their ability to supply. This issue was more common among generic manufacturers (n=20, 45%) than among manufacturers of APIs (n=17, 31%) and by far least common among manufacturers of patented medicines (n=5, 11%). This is consistent with remarks made by numerous stakeholders, from different groups, about the often very low profit margins for generic medicines. Patented medicines are typically associated with higher profit margins. Consequently, suppliers of patented medicines are more inclined to take all possible actions to prevent shortages on these profitable products. A more in-depth discussion of shortages caused by permanent market withdrawals is provided in Section 5.7.

5.4. Unexpected increased demand

Data from the shortage registries indicate that unexpected demand increases are another important driver of shortages (9% of notified shortages with reporting of a root cause) that has steadily increased in importance. This observation is confirmed by stakeholders in interviews and survey responses. Among surveyed supply chain actors[116], 65% (153 out of 234) indicated that unexpected demand increases had been among the three most common causes of shortages for their organisation in the past five years. For their part, representatives of NCAs in 10 out of 14 (72%) responding Member States[117] confirmed that such demand increases had been a main source of shortages in their countries in the past five years. According to surveyed pharmacists, the main causes of these sudden changes in demand are the adoption of a new treatment regimen (n=30, 45%) and the introduction of generics or therapeutically equivalent alternatives (n=29, 44%). The specific impacts of COVID-19 on increased demand and product shortages are further discussed in Section 5.8.

The impact of the introduction of new treatment guidelines is most visible when a medicine is suddenly needed in very significant quantities. This happens, for instance when a new vaccine is introduced into a national immunisation programme (NIP). This creates a sudden very large demand increase. Given the lengthy production process for vaccines, absorbing such significant demand shocks takes time. Interviewed vaccine manufacturers have indicated that it is thus essential for manufacturers and the public health organisations responsible for decision-making and implementation of national immunisation programmes to discuss well in-advance the expected supply needs so that manufacturers can anticipate and, where necessary, increase their production capacity.

Demand for a particular product can also surge when other suppliers of the same (or a similar) product leave the market or are temporarily unable to supply, thus leaving others to fill the supply gap. Interviewed manufacturers indicate that it is often not possible to rapidly ramp up production as pharmaceutical production must be planned well in advance and production lines cannot always quickly be retooled.[118] This can create a 'domino' effect whereby products in the same therapeutic group successively experience shortages when supply gaps for one product are filled with another.

Data from the national shortage registries show that between 2005 and 2019 (prior to COVID-19), increases in demand as the reported cause for shortages were relatively most often associated[119] with anti-infectiveantiinfectiveantiinfective products (ATC J), oncology medicines (ATC L) and medicines to treat blood-related disorders (ATC B) (Table 13). No further data were collected that could help interpret these observations. The outbreak of COVID-19 increased demand for other types of medicines, resulting in shortages, as discussed further in Section 5.8.

[116] Manufacturers of APIs/intermediates, generic medicines and innovative medicines; wholesalers-distributors; and parallel traders.

[117] Belgium, Denmark, Estonia, Finland, Germany, Ireland, Latvia, the Netherlands, Portugal, Slovenia and Spain.

[118] More information on complexity of pharmaceutical production planning can be found, for instance, in: Moniz S, Paula Barbosa-Póvoa AP, Pinho de Sousa J (2015). Recent Trends and Challenges in Planning and Scheduling of Chemical-Pharmaceutical Plants. Operations Research and Big Data, p.123-130.

[119] Calculated as the proportion of reporting of the root cause within each therapeutic area relative to the overall proportion of reporting of the root cause.

Table 13 Association between unexpected increased demand as a root cause of shortages and therapeutic area

ATC1	Relative frequency	# Shortages	ATC1	Relative frequency	# Shortages
J	1.80	55	**D**	0.93	13
L	1.64	24	**T**	0.92	2
B	1.41	10	**N**	0.86	42
S	1.31	12	**V**	0.80	2
C	0.98	34	**A**	0.59	15
G	0.95	16	**H**	0.59	3
M	0.93	17	**R**	0.44	9
Grand Total					**255**

Source: Technopolis Group, based on data from national shortage registries.

5.5. Distribution issues

Distribution issues have been reported as a root cause for 8% of all notified shortages for which root causes were indicated. For the few notifications for which more detailed information is provided, this points mainly towards logistical issues. Although the definition of distribution issues offered by the SPOC Network intends to also capture parallel trade[120], quotas and supply chain policy factors, such information is typically not captured in the information in the national shortage registries. As such, parallel export cannot be properly recognised as the root cause of a shortage in the data provided by NCAs.[121]

Among various interviewed stakeholder groups there is nonetheless a strong sense that parallel exports are exacerbating the shortages problem. Some academic literature likewise identifies parallel trade as a contributing factor to shortages in "lower price" countries, including a number of Eastern and Central European countries and Portugal.[115,122]

As discussed in more detail in Section 6.1, various Member States have introduced 'parallel export authorisation lists' with specific medicines for which the export to another EU country is restricted. Around a quarter (n=25, 26%) of surveyed manufacturers of innovative medicines indicated that intercountry stock movements and parallel trade were among the factors that had most affected their ability to ensure supply. This was less common among manufacturers of generic medicines (n=6, 14%). This is consistent with remarks made by interviewed representatives of both types of industry: innovative manufacturers are generally more concerned about the effects of parallel trade than generics manufacturers.

According to Affordable Medicines Europe (AME), the industry association for European parallel traders, the large majority of parallel traded products concern innovative medicines (approx. 95% in EUR sales; approx. 89% in unit sales). AME furthermore estimates that less than 0.7% of the generics market is parallel traded.[123] Paired with the observation that most shortages occur for generic medicines (see Section 4.3), AME argues that parallel trade is unlikely to be a significant driver of shortages. Moreover, the organisation emphasises that many countries already have restrictions in place on the export of critical medicines and that Public Service Obligations (PSO) further ensure that no products are exported beyond the levels required to supply patients in a given Member State. Without further data that could link parallel exports to specific product shortages at the country level, it is not possible to estimate what the precise contribution of parallel export to shortages is. Qualitative evidence from stakeholder interviews, as well as the estimated impact of parallel export restrictions on the frequency of shortages described in Section 6.2, nonetheless suggest that, at least in some countries, parallel exports may contribute to shortages.

[120] In the context of this report, parallel trade is understood exclusively as the import and export of pharmaceutical products between countries *within* the EU/EEA region.

[121] Notifying companies may not be able to independently demonstrate the role of parallel trade in the shortage situation.

[122] Weerdt, E. De et al. (2015) 'Causes of drug shortages in the legal pharmaceutical framework', Regulatory Toxicology and Pharmacology, 71(2), pp. 251–258. doi: 10.1016/j.yrtph.2015.01.005.

[123] Aguiar E, Ernest K (2020). Study of the trade flows of parallel imported medicines in Europe. Affordable Medicines Europe. Available at: https://affordablemedicines.eu/wp-content/uploads/2020/06/Trade-Flow-Study-FINAL-big-file.pdf. Last accessed 6 August 2021.

For their part, parallel traders and wholesale distributors point towards the role of manufacturer supply quotas in causing (temporary) shortages. Most surveyed wholesale distributors (n=61, 80%) indicate that their ability to supply has been affected by supply quotas and restrictions, and that they consider these to be the factor that has most impacted their ability to supply. Nearly all parallel traders (n=23, 96%) agree with this assessment. In its position paper on medicine shortages, AME calls for a ban on 'black-box' quotas (further discussed in Section 8.4) and recommends that supply quotas must be "sufficiently transparent, flexible and justified".[124] According to survey responses by representatives of NCAs, various countries[125] have introduced, or are considering introducing, measures to require industry to provide greater transparency of supply quotas and wholesalers to report transactions to the relevant national authorities.

5.6. Regulatory issues

In the 2019 FDA report on shortages, regulatory challenges are identified as one of the three most important root causes of medicine shortages.[99] By contrast, analysis of reported root causes for notifications in the European national shortage registries finds that no more than 4% of all notified shortages can be traced to regulatory issues. The FDA study, however, clarifies that regulatory factors are not necessarily the direct cause of shortages but rather make it more difficult for markets to recover after a disruption. For instance, when companies – in response to shortage situations – wish to increase their production by modifying or building production sites this requires regulatory approval by competent authorities. Routine variations to the production process, such as when APIs and raw materials are sourced from new suppliers or when a production method is changed also necessitate regulatory approval. When products are marketed in multiple territories or countries, separate approval is required from all relevant competent authorities. Problems with obtaining such approvals were discussed in-depth by interviewed vaccine manufacturers who emphasise that, because vaccines are complex products, variations are very common and often affect many individual licences.[126] When each authority must separately review and approve these changes, this can create long delays before a new production line can be used. Data from the national shortage registries are unable to confirm whether regulatory issues have an especially pronounced impact on vaccines. Only one out of 257 notified vaccine shortages (ATC J7) for which a root cause was provided linked the shortage directly to regulatory issues.[127] As the number of notifications citing regulatory issues is low overall, no conclusive associations can be drawn between regulatory issues and either therapeutic area or form.

A further challenge that is particular to the European context is the diversity of presentations and national labelling requirements across Member States. These can create barriers in mitigating shortages when the movement of products between countries is delayed because medicines need to be repackaged to meet local requirements. European pharmaceutical industry associations thus call for increased regulatory flexibility, including acceptance of multi-country packages in case of confirmed shortages and facilitation of post-approval changes (PACs), to avoid and help mitigate shortages.[101]

5.7. Market withdrawals as a cause of shortages

Alongside disruptions to the global supply chain that may cause shortages, unavailability of products can occur when an MAH decides to withdraw a product temporarily or permanently from a market. Under current EU legislation, companies are not obliged to maintain medicines on a market. According to Directive 2001/83/EC:[44]

- MAHs are required, other than in exceptional circumstances, to give *advance notification* to the relevant NCAs if a product ceases to be placed on the market of a Member States, either temporarily or permanently (Article 23a); and,
- MAHs and wholesalers are required, within the limits of their responsibilities, to ensure appropriate and continued supplies *of marketed products* to cover the needs of patients (Article 81).

[124] Ernest K. (2020) Medicine shortages: position paper. Affordable Medicines Europe. Available at: https://affordablemedicines.eu/wp-content/uploads/2020/06/Position-Paper-on-Medicine-Shortages.pdf. Last accessed 6 August 2021.

[125] Introduced in Germany; under consideration in Estonia, Iceland, Latvia and Portugal.

[126] Vaccines are often produced in a variety of combinations (multivalent vaccines) and presentations, such that changes to one of the antigens can affect numerous separate products.

[127] For the product Fluarix, a vaccine against influenza.

Additionally, Article 123 paragraph 2 of the same Directive obliges the MAH to "*notify* the Member States concerned forthwith of any action taken by the holder to suspend the marketing of a medicinal product, to withdraw a medicinal product from the market, to request the withdrawal of a marketing authorisation or not to apply for the renewal of a marketing authorisation, together with the reasons for such action". Furthermore, according to Article 24 paragraph 5, "when an authorised product previously placed on the market in the authorising Member State is no longer actually present on the market for a period of three consecutive years, the authorisation for that product shall cease to be valid."

However, the provisions of the Directive do not require MAHs to maintain products on the EU market. Consequently, the decision on whether and when to (permanently) withdraw a product from a particular market is at the discretion of the MAH. Market withdrawals may occur over safety or efficacy concerns but are more frequently the result of commercial decisions. For instance, data from the National Agency for Medicines and Medical Devices of Romania suggests that in Romania around 70% of current withdrawal notifications are the result of commercial reasons.[128] Because commercial considerations are linked to a product's profitability in a particular market, products may be withdrawn in some markets but not in others and thus contribute to inequitable access to these products between Member States.

In interviews and group discussions, various representatives of Member States, pharmacists and patient organisations have expressed strong concerns about shortages caused by selective market withdrawals for commercial reasons. Their view is that both selective market entry[129] and selective market withdrawal violate the right to treatment of patients. In a briefing paper, Members of the European Parliament call on the Commission and the Council to "explore mechanisms to address the withdrawal of effective medicines from the market for purely commercial reasons and take action to remedy these shortages".[130] From the perspective of MAHs, however, these withdrawals are sometimes the basic consequence of the economic need to balance costs associated with operating in specific markets with profits.

To further assess how often market withdrawals affect product availability, data from the national shortage registries were examined. As part of the study's team data request, NCAs were asked to indicate whether, irrespective of the root cause, the shortage notification involved a product that had been temporarily or permanently withdrawn. In total, NCAs indicated 2,055 shortages (9%) were for products that had been permanently withdrawn from a market. Data indicating permanent market withdrawals were received for 21 countries (Table 14). Nearly a third (32%) of all permanent withdrawals were reported by Slovenia. It is possible that the relatively low level of reports in some countries is because product withdrawals are recorded separately and not included in the national shortage registries. The presented data thus do not necessarily reflect the full extent to which countries experience permanent market withdrawals. Since 2010, there has been a steady increase in the number of products annually reported as permanently withdrawn (Figure 14).

Table 14 Permanent market withdrawals as indicated by NCAs

Country	# Shortages	Country	# Shortages
Austria	118	Hungary	69
Belgium	189	Ireland	67
Bulgaria	1	Italy	94
Croatia	21	Netherlands	604
Czechia	269	Norway	59
Estonia	162	Portugal	99

[128] Medicine withdrawals are deepening shortages and blocking patients' access to essential treatments in Romania. Parallel import – yet an unexplored solution to shortages. (27 April 2021) Affordable Medicines. Available at: https://accesstomedicine.eu/articles/medicine-withdrawals-are-deepening-shortages-and-blocking-patients-access-to-essential-treatments-in-romania-parallel-import-yet-an-unexplored-solution-to-shortages/. Accessed 9 August 2021. The website https://accesstomedicine.eu is supported by Affordable Medicines Europe and the Belgian Association of Parallel Importers and Exports (BAPIE) and as such reflects the perspectives of the parallel trade sector in Europe.

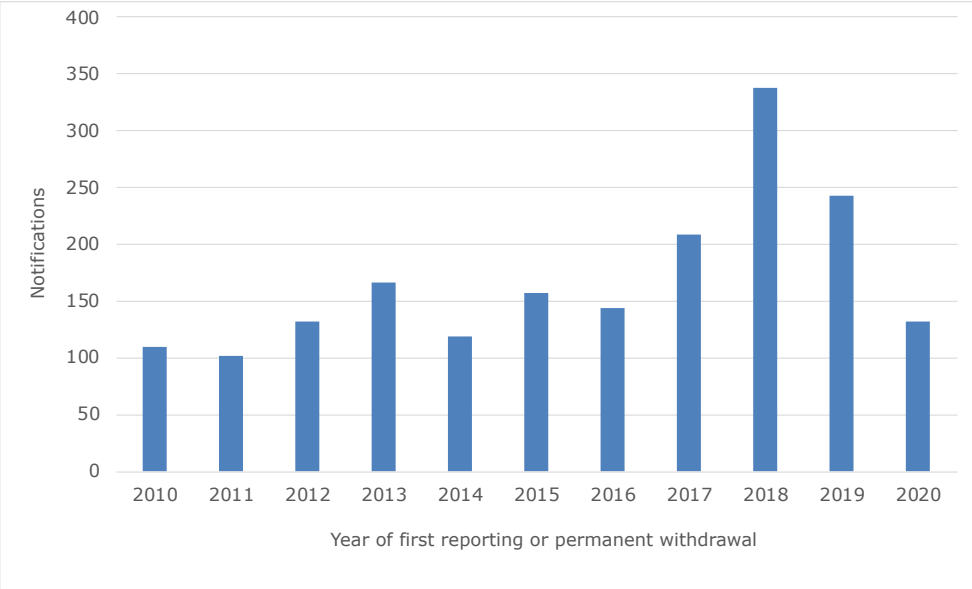
[129] Whilst selective market entry is a major factor in whether patients have access to a medicine, it is out of the scope of this study.

[130] Scholz N. Members' Research Service (April 2020). Addressing shortages of medicines. European Parliamentary Research Service. Available at: https://www.europarl.europa.eu/RegData/etudes/BRIE/2020/649402/EPRS_BRI(2020)649402_EN.pdf. Accessed 9 August 2021.

Country	# Shortages	Country	# Shortages
EU-wide (EMA)	1	Romania	159
Finland	72	Slovakia	160
France	99	Slovenia	1,187
Germany	6	Spain	177
Greece	4	Sweden	37
Total 3,654			

Source: Technopolis Group, based on data from national shortages registries. The total of notifications indicated exceeds the total number of product shortages for which market withdrawal has been indicated because shortages may have been reported in multiple countries.

Figure 14 Permanent market withdrawals over time (as reported by NCAs)



Source: Technopolis Group, based on national shortage registries and data provided by NCAs. Only data from 2010 onwards have been presented because low numbers of reports in previous years obscure the trend. Data collection for 2020 is incomplete. The year indicated is the year the product was first reported as permanently withdrawn in any Member State. In some Member States the product may have been withdrawn later.

Most (71%) permanent withdrawals affected more than one Member State. On average, 4.5 countries reported a specific product as having been permanently withdrawn. The most extreme case was the EU-wide withdrawal of the cancer medicine Lartruvo (olaratumab), as reported by the EMA. This followed a 2019 recommendation by the EMA that the conditional marketing authorisation be withdrawn after the Agency found that the medicine did not offer benefit over existing treatment options.[131] In the case of Celebrex (celecoxib) an anti-inflammatory medicine used to treat rheumatoid arthritis, 14 Member States reported the product as having been permanently withdrawn.[132] However, such wide-scale permanent withdrawals appear to be rare. Only ten out of the 2,055 reported withdrawals affected ten or more Member States. Widespread permanent withdrawals are mostly done for concerns over safety or efficacy.

There are no clear patterns showing a combination of countries that are most often the subject of permanent withdrawals. However, it was relatively common for Czechia to be affected together with Slovenia (n=218), Slovakia (n=96) or both (n=23). This may reflect the fact that all three countries report relatively high numbers of permanent market withdrawals.

[131] EMA recommends withdrawal of marketing authorisation for cancer medicine Lartruvo. (22 August 2019). European Medicines Agency. Available at: https://www.ema.europa.eu/en/medicines/human/referrals/lartruvo. Last accessed 9 August 2021.

[132] Austria, Belgium, Czechia, Estonia, Finland, Hungary, Ireland, Norway, Portugal, Romania, Slovakia, Slovenia, Spain, and Sweden.

Of the 350 permanent withdrawals for which a separate root cause is also reported, 247 (71%) indicate commercial reasons as the root cause of the shortage and 59 (17%) directly refer to market withdrawal as the cause without specification of the underlying reasons. A further 61 notifications (17%) report that the product was withdrawn following quality or manufacturing issues. None of the 350 withdrawal notifications with a specified root cause include information that suggests the product was withdrawn over safety or efficacy concerns. These data thus suggest that most permanent withdrawals can be attributed to commercial reasons rather than to problems with safety or efficacy.

Products that have been reported as permanently withdrawn include both generic/biocomparable medicines (49%) and non-generic medicines (43%).[133] Among permanently withdrawn products for which the root cause is indicated as 'commercial reasons', the share of generic/biocomparable products somewhat increases to 54%. This finding supports the observation made by many stakeholders during consultations and in position papers that generic products are more likely to be withdrawn due to their lower profit margins.

To further explore the relationship between permanent market withdrawals and profitability, sales volumes prior to market withdrawal were analysed. The analysis focused on those products that, according to data provided by the NCAs, had been permanently withdrawn and for which quarterly sales in the reporting Member States had permanently declined to zero after four consecutive quarters of no sales.[134,135] This analysis is limited by the fact that quarterly turnover data were not available for all notified permanent withdrawals. The analysis group contained 388 shortages reported across 15 different Member States.[136] All except seven involved products with average aggregated quarterly sales below EUR 1 million (Table 15).[137] Most (78%) even had average quarterly sales below EUR 30,000 and their sales decreased over time. Whilst sales do not equate to profits, it is likely that these products were of limited commercial value to the MAHs. These withdrawals mainly concerned products that had been on the market for over 20 years (76%) and many (65%) were non-generic medicines. Whilst it was not possible from the available data to establish whether, at the time of withdrawal, there were generic substitutes available for these products in the countries concerned, it is very possible that some of these originator products were withdrawn after generic competition had eroded their market share. Withdrawals for products with sales below EUR 30,000 range from over-the-counter cold medicines to oncology medicines.

Another explanation could be that treatment populations were too small in the countries where the product was discontinued. This could happen, for instance, with medicines used to treat rare diseases. However, none of the permanent withdrawals identified by the NCAs concern products that appear on the EU Community Register of Orphan Medicinal Products.[138]

Table 15 Average quarterly sales prior to permanent market withdrawal

Average quarterly sales (maximum)	Frequency
EUR 5,000	157
EUR 10,000	44
EUR 20,000	59
EUR 30,000	23
EUR 40,000	19
EUR 50,000	18
EUR 60,000	10
EUR 70,000	6
EUR 80,000	2
EUR 90,000	5

[133] Non-generic medicines include innovative, single-source medicines but also reference products for which there are generic versions available. Other product categories in the data set include "non-categorized" and "other" products.

[134] A minimum of one quarter of sales had to be provided in the IQVIA MIDAS data set.

[135] Quarterly sales volume (in standard units) were summed across all countries where the medicine had been reported in shortage.

[136] Austria, Belgium, Czechia, Estonia, France, Hungary, Ireland, Italy, the Netherlands, Norway, Portugal, Romania, Slovakia, Slovenia and Spain.

[137] Quarterly sales aggregated over the countries where the product was withdrawn.

[138] European Commission (no date). Community Register of orphan medicinal products. Available at: https://ec.europa.eu/health/documents/community-register/html/reg_od_act.htm?sort=a. Accessed 24 August 2021.

EUR 100,000	5
EUR 150,000	13
More than EUR 150,000	27

Source: Technopolis Group, based on data from the national shortage registries and sales data from IQVIA MIDAS.

Whether there is a sufficient economic rationale to maintain market presence depends on the ratio between profits and marginal costs of staying in a particular market. These costs include expenditures associated with local presence required to market and distribute a product, fees for maintaining a marketing authorisation and other operational costs. They may vary depending on the type of product and the size of the local market. Costs will also be different for different groups of operators. Estimates were collected from supply chain actors on the overall costs per product for operating in the EEA (excluding manufacturing) (Table 16).

Table 16 Average costs of maintaining a marketing authorisation per product per year

Supply chain actor	Registration costs	Staff costs	Other costs	**Total costs**
Generics industry	EUR 87,000	EUR 40,000	EUR 53,000	**EUR 180,000**
Innovative industry	EUR 326,000	EUR 530,000	EUR 238,000	**EUR 1,096,000**

Source: Technopolis Group, survey of supply chain actors.

The calculated average costs are, however, based on a very small number of survey responses and the estimates show great variation between them. Consequently, the calculated averages have a high degree of uncertainty. Moreover, they do not provide an indication of the *incremental* costs for operating in a specific market. The above costs pertain only to registration through the EMA's centralised procedure and thus relate to all Member States in which the supply chain actor is active. For an analysis of profitability, however, the incremental cost of presence in any additional Member State is required. If an MAH is only present in one Member State, the above costs equal the marginal costs, but if the MAH is active in more than one Member State the incremental cost will be lower or almost absent. In the context of the observed (very) low sales for many of the permanently withdrawn products, it is conceivable that if a supply chain actor is active in one Member State only, the registration costs are significant enough to force profits below the point where there is sufficient economic justification for a company to stay in a market.

No data were collected on the costs of maintaining a marketing authorisation obtained through national or decentralised procedures, as these costs vary substantially between countries. The decentralised procedure is, however, the most common route of authorisation for generic medicines. In the case of products authorised through this route, the total costs may be lower, depending on where the product has been authorised, but the incremental costs may be more substantial as each country requires a separate registration.

It can be asked if low (or no) profitability in a particular market offers sufficient justification for a withdrawal of the product if 1) the product generates sufficient sales in other markets such that, overall, the product would remain profitable or 2) the MAH generates significant profits on other parts of its portfolio to remain profitable. This applies particularly to companies with presence in many markets and large product portfolios, as these are most able to offset losses in one place with profits elsewhere.

Analysis of the group of 2,055 permanently withdrawn products indicates that these products were marketed by 144 companies. Over half (n=1,234; 60%) of the withdrawals were traced to just eight companies, including both R&D based pharmaceutical firms and companies that predominantly produce generic medicines.[139] All are large, internationally operating firms that have reported healthy profit margins. Whilst their decision to discontinue marketing may make economic sense at the level of the individual market, the financial impacts from continuing to operate in that market on the company's overall operating profit may thus be comparatively small. In such cases, it could be argued that the commercial considerations may not sufficiently justify the possible negative impact on patients. This will depend, however, also on the product's importance to patients and the availability of appropriate substitutes.

[139] Teva (n=264), Novartis (n=233), GlaxoSmithKline (n=122), Krka (n=116), Stafa (n=95), Merck & Co (n=89), Aurobindo (n=82), Mylan (n=79), Bayer (n=79) and Pfizer (n=75). Data have been aggregated across divisions and local subsidiaries to the level of the parent company.

Low sales revenues can reflect limited interest in the product on the part of patients, for instance because newer products have become available that are deemed to be clinically superior, have a better benefit-risk profile or because of increased competition from generic versions. In such cases, the product's discontinuation may have relatively little impact on quality of care, provided these other products are suitably available. On the other hand, products may be critical to specific groups of patients, despite their low sales volumes. This could be the case, for instance, for products used to treat (very) rare diseases or for use in small patient populations, such as children. In these cases, market withdrawal may have catastrophic repercussions to these patients when no therapeutic alternatives are available. From the data provided by the NCAs, it is not possible to determine what the importance of discontinued products is to patients as no information has been included on criticality (see also Section 4.6). For Romania, it was suggested that for 20% of all discontinued products there was no generic substitute.[128]

5.8. Impact of COVID-19

Whilst the issue of medicines shortages predates the COVID-19 pandemic, it has led to increased concerns about the availability of critical medicines. In the first months after the pandemic reached Europe, many European countries reported increases in shortages of medicines used in intensive care units to treat COVID-19 and its complications. In the early stages of the pandemic, the surge in demand for these medicines led to decreased stocks in many hospitals, with many hospital pharmacists unable to dispense in a timely manner to meet demand.[140] The EMA reported at the time that affected medicines included anaesthetics, antibiotics, muscle relaxants and medicines used off-label to treat COVID-19.[141] In the United States, the American Medical Association reported COVID-19 related shortages of analgesics, sedatives (psycholeptics) and paralytics (muscle relaxants).[142]

Data from the national registries, comparing notifications made during the final two quarters of 2019 ('pre-COVID-19') to the first two quarters of 2020 ('first wave COVID-19') confirm these reports. It shows particularly strong increases in the number of shortage notifications for analgesics, medicines for obstructive airway diseases, psycholeptics, anaesthetics, and antibacterials for systemic use (Figure 15). Other notable increases were seen for immunosuppressants, antivirals for systemic use and muscle relaxants. These classes all contain medicines used in the treatment of COVID-19, including during mechanical ventilation of patients. However, significant increases were also observed in many other product classes (e.g. diabetes medicines) that have no apparent use in treatment of COVID-19 patients. Whilst these increases are not likely the result of increased demand due to use in COVID-19 treatment, it is possible that these product classes were still impacted by COVID-19 related global supply disruptions. Such disruptions occurred in part because, during the quarantine period, some manufacturers of active pharmaceutical ingredients (APIs) and generic medicines in China were forced to suspend or reduce their production.[143] A survey by the Institute for Supply Management conducted between February and March 2020 found that 50% of suppliers (across industries) were operating at only 50% capacity.[144] India, furthermore, curbed the export of multiple APIs and formulations.[143]

[140] Vinci DL, Milković N, Batista A, Amann S, Makridaki D. (2021) Lessons learnt from the COVID-19 pandemic: results of EAHP survey on the future crisis preparedness of hospital pharmacies. European Journal of Hospital Pharmacy. BMJ Journals. Available at: http://dx.doi.org/10.1136/ejhpharm-2021-002944.

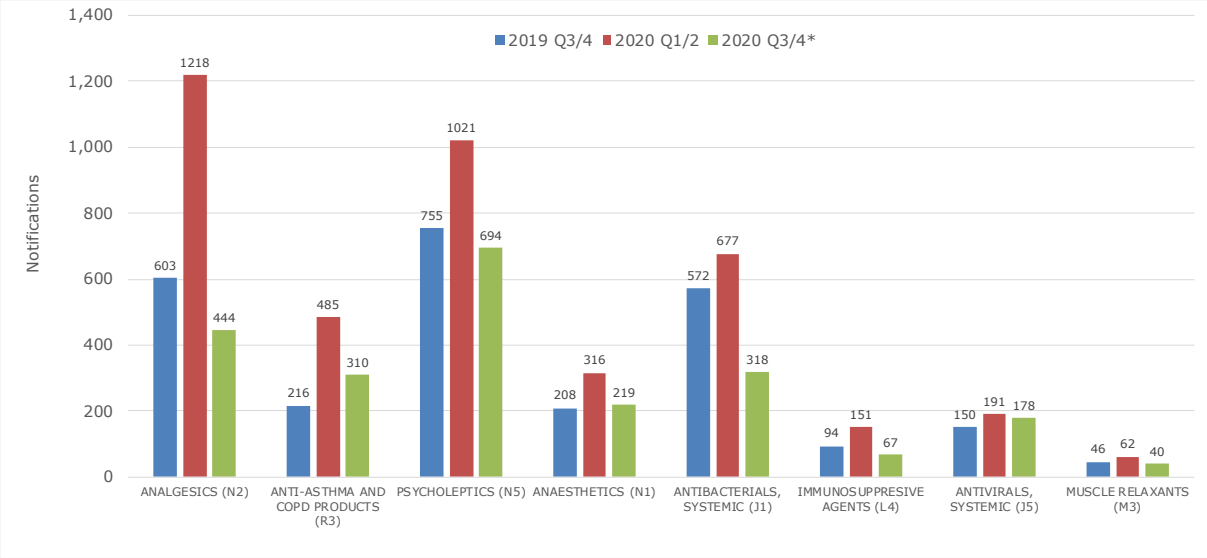
[141] EMA press release, April 2020. Available at https://www.ema.europa.eu/en/news/eu-authorities-agree-new-measures-support-availability-medicines-used-covid-19-pandemic

[142] Berg S. (17 November 2020). American Medical Association. COVID-19 exacerbates drug shortages. AMA details next steps. Available at: https://www.ama-assn.org/delivering-care/public-health/covid-19-exacerbates-drug-shortages-ama-details-next-steps.

[143] Everstream Analytics (no date). COVID-19: impact on API production and global pharmaceutical supply chains. Available at: https://www.everstream.ai/risk-center/special-reports/covid-19-impact-on-pharma/. Accessed 4 August 2021.

[144] Institute for Supply Management (2020). Available at: https://www.ismworld.org/supply-management-news-and-reports/reports/covid-19-resource-center/infographic/. Accessed 4 August 2021.

Figure 15 Notifications by product category (anatomical classification level 2) for categories containing products most commonly used in COVID-19 treatment.



Source: Technopolis Group, based on data from national shortage registries. The period 2019 Q3/4 (shown in blue) represents the situation before the outbreak of COVID-19 in Europe; the period 2020 Q1/2 (shown in red) represents the 'first wave' of the outbreak, as first cases of COVID-19 in the EU were confirmed in February/March 2020; during the period 2020 Q3/4 (shown in green) many countries experienced new waves of COVID-19 infections but supply disruptions were less severe. *Data for Q4 2020 were incomplete for some countries at the time of data collection, as the first data sets were collected in October 2020. The final number of notifications for the period Q3/4 2020 will thus be higher than what has been shown here.

Although the data for the final quarter of 2020 were incomplete at the time of collection, data for the third and fourth quarters of 2020 suggest that for the most affected product classes the effects of the surge demand had largely dissipated, and that the number of notifications had declined to levels closer to those before the outbreak of COVID-19 in Europe.

The impact of COVID-19 on medicines availability was also confirmed by consulted stakeholders. Surveyed pharmacists and representatives of national health authorities highlighted problems with the supply of anaesthetics, antibiotics and antivirals. A third (33%) of NCAs indicated that shortages of anaesthetics reached critical levels and endangered the quality of care (Figure 25). Nearly all NCAs reported a surge in demand for various types of medicines, including medicines used in treatment of COVID-19 patients but also common over-the-counter pain medication and medicines for which patients feared shortages. Some NCA representatives reported being aware of manufacturers that had changed their production lines to increase manufacturing of medicines associated with COVID-19 treatment.

Surveyed pharmaceutical manufacturers confirmed the COVID-19 related disruptions to their ability to supply, attributing these mostly to travel restrictions, increased complexity in transportation of goods and reduced manufacturing capacity because of lockdowns (

Figure 78). However, in a paper produced by the European Federation of Pharmaceutical Industry Associations (EFPIA), the Federation indicated that its member companies had mostly been able to meet the needs of patients by increasing production, especially for medicines used in intensive care units and for COVID-19 treatment candidates.[145]

Many stakeholders have pointed towards the detrimental impact of international export restrictions and increased stockpiling of medicines used to treat COVID-19 patients by national authorities, hospitals, and citizens. These practices were seen by many as disruptive. A study of shortages for selected products in the United States suggested that these shortages were directly related to India's export restriction of APIs.[146] In Europe, export restrictions likewise affected the entry of

[145] EFPIA (no date) Policy Proposals to Minimise Medicine Supply Shortages in Europe. Available at https://efpia.eu/media/15427/policy-proposals-to-minimise-medicine-supply-shortages-in-europe-march-2014.pdf. Accessed 17 June 2021.

[146] Piatek, O. I., Ning, J. C. and Touchette, D. R. (2020) 'National drug shortages worsen during COVID-19 crisis: Proposal for a comprehensive model to monitor and address critical drug shortages', American Journal of Health-System Pharmacy, 77(21), pp. 1778–1785.

pharmaceutical products and ingredients into the Union. Export restrictions on movement of products within the Union were also considered by Member States to ensure availability of products on their territory. In response, on 8 April 2020, the European Commission recalled the principle of solidarity and called on all Member States "to lift unjustified export bans for medicines within the internal market" and urged that "any stockpiling by Member States should be at national level and for moderate quantities based on epidemiological indications" to avoid the creation of shortages of critical medicines.[147]

Summary

Analysis of reported root causes of shortages in the EU/EEA suggests that around half of all cases, irrespective of the therapeutic application of the medicine, can be traced back to issues with quality and manufacturing. There are indications that certain product formulations, such as lyophilised products for injection, are more sensitive to manufacturing issues, but the available data from the national shortage registries are insufficiently detailed to corroborate this.

Around a quarter of notified shortages are reportedly due to commercial reasons, although this may underestimate the true role of economic factors. This is because even when the stated root cause of a shortage is an issue 'upstream' in the pharmaceutical value chain, the consequences of this issue may be felt differently across countries depending on national economic and market structure factors. Inexpensive off-patent medicines, including many older oncology medicines, are at highest risk of shortage because of economic reasons. Market factors play an especially important role in product withdrawals, which have been happening with increasing frequency. Most medicines that were permanently withdrawn from a particular market generated low sales revenues in those markets, suggesting this revenue was no longer sufficient to outweigh the costs to the MAH of keeping the product on that market.

Unexpected demand increases are another important driver of shortages that has steadily increased in importance. Sudden demand increases can occur, for instance, as a result of adoption of a new treatment regimen or introduction of a new vaccine into national immunisation programmes, seasonal fluctuations or when there is a supply gap to fill left by the short supply of another product. Sudden large demand increases often are difficult to absorb because of issues with production planning and the complexity of production processes. The onset of the COVID-19 pandemic exemplifies a situation whereby sudden large surges in demand for critical medicines used in the treatment of COVID-19 patients posed a challenge to the continuity and quality of care for COVID-19 and other indictations reliant on the same medicines.

Although in the EU/EEA regulatory issues are not frequently cited as a direct cause for shortages, regulatory factors play a significant role in the ability to absorb supply disruptions and efficiently mitigate the impact of shortages. A particular challenge in the European context is the diversity of presentations and national labelling requirements across Member States. These can create barriers in mitigating shortages when the movement of products between countries is delayed because medicines need to be repackaged to meet local requirements.

The available information is, at present, insufficient to quantify the importance of outsourcing of pharmaceutical production (including the production of APIs) and of parallel distribution as potential risk factors for shortages.

Proper understanding of the root causes of shortages, however, remains substantially challenged by inconsistent and limited reporting. Moreover, reporting of root causes is generally reductionist, singling out the most acute cause but without considering the underlying more systemic issues and market-related factors.

[147] Communication from the Commission: Guidelines on the optimal and rational supply of medicines to avoid shortages during the COVID-19 outbreak (C2020) 2272 final), European Commission (8 April 2020). https://ec.europa.eu/health/sites/health/files/human-use/docs/guidelines_isc_en.pdf.

6. EVALUATION OF THE EU LEGAL FRAMEWORK

As indicated in Section 1.3, there are two provisions within the EU general pharmaceutical legislation, Directive 2001/83/EC on the Community code relating to medicinal products for human use, that aim to protect the supply of medicinal products to the Union:

- Article 23a paragraph 2, requires a MAH, other than in exceptional circumstances, to submit a pre-notification to the relevant national competent authorities (NCAs) if a product ceases to be placed on the market of a Member States, either temporarily or permanently; and,
- Article 81 paragraph 2, requires MAHs and wholesale distributors of a medicine that is placed on the market to "ensure appropriate and continued supplies", within the limits of their responsibilities, to cover the needs of patients.

Member States are required to pass appropriate implementing measures and write these into national laws, in a process known as 'transposition'. To better understand how Member States have done so and to assess whether these measures have resorted any effect in preventing or mitigating the impact of shortages, an evaluation was performed of the EU legal framework. This evaluation considered the criteria of effectiveness, efficiency, coherence, relevance and EU added value. The evaluation first considers how Member States have transposed the different articles into their national legislation and takes stock of additional measures countries have introduced to address shortages (Section 6.1). The following sections cover the assessment against the evaluation criteria. Specifically, they address the following study questions:

- Are the current legal provisions at EU level (articles 23a and 81) adequate to prevent or mitigate medicines shortages?
  - To what extent have these provisions contributed to the prevention/mitigation of effects of shortages, in comparison to the situation before their adoption?
  - What (additional) measures have Member States introduced at national level to prevent or address shortages? What has been their effect?
- Are there/what are the costs linked to the application of these provisions (EU/national level) and who is bearing these costs?
  - What are the benefits linked with the application of these provisions (EU/National level) and who is getting those benefits?
  - Are the costs reasonable in terms of benefits provided to the concerned actors
- How do EU/national actions complement each other?
  - Are there any inconsistencies and/or synergies between the provisions on shortages at EU/national/international level?
  - What has been the impact of voluntary cooperation at EU-level?
- Were these provisions appropriate to solve the problem of shortages in the EU at the time of their adoption?
  - Are these provisions still appropriate to tackle the issue of shortages in the light of the developments in the sector?
  - Do these provisions at EU level provide added value in comparison to what could have happened in their absence?

As indicated in Section 2.6, the evaluation is limited by the absence of suitable comparators and is based primarily on qualitative information collected through consultations with key stakeholders.

6.1. Transposition and implementation of Articles

All 27 Member States have transposed both Articles 23a and 81 in some form. A comparative analysis of transposing measures shows that the approaches of Member States in the implementation of both provisions varies significantly across Member States, and that a great number of additional measures have been adopted to prevent and mitigate impacts of shortages of pharmaceutical products. Some countries, such as Finland, have only recently transposed or amended their transposing provisions.

Article 23a of Directive 2001/83/EC

The notification obligation on the future (temporary or permanent) market withdrawal of a medicinal product has been transposed in all Member States. Half of the Member States (n=14) have transposed this provision in an almost literal 'a minima' manner, referring to the absence of broader,

additional and/or more stringent obligations for MAHs or distributors in terms of a longer notification timeframe or wider material/personal scope. Seven Member States have extended the notification timeframe for all medicinal products or reimbursed medicines to between three and six months (Table 17). Whilst not considered an extension of the notification obligation, 16 Member States have also introduced public publication of the notifications and two have defined exceptional circumstances.

Among survey respondents from 15 countries, all NCA representatives confirmed that in their countries some form of early notification system for expected shortages had been introduced (n=14) or was under consideration (n=1)(Annex H, Figure 43). Most (n=12) also publish a national list of medicines currently in shortage that can be accessed by patients and healthcare professionals.

Article 81 of Directive 2001/83/EC

All Member States have transposed the obligation for MAHs and wholesalers to ensure, within the limits of their responsibilities, appropriate and continued supplies of the medicinal product placed on the market to pharmacies and persons authorised to supply medicinal products. Nearly a third of the Member States (n=8) have transposed Article 81 'a minima', thus without further extension of this obligation (Table 18). In some cases, the obligation is limited in its scope of coverage, for instance to wholesale distributors or MAHs. Beyond this obligation, many countries have added new requirements or set more specific provisions for MAHs and distributors that concern the continuity of supply. These include, for instance, the application of a 'public service obligation' (PSO) on distributors (n=6), the obligation to supply medicines within a specific timeframe (n=7), the obligation to maintain stocks such as mandatory reserve supplies or pharmacy stocks (n=9) and a definition of appropriate and continued supply (n=2). Other measures include the requirement for the MAH to set up a shortage management plan (n=2) or for dialogue and cooperation with authorities (n=2). Some Member States, such as Austria, have recently amended their transposing provisions.

In survey responses, representatives for Denmark and the Netherlands indicated that these countries have introduced stock holding requirements on MAHs and distributors even though these requirements were not confirmed in the desk research or NCA interviews (Annex H, Figure 43).

In four Member States, some potential conformity issues linked to the transposition of Article 81 were identified:

- Belgium and Malta restrict the obligation on distributors to wholesale distributors
- Slovakia restricts the obligation of continued and appropriate supply to reimbursed medicinal products
- In the Netherlands, the transposing provision does not extend to distributors but only applies to MAHs.

Some NCA representatives (Belgium, Finland, France, Romania) have highlighted the difficulty and complexity of enforcing the obligation of continued supply, finding that in practice it is often hard to demonstrate the violation of such an obligation (e.g. where limited stocks are available). This view was shared also by several NCAs, healthcare professionals and patient representatives during focus group discussions.

Additional national measures

As a complement to the EU obligations under Article 23a and Article 81, many Member States have introduced additional national measures to prevent or mitigate the impact of shortages (Table 19). These measures cover a variety of elements, such as stock keeping and supply obligations, mandatory reporting on available stock levels, regulatory flexibilities on import and use of unauthorised medicines. Restrictions on parallel export have been introduced in 16 Member States.

In survey responses, NCA representatives confirm the introduction or consideration of various additional measures, beyond those discussed in connection to the transposition of Articles 23a and 81 (Annex H, Figure 43). These include the establishment of national lists of essential medicines and medicines at high risk of shortage, use of national stockpiles and restrictions on parallel export. An additional mitigation measure introduced in at least seven countries is the option for pharmacists to substitute certain medicines without intervention of a prescribing physician. Although several countries have indicated that they are considering introducing requirements on transparency of industry supply quotas and wholesalers' transactions for the relevant Member State authorities, thus far no country reports having implemented this.

Table 17 Transposition of Article 23a paragraph 2 Directive 2001/83/EC in EU Member States

Country	AT	BE	BG	CY	CZ	DE	DK	EE	EL	ES	FI	FR	HR	HU	IE	IT	LT	LU	LV	MT	NL	PL	PT	RO	SE	SI	SK
Year of transposition	2005	2006	2007	2006	2007	2005	2005	2005	2006	2007	2005	2007	2013	2005	2007	2006	2006	2006	2007	2007	2007	2013	2006	2006	2006	2006	2006
State of the transposition																											
Literal a minima transposition																											
Different notification timeframe		a							b	a,c		h		a		d								e			
Extended transposition of Article 23a																											
Public register based on Art. 23a notifications																											
Definition of exceptional circumstances																											
Possibility for NCAs to request information		f	f	f								f	f						f						g		f
Notification on supply disruption to other actors																											

Source: Milieu Law & Policy Consulting, based on interviews with NCA representatives and desk research. Green shading = Yes; Red shading = No; a = 6 months for reimbursed medicines; b = 3 months; c = as of 2019; d = 4 months; e = 6 months, 12 for commercial discontinuations; f = obligation on MAH; g = informal; h= 1 year for medicines with major therapeutic interest; i = distributors.

Table 18 Transposition of article 81 paragraph 2 Directive 2001/83/EC in EU Member States

Country	AT	BE	BG	CY	CZ	DE	DK	EE	EL	ES	FI	FR	HR	HU	IE	IT	LT	LU	LV	MT	NL	PL	PT	RO	SE	SI	SK
Year of transposition	2005	2006	N/A	2006	2007	2009	2005	2005	2003	2006	2005	2008	2003	2007	2007	2006	2006	2012	2007	2007	2013	2013	2006	2006	N/A	2006	2011
State of the transposition																											
A minima transposition																											
Limited transposition (personal or material)	b	b	b	b		b	b	b		b	b	b			b			b	b	d	e,f	b		b	b	b,d	b,c
Extended obligations onto MAHs and/or distributors																											
Public service obligation (PSO) on distributors																											
Timeframe to supply upon request																											
Stock obligations on MAH and/or distributors (excl. pharmacies)		a				g										c											
Mandatory reporting on available stocks																											
Specific supply obligations of MAHs towards distributors																											
More stringent obligations for categories of medicines (e.g. essential, subsidised)																											
Definition of continued and appropriate supply																											
Supply/shortage management plans by MAHs																											
Requirement of cooperation and dialogue with NCA																											

Source: Milieu Law & Policy Consulting, based on interviews with NCA representatives and desk research. Green shading = Yes; Red shading = No measure identified. a = within the frame of the PSO; b = transposition of distributors as "wholesale distributors" or limitation to full-line distributors; c = limited to reimbursed medicinal products; d = obligation limited to distributors; e = only applicable to MAHs; f = no transposition of the continuous requirement, g = limited to full-line wholesalers.

Table 19 National measures to address shortages introduced by EU Member States (as of January 2021)

Country	AT	BE	BG	CY	CZ	DE	DK	EE	EL	ES	FI	FR	HR	HU	IE	IT	LT	LU	LV	MT	NL	PL	PT	RO	SE	SI	SK
Exports																											
Restrictions on parallel exports (and supporting measures)																											
Mandatory notification of exports																											
Imports and distribution																											
Exceptional imports of medicines not authorised in the MS																											
Possibility to set quotas for the distribution of medicines																											
Possibility to issue authorisations in absence of application																											
Temporary derogatory authorisation of medicines (e.g. packaging in another language; products close to expiry date; formal error in application)																											
Additional obligations on MAHs and distributors																											
Obligation to supply directly to pharmacies and other end-distributors upon request																											
Obligation to import alternative medicines in case of shortage																											
Information																											
Advanced disclosures on stocks available and/or operations of MAHs and distributors									a																		
Specific disclosure requirements in case of withdrawal																											
Pharmacies, medical institutions, and end-users																											
Minimum stock by pharmacies or healthcare units																											
Daily reporting on stocks by pharmacies																											
Warning of supply issues by pharmacists (and patients)																											
Reimbursement of medicines																											
Limited reimbursement of medicines as a result of shortages																											
Other																											
Exceptional manufacturing activities by the State																											

Country	AT	BE	BG	CY	CZ	DE	DK	EE	EL	ES	FI	FR	HR	HU	IE	IT	LT	LU	LV	MT	NL	PL	PT	RO	SE	SI	SK
Centralised purchasing and stockpiling at national level																											
Prevention and/or mitigation plans required from MAHs																											
Obligation to collaborate with the authorities																											
Possibility for the NCA to declare shortages or risk thereof independently of notifications																											
Ad-hoc agreements with MAHs																											

Source: Milieu Law & Policy Consulting, based on interviews with NCA representatives and desk research. Green shading = Yes; Red shading = No measure identified. Not included: temporary COVID-19 specific measures identified in national reports; future legislation planned and announced by Member States. a = in case of export restriction.

6.2. Effectiveness

As specified by the Better Regulation guidelines, effectiveness analysis considers how successful an action has been in achieving or progressing towards its objectives, the extent to which progress has fallen short of the target and what factors have influenced why something hasn't been successful or why it has not yet been achieved.[148] It also considers whether any unexpected or unintended effects have occurred. In the context of this study, effectiveness analysis focuses on the extent to which the obligations laid out in Articles 23a and 81 have contributed to the prevention or mitigation of shortages in the Member States.

Timely notification in case a product ceases to be placed on the market

The objective of Article 23a is to provide NCAs with adequate warning about temporary or permanent market withdrawals of pharmaceutical products. As such, it is aimed at improving the ability of authorities to prepare for impending shortages and mitigate their impact rather than at preventing shortages. Assessment of effectiveness should thus not consider whether fewer supply disruptions or market withdrawals have occurred, but whether NCAs have been given sufficient advance warning about impending supply disruptions to take appropriate action. It should be noted that the obligation laid down in Article 23a to notify two months in advance is designed for a situation in which the MAH knows ahead of time that they will be unable to supply a market, either temporarily or permanently.

In the national shortage registries, eight countries provide not only information on the start data of the shortage but also register a 'date of notification'.[149] In theory, it should be possible to determine from this how much in advance MAHs notify the relevant NCA in case of an expected product discontinuation and what the compliance is for the notification obligation under Article 23a. However, closer inspection of the data in these registers shows that many notifications were entered into the registries many months or even years after the shortage started. It is unlikely that for all these shortages, the responsible MAH waited this long before notifying the relevant authorities of the situation. It appears that these shortages were included in the shortage registers retroactively and that the provided 'date of notification' does not represent the time the MAH first notified the NCA but rather the time the NCA entered the information into the register. Furthermore, of these eight countries, three (Croatia, Iceland and Norway) did not provide information that would allow distinguishing between foreseen discontinuations and unplanned shortages. Importantly, it is not known to what extent all NCAs include product withdrawals in their national shortage registers as they may opt to record these separately. For these reasons, **quantitative analysis of the compliance with the notification obligation is hampered by lack of reliable data from the NCAs**. No other public reporting was identified on the compliance of MAHs with the notification obligation. Assessment of compliance with and effectiveness of the obligation thus rests principally on reports by consulted NCAs.

NCA representatives differ in whether they consider the two-month timeframe for notification effective. Six Member States (Belgium, Greece, Hungary, Italy, Romania and Spain) have opted to impose longer notification requirements of between four and six months. However, most other countries have left the obligation at two months. NCA representatives from five countries (Austria, Hungary, Lithuania, the Netherlands and Slovakia) felt that Article 23a has generally been helpful in mitigating the impact of shortages and related consequences, whilst enabling the sharing of information to the rest of the supply chain. Representatives for Czechia and Estonia added that the two month-period usually provides sufficient time to turn to alternative suppliers, if these exist.

Various consulted NCA representatives have highlighted that for shortages that are caused by unforeseen supply disruptions, the MAH frequently only notifies the NCA at, or even after, the actual time the shortage occurs, citing 'exceptional circumstances'. NCAs generally recognise the challenge of providing early notification in such situations and usually do not fault the MAH for the late notification. It is unlikely that in these situations stricter advance notification obligations would make a difference. Representatives of pharmaceutical manufacturers have also suggested that many

[148] European Commission (no date). Better Regulation Toolbox. Tool #47 Evaluation criteria and questions. Available at: https://ec.europa.eu/info/sites/default/files/better-regulation-toolbox.pdf. Accessed 5 September 2021.

[149] Belgium, Croatia, Estonia, the Netherlands, Norway, Slovakia and Slovenia.

supply issues can be resolved before they result in shortages. They argue that notifications made too far in advance will lead to many false alarms and unnecessarily increase the administrative burden on companies and NCAs alike. In submitted comments by a representative of the Dutch NCA, it was suggested that most notifications it receives are submitted out of precaution for fines and do not result in actual shortages in the market. Theoretically, pre-emptive notifications could create problems when distributors and pharmacies, in anticipation of a shortage that may not materialise, start stockpiling the product and disrupt the equilibrium between demand and supply.

Most (80%) surveyed NCA representatives responded that the early notification of expected shortages[150] is somewhat or very effective in reducing the frequency of shortages (Annex H, Figure 45). Pharmacists were surveyed on whether they receive advance notice of shortages. Of these, nearly a third (n=16, 30%) indicated they frequently or always receive this, whilst nearly all others said they rarely received these (n=34, 64%).[151] This could either mean that in these cases the MAH has not given the NCA advance notice or that the NCA has not actively passed this information on to pharmacists. Pharmacists were furthermore asked about the impact of the notification obligation under Article 23a (Annex H, Figure 70). Many (42%) felt it had enabled more timely identification of treatment alternatives.[152] Additionally, around a third (31%) suggested that this notification had enabled more timely identification of alternative sources of the same medicine, for instance by importation.[153] On the part of the MAHs, 78% of survey respondents felt that the notification obligation under Article 23a had not had any impact on their operations (Annex H, Figure 87).[154] This suggests companies consider such notifications part of their routine operations and that complying with the obligation does not require significant investment of resources.

Overall, the assessment indicates that Article 23a is relatively effective in enabling authorities to prepare for planned product discontinuations but is less effective in providing timely information about shortages due to unforeseen supply disruptions. For the latter, longer or stricter notification obligations are unlikely to lead to more advance notification unless somehow these situations become more predictable.

During focus group discussions and in the consultation on possible solutions to shortages, many different stakeholders have emphasised the importance of regular open communications between national authorities, manufacturers, distributors and pharmacists to discuss any relevant issues in the supply chain and their possible impact on product availability. They argue that these discussions should be allowed to take place without triggering a formal shortage notification and in a "no-blame culture".

Ensure appropriate and continued supply

Whilst Article 23a is primarily concerned with obtaining timely notifications about expected product discontinuations, Article 81 is broader in that it imposes obligations on both MAHs and wholesaler-distributors to make best efforts to ensure the continuity of supply of all medicines they place on the market. Because of this, the effectiveness of Article 81 can be measured more directly by the incidence of shortages. It could be assumed that a reduction in the frequency with which shortages occur, or even a slowing down of an otherwise upward trend could be evidence of some effect of supply obligations.

As shown previously in Section 4.1 (Figure 2), the number of notified shortages is still increasing year-on-year, even after accounting for an increase in the number of countries that are collecting this information. The increase has continued even though all Member States have transposed the obligation into national legislation in at least some form. Whilst this could be taken to mean that Article 81 has not been sufficiently effective, it cannot be determined directly from the register data what the situation would have been like *without* this obligation. Only in France and the Netherlands was Article 81 transposed *after* the start of data collection (two and five years after respectively).

[150] The question asked respondents for their view on the effectiveness of early notification of expected shortages but did not here to distinguish between market withdrawals and other anticipated shortages.
[151] The question did not differentiate between shortages caused by product discontinuations and those linked to supply chain disruptions.
[152] Hospital pharmacists: n=19 (44%); Retail pharmacists: n=5 (36%)
[153] Hospital pharmacists: n=16 (37%); Retail pharmacists: n=2 (14%)
[154] Generic pharmaceutical industry: n=20 (80%); innovative pharmaceutical industry: n=20 (77%)

Moreover, consultations with NCA representatives and supply chain actors suggest that, even in countries where national shortage registers have existed for longer, both the notification criteria and the way in which NCAs enforce notification may have changed during this time. Both these factors could have resulted in increased notification of shortages even when the true number of shortages, as experienced by pharmacists and patients, did not increase in the same way. The importance of these confounding factors cannot be objectively quantified. Most consulted stakeholders, particularly NCA representatives and pharmacists, nonetheless experience that the actual frequency with which shortages occur has significantly increased over time and that this is not simply a matter of improved reporting or increased public attention (See also Section 4.1).

NCA representatives for Austria, Czechia, Romania, Sweden and Slovakia all highlighted that the supply obligation laid down Article 81 is framed in rather broad terms, which makes it hard to enforce directly when transposed literally or 'a minima'. Consequently, **many countries have stipulated additional obligations and introduced complementary national measures to further operationalise the supply obligation**. A further issue observed by some authorities is the interpretation of the obligation itself and what is covered by it. For instance, Dutch authorities felt that the understanding of what constitutes 'continued and appropriate supply', the conditions under which the supply obligation can be considered fulfilled, and the external justifications that can be used by MAHs and distributors to explain non-observance of the obligation are all insufficiently defined by Article 81. The difficulty in establishing what products are covered by the supply obligation and to whom the obligation pertains is illustrated by the situation in Finland. Here, medicines that are imported by distributors – but which are not placed on the market directly by the MAH – can be validly considered as a medicine "actually placed on the [Finnish] market" and thus fall under the scope of the obligation. A similar situation exists in Belgium: after a change in the legislation, the notification obligation extends to parallel distributors and importers. However, parallel distributors' ability to supply a market depends on their own access to products[155] and whether they can resell these products at a reasonable profit. As a result, their supply is by nature non-continuous. This leads to issues when authorities need to assess whether distributors have done enough, within the limits of their responsibility, to ensure continued and appropriate supply.

As indicated previously, the additional obligations introduced by Member States to operationalise the public service obligation enshrined in Article 81 cover a combination of measures. These range from measures imposed on MAHs to define their obligations towards distributors, stocking requirements (on MAHs and/or distributors) and information disclosure obligations (e.g. mandatory stock reporting). Additional measures can be associated with the specific market structure of a country (e.g., smaller markets; cheaper medicinal product prices compared to other Member States; parallel exports). Some Member States can be less attractive for MAHs and be subject to parallel exports to other Member States where medicinal products can be sold at a higher price.

Because of these underlying differences in what (combination of) measures countries have introduced, the operational specifics of these measures and variations in national market structures, it is difficult to extrapolate from one country's experience to another about the effectiveness of individual measures. Rather than attempt to analyse this at the individual country level, an assessment was performed of clusters of measures by comparing groups of countries where elements of these clusters had been introduced. The main clusters of measures identified as part of this concern provisions regarding distributors' obligations to restrict exports and measures to impose stock obligations. Due to limited data only the impact of stock obligation measures could be assessed, by comparing countries with and without such an obligation, but otherwise similar regimes (i.e. Groups C and E, thereby correcting for the overlap between these two groups). (Table 20). To account for limitations in the completeness and comparability of data between countries, the analysis focused on the shortages per Member State in each group for the period 2017-2019 only, as this is the period for which nearly all Member States provided data.[156]

[155] Depending on whether there is any surplus product in the market from which the company can import.

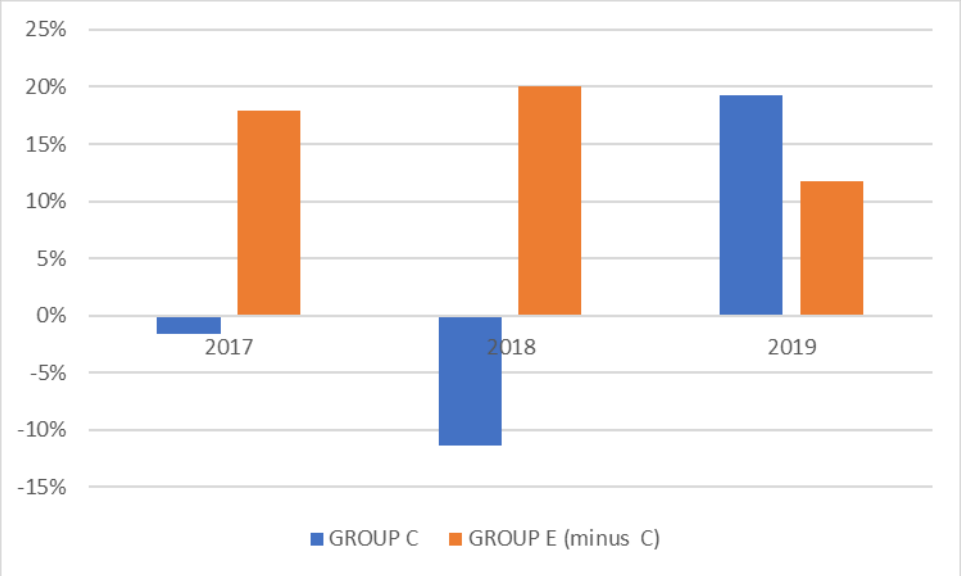
[156] The exceptions are Ireland and Greece. For these countries shortage data start from 2017 and 2019 respectively.

Table 20 Country groups clustered by additional measures to ensure appropriate and continued supply

Group	Provisions	Countries
Group A	A minima transposition of MAHs and distributors' obligations	Cyprus, Denmark, Croatia, Malta
Group B	A minima transposition + provisions allowing export restrictions	Austria, Greece, Latvia, Poland
Group C	Extended obligations onto MAHs and/or distributors + export restrictions (i.e. excludes group B)	Belgium, Bulgaria, Czechia, Estonia, Spain, Finland, France, Hungary, Italy, Portugal, Romania, Slovakia
Group D	Stock obligations (excl. pharmacies)	Belgium, Germany, Spain, Finland, France, Italy, Luxembourg, Netherlands, Portugal
Group E	Stock obligations (excl. pharmacies) + export restrictions	Belgium, Spain, Finland, France, Italy, Portugal

Between 2017 and 2019, shortages continued to increase year-on-year but at different rates in the two groups (Figure 16). The rate of growth in shortage notifications was slower in countries without stock obligations (Group C, excluding Group E) than in those with such obligations (Group E). It shows that there are differences in year-on-year growth for these two groups, but there is no clear pattern. This finding, and the short time period for the comparison, makes it impossible to draw any firm conclusions about the impact of stock obligations on the level of (notified) shortages in the countries where they were introduced.

Figure 16 Year on year change in ongoing shortages (2017-2019) by type of provisions



Source: Ecorys, Milieu Law & Policy. Based on data provided in national shortage registries and information on transposing measures collected via desk review interviews with NCA representatives.

The study did not identify *legal* requirements pertaining to procedures or rules of public procurement that were directly aimed at preventing shortages. Nonetheless, several Member States have introduced practices, which are not enshrined in law, to prevent or mitigate shortages within the remit of existing procurement rules. For instance:

- France has introduced the possibility to include clauses according to which the contractor must ensure supply of medicinal products via other suppliers if they cannot distribute the products themselves. Alternatively, the purchasing entity may arrange the supply with another supplier while the original contractor must bear the costs of this new purchase.

- In Spain, urgent public procurement needs can be fulfilled via a negotiated procedure, also for medicinal products for which a MAH has exclusive rights.
- Hungary uses multi-winner award of public procurement to avoid shortages due to force majeure.
- Sweden makes a use of a substitutability criterion for the supply of medicines. The national competent authority considers this an important means mitigation measure.
- In Denmark, public procurement of medicines is delegated to a public purchasing company, which gathers monthly information on hospital pharmacies' needs, to inform MAHs immediately of changes on the demand side. This allows them to better prepare for demand fluctuations and adjust supply accordingly.

Monitoring and enforcement of the EU legal framework

Neither Article 23a nor 81 defines specific sanctions when the notification obligations are not met. Rather, it is the responsibility of the Member States to monitor and enforce the obligations and impose "effective, proportionate and dissuasive penalties pursuant to Article 118a of the Community Code" if the obligations are not met.

Around half of Member States[157] have specified sanctions for non-compliance with the obligations. The remaining ones set 'catch-all' sanctions that cover any type of infringement. Survey responses from NCA representatives, however, suggest that sanctions that address continuity of supply – in line with Article 81 – have been incorporated into procurement procedures only in Spain, Finland, Latvia and the Netherlands (Annex H, Figure 43). Most sanctions are administrative fines. Based on information shared by some NCA representatives during group discussions, there is substantial divergence between Member States in the size of the fines and in how often countries apply these. No comprehensive data was collected from NCA on when or why fines have been levied and how high the fines were. Some reports nonetheless offer insight into the wide range of possible fines. For instance, in 2018 the Netherlands raised the maximum imposable fine on MAHs for culpable failure to meet supply obligations from EUR 150,000 to EUR 820,000.[158] In a 2019 report it was indicated that the effects of the enforcement of this measure were not yet known and could be either positive or negative.[159] The report indicated that sanctions had been imposed twice and that several more investigations were ongoing. It did not offer information about the amounts fined. In France, in 2018, the National Authority for Medicines and Health Products Safety (ANSM) imposed a fine of EUR 348,623 on a pharmaceutical company for not meeting its supply obligation.[160] It deemed the company had neglected to adequately plan for possible shortages of the medicines that it considered to be of major therapeutic interest.[161] However, two fines imposed the year after amounted to only EUR 830 and EUR 5,807.[162]

[157] Bulgaria, Belgium, Croatia, Czechia, Cyprus, Estonia, France, Greece, The Netherlands, Portugal, Poland Romania Slovakia, Slovenia.

[158] Tweede Kamer der Staten-Generaal. (2016) Wijziging van de Geneesmiddelenwet in verband met technische verbeteringen en verhoging van het boetemaximum. Nr.3 Memorie van Toelichting. Available at: https://zoek.officielebekendmakingen.nl/kst-34694-3.html. Accessed 3 September 2021.

[159] Weda M. Et al. (2020). Maatregelen geneesmiddelentekorten; stand van zaken najaar 2019. RIVM-briefrapport 2019-2020. Rijksinstituut voor Volksgezondheid en Milieu. Ministerie van Volksgezondheid, Welzijn en Sport. Available at: https://www.rivm.nl/bibliotheek/rapporten/2019-0220.pdf. Accessed 3 September 2021.

[160] ANSM. (2018) Bilan 2019 des sanctions financières prononcées par l'ANSM. Available at: https://archiveansm.integra.fr/Decisions/Injonctions-decisions-de-police-sanitaire-sanctions-financieres-interdictions-de-publicite-Sanctions-financieres/Bilan-2018-des-sanctions-financieres-prononcees-par-l-ANSM. Accessed 3 September 2021.

[161] Allen & Overy. (2019) French regulator (ANSM) imposes major financial penalty on a pharmaceutical company for shortage of medicine. Available at: https://www.allenovery.com/en-gb/global/blogs/life-science/french-regulator-ansm-imposes-major-financial-penalty-on-a-pharmaceutical-company-for-shortage-of-medicine. Accessed 3 September 2021.

[162] ANSM. (2019) Bilan 2019 des sanctions financières prononcées par l'ANSM. Available at: https://archiveansm.integra.fr/Decisions/Injonctions-decisions-de-police-sanitaire-sanctions-financieres-interdictions-de-publicite-Sanctions-financieres/Bilan-2019-des-sanctions-financieres-prononcees-par-l-ANSM. Accessed 3 September 2021.

In stakeholder consultations (interviews, focus groups), multiple NCA representatives have expressed doubts about the effectiveness of sanctions on failure to meet supply obligations. Authorities in several Member States (Hungary, Italy, Latvia and Slovenia) have suggested that the current level of sanctions may be insufficient to be effective. Some even fear that the threat of sanctions could be a deterrent for pharmaceutical companies when deciding in which markets to place their products or that differences in the fines between countries could lead MAHs to preferentially supply countries with fines over those without. A further point that was noted is that the use of sanctions requires proper monitoring and enforcement of obligations, but that many authorities lack the financial resources or capacity to verify if the MAH or wholesaler has done everything in their power to fulfil their obligations.

Overall, some stakeholders have taken the view that the continued and rising problem of medicine shortages in the EU, even after adoption of Directive 2001/83/EC and the transposition of Articles 23a and 81 into national law, is clear evidence that, by itself, the EU legal framework is insufficiently effective in achieving the aim of protection of public health. They underline that the obligations laid down in the Articles are nonetheless relevant but that they should be complemented with additional measures (e.g. extension of the temporal scope of Article 23a, or the definition of certain notions such as "appropriate and continued supplies" and MAHs and distributors "responsibilities" of Article 81).

6.3. Efficiency

Efficiency refers to "the relationship between the resources used by an intervention and the changes generated by the intervention (which may be positive or negative)."[163] Analysis of whether an intervention can be considered efficient should thus take into consideration whether and how the same benefits, or greater, could have been achieved at less cost had the intervention been approached or conducted differently. Whether the current EU legal framework, in particular the obligations under Articles 23a and 81 of Directive 2001/83/EC, can be considered efficient thus depends on the balance between the benefits derived from the provisions tied to the framework and the costs associated with the implementation and enforcement of these provisions. The following sections respectively consider the main types of costs and benefits of different measures to address shortages and attempt to quantify these. Importantly, it does not refer to the costs of shortages themselves; rather, these appear in the analysis of benefits – by virtue of costs avoided – of measures to prevent or mitigate shortages, as discussed in section 6.3.2.

6.3.1. Estimation of costs

The costs associated with implementation and enforcement of the obligations laid down by the EU legal framework are borne primarily by the national competent authorities responsible for monitoring and enforcing compliance with obligations, and the MAHs and wholesale distributors to whom the obligations fall. Costs to these groups were considered for two main categories of measures:

- Notification requirements of (expected) shortages – linked to Article 23a
- The obligation to ensure continuity of supply (public service obligations) – linked to Article 81

Within each of these categories, different types of costs can be expected (Table 21). The main costs in connection to Article 23a are those for the development and maintenance of (electronic) reporting systems and those associated with processing of notifications and interactions between authorities and suppliers to discuss shortage situations. These costs can logically be assumed to consist of both a **fixed component** (e.g. development and maintenance of systems, involvement of staff) and a **variable component** (associated with the processing of each individual notification). The main types of costs connected to Article 81 are staff costs for authorities needed to monitor and enforce supply obligations and costs to suppliers from stockholding requirements. In the analysis of effectiveness of the legal framework (Section 6.2) also the role of export restrictions was considered. Whilst such

[163] European Commission (no date). Better Regulation Toolbox. Tool #47 Evaluation criteria and questions. Available at: https://ec.europa.eu/info/sites/default/files/better-regulation-toolbox.pdf. Accessed 5 September 2021.

restrictions do not any impose costs on MAHs, they can result in loss of revenue for other supply chain actors, most notably parallel traders. The restrictions are, however, not part of the EU legal framework and thus not considered within the scope of the cost-benefit analysis.

Table 21 Cost elements considered in efficiency analysis of the EU legal framework

Stakeholder group	Type of measure	Type of costs	Estimates	Sources
National competent authorities	**Notification obligations (Art 23a)**	Development and maintenance of notification system (fixed, largely independent of number of notifications)	None available	--
		Time spent on verification of notifications and enforcement of notification requirements	Estimated at EUR 800 in staff costs per shortage notification. Approx. EUR0.5 million (7 full time equivalents) per year per Member State	Interviews, survey, focus groups
	Supply obligations (Art. 81)	Time spent on monitoring and enforcing supply obligations		
MAH and wholesalers	**Notification obligations (Art 23a)**	**Administrative costs:** Time spent on notification; fees associated with notification; possible penalties for breach of obligation	Approx. EUR 300 per notification per Member State (n=1 MAH). Penalties for non-compliance differ by Member State.	Interviews, survey, solution panel consultation
	Supply obligations (Art. 81)	**Adjustment costs:** (Increased) stock holding; possible penalties for breach of obligation	Approx. EUR 150,000 per stock keeping unit per month when PSO applies	Survey

National competent authorities

Surveyed NCA representatives were asked to estimate the resources dedicated (in euros and staff time) for all activities directly associated with the obligations tied to Articles 23a and 81, specifically:

- Collecting, processing, and analysing shortage notifications (Art. 23a)
- Monitoring and enforcing compliance with notification obligations (Art. 23a)
- Monitoring and enforcing compliance with supply obligations (Art. 81)
- Reporting on compliance with obligations (Art. 23a and 81)

No separate information was requested on the development and maintenance of the technological infrastructures needed to support the implementation of the obligations as these are considered a fixed and one-time investment.

Information was received from 14 NCAs. Based on their responses, the average number of staff involved in application of both provisions together is estimated to amount to just over 7 full-time equivalents per Member State (Annex H,

Figure 42). This implies that annual costs of direct staff involved in application of these provisions are on average approximately EUR 0.5 million per Member State per year and around EUR 13 million for the whole EEA.[164] If related to the number of shortages reported in 2019, the costs amount to on average EUR 1,600 per shortage per Member State. These staff numbers are understood to cover

[164] In this estimate only direct labour costs have been taken into account, so excluding overhead or indirect costs. An average salary cost of EUR 60,000 to 70,000 per year has been assumed for the government staff in the described activities.

directly involved staff only. In this respect, the above costs are likely to be an underestimation of the annual costs related to the provisions.

In interviews, most national authorities underlined that they generally do not maintain separate budget lines or cost overviews for activities linked to the implementation, monitoring or enforcement of either of the obligations. Therefore, they could not provide reliable estimates of their *absolute* costs. This data therefore also does not exist in the public domain and no other data sources could be identified to inform the analysis on this aspect.

Only eight surveyed NCAs provided estimates of the *relative* impact of specific measures on their operational costs[165] (Annex H, Figure 47). Out of those eight countries, seven provided estimates of the relative impact of the requirement for early notification of expected shortages[166]. This was said to have substantially increased operational costs (greater than 10% increase) in one country and somewhat increased costs (by 5-10%) in a further two countries. The other four responding countries indicated this had only a very small (0-3%) increase or no impact at all.

Since the supply obligation connected to Article 81 has been operationalised differently in different countries, it is not possible to arrive at a single cost estimate for the implementation and enforcement of this obligation. A limited number of surveyed NCAs offered some insight into the impact of different operational measures on their costs (Annex H, Figure 47). Three NCAs indicated that the stockholding requirements for MAHs and distributors they had introduced had, on average, a very small impact on their own operational costs.[167] Similarly, responding NCAs indicated that introduction of procurement practices to include criteria for continuity of supply, including penalties, did not come with significant costs to the NCA.[168] These findings are expected as, from the perspective of the NCA, the measures are largely administrative whilst the associated costs are predominantly carried by the MAHs and distributors.

Marketing authorisation holders and wholesale distributors

Very little quantitative data about the costs for compliance with the obligations imposed by the legal framework could be obtained from MAHs and wholesalers. In interviews, MAHs explained that the costs for compliance with notification obligations, as covered by Article 23a, depend strongly on the number of countries in which they operate and on the specific national requirements set for notification (e.g. when (expected) shortages should be notified and for which products) and on the duration of shortage. Longer shortages may necessitate more frequent and sustained interaction between the company and the regulatory authority to discuss plans for resolving the shortage and mitigating its impacts. Only one company offered an estimated cost for notification of a shortage, at EUR 300 per product per country. **Whilst the cost of notification itself thus appears relatively small, a potential significant extra cost can be incurred if a company is found to be in breach of its notification obligation and a sanction is imposed**. As discussed previously (Section 6.2), the size of sanctions can differ greatly between countries and further depends on how serious the authorities deem the breach to be but, in practice, sanctions are seldom imposed.

Interviewed manufacturers indicate that most of their activities conducted to ensure appropriate and continued supply of marketed products are part of normal business operations and are not performed specifically to comply with nationally imposed supply obligations. This includes elements such as demand forecasting, stockholding and optimisation of production and logistics processes. Because of this, **costs associated with compliance with supply obligations, as mandated by Article 81, are not readily distinguishable within the company's operating costs**.

One surveyed MAH estimates the costs of stock keeping at EUR 150,000 per stock keeping unit per month. However, it did not indicate whether these costs are additional because of greater levels of stock holding needed to comply with supply obligations or are part of standard industry stock keeping

[165] Finland, Germany, Iceland, Latvia, the Netherlands, Portugal, Slovenia, Spain. However, Iceland did not provide estimates on the requirement for early notification of expected shortages.

[166] The survey question did not distinguish between notification of product withdrawals and foreseen suspension of operations and notification of shortages caused by unforeseen supply disruptions.

[167] N=3, with n=1 for small impact (5-10% increase), n=1 for very small impact (0-3%) and n=1 for no impact on operational costs.

[168] N=5, with n=1 for small impact (5-10% increase), n=2 for very small impact (0-3%) and n=2 for no impact on operational costs.

levels. No other reliable public data could be identified from which to estimate the average cost of stock holding of medicines. It is likely that **stock keeping costs are substantially influenced by product-specific characteristics** such as storage requirements (for instance, the temperature at which the product needs to be stored and transported) or box and pack sizes. Another relevant factor is whether stock is held in the form of finished products or as semi-finished or intermediate products. For semi-finished products or intermediate products, the MAH has not yet incurred costs for packaging and labelling in accordance with country-specific requirements and is more flexible in where it distributes the products.

Overall, very few objective and reliable estimates exist of the costs for national authorities on the one hand and MAHs and wholesalers on the other, in direct connection to the obligations laid down by the EU legal framework. Moreover, available estimates may obscure substantial variations between products and Member States. From the limited data available, it appears that the adjustment and administrative costs for compliance with the obligations are relatively small for MAHs in relation to their general operational costs and, in particular in relation to supply obligations, are substantially covered by normal operations that would have been conducted even in the absence of the provisions. Potentially greater administrative costs, in the form of sanctions, could be incurred by these parties if they fail to meet obligations though limited enforcement means that these costs are not frequently incurred.

6.3.2. Estimation of benefits

In assessing the benefits for the various stakeholders, a situation in which a preferred medicine is unavailable to the patient (i.e. in shortage) was compared to the normal situation (i.e. without a shortage), irrespective of the cause of the unavailability. Unavailability of the product could, for instance, be the result of production problems, distribution problems or unexpected increased demand but also of a commercial decision by the MAH to suspend marketing.

A situation in which a medicine for which there is a demand from patients is (temporarily) not available causes costs for various stakeholders. If a policy measure is effective in avoiding the particular shortage such costs are also avoided. These avoided costs are seen as a benefit derived from that measure. Apart from the stakeholders that directly incur costs in case of a shortage, as described in the previous section, also patients and health professionals benefit from an avoided shortage.

The occurrence of shortages brings with it a financial cost (distinct from the costs associated with the *measures* to prevent or mitigate shortages, described in section 6.3.1). For patients, the consequences of shortages can be both financial and non-financial. Financial costs, either for patients or for payers (health systems or insurers) can arise if the patient cannot be dispensed the preferred medicine and instead is given another more expensive (e.g. branded) medicine.[169] Non-financial consequences include potentially poorer treatment outcomes when less-than-optimal alternatives are used or when treatment is suspended for lack of suitable alternatives. To health professionals, the cost of shortages stems mainly from the time and resources they need to invest in identifying and sourcing suitable treatment alternatives, as well as communicating with physicians and patients. In health systems wherein the cost of medicines is largely covered by insurance or national health systems, the costs for more expensive alternatives are largely carried by payers (who, in response, may raise deductibles or insurance premiums, thereby transferring the costs back to society). When a shortage can be avoided, the associated costs are also avoided. Thus, in economic terms, the benefits of measures that prevent or mitigate shortages generally consist of "avoided costs".

From the perspective of national authorities, MAHs and wholesalers the avoidance of shortages implies that some of the costs derived from notification and management of shortages (described in section 6.3.1) can also be avoided. Additionally, to MAHs and wholesalers a shortage situation represents a loss of revenue. To them, the avoidance or quick resolution of a shortage will constitute a direct financial benefit. In summary, the possible benefits from prevention and mitigation of shortages fall on a wide group of stakeholders, as summarised in Table 22.

[169] For instance, if the medicine has a higher co-payment or is paid for out-of-pocket.

Table 22 Benefits considered in efficiency analysis of the EU legal framework

Stakeholder group	Type of benefits	Estimates	Sources
Patients	Avoidance of higher co-payments or out-of-pocket expenses; Avoidance of costs and health consequences associated with delayed or sub-optimal treatment	Not quantifiable	Literature, EAHP survey
Health professionals	Time avoided on having to deal with shortages, such as by conferring with prescribers and having to source suitable alternatives	Approx. EUR 25,000 per notification per Member State	PGEU & EAHP surveys; study survey of pharmacists
Health systems / payers	Avoidance of costs for reimbursement of more expensive medicines or higher healthcare costs resulting from delayed or sub-optimal treatment.	None available	--
MAHs and wholesalers	Avoidance of costs associated with notification of shortages and actions required to resolve shortages; Avoidance of loss of revenue from products in shortage	Inverse of estimate per notification in Table 21 Avoided loss of revenue dependent on price and sales volume of product for which shortage is avoided	See Table 21 No data on loss of revenue to MAH due to shortages
NCAs	Avoidance of costs associated with processing shortage notifications; reduced costs of monitoring and enforcement of compliance with notification and supply obligations	Inverse of estimate per notification in Table 21	See Table 21

Limited data exist on the costs to patients from medicine shortages. A 2019 review identified five studies that reported increased out of pocket costs to patients resulting from medication shortages. These costs happened because patients had to pay for more expensive alternatives or were forced to procure their medicines at a private sector pharmacy.[170] The findings were, however, largely based on qualitative reports by patients or pharmacists or were limited to specific medicines. From these data, it is not possible to derive an average impact on increased out-of-pocket costs to patients stemming from shortages. The review also noted higher rates of medication errors, adverse events and even mortality but did not attempt to express this in economic terms. The 2019 EAHP survey found that a majority (62%) of surveyed hospital pharmacists, physicians and other health professionals had observed negative impacts on patient care in their hospital due to shortages, most commonly involving delays in care, suboptimal treatment and cancellation of care.[19] The EAHP survey also included responses from 158 patients, many of whom (30%, n=48) confirmed having experienced delays in care. Others reported consequences such as failure of treatment (12%, n=20) or increased length of stay in hospital (11%, n=18). However, none of these observed impacts was expressed in quantifiable terms (e.g. QALY's lost or length of hospitalisation). Consequently, the benefits that befall patients from the avoidance or fast resolution of shortages cannot easily be estimated in economic terms.

Some more data exist about the consequences of shortages for pharmacists and thus of the costs averted when shortages are prevented. For instance, a 2019 study conducted among 365 hospital pharmacies in the United States estimated that the financial impact of having to manage medicines shortages added up to 8.6 million hours of additional labour, amounting to just under EUR 316 million

[170] Phuong JM, Penm J, Chaar B, Oldfield LD, Moles R. (2019). The impacts of medication shortages on patient outcomes: a scoping review. PLoS One 14(5). Available at: https://10.1371/journal.pone.0215837. Accessed 6 September 2021.

per year.[171] A 2017 study in 25 Flemish community pharmacies, estimated that these pharmacies spent about half an hour per week on dealing with medicine shortages.[172] The 2020 conducted by the PGEU offers a considerably higher estimate, suggesting that across Europe pharmacy staff spend an average of 6.3 hours per week on this.[18] An even higher estimate is given in a 2019 report by the Royal Dutch Pharmacists Association (KNMP), according to which surveyed pharmacy teams spend 17.5 hours per week solving shortage situations (5.5 hours by the pharmacist and a further 12 hours by other pharmacy staff).[173] None of these reports convert time spent directly into a financial cost.

This study also surveyed pharmacists on their time spent on dealing with shortages. Based on the responses of 54 pharmacists, the average time spent is estimated to be around 4 hours per week (Annex H, Figure 56). Considering the volume of all shortages in a calender year (i.e. around 8,000 in 2019), this would represent a cost of around EUR 25,000 per shortage per Member State. However, as indicated, available estimates of time spent by pharmacists on dealing with shortages show significant variation.

EU Member States have different types of health systems, ranging from fully public national health systems to health systems that are substantially privatised. Countries consequently differ in how the costs from medicine shortages are shared between patients and payers. This makes it difficult to determine how the cost of shortages in one country should be compared to that in another. Irrespective of this, this study was not able to identify reports of the costs of shortages to EU health systems. In November 2017, it was reported that the United Kingdom's National Health System (NHS) was spending around EUR 43 million to boost stocks of medicine in shortage at emergency prices.[174] However, such costs are incidental rather than structural and offer no insight into how much having to reimburse more expensive medicines are costing countries. Likewise, in 2019, the Dutch government announced it planned to build up an 'iron stock' of medicines, worth five months of supply to cover around 85% of temporary shortages and reduce its reliance on more expensive replacement medicines.[175] The plan was estimated to cost EUR 25 million. Following discussion in Parliament, it was decided to first conduct a pilot project with stock of selected medicines worth two months of supply.[176] The pilot was initiated in April 2021 and results are not yet available.

The potential for cost savings by effective prevention of medicine shortages is underlined also by data from the United States, which suggests that the annual cost of purchasing alternative medicines to hospital pharmacies amounts to around USD 215 million (around EUR 185 million).[177] Differences in the prices of prescription medicines, reimbursement systems and treatment guidelines between the US and EU Member States all mean that this estimate should not be directly applied to the EU situation but it nonetheless offers meaningful insight into the order of magnitude of the issue. Importantly, none of the estimated costs and savings described here take into account the costs that could result from delayed or foregone treatment in cases where no suitable substitutes are available

[171] Vizient (June 2019). Drug shortages and labor costs. Measuring the hidden costs of drug shortages on U.S. hospitals. Available at: https://newsroom.vizientinc.com/sites/vha.newshq.businesswire.com/files/doc_library/file/Drug_Shortages_Labor_Cost_Report_Vizient.pdf. Accessed 6 September 2021. Currency converted from US$ to EUR using historical exchange rate on 26 June 2019 via Fxtop.com

[172] De Weerdt E, Simoens S, Casteels M, Huys I. (2017) Time investment in drug supply problems by Flemish community pharmacies. Front. Pharmacol. Available at: https://doi.org/10.3389/fphar.2017.00568.

[173] KNMP (2019) Onderzoek geneesmiddelentekorten 2019. Available at: https://www.knmp.nl/downloads/rapport-knmp-onderzoek-geneesmiddelentekorten-2019.pdf. Accessed 6 September 2021.

[174] Iacobucci G. (2017). Drug shortages cost £38m in November. BMJ 359. Available at: https://doi.org/10.1136/bmj.j5883. Accessed 6 September 2021. Currency converted to EUR at 2017 historical exchange rate using fxtop.com.

[175] Rijksoverheid. (4 November 2019) Minister Bruins: oplossing voor geneesmiddelentekorten. Available at: https://www.rijksoverheid.nl/actueel/nieuws/2019/11/04/minister-bruins-oplossing-voor-geneesmiddelentekorten. Last accessed 7 October 2021.

[176] Van Ark T. (16 April 2021). Voortgangsbrief ijzeren voorraad geneesmiddelen. Available at: https://www.rijksoverheid.nl/binaries/rijksoverheid/documenten/kamerstukken/2021/04/16/voortgangsbrief-ijzeren-voorraad-geneesmiddelen/voortgangsbrief-ijzeren-voorraad-geneesmiddelen.pdf. Last accessed 7 October 2021.

[177] Morrisey J. (2012) The drug shortage. Hospitals & health Networks. 81(12): 46-50, 1.

or the additional healthcare costs that could result from sub-optimal treatment or increased occurrence of adverse events in case the dispensed alternative is not fully equivalent to the medicine in shortage.

6.3.3. Overall assessment of efficiency

Because of the previously described data limitations in determining the results of specific measures to prevent or mitigate shortages (considered as part of the effectiveness assessment in Section 6.2) as well as the lack of reliable estimates of the respective costs and benefits, the assessment of efficiency is severely challenged.

No data were identified that would allow to quantify the specific benefits of the notification obligation on MAHs as laid down in Article 23a. In general, more timely notification allows authorities and health professionals to identify alternatives and devise mitigation strategies but it cannot be determined how this translates into economic or health benefits to any of the affected parties. Moreover, the notification obligation does not prevent the MAH from discontinuing the marketing of the product, meaning that it does not negate the costs health professionals must make to identify and source suitable alternatives. Likewise, patients may still incur the costs of having to pay for more expensive alternatives or experience the negative health outcomes associated with the unavailability of their preferred medicine. Nonetheless, early notification can help to reduce these costs as authorities are given more time to devise both effective and cost-efficient mitigation strategies. Although the absolute costs to MAHs associated with having to comply with this obligation could not be quantified, the costs per notification of product discontinuations are likely relatively small particularly as such discontinuations are not the main reason for shortages. Notification of unexpected shortages can reasonably be assumed to be a more significant expense.

Interviewed representatives of authorities in some Member States consider the absence of harmonised notification templates a barrier to the exchange of information between countries, which results in lack of coordination and inefficiencies. Authorities in the Netherlands also highlighted the lack of harmonised grounds for justifications of a late notification by MAHs as a potential source of inefficiency. It was indicated that detailed, manual analysis of the provided justifications for all notifications would entail a significant workload and require substantial commitment of resources. The supply obligation under Article 81 is phrased in such general terms that efficiency assessment cannot be done at the level of the obligation itself.

This implies that the effectiveness of neither the notification requirement, nor the supply obligation or additional measures (such as export restrictions) could be properly quantified and, consequently, neither can the efficiency. In general terms, however, it can be concluded that any measure that is effective in avoiding medicine shortages may have various benefits for the following groups:

- For patients: avoidance of negative health impact resulting from delays in treatment and/or treatment with suboptimal medication
- For patients and tax or health insurance payers: avoidance of higher financial costs of more expensive alternative medicines
- For health professionals: avoidance of time costs involved in dealing with the medicine shortage, estimated at around EUR 25,000 per shortage per Member State per year (based on four hours per week per pharmacist in dealing with medicine shortages)[178]
- For MAHs and/or wholesale distributors: avoidance of administrative costs of notification, estimated at EUR 300 per notification per Member State[179]

[178] This implies that time costs of health professionals in a Member State with 400 notifcations are on average EUR 10 million per year.

[179] MAHs and/or wholesale distributors may also experience an impact on their net operating profit. This impact may,however, be negative of positive, depending on the specific situation. For instance, in case a medicine is withdrawn for commercial reasons (e.g. production or distribution is loss making) the impact would be positive. However, like in the case of the impact for patients, the impact is vary situation specific and no general conclusion can be drawn.

- For NCAs: avoidance of costs of registration of, analysis and reporting on the shortage notification.

Compared to the avoided costs for MAHs and health professionals, the benefits for patients expressed in monetary terms can be substantial. The size of these benefits, however, depends on factors that may greatly vary per medicine, such as the number of patients affected, the type of illness of these patients, the duration of the shortage and the availability and quality of alternatives. These factors will vary considerably for individual shortages, meaning that no general conclusions can be drawn. This also means that no quantitative conclusion can be drawn on the efficiency of the obligations introduced in the past decades. Ultimately, whether these measures can be considered efficient is a matter not only of the balance between the costs of measures to prevent shortages and the benefits of avoided shortages, but also of the importance that governments and health systems place on being able to provide the highest standard of healthcare, including the dispensing of preferred medicines without delay.

Representatives of the national authorities in Spain and Hungary felt that the possible benefits, especially health benefits to patients, from the implementation of notification and supply obligations justify the related cost.

6.4. Coherence

The analysis of coherence involves looking at how well or not different actions work together and highlights where there are synergies or tensions between actions (e.g. objectives that are potentially contradictory, or approaches which are causing inefficiencies).[148] In the context of this study, the question is whether the relevant provisions of the Community code relating to medicinal products for human use (Directive 2001/83/EC, Articles 23a and 81) are internally coherent with the EU legal framework. It also considers how these provisions complement actions introduced by the Member States and are externally coherent with national legal frameworks regulating the continuity of supply of medicines.

Internal coherence

Two amending Directives are directly relevant to the consideration of internal coherence in the context of the EU legal framework:

- Directive 2010/81/EU, as regards pharmacovigilance[180]
- Directive 2011/62/EU, as regards the prevention of the entry into the legal supply chain of falsified medicinal products[181]

Article 116 of Directive 2010/81/EU allows competent authorities to suspend, revoke or vary a marketing authorisation when, following evaluation of data resulting from pharmacovigilance activities, the view is taken that the product is "harmful or that it lacks therapeutic efficacy, or that the risk-benefit balance is not favourable or that its qualitative and quantitative composition is not as declared." The situation in which competent authorities decides that a product should be removed from the market is distinct from one in which the MAH itself decides to discontinue operations. As such the notification obligation of Article 23a of Directive 2001/83/EC does not apply here. Moreover, it is in the interest of public health that products that are deemed to be unsafe are removed from the market as quickly as possible. The revocation of the marketing authorisation also means that the supply obligation of Article 81 no longer applies. However, Article 117 of Directive 2010/81/EU specifies that the competent authority may "for a medicinal product for which the supply has been prohibited or which has been withdrawn from the market […], in exceptional circumstances during a

[180] European Parliament and Council (15 December 2010). Directive 2010/84/EU amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. Official Journal of the European Union. L 348/74. Available at: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF

[181] European Parliament and Council (8 June 2011). Directive 2011/62/EU amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products. Official Journal of the European Union. L174/74. Available at: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf.

transitional period allow the supply of the medicinal product to patients who are already being treated with the medicinal product."

Directive 2011/62/EU, known as the Falsified Medicines Directive (FMD), introduced new packaging and labelling requirements for medicinal products, imposed stricter rules on the import of APIs and strengthened record-keeping requirements for wholesale distributors.[182] The Directive was adopted in 2011 and has applied since January 2013. The implementation of the Directive has been accompanied by the introduction of an Electronic Medicines Verification System (EMVS).[183] Although the FMD has no direct bearing on either of the obligations to MAHs and wholesaler-distributors laid down by Articles 23a and 81 Directive 2001/83/EC, there are several points of intersection between the FMD and the appropriate and continued supply of medicines.

First, in 2012, there were concerns that the requirement that all imported APIs are manufactured in compliance with GMP standards or acceptable equivalent standards would lead to an increase in shortages.[184] However, half a year after the FMD went into effect, both the European Commission and EFPIA indicated they had not observed any increase in shortages resulting from interruptions in API supply.[185] It was reported that not only had suppliers stockpiled APIs in preparation for the measure, but that API suppliers in third countries also were sufficiently prepared to provide written confirmation.[186] It was not a in the scope of the study to assess whether the measures introduced by FMD were sufficient to ensure the quality of APIs. The data from the national shortage registries reviewed for this study are insufficiently granular to determine whether there has been an increase in shortages caused by problems with the importation of APIs in the years since the implementation of the FMD. However, no specific concerns about this were raised in interviews with either manufacturers or competent authorities, suggesting the concern was mostly unfounded.

The FMD also introduced the need for the packaging of all prescription medicines to be serialised, which includes barcoding. These requirements are detailed in the Commission Delegated Regulation 2016/161 and have applied as of February 2019.[187] The European industry association for the generic medicines industry has publicly stated that the serialisation requirements have slowed down manufacturing (packaging) processes.[188] No public data on pharmaceutical manufacturing times and the role of serialisation were found that establish the extent to which this has happened. In interviews, suppliers did indicate that the FMD requirements on safety features (anti-tampering devices and unique identifiers) are complicating the repacking and relabelling of products for sale in another market. It may also impact on the speed with which suppliers can (re)allocate stock of finished and packaged products to meet unexpected increased demand in specific markets. As the Delegated Regulation was implemented only recently (2019), no formal evaluation of the Regulation's

[182] European Commission (no date). Falsified medicines. Available at: https://ec.europa.eu/health/human-use/falsified_medicines_en. Accessed at 7 September 2021.

[183] European Medicines Verification Organisation. (no date). Introduction to the European medicines Verification System (EMVS). Available at: https://emvo-medicines.eu/mission/emvs/.

[184] Gaffney A. (12 December 2012). EU Falsified Medicines Directive could result in drug shortages. Regulatory Focus. Available at: https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2012/12/eu-falsified-medicines-directive-could-result-in-drug-shortages. Accessed 7 September 2021.

[185] Taylor P. (9 December 2013) API imports in the EU: gauging the FMD's impact. Pharmafile. Available at: http://www.pharmafile.com/news/181764/api-imports-eu-gauging-fmd-s-impact. Accessed 7 September 2021.

[186] Bennett S. (10 June 2014) API supply lines: examining the impact of the EU Falsified Medicines Directive and global GMP certifications. ValueChainInsights. Thomson Reuters. Available at: https://www.dcatvci.org/292-api-supply-lines-examining-the-impact-of-the-eu-falsified-medicines-directive-and-global-gmp-certifications. Accessed 7 September 2021.

[187] European Commission. (2 October 2015) Commission delegated regulation (EU) 2016/161, supplementing Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, and in particular Article 54a(2) thereof. Official Hournal of the European Union L32/1. Available at: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-1/reg_2016_161/reg_2016_161_en.pdf. Accessed 7 September 2021.

[188] Rees V. (10 February 2020) Resolving and mitigating medicine shortages in the EU. European Pharmaceutical Review. Available at: https://www.europeanpharmaceuticalreview.com/article/112301/resolving-and-mitigating-medicine-shortages-in-the-eu/.

impact has taken place and no data are available on how the introduction of mandatory safety features has impacted on the ability of MAHs and wholesalers to ensure appropriate and continued supply of medicines in the Member States. There are no indications that the introduction of the system has led to widespread shortages in the EU.

External coherence

As indicated in previous sections, many Member States have introduced additional legal provisions and actions in their efforts to prevent or mitigate shortages. These include complementary measures for the realisation of the objectives of Article 23a, as well as measures to further operationalise Article 81. Review of these provisions and consultations with national authorities did not reveal any material conflicts between these national measures that would limit the effects of Articles 23a and 81 of Directive 2001/83/EC.

Although, under Article 168 of the Treaty on the Functioning of the European Union (TFEU)[189], public health is a competence shared between the European Union and its Member States, the responsibility for tendering and procurement of pharmaceutical products rests with the individual Member States. Nonetheless, tenders above the European threshold for public procurement are subject to EU public rules. The Public Procurement Directive 2014/24/EU (PPD) requires contracting authorities to award the 'most economically advantageous tender' (MEAT).[190] The Directive (paragraph 90) leaves it up to the individual contracting authority to decide what quality factors, if any, to consider and how to weigh these into the tender evaluation, as long as this is done transparently. Consultation with different groups of stakeholders suggests that, at present, national contracting authorities still focus predominantly on lowest price and that assessment criteria do not often include factors relating to supply chain security. An in-depth assessment of national tendering procedures for medicines and the criteria used therein was outside the scope of this study. However, as the PPD explicitly allows authorities to select tenders based on price or cost-effectiveness only, these national procurement practices are not in direct contradiction with the current provisions of the EU legal framework.

Under the PPD, contracting authorities are also free to set "adequate quality standards by using technical specifications or contract performance conditions". This allows Member States to impose their own conditions on suppliers, such as stock holding obligations and mandatory reporting of stock, and decide appropriate penalties for non-compliance with the conditions, such as the supplier bearing the difference of the costs in the case the contracting authority has to procure product from another, more expensive supplier due to a shortage. The measures introduced by some Member States to operationalise and further strengthen the supply obligation of Articles 81 of Directive 2001/83/EC, as shown in Table 18 are thus coherent with the PPD.

An important point of possible tension between the EU legal framework and national measures to protect the continuity of supply of medicines concerns the use of export restrictions. Parallel trade of medicines is a contentious issue: the fear is that what represents a solution for one country may create a problem for another. Article 26 of the TFEU enshrines the free movement of goods within the internal market, whilst Articles 34 and 35 "define the scope and content of the principle by prohibiting unjustified restrictions on intra-EU trade".[191] Article 36 provides for derogations to the internal market that allow Member States to restrict this movement when "justified by general, non-economic considerations", as long as the restrictions are not imposed arbitrarily against another country and do not go "beyond the necessary level". This exception allows Member States to place restrictions on the export of medicines if this is deemed to be in the interest of the protection of health, but these cannot be applied "if the health and life of humans can be as effectively protected by measures which are less restrictive to intra-EU trade". In 2018, the Commission further elaborated

[189] European Union. (2012) Consolidated version of the Treaty on the Functioning of the European Union. Official Journal of the European Union C326/47. Available at: http://data.europa.eu/eli/treaty/tfeu_2012/oj. Accessed 7 September 2021.

[190] European Commission. (26 February 2014) Directive 2013/24/EU on public procurement and repealing Directive 2004/18/EC. Official Journal of the European union L 94/65. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014L0024&from=NL. Accessed 7 September 2021.

[191] European Commission. (23 March 2021) Commission notice: guide on Articles 34-36 of the Treaty on the Functioning of the European Union (TFEU). Available at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52021XC0323(03)&from=EN. Accessed 7 September 2021.

on the conditions under which supply for specific listed medicines could be restricted, indicating this could be considered suitable only if:[192]

- The list applies only to pharmaceuticals for which a shortage is likely or certain, such as those medicines where the volume available does not meet current needs of patients in the Member State
- The list is established through criteria that are known in advance
- The list takes into account the availability of alternative treatments in the Member State
- The list is revised on a regular basis, taking into account the latest occurrences or risks of shortages of medicines for public health
- The decisions implementing its application are taken within a reasonable time period
- The decisions are open to be contested before the relevant administrative bodies or courts of justice

The European association for the parallel distribution industry (Affordable Medicines Europe) has indicated that 11 EU Member States have introduced legislation to restrict export of medicines and suggested that some of this legislation had been deemed by the European Commission to be in violation of the TFEU.[193] As described in Section 5.8, the COVID-19 pandemic has renewed scrutiny of export restrictions, as these restrictions can help in protecting against shortages in one country but may do so at the expense of others, challenging the principle of European solidarity.

The EU legal framework does not address problems with the availability and continued supply of medicines linked to national market structures. Relevant factors can include, for instance, market size (e.g. Slovenia, Latvia) or strong price pressures (e.g. the Netherlands) that make these markets less economically attractive to suppliers and place them at greater risk of shortages. There are currently no obligations on MAHs to place centrally authorised products on all EU/EEA markets and maintain a presence there.

The national actions taken by individual Member States have been complemented by various forms of voluntary cooperation, either at EU-level or between groups of Member States. As previously described in Section 1.2, voluntary cooperation and information sharing between all EU Member States has been coordinated via a dedicated HMA/EMA Task Force and the establishment of the EU SPOC network. The network has been instrumental in the development of a harmonised shortage definition and of guidance for MAHs on detection and notification of shortages. Whilst from consultation of NCA representatives it is apparent that Member States widely value these platforms for information exchange and coordination, this study did not conduct an in-depth analysis of the functioning of the Taskforce or of the SPOC network. No information was available on whether or how the work of these bodies has impacted on the incidence, duration or impact of shortages. The COVID-19 pandemic has given further impetus to EU-wide coordination, through the EMA, on monitoring and mitigating the risk of critical medicines in response to major events.

In response to wider challenges in the area of access to medicines, not limited to shortages, several initiatives for multilateral cooperation between Member States have been created.[194] These collaborations typically are formed between countries that are geographically close and/or have similar socioeconomic backgrounds that make their markets commercially less attractive to MAHs. Key activities conducted through the initiatives include joint procurement, joint health technology assessment, horizon scanning or pricing and reimbursement. Joint procurement may be used as a strategy to create larger and thus more economically attractive markets that may be less vulnerable

[192] European Commission. (2018) Paper on the obligation of continuous supply to tackle the problem of shortages of medicines. Available at https://ec.europa.eu/health/sites/default/files/files/committee/ev_20180525_rd01_en.pdf. Accessed 10 September 2021.

[193] Affordable Medicines Europe. (no date) Shortages: parallel trade does not drive shortages. Available at: https://affordablemedicines.eu/shortages/. Accessed 7 September 2021.

[194] World Health Organization. (2020) Cross-country collaborations to improve access to medicines and vaccines in the WHO European Region. Copenhagen. Licence: CC BY-NC-SA 3.0 IGO.

to commercial reasons for supply disruptions and market withdrawals. Additionally, one of the objectives of the Baltic Procurement Initiative, formed between Estonia, Latvia and Lithuania, is to prevent or address supply shortages through a lending agreement for centrally procured medicines, meaning that any country in the initiative can lend a medicine in shortage from any of the other countries for free (assuming it is available in sufficient quantities there) and will return the borrowed products once normal supplies have resumed. Since the lending mechanism was instituted in 2012, there have been several such lending processes.[195] Bilateral sharing of medicines has also been reported between Belgium and Luxembourg.[196] It is possible this type of sharing arrangement is conducted on a case-by-case basis between other countries as well. This study, however, did not include a comprehensive investigation of bilateral voluntary collaboration between Member States to mitigate shortages.

6.5. Relevance

Analysis of relevance considers the relationship between the needs and problems identified as the grounds for introduction of an intervention and the objectives of that intervention.[147] It, furthermore, requires a consideration of how the objectives of the intervention correspond to wider policy goals and priorities.

Article 23a of Directive 2001/83/EC was introduced as a way of providing competent authorities advance warning about the discontinuation of medicines and allow them to prepare for the consequences of that withdrawal. It was, as such, not designed specifically as an intervention to prevent shortages. Moreover, the MAH is exempted from the notification obligation in case of 'special circumstances', wherein the MAH could not reasonably foresee the supply disruption. Whilst the relevance of the Article in obtaining information from MAHs about expected supply discontinuations was not disputed by any of the consulted national authorities, its scope is insufficient for the purpose of addressing the issue of shortages.

The supply obligation of Article 81 of Directive 2001/83/EC was introduced to ensure that MAHs and wholesalers strive, to the best of their ability and within their responsibilities, to protect continuity of supply in the interest of public health. The observation that shortages have continued to increase, even after the introduction of supply obligations, suggests that many shortages are either happening *despite* the best efforts of MAHs and wholesalers – meaning that these shortages are caused by factors beyond their immediate influence – or that these parties are still insufficiently endeavouring to fulfil their obligations. The general perception among many consulted stakeholders is that both are true. Various stakeholders, both from industry and among NCAs, feel that market forces (e.g. price pressures, off-shoring of manufacturing, industry consolidation) have made the global pharmaceutical supply chain more vulnerable. Consequently, MAHs may struggle to absorb sudden external shocks even when they have proper supply chain management plans in place. Nonetheless, national authorities and patient groups observe a degree of culpability with MAHs, suggesting the industry is more concerned with profit maximisation in more lucrative markets than with ensuring continued supply in all markets. The observation that relatively few shortages happen concurrently in multiple Member States indeed points towards problems with the equitable distribution of medicines across the European Union, although it cannot be determined from the available data to what degree this is influenced by the procurement behaviour of Member States or by the commercial strategies of suppliers. Overall, the grounds for inclusion of Article 81 can be said to remain valid and are even gaining in importance, both generally and in times of crisis, as underscored in comments by the national authorities of Czechia and Estonia. Although the relevance of the Article itself is somewhat challenged by its overly broad formulation and a lack of specification of the responsibilities that apply to the parties that are subject to the supply obligation, this can be remedied at the Member State level through the transposition process and the introduction of further operational measures.

[195] Espin J, Rovira J, Calleja A, Azzopardi-Muscat N, Richardson E, Palm W, Panteli D. (2016) Policy Brief 21: How can voluntary cross-border collaboration in public procurement improve access to health technologies in Europe? European Observatory on Health Systems and Policies. World Health Organization.

[196] RTL Today. (28 August 2019) Luxembourg – Medicine shortages: Pharmacies deplore lack of communication from suppliers. Available at: https://today.rtl.lu/news/luxembourg/a/1395393.html. Accessed 25 October 2021.

Several factors could affect the issue of medicine shortages in future. First, an increasing number of newly authorised medicines are classified as biological medicines. Compared to small molecule based medicines, competition for biological medicines – in the form of biosimilar medicines – thus far has tended to be slow to emerge and typically involves a much smaller number of competitors. The entry of only a limited number of biosimilar medicines often also does not have a very substantial effect on the price of the originator medicine.[197] This has led some to suggest that biological medicines enjoy a "natural monopoly".[198] This prolonged (possibly even perpetual) reliance on a single source of supply, or very limited number of sources, may pose an increased risk to the continuity of supply, particularly if the production is also highly centralised. At the same time, the fact that the originator product can be sold at higher profit margins for longer, due to the absence of competition, may offer additional incentives to the MAH to take all possible measures to protect the supply, similar to what is currently observed with most still-patented medicines. No information was collected from stakeholders about their expectations regarding how a shift towards biological medicines may impact the likelihood and impact of shortages. The current EU legal framework for the prevention or mitigation of shortages does not differentiate between types of medicines, nor does it distinguish between (suppliers of) single- or multisource products. Thus, whilst the relevance of the EU legal framework itself could be affected by the development in terms of the number of shortage situations that fall within its scope, there is at present no reason to assume that the relevance of the content of the framework would be directly affected.

A second consideration is the impact of the COVID-19 pandemic and potential future pandemics or health threats. COVID-19 has further exposed vulnerabilities in the current structures of the global pharmaceutical supply chain and highlighted the importance of quick and effective collaboration between Member States to minimise the impact of supply chain disruptions and protect the health of EU citizens. Under normal circumstances, the provision of health care – including the procurement, reimbursement and distribution of medicines, – is a national competency of the Member States and many consulted stakeholders, in particular NCA representatives, have indicated that national governments should maintain the capacity to institute those policy actions (including obligations and restrictions) that are deemed most relevant in their national context. However, stakeholders from across all consulted groups have also emphasised the need for special coordination structures and mechanisms for crisis situations. No further analysis was conducted of what role stakeholders foresee in the prevention or mitigation of shortages in crisis situations for newly created structures such as the European Health Emergency preparedness and Response Authority (HERA) or the rescEU mechanism, a European reserve of resources that includes a stockpile of medical equipment.[199]

6.6. EU added value

A key consideration in the assessment of EU interventions is whether it has achieved changes beyond what could reasonably have been expected from national actions by the Member States, known as EU added value.[147] In the context of this study, it should be borne in mind that the evaluation here does not concern an EU Regulation or complete Directive. Instead, the analysis has focused on only two Articles (Article 23a and 81) within the Community code relating to medicinal products for human use (Directive 2001/83/EC). The assessment of the added value of the complete Community code is beyond the study scope, as it has limited bearing on the issue of medicine shortages.

Both provisions considered (Articles 23a and 81) apply to all medicinal products placed on the market in a Member State, regardless of whether these have been centrally authorised or authorised through a national procedure. As such, the number of products that fall within the scope of the Articles may vary between countries, depending on what products have been placed on those markets but there are no differences in which types of products are covered. This ensures a degree of harmonisation

[197] IQVIA Institute. (29 September 2020) Biosimilars in the Uited States 2020-2024. Competition, savings, and sustainability.

[198] Atteberry P, Bach PB, Ohn JA, Trusheim MR. (15 April 2019) Biologics are natural monopolies (Part 1): why biosimilars do not create effective competition. Health Affairs Blog. Available at: https://www.healthaffairs.org/do/10.1377/hblog20190405.396631/full/.

[199] European Commission. (16 September 2021) European Health Emergency preparedness and Response Authority (HERA): Getting ready for future health emergencies. Available at: https://ec.europa.eu/commission/presscorner/detail/en/IP_21_4672. Accessed 25 October 2021.

between Member States, although variations in other aspects are still introduced by the different ways the Articles have been transposed. National authorities in five countries (Austria, Spain, Hungary, Lithuania and Sweden) have suggested that the EU added value of the provisions could be improved by further harmonisation of criteria, specific operational measures and enforcement. The absence of harmonised practical rules to ensure that MAHs and distributors fulfil their supply obligations, pursuant to Article 81, creates some distortions in the costs incurred by suppliers for compliance with implementing national legislation, depending on the location of their operations.

The lack of EU-wide provisions for the effective enforcement of the provisions also poses some risks. As discussed previously, the greater threat of financial sanctions in some countries than others if supply obligations are not met, may have the consequence of MAHs prioritising supply to these countries over others. Consulted competent authorities in some countries, as well as patient organisations have suggested that this risk should be reduced by improved alignment between countries on sanctions and enforcement, possibly with EU-level coordination.

As discussed in Section 6.3.1, the obligations introduced by the relevant provisions in Directive 2001/83/EC are generally considered to have had limited financial and administrative impact on the operations of MAHs. In fact, many Member States have introduced additional or stricter obligations on suppliers. This suggests that the provisions themselves, not including national implementing measures, are relatively minimal and may be considered proportional to the intended objectives.

Many different stakeholders, especially NCA representatives, have argued throughout the consultation process in favour of stronger EU coordination in addressing the problem of shortages in general, although they emphasise the need to remain mindful of national differences in, for instance, pricing policies and the availability and acceptability of substitute medicines. Particularly countries with smaller and commercially less attractive markets, such as Estonia and the Netherlands, expect to benefit from stronger EU-level coordination, noting that such countries have less power to regulate large, global market players. Various authorities, including those in Czechia, Slovenia and Finland, have indicated seeing great value in a common approach to the supply of pharmaceutical products in Europe, such as experienced during the COVID-19 pandemic. The EU added value of different proposed solutions, beyond what the current EU legal framework foresees in, is further explored in Chapter 8.

Summary

Directive 2001/83/EC contains two provisions which can help prevent and mitigate shortages. Article 23a requires MAHs to notify the NCA at least two months in advance of their intent to suspend the marketing of a product it has placed on that market, whilst Article 81 mandates MAHs and wholesalers to ensure, within the limits of their responsibility, the continued and appropriate supply of medicines placed on the market. This study shows that all Member States have transposed these provisions into national legislation but have operationalised them in different ways.

Because in most countries the transposition took place years before the introduction of a shortage notification registration system, the data to substantiate where these provisions have enabled Member States to effectively slow down the incidence of shortages is largely lacking. The notification obligation imposed by Article 23a has generally been helpful to authorities in preparing for discontinuations of supply and mitigating the impact thereof. The supply obligation dictated by Article 81 is, by itself, very generally formulated and many Member States have introduced a variety of measures to impose more specific obligations on MAHs and, in some cases, other parties. These vary from stock keeping obligations to mandatory reporting on stock levels and export restrictions. Based on the limited availability of data and the concurrent presence of different preventative or mitigating measures, only the effects of stock keeping obligations on the growth in notified shortages could be isolated. However, no firm conclusions could be drawn from this analysis about the impact of stock obligations on the level of (notified) shortages in the countries where they were introduced. It can be argued that the continued and rising problem of medicine shortages in the EU, even after adoption of Directive 2001/83/EC and the transposition of Articles 23a and 81 into national law, means that, by itself, the EU legal framework is insufficiently effective in achieving the aim of protection of public health and needs to be complemented with additional (national or EU-level) measures.

The costs that could be attributed directly to the obligations under the EU legal framework are difficult to quantify as, to a significant degree, these are absorbed by the normal operational costs of the parties on whom the obligations fall. On the other hand, there are important benefits to patients and health systems from avoided shortages or from shortages that are resolved more quickly or mitigated better, in the form of costs avoided and continuation of care. These benefits, which have also been insufficiently quantified to substantiate a proper efficiency analysis, may be viewed as adequate justification for the costs. Articles 23a and 81 are, for the most part, internally coherent with the objectives and provisions of the broader EU legal framework.

The two Articles are largely coherent with both the wider EU legal framework, including the amending Directives on pharmacovigilance and the Falisified Medicines Directive, despite some initial fears that the introduction of the latter could (temporarily) result in a rise in shortages. Measures introduced by the Member States nationally, or through voluntary cross-country collaboration, have complemented the EU legal framework. This has been done particularly to address problems with the availability and continued supply of medicines linked to national market structures.

The persistence of the issue of shortages suggests that EU intervention remains relevant and may grow in importance as new challenges, like the COVID-19 pandemic, emerge. Vulnerabilities in the global pharmaceutical supply chain, including a growing reliance on a limited number of manufacturers and suppliers, call for concerted action from all involved stakeholders to not only prevent supply disruptions but also ensure a more equitable distribution of available supplies thanc urrently observed.

EU-level coordination has already resulted in the development of useful new guidance and structures for dialogue and cooperation to tackle medicine shortages. However, there remains considerable scope for improvement through greater adoption of harmonised definitions and criteria and uniform implementation of guidelines.

7. PRODUCT CASE STUDIES

To further illustrate the causes of shortages and their impacts on patients, health providers and health systems, we have developed a series of product case studies.[200] Here, summaries of these case studies are presented, with the full cases available in Annex I.

7.1. EpiPen

Epipen is a brand of epinephrine (adrenaline) filled auto-injectors used as an emergency treatment in case of a severe allergic reaction.[201] Epinephrine is included on the WHO Essential Medicines List. The auto-injector is a spring-loaded syringe pre-filled with a fixed dose of epinephrine.[202] It is designed to be carried by those at risk of anaphylaxis and can be used without medical expertise.

The EpiPen brand is currently owned by Mylan, which markets two versions of the EpiPen: a 300 microgram formulation (EpiPen®) and a 150 microgram formulation specifically for young children, the EpiPen Jr®. Both versions have been approved in all EU Member States.[282] The devices for both versions are manufactured at a single plant in the United States. [203] Although other epinephrine auto-injectors are marketed both in the US and in Europe, thus far none have achieved the brand recognition of the EpiPen.[204]

In Spring of 2018, shortages of EpiPens were being signalled in Britain, Canada and the United States.[287] Mylan acknowledged the supply problems and attributed these to otherwise unspecified "production delays" at its device production site. Mylan's supply problems lasted for over a year.[286] Data from the national shortage registries confirm that shortages were happening throughout much of the EU in 2018 and 2019.

The situation had a severe impact on patients, parents, pharmacists and clinicians who had to deal with finding remaining supplies or suitable alternatives.[205] Because of Mylan's dominant market share, the gap left by its inability to meet demand was very substantial and could not easily be filled by competitor brands or generic alternatives. To mitigate the impact of the EpiPen shortage the UK's Medicines and Healthcare products Regulatory Agency (MHRA) allowed extension of the expiration date for not only the EpiPen but also for one of the EpiPen's competitor product, the Jext pen.[206] It is unclear if any of the affected EU Member States took similar measures or to what extent patients had to use EpiPens beyond their expiration date. Because of critical shortages for the EpiPen Jr, UK community pharmacists were furthermore instructed to prioritise supplies for smaller children.[207]

The EpiPen shortage highlights the vulnerability of the supply chain in situations where there is a particularly dominant supplier and where the production capacity is highly concentrated. Some

[200] Three product case studies have so far been included in this report. Case studies on amoxicillin and midazolam are under development and will be added to the final report.

[201] Committee for Medicinal Products for Human Use. (2015) CHMP Assessment report. Available at: www.ema.europa.eu/contact. Accessed 16 June 2021.

[202] Rimler R. (Updated 9 April 2020) The Long, Strange History of the EpiPen. Available at: https://www.healthline.com/health-news/strange-history-of-epipen#Discovery-of-adrenaline. Accessed 16 June 2021.

[203] Hirschler B. (10 May 2018) In Europe, Mylan's rivals try to plug EpiPen shortages | Reuters. Available at: https://www.reuters.com/article/us-mylan-epipen-idUSKBN1IB26Z. Accessed 16 June 2021.

[204] Whooley S. (20 August 2019) Teva launches generic EpiPen Jr. Drug Delivery Business. Available at: https://www.drugdeliverybusiness.com/teva-launches-generic-epipen-jr/. Accessed 17 June 2021.

[205] Ward M. (10 July 2019) How to Get EpiPen: US Shortage Enters Second Year - Bloomberg. Available at: https://www.bloomberg.com/news/articles/2019-07-10/-there-s-nothing-to-give-them-the-hunt-for-lifesaving-epipens. Accessed 17 June 2021.

[206] Palmer E. (17 October 2018) U.K. fights EpiPen shortage by extending injector expiry dates | FiercePharma. Available at: https://www.fiercepharma.com/manufacturing/uk-fights-epipen-shortage-by-extending-injector-expiry-dates. Accessed 16 June 2021.

[207] The Pharmaceutical Journal. (18 October 2018) Small children prioritised under emergency protocol to tackle "critical" EpiPen shortage. Available at: https://pharmaceutical-journal.com/article/news/small-children-prioritised-under-emergency-protocol-to-tackle-critical-epipen-shortage. Accessed 25 August 2021.

analysts expect that with the launch of a generic EpiPen by Teva and other auto-injectors, the position of Mylan could weaken and that the market will become more diverse and resilient.[208]

7.2. 5-Fluorouracil (5FU)

5-Fluorouracil (5FU) is a common cancer therapeutic used in the treatment of many adult and paediatric cancers.[209] It came into medical use in 1962 and is included in the WHO Essential Medicines List.[210,211] Today, it is predominantly sold as a generic medicine. Two prodrugs of 5FU are also in use in the EU: 1) Tegafur (available as part of the combined product Teysuno) which is approved for treatment of rectal, colon gastric, and breast cancer, as well as some types of brain tumours; and 2) Capecitabine (brand name, Xeloda) currently authorised for the treatment of colorectal, gastric and breast cancers. In 2018, in the EEA, about 600,000 patients were treated with 5FU and its prodrugs in oncological indications and about 1,500,000 patients were treated with topical 5FU products.[212]

Between 2010 and 2021, there have been multiple 5FU shortages, of varying severity, across about half of EU Member States. The first major shortage was recorded in 2012 in Germany when Teva Pharmaceuticals discontinued sales of 5FU.[213] This left the country with only a sole (German) MAH, who struggled to meet the increased demand.[214] The resulting knock-on effect was felt across eastern and central Europe as Germany resorted to parallel importing 5FU from lower-price countries. Data from the national shortage registries confirms that, in 2013 and 2014, there were several more instances of shortages of 5FU due to a combination of permanent market withdrawals, linked to the product's low profitability, and manufacturing or distribution issues.

The 2012, the 5FU shortage in Germany meant that about 170,000 patients with colon cancer could not be treated properly.[214] Recent publications suggest that shortages of several essential, generic oncology medicines, among them 5FU, continue to recur periodically affecting the availability of treatments for patients.[312,310,215] For some indications, such as colorectal, gastric and breast cancers, capecitabine can be used as a substitute for 5FU in which case the consequences of the shortages can be less severe. [216,217]

7.3. Diphtheria, tetanus, pertussis, and polio vaccines

Vaccines against diphtheria, tetanus, pertussis (whooping cough) and polio (DTPP), commonly administered as a combination vaccine, are given to children to reduce the incidence of several life-

[208] Edwards C. (April 2019) Epipen: from monopoly to multiplicity. Medical Technology 14. Available at: https://medical-technology.nridigital.com/medical_technology_apr19/epipen_from_monopoly_to_multiplicity. Accessed 16 June 2021.

[209] World Health Organization. (no date) Fluorouracil. Electronic essential medicines list. Available at: https://list.essentialmeds.org/medicines/91. Accessed 12 June 2021.

[210] Chu, E. (2007) 'Clinical Colorectal Cancer: "Ode to 5-Fluorouracil"', *Clinical Colorectal Cancer*, 6(9), p. 609. Available at: https://doi.org/10.3816/CCC.2007.n.029.

[211] World Health Organization. (2019) World Health Organization Model List of Essential Medicines 21st list 2019. Available at: http://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?sequence=1&isAllowed=y. Accessed 25 August 2021.

[212] Boshnakova, A. et al. (2017) 'Cancer medicines shortages in Europe - Policy recommendations to prevent and manage shortages', The economist intelligence unit, European Society for Medical Oncology. Available at: https://www.eiu.com/graphics/marketing/pdf/ESMO-Cancer-medicines-shortages.pdf.

[213] Brazil, R. (30 May 2019) 'Shortages of generic cancer medicines are harming patients. So why can't we fix it?'. Cancerworld. Available at: https://archive.cancerworld.net/spotlight-on/shortages-of-generic-cancer-medicines-are-harming-patients-so-why-cant-we-fix-it/.

[214] The Economist. (2019). Country profile: cancer medicines shortages. Germany. The Economist Intelligence Unit Limited, supported by the European Society for Medical Oncology. Available at: https://www.esmo.org/content/download/197312/3552896/1/ESMO-Country-profile-Germany.pdf. Accessed 19 August 2021.

[215] European Cancer Organisation. (2020) Response of the European Cancer Organisation to the Roadmap consultation on a new EU Pharmaceutical Strategy.

[216] EMA Pharmacovigilance Risk Assessment Committee. (2020) Fluorouracil and fluorouracil related substances (capecitabine, tegafur and flucytosine) containing medicinal products. Assessment report.

[217] Alpert, A. and Jacobson, M. (2019) 'Impact of Oncology Drug Shortages on Chemotherapy Treatment', *Clinical Pharmacology & Therapeutics*, 106(2), pp. 415–421. doi: 10.1002/cpt.1390.

threatening diseases and child mortality. The most common combination vaccine is that against diphtheria, tetanus and pertussis (DTP) and has been used since the 1940s.[218] DTP vaccines are essential components of national immunisation programmes. Various combination products have been authorised in EU Member States. The two main manufacturers are GlaxoSmithKline (GSK) and Sanofi/Sanofi-Pasteur.[219] The vaccines are delivered through injections and as such are supplied as suspensions, solutions, or pre-filled syringes.[220]

In 2015, the ECDC reported a major shortage of acellular pertussis-containing vaccines caused by a reduction of production capacity for the pertussis antigen.[221] A 2019 survey found that six EU countries had experienced vaccine shortages between 2016 and 2018.[222] The 2015 shortage was reflected in the data provided by the NCAs. Most shortage notifications for DTP(P) occurred between 2015 and 2019. Shortages of DTP(P) combination vaccines were reported in 15 Member States, most often attributed to manufacturing issues. Vaccine shortages are not limited to Europe but are a global problem. Underlying issues include increasing global demand owing to large immunisation programmes in Africa and Asia, and concentration of production in a handful of large pharmaceutical companies.[223,224]

Non-availability of vaccines for immunisation presents a major threat to public health. In theory, shortages of combination vaccines could be mitigated by use of individual vaccines or other combinations supplemented by individual vaccines, where possible. However, the 'monovalent' vaccines are hardly manufactured anymore.[221,223] The shortage of acellular pertussis-containing combination vaccines in 2015 prompted some Member States to adjust their immunisation policies by delaying specific immunisations, modifying the vaccine formulations used and prioritising primary immunisations over subsequent immunisations.[221]

7.4. Midazolam

Midazolam is a short-acting sedative medicine used to relieve anxiety or cause a state of decreased consciousness in seriously ill people in intensive care units (ICUs) or before surgery.[225] It is used regularly as a pre-anaesthetic after which anaesthesia is deepened with another intravenous anaesthetic. The tablet form of midazolam is used mainly for sleep disorders but also for sedation (calming) and anxiolysis (reducing anxiety). Terminally ill patients are sometimes administered midazolam to give rest in the last stages of life. As of 2010, it is the most used benzodiazepine in

[218] World Health Organization. (2014) Information sheet. Observed rate of vaccine reactions – Diphtheria, pertussis, tetanus vaccines. Available at: https://www.who.int/vaccine_safety/initiative/tools/DTP_vaccine_rates_information_sheet.pdf. Accessed 12 June 2021.

[219] European Medicines Agency. (2021) List of nationally authorised medicinal products. Active substance: diphtheria / tetanus / pertussis (acellular, component) and poliomyelitis (inactivated) vaccine (adsorbed), diphtheria / tetanus / pertussis (acellular, component) and poliomyelitis (inactivated)vaccine (adsorbed) reduce antigens content. Procedure no.: PSUSA/00001126/202007.

[220] Drugbank Online. (no date) Bordetella pertussis pertactin antigen. Available at: https://go.drugbank.com/drugs/DB10789. Accessed 12 June 2021.

[221] European Centre for Disease prevention and Control. (2015) Shortage of acellular pertussis-containing vaccines and impact on immunisation programmes in the EU/EEA. Available at: https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/vaccine-shortage-rapid-risk-assessment-october-2015.pdf Accessed 12 June 2021.

[222] Filia, et al. (2020) Are vaccine shortages a relevant public health issue in Europe?, European Journal of Public Health, 30 (Supplement 5), pp. ckaa165.670. Available at: https://doi.org/10.1016/j.ijid.2020.09.1261.

[223] SWI (2017) What's behind Switzerland's vaccine shortage? Available at: https://www.swissinfo.ch/eng/drug-dilemma_what-s-behind-switzerland-s-vaccine-shortage/43412750 Accessed 12 June 2021.

[224] Filia, et al. (2021) 'Report on previous experiences with vaccine shortages in EU countries (and non-EU consortium member countries), and responses at national and European levels', European Joint Action on Vaccination report

[225] The American Society of Health-System Pharmacists. (no date) Midazolam. Drugs.com. Available at: https://www.drugs.com/monograph/midazolam.html. Accessed July 2021.

anaesthetic medicine.[226] Midazolam is included in the World Health Organization's List of Essential Medicines.[227]

Midazolam is branded as Dormicum and marketed by Roche. It is also widely available as a generic medication.[228] In 2011, the EMA granted a marketing authorisation to Shire Pharmaceuticals (now Takeda) for a buccal[229] application form for the treatment of prolonged, acute, convulsive seizures in children, sold under the trade name Buccolam.[230]

Prior to 2020, there had been several instances of shortages of Midazolam. In April 2014, several Member States temporarily recalled Buccolam from the market following deficiencies in the manufacturing process.[231] The issue was resolved in March 2015. Data from the national shortage registries also show that between 2017 and 2019 at least seven Member States experienced shortages of Midazolam from different suppliers. Most were attributed to distribution issues. In 2020, following the onset of the COVID-19 pandemic, demand for Midazolam suddenly sharply increased as the medicine was used as a first-line sedative in the management of COVID-19 patients.[232] Supply of Midazolam could not keep up with the rapidly increased demand. As a direct result, shortages of Midazolam were recorded in many Member States.

The shortage of sedatives, including Midazolam, caused by the COVID-19 crisis put not only COVID-19 patients in ICUs at risk but also non-COVID-19 patients in need of surgery.[233] In response to this, France centralised management of procurement and stocking of critical medicines, including Midazolam. Mitigation strategies have been suggested that focus on reducing usage of sedatives in ICU patients to reduce (the risk of) shortages. [234] In case a patient requires light sedation, an escalation strategy could be used whereby alternative agents are promoted for patients with lower sedation needs and infusions are reserved for patients who need deeper sedation. Protocolised and targeted sedation could prevent over-sedation and unnecessary sedative usage and shorten the duration of mechanical ventilation.

7.5. Amoxicillin(/clavulanic acid)

Amoxicillin/clavulanic acid, also known as co-amoxiclav is a broad-spectrum antibiotic used as a first choice medication for adults and children for many common bacterial infections. It is a combination of amoxicillin, a derivative of penicillin, and clavulanic acid. The ratio of amoxicillin to clavulanic acid

[226] Oparil S, Weber M (22 April 2005). Hypertension: a companion to Brenner and Rector's the kidney (2 ed.). Philadelphia: Elsevier Mosby. p. 816. ISBN 978-0-7216-0258-5.

[227] World Health Organization. (2019) World Health Organization model list of essential medicines: 21st list 2019. Geneva: World Health Organization. hdl:10665/325771. WHO/MVP/EMP/IAU/2019.06. License: CC BY-NC-SA 3.0 IGO.

[228] Hamilton R (2015). Tarascon Pocket Pharmacopoeia 2015 Deluxe Lab-Coat Edition. Jones & Bartlett Learning. p. 21. ISBN 9781284057560.

[229] In buccal administration, a medicine is absorbed into the bloodstream after being held in the mouth to allow for diffusion through the cheek tissue.

[230] European Medicines Agency. (2011) European public assessment report (EPAR) for Buccolam. EMA/522148/2011. Available at: https://www.ema.europa.eu/en/documents/overview/buccolam-epar-summary-public_en.pdf.

[231] European Medicines Agency. (2015) Buccolam Midazolam Shortage – Europe. Available at: https://www.ema.europa.eu/en/documents/shortage/buccolam-midazolam-supply-shortage_en.pdf.

[232] Royal College of Anaesthetics, Association of Anaesthetics. (2020) Guidance on potential changes to anaesthetic drug usage and administration during pandemic emergency pressures. Available at: https://icmanaesthesiacovid-19.org/drug-demand-supply-anaesthetic-drug-usage-and-administration.

[233] Montmeat et. al., (2020). Shortage of sedatives and neuromuscular blockers during COVID-19 pandemic: The result of an overstocking procedure in French hospitals?. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7326429/.

[234] Kanji, S., Burry, L., Williamson, D. et al. Therapeutic alternatives and strategies for drug conservation in the intensive care unit during times of drug shortage: a report of the Ontario COVID-19 ICU Drug Task Force. Can J Anesth/J Can Anesth 67, 1405–1416 (2020). Available at: https://doi-org.vu-nl.idm.oclc.org/10.1007/s12630-020-01713-5.

has varied over the years according to needs.[235] Amoxicillin/clavulanic acid has been on the WHO's List of Essential Medicines since 1997 and is classified as a critically important human medicine. [236,237]

The oral formulations of the combination product have been available worldwide since 1981 and the intravenous formulation since 1984, under the brand name Augmentin. The product has been available as a generic medication since 2002 when the original patents protecting Augmentin expired. The medicine is now marketed globally under numerous generic and trade names.

The availability of amoxicillin and combination products containing amoxicillin has fluctuated in recent years, but shortages occur frequently, as confirmed by data from the national shortage registries. Co-amoxiclav was reported as one of the top 10 medicines in shortage in European hospitals by the EAHP's 2018 Survey on Medicines.[238] According to a 2017 report by Medicines for Europe, price pressure is one of the leading causes affecting the availability of injectable amoxiclav.[239] In a 2016 report following a shortage of injectable amoxicillin in 2013, the French Agency for the Safety of Health Products concluded that the supply of amoxicillin is vulnerable because of the very limited number of manufacturers of the active substance worldwide.[240] Following the COVID-19 outbreak, shortages of antibiotics – including amoxicillin – were noted both within and outside of the EU, due to a combination of increased demand and supply disruptions.[241,242] In March 2020, Great Britain included all forms of amoxicillin on its list of medicines that cannot be exported from the UK. [243]

When first-choice antibiotics are not available and patients are instead provided a suboptimal antibiotic with a different therapeutic spectrum, this can lead to poorer patient outcomes and an increased risk of adverse effects.[244] It can also contribute to a rise in AMR, particularly if the alternative has a broader spectrum, and increased healthcare costs.[245]

---

[235] European Medicines Agency. (2009) Review of Augmentin. Annex II. Available at: https://www.ema.europa.eu/en/documents/referral/augmentin-article-30-annex-ii_en.pdf Accessed 12 June 2021.

[236] World Health Organization. Model list of essential medicines. Available at: https://list.essentialmeds.org/medicines/310. Accessed 12 June 2021.

[237] World Health Organization. (2019) Critically important antimicrobials for human medicine. Available at: http://apps.who.int/iris/handle/10665/312266 Accessed 12 June 2021.

[238] Miljković et al. (2019) Results of EAHP's 2018 Survey on Medicines Shortages, European Journal of Hospital Pharmacy 2019;26:60-65. Available at: https://ejhp.bmj.com/content/26/2/60

[239] Medicines for Europe. (2017) Patient access to medicines: how to prevent medicine shortages? Available at: https://www.medicinesforeurope.com/docs/20171106_Overall_presentation_final.pdf Accessed 12 June 2021.

[240] The French Agency for the Safety of Health Products. (2016) Situation Report on the active substance amoxicillin. Available at: http://dev4-afssaps-marche2017.integra.fr/var/ansm_site/storage/original/application/cae8a3e3e3ec6ef704b2ff963d02d310.pdf Accessed 11 August 2021).

[241] Guarascio F. (8 July 2020) EU scrambles to buy intensive care drugs to tackle COVID shortages. Reuters. Available at: https://www.reuters.com/article/us-health-coronavirus-eu-patients-idINKBN2492D5. Accessed 19 August 2021.

[242] For example, in the US: CBS News (2020) Coronavirus outbreak causes first drug shortage in U.S., FDA says. Available at: https://www.cbsnews.com/news/coronavirus-human-drug-shortage-food-drug-administration/ Accessed 11 August 2021).

[243] Department of Health and Social Care and Medicines and Healthcare products Regulatory Agency. (3 October 2019, last updated 3 August 2021). List of medicines that cannot be exported from the UK or hoarded. Available at: https://www.gov.uk/government/publications/medicines-that-cannot-be-parallel-exported-from-the-uk. Accessed 11 August 2021).

[244] Beraud G. (12 February 2021). Shortages without Frontiers: Antimicrobial drug and vaccine shortages impact far beyond the individual! Frontiers in Medicine. Available at: https://doi.org/10.3389/fmed.2021.593712.

[245] (March 2020). Shortages and AMR – why should we care? 4 consequences of antibiotic shortages. Available at: https://www.reactgroup.org/news-and-views/news-and-opinions/year-2020/shortages-and-amr-why-should-we-care-4-consequences-of-antibiotic-shortages/.

7.6. Lessons from product case studies

Whilst these case studies make it clear that each shortage has its own combination of causes and consequences, together they illustrate several key points:

- Continuity of supply is particularly vulnerable when there are very **few suppliers** in the market. For instance, the market dominance of Mylan meant that its production issues with the EpiPen had a very significant impact on product availability, with very few other suppliers available to help fill the supply gap. Vaccine production is likewise heavily concentrated, with very few suppliers globally.
- Even when generic competition exists and products can be sourced from multiple suppliers, **consolidation** of the pharmaceutical supply chain further **upstream** can lead to vulnerabilities. In the case of amoxicillin, the production of the API was limited to a small number of suppliers. Production issues at this part of the supply chain can then have an impact on all manufacturers who use the same API supplier.
- Vulnerabilities are introduced not only by the structure of supply chains but also by market-related factors. In the cases of both 5-FU and amoxicillin/clavulanic acid, **strong price pressures** were identified as a significant contributor to product discontinuations and shortages.
- **Large, unexpected demand increases** can be **difficult to absorb**, as illustrated by the cases of Midazolam and amoxicillin where the COVID-19 pandemic caused demand to surge. Identification of critical medicines, creation of buffer stocks of such medicines and centralised distribution of this stock can all be part of crisis preparedness and management strategies, though it will depend on both product characteristics (e.g. batch size, pack sizes, shelf life), therapeutic application and other factors which strategies are best suited.
- For some products **therapeutic substitution** can be a viable mitigation strategy. In some circumstances, 5FU and amoxicillin could be substituted for other products from the same class of medicines. This substitution with less favoured medications may, however, reduce treatment effectiveness and increase the risk of side effects.
- Other mitigation strategies can include **changes to treatment protocols** to reduce use of the product. In the case of Midazolam, more targeted sedation protocols have been suggested to reduce reliance on Midazolam. Shortages of DTP-based vaccines have also been mitigated by making changes to national immunisation schedules and delaying introduction of specific antigens in the vaccination programme.
- Another, more exceptional, measure is the **extension of a product's expiration date** to allow products that otherwise would have been destroyed to remain in circulation, as was done for the EpiPen. The EpiPen is, however, somewhat atypical as it concerns a product that is used only in emergency situations. This means that at any time many users of EpiPens will still have unused products in their possession. For products that are used more routinely and where prescriptions need to be regularly refilled, the measure may be less effective. The relevance of the strategy furthermore depends greatly on the product's chemical stability and shelf-life.

8. POTENTIAL SOLUTIONS ADDRESSING MEDICINAL SHORTAGES

As outlined in various parts of this report, the observed increase and the attention given to shortages have caused many different parties to propose or introduce measures aimed at preventing and mitigating the impact of shortages. One of the purposes of this study was to include a set of potential future actions to address shortages, either at EU-level or at national level. For this, a long list of possible actions was drawn up which formed the starting point of a stakeholder consultation process. As outlined in Section 2.8, different groups of stakeholders were asked to reflect on this overview of longlisted solutions and rate these on multiple assessment criteria. Based on the ratings thus provided, a selection of solutions was drawn from the longlist and submitted to a second round of assessment on different criteria. The selection was informed by the need for actionable recommendations that are relevant in today's context and that consider the different perspectives and interests of a wide range of stakeholders. The assessment scores from both consultation rounds, as well as an ensuing discussion with a group of participating stakeholders, contributed to the development of a final set of 16 recommended solutions.

The identified solutions are presented alongside the specific problems they are expected to address. The support of stakeholders is also outlined below, as well as the actions that are needed to implement these solutions. However, as some of the proposed solutions are relatively high-level and still lack operational detail, actions are also mostly framed in general terms. The reasons for excluding some solutions from the final list is also explained, either due to a lack of suitability or consensus from stakeholders. The lack of consensus does not necessarily imply these measures could not be effective, but other considerations – such as expected costs to specific stakeholder groups – were deemed to pose a substantial barrier to their implementation.

In connection to the study questions, this chapter address the following:

- According to stakeholders, what are the (potential) solutions to address shortages?
- What are EU and national solutions to address shortages of medicines?
- What positions do stakeholders have in relation to different solutions?

8.1. Harmonisation of shortage definitions and notification criteria

Problem description

As detailed in Chapter 3, the coexistence of a wide variety of definitions of what constitutes a shortage hinders effective information sharing between stakeholders and creates inefficiencies. Many stakeholders have thus called for a harmonised definition to be used across the EU. Whilst this may not help prevent shortages directly, it is viewed as an important basis for devising more actionable, structural solutions. The definition already agreed by the HMA/EMA and stakeholders[59] is widely considered a suitable definition that should be mainstreamed across the EU, even though some stakeholders have emphasised that definitions should match the needs and characteristics of specific markets. In this light, the question is not so much the phrasing of the high-level definition but rather the operationalisation thereof (i.e. product scope, timeframes, level at which to apply it).

Building on the notion of how best to operationalise shortage definitions, many stakeholders would welcome the establishment of a more harmonised set of notification criteria across Member States. This would include standardisation of the information reported, including medicines identifiers and classification of root causes. This study, and others before it, has clearly shown how the present lack of standardisation hinders proper comparative analysis of the characteristics of medicines shortages and their root causes. Although some MAHs have called for centralised reporting at EU-level, already greater harmonisation of reporting requirements and systems is seen as helpful to cooperation and information sharing between Member States. It is also expected to reduce inefficiencies for MAHs and wholesalers having to report shortages into many different systems.

To facilitate harmonisation of practices and coordination between national authorities, the EMA has already taken several measures, including the creation of a Single Point of Contact (SPOC) network for shortages. It has also supported the development of templates and guidelines to support standardisation. As mentioned in section 3.2, the HMA/EMA has issued guidance to MAHs for reporting of shortages that includes a template detailing what information to include.[59] This template is designed to not only collect data on shortage characteristics but also to proactively propose

mitigation options (e.g. potential substitutions). However, this template has been proposed only for use in situations where there is no reporting template available at national level and it does not supersede the requirements of individual Member States. The classification of root causes developed by the SPOC network, designed to reach common understanding when communicating market disruptions through the SPOC system, similarly represents an attempt at EU-wide standardisation. In interviews, several NCA representatives signalled that Member States should be encouraged to make greater use of such common templates and classifications to facilitate exchange of information.

Some authors have suggested that, despite these initiatives to improve coordination and information exchange at a European level, several important issues remain unaddressed.[246] These are said to include:

- Procedures to assess the degree of urgency and the impact shortages may have on the patients are not described, leaving them open for interpretation and subsequent fragmentation of response among Member States
- Current notification processes are not sufficient to detect risk of shortages caused by unavailability of raw materials and mitigation is not quite adequate

Many stakeholders, especially NCA representatives, emphasised a special need for centralised reporting for crisis situations, such as for COVID-19. Such crisis reporting should be facilitated and/or coordinated by the Commission or EMA and can build on existing coordination tools. The issue of the need for stronger and centralised coordination in monitoring of shortages was mentioned also in the context of critical and essential medicines. Many stakeholders advocate for an EU-wide list of medicines for which shortages are the most critical and for which specific or additional mitigation and prevention measures are desirable. Importantly, by itself the list will not be effective in preventing or mitigating the impact of shortages, unless it contains recommendations on measures to address the (potential) shortage situation of an included medicine.

Considered and recommended solutions

Based on the issues here described and consultations with stakeholders about suitable solutions, three main solutions have been identified:

- Establish and follow a centralised and harmonised EU-wide definition of medicine shortages
- Establish and mainstream harmonised reporting criteria for shortages
- Develop an EU-wide list of medicines for which shortages are the most critical and develop policies and/or regulations to improve their availability

For all three measures, the consultation reveals substantial support across all stakeholder groups. The establishment of a harmonised definition and of centralised reporting criteria score highly on all considered assessment criteria, meaning that stakeholders do not observe major obstacles (Figure 105 and Figure 106 respectively). A separately proposed solution suggesting the establishment and mainstreaming of a centralised or interoperable interface for monitoring of shortages was somewhat favourable judged but, as it scored comparatively low on feasibility, was excluded from further consultation (Figure 89).

Some concern is noted among civil society and health professionals that the introduction of an EU-wide list of most critical and essential medicines could lead to unintended consequences (Figure 109). This is grounded in the risk that such lists could result in discrimination against specific medicines or groups of patients. They argue that, at the level of the individual patient, any medicine can be important and should be readily available. It is feared that prioritising some medicines over others may create discriminatory practices and lead to preferential procurement. It is emphasised that an EU-list should not preclude Member States from issuing their own lists, as these may better reflect local needs and priorities.

All three measures are expected to be cost-efficient. This is likely based in the fact that implementation of these measures does not require very significant investment of resources. New or

[246] Musazzi, U. M., Di Giorgio, D. and Minghetti, P. (2020) 'New regulatory strategies to manage medicines shortages in Europe', International Journal of Pharmaceutics. Elsevier, 579(February), p. 119171. doi: 10.1016/j.ijpharm.2020.119171.

changed notification criteria can be introduced relatively easily into existing reporting systems, as confirmed by the fact that stakeholders consider the solutions highly feasible and easy to implement.

To implement these solutions, action is needed at two main levels. First, the development of harmonised definitions, criteria and lists should be done through EU-level agencies and coordinating bodies such as the EMA and HMA. This action is already substantially underway but requires continued efforts. Second, to effectively implement the solutions, action will need to be taken by the NCAs of the individual Member States to operationalise the guidance offered and embed it into national reporting systems.

8.2. Stakeholder dialogue and coordination

Problem description

Throughout the study, many stakeholders have called for enhanced dialogue on medicines shortages between regulators, supply chain actors, healthcare providers and patients. They believe this would improve trust, communication, and collaboration between actors to help jointly devise strategies for handling shortages. Surveyed NCA representatives with experience in cooperative forecasting and planning report generally finding this type of dialogue to be effective or even very effective (Figure 45).

At present, many consulted stakeholders have expressed that there is a culture of assigning blame that is unhelpful in finding solutions to resolve shortages and hinders the open exchange of timely information. It has been argued that, for these discussions to be constructive, they should be 'blame free' and solutions-oriented, involving all relevant stakeholder groups. In addition to inclusive, broad dialogue, there is room for further dialogue between specific technical subgroups (e.g. actors involved in medicines for different therapeutic areas).

In parallel to this study, as mentioned in Section 1.2, the European Commission has already launched a structured dialogue with and between actors in the pharmaceutical manufacturing value chain and public authorities to propose actions to strengthen the continuity and security of supply in the EU. This dialogue is expected to assist in the further development of guidelines, measures, and tools to address structural shortages.

Considered and recommended solutions

Following the consultation process, a recommended solution is to:

- Set up stakeholder dialogue platforms for/between supply chain stakeholders, patients, and healthcare providers, respectively at Member States level

The solution is uncontroversial among the stakeholders involved in the consultation process (Figure 126). All acknowledge that such a dialogue may help to prevent future shortages or allow to better mitigate against their impacts. They do not expect significant problems or unintended consequences from this. No in-depth discussion was had on who should be the convenor of this type of dialogue but, given their central role and connections to all other parties, it is likely this is best done by a (national) competent authority. The solution is expected to be relatively low-cost: the main investment required is a time commitment by all parties involved in the dialogue for organisation and attendance of these meetings.

8.3. Monitoring, enforcement and use of sanctions

Problem description

As described in Section 6.2, the effectiveness of the EU legal framework and of national measures to prevent and mitigate shortages is limited by the ability of authorities to monitor and enforce the obligations enshrined therein. Obligations are typically not enforced in the sense that penalties are levied when these obligations are not complied with.

Member States have general provisions to apply administrative sanctions and fines to breaches of their pharmaceutical legislation. Sanctions may be imposed if notification requirements and/or supply responsibilities are not met. However, as discussed in Section 6.2, these sanctions are often not enforced because of lack of capacity and difficulties in proving culpability. In some Member States sanctions are said to be so low as to be meaningless. Moreover, national authorities have been careful

to not unnecessarily damage their relationship with manufacturers to ensure sustained supply to their respective markets. Whilst national authorities are thus fearful of imposing financial sanctions, other parties view it as a necessary tool to hold suppliers accountable.

It has previously been noted that, if there is no consensus between Member States about the use of sanctions, they may be even harmful; if sanctions are imposed in some countries but not in others, this may cause suppliers to prioritise markets where they would otherwise incur sanctions. Some stakeholders have thus argued to implement more coherent and uniformly binding sanctions across the entire EU, designed such that they may help in preventing shortages without jeopardy to patients' treatment. It is generally felt that this requires a somewhat 'soft' approach, where the preferred modus operandi is cooperation between parties to resolve a situation, with sanctions being triggered only as a last resort. The solution, therefore, lies in creating a uniform and coherent framework that allows for the imposition of sanctions while prioritising solutions-focused approaches whenever possible.

Considered and recommended solutions

Based on the outcomes of the consultation process, it is recommended to:

- Develop EU-wide and uniform legislation allowing for imposing financial sanctions if notification requirements and/or supply responsibilities are not met

Whilst this measure enjoys substantial support from NCAs, civil society organisations and health professionals, distributors, and parallel traders, it is considerably less welcomed by MAHs (Figure 116 and Figure 117). This resistance is expected, as MAHs would generally be the parties on whom the sanctions are imposed. They assess the solution unfavourably on all assessment criteria. It is thus very likely that they will show substantial opposition to attempts by NCAs or European authorities to introduce legislation, which may encourage the greater use of sanctions.

The risk of unintended consequences, such as MAHs deciding to bypass markets where they may be subjected to substantial fines, is well recognised by NCAs and civil society. As an alternative to financial sanctions for failure to meet supply obligations, the possibility of introduction of a "PSO-responsible pay" principle has been suggested, whereby MAHs are obliged to pay the price difference (if positive) between emergency or parallel imports and the normal reimbursement price for products in shortage in a given Member State.[124] This measure, however, did not receive sufficient support in the consultation process to be recommended here, as it was assessed relatively poorly by both manufacturers and NCAs (Figure 112). As with the imposition of financial sanctions, NCAs appear to be particularly fearful of unintended consequences and expect the measure to be complicated to implement.

The stakeholder consultation process did not include in-depth discussion on further specifics of what such legislation should look like and how prescriptive it should be with regards to, for instance, the conditions for when sanctions should be imposed, on what grounds these could be waived or the height of penalties. These factors could all influence the effectiveness of the solution, as well as its ultimate acceptability to stakeholders.

The possibility to further strengthen and enforce notification obligations, such as by stipulating earlier notification requirements and setting stricter criteria on what information MAHs must provide was explored. Among MAHs this suggestion predictably was met with considerable opposition, with many questioning the practical implementation of it and expecting unintended consequences (Figure 108). Indeed, the identified issues with the current monitoring and enforcement of already existing obligations justify some reservation about the expected effectiveness of the solution if not accompanied by a greater capacity to monitor and enforce these. The solution has thus not been included in the recommendations.

8.4. Supply chain transparency

Problem description

Throughout this study, stakeholders have commented on the lack of transparency throughout the supply chain. No single party has full information on where products are in the supply chain and on what the demand is. As a result, it is difficult to get a good and full understanding of the issue of shortages at the level of the EU. Many stakeholders have thus called for greater transparency,

including through use of centralised and interconnected data repositories and data sharing between parties at different parts of the supply chain and competent authorities.

A particular point where representatives of wholesalers and parallel traders have expressed concern about the lack of transparency is in connection to supply quotas. These quotas are set by MAHs to define the quantity of a certain medicine with which they supply a wholesaler or pharmacy. MAHs indicate that supply quotas allow them to better regulate the distribution of medicines across countries to ensure that patient demands are met. Supply quotas have been linked to shortages when wholesalers are not able to fulfil orders because their quotas have been reached. This can create interruptions in the supply to pharmacies and thus in the availability of products to patients. Normal supply is resumed only when the manufacturer resupplies the wholesale distributor at the start of the next supply period. These shortages are thus not caused by an actual insufficient availability of the product but are created artificially because supply is 'throttled'. Supply quotas can also have the effect of limiting parallel exportation from certain countries by prohibiting the accumulation of surplus.[124] According to AME, territorial supply quotas can be contrary to the functioning of the internal EU market unless there is a clear and acceptable reason, such as production problems, that would warrant rationing. It is argued that, in all circumstances, quotas should be sufficiently transparent and flexible to account for normal market fluctuations.

In practice, however, quotas are often found to be tight and wholesalers are not always informed of how much stock they will receive per week or month, so-called 'black-box quotas'. When supply quotas are not transparently defined and communicated, wholesale distributors are not able to foresee supply problems or inform pharmacies and authorities of their inability to supply in a timely way. Greater transparency on quotas would enable wholesale distributors to predict shortages and inform pharmacies accordingly, so that they may take timely action to mitigate the impact of the expected shortage.

Considered and recommended solutions

The call for increased supply chain transparency in general is supported by most stakeholders but clear differences are observed in the areas in stakeholders see the value of such transparency. Based on the average assessment of proposed solutions, it is recommended to:

- Require greater transparency of industry supply quotas as well as parallel traders' and wholesalers' transactions

Whilst this solution is generally positively assessed by most NCAs and by civil society organisations and health professionals, it is rather strongly opposed by MAHs on all criteria. These may thus be expected to resist any efforts by authorities to impose greater transparency. For their part, distributors and parallel traders have expressed strong concerns about full disclosure of their transactions towards MAHs. There is mutual reluctance between MAHs on the one hand and distributors on the other to disclose commercially sensitive information to the other party. There is, however, greater willingness to share this information with the NCAs, provided this is then kept confidential from others. Increasing transparency towards national authorities about the use of quotas and about transactions between supply chain actors could allow NCAs to better prepare for and mitigate the impact of impending shortages.

It has also been suggested by the pharmaceutical industry that the EMVS, used to track and verify medicines throughout the supply chain, can be used to increase transparency and help prevent shortages. The industry associations for both the innovative and generic medicines industry have strongly advocated, both publicly and in stakeholder consultations conducted as part of this study, for using the data stored within the EMVS to increase supply chain transparency, improve management of production and supply, and monitor shortages.[247,248] However, other parties have argued that the EMVS is not fit for this purpose. The industry association for pharmaceutical

[247] Bouvy F, Rotaru M. European Federation of Pharmaceutical Industries and Associations. (2021) Medicine Shortages: From assumption to evidence to action – a proposal for using the FMD data repositories for shortages monitoring. Frontiers in Medicine. Available at: https://doi.org/10.3389/fmed.2021.579822.

[248] Medicines for Europe. (27 September 2017) Position paper medicines shortages. Available at: https://www.medicinesforeurope.com/docs/20170927_Positionpaper_medicines%20shortages.pdf. Accessed 7 September 2021.

wholesalers, GIRP, has stated that because of intrinsic limitations the system systematically overstates supply and underestimates demand.[249] On behalf of pharmacists, the PGEU has also issued a statement in which it outlines the system's legal and technical limitations and indicates that it considers that "the EMVS, as it is designed, is not an appropriate and reliable tool to monitor shortages of medicines".[250] A solution to increase supply chain transparency by use of appropriate systems and tools, without specifically suggesting use of the EMVS for this purpose, was rejected from recommendation for insufficient agreement between consulted stakeholders about, in particular, the feasibility and ease of implementation of this (Figure 107).

8.5. Risk assessment and shortage mitigation plans

Problem description

Under Article 81 of Directive 2001/83/EC, MAHs and wholesalers have a responsibility to ensure the continued supply of medicines within the limits of their responsibility. Despite this, as presented in Chapter 4, data from the national shortage registries confirm that shortages still regularly happen across all Member States. The review of available information on the root causes of shortages, described in Chapter 0, furthermore, shows that many shortages are the consequence of problems with manufacturing or stem from sudden fluctuations in demand. Even though these problems can materialise without advance warning, it is possible for manufacturers to proactively assess the main production and distribution risks and plan for these accordingly. Thus, regulatory authorities may require manufacturers to submit shortage mitigation and prevention plans. Such strategies could outline, for example, approaches to handling a shortage, steps to mitigate the core issue, prospective action-timelines or information on alternatives in case a shortage occurs. Furthermore, they could include clear communication guidelines and channels, which can become activated in case of a shortage (e.g. how will NCAs, practitioners or other stakeholders be informed?). Legal obligations on MAHs to develop shortage mitigation or prevention plans already exist in several countries, e.g. France and Spain.

Considered and recommended solutions

The consultation process shows there is strong support for the use of shortage prevention and mitigation plans. It is thus recommended to:

- Require suppliers to have adequate shortage prevention and mitigation plans in place

This would, for instance, require suppliers to provide proof of adequate quality management systems and information on market forecasting methods or inventory management techniques. Even though MAHs have expressed somewhat greater reservations about this solution than other stakeholders, mostly because they view the measure is complicated to implement, they still recognise its possible value. The solution is viewed as likely to be effective and offering greatest value when implemented at EU-level (Figure 110). However, in discussion some stakeholders expressed doubts about how such plans would work in practice, in terms of compliance and enforcement.

Although the recommended solution focuses on a requirement on suppliers, the responsibility for planning for shortage situations need not be limited there. Authorities and pharmacists also can play active roles in signalling the risk of shortages and devising mitigation strategies. Several EU countries already use a risk-assessment approach to tackle medicine shortages.[251] For life-saving medicines, national authorities in Denmark, Finland, Germany, Hungary, and Italy perform risk assessment for medicines affected by shortages. Irish medicine shortage management guidelines that encompass risk assessments have also been developed. In the first consultation round, stakeholders were asked

[249] European Healthcare Distribution Association GIRP. (February 2021) European Medicines Verification System data: GIRP reflections on potential use of data contained in the EMVS for shortages monitoring. Available at: http://girp.eu/sites/default/files/documents/girp_position_on_use_of_emvs_for_monitoring_of_shortages_-_updatedfeb21.pdf. Accessed 7 September 2021.

[250] Pharmaceutical Group of European Union PGEU. (2020) PGEU statement on the potential use of the data contained in the EMVS to monitor shortages. Available at: https://www.pgeu.eu/wp-content/uploads/2020/08/PGEU-Statement-on-the-potential-use-of-the-EMVS-to-monitor-shortages.pdf. Accessed 7 September 2021.

[251] Miljković, N. et al. (2020) 'Prospective Risk Assessment of Medicine Shortages in Europe and Israel: Findings and Implications', Frontiers in Pharmacology, 11(March), pp. 1–14. doi: 10.3389/fphar.2020.00357.

for their opinion on a solution focused on supporting cooperation on national strategies for demand forecasting, planning and shortage mitigation across the Member States. Although this solution was removed from further consultation, for lack of broad consensus, it enjoyed high support among NCAs, manufacturers, civil society organisations and health professionals (Figure 91). The solution was mostly opposed by distributors and parallel traders. However, as these parties would not be directly involved in the implementation of the solution and are themselves not placed under any obligations, there is scope for the Member States to further explore this potential solution.

Pharmacists are the final link in the supply chain and connect directly to the patient. As such, they play a significant role in mitigating the impact of a shortage at the patient level. To assist them in such efforts, they could be encouraged and equipped to develop prospective risk assessments, considering the potential impact of a shortage and any actions that could be taken to either obtain a product another way or offer appropriate substitutes. Although a full overview of countries where this has been introduced was not available, review of the literature shows that, in Hungary, the Professional College of Healthcare has developed a practical guide for health providers on how to respond to pharmaceutical shortages.[252] According to this guide, key steps and measures to be taken in such an event include: i) preparation of a strategic plan, ii) determining the duration of the respective shortage, iii) identifying alternative treatments, iv) estimating the impact of concerned shortage, v) securing communication and patient safety, as well as, vi) collaboration and consultation with external stakeholders. A proposed solution to encourage pharmacists to increase the use of prospective risk assessments for the mitigation of medicines shortages received moderately strong support in the first consultation round (Figure 90). As with the proposed solution on cooperation between Member States on planning and mitigation, the overall assessment was lowered by opposition from distributors and parallel traders who doubt the solution's relevance and are unconvinced it will prove to be feasible or efficient.

8.6. Stock keeping obligations

Problem description

As a result of pressure to minimise cost, pharmaceutical manufacturers generally operate their supply chains based on 'just-in-time' management principles, involving low inventory levels. Cost containment considerations likewise encourage pharmacists to maintain low levels of stock and to rely on the ability of wholesale distributors to resupply quickly as and when needed. These low stock-keeping levels mean that sudden supply disruptions or increases in demand cannot easily be absorbed by available supplies. The speed with which shortages can be resolved then depends greatly on the speed with which new products can be produced and distributed. Although this study did not investigate average manufacturing and resupply times or stock levels at different points throughout the value chain, many NCAs view increased stocking as a potential solution for shortages. In 12 European countries MAHs and/or wholesalers already have the obligation to keep a stock of defined medicines for a certain period (usually at least three months).[255] Such stocking requirements have also been built into tender contracts in, for instance Albania and Denmark. Interviewed NCA representatives indicated that, in Estonia, authorities have proposed introducing requirements on MAH to hold sufficient stocks whilst, in Latvia, it has been proposed to mandate stock holding at pharmacy level. The COVID-19 pandemic has further impressed on Member States the importance of having emergency reserves of essential medicines.

In the survey of national authorities, all respondents from countries that had experience with stockholding obligations on suppliers found this measure effective, with 30% even considering it 'very effective' (Figure 45). As discussed in Section 6.2, it was not possible on the basis of data from the national shortage registers to verify whether countries that have introduced stock keeping obligations have indeed derived some benefit from this measure. Nonetheless, national stockpiling is frequently considered as a safeguard against (temporary) shortages.

Although stockpiling of medicines may help to protect a country against shortages, it may have the unwanted by-effect of increasing (the risk of) shortages in another. When there is a limited overall

[252] Bochenek, T. et al. (2018) 'Systemic Measures and Legislative and Organizational Frameworks Aimed at Preventing or Mitigating Drug Shortages in 28 European and Western Asian Countries', Frontiers in Pharmacology, 8, p. 942. doi: 10.3389/fphar.2017.00942.

supply, stockpiling by some could mean that others cannot be sufficiently supplied anymore. Products that are kept in national (or regional) stockpiles cannot easily be redistributed to other markets in need, due to country-specific packaging and labelling requirements. For equitable product availability between Member States, it is thus important that there is a clear and transparent relation between supply and demand and that individual Member States are discouraged from locking in critical supplies through excessive stockpiling.

Although excessive national or regional stockpiling is counter to equitable access, holding sufficient stock of medicines of major therapeutic interest can be an effective tool to protect against shortages, if done jointly (such as at EU-level) and when managed properly. Marketing authorisation holders and/or wholesalers could be obligated to hold sufficient stock, not only of finished products but potentially also of raw materials and of unfinished/unpackaged products that can be prepared to meet specific national requirements. Stockholding can also be centrally coordinated at the EU-level for particular products. In 2020, against the backdrop of COVID-19, the Commission introduced the first strategic EU-coordinated stockpile (rescEU) for medical equipment, vaccines and therapeutics. For other medicinal products thus far a coordinated approach to stockpiling at the EU-level does not exist.

Considered and recommended solutions

Outcomes of the stakeholder consultation support the recommendation to:

- Introduce legal obligations for MAHs and wholesalers to maintain a safety stock of (unfinished) products for medicines of major therapeutic interest at EU-level

Initially, stakeholders were asked for their opinion on the usefulness of requiring MAHs and wholesalers to maintain a safety stock of *finished* products at EU-level. This proposal was widely dismissed by manufacturers who feel that the differences between requirements of Member States in terms of presentation and labelling are so substantial that this stock could not easily be used to supply different markets (Figure 119). Holding safety stock of finished products at the (sub-)national level instead was not viewed as a good alternative as this potentially creates substantial waste.

Following discussion, it was deemed more viable to require holding stock of *unfinished* goods and of the ingredients and materials needed to produce finished goods. When there an impending shortage situation, production capacity can be mobilised to manufacture or finish additional supplies of the affected medicines. Nonetheless, stockpiling is mostly seen as an "in-case of emergency" option rather than as a structural solution and one that should be focused on the most critical medicines.

EU-coordinated strategic stockpiling of specific medicines was generally well supported by NCAs but much less so by supply chain actors (Figure 102). For this reason, this solution was not taken further in the consultation process and has not been recommended. This should, however, not be interpreted to mean that initiatives such as rescEU are not considered to have merit.

An important consideration in the introduction of stock holding requirements are the potential negative impacts and the allocation of costs across parties. Increased stock holding requirements will come at a substantial cost: manufacturers will have to produce greater volumes of product that may end up having to be destroyed as reserve stock goes unused and expires, and the excess stock will need to be appropriately warehoused. If MAHs or wholesalers are required to carry the additional costs themselves, they are likely to push at least some of these costs onto payers by increasing medicine prices. The potentially greater need to destroy expired medicines also runs counter to efforts to reduce pharmaceutical waste and increase the environmental burden. As such, legal obligations should carefully consider the appropriate stock levels on a product-by-product basis, and account for both the risk of shortages and the criticality of the product.

8.7. Local production of APIs, raw materials and medicines

Problem description

As illustrated by the case study on amoxicillin (Section 7.5), even in a market where there are multiple suppliers of a (generic) medicinal product, these suppliers frequently rely on raw materials and APIs from a very limited number of sources. Any disruptions to the operations of these upstream suppliers thus can have large scale domino effects on the manufacturers who rely on their products. Although the level of detail national shortage registries report on the root causes of shortages in the

(Section 5.2) was insufficient to estimate how large of a role API shortages play in the occurrence of medicine shortages, insufficiently diversified supply chains are widely recognised as an issue of concern.

Furthermore, at present a large part of all APIs and raw materials are produced in non-EU countries, which leads to limited oversight and control over supply chains. Non-EU based production also means that the supply of medicines to the EU is at increased risk from export restrictions or from events and policies that affect operations elsewhere. This was illustrated by the COVID-19 pandemic when API production in China was suspended due to local lockdowns.

A possible strategy to reduce the risk of shortages is thus to introduce measures that incentivise the diversification of the production of APIs, raw materials and medicines. These measures could be both economic and legislative nature. Economic measures may involve subsidies, grants or tax breaks, whilst regulations could be introduced to mandate MAHs to source materials from multiple suppliers.

Considered and recommended solutions

The consultation assessed stakeholders' perspectives on the introduction of measures to create an economic and regulatory framework incentivising the local production of APIs, raw materials and medicines to better protect continuity of supply and reduce Europe's dependence on pharmaceutical manufacturing elsewhere. Although the solution was generally favoured by NCAs, distributors and parallel traders, there was a significant lack of stakeholder consensus on whether the solution would be easy to implement and a fear of unintended consequences (Figure 111). Manufacturers in particular note that reshoring of production will likely increase production costs. For products where profit margins are low, as with many generic medicines, this could make production and marketing economically unworkable unless health authorities are willing to pay higher prices for these medicines to absorb the cost increases. Because of the lack of consensus and the significant concerns of manufacturers, who are responsible for production, this solution could not be recommended here in the proposed form. Further dialogue between authorities and manufacturers, such as that currently taking place in the EU structured dialogue, may deepen the understanding of what measures are most appropriate to improve supply chain resilience and what role reshoring of pharmaceutical production can play in this.

8.8. Parallel distribution

Problem description

Although the data from the national shortage registries analysed in this study did not allow for any firm conclusions to be drawn about the role of parallel exportation of medicines from one Member State to another (Section 5.5), parallel trade has often been cited as one of the demand-related causes of medicines shortages.[253] This has spurred some countries to restrict the flow of certain medicines, even in the context of the European internal market. For instance, in 2015, the Polish Ministry of Health introduced a list of medicinal products and other medical and health items prone to unavailability to better track and manage export flows. Similar measures against export are also in place in other Member States with many variations.[254,255] In Poland, but also in France, the export restriction applies to all medicinal products of high therapeutic value that are in shortage. In Greece and Latvia, the restriction extends to all medicinal products in shortage. In Spain, export is restricted only for medicinal products without therapeutic equivalents.

Whilst this study was not able to quantify the effect of export restrictions on the occurrence of shortages (see Section 6.2), NCA representatives of countries that have introduced such measures often feel that these restrictions are a necessary part of their ability to protect the supply of critical medicines. However, national restrictions have not always been deemed to be in conformance with

[253] Weerdt, E. De et al. (2015) 'Causes of drug shortages in the legal pharmaceutical framework', Regulatory Toxicology and Pharmacology, 71(2), pp. 251–258. doi: 10.1016/j.yrtph.2015.01.005.

[254] Musazzi, U. M., Di Giorgio, D. and Minghetti, P. (2020) 'New regulatory strategies to manage medicines shortages in Europe', International Journal of Pharmaceutics. Elsevier, 579(February), p. 119171. doi: 10.1016/j.ijpharm.2020.119171.

[255] Vogler, S. and Fischer, S. (2020) 'How to address medicines shortages: Findings from a cross-sectional study of 24 countries', Health Policy. Elsevier Ireland Ltd, 124(12), pp. 1287–1296. doi: 10.1016/j.healthpol.2020.09.001.

the EU legal framework, as discussed in Section 6.4. Common principles across Member States could help to improve transparency and predictability of the legal frameworks and ensure that the policies of some Member States are not to the detriment of others.

Practical evidence suggests that in case of shortages, excess stocks of the medicine in question are typically available elsewhere. Although parallel trade has been maligned as a cause of shortages, it is also used by countries to fill their supply gaps when there is excess product in others. Under the right circumstances, parallel distribution can thus be used to mitigate shortages. Parallel import is already used routinely by some countries, like Portugal and the Netherlands, that are frequently affected by shortages and by decisions of MAHs not to operate in those markets. Particularly in crisis situations, countries could make better use of parallel importation, for instance by having procedures in place for emergency imports and issuing emergency import licenses. To tackle shortages, several European countries have simplified regulatory procedures related to the import, authorisation and dispensing of medicines procured on the world market.[252,256] Exceptions have been granted with regard to labelling requirements of packages and product information leaflets in other languages were permitted. Malta has used Article 126a of Directive 2001/83/EC, which effectively allows Maltese authorities to place a product with a license in another EU Member State on the domestic market even if a domestic license has not been issued yet. This measure has also partially been implemented by Latvia.[257]

To prevent excessive stock held in some EU Member States while others are experiencing shortages, common principles may be adopted that lay the foundation for export restrictions or the reduction thereof. Member States may therefore be requested to abolish the distortive effects of national schemes incentivising parallel imports and instead promoting the application of the non-extraterritoriality principle.

Considered and recommended solutions

Despite the contentious nature of discussions on the role of parallel distribution, there was determined to be sufficient stakeholder support and consensus to recommend:

- Adopting common principles for the introduction of national restrictions on intra-EU trade
- Allowing for greater flexibilities for emergency imports of specific products in case of market withdrawals and other critical shortages

Expectedly, parallel traders show greatest concern at the proposal to introduce common principles for export restrictions, particularly if these would lead to increased use of such restrictions (Figure 115). NCAs anticipate problems with the practical implementation but generally do expect that it can be effective. Whilst there is overall support for the basic idea of incorporating such requirements, the solution is more often seen in terms of more general guidance rather than in prescriptive regulations.

The parallel distribution industry has publicly emphasised the role of parallel import as a solution for shortages, so it is not surprising they strongly support allowing for greater flexibilities for emergency imports (Figure 114). The solution is, however, also favoured by others, including many NCAs.

Because the free movement of goods within the EU/EEA internal market is enshrined in the TFEU, any solutions introduced that could restrict this need to be carefully tested for their coherence with the EU legal framework. Member States should be aware of the legal limits on their national actions. Conversely, the design of more specific solutions to facilitate emergency imports should carefully consider the objectives of the regulatory framework that normally restrict these. For instance, in deciding whether to allow the emergency import of products from a supplier that does not already have an authorisation in the target market, competent authorities need to consider not only the benefits of allowing the import but also the potential risks.

[256] WHO Regional Office for Europe (2020) Assessing the magnitude and nature of shortages of essential medicines and vaccines and nature of shortages. Copenhagen.

[257] Musazzi, U. M., Di Giorgio, D. and Minghetti, P. (2020) 'New regulatory strategies to manage medicines shortages in Europe', International Journal of Pharmaceutics. Elsevier, 579(February), p. 119171. doi: 10.1016/j.ijpharm.2020.119171.

8.9. Procurement and tendering processes

Problem description

Procurement practices can have a major impact on the medicines supply chain. Some current practices, aimed primarily at reducing healthcare expenditure on medicines, can directly affect market dynamics and the level of competition.

By granting tenders primarily based on price, procurement agencies are incentivising manufacturers to obtain materials at the lowest cost without due consideration of the importance of multi-sourcing. Moreover, the low margins on many pharmaceutical products – especially older and generic medicines – make it unattractive for manufacturers to continue operating in specific markets, or even manufacture a particular product, if they have been excluded from the market for a longer time because they did not win a tender. This reduces the competition and leaves markets vulnerable when remaining suppliers experience disruptions or if demand for a product suddenly increases beyond the level the selected supplier is able to provide. The European association for the generics industry has published a position paper on best procurement practices, recommending the use of multi-winner tenders and adjusting the number of procurement winners according to the market, product and country characteristics.[258]

As shown in Section 5.3, the analysis of reported root causes shows that a very substantial share of shortages is directly attributed to 'commercial reasons' and that such commercial factors may be a further aggravating factor in shortages caused by other issues. As such, there is a clear imperative to devise solutions that improve the balance between cost containment measures and maintaining a healthy and competitive pharmaceutical market. Potential solutions may lie in smaller and more frequent tenders and reduced use of 'winner-takes-all' tenders. Procurers could furthermore be encouraged or even obligated to evaluate tenders not only on price but also on criteria such as supply chain robustness. Procurement contracts could have built in security provisions, specifying how the provider intends to protect against the risk of shortages and how these would be mitigated should they occur. Dutch pharmaceutical policy experts, for instance, have called for the establishment of specific requirements, such as for manufacturers to demonstrably have several production locations or to include two suppliers of raw materials for necessary medicines in their respective registration files.[259] Interviewed Swedish authorities indicated considering a similar measure whereby MAHs would be required to list at least two manufacturers when applying for the authorisation of pharmaceutical product.

Considered and recommended solutions

Based on solutions discussed with stakeholders throughout this study, the consultation process focused on how (public) procurement agencies could improve their tendering practices to achieve greater resilience of supply. This has resulted in the specific recommendation to:

- Incorporate requirements for having more diversified, multiple tenderers and thereby supply sources in public procurement tenders

The measure receives moderately strong support from all stakeholder groups and generally scores well on all criteria (Figure 118). There was, however, some concern that national procurement agencies may not currently be equipped to mainstream more diversified procedures. It was also noted that the complexity of global supply chains is such that different manufacturers of finished products may still rely on the same suppliers of APIs, raw materials and intermediates, which can make it difficult for procurement agencies to identify if their suppliers are truly diversified. In a related question, stakeholders were asked whether anchoring supply security provisions in procurement contracts would constitute a potential solution for shortages. Although most stakeholder groups saw potential in this solution, it was discarded from further consultation because of lack of support from distributors and parallel traders and because it was considered too similar to other already recommended solutions to offer much added value.

[258] Medicines for Europe. (2019) Position paper on best procurement practices. Available at: https://www.medicinesforeurope.com/wp-content/uploads/2019/04/M-Best-procurement-practices-position-paper_final-version.pdf. Accessed 10 September 2021.

[259] Marselis, D. (2017) 'Zwartepieten over het geneesmiddelentekort', Nederlands Tijdschrift voor Geneeskunde.

The consultation included two more solutions involving tendering and procurement practices. These included adjusting national tendering procedures to include criteria other than price and introducing smaller and more frequent tenders aimed at maintaining health market competition. Although, on average, there was a moderate level of support for these solutions, there was insufficient agreement between all involved stakeholders for these solutions to be selected as recommendations. Nonetheless, the solutions are here still discussed in somewhat more detail.

Manufacturers universally encouraged the inclusion of quality-related criteria in national tendering procedures (Figure 99). Importantly, this solution also received significant report from NCAs who, whilst not typically directly responsible for procurement, are the closest representatives of the Member States who ultimately bear much of the cost of medicines. In discussions, stakeholders clarified that they would like to see procurement agencies reward tenderers not only for having diversified supply chains but also for minimising the environmental impact of manufacturing. As with the discussed solution around reshoring of pharmaceutical manufacturing, moving away from price-only selection of tenderers may be expected to increase the price of medicines but the exact impact of this is difficult to predict. It will depend on such factors as the overall level of competition for a product (when there are few suppliers in a market, procurement agencies have limited choice), and the price difference between suppliers. The use of criteria beyond price to evaluate tenders is already encouraged by the EU Public Procurement Directive, as discussed in 6.4, but the Directive is not prescriptive in what criteria Member States should use or how to weigh these. This study did not look at how widely procurement agencies currently use quality criteria in the evaluation of tenders, what these criteria are and how they consider security of supply.

Most consulted stakeholders saw only modest benefit in the introduction of smaller and more frequent tenders and were weary of the effect that increased uncertainty could have on suppliers (Figure 97). Even though large and long-running contracts can have the consequence of driving unsuccessful tenderers out of a market, they offer the winning tenderer the financial security needed to justify investments in production capacity. Whilst there is discussion in the academic literature[56] on the role of procurement practices in drug shortages, no quantitative data were available on how different procurement practices can influence medicine costs on the one hand and supply chain resilience on the other.

As a counterpoint to introduction of smaller tenders, some countries have sought to increase their bargaining power towards suppliers by engaging in pooled procurement. In the first consultation round, the use of centralised or pooled procurement was seen as a good possible solution by NCAs, civil society organisations and health professionals but widely rejected by manufacturers (Figure 100). Because of the lack of consensus, the measure has not here been included as a recommended solution although there may be specific situations, such as in the case of products with low sales volumes or in emergency situations, where pooled procurement is a viable strategy to negotiate contracts imposing stricter obligations on suppliers for ensuring the continuity of supply.

8.10. Regulatory simplification

Problem description

It has been suggested that inefficient regulatory procedures are contributing to the incidence of shortages and extending them. The first identified area of concern involves the registration of post-approval changes (PACs). Any time a manufacturer changes the production of a medicine, for instance because ingredients are sourced from new suppliers or because the production method has changed, they need to submit a PAC application Although this study could not find quantifiable evidence that the need to register PACs is contributing to the incidence of shortages, as this is not reported as a root cause for shortages, some manufacturers have indicated that the associated regulatory burden is delaying manufacturing and distribution of products. This issue was raised especially for vaccines, where chemical, manufacturing and control (CMC) variations are common. Manufacturers thus strongly favour changes to align guidelines for post-approval changes. They expect this will lead to more rapid introduction of products and improved product availability. It is expected that this solution will most benefit availability of vaccines and older medicines for which the cost of upkeep of the marketing authorisation is high in comparison with the perceived commercial interest. Stakeholders also would welcome more automated dossier submission options.

Further issues were raised in connection to authorisation procedures. The Mutual Recognition Procedure (MRP) is used by companies to apply for a marketing authorisation in multiple EU Member States in succession. The MRP is a European marketing authorisation procedure based on the principle of recognition of the evaluation performed by the reference Member State. If a European Member State has already issued a marketing authorisation, other Member States may refer to, and rely on this authorisation instead of having to run their own authorisation procedures. Under an accelerated MRP, other Member States would not require a full review of the same dossier, but rather focus on the most relevant aspects such as the fulfilment of the local regulatory obligations in the given country. In the context of shortages, this could be useful when the impact of a particular shortage can be mitigated by use of another (generic) version of the product or a therapeutic equivalent. If these other medicines have not previously been authorised, faster approval could help to make these products available more quickly. After completion of the first MRP, an MAH may use the MRP repeatedly to obtain marketing authorisation for the same product in additional Member States. This is known as the Repeat Use Procedure (RUP). As with allowing for accelerated MRP, improving the efficiency of the RUP is expected to help mitigate the impact of shortages by allowing for faster approval of alternative products into a market.

The data analysed in this study focus only on products in shortage but offer no insight into whether suitable substitutes have already been authorised in the country reporting the shortage or whether the shortage could have been mitigated more quickly through use of accelerated authorisation procedures. As such, the relevance of proposed solutions rests entirely on the perceptions of stakeholders involved in the consultation.

Considered and recommended solutions

Although the link between shortages and potentially inefficient regulatory procedures could not be established in this study, solutions aimed at improving this efficiency enjoy substantial stakeholder support. It is thus recommended:

- For EU authorities to reduce the administrative and cost burden submission of post-approval changes
- To enable an accelerated mutual recognition procedure (MRP) within the EU
- To enable a (more) efficient Repeat Use Procedure

It should be noted that NCAs are generally least supportive of reducing the burden associated with PAC submissions, possibly out of concern that this could compromise the regulatory oversight of the quality and safety of medicines (Figure 124). Supply chain actors are the main proponents of the measure. It was not explicitly discussed to what extent the solution should be applied to specific products deemed critical and at risk of shortage.

Consulted stakeholders were generally supportive of solutions based on accelerated and improved authorisation procedures (MRP and RUP) (Figure 122 and Figure 123). It is, however, noted that use of this should be conditional upon the product dossier being up-to-date (i.e. all variations appropriately filed in line with EU legislations) and the product having a valid license in at least one Member State. It is also noted that implementation of an accelerated MRP may require improved alignment of regulatory systems across the Member States. As with the facilitation of PACs, it was not specified for which products or under which circumstances this measure would be applied.

This study does not have sufficient insight into the specifics of the regulatory procedures involved to determine the scope for efficiency gains and whether these would achieve the desired impact of alleviating shortages. The ongoing evaluation and ex-ante impact assessment of the general pharmaceutical legislation may offer further understanding of the role of these procedures and the feasibility to optimise them.

8.11. Packaging and labelling

Problem description

The analysis presented in Sections 4.2 and 4.7.1 confirms that medicine shortages rarely affect more than a few EU Member States at the same time. Although the internal market allows for products to be redistributed from countries where there is surplus to countries where there is a shortage through

parallel distribution, the current requirement of national labelling on packaging reportedly restricts the ability of MAHs and Member States to mitigate shortages by moving supplies of medicines between countries in a timely manner. It has thus been suggested that increased use of multi-language packs could help to reduce the duration of shortages and allow for supply to be redistributed more quickly to where the demand is. In Malta, pharmaceutical products are allowed to be marketed in both Maltese and English, and joint packs with other English-speaking countries have been pursued as a common strategy. [260]

An approach allowing for multi-language packaging would be to implement labelling that refers to an online, electronic version of the full package labelling and/or patient information via a code on the pack. During dispense, the pharmacist provides details of the dose regimen that needs to be followed in the national language thereby ensuring that the medicine is taken correctly: the rest of the information could then be accessed electronically. For those patients that cannot access online labelling, the pharmacist would be able to print out the needed material in the local language. The goal could be the mainstreaming of Electronic Product Information Leaflets (ePIL), which would provide additional options to improve patient understanding of their medicines and how they should be used, for instance in the form of videos included in the ePIL demonstrating their correct use.

Considered and recommended solutions

Considering the perspectives of all consulted stakeholders, it is recommended to:

- Develop an EU-wide medicines packaging and labelling regulation that included flexibilities for digital leaflets and multi-country/multi-language packaging and labelling

Most stakeholder groups view flexibilities in the packaging and labelling of medicines (not including mandatory safety features and national product identifiers) as a viable solution to reduce or prevent shortages by facilitating redistribution of medicines between markets when these are in short supply for some markets but not others (Figure 125). It is expected to improve resilience against demand fluctuations. Nevertheless, civil society and patient organisations have expressed concerns about the use of technological solutions, including digital leaflets, that could harm less digitally versed patient groups, such as the elderly or those with less education or those without access to computers or the Internet. This also applies to use of leaflets in languages other than the majority language of a country or region.

At the same time, manufacturers health professionals that participated in interviews and consultation discussions highlighted that for certain medicines, particularly those administered in the hospital setting by certified health personnel, the use of digital leaflets and/or packaging and leaflets in different languages could be implemented more readily without risk or inconvenience to patients. This applies, for instance, to vaccines, which are only administered by health professionals.

Although the introduction and increased use of digital solutions may be expected to require some initial investments by MAHs, for instance to build online platforms to make information available online for health professionals and patients and to print new leaflets, in the longer run these may be expected to result in cost savings.

For pharmacists and physicians, the use of multi-language and digital leaflets could pose an extra burden, both financially and in terms of effort needed. As the point of contact with patients, these parties would need to play an important role in helping patients access and understand relevant information, for instance by printing out leaflets in the local language. An added issue that could arise is one of liability if a health professional incorrectly translates important patient information. This issue was not further discussed during the consultation process but would be important to consider in the further elaboration of the solution.

[260] Musazzi, U. M., Di Giorgio, D. and Minghetti, P. (2020) 'New regulatory strategies to manage medicines shortages in Europe', International Journal of Pharmaceutics. Elsevier, 579(February), p. 119171. doi: 10.1016/j.ijpharm.2020.119171.

8.12. Therapeutic substitution and pharmacy preparations

Problem description

Depending on the country, if a prescribed medicine is not available in the exact strength and formulation indicated on the prescription, pharmacists may not have the authority to issue another version of the product or a therapeutic alternative. In such cases, the pharmacist first needs to contact the prescriber to discuss an appropriate alternative and a new prescription needs to be issued. This creates significant additional work for both the pharmacist and the prescriber and can result in delays in dispensing of the medicine to the patient.

A potential solution to mitigate the impact of shortages, is to enable pharmacists to independently decide on appropriate substitutions for a medicine in shortage and dispense this directly to the patient without mandating consultation with a prescriber. This would decrease the administrative and cost burden on the involved health professionals and decrease the impact on the patient. Competent authorities could thus consider extending the mandate for pharmacists to independently issue substitutions, whilst clarifying the conditions under which such substitution would and would not be allowed.

To enable these mitigating measures, more systematic and better information is needed about the availability and suitability of substitutes. Therefore, shortage databases could also provide information about available alternative medicines that may be dispensed if a shortage occurs. These alternatives should then be decided upon a-priori by competent authorities.

Besides dispensing available substitutes, it is also possible for pharmacists to produce medicines that are in shortage directly or to have these produced in compounding pharmacies. For patented medicines, this is allowed only under a prescribed set of conditions and only for the pharmacy's own patient population. Expanding the regulatory framework to increase the scope for use of pharmacy preparations could help reduce shortages provided raw materials are still available.

Considered and recommended solutions

Among all proposed solutions, the consultation showed strongest, near unanimous support for the recommendation to:

- Include information about available alternative medicines in national shortage databases

This would allow pharmacists to rapidly identify, procure and dispense such alternatives and would allow the impact of shortages on patients to be mitigated. However, whilst there is great support for the measure in theory, in practice support for the measure will depend on how it is implemented (Figure 121). Health professionals and representatives of patient organisations emphasised that, as a non-debatable core principle, patient safety should not be compromised. This means that alternatives should only be dispensed if they do not pose avoidable and unjustifiable risks to the patient. Consequently, information on alternatives will need to be as contextual and specific (e.g. dosage, potential side effects) as possible to enable pharmacists and prescribers to make well-informed choices when dispensing these alternatives. Because of differences in treatment guidelines and availability of alternatives, this information needs to be tailored to the national situation in each Member State. There also needs to be clarity on whether pharmacists can make the suggested substitution autonomously or whether a physician needs to first be consulted. This requires intensive collaboration between competent authorities, pharmacists and physicians to discuss scientific and health-relevant factors.

Devising suitable alternatives may be approached from different angles: i) sourcing the same medicine from alternative authorised sources; ii) reverting to the same medicine with a different strength, if available, and adjusting the treatment regimen accordingly; iii) therapeutic substitutions with another medicine from the same class; iv) or import of the medicine from elsewhere.

Two additional potential mitigation strategies involving pharmacists were proposed as potential solutions. The first concerned allowing the use of pharmacy preparations as alternatives in case of shortages. Although in the first round of consultation, this solution received substantial support from most stakeholders, it was generally rejected by manufacturers (Figure 103). This position is expected as allowing pharmacy preparations effectively grants pharmacists the authorisation to override the

patents of MAHs and MAH will actively seek to protect these, where necessary through legal challenges. Consequently, the solution could proof to implement in most situations.

Separately, the possibility of allowing pharmacies to supply a part of a unit pack to avoid waste in case of shortages was explored with stakeholders (Figure 120). However, during the consultation process, it was suggested that in some countries the national legal framework does not allow this. Within the scope of the study, this could not be independently verified. Because of these uncertainties, the solution was not selected for recommendation.

9. CONCLUSIONS

9.1. What this study adds to the existing evidence

This study adds to a fast-growing body of work, produced by academic researchers as well as by professional and industry associations, that has looked at the problem of medicine shortages, their impacts and root causes. It confirms many of the various observations made by these others, such as that the occurrence of shortages is commonplace across the European Union, that these shortages are driven by a combination of factors and that they are placing a substantial burden on health systems and patients. The present study adds to the existing evidence-base in various ways:

- It has compiled and analysed the thus-far largest set of data from across the EEA, using data from the national shortage registries of 22 EEA countries
- It includes a comprehensive analysis of these data sets on key product characteristics, comparing findings against a matched set of medicines not in shortage to determine whether certain characteristics predispose products for greater risk of shortage
- It has applied guidance developed at the EU-level to standardise information of reported root causes of shortages and allow for an aggregated analysis across national data sets
- It evaluated, to the extent possible, whether the current EU legal framework, specifically Articles 23a and 81 of Directive 2001/83/EC, has been effective in preventing and mitigating shortages, whilst considering how this framework is consistent with and has been complemented by actions taken nationally by the Member States
- It included a broad-based consultation with stakeholders to discuss the underlying issues and derive a set of recommended solutions

9.2. Key findings from this study

Defining and reporting of medicine shortages

There are significant variations within the EU in how countries define a shortage with further differences in how and when these definitions are used. In response to this problem, in 2019, the EMA and HMA released an agreed "shortage" definition.[261] Stakeholders widely view this as a useful step, though some feel the definition does not adequately differentiate between critical and non-critical shortages. Member States also are far from uniform in their standards and systems for notification of shortages and in the information they request. The lack of standardisation and harmonisation is hampering information sharing and comparative analysis between countries. It also creates inefficiencies for parties tasked with notification of shortages. Improved harmonisation is widely viewed as a prerequisite for the development of effective and appropriately tailored actions to prevent and mitigate shortages.

Trends and characteristics of medicine shortages

Based on the comprehensive analysis of data from the shortage registries and the consultation with stakeholders, several conclusions can be drawn. First, notified shortages have strongly increased over the last five to ten years. Although the increase can be partially explained by more widespread and better notification, it also reflects a real increase in the number of times a pharmacist is not able to offer a patient their preferred medicine and the impact of this is felt in several ways. It creates a significant burden on pharmacists and physician tasked with providing the best possible treatment alternative. Even more crucially, it puts patients at risk from worse health outcomes and causes distress. However, what this study has also shown is that shortages are only rarely the result of globally low levels of supply. Most shortages are localised and impact some countries but not others, pointing towards issues with inequitable distribution and access.

Shortages can arise for any type of medicine, but those at highest risk include pain relief medication, antihypertensives, anti-infectives and oncology medicines. Most shortages involve older, off-patent and generic medicines, which has been widely attributed to the low profit margins associated with these products. Although for most products in shortage an alternative may be found through, for instance, generic substitution or importation, for approximately a quarter of cases the product in shortage may represent the only available version. The shortage registries, however, offer very

261 HMA/EMA (2019) Good practice guidance for communication to the public on medicines' availability issues.

limited insight into the criticality of product shortages and their impact on the quality and continuity of treatment to patients.

Root causes of shortages

Despite a multitude of position papers and studies, proper understanding of the root causes of shortages remains substantially challenged by inconsistent and limited reporting. Moreover, reporting of root causes is generally reductionist, singling out the most acute cause (e.g. a problem at the production site) but without considering the underlying more systemic issues (e.g. consolidation of manufacturing, resulting in a very limited number of production sites) and market-related factors (e.g. single-winner procurement practices). Reporting of root causes of shortages suggests that around half of all cases can be traced back to issues with quality and manufacturing. Commercial reasons, including market withdrawals, and unexpected increases in demand are other important causes of shortages. The COVID-19 pandemic posed a major challenge to the continued availability of critical medicines used in the treatment of COVID-19 patients.

The available information is, at present, insufficient to quantify the importance of outsourcing of pharmaceutical production (including the production of APIs) and of parallel distribution as potential risk factors for shortages. More generally, austere pricing policies and industry consolidation are viewed as systematic factors that contribute to or aggravate shortages. Market factors play an especially important role in product withdrawals for commercial reasons, which have been happening with increasing frequency in recent years. The large majority of medicines that are permanently withdrawn from a particular market involve products with low sales revenues in those markets, for which the MAH has decided that the generated revenue on the product no longer justifies the costs of maintaining the product on that market. This may be the case if the demand for the product has declined, for instance because better products have become available, but also if the market conditions no longer enable the MAH to earn a sufficient profit margin on the product.

Evaluation of the EU legal framework

The current EU legal framework, through the Community Code relating to medicinal products for human use (Directive 2001/83/EC), contains two provisions Member States can use to help prevent and mitigate shortages. Article 23a requires MAHs to notify the NCA at least two months in advance of their intent to suspend the marketing of a product it has placed on that market, whilst Article 81 mandates MAHs and wholesalers to ensure, within the limits of their responsibility, the continued and appropriate supply of medicines placed on the market. This study shows that all Member States have transposed these provisions into national legislation but have operationalised them in different ways.

Because in most countries the transposition took place years before the introduction of a shortage notification registration system, the data to substantiate where these provisions have enabled Member States to effectively slow down the incidence of shortages is largely lacking. The notification obligation imposed by Article 23a has generally been helpful to authorities in preparing for product withdrawals and mitigating the impact thereof. The supply obligation dictated by Article 81 is, by itself, very generally formulated and many Member States have introduced a variety of measures to impose more specific obligations on MAHs and, in some cases, other parties. These vary from stock keeping obligations, to mandatory reporting on stock levels and export restrictions. There is some, albeit rather poorly substantiated, evidence to support that export restrictions have allowed countries that have imposed these to reduce the number of shortages experienced. It was not possible to isolate the effects of other measures, including stock keeping obligations.

The costs that could be attributed directly to the obligations under the EU legal framework are difficult to quantify as, to a significant degree, these are absorbed by the normal operational costs of the parties on whom the obligations fall. On the other hand, there are important benefits to patients and health systems, in the form of costs avoided and continuity of care, from avoided shortages or from shortages that are resolved more quickly or mitigated better. These benefits may be viewed as adequate justification for the costs.

Articles 23a and 81 are, for the most part, internally coherent with the objectives and provisions of the broader EU legal framework. EU-level coordination has already resulted in the development of useful new guidance and structures for dialogue and cooperation to tackle medicine shortages. However, there remains considerable scope for improvement through greater adoption of harmonised definitions and criteria and uniform implementation of guidelines.

9.3. Recommendations

Following extensive consultation with stakeholders, a series of 16 solutions has been recommended to address different aspects of the issue of shortages. These solutions collectively cover areas related to the collection and sharing of data and information between parties, supply chain issues, market

issues and mitigation strategies. Specifically, it is recommended for the European Commission, the EMA and/or Member States to:

- Establish and follow a centralised and harmonised EU-wide definition of medicine shortages
- Establish and mainstream harmonised reporting criteria for shortages, collecting sufficiently detailed information on key parameters (e.g. product details, MAH, details on the shortage and impact)
- Develop an EU-wide list of medicines for which shortages are the most critical and develop policies and/or regulations to improve their availability
- Set up stakeholder dialogue platforms for/between supply chain stakeholders, patients, and healthcare providers, respectively at Member States level
- Develop EU-wide and uniform legislation allowing for imposing financial sanctions if notification requirements and/or supply responsibilities are not met
- Require greater transparency of industry supply quotas as well as parallel traders' and wholesalers' transactions
- Require suppliers to have adequate shortage prevention and mitigation plans in place
- Introduce legal obligations for MAHs and wholesalers to maintain a safety stock of (unfinished) products for medicines of major therapeutic interest at EU-level
- Adopt common principles for the introduction of national restrictions on intra-EU trade
- Allow for greater flexibilities for emergency imports of specific products in case of market withdrawals and other critical shortages
- Incorporate requirements for having more diversified, multiple tenderers and thereby supply sources in public procurement tenders
- For EU authorities to reduce the administrative and cost burden submission of post-approval changes
- Enable an accelerated mutual recognition procedure (MRP) within the EU
- Enable a (more) efficient Repeat Use Procedure
- Develop an EU-wide medicines packaging and labelling regulation that included flexibilities for digital leaflets and multi-country/multi-language packaging and labelling
- Include information about available alternative medicines in shortage databases

Implementation of these recommendations will require action by different sets of stakeholders, with some requiring coordination at the level of the European Commission or the EMA whilst others will need to be supported and coordinated by competent authorities or similarly responsible bodies in the Member States. The recommended solutions still lack operational detailing. The development of this will require further consultation and reflection by policy makers.

Importantly, the recommendations offered were selected based on inputs collected from stakeholders with sometimes opposing interests. The scoring framework used allowed for the interests of different groups of stakeholders to be given equal weight. This was done to arrive at a set of recommendations for which there could be deemed to be sufficient support for the solutions to be actionable. However, it also allowed for solutions to be rejected from the list of recommendations even if they could offer substantial benefit but were strongly opposed by certain groups of stakeholders. Ultimately, it will be up to national and European authorities to decide if such solutions should still be pursued in the face of potentially strong opposition.

9.4. Final reflections

Despite persisting data limitations, it is evident that medicine shortages are an important problem. There is no reason to believe this problem is temporary or that it will go away on its own. It is thus safe to say that action is needed: action by those working in the different parts of the pharmaceutical value chain but also action by policymakers, at both the national and European levels. Crucially, any policy actions policies should aim to maximise the potential for achievement of its objectives while minimising the risk of unwanted consequences. This requires evidence of what works and what does not, under which circumstances and at what cost.

In recent years, many countries have started collecting important data on shortages and their causes. That is a step in the right direction. However, this study, as others before it, has shown that the data can and must be further improved. Continuous effort will thus be needed to optimise the data and keep feeding into the evidence base.

This study has confirmed that shortages often are not so much a problem of whether a medicine is available but one of where it is available. Even in the context of the European Union, founded on principles of solidarity, some countries are fighting shortages daily whereas others hardly experience them at all. This points towards some fundamental issues that have little to do with sourcing and manufacturing and much more with commercial decisions by suppliers on the one hand and national policies on the other. Here, many parties share responsibility. Suppliers take decisions based on considerations of profitability, selecting markets to supply based on willingness and ability to pay and ignoring others. Governments have also put pressure on prices that has led to supply chains that are lean to the point of vulnerability. This requires critical reflection on the part of all stakeholders not only of the roles of others but also of their own responsibilities.

The solutions recommended combine fairly uncontroversial and easily implemented actions with proposals for more radical and systemic changes to the pharmaceutical value chains. These systemic changes will be harder to make and they carry with them a cost but may ultimately prove to be the most essential.

Annex A. STUDY QUESTIONS AND SCOPE

Following the inception phase of this study, the study questions as presented in Table 23 were agreed between the contractor and the Commission. The reference period for this study was the period from 2004 to 2020. The study covers all countries within the European Economic Area (EEA).

Table 23 Study questions

#	Study questions
1	What are the positions of the main stakeholders regarding medicines shortages?
2	According to stakeholders, what are the main reasons for shortages?
3	According to stakeholders, what are the (potential) solutions to address shortages?
4	How do stakeholders define a shortage (essential elements of the definition)?
5	How do stakeholders feel shortages should be measured?
6	What are the most recent and relevant developments in the pharmaceutical sector and their impact on medicines shortages?
7	What are the national definitions of a shortage in the EEA? What are their advantages and disadvantages?
8	What are the national criteria for notifying a shortage in the EEA? What are their advantages and disadvantages?
9	How many and which medicines are currently in shortage in the EEA (taking into account different definitions and reporting requirements)?
10	What (groups of) medicines are at highest risk of being in shortage in the EU?
11	Has the profile of medicines in shortage changed over time (time trend analysis)? If so, in what ways?
12	What are the root causes of shortages in the EEA?
13	Are the root causes different depending on the type of medicine in shortage?
14	Are the current legal provisions at EU level (articles 23a and 81) adequate to prevent or mitigate medicines shortages? To what extent have these provisions contributed to the prevention/mitigation of effects of shortages, in comparison to the situation before their adoption? What (additional) measures have Member States introduced at national level to prevent or address shortages? What has been their effect?
15	Are there/what are the costs linked to the application of these provisions (EU/national level) and who is bearing these costs? What are the benefits linked with the application of these provisions (EU/National level) and who is getting those benefits? Are the costs reasonable in terms of benefits provided to the concerned actors?
16	How do EU/national actions complement each other? Are there any inconsistencies and/or synergies between the provisions on shortages at EU/national/international level? What has been the impact of voluntary cooperation at EU-level?
17	Were these provisions appropriate to solve the problem of shortages in the EU at the time of their adoption? Are these provisions still appropriate to tackle the issue of shortages in the light of the developments in the sector? Do these provisions at EU level provide added value in comparison to what could have happened in their absence?
18	What are EU and national solutions to address shortages of medicines?
19	What positions do stakeholders have in relation to different solutions?

Annex B. LITERATURE REVIEW

Peer-reviewed and grey literature published in English, French or German was identified on:

- Definitions (both official and less formal) of shortages in the EEA, including national definitions and notification criteria
- Systems used to measure and report shortages (both publicly available and those used exclusively e.g. by a Ministry of Health, where information is available)
- Requirements (legal obligations or other standards) that different parties along the full supply chain e.g. manufacturers, wholesalers, pharmacies, and patients have in relation to preventing and reporting shortages
- Measures national governments or multilateral organisations such as WHO are taking or have proposed in response to shortages
- Worldwide trends in shortages and stakeholder views
- Developments in the pharmaceutical sector and their (potential) impact on medicines shortages

Peer-reviewed literature was identified by using suitably adapted search strings containing combinations of the following search terms (* denotes a wildcard):

- Drug* OR Medicine*
- shortage*
- "Drug shortage" OR "Medicine shortage"
- definition OR notification OR reporting OR measurement OR response OR trends OR developments OR impact

A search was conducted of the following online databases: PubMed (including MEDLINE), Scopus, The Cochrane Library.

For **grey literature**, i.e. literature that has not been peer-reviewed such as data or survey reports, commissioned or internal studies, position papers and other information, we conducted searches using terms such as "Drug shortages OR Medicine shortages OR Medicines shortages" in the following:

- Online search engines e.g. Google
- Google Scholar
- EC and EMA websites
- Websites of international organisations such as OECD and WHO

Additionally, we checked the reference lists of all the literature identified and further identified relevant studies.

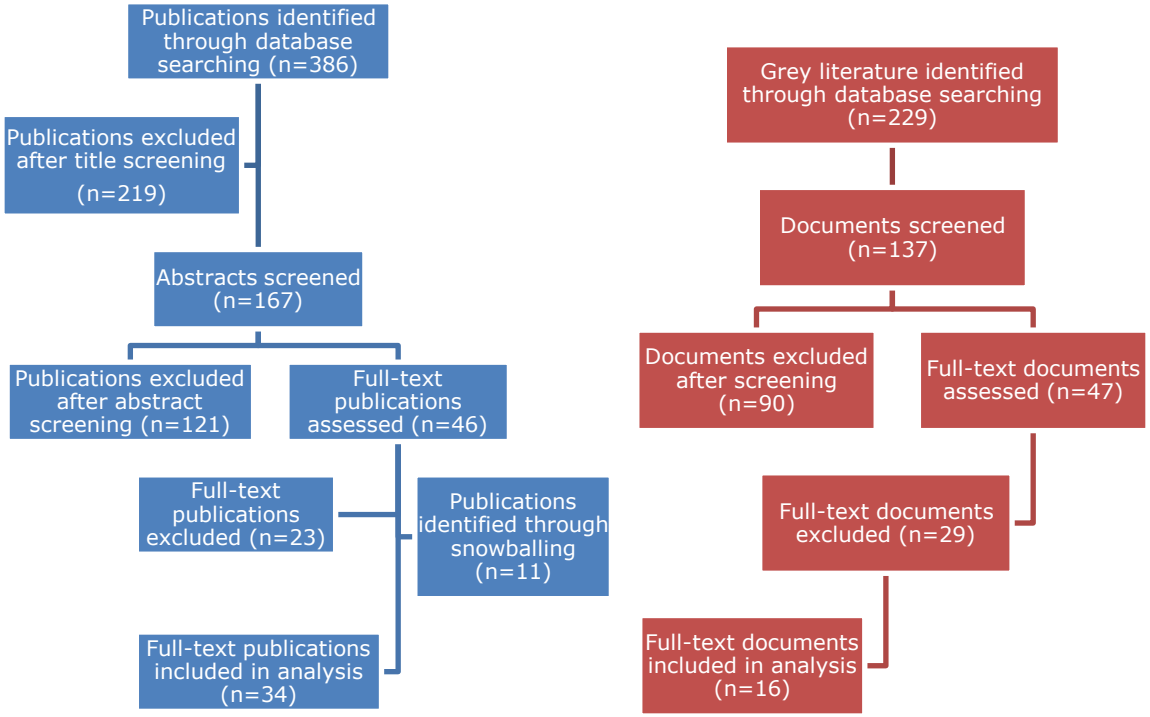
Literature was included in the literature review if it met the inclusion and exclusion criteria described below.

- Inclusion criteria
  - English, French or German language papers/documents
  - Papers/documents related to EU and its member states, US, Canada, Australia, UK, worldwide scope (i.e. those with international perspective rather than those about one country)
  - Papers/documents from last 5 years (mid 2015 to mid 2020) except for definitions, notification criteria and measurement systems where older documents were included if they were the most recent
- Exclusion criteria
  - Papers/documents about individual medicines, including those on supply of raw materials (both APIs and excipients), production and distribution of individual medicines, and individual indications

- Documents covering information on enforcement of relevant EU legislation, measures to address shortages of medicine, pricing and tendering procedures in Member States

The included literature was analysed and synthesised thematically. Although the literature review was not a standard scientific and systematic literature review, we prepared the following PRISMA flow chart to provide a record of numbers of documents/papers retrieved, screened, excluded and included.

Figure 17 PRISMA charts[262] for peer-reviewed (left panel) and grey literature (right panel)



[262] The PRISMA flow chart is a structured tool for showing the flow of information through the different phases of a systematic review. For more information, see: http://prisma-statement.org/prismastatement/flowdiagram.aspx.

Annex C. STAKEHOLDER CONSULTATIONS

Table 24 Stakeholders included through individual or group interviews

#	Name	Country/sector	Organisation
National competent authorities			
1	[Anonymised]	Czechia	State Institute for Drug Control
2	[Anonymised]	Estonia	The Estonian State Agency of Medicines
3	[Anonymised]	France	French National Agency for Medicines and Health Products Safety
4	[Anonymised]	Germany	Federal Institute for Drugs and Medical Devices Paul Ehrlich Institute
5	[Anonymised]	Ireland	Health Products Regulatory Authority
6	[Anonymised]	Latvia	State Agency of Medicines
7	[Anonymised]	Netherlands	Medicines Evaluation Board
8	[Anonymised]	Portugal	National Authority of Medicines and Health Products
9	[Anonymised]	Spain	Spanish Agency for Medicines and Health Products
10	[Anonymised]	Sweden	Medical Products Agency
11	[Anonymised]	Slovenia	Agency for Medicinal Products and Medical Devices of the Republic of Slovenia
European trade associations			
12	[Anonymised]	Innovative industry	European Federation of Pharmaceutical Industries and Associations (EFPIA), members of the shortages working group
13	[Anonymised]	Innovative industry	Vaccines Europe (VE)
14	[Anonymised]	Innovative industry	European Confederation for Pharmaceutical Entrepreneurs (SMEs) EUCOPE
15	[Anonymised]	Generics industry	Medicines for Europe (MfE)
16	[Anonymised]	Wholesale-distribution industry	European Healthcare Distribution Association (GIRP)
17	[Anonymised]	Parallel distribution industry	Affordable Medicines Europe (previously EAEPC)
18	[Anonymised]	Chemical manufacturing industry	European Chemical Industry Council (CEFIC)
Professional associations			
19	[Anonymised]	Hospital pharmacy	European Association of Hospital Pharmacists (EAHP)
20	[Anonymised]	Community pharmacy	Pharmaceutical Group of the European Union (PGEU)
21	[Anonymised]	Pharmacy	Portuguese National Association of Pharmacists (ANF)

Table 25 Participation in online focus group (7 May 2021)

Name	Country / sector	Organisation
National competent authorities		
[Anonymised]	Austria	Austrian Medicines and Medical Devices Agency
[Anonymised]	Austria	Austrian Medicines and Medical Devices Agency
[Anonymised]	Croatia	Agency for Medicinal Products and Medical Devices
[Anonymised]	Czechia	State Institute for Drug Control
[Anonymised]	Estonia	Estonian Medicines Agency
[Anonymised]	Finland	Finnish Medicines Agency
[Anonymised]	Finland	Finnish Medicines Agency
[Anonymised]	Finland	Finnish Medicines Agency
[Anonymised]	Finland	Finnish Medicines Agency
[Anonymised]	Germany	Paul Ehrlich Institute
[Anonymised]	Germany	Paul Ehrlich Institute
[Anonymised]	Hungary	National Institute of Pharmacy & Nutrition
[Anonymised]	Iceland	Icelandic Medicine Agency
[Anonymised]	Ireland	Health Products Regulatory Authority
[Anonymised]	Italy	Italian Medicines Agency
[Anonymised]	Luxembourg	Luxembourg Health Directorate
[Anonymised]	Malta	Malta Medicines Authority
[Anonymised]	Malta	Malta Medicines Authority
[Anonymised]	Norway	Norwegian Medicines Agency
[Anonymised]	Norway	Norwegian Medicines Agency
[Anonymised]	Portugal	National Authority of Medicines and Health Products
[Anonymised]	Slovakia	Department of Drug Distribution Inspection and Pharmacy Inspection
[Anonymised]	Slovenia	Agency for Medicinal Products and Medical Devices of the Republic of Slovenia
[Anonymised]	Slovenia	Agency for Medicinal Products and Medical Devices of the Republic of Slovenia
[Anonymised]	Sweden	Swedish Medical Products Agency
[Anonymised]	The Netherlands	Medicines Evaluation Board
[Anonymised]	The Netherlands	Medicines Evaluation board
[Anonymised]	The Netherlands	Medicines Evaluation Board
Health professionals		
[Anonymised]	Medical associations	Standing Committee of European Doctors (CPME)
[Anonymised]	Pharmacy associations	Pharmaceutical Group of the European Union (PGEU)
[Anonymised]	Health professional	Portuguese National Association of Pharmacists (ANF)
[Anonymised]	Health professional	University Hospital Leuven (Belgium)
Patient and consumer organisations		
[Anonymised]	Patient organisation	The Association of European Cancer Leagues (ECL)
[Anonymised]	Patient organisation	French Cancer League (LNCC)
[Anonymised]	Consumer organisation	The European Consumer Organisation (BEUC)
[Anonymised]	Consumer organisation	France Assos Santé
[Anonymised]	Patient organisation	EURORDIS

[Anonymised]	Patient organisation	European Patients Forum
[Anonymised]	Patient / consumer organisation	European Public Health Alliance
[Anonymised]	Malta	University of Malta
Trade associations		
[Anonymised]	Wholesale-distribution industry	GIRP
[Anonymised]	Wholesale-distribution industry	GIRP
[Anonymised]	Wholesale-distribution industry	Affordable Medicines Europe
Other		
[Anonymised]	EU regulatory authority	European Medicines Agency
Not all participants logged in using recognisable identifiers. Therefore not all participants could be identified and the here presented list of participants is incomplete.		

Annex D. SURVEY METHODOLOGY

Separate **surveys** were developed for three specific categories of stakeholders:

- National competent authorities
- Supply chain actors (associations for producers, wholesalers and distributors)
- Healthcare professionals (effectively answered by pharmacists)

These surveys each follow a similar three-part structure:

- Assessment of the problem (definition of a shortage, measuring and reporting of shortages)
- Identification of the root causes of shortages
- Identification of potential solutions for medicine shortages

The link to the different surveys was distributed at the end of December 2020. National competent authorities were contacted directly by the study team, whereas the other two survey versions were distributed via intermediary umbrella associations. Following the end of the administration period of the survey we have been able to collect:

- 18 answers from NCAs representing 14 different EEA countries;
- 101 answers representing pharmacists (78 answers from organisations representing hospital pharmacists and 23 representing retail pharmacists)
- 205 answers from organisations representing pharmaceutical companies

To ensure a maximum of answers and openness in the comment sections (analysed by the study team and not included in the present annex), survey responses were collected without collection of identifying information (e.g. personal or organisation name). A number of methodological safeguards were implemented to protect the data presented here:

- the link to the survey was not publicly shared. We relied on serious and vouched proxy organisations for distribution, which were the initial pilot testers, ensuring a pool of reliable respondents
- we used specific additional identification elements (notably the IP address) to clean our answers base. In the treatment of the data, we filtered duplicates from the same IP address and only kept answers from the same IP address that were people clearly representing different divisions of the same company (innovative manufacturers and generics for example). Manual control of the quality of our data was ensured.
- finally, all data treatment was filtered by stakeholder groups and information triangulated with our interview campaign results.

Below are the three PDF extracts of questions as they were displayed in the surveying tool for each version of the stakeholder survey we administered during the study. It is to be noted that the questions were formulated in the tools with filters and references to previous questions that can make them difficult to read in a PDF format. For example, on question 10.2 of the supply chain actors survey, the "MAHC2_SQ001.question" corresponds to a display for MAH respondents of the first answer in the question identified as "C2" by the tool (Question 10.1, "Factory closures" in this case), only if they had selected it in this question.

National Competent Authorities

Section A: Identification

Stakeholder identification and routing

A1. 1. What type of organisation do you represent ? Please indicate the option that (best) matches the organisation you represent ?

- ☐ National medicine pricing and reimbursement authority
- ☐ National medicine agency
- ☐ Ministry of Health
- ☐ National health system
- ☐ Other, please specify :

Other, please specify :

A2. 2. What country do you represent ?

- Austria ☐
- Belgium ☐
- Bulgaria ☐
- Croatia ☐
- Cyprus ☐
- Czech Republic ☐
- Denmark ☐
- Estonia ☐
- Finland ☐
- France ☐
- Germany ☐
- Greece ☐
- Hungary ☐
- Iceland ☐
- Ireland ☐
- Italy ☐
- Latvia ☐
- Liechstenstein ☐
- Lithuania ☐
- Luxembourg ☐
- Malta ☐
- Netherlands ☐
- Norway ☐
- Poland ☐
- Portugal ☐
- Romania ☐
- Slovakia ☐
- Slovenia ☐
- Spain ☐
- [illegible] ☐
- Other, please specify : ☐

Section B: Assessing the problem

B1. 3. What definition of a medicine shortage is used in your country ?

EMA's Definition ("A shortage of a medicinal product for human or veterinary use occurs when supply does not meet demand at a national level") ☐

National Definition - please specify by inserting the national definition itself or a weblink to such in the comment box ☐

No standard definition ☐

B2. 4. What elements do you consider to be necessary in the reporting of a medicine shortage ?

MAH name ☐

Product name ☐

Composition ☐

Country of authorisation ☐

Shortage status (e.g. expected, ongoing...) ☐

Expected start/end date ☐

Point in chain where disruption occurs ☐

Reason for the disruption ☐

Mitigation plan ☐

Market size ☐

Other, please specify : ☐

Other, please specify :

B3. 5. Can you estimate the proportion of the shortages in your country where (in percentages, the total being 100%) :

The pharmacy can issue an alternative treatment without further consulting a prescribing physician

It is necessary to consult with a prescribing physician before dispensing an alternative treatment

x

No alternative is available ☐

B4. **Comment box :**

B5. **6. How has the frequency with which medicine shortages occur in your country changed in the past :**

	Increased more than 10%	Increased between 0 and 10%	Remained unchanged	Decreased between 0 and 10%	Decreased more than 10%	Not known/no information available
2 years	☐	☐	☐	☐	☐	☐
5 years	☐	☐	☐	☐	☐	☐
10 years	☐	☐	☐	☐	☐	☐
15 years	☐	☐	☐	☐	☐	☐

B6. **Comment box :**

B7. **7. What proportion (in %) of all medicine shortages is typically resolved (supply of shortages medicine is meeting national demand again / suitable alternative proposed to patients) in :**

	None	Up to 20%	20-40%	40-60%	60-80%	80-100%	Not known/no information available
Days	☐	☐	☐	☐	☐	☐	☐
Weeks	☐	☐	☐	☐	☐	☐	☐
Months	☐	☐	☐	☐	☐	☐	☐
Years	☐	☐	☐	☐	☐	☐	☐
Never	☐	☐	☐	☐	☐	☐	☐

B8. **8. To what extent has the COVID-19 pandemic thus far impacted the national availability of the following types of medicines due to a surge in demand (not taking into account potential future impacts)**

	In critical shortage; quality of care endangered	In shortage; quality of care not affected	Decreased, but not in shortage	Unaffected
Antibiotics	☐	☐	☐	☐
Antiparasitic products	☐	☐	☐	☐
Antivirals	☐	☐	☐	☐
Anaesthetics	☐	☐	☐	☐
Other (please specify in the comment box below)	☐	☐	☐	☐

B9. **Comment box :**

B10. **9. To what extent has the COVID-19 pandemic thus far impacted the national availability of medicines due to factors other than a surge in demand?**

- ☐ Remained unchanged
- ☐ Availability decreased between 0 and 10%
- ☐ Availability decreased more than 10%
- ☐ Not known/no information available

B11. **Comment box :**

B12. **10. Which of the following disruptions have affected the availability of medicines in your country as a result of the COVID-19 pandemic ?**

- ☐ Temporary lockdown of manufacturing sites
- ☐ Travel restrictions impacting import and export of medicines and ingredients
- ☐ Export bans between EU Member States
- ☐ International export bans (outside of the EU/EEA)
- ☐ Increased demand for medicines used to treat COVID-19 patients
- ☐ Increased stockpiling by hospitals, individual citizens or at Member State level

Other, please specify :

Other, please specify :

B13. Comment box :

Section C: Root causes

C1. 11. Please select the 3 most common causes of medicine shortages observed in your country in the past 5 years

- Quality issues and batch recalls
- Manufacturing issues
- Regulatory issues
- Safety and efficacy issues
- Unpredicted major events or natural disasters
- Unexpected increased demand
- Other, please specify :

Other, please specify :

C2. 12. To what extent are shortages in your country influenced by external shocks and international trends ?

- Not at all
- Minimally
- Moderately
- Considerably

C3. **13. Does your country have a reporting system for shortages ? If answer option "no", this quiz will continue at question n°23**

- Yes ☐
- No ☐

C4. **13.1 When was a system for shortage reporting first introduced in your country ?**

- 2020 ☐
- 2015-2019 ☐
- 2010-2014 ☐
- 2004-2009 ☐
- Before 2004 ☐

C5. **13.2 Do you list root causes in your reporting system ?**

- Yes, in line with SPOC definitions ☐
- Yes, according to own definitions ☐
- No ☐

C6. **14. What is the proportion of observed shortages where the reason remains unreported ?**

Percentage of shortages with unreported reason ☐☐☐☐☐☐☐☐☐☐

C7. **15. At what moment in time are shortages required to be reported in your country ?**

- Prospective (beforehand) ☐
- Instantly (at the moment when a shortage occurs) ☐
- Retrospective (after a shortage has occurred) ☐

C8. **15.1. Please indicate the number of months in advance shortages are required to be reported in your country**

☐☐☐☐☐☐☐☐☐☐

C9. **16. At what moment are shortages effectively reported in your country**

- Prospective (beforehand) ☐
- Instantly (at the moment when a shortage occurs) ☐
- Retrospective (after a shortage has occurred) ☐

C10. **16.1. Please indicate the number of months in advance shortages are effectively reported in your country**

☐☐☐☐☐☐☐☐☐☐

C11. **Comment box :**

C12. **17. Who provides information and data on medicine shortages in your country to national authorities ?**

- ☐ Marketing authorisation holder
- ☐ Manufacturer
- ☐ Wholesaler
- ☐ Medicines agency
- ☐ Ministry of Health
- ☐ Pharmacy organisations
- ☐ Other, please specify :

Other, please specify :

C13. **18. Who reports the cause of a medicine shortage in your country ?**

- ☐ Marketing authorisation holder
- ☐ Manufacturer
- ☐ Wholesaler/distributor
- ☐ Medicines agency
- ☐ Ministry of Health
- ☐ Pharmacy organisations
- ☐ Other, please specify :

Other, please specify :

C14. **19. Does your organisation have staff responsible for verifying and enforcing the timely notification of a shortage ?**

Yes ☐

No ☐

C15. **19.1. Can you give an estimation of the number of staff involved in this (in full time equivalents) ?**

C16. **Comment box :**

C17. **20. Does your organisation have staff responsible for monitoring/enforcing any public service obligation by MA holders or distributors ?**

Yes ☐

No ☐

C18. **20.1. Can you give an estimation of the number of staff involved in this (in full time equivalents)**

C19. **Comment box :**

Section D: Identification of potential solutions

D1. 21. Please indicate which of the following measures have been implemented or are under consideration in your country :

	Implemented	Under consideration
Early notification of expected shortages	☐	☐
Requiring stockholding by marketing authorisation holders and distributors	☐	☐
National stockpiling	☐	☐
Restrictions on parallel exports	☐	☐
Requiring transparency of industry supply quotas and wholesalers' transactions for the relevant Member State authorities	☐	☐
Establishing national lists of essential medicines and medicines at high risk of shortage	☐	☐
Publication of national lists of medicines currently in shortage that can be accessed by patients and health professionals	☐	☐
Publication of lists of past shortages by company	☐	☐
Cooperation between NCA, MAH holders and distributors on forecasting and planning the demand side	☐	☐
Allowing pharmacists to substitute medicines without intervention of a prescribing physician	☐	☐
Incentives for local production of APIs	☐	☐
Incentives for local manufacturing of finished products	☐	☐
Procurement procedures at national level to include criteria (e.g. penalties) that address continuity of supply	☐	☐
Incentivising multiple active marketing authorisations to promote (generic) market competition	☐	☐
Other (please specify in the comment box that will appear)	☐	☐

D2. Comment box :

D3. 22. Which policies do you think would be relevant solutions to address medicine shortages at the EU/international level ?

Adopting commong principles for the introduction of national restrictions on exports to other Member States	☐
Coordinating a list of essential medicines at the EU level and medicines at high risk of shortage	☐

Amending the EU GMP guidelines to require marketing authorisation holders and manufacturers to have a shortage prevention or mitigation plan ☐

Establishing EU stockpiles under the EU Civil Protection Mechanism ☐

Developing joint procurement modalities between countries ☐

Encouraging Member States to accept or promote multi-country packages to allow more flexibility for companies when allocating supply ☐

D4. 23. How effective have the measures implemented in your country been in reducing the :

Frequency of shortages

	Very effective	Somewhat effective	No effect
{D1_SQ001.question}	☐	☐	☐
{D1_SQ002.question}	☐	☐	☐
{D1_SQ003.question}	☐	☐	☐
{D1_SQ004.question}	☐	☐	☐
{D1_SQ005.question}	☐	☐	☐
{D1_SQ006.question}	☐	☐	☐
{D1_SQ007.question}	☐	☐	☐
{D1_SQ008.question}	☐	☐	☐
{D1_SQ009.question}	☐	☐	☐
{D1_SQ010.question}	☐	☐	☐
{D1_SQ011.question}	☐	☐	☐
{D1_SQ012.question}	☐	☐	☐
{D1_SQ013.question}	☐	☐	☐
{D1_SQ014.question}	☐	☐	☐
{D1_SQ015.question}	☐	☐	☐

D5. **23. How effective have the measures implemented in your country been in reducing the :**

Duration of shortages

	Very effective	Somewhat effective	No effect
{D1_SQ001.question}	☐	☐	☐
{D1_SQ002.question}	☐	☐	☐
{D1_SQ003.question}	☐	☐	☐
{D1_SQ004.question}	☐	☐	☐
{D1_SQ005.question}	☐	☐	☐
{D1_SQ006.question}	☐	☐	☐
{D1_SQ007.question}	☐	☐	☐
{D1_SQ008.question}	☐	☐	☐
{D1_SQ009.question}	☐	☐	☐
{D1_SQ010.question}	☐	☐	☐
{D1_SQ011.question}	☐	☐	☐
{D1_SQ012.question}	☐	☐	☐
{D1_SQ013.question}	☐	☐	☐
{D1_SQ014.question}	☐	☐	☐
{D1_SQ015.question}	☐	☐	☐

D6. **24. To what extent have the measures implemented in your country increased the operational costs (including compliance, monitoring, enforcement...) of the national authority?**

	No impact on operational cost (0%)	Very small impact (0-3% increase in costs)	Small impact (5-10%) increase in costs	Substantial impact (>10% increase in costs)
{D1_SQ001.question}	☐	☐	☐	☐
{D1_SQ002.question}	☐	☐	☐	☐
{D1_SQ003.question}	☐	☐	☐	☐
{D1_SQ004.question}	☐	☐	☐	☐
{D1_SQ005.question}	☐	☐	☐	☐
{D1_SQ006.question}	☐	☐	☐	☐
{D1_SQ007.question}	☐	☐	☐	☐
{D1_SQ008.question}	☐	☐	☐	☐
{D1_SQ009.question}	☐	☐	☐	☐
{D1_SQ010.question}	☐	☐	☐	☐
{D1_SQ011.question}	☐	☐	☐	☐
{D1_SQ012.question}	☐	☐	☐	☐
{D1_SQ013.question}	☐	☐	☐	☐
{D1_SQ014.question}	☐	☐	☐	☐
{D1_SQ015.question}	☐	☐	☐	☐

D7. **Comment box :**

D8. **We are looking for additional data on costs. If you are able to provide such information, please complete the Excel template that you can download at the following LINK and upload here (before submitting the survey) or send it via e-mail to us at *shortages@technopolis-group.com***

The following Excel template was accessible to NCA survey respondents to provide cost elements:

This form is intended to collect additional information on **staff costs associated with measures to prevent or mitigate shortages of human medicines to national health authorities of EU/EEA Member States**. The information will be used in the EU commissioned study on medicine shortages that is being conducted by the consortium of Technopolis Group, Ecorys BV and Milieu Policy Consulting.

This form is an **integral part of the online survey** and we therefore ask you not to distribute this form to others ourside of your own organisation. The form can be shared within your organisation to facilitate completion of the information but **no more than one form per organisation should be submitted**. The form can be submitted at a different date and time than the survey responses. Submission is done by uploading the complete file to the dedicated question in the survey or by sending it to shortages@technopolis-group.com via e-mail.

We realise that information may be difficult to obtain or to provide in a clear, standardised way. We therefore provide a relatively open format for the information requested in columns C, D and E but ask you to provide us sufficient explanatory information in Column G. It is appreciated if you can share with us also contact information (Cell C8) for whom we could approach in case further discussion to interpret the information is needed.

Respondent information
Name of authority for which information is provided
Country of authority for which information is provided
Contact information (optional) (name, email, phone number)

PLEASE SPECIFY WHETHER THE COSTS RELATE TO ACTIVITIES FOLLOWING FROM EU REGULATION, FROM NATIONAL REGULATION OR FROM BOTH

Cost element	Number of labour hours directly resulting from the activity per year (in staff hours)	Average associated labour cost (Euro per hour)	Associated extra staff costs per year (Euro)	Inclusive of indirect or overhead costs (yes / no)	Do these costs relate to activities following from EU regulation, from national regulation or from both?	Explanatory information, for instance: - over which year(s) was the data collected - were there any relevant changes to activities that impacted on cost
MONITORING SHORTAGE NOTIFICATIONS						
Collecting and storing reports on shortages						
Analysing reports on shortages						
Monitoring of adherence to the reporting obligation on shortages by industry / distributors						
Enforcement of the obligation of shortages: sending out reminders, additional enforcement steps						
MONITORING STOCKS / CONTINUOUS SUPPLY						
Monitoring of current stock keeping obligations						
Monitoring the adherence of obligation of contiuous supply						
Preparing (public) reports on shortage notifications received						
Preparing (public) reports regarding the adherence of MA holders to continuous supply obligation						
OTHER						
Please specify						

Supply chain actors:

Section A: Identification

A1. 1. In what type of industry does your organisation operate ?

- ☐ Innovative pharmaceutical industry
- ☐ Generics pharmaceutical industry
- ☐ Pharmaceutical manufacturing industry (API and/or finished products)
- ☐ Pharmaceutical distributors or wholesalers
- ☐ Parallel trade industry
- ☐ Other, namely :

Other, namely :

A2. 2. In what EU/EEA countries is your organisation active ?

- ☐ The entire EU/EEA
- ☐ Austria
- ☐ Belgium
- ☐ Bulgaria
- ☐ Croatia
- ☐ Cyprus
- ☐ Czech Republic
- ☐ Denmark
- ☐ Estonia
- ☐ Finland
- ☐ France
- ☐ Germany
- ☐ Greece
- ☐ Hungary
- ☐ Iceland
- ☐ Ireland

Italy ☐
Latvia ☐
Liechstenstein ☐
Lithuania ☐
Luxembourg ☐
Malta ☐
Netherlands ☐
Norway ☐
Poland ☐
Portugal ☐
Romania ☐
Slovakia ☐
Slovenia ☐
Spain ☐
Sweden ☐
Other, please specify : ☐

Other, please specify :

Section B: Assessing the problem

B1. **3. What definition of a medicine shortage is used within your organisation ?**

The EMA's definition is the following : " a shortage of a medicinal product for human or veterinary use occurs when supply does not meet demand at a national level"

- ☐ No standard definition
- ☐ EMA's definition
- ☐ Company's own definition, please specify by inserting the definition :

Company's own definition, please specify by inserting the definition :

B2. **4. In your opinion, is this definition adequate to identify medicine shortages ?**

- ☐ Yes
- ☐ No

B3. **Please specify in what way you consider this definition inadequate :**

B4. **5. What elements do you consider to be necessary in the reporting of medicine shortages ?**

- ☐ MAH name
- ☐ Product name
- ☐ Composition
- ☐ Country of authorisation
- ☐ Shortage status (e.g. expected, ongoing...)
- ☐ Expected start/end date
- ☐ Point in chain where disruption occurs
- ☐ Reason for the disruption
- ☐ Mitigation plan

Market size ☐

Other, please specify : ☐

Other, please specify :

B5. **6. How has the frequency with which medicine shortages occur changed in the country/countries in which your organisation/your member organisations are active in the past :**

	Increased by more than 10%	Increased between 0 and 10%	Remained unchanged	Decreased by between 0 and 10%	Decreased by more than 10%	Not applicable
2 years	☐	☐	☐	☐	☐	☐
5 years	☐	☐	☐	☐	☐	☐
10 years	☐	☐	☐	☐	☐	☐
15 years	☐	☐	☐	☐	☐	☐

B6. **Comment box :**

B7. **7. How has the frequency with which shortages of active pharmaceutical ingredients occur changed for your organisation/your member organisations in the past :**

	Increased by more than 10%	Increased between 0 and 10%	Remained unchanged	Decreased by between 0 and 10%	Decreased by more than 10%	Not applicable
2 years	☐	☐	☐	☐	☐	☐
5 years	☐	☐	☐	☐	☐	☐
10 years	☐	☐	☐	☐	☐	☐
15 years	☐	☐	☐	☐	☐	☐

B8. **Comment box :**

B9. **8. Please indicate which of the following events have affected your supply chain/the supply chain of your member organisations in the course of the COVID-19 pandemic ?**

- [ ] Temporary lockdown of manufacturing sites and/or distribution sites
- [ ] Travel restriction impacting import and export
- [ ] Export bans
- [ ] Increased demand for medicines used to treat COVID-19 patients
- [ ] Decreased demand for medicines not associated with the treatment of COVID-19 patients
- [ ] Increased complexity in transport
- [ ] Unilateral behaviours by EU/EEA governments
- [ ] Increased stockpiling by hospitals
- [ ] Increased stockpiling by pharmacies
- [ ] Increased stockpiling by individual citizens
- [ ] Increased stockpiling at the Member State level
- [ ] Other, please specify :

Other, please specify :

Section C: Root causes

C1. **9. Please select the 3 most common causes of medicine shortages that your organisation/your member organisations experienced in the past 5 years :**

- [ ] Quality issues and batch recalls
- [ ] Manufacturing issues (other than quality)
- [ ] Regulatory issues
- [ ] Safety and efficacy issues
- [ ] Unpredicted major events or natural disasters
- [ ] Unexpected increased demand

Other, please specify :

Other, please specify :

C2. 10.1 Which of the following factors have most affected the ability of your organisation/your member organisations to ensure appropriate and continued supply of medicines? Select up to 5 answers

	Select your answers
Factory closures	☐
Quality issues	☐
Environmental factors impacting manufacturer and raw materials	☐
Raw material related (from 3rd party)	☐
Component related (from 3rd party)	☐
API related	☐
Non-quality issue (e.g. mechanical or software failure)	☐
Capacity issues	☐
Increased manufacturing complexity	☐
Industry consolidation	☐
Mandatory inventory policies	☐
Supply chain disruptions (logistics/transport disruptions)	☐
Changes in demand	☐
Supply quotas/restriction of supply by manufacturers	☐
Product registration or approval issues	☐
Profitability issues	☐
Intercountry stock movements and parallel trade	☐
Regulatory complexity	☐
Penalties due to non-compliance of delivery agreement	☐
Lack of information/insufficient notification about shortages	☐
Other (please specify in the comment box that will appear)	☐

C3. **Comment box :**

C4. **10.2 Out of the selected factors, which had the strongest impact on your operations ?**

{MAHC2_SQ001.question}
{MAHC2_SQ002.question}
{MAHC2_SQ003.question}
{MAHC2_SQ004.question}
{MAHC2_SQ005.question}
{MAHC2_SQ006.question}
{MAHC2_SQ007.question}
{MAHC2_SQ008.question}
{MAHC2_SQ009.question}
{MAHC2_SQ010.question}
{MAHC2_SQ011.question}
{MAHC2_SQ012.question}
{MAHC2_SQ013.question}
{MAHC2_SQ014.question}
{MAHC2_SQ015.question}
{MAHC2_SQ016.question}
{MAHC2_SQ017.question}
{MAHC2_SQ018.question}
{MAHC2_SQ019.question}
{MAHC2_SQ020.question}
{MAHC2_SQ021.question}

C5. **10.1 Which of the following factors have most affected the ability of your organisation/your member organisations to ensure appropriate and continued supply of medicines? Select up to 5 answers**

	Select your answers
Mandatory inventory policies	☐
Supply chain disruptions (logistics/transport disruptions)	☐
Changes in demand	☐
Supply quotas/restriction of supply by manufacturers	☐
Product registration or approval issues	☐
Profitability issues	☐
Intercountry stock movements and parallel trade	☐
Regulatory complexity	☐
Penalties due to non-compliance of delivery agreement	☐
Lack of information/insufficient notification about shortages	☐
Other (please specify in the comment box that will appear)	☐

C6. **Comment box :**

C7. **10.2 Out of the selected factors, which had the strongest impact on your operations ?**

{DISTRIBC2_SQ011.question}	☐☐☐☐☐
{DISTRIBC2_SQ012.question}	☐☐☐☐☐
{DISTRIBC2_SQ013.question}	☐☐☐☐☐
{DISTRIBC2_SQ014.question}	☐☐☐☐☐
{DISTRIBC2_SQ015.question}	☐☐☐☐☐
{DISTRIBC2_SQ016.question}	☐☐☐☐☐
{DISTRIBC2_SQ017.question}	☐☐☐☐☐
{DISTRIBC2_SQ018.question}	☐☐☐☐☐

{DISTRIBC2_SQ019.question}

{DISTRIBC2_SQ020.question}

{DISTRIBC2_SQ021.question}

C8. 10.3 Which production methods and/or types of products are most associated with shortages ?

- [ ] Lyophilisation
- [ ] Fermentation
- [ ] Small batches/pack size volumes
- [ ] Narcotics
- [ ] Cold chain
- [ ] Other, please specify :

Other, please specify :

C9. Please rank your selected answers from highest to lowest :

{C4_SQ001.question}

{C4_SQ002.question}

{C4_SQ003.question}

{C4_SQ004.question}

{C4_SQ005.question}

{C4_other}

C10. Unfortunately, the option "other" cannot be multiplied in this tool, if you added more than one answer in the "other" box in question 10.3, please specify their ranking here :

C11. **11. To what extent are shortages of medicines produced, marketed and/or traded by your organisation / your member organisations influenced by external shocks and international trends ?**

- To a very large extent ☐
- To a large extent ☐
- To some extent ☐
- Not at all ☐

C12. **12. For market authorisations obtained at the EEA level (through the centralised procedure), please estimate the average cost (in euros) per medicine per year associated with the maintaining of this authorisation for each of the following cost components.**

Registration costs	
Staff costs (updating of the information)	
Other costs	
Total costs	

C13. **We are looking for additional data on costs. If you are able to provide such information, please complete the Excel template that you can download at the following LINK and upload here (before submitting the survey) or send it via e-mail to us at *shortages@technopolis-group.com***

Section D: Identification of potential solutions

D1. **13. To what extent do you consider manufacturers and business associations to be in a position to address causes of medicine/API shortages ?**

- To a very large extent ☐
- To a large extent ☐
- To some extent ☐
- Not at all ☐

D2. **Comment box :**

D3. **14. Has your organisation implemented any of the following measures to address medicine/API shortages in your operations ?**

- Securing of key API and starting materials for key molecules ☐

Securing manufacturing by reshoring manufacturing plants in the EU	☐
Assess and optimise allocation of stock	☐
Optimise production and distribution capacity	☐
Identify and secure logistics capacity	☐
Assess realistic final-customer demand	☐
Developing and improving demand forecasting techniques	☐
Agile allocation of production capacity in response to increased sudden demands	☐
Initiatives for access to shared supply	☐
Develop prevention and response plans	☐
Other, please specify which ones :	☐

Other, please specify which ones :

D4. **15. At the level of the EU, which of the following measures do you consider necessary in addressing medicine shortages ? Please select up to 5 answers**

	Select your answers
Promoting balanced tender processes	☐
Incentivising multisource sompetition	☐
Provide guidance on criteria for security of supply	☐
Strengthened public service requirements at EU level for manufacturers	☐
Shortages early warning systems	☐
Transparency across entire supply chain	☐
Other (please specify in the comment box that will appear)	☐

D5. **Comment box :**

D6. **16. Did the implementation of the European obligation for market authorisation holders to notify competent authorities if a product ceases to be placed on the market (temporarily or permanently) have an impact on your operations ?**

Yes ☐

No ☐

D7. **How ?**

D8. **Please estimate the costs (in euros per year, notification) associated with this obligation to notify ?**

D9. **Are these costs dependent on the 2 month time period specified in the obligation (would they be different with a different notification period) ?**

Yes ☐

No ☐

D10. **Comment box :**

Thank you for participating in this survey. Your responses have been received. You can now close this window.

The following Excel template was accessible to supply chain actors responding to the survey to provide cost elements:

This form is intended to collect additional information on **costs associated with measures to prevent or mitigate shortages of human medicines** to industry stakeholders in the **EU/EEA Member States**. The information will be used in the EU commissioned study on medicine shortages that is being conducted by the consortium of Technopolis Group, Ecorys BV and Milieu Policy Consulting.

This form is an **integral part of the online survey** and we therefore ask you not to distribute this form to others ourside of your own organisation. The form can be shared within your organisation to facilitate completion of the information but **no more than one form per organisation should be submitted**. The form can be submitted at a different date and time than the survey responses. Submission is done by uploading the complete file to the dedicated question in the survey or by sending it to shortages@technopolis-group.com via e-mail.

We realise that information may be difficult to obtain or to provide in a clear, standardised way. We therefore provide a relatively open format for the information requested in columns C, D and E but ask you to provide us sufficient explanatory information in Column G. It is appreciated if you can share with us also contact information (Cell C8) for whom we could approach in case further discussion to interpret the information is needed.

Respondent information
Name of organisation for which information is provided
Country of orgnisation for which information is provided **(if applicable)**
Contact information (optional) (name, email, phone number)

Cost element	Number of labour hours directly resulting from the activity per year (in staff hours)	Average associated labour cost (Euro per hour)	Associated extra staff costs per year (Euro)	Inclusive of indirect or overhead costs (yes / no)	To which Member States these data apply?	Do these costs relate to activities following from EU regulation, from national regulation or from both?	Explanatory information, for instance: - over which year(s) was the data collected - were there any relevant changes to activities that impacted on cost
IMPACT ON STAFF COSTS DUE TO (ACTIVITIES):							
Procurement of raw materials							
Production of medicines							
Storage of medicines							
Innovation (development of new medicines)							
Distribution of medicines							
Procurement of medicines (trading)							
Preparing notifications							
Monitoriong medicine stock levels							
Financing							
Management							
Other ***(please specify)***							

Cost element	Annual extra costs (Euro)	or: extra costs as % of annual total costs of purchases	To which Member States these data apply?	Do these costs relate to activities following from EU regulation, from national regulation or from both?	Explanatory information, for instance: - over which year(s) was the data collected - were there any relevant changes to activities that impacted on cost
IMPACT ON PURCHASES OF (RAW) MATERIALS, SERVICES IN RELATION TO:					
Procurement of raw materials					
Production of medicines					
Storage of medicines					
Innovation (development of new medicines)					
Distribution of medicines					
Procurement of medicines (trading)					
Preparing notifications					
Monitoriong medicine stock levels					
Financing					
Management					
Other ***(please specify)***					

For **hospital and retail pharmacists**:

Section A: Identification

A1. 1. What group of health professionals do you belong to/does your organisation represent?

- ☐ Hospital medical practitioners
- ☐ General healthcare practitioners
- ☐ Hospital pharmacists
- ☐ Retail pharmacists
- ☐ Other, please specify :

Other, please specify :

A2. 2. In what country(ies) are you/is your organisation active?

- ☐ All EU/EEA countries
- ☐ Austria
- ☐ Belgium
- ☐ Bulgaria
- ☐ Croatia
- ☐ Cyprus
- ☐ Czech Republic
- ☐ Denmark
- ☐ Estonia
- ☐ Finland
- ☐ France
- ☐ Germany
- ☐ Greece
- ☐ Hungary
- ☐ Iceland
- ☐ Ireland
- ☐ Italy

Latvia ☐
Liechstenstein ☐
Lithuania ☐
Luxembourg ☐
Malta ☐
Netherlands ☐
Poland ☐
Portugal ☐
Romania ☐
Slovakia ☐
Slovenia ☐
Spain ☐
Sweden ☐
Other, please specify : ☐

Other, please specify :

Section B: Assessing the problem

B1. **3. What definition of a medicine shortage is used in the country(ies) where you are/your organisation is active ?**

EMA's definition : "A shortage of a medicinal product for human or veterinary use occurs when supply does not meet demand at a national level"

No standard definition ☐
EMA's definition ☐

National definition, please specify by inserting the national definition itself or a weblink to such : ☐

National definition, please specify by inserting the national definition itself or a weblink to such :

B2. **4. In your opinion, is this definition adequate to identify medicine shortages?**

Yes ☐

No ☐

B3. **Please specify :**

B4. **5. What elements do you consider to be necessary in the reporting of a medicine shortage?**

MAH name ☐

Product name ☐

Composition ☐

Country of authorisation ☐

Shortage status (e.g. expected, ongoing...) ☐

Expected start/end date ☐

Point in chain where disruption occurs ☐

Reason for the disruption ☐

Mitigation plan ☐

Market size ☐

Other, please specify : ☐

Other, please specify :

B5. **6. How has the frequency with which prescriptions cannot be filled (without making substitutions) been affected in the country/countries where your organisation/member organisations is/are active changed in the past :**

	Increased by more than 10%	Increased between 0 and 10%	Remained unchanged	Decreased by between 0 and 10%	Decreased by more than 10%
2 years	☐	☐	☐	☐	☐
5 years	☐	☐	☐	☐	☐
10 years	☐	☐	☐	☐	☐
15 years	☐	☐	☐	☐	☐

B6. **Comment box :**

B7. **7. In what proportion of unfilled prescriptions is there an alternative treatment available (generic or therapeutic substitution)?**

- 0-25% ☐
- 25-50% ☐
- 50-75% ☐
- 75-100% ☐
- Unknown/no information available ☐

B8. **8. What proportion (in%) of all medicine shortages is typically resolved (supply of shortaged medicine is meeting national demand again / suitable alternative proposed to patients) in:**

	None	Up to 20%	20-40%	40-60%	60-80%	80-100%	Unknown / no information available
Days	☐	☐	☐	☐	☐	☐	☐
Weeks	☐	☐	☐	☐	☐	☐	☐
Months	☐	☐	☐	☐	☐	☐	☐
Years	☐	☐	☐	☐	☐	☐	☐
Never	☐	☐	☐	☐	☐	☐	☐

B9. **9. To what extent has the COVID-19 pandemic thus far impacted the national availability of the following types of medicines due to a surge in demand (not taking into account potential future impacts) ?**

	In critical shortage; quality of care endangered	In shortage; quality of care not affected	Decreased, but not in shortage	Unaffected
Antibiotics	☐	☐	☐	☐
Antiparasitic products	☐	☐	☐	☐
Antivirals	☐	☐	☐	☐
Anaesthetics	☐	☐	☐	☐
Other (please specify in the comment box that will appear)	☐	☐	☐	☐

B10. **Comment box :**

B11. **10. To what extent has the COVID-19 pandemic thus far impacted the national availability of medicines due to factors other than a surge in demand ?**

- ☐ Remained unchanged
- ☐ Availability decreased between 0 and 10%
- ☐ Availability decreased more than 10%
- ☐ Not known/no information available

B12. **Comment box :**

B13. **11. On average, how much time per week do the health professionals from the group that you represent spend on managing shortages and the effects of such (e.g. finding alternative means of treatment and patient care)**

- ☐ 1 hour
- ☐ 2-5 hours
- ☐ 5-10 hours
- ☐ 10-15 hours
- ☐ more than 15 hours

B14. **12. Please indicate which of the following financial consequences you/the health professionals that your organisation represents have experienced as a result of medicine shortages?**

Please estimate these costs in euros/year in the boxes on the right

☐ Increased staff time

Comment

☐ Increased stocking costs

Comment

☐ Increased other operational costs (please specify in the comment box below)

Comment

☐ Increased costs for patients

Comment

☐ Not applicable/do not know

Comment

☐ Other costs, please specify :

Other costs, please specify :

B15. **Comment box :**

In addition to the time spent with dealing with shortages,have you had any other costs than mentioned above, identify the main cost elements and estimate them in euros

B16. **13. What was the extent of these financial consequences?**

- Very severe ☐
- Significant ☐
- Small ☐

B17. **Comment box :**

B18. **14. Please indicate if you are personally aware of any of the following consequences of a medicine shortage ? Rank them according to their frequency (from most to least frequent)**

- No treatment provided ☐
- Wrong medicine administered/dispensed ☐
- Wrong dose administered/dispensed ☐
- Wrong frequency of administration ☐
- Wrong administrative route ☐
- Reduced or no treatment adherence with substitute medication ☐
- Other (please specify in the comment box that will appear) ☐

B19. **Comment box :**

B20. **15. Please indicate how often the following patient outcomes occur as a consequence of a medicine shortage?**

	Rarely	Sometimes	Often
Alternative medicine used	☐	☐	☐
Delay of therapy	☐	☐	☐
Increased patient monitoring necessary	☐	☐	☐
Suboptimal treatment	☐	☐	☐
Increased length of care	☐	☐	☐
Treatment failure	☐	☐	☐
Cancellation of care	☐	☐	☐
Patient transferred to an institution with a supply of the needed medication	☐	☐	☐
Re-admission caused by treatment failure	☐	☐	☐
Death	☐	☐	☐
Other (please specify in the comment box that will appear)	☐	☐	☐

B21. **Comment box :**

Section C: Root causes

C1. **16. In the case of medicine shortages related to sudden changes in demand, what are the main causes of these demand-side changes?**

- ☐ Adoption of a new treatment regimen
- ☐ Development of generics/therapeutically equivalent alternatives
- ☐ Product specific concerns (previously unknown side-effects, change in coating...)
- ☐ Other, please specify :

Other, please specify :

C2. **17. Does your country/countries of operation have a reporting system for shortages ?**

- [ ] Yes
- [ ] No

C3. **17.1. Who reports the occurrence of a medicine shortage to relevant stakeholders in your country/countries of operation?**

- [ ] Marketing authorisation holders
- [ ] Manufacturers
- [ ] Wholesalers/distributors
- [ ] Medicines agency
- [ ] Ministry of health
- [ ] Pharmacy organisations
- [ ] Healthcare professionals
- [ ] Other, please specify :

Other, please specify :

C4. **18. Who determines the cause of a specific medicine shortage in your country/countries of operation?**

- [ ] Marketing authorisation holders
- [ ] Manufacturers
- [ ] Wholesalers/distributors
- [ ] Medicines agency
- [ ] Ministry of health
- [ ] Pharmacy organisations
- [ ] Healthcare professionals
- [ ] Other, please specify :

Other, please specify :

C5. **19. To whom can healthcare professionals turn for professional advice and information how to deal with a medicine shortage?**

- ☐ Marketing authorisation holders
- ☐ Medicines agency
- ☐ Ministry of Health
- ☐ Pharmacy organisations
- ☐ Health professional associations
- ☐ Other, please specify :

Other, please specify :

C6. **20. To what extent do you consider the criteria for notifying a shortage used in your country appropriate?**

- ☐ Very
- ☐ Somewhat
- ☐ Not at all

C7. **Comment box :**

Section D: Identification of potential solutions

D1. **21. To what extent do you consider prescribing physicians to be in a position to prevent or mitigate medicine shortages**

- ☐ To a very large extent
- ☐ To a large extent
- ☐ To some extent
- ☐ Not at all

D2. **22. To your knowledge, have prescribing physicians or their representing organisations implemented any measures to prevent or mitigate medicine shortages ?**

- ☐ Yes
- ☐ No

D3. **Can you please specify which measures?**

D4. **21. To what extent do you consider pharmacists to be in a position to address medicine shortages?**

- ☐ To a very large extent
- ☐ To a large extent
- ☐ To some extent
- ☐ Not at all

D5. **22. To your knowledge, have pharmacists or their representing organisations implemented any measures to prevent or mitigate shortages in their operations?**

- ☐ Yes
- ☐ No

D6. **Can you please specify which measures?**

D7. **23. To your knowledge, do the health professionals that you represent receive advance notices of shortages?**

- ☐ Never
- ☐ Rarely
- ☐ Frequently
- ☐ Always
- ☐ Unknown/does not apply

D8. **24. Please indicate which of the following measures have been implemented in the country/countries where you operate?**

- ☐ Early notification of expected shortages
- ☐ Requiring stockholding by marketing authorisation holders and distributors

- [ ] National stockpiling
- [ ] Restrictions on parallel exports
- [ ] Requiring transparency of industry supply quotas and wholesalers' transactions for the relevent Member State authorities
- [ ] Establishing national lists of essential medicines and medicines at high risk of shortage
- [ ] Publication of national lists of medicines currently in shortage that can be accessed by patients and health professionals
- [ ] Publication of lists of past shortages by company
- [ ] Cooperation between NCA, MAH holders and distributors on foreasting and planning the demand side
- [ ] Allowing pharmacists to substitute medicines without intervention of a prescribing physician
- [ ] Incentives for local production of APIs
- [ ] Incentives for local manufacturing of finished products
- [ ] Procurement procedures at national level to include criteria (e.g. penalties) that address continuity of supply
- [ ] Incentivising multiple active marketing authorisations to promote (generic) market competition
- [ ] Other, please specify :

Other, please specify :

D9. 25. What did the implementation of these solutions have on your operating costs?

- [ ] No impact on costs
- [ ] Relatively small impact on costs (0-5%)
- [ ] Substantial impact on costs (>5%)

D10. 25. What did the implementation of these solutions have on treatment costs?

- [ ] No impact on costs
- [ ] Relatively small impact on costs (0-5%)
- [ ] Substantial impact on costs (>5%)

D11. 26. Which policies do you think would be revelant solutions to address medicine shortages at the EU level

- [ ] Adopting common principles for the introduction of national restrictions on exports to other Member States
- [ ] Coordinating a list of essential medicines at the EU level and medicines at high risk of shortage
- [ ] Amending the EU GMP guidelines to require marketing authorisation holders and manufacturers to have a shortage prevention or mitigation plan

Establishing EU stockpiles under the EU Civil Protection Mechanism ☐

Encouraging Member States to accept or promote multi-country packages to allow more flexibility for companies when allocating supply ☐

Other, please specify : ☐

Other, please specify :

D12. **27. Did the implementation of the European requirement on marketing authorisation holders to provide notification when a product ceases to be placed on the market (temporarily or permanently) at least 2 months in advance have any of the following impacts on your operations**

No impact at all ☐

It enabled more timely identification of treatment alternatives ☐

It enabled more timely identification of alternative sources of the same medicine (e.g. through import) ☐

Other impact, namely : ☐

Other impact, namely :

D13. **Comment box :**

Thank you for participating in this survey. Your responses have been received. You can now close this window.

Annex E. ANALYSIS OF SHORTAGE REGISTRY DATA

Overview of data sources

Data collection from national shortage registries began in October 2020 with requests sent to the NCA representatives of the SPOC network. All received data were cleaned and recoded for improved standardisation. Because data sets were received at different points in time (between October 2020 and January 2021), there was inconsistency in what was considered a current or historical shortage. To standardise this, any shortage with an end date or estimated end date reported before 1 October 2020 was considered a historical shortage. Any shortage with end date reported after this date, or unknown but with a reported start date (approximately 17% of all shortage notifications) was considered as a current shortage.

The IQVIA MIDAS database covering Q1 2008 up until Q3 2020, was also further restructured. After cleaning, the country datasets were merged and linked to the IQVIA MIDAS data to create an overview of medicines in shortage and enable a comparison of key characteristics of shortage medicines versus non-shortage medicines. Linking allowed the use of revenue and volume data, as provided by the IQVIA MIDAS data, as additional variables in the analysis of shortage notifications. Data on root causes of shortages provided by countries was recoded using the SPOC network classification system and at a more granular level for countries that provided sufficient detail.

No country was able to report all requested variables. However, some were able to provide notably more complete data than others (Table 26). There are also notable differences in the timespan covered by the notifications included in the data sets (Table 27). The analyses presented in this report are naturally limited by the data availability.

Table 26 Variables included in national shortage registries included in study

Country	Austria	Belgium	Croatia	Czechia	Denmark	Estonia	Finland	France	Germany	Greece	Hungary	Iceland	Ireland	Italy	Netherlands	Norway	Portugal	Romania	Slovakia	Slovenia	Spain	Sweden	SPOC registry	**Total**
Product Name (local or international)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	**23**
MAH	X	X	X			X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		**19**
Active Ingredients	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X		**20**
NFC3																								**0**
ATC4		X				X	X	X	X		X	X	X			X	X			X	X			**12**
Location(s) of API Manufacturer												X					X							**2**
Form	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	**22**
Route of Administration		X				X	X	X				X					X			X				**7**
Strength	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	**22**
Availability of alternatives	X	X												X										**5**
Import/export data																								**0**
Date of notification		X	X			X		X	X						X	X			X	X			X	**10**
Start Date of Shortage	X	X	X		X	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	**19**
Estimated End Date of Shortage		X			X	X				X	X	X	X	X	X	X	X		X	X	X	X	X	**16**
Status of Shortage	X	X	X			X		X				X	X	X	X	X	X	X	X	X	X		X	**16**
Root Cause of Shortage	X	X	X		X	X		X			X	X	X	X	X	X	X	X			X	X	X	**17**
Total	**9**	**13**	**9**	**2**	**7**	**13**	**7**	**10**	**6**	**7**	**9**	**12**	**10**	**10**	**10**	**12**	**12**	**8**	**8**	**10**	**10**	**8**	**8**	

Table 27 Summary of reporting dates per country

Country	Earliest reported shortage start date	Latest reported shortage start date
Austria	14/12/2015	13/11/2020
Belgium	01/01/2015	15/06/2021
Croatia	25/09/2013	01/11/2020
Czechia	NA*	NA
Estonia	10/10/2011	01/08/2021
Finland	NA	NA
France	06/07/2005	30/12/2022
Germany	NA	NA
Greece	01/01/2019	01/04/2021
Hungary	08/03/2007	21/01/2021
Ireland	31/01/2017	01/02/2021
Italy	01/01/2009	01/05/2023
The Netherlands	01/01/2008	01/05/2022
Norway	01/01/2016	10/10/2021
Portugal	03/01/2014	31/07/2021
Romania	09/03/2016	15/03/2021
Slovakia	02/11/2012	01/08/2019
Slovenia	12/01/2007	30/06/2021
Spain	27/09/2007	15/03/2021
Sweden	03/10/2016	01/02/2021
SPOC-registry	31/08/2011	01/12/2020

*NA (Not applicable) indicates that the data provided did not include start and/or end dates per shortage

All data returned by the NCAs or retrieved from public registries was cleaned and structured according to a data collection template. Most cleaning was performed on the matching variables:

- Product name (International non-proprietary name)
- Marketing authorisation holder
- Form
- Active Ingredient(s)

For each of these, IQVIA was used as a reference. Cleaning was done using a combination of automated and manual steps. The formulation variable was also cleaned into more simplified codes (Table 28).

Table 28 Form framework used to reclassify country reported medicine forms (non-exhaustive)

Simplified coding	NCA Form descriptions (non-exhaustive)
Tablet	Tablet, tabs, orodispersible, effervescent tablet, chewable tablet, coated tablet, sublingual tablet
Capsule	Capsule, caps, hard capsule modified release, gastro resistant capsule
Oral solid other	Lyophilisate, medical chewing gum, oral paste, lozenge
Oral powder	Oral powder, oral granules
Oral liquid	Oral solution, syrup, oral drops, concentrate for solution, mouthwash, oral suspension, oromucosal
Injections/infusions	Injections, infusion bags, infusion, injection, pre-filled syringe, implant in syringe, solution for injection

Rectal	Rectal, enema, suppository enemas, suppositories
Nasal	Nasal aerosols, drops
Other	Hormone implant, kit for radiopharmaceutical, matrix for sealant in surgery, rods for use in the urethra
Topical	Cream, gel, topical, cutaneous, medicated plaster, shampoo. Includes treatments for mouth e.g. lozenge to relieve oral ulcer, nail lacquer
Ophthalmic	Eye drops, ointments, ophthalmic creams, eye, intravitreal
Otic	Otic, ear drops, creams
Lung	Inhaler capsules nebuliser, aerosol
Vaginal	Vaginal tablets, vaginal devices, pessary

Further cleaning was also conducted on the variables needed in subsequent analyses:

- Shortage dates
- Root causes
- Shortage status

Cleaning of information classification on reported root causes and recoding into the categories provided by the SPOC was largely a manual process (Table 29). The current SPOC classification of root causes differentiates between quality and manufacturing issues. However, this distinction was not made in the same way before November 2019 and thus some entries had been classified as 'quality/manufacturing issues'. Moreover, the information provided on the cause of the shortage is not always sufficiently detailed in the NCA reporting to establish whether the issue is one of quality or of manufacturing. Therefore, these were grouped into 'quality and manufacturing issues'. It should be recognised that this manual recoding is challenged by the limited information available and is inherently subjective. It is also not clear what the source for the information provided in the registries is and whether the NCA has independently verified this.

Table 29 Reclassification of reported root causes in national shortage registries according to SPOC classification

SPOC classification	SPOC definition	NCA coding examples (non-exhaustive)
Quality and manufacturing issues	Quality: Unforeseen disruptions within the manufacturing process leading to quality defects (API or finished product), including recalls. Manufacturing: Unforeseen disruptions within the manufacturing process caused by GMP compliance problems (API or finished product). Manufacturing issues also include capacity issues.	Quality defect Quality investigation at manufacturing site has halted production Quality event at manufacturing site has resulted in temporary cessation of release and production activities Manufacturer not GMP compliant Production on hold globally due to quality issue with primary packaging API impurity API supplied did not meet specification size and was rejected, impacting FP manufacture Recall - sterility issue due to cracked vials Packaging issues Manufacturing delays (due to unavailability of bulk product, on packaging line, break down on production line) Delay in production / quality control API delay / unavailability (due to upgrades at API facility) Technical issue on packaging line has delayed FP manufacture Capacity constraints (at CMO, for bulk production, on manufacturing line, capacity issues at plant)

		Reduced capacity & quantity of personnel at site
Regulatory issues	When requirements or obligations relating to the grant of the authorisation have not been fulfilled after authorisation and 'placing on the market'. Failure to implement safety features (i.e. MAH failure to implement the unique identifier and the tamper evident features on the pack) are also considered regulatory issues.	Implementation of Falsified Medicine Directive requirements Delays implementing serialisation Delay adding new QP release site Delay in release to market due to nitrosamine testing Incorrect info on pill Regulatory authority inspection Delay in submissions MA non-compliance RMS transfer Brexit Variation to licence has delayed release of manufactured product
Safety and efficacy issues	If the medicinal product lacks therapeutic efficacy (or decrease efficacy), there are new safety risks identified requiring precautionary action, or the risk-benefit balance of the medicine is no longer favourable.	(None reported)
Unpredicted major events or natural disasters	May indirectly lead to shortages of medical products, e.g. the ongoing swine fever in China or the earthquake in Japan in 2011	COVID-19 demand Delay in delivery due to COVID related capacity constraints at warehouse in France Temporary reduction in capacity at manufacturing site due to COVID-19 Manufacturing delay - leaflet delayed due to COVID Priority manufacturing being given to COVID-19 products Stock delayed due to impact of hurricane near CMO
Unexpected increased demand	Due to previous defects, due to market cessation/shortage of alternative products (e.g. generics), due to great awareness about a specific disease prevention or new treatment guidelines and/or recommendations of physicians'/veterinarians'/other healthcare professionals' organizations, change in reimbursement conditions, change in epidemiology	Increase in demand as a result of shortage of lower strength Increase in demand due to flu season Increase in demand due to recall/shortage of competitor product Increase in demand for stock
Distribution issues	Distribution channel structures, parallel trade (also includes export to outside of the EU), quotas, supply chain policy (e.g. DTO), logistic issues	Local delay in confirming order Shipping delay Technical issue with ordering software Delay in delivery from supplier Delay in delivery of bulk product to CMO Delay in order delivery due to bank holiday, short on other markets for various reasons Missed delivery - MAH investigating how this happened

Commercial reasons	Company-driven decisions linked to business aspects such as pricing negotiations; discontinuation; change in reimbursement status; low sales (i.e. low number of patients); business strategies prioritising other markets.	Change of the marketing authorisation holder CMO does not have enough orders to meet minimum batch size Batch rejected by manufacturer (none on market) Delay in receipt of export permit CMO has gone into administration MAH transfer Delayed release documentation Delay in setting up a new SKU Product not commercially viable Incorrect forecasting/sales planning Low market potential Overselling abroad Order not placed in time Overdue order Product withdrawn Market withdrawal
Other	(Not included in SPOC classification)	End of the vaccination season in the 2018/2019, the current inability to supply the market Bioassay testing site no longer able to release as they are shutting down due to mounting pressure from animal rights activists Cyber attack Product never placed on market and not used clinically Ongoing variation (too vague) Supply chain issue (too vague)

Source: List of definitions and classification of different shortage root causes provided by the SPOC network (HMA/EMA (22 January 2020). Annex 1 – List of definitions and classification of different shortage root causes. EMA/912132/2019 Rev.3.). Reported root causes included in national shortage registries. Recoding by Technopolis Group.

Once the data were cleaned, a four-step matching process was followed to link shortage data reported by the NCAs to IQVIA sales data. In the first instance, products in shortage were matched based on product name, active ingredient(s), form, and manufacturer.[263] Medicines that could not be matched this way were then matched only based active ingredient(s), form, and manufacturer (excluding product name). Medicines that could still not be matched were matched using their product name and form only. The final set of remaining products were then matched using only their product name. Steps involving manufacturer used a 'fuzzy matching' approach to allow for minor variations caused by, for instance, differences in the spelling or use of abbreviations of manufacturer names (for instance, GSK versus GlaxoSmithKline) or mention of different national subsidiaries. The rate of matching differed between countries, varying from 66% (Slovakia) to 97% (SPOC register) (

[263] In the IQVIA MIDAS data set, these variables are named INTPRD (International product name), MOL_LIST, NFC (New form code) and MNF (manufacturer).

Table 30).

Table 30 Summary of the completeness and matching success of reported shortages per reporting country/entity

Reporting country/entity	# Shortages reported	Completeness of returned template/public registry according to data collection template	Matching success rate
Austria	482	62%	75%
Belgium	8,082	71%	85%
Croatia	201	49%	75%
Czechia	10,526	9%	74%
Estonia	1,425	73%	93%
Finland	1,268	51%	90%
France	6,651	64%	82%
Germany	925	28%	24%
Greece	108	33%	73%
Hungary	1,382	35%	73%
Ireland	1,574	50%	88%
Italy	2,557	42%	67%
Netherlands	14,989	44%	75%
Norway	9,212	44%	73%
Portugal	9,250	67%	87%
Romania	684	38%	73%
Slovakia	3,080	35%	66%
Slovenia	7,326	57%	85%
Spain	7,037	45%	85%
Sweden	2,692	50%	74%
SPOC register	133	58%	97%

As not all national level shortage data could be linked to the sales data, tests were conducted to assess whether any bias had been introduced via the linking process. For example, medicines of a certain therapeutic area could have been more likely to be linked than others because of more wide-spread use. However, inspection of the distribution across medicinal forms (Figure 18) or ATC1 codes (Figure 19) or linked shortages was similar to the overall distribution. It is therefore assumed that the linking process did not introduce bias that would affect the validity of the study analyses.

Figure 18. Proportions of ATC1 medicines for linked shortage data and all (linked and not linked) shortage data

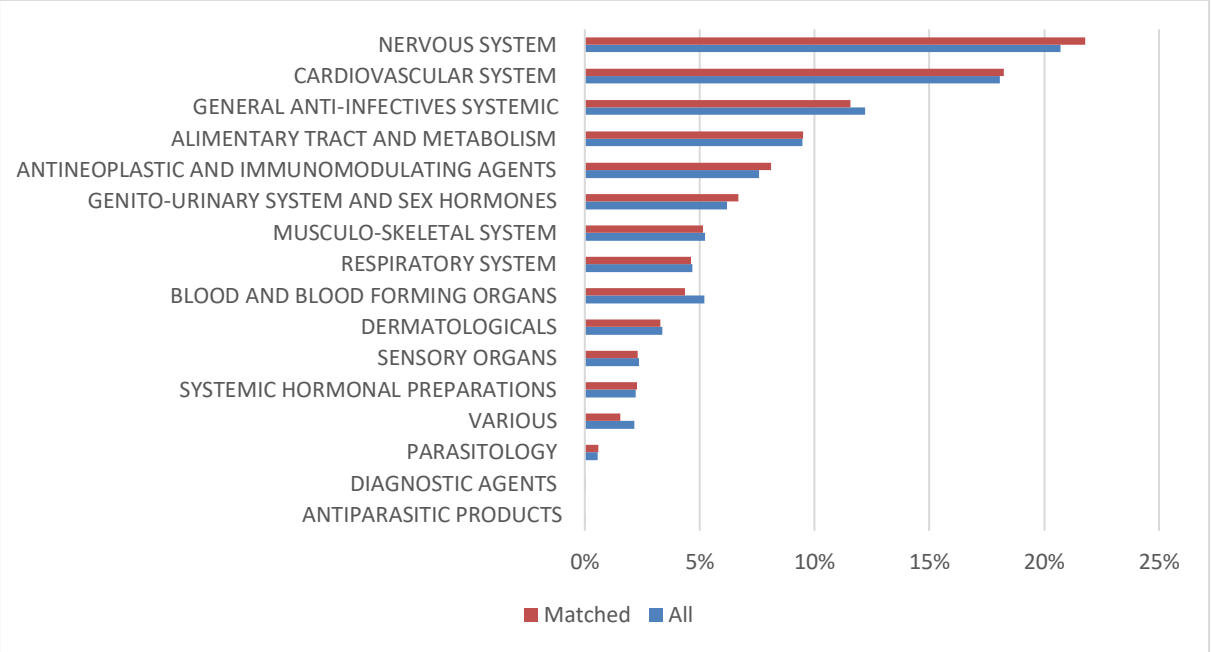
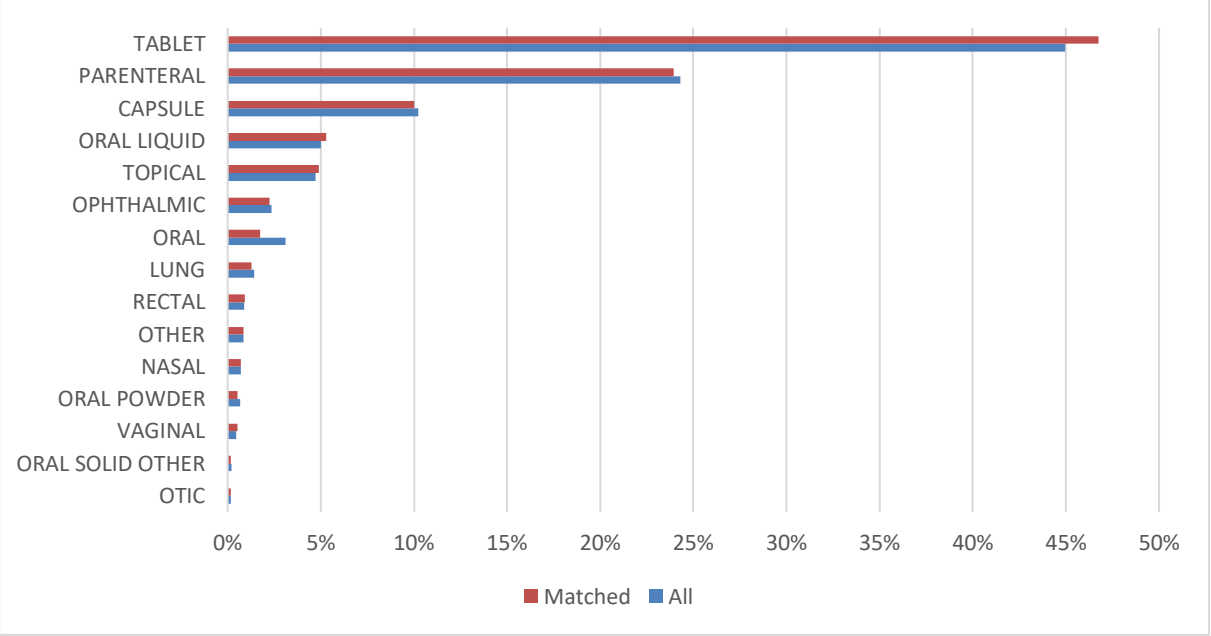


Figure 19 Proportions of medicine formulation for linked shortage data and all (linked and not linked) shortage data



Summary statistics of included medicine shortages

This section presents only those summary statistics that have not already been included in the main text of this report.

Table 31 Total shortage duration per product (in days) for products included on the WHO EML

EML Status	Minimum	Median	Mean	Maximum	N
Excluded	1	132.6	102	400	6,261
Included	1	134.0	103.5	400	3,270

Table 32 Number of shortage events per product across all reporting countries

Minimum	Median	Mean	Maximum
1	2	4.5	207

Key characteristics (Chi-square analysis)

The differences of key characteristics between shortage and non-shortage products were assessed using a Chi-square test. A Chi-square test is a non-parametric statistical tool used to assess differences in proportions in characteristics between groups. Chi-square does not require the underlying data to be normally distributed.[264] This test has been used in the context of medicines shortages previously to compare and describe differences in medicines listed as shortage between locations[265,266] and medicine types.[267]

The strength of association of statistically significant results was assessed using 'Cramer's V' statistic. The values from this test range from 0 to 1 with larger values of V indicating stronger (i.e. more meaningful) associations in the variables. Values of over 0.1 or 0.2 are generally considered to be a suitable threshold for suggesting there is a substantive relationship between variables.

Table 33 provides an overview of the results of all Chi-square tests that were performed, along with their respective Chi-square statistics, p-values and Cramer's V. There is a statistically significant difference in the distribution of all tested variables between shortage and non-shortage products. This is likely to be a result of the large sample size, which increases the likelihood of statistically significant differences, which is where Cramer's V is useful as a means of assessing the strength of association.

Table 33. Pearson's Chi-square and Cramer's V analysis of key characteristics between shortage medicines and non-shortage medicines

Key characteristic	Number of categorical variables	Chi-square value	P- value	Cramer's V value
Generic status	7[b]	9,404.1	<0.0001	0.221
Top 10 manufacturers	10[c]	9424.4	<0.0001	0.221
ATC2	100	6,243.5	<0.0001	0.180
ATC1	16	4,059.0	<0.0001	0.145
Form	13	1,854.8	<0.0001	0.100
On WHO Essential Medicine List	2[a]	1,242.0	<0.0001	0.080
Manufacturer history of GMP non-compliance	2	716.2	<0.0001	0.061
List price (percentiles)	100	593.5	<0.0001	0.059
List price (deciles)	10	344.2	<0.0001	0.045
Time since launch	13[d]	257.3	<0.0001	0.044
Patent status	2[e]	27.2	<0.0001	0.011

a) To reduce error, Yates continuity correction was applied where the number of categorical variables was 2; b) As defined in IQVIA MIDAS: Generic medicines, Non generic medicines, Biocomparable medicines, Early entry generic medicines,

[264] McHugh, Mary L. "The chi-square test of independence." Biochemia medica: Biochemia medica 23.2 (2013): 143-149.

[265] Yang, Caijun, et al. "The current status and effects of emergency drug shortages in China: Perceptions of emergency department physicians." PloS one 13.10 (2018).

[266] Alsheikh, Mona, et al. "A comparison of drug shortages in the hospital setting in the United States and Saudi Arabia: an exploratory analysis." Hospital pharmacy 51.5 (2016): 370-375.

[267] Chen, Serene, "Trends in National Shortages of Acute Care Drugs, 2001-2014" (2015). Yale Medicine Thesis Digital Library. 1956. https://elischolar.library.yale.edu/ymtdl/1956

Multiple, Non categorized medicines, Other medicines[268]; c) Top 10 manufacturers in terms of frequency of occurrence in IQVIA MIDAS (includes both shortage and non-shortage medicines) d) In decades since 1900; e) Products with expiration dates before 1 January 2021 were classed as expired.

As part of Chi-squareanalysis, Pearson residuals are also calculated which specify the categories within each variable that are contributing to the difference in distributions. This contribution can be expressed as a percentage so show the relative importance of said variable to the overall difference. The residuals can therefore be used to determine the characteristics of a medicine that make it more or less likely to be in shortage. Table 34 provides a summary of these residuals, specifying the categories within each characteristic where shortages are the most or the least likely.

Table 34 Analysis of Pearson residuals based on Chi-square tests

Variable	Categories where shortage medicines are most likely to occur	Relative importance to the effect[a]	Categories where shortage medicines are least likely to occur	Relative importance to the effect
ATC1	N – Nervous System	17.3%	V - Various	39.2%
ATC2	N2 – Analgesics	4.4%	V3 – All other therapeutic products	20.0%
On WHO Essential Medicine List	On EML list	67.2%	Not on EML list	21.2%
Form	Tablets Injectables/Infusions	17.0% 12.6%	Topical Oral liquids	22.8% 20.3%
Manufacturer history of GMP non-compliance	GMP non-compliance	85.6%	GMP compliance	1.9%
Generic status	Multiple[a] Generic	42.3% 7.6%	Non-categorised	33.5%
Top-10 manufacturers	Top-10 manufacturers	71%	Non-top 10 manufacturers	17%
Time since launch	Products launched between 1980-1989	29.0%	Products launched between 1990-1999	17.0%
Patent status	Patent expired	1.1%	Patent not expired	88.2%
List price (deciles)	Products in the 6th price decile of their formulation group	16.3%	Products in the 1st price decile of their formulation group	48.4%
List price (percentiles)	Products in the 55th price percentile of their formulation group	2.1%	Products in the 1st price percentile of their formulation group	26.0%

a. Contribution to the Chi-square statistic (based on Pearson residuals) / b. 'Multiple' indicates that the same medicine has differing generic statuses across countries.

[268] These categories derive directly from the IQVIA MIDAS data set where they have been defined as follows: Biocomparable = A biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the EEA; early entry generic products = generic products that have entered the market prior to patent expiry with permission of the manufacturer; generic products = a product that is developed to be the same as a medicine that has already been authorised; non-categorised products = a product for which generic status was not known as per IQVIA MIDAS; non-generic products – includes innovative products; other products = specific products that fall outside of other categories e.g. vitamins.

Table 35 Co-occurrence of shortages between countries

	Austria	Belgium	Croatia	Estonia	France	Hungary	Ireland	Italy	Netherlands	Norway	Portugal	Slovakia	Slovenia	Spain	Sweden
Austria	-	2	1	0	4	1	1	0	1	2	1	0	1	4	3
Belgium	2	-	0	3	13	4	9	0	10	14	28	8	12	15	17
Croatia	1	0	-	1	1	2	1	1	0	0	0	1	3	1	1
Estonia	0	3	1	-	0	0	0	2	2	3	8	1	7	4	4
France	4	13	1	0	-	1	3	0	5	4	8	0	5	8	6
Hungary	1	4	2	0	1	-	2	0	0	3	3	2	4	5	5
Ireland	1	9	1	0	3	2	-	0	3	12	10	0	7	9	19
Italy	0	0	1	2	0	0	0	-	0	0	0	0	2	1	0
Netherlands	1	10	0	2	5	0	3	0	-	4	10	1	1	7	2
Norway	2	14	0	3	4	3	12	0	4	-	17	4	8	8	18
Portugal	1	28	0	8	8	3	10	0	10	17	-	7	11	15	20
Slovakia	0	8	1	1	0	2	0	0	1	4	7	-	2	2	3
Slovenia	1	12	3	7	5	4	7	2	1	8	11	2	-	11	10
Spain	4	15	1	4	8	5	9	1	7	8	15	2	11	-	10
Sweden	3	17	1	4	6	5	19	0	2	18	20	3	10	10	-

Source: Technopolis Group based on data from national shortage registries. Concurrent shortages have been defined as shortages that affect four or more countries with a shortage start date reported in the same quarter. The indicated number express how often a concurrent shortage occurred in the combination of countries indicated on the horizontal and vertical lines.

Trends in revenue, volume and price

In line with the FDA analysis[269] of medicine shortages in the US, the market trends of medicines associated with shortages were analysed and compared to similar non-shortage medicines. The economic trend analysis further helps to characterise shortage medicines from an economic perspective, highlighting differences, if any, from similar non-shortage medicines.

To compare shortage medicines to similar non-shortage medicines, these were linked using 'nearest neighbour' matching. Nearest neighbour analysis allowed the matching of a control group (i.e. the non-shortage group) using a pre-defined set of variables. The FDA analysis matched each shortage medicine to its 50 'nearest neighbour' non-shortage medicine based upon the variables: route of administration, time on the market, list price and volume sold to matched non-shortage medicines (in addition to the non-shortage medicine having never been in a shortage for the duration of the time for which there is data). In this study, shortage medicines were matched to five 'nearest neighbours' as defined by their ATC2 code, pharmaceutical form, and time on the market (calculated based on the product launch date as reported in IQVIA MIDAS). A ratio of 1-to-5 (shortage to non-shortage products) was used as this is in line with the number of shortage products identified by this study (approximately 22.5K) relative to the number of remaining non-shortage datasets in the IQVIA dataset (approximately 170K) and does not produce errors when running the matching algorithm.

For the computation of trends and average quarterly figures, the following steps were followed:

- For every shortage medicine, all quarters available in the IQVIA MIDAS dataset preceding the quarter in which the first recorded shortage occurred were considered
- The quarter prior to the first shortage occurring was used to standardise all preceding quarters for shortage medicines
- Next, a simple linear regression was fitted to all available quarters for shortage medicines, from which the regression coefficient was extracted. In this process, shortage medicines for which no data was available for the quarters under consideration were excluded (as no regression could then be fitted)
- For all medicines (shortage and non-shortage), the relative quarterly change was calculated for all available quarters, which was subsequently averaged, resulting in a single figure for average quarterly change per product, expressed as a percentage
- The data was then grouped based on the direction of the trend (increasing or decreasing) across quarters preceding the shortage occurring for shortage products
- Per group, the mean of all average quarterly changes is computed separately for shortage and non-shortage products
- This process was followed a total of three times: once for quarterly revenue data, once for quarterly volume data, and once for quarterly price data

The results of this analysis are presented in Table 36, from which two main observations can be made. First, the average quarterly change goes negative for volume and price for shortage products with a decreasing trend prior to the shortage occurring. Similarly, for non-shortage products, the average quarterly change in the indicator is consistently higher for products with a positive trend compared to those with a decreasing trend. However, for shortage products, the average quarter-on-quarter change in revenue is higher for products with a decreasing trend than for those with an increasing trend. This suggests that consistently decreasing trends in revenue for any product are relatively rare and are therefore outweighed by medicines with largely stable or increasing trends. Another possible explanation is that medicines with overall decreasing trends occasionally experience large upward spikes in terms of quarter-to-quarter change.

Table 36 Summary of market trend analysis results

Indicator	Indicator trend prior to shortage	Average quarterly change of indicator in shortage medicine prior to shortage (%)	N (shortage medicines)	Average quarterly change of indicator in non-shortage medicine during equivalent shortage time period (%)	N (non-shortage medicines)
Revenue	Decreasing	+386%	324	+89%	1,620
	Increasing	+245%	470	+202%	2,350

[269] US. Food & Drug Administration (2019). Drug shortages: Root causes and potential solutions. Executive summary. Available at: https://www.fda.gov/media/132058/download.

Volume	Decreasing	-14%	313	+88%	1,565
	Increasing	+248%	481	+204%	2,405
Price	Decreasing	-1%	921	+5%	4,605
	Increasing	+37%	341	+8%	1,705

Relative importance of shortage products to its manufacturer

The process of nearest neighbour matching described above also served as the basis for an analysis of the relative (economic) importance of shortage products to their manufacturer, compared to that of non-shortage products. For every product available in the IQVIA dataset, all quarterly revenue data was summed up which was subsequently divided by the total revenue for all products by the corresponding manufacturer to obtain the proportion of manufacturer revenue each products accounts for. When coupled with the outputs of the nearest neighbour analysis, the relative importance of shortage products to their manufacturers is compared to that of non-shortage products. As can be seen in Table 37, the relative importance between shortage and non-shortage products to their manufacturer differs by only a tenth percentage point.

Table 37 Relative importance of shortage and non-shortage products to their manufacturers

Average relative importance of shortage products to manufacturer	Average relative importance of non-shortage products to manufacturer
4.8%	4.9%

Annex F. COST-BENEFIT ANALYSIS

F. 1 Effectiveness analysis

Analysis of the compliance with the notification obligation is prevented by lack of reliable data from the NCAs on the time between notification and start of a shortage and an absence of comparators. Consequently, it was not possible to quantify the effectiveness of Article 23a of Directive 2001/83/EC. With regards to Article 81, Member States have transposed thisthis in different ways and at different levels of 'intensity'. The first concerns the "literal a minima" transposition, without any additional national provisions imposed. Besides this first level transposition, Member States may have introduced additional provisions in their legislation. Based on the provisions, Member States have been grouped into three distinct groups:

Group	Provisions	Countries
Group A	A minima transposition of MAHs and distributors' obligations	Cyprus, Denmark, Croatia, Malta
Group B	A minima transposition + provisions allowing export restrictions	Austria, Greece, Latvia, Poland
Group C	Extended obligations onto MAHs and/or distributors + export restrictions (i.e. excludes group B)	Belgium, Bulgaria, Czechia, Estonia, Spain, Finland, France, Hungary, Italy, Portugal, Romania, Slovakia
Group D	Stock obligations (excl. pharmacies)	Belgium, Germany, Spain, Finland, France, Italy, Luxembourg, Netherlands, Portugal
Group E	Stock obligations (excl. pharmacies) + export restrictions	Belgium, Spain, Finland, France, Italy, Portugal

As can be seen from the table the groups overlap in that several countries in Group E are also included in Groups C and D. For a meaningful quantitative analysis of the effectiveness of provisions distinct groups are required covering countries which have broadly similar provisions. Another requirement is that complete (i.e. with start and end date of the shortage) information on reported shortages is available for all or several of the countries in a particular group. Based on these requirements only a limited quantitative analysis of effectiveness was possible.

For Group A only complete data on one country was available (Croatia), while for Group B data for none of the countries was complete (end dates missing for several countries). The only meaningful comparison possible was between Group E and the countries in Group C that are not also coverd in Group C. In other words, by comparing shortage information for Estonia, Hungary and Slovakia (part of Group C) with data for Belgium, Spain, Finland, France, Italy and Portugal on the other (Group E), the impact stock obligations (being the difference between the two groups) could be analysed. The other countries in Group C (Bulgaria, Czechia and Romania) could not be included due to missing information, mostly on the end date of shortages.

Because of variations in the starting dates in reporting, the analysis focused on a period in which most of the countries for which data were available had started reporting: the years from 2016 until 2019.[270] Shortages notified in 2020 were excluded as these data were collected before the end of the calendar year and thus were incomplete.

Table 38 shows the number of ongoing shortages in each of the groups of Member States between 2016 and 2019.[271]

Table 38 Number of ongoing medicine shortages in 2017-2019, by group of Member States

Group	2016	2017	2018	2019	Average change per year
C (excluding E) [a]	375	369	327	390	2%
E [b]	3,016	3,556	4,271	4,773	17%
C (excluding E) + E	3,391	3,925	4,598	5,163	15%
All[c]	3,758	4,458	5,778	7,118	24%

[270] Only Greece, Ireland, Romania and Sweden started after 2016.

[271] Ongoing shortages include not only the shortages that started in a calendar year, but also those that started in previous year(s) but were still ongoing.

a: Estonia, Hungary, Slovakia; b: Belgium, Spain, Finland, France, Italy and Portugal; c: covering shortages with complete information for Belgium, Croatia, Estonia, France, Hungary, Ireland, Italy, Netherlands, Portugal, Slovakia, Slovenia, Spain and Sweden. Source: Analysis by Ecorys BV of data from national shortage registries

Table 38 shows the average growth rate in shortages for the two groups of countries separately andtogether. It also shows the total number of ongoing shortages in the 13 countries for which complete data were available for the years 2016-2019.[272] The total number of ongoing shortages recorded by the individual Member States involved increased substantially over the period 2016-2019, from 3,800 to 7,1600; the average growth rate in these years was nearly 24% per year. This increase may either reflect a strong increase in the incidence of shortages, a better reporting of shortages over time or a combination of the two.

When focusing on the two groups C (excl. E) and E, it appears that the absolute number of ongoing shortages differs considerably between the two groups, also when differences in the number of countries reporting are taken into account (Group C (minus E) covers three countries, Group E five). The number of shortages is considerably higher in the group with stock obligations (Group E) . Group E includes Member States such as Portugal, Belgium, France and Spain, which are Member States with, on average, a relatively high number of reported shortages.

Also the development in the volume of reported shortages differs between the two groups. The group of Member States that also had stock obligations had a higher average growth over 2017-2019, but growth in 2019 was lower as compared to to the group without stock obligations.

Although the level of reporting may differ between Member States, the way of reporting of an individual Member State could be assumed to be more stable over these four years. If true, the data suggest that stock obligations may not have had a downward effect on the incidence of medicine shortages in the Member States that imposed them but the quality and heterogeneity of the data are such that such a conclusion cannot be drawn.

F.2 Cost analysis

Actions taken to prevent shortages

To avoid or minimise shortages, pharmaceutical companies take various preventive actions. Such actions can be seen as being part of normal operating procedures, aimed at realising a stable supply of medicines to the market. Based on inputs from stakeholders in interviews and through surveys, common measures taken by **pharmaceutical manufacturers** include:

- Demand forecasting
- Optimisation of stocks and production capacity
- Optimising logistics capacity
- Dual sourcing: ensuring the supply of critical supplies (e.g. APIs) by using more than one supplier, even if costs are higher
- Keeping higher stocks of critical supplies such as APIs
- Keeping higher stocks of finished products
- Ensure that packaging and leaflets are available in more languages

Such measures involve operating costs, but these operating costs can be seen as being part of the normal operating procedures of companies to ensure supply.

For **wholesale distributors** preventive actions focus mostly on demand forecasting, optimisation of stock allocation and logistics measures to deal with shortages. However, like for pharmaceutical industry, such measures may be seen as being part of their normal operations and are not specifically related to the legal provisions aimed at preventing / mitigating shortages.

Pharmacists are not normally in a position to take measures to avoid shortages of medicines, apart from keeping extra stocks. The possibility to keep extra stock will, however, in most cases be limited, unless the pharmacy function is combined with a distribution function within the same company.

Actions, impacts and costs in the event of a medicine shortage

Stakeholders take various actions to prevent shortages arising. When a shortage arises, stakeholders are affected in different ways. This section briefly describes in what way stakeholders are affected

[272] The other Member States were not included in this analysis as the information on shortages in these countries did not contain all information, such as end dates of shortages. For this reason the number of ongoing shortages could not be established for these Member States.

and what this means in terms of extra costs or benefits foregone associated with the use of medicines.

In response to a shortage, **pharmaceutical companies** may decide to take the following actions:

- Production capacity may be expanded
- Stock of final product stocks may be relocated from one Member State to another, requiring distribution

The result of both types of action may be that the shortage is solved and sales can resume, such that the company can derive a profit from these sales. Whether the actions taken result in additional costs and subsequently in a lower profit margin or are reflected in a higher retail price of the medicine will depend on the specific situation. In case shortages cannot be addressed sufficiently, companies would risk sales revenues and the profit margin associated with it, as well as potentially fines for non-compliance with supply obligations.

Wholesale distributors cannot influence the production of a medicine but may be able to relocate final product stock from another Member State to the Member State where the shortage arises, which possibly involves extra logistics costs. If such action cannot be taken, the shortage will continue, and turnover (and profit margin) are foregone. As wholesalers are also subject to the supply obligations under Article 81, they may be liable for financial sanctions for non-compliance.

A medicine shortage means that the medicine that is the preferred option for treating a patient is (temporarily) not available or less available. The impact thereof on **health care professionals** (pharmacists and prescribers) depends on various factors. A main factor is the availability of an appropriate alternative. Surveyed health care professionals indicated that in 50-60% of shortages an alternative is available, although extra time may be needed to identify and source that alternative. In the remaining 40-50% of cases, there may be a more substantial impact, both for the healthcare professionals and the patients due to sub-optimal or interrupted treatment. In the survey carried out for this study, it was found that pharmacists spend on average around 4 hours per week in managing the effects of medicine shortages. Taken this number and relating it to the number shortages in 2019, it is estimated that pharmacists in the EU27 spent in total approximately 10 million hours in 2019 on dealing with medicine shortages, or around 500 hours per shortage per Member State per year. The time costs equal roughly EUR 25,000 euro per Member State per shortage in that year.

The non-availability of medicines can have serious effect on the health of **patients**. In 2019, around 8,000 cases of an ongoing shortage of a medicine were reported in the group of 19 EU Member States for which data were included in this study. In 40-50% of cases a replacement was not readily available. In about half of the cases, the shortage was reportedly solved within a matter of days or weeks. Based on the survey data, it is tentatively concluded that in about 25% of the cases the treatment of the patient can be resumed within a matter of days or weeks. The health impact of this delay may be limited depending on the treatment. For a further 25% of cases it takes considerably longer to solve the shortage. In these cases, alternative treatment would be required during the shortage period, which could have a negative health impact on these patients. The size of this impact very much depends on the specific situation (i.e. the type of medicine, how the alternative treatment compares, etc.).

Table 39 summarises the applicable costs associated with medicine shortages for these four groups of actors.

Table 39 Potential impacts and costs arising from shortages

Affected group	Impacts	Costs
Pharmaceutical companies	Possibly expansion of production, relocation of finished products	No extra costs, part of normal operations
Wholesalers/traders	Possibly relocation of finished products	No extra costs, part of normal operations
Health care professionals	Extra time spent on finding alternative medicines / treatments, patient care	Approximately 500 hours per shortage per MS per year
Patients	Extra costs for alternative medicines	Depends on the situation, no general assessment possible
	Possible negative impacts due to unavailability of medicine / delay in treatment	Depends on the situation, no general assessment possible

Costs associated with the legal provisions

During the study, evidence has been collected on costs borne by the stakeholders directly affected by the provisions under Articles 23a and 81, namely the NCAs, MAHs and wholesalers/distributors. The evidence is predominantly based on the results from the surveys and interviews.

As shown by the analysis of shortages, **NCAs** record sometimes several shortage notifications per week. For instance, the 19 Member States for which data are available together registered over 10,000 shortage notifications during 2019, which means an average of 10 notifications per Member State each week. Although the notification process is predominantly an electronic process, the NCAs incur costs in relation to the notification, and other provisions. Surveyed NCAs identified the following types of costs associated with the provisions:

- the costs of developing and maintaining the notification system
- the costs associated with registration of the notifications
- the costs associated with enforcement of the notification requirements
- the costs associated with enforcement of supply obligations

No information is available on the development and maintenance of the IT-infrastructure that is used for the notification. This is less of a problem, though, as the costs of this infrastructure are largely a onetime investment and are not likely to be dependent on the number of notifications.

For the other activities the following type of costs are identified:

- costs of staff involved in verification and enforcement of the shortage notification system
- costs of staff involved in monitoring and enforcing of the public service obligation

Based on the survey results, the average number of staff involved in these two activities together amounts to slightly over 7 full time equivalents per Member State. This would imply that annual costs of direct staff involved in application of these provisions could be around EUR 13 million for the whole EEA, or on average EUR 0.5 million per Member State. If related to the number of shortages reported in 2019, the costs amount to on average EUR 1,600 per notified shortage per Member State. These staff numbers are understood to cover directly involved staff only. In this respect the above costs is likely to be an underestimation of the annual costs related to the provisions.

The legal provisions affect MAHs and wholesalers in two ways:

- the obligation to notify NCAs of expected shortages requires notification actions
- the obligation to ensure continued and appropriate supply may impose additional costs

The costs to **MAHs** resulting from the obligation to notify shortages relate to the time spent by staff responsible for notification. According to surveyed industry sources, those costs depend on the number of countries in which the company is active, the notification period (the longer the period, the higher the process costs) and the number of times a notification needs to be registered. Based on data from one company, it is assessed the average cost is around EUR 300 per notification of a shortage with a particular NCA. Another cost related to the notification obligation are the penalties that may be applied if companies do not comply with the obligation. Such penalties differ by Member State. Industry estimates vary from EUR 10,000 to more than EUR 800,000 per incident.

If the obligation to supply is operationalised with a stock obligation on the MAH or wholesale distributor, this may result in additional stocks being kept. The additional costs of stocks are estimated by industry to be EUR 150,000 per stock keeping unit (SKU) per month but will vary substantially depending on product needs and shelf-life.

Additional provisions that involve export restrictions do not directly impose costs on industry. Indirectly export restrictions may affect industry, as these restrictions limit the possibility to generate revenues (and subsequently profits) of the manufacturers / distributors. However, as such costs are not directly connected to the EU legal framework, they are excluded from the analysis.

The evidence collected during the study suggests that both NCA's and manufacturers / distributors are faced with costs as a result of the provisions following from Articles 23a and 81 and any additional national provisions (Table 41).

Table 40 Cost elements considered in efficiency analysis of the EU legal framework

Stakeholder group	Type of measure	Type of costs	Estimates	Sources
National competent authorities	**Notification obligations (Art 23a)**	Development and maintenance of notification system (fixed, largely independent of number of notifications)	None available	--
		Time spent on verification of notifications and enforcement of notification requirements	Estimated at EUR 800 in staff costs per shortage notification. Approx. EUR 0.5 million (7 full time equivalents) per year per Member State	Interviews, survey, focus groups
	Supply obligations (Art. 81)	Time spent on monitoring and enforcing supply obligations		
MAH and wholesalers	**Notification obligations (Art 23a)**	Time spent on notification; fees associated with notification; possible penalties for breach of obligation	Approx. EUR 300 per notification per Member State (n=1 MAH). Penalties for non-compliance differ by Member State.	Interviews, survey, solution panel consultation
	Supply obligations (Art. 81)	(Increased) stock holding; possible penalties for breach of obligation	Approx. EUR 150,000 per stock keeping unit per month when PSO applies	Survey

F.3 Benefits of shortages avoided and mitigated

Medicine shortages result in additional costs to society. When a shortage can be avoided, the associated costs are also avoided. Thus, generally speaking, the benefits of measures that reduce shortages consist of "avoided costs of shortages". This section describes the effects for each of these groups of stakeholders per avoided medicine shortage.

NCAs have transposed the provisions in national regulations. In many cases, this transposition is accompanied by various obligations of pharmaceutical companies and/or wholesale distributors. The NCAs, in turn, have an obligation to collect and analyse data, and to enforce the provisions. The costs of the NCAs are therefore to a large extent related to setting up a reporting system for all medicine shortages that may arise. The marginal costs for an individual shortage could be limited. As a proxy for the incremental costs, 50% of the average operating costs per shortage related to registration and enforcement for NCAs is taken. The incremental costs savings per avoided shortage are thus calculated at EUR 800 per year for a Member State.

To **manufacturers**, the primary benefit of avoided shortages is the ability to continue deriving revenue from the sales of the medicines. Additionally, the avoidance of a shortage situation means that the MAH may forego the costs associated with the notification of shortages (provided that the shortage was avoided before the point where a notification needed to be made).

Health care professionals spend on average 4 hours per week in dealing with shortages. This involves time needed for the search of an alternative and patient care. These time costs can be saved in case a medicine shortage is prevented. Mirroring the estimated costs of dealing with shortages, the benefit of avoided shortages can be estimated at around EUR 25,000 per shortage avoided per Member State per year.

For **patients** the impact of an avoided shortage will differ case by case. In cases where an appropriate alternative medicine is readily available, the impact may be limited to avoiding that a potentially a higher price has to be paid for the substitute medicine but this will differ by product and no data are available to estimate an average impact.

For the 40-50% of cases in which an alternative is not readily available, the impact depends on the type of effects that otherwise might have occurred for the patient as a result of the delay in treatment. Such effects can theoretically range from relatively minor impact on the patient, to a very serious impact in case the non-availability of a medicine would have resulted in avoidable death. Also the size of this effect, which potentially is quite large, could not be established. Likewise, patients may have to invest their own time to obtain their preferred medicine or an appropriate alternative

from another pharmacy or to get another consult with their physician to discuss alternative treatment options. No estimates are available on the average time or resources spent by patients on dealing with medicine shortages.

Based on the above, the following estimates of benefits (costs avoided and/or other benefits) are made for an average marginal medicine shortage per Member State:

- For pharmacists: EUR 25,000 per medicine
- For patients: price difference between cost of preferred and substitute medicine[273]; preserved quality of treatment; avoided time and resources from having to manage shortage of their preferred medicine
- For NCAs: EUR 800 euro per notification
- For industry: EUR 300 euro per notification

Apart from the impact for patients, average marginal benefit of avoiding one shortage in terms of staff costs is thus calculated at EUR 26,000 per shortage notification per Member State, most of which is related to the time spent by pharmacists in dealing with shortages.

On top of that there is a potentially large impact for patients. This relates to a potential delay in treatment for those patients that need a medicine for which a shortage cannot be solved within a few months. The exact impact of this patients cannot be estimated, as it is dependent on the type of medicine, the type of illness and the number of patients being affected by the temporary unavailability of the medicine. However, given the size of the staff cost impacts described above and the possible health impact of a delay in treatment, the impact for patients is likely to be substantially larger than the impact on staff costs of health care professionals, pharmaceutical companies and NCAs together, as outlined above.

[273] Limited to the proportion of the price that is covered by the patient, either in the form of co-payment or under their insurance deductible. The remaining difference is paid for by the health system or insurer.

Annex G. LITERATURE FINDINGS ON DEFINING AND REPORTING SHORTAGES

Definitions of shortages in use

Table 41 Definitions of shortages used internationally

Source	Definition	Supply vs demand	Duration	Criticality
WHO	On the supply side: a "shortage" occurs when the supply of medicines, health products or vaccines identified as essential by the health system is considered to be insufficient to meet public health and patient needs. This definition refers only to products that have already been approved and marketed, in order to avoid conflicts with research and development agendas. On the demand side: a "shortage" will occur when demand exceeds supply at any point in the supply chain and may ultimately create a "stockout" at the point of appropriate service delivery to the patient if the cause of the shortage cannot be resolved in a timely manner relative to the clinical needs of the patient.			
EMA	A shortage of a medicinal product for human or veterinary use occurs when supply does not meet demand at a national level.			
EFPIA	A shortage happens if supply of critical and essential medicines does not meet patient demand for a period longer than 2 weeks			
FDA	A period when the demand or projected demand for a medicine within the United States exceeds the supply of the medicine			

Source: Green indicates inclusion of the aspect in the definition; red indicates the element is not explicitly included.

Table 42 Definitions of shortages used in EU Member States

Source	Definition	Supply vs demand	Duration	Criticality
Belgium	Medicine that is temporarily unavailable or for which the commercialisation is interrupted or stopped			
Estonia	Medicines that are not available due to difficulties in the supply or distribution.			
France	The inability for a community or hospital pharmacy to deliver a medicine to a patient within 72 hours			
Germany	A delivery bottleneck is an interruption of delivery to the usual extent that is likely to last more than 2 weeks or a significantly increased demand that cannot be adequately met.			
Greece	Deficiencies, reduced availability, delivery disruptions.			
Italy	All manufacturing-related shortages including also those caused by MAH voluntary withdrawal (temporary or permanent); unavailability of a medicinal product in a specific geographical area due to inefficiencies of the pharmaceutical distribution chain			
Ireland	When the supply of a medicinal product is inadequate to meet the needs of the patient.			
Slovenia	Market situation where the business entities responsible for supplying the market of the Republic of Slovenia fail to provide the necessary quantities of the medicinal product within the appropriate time.		*	
Spain	A supply problem is a situation in which the available units of a medicine in the pharmaceutical channel are less than the national or local consumption needs.			
Sweden	A medicine is called residual when a pharmaceutical company fails to deliver it for a period.		*	

Green indicates inclusion of the aspect in the definition; red indicates the element is not explicitly included. * = mentioned only in general terms, but not detailed

Table 43 National registers to notify shortages as of April 2020

Country	In place	Obligation	Managed by	Reports from	Medicines covered	Reporting time-lines
Austria	Yes	Obligatory (since April 2020; before: voluntary), no sanctions	Medicines Agency	MAH	POM	At least 2 months in advance if known; "immediately" for unforeseen shortages
Albania	No	*Not appl.*	*Not appl.*	*Not appl.*	*Not appl.*	*Not appl.*
Bulgaria	No	*Not appl.*	*Not appl.*	*Not appl.*	*Not appl.*	*Not appl.*
Canada	Yes	Obligatory, sanctions possible	Medicines Agency	MAH	POM and NPM administered under practitioner's supervision	6 months in advance, if known or within 5 days of becoming aware
Cyprus	Yes	Obligatory, no sanctions (but their introduction is being discussed)	MoH and Health Insurance Organisation	Local distributors	Reimbursed POM	"Immediately"
Czech Republic	Yes	Obligatory, sanctions possible	Medicines Agency	MAH	Any medicine	At least 3 months in advance
Denmark	Yes	Obligatory, sanctions possible	Medicines Agency	MAH	Any medicine if shortage is expected to influence the treatment of patients	At least 2 months in advance
Finland	Yes	Obligatory, no sanctions (but their introduction is being discussed)	Medicines Agency	MAH	Any medicine	2 months in advance
Germany	Yes	Obligatory (since April 2020; earlier: voluntary), sanctions possible	Medicines Agency	MAH, wholesalers	POM that are relevant or critical for supply	Existing or upcoming shortage (no timeline defined)
Israel	Yes	Obligatory, sanctions possible	MoH	MAH	Any medicine	3 or 6 months in advance (unless "immediately" in case of immediate shortage)
Italy	Yes	Obligatory, sanctions possible	Medicines Agency	MAH	Any medicine	At least 4 months in advance except for unpredictable circumstances[a]
Latvia	Yes	Obligatory, sanctions possible	Medicines Agency	MAH, wholesalers[b]	Any medicine	2 months in advance
Lithuania	Yes	Obligatory	Medicines Agency	MAH	Any medicine	"Immediately", in some cases at least 3 months in advance
Malta	Yes	Voluntary	Medicines Agency	MAH	Any medicine	As soon as possible, but at least 2 months in advance
Moldova	No	*Not appl.*	*Not appl.*	*Not appl.*	*Not appl.*	*Not appl.*
Netherlands	Yes	Obligatory[c], sanctions possible	Medicines Agency	MAH	Any medicine	2 months in advance
Norway	Yes	Obligatory, no sanctions	Medicines Agency	MAH	Any medicine	As soon as possible, but at least 2 months in advance
Portugal	Yes	Obligatory, sanctions possible in cases of non-reporting or delayed reporting without justification	Medicines Agency	MAH	Any medicine	2 months in advance
Romania	Yes	Obligatory, sanctions possible	Medicines Agency	MAH	Any medicine	Apart from exceptional cases, at least 6 months (and 12 months for commercial reasons)
Russia	No	*Not appl.*	*Not appl.*	*Not appl.*	*Not appl.*	*Not appl.*
Slovenia	Yes	Obligatory, sanctions possible	Medicines Agency	MAH	Any medicine	At least 2 months in advance
Sweden	Yes	Obligatory, no sanctions	Medicines Agency	MAH	POM	At least 3 months in advance
Switzerland	Yes	Obligatory[c], no sanctions	Medicines Agency[c]	MAH	Defined essential medicines, including vaccines	5 days in advance for a shortage of a defined medicine to last for more than 14 days
UK	Yes	Obligatory (since January 2010), sanctions possible	Department of Health	MAH	Any health service (i.e. reimbursed) medicine	At least 6 months in advance (or at least, as soon as the MAH becomes aware)

MAH = marketing authorisation holders, not appl. = not applicable, NPM = non-prescription medicines, POM = prescription-only medicines.
[a]Legal change in 2019: timeline of reporting was changed from 2 to 4 months in advance.
[b]Anyone can report to the register but MAH are obliged to do so; wholesalers have to report about their stock on a daily basis.
[c]In addition, voluntary registers are run by the Dutch Pharmacy Association (in the Netherlands) as well as a hospital pharmacy in Basel and a private consultancy firm (in Switzerland). Any medicine can be reported to the voluntary registers.

Source: Vogler S. Fischer S. (2020) How to address medicines shortages: Findings from a cross-sectional study of 24 countries. Health Policy 124(12):1287-1296. DOI: 10.1016/j.healthpol.2020.09.001

Table 44 Consistency in reporting medicine shortages in the EU/EEA

Country	Legislation exists	Policy exists	Mechanism exists	Data are exported
Austria	No	Yes	Yes	Yes
Belgium	Yes	Yes	Yes	Yes
Croatia	No	No	Yes	Yes
Cyprus	Yes	Yes	Yes	Yes
Czechia	No	Yes	Yes	Yes
Denmark	Yes	Yes	Yes	No*
Estonia	Yes	Yes	Yes	Yes
Finland	Yes	Yes	Yes	No
Germany	Yes	Yes	Yes	Yes
Greece	Yes	Yes	Yes	Yes
Hungary	Yes	Yes	Yes	Yes
Iceland	Yes	No	Yes	No*
Ireland	Yes	Yes	Yes	Yes
Latvia	Yes	Yes	Yes	Yes
Lithuania	Yes	Yes	No	Yes
Luxembourg	Yes	No	No	No
Malta	Yes	Yes	Yes	Yes
Norway	Yes	No	No	Yes
Portugal	No	Yes	Yes	No
Romania	No	Yes	Yes	No
Slovenia	Yes	Yes	Yes	Yes
Spain	Yes	Yes	Yes	Yes
Sweden	Yes	Yes	Yes	Yes

Source: WHO Regional Office for Europe. (2020) Assessing the magnitude and nature of shortages of essential medicines and vaccines: focus on the WHO European Region. * Countries may have reporting systems but not provide public reports.

Annex H. SURVEY RESULTS

G.1 NCAs

Table 45 What type of organisation do you represent? Please indicate the option that (best) matches the organisation you represent?

Category	Respondents (n)
National medicines agency	16
National health system	1
Other	1

Table 46 What country do you represent?

Country	Respondents (n)
Germany	3
Belgium	2
Slovenia	2
Austria	1
Denmark	1
Estonia	1
Finland	1
Iceland	1
Ireland	1
Latvia	1
Netherlands	1
Portugal	1
Spain	1
Sweden	1

Figure 20 What definition of a medicine shortage is used in your country?

Definition	Responses (%)	Countries
EMA	10 (56%)	Denmark, Estonia, Finland, Germany (PEI)[274], Iceland, Latvia, Slovenia (n=2), Spain, Sweden
National	8 (44%)	Austria, Belgium (n=2), Germany (BfArM, n=2), Ireland, the Netherlands, Portugal

[274] In the case of Germany, three answers were submitted, two from Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical devices, BfArM) and one from the Paul-Ehrlich Institut (PEI) which is the federal Institute for Vaccines and Biomedicines. For some questions the answers differ but typically have been jointly displayed as 'Germany'.

Figure 21 What elements do you consider to be necessary in the reporting of a medicine shortage?

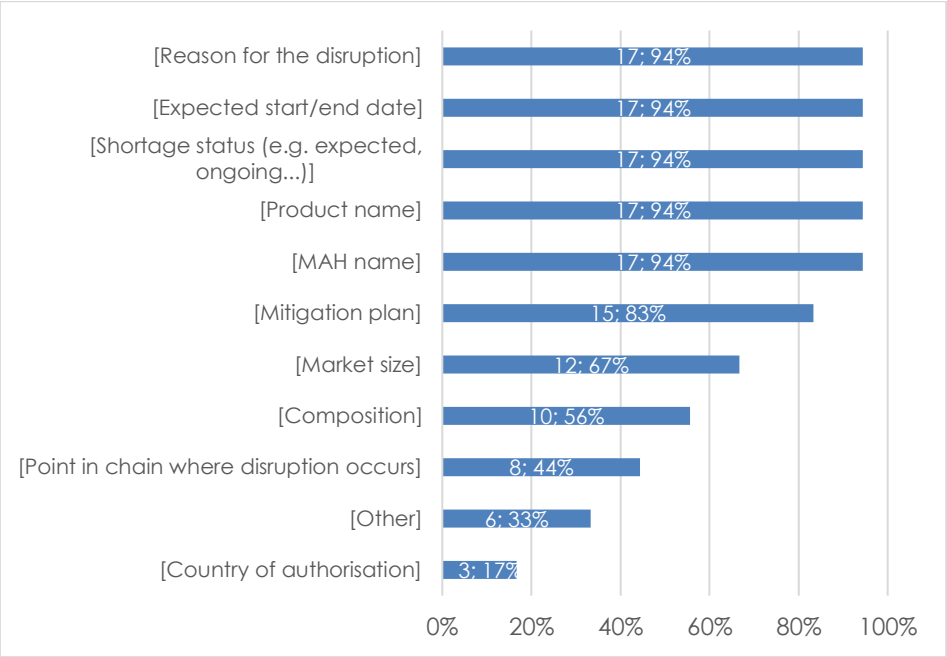
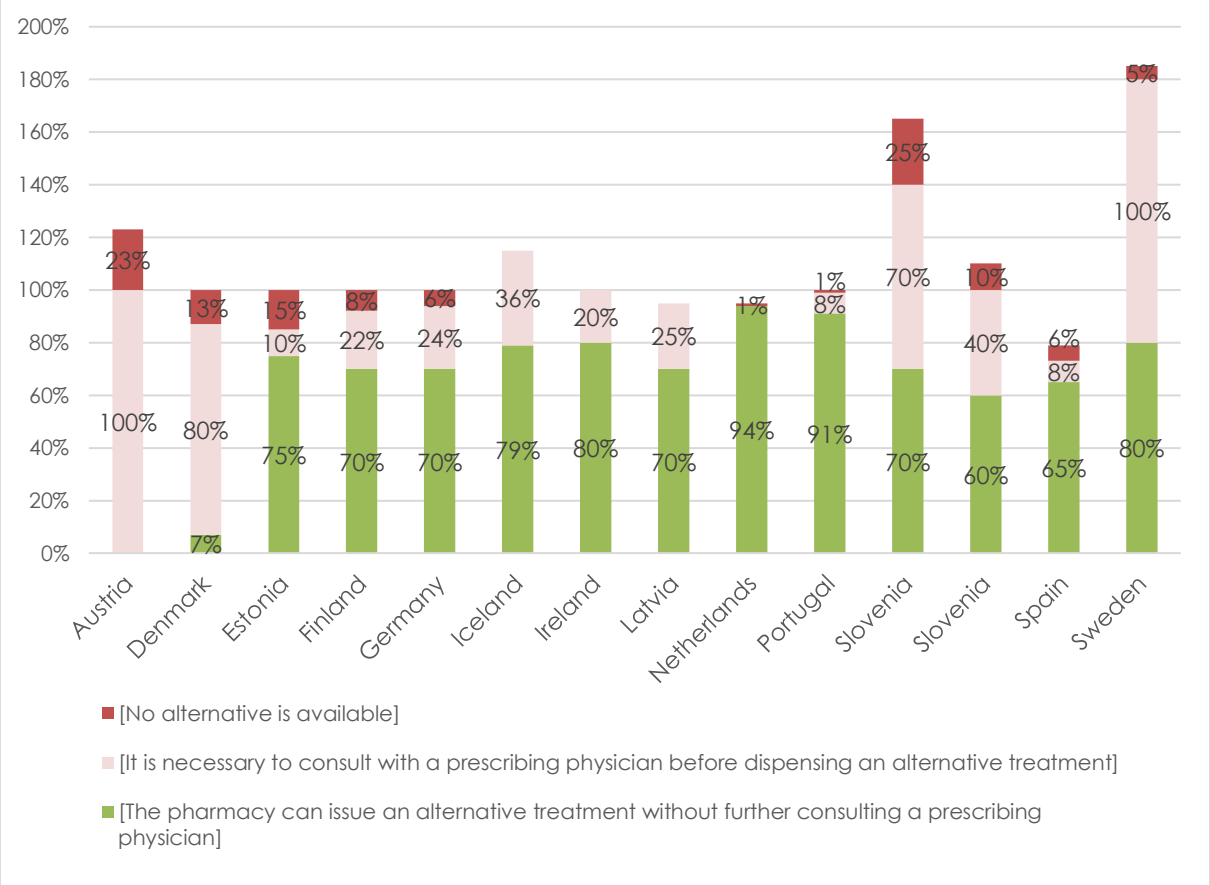


Figure 22 Can you estimate the proportion of the shortages in your country where (in percentages, the total being 100%):

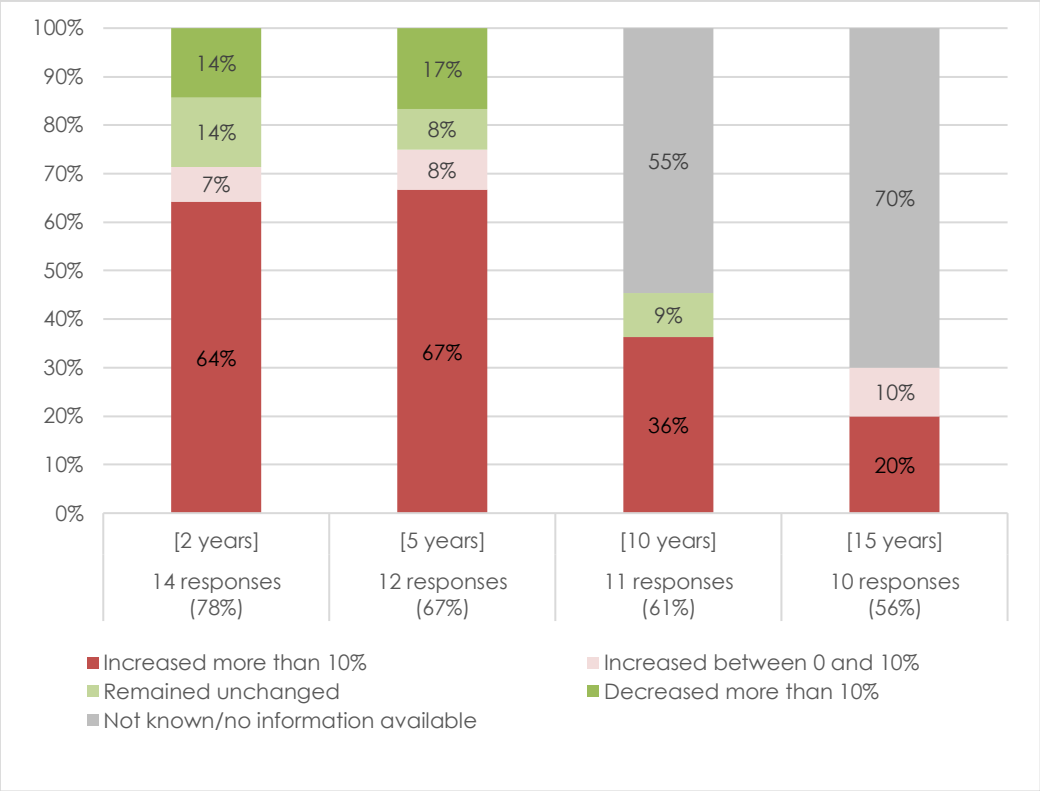


Note: the survey tool did not allow automatic limiting to 100%. Consequently, responses from Slovenia and Sweden were allowed to exceed 100%.

Figure 23 How has the frequency with which medicine shortages occur in your country changed in the past:[275]

Years	Increased by > 10%	Increased between 0 and 10%	Remained unchanged	Decreased	No information available
2	Austria, Denmark, Estonia, Finland, Germany, Iceland, Latvia, the Netherlands, Spain	Sweden	Ireland, Slovenia	Slovenia, Germany	-
5	Austria, Denmark, Estonia, Finland, Germany, Netherlands, Spain, Sweden	Latvia	Slovenia	Germany, Slovenia	-
10	Austria, Finland, Spain, Sweden	-	Latvia	-	Denmark, Estonia, the Netherlands, Portugal, Slovenia
15 by >	Finland, Spain	Sweden	-	-	Austria, Denmark, Estonia, the Netherlands, Portugal, Slovenia

Figure 24 How has the frequency with which medicine shortages occur in your country changed in the past:



[275] For Germany and Slovenia, it is unknown why different respondents from the same country provided different answers to this question, nor which answers are most accurate.

Figure 25 What proportion (in %) of all medicine shortages is typically resolved (supply of shortages medicine is meeting national demand again / suitable alternative proposed to patients) in days?[276]

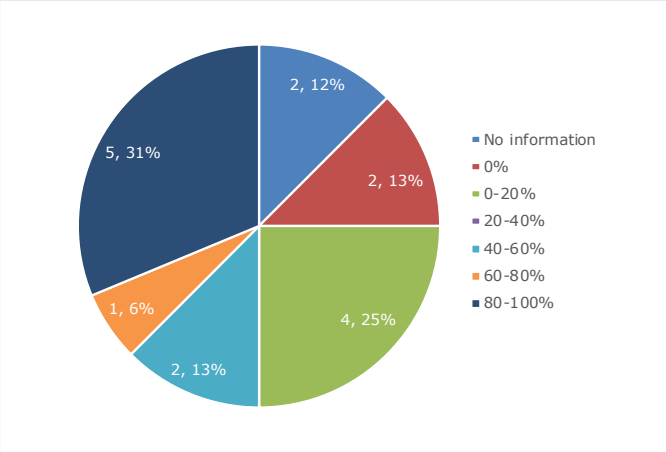
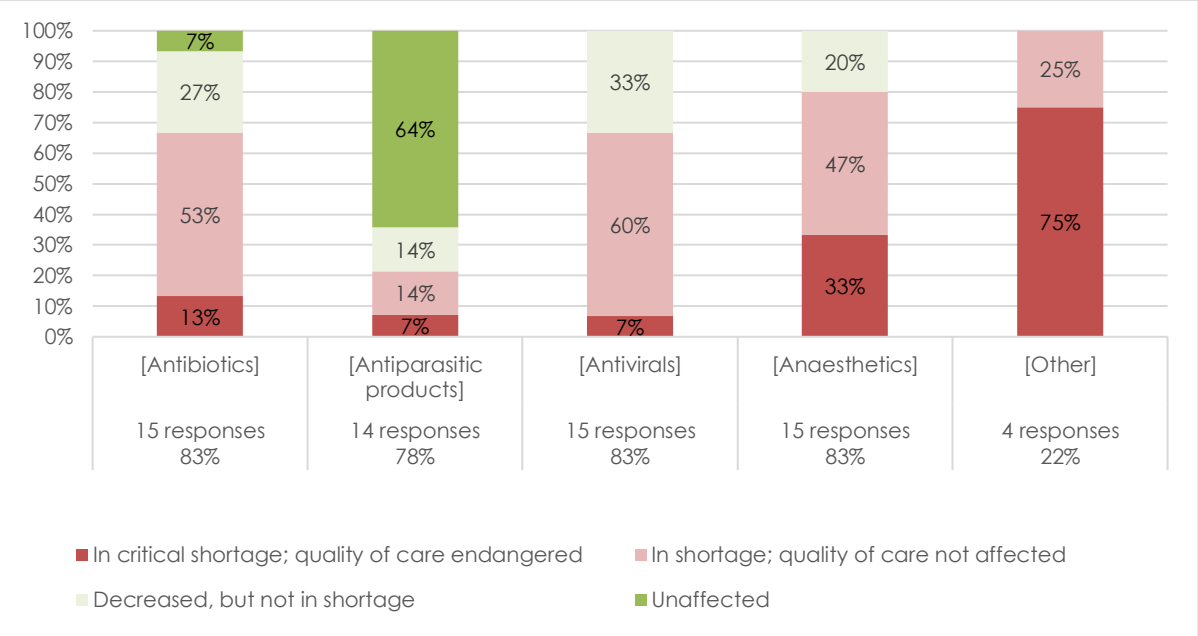


Figure 26 To what extent has the COVID-19 pandemic thus far impacted the national availability of the following types of medicines due to a surge in demand (not taking into account potential future impacts)?[277]



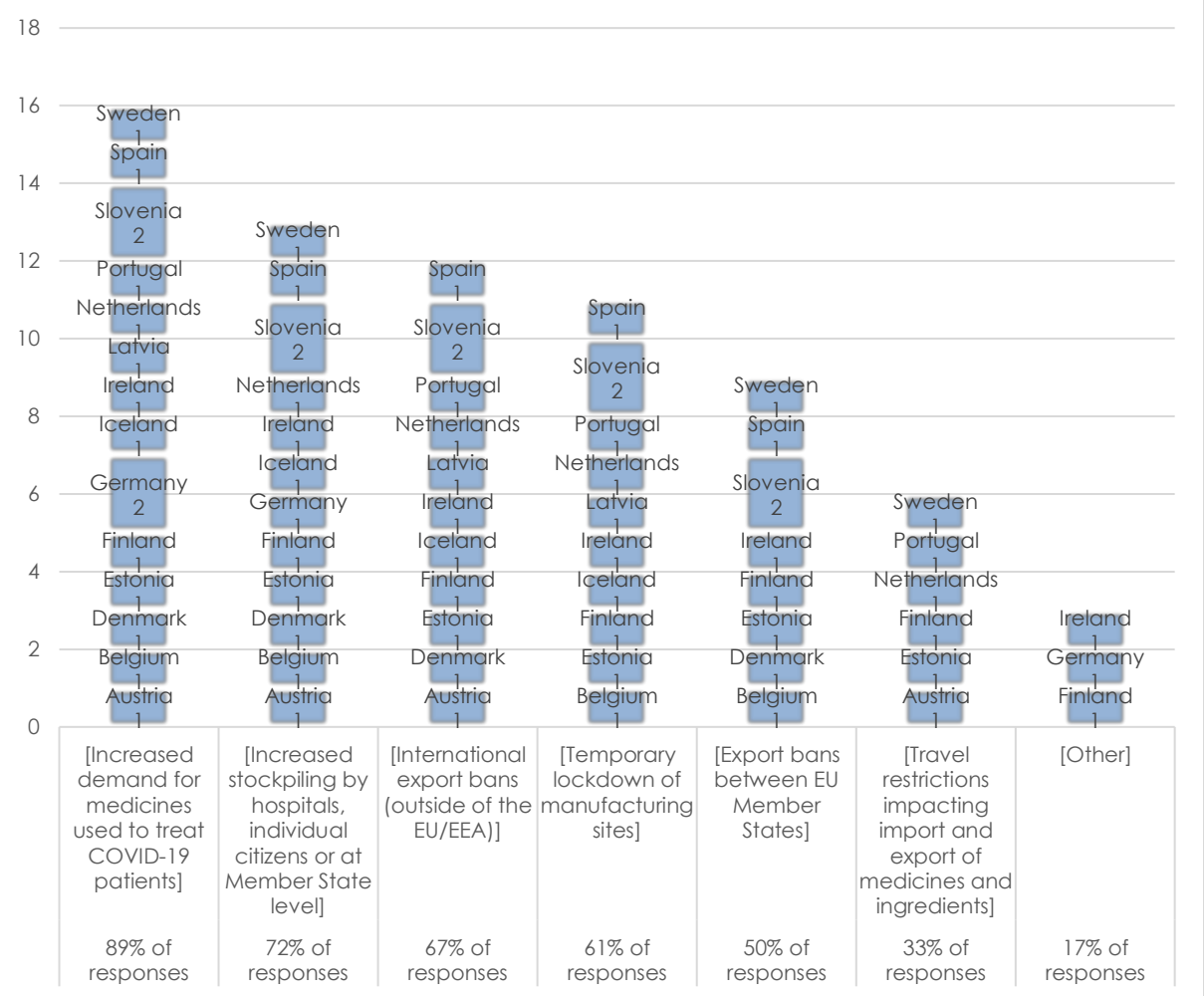
[276] This question was originally formulated as "What proportion (in %) of all medicine shortages is typically resolved (supply of shortages medicine is meeting national demand again / suitable alternative proposed to patients) in days, weeks, months or years?" However, respondents interpreted the choices as either cumulative (if a shortage is resolved in days, it is also resolved in years) or mutually exclusive (a shortage is either resolved in days, weeks, months or years) making the results for "weeks", "months" and "years" unexploitable for our analysis.

[277] The 4 respondents that selected "Other" mentioned the following medicines: vaccines (specifically Pneumococcal vaccines and Influenza vaccines), neuromuscular blockers and sedatives, PPI, opioid antagonists and muscle relaxants.

Figure 27 To what extent has the COVID-19 pandemic thus far impacted the national availability of medicines due to factors other than a surge in demand?[278]

Change	Responding countries
Availability decreased more than 10%	Austria, Finland, Iceland, Slovenia
Availability decreased between 0 and 10%	Estonia, Germany, Ireland, Latvia, Portugal, Slovenia, Spain, Sweden
Remained unchanged	Belgium, Denmark, Germany, the Netherlands

Figure 28 Which of the following disruptions have affected the availability of medicines in your country as a result of the COVID-19 pandemic?



[278] As the COVID pandemic was still ongoing at the time this survey was conducted, the perception of its impact on availability could still vary between respondents.

Figure 29 Please select the 3 most common causes of medicine shortages observed in your country in the past 5 years

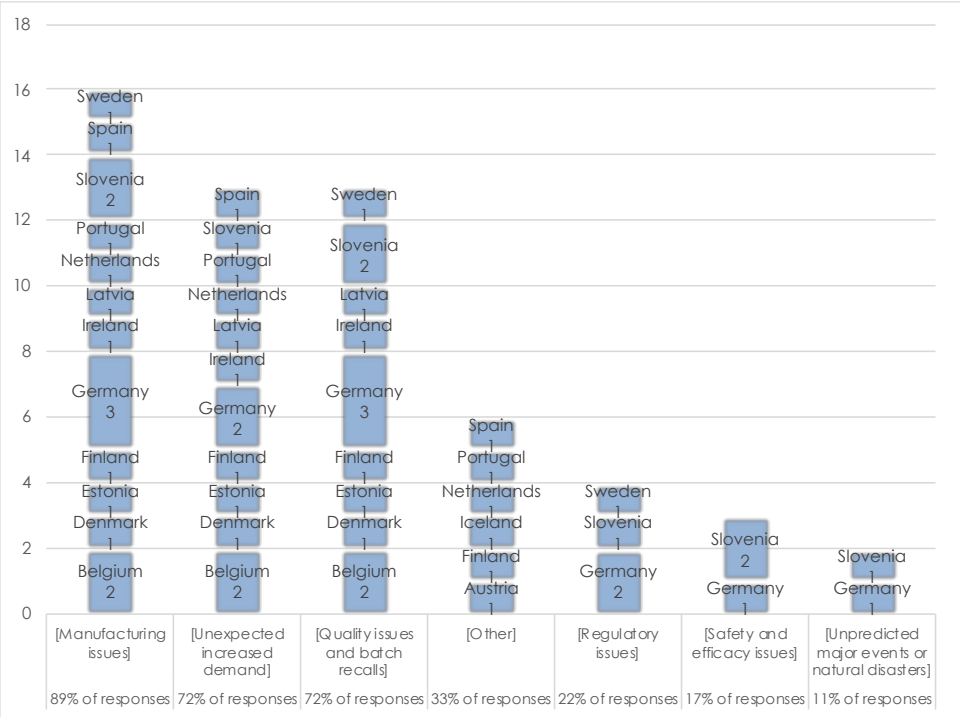


Figure 30 To what extent are shortages in your country influenced by external shocks and international trends?

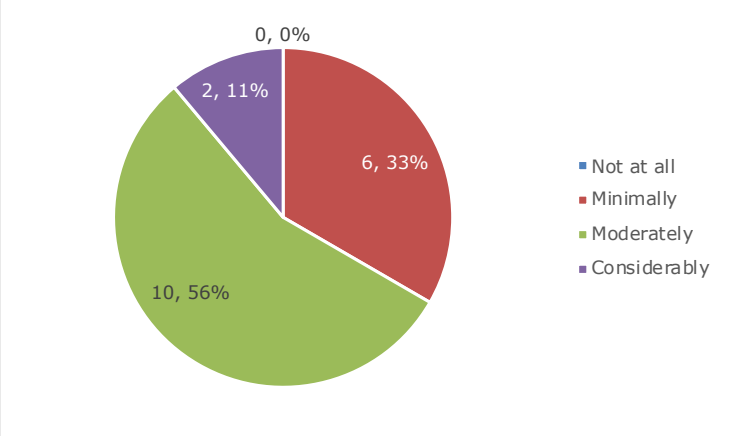


Figure 31 When was a system for shortage reporting first introduced in your country?[279]

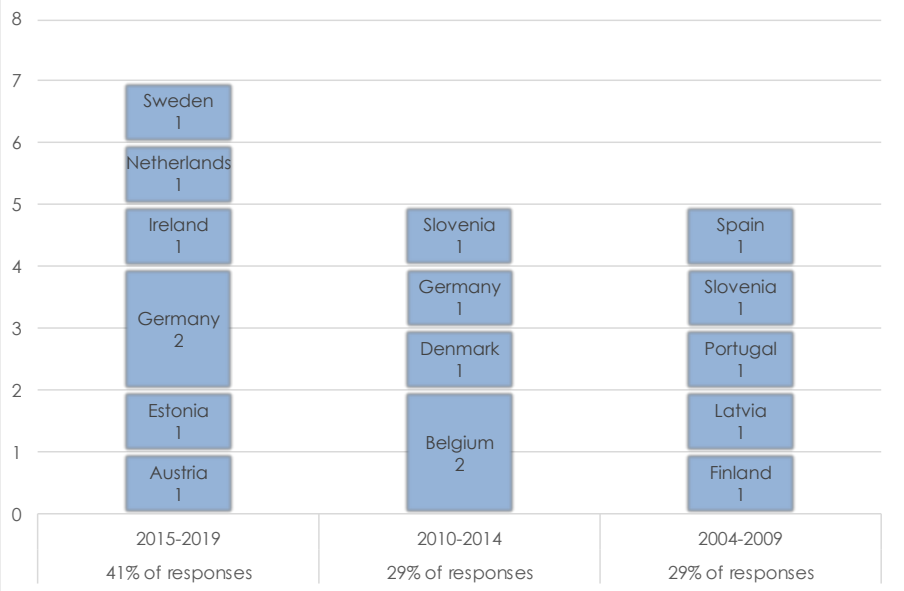


Figure 32 Do you list root causes in your reporting system?

Answer	Countries
Yes, according to own definitions	Belgium, Denmark, Germany, Ireland, the Netherlands, Portugal
Yes, in line with SPOC definitions	Finland, Germany, Spain
No	Austria, Estonia, Latvia, Slovenia, Sweden

[279] The incoherence between answers from Germany may be explained by the fact that, while the reporting system monitoring medical shortages was introduced in 2010-2014, compulsory monitoring by pharmaceutical companies only became mandatory in 2015-2019.

Figure 33 At what moment in time are shortages required to be reported in your country?[280]

Moment	Responses	Countries
Prospectively (beforehand)	16 (94%)	Belgium, Denmark, Estonia, Finland, Germany, Iceland, Ireland, Latvia, the Netherlands, Portugal, Slovenia, Spain, Sweden
Instantly (at time of occurrence)	1 (6%)	Austria

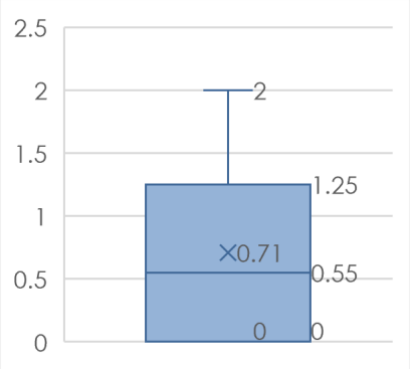
Figure 34 Please indicate the number of months in advance shortages are required to be reported in your country

Months	Responses	Countries
2	14 (88%)	Belgium, Denmark, Estonia, Finland, Iceland, Ireland, Latvia, the Netherlands, Portugal, Slovenia, Spain, Sweden
1	1 (6%)	Germany
0	1 6%)	Germany

Figure 35 At what moment are shortages effectively reported in your country?

Moment	Responses	Countries
Before occurrence	12 (67%)	Belgium, Denmark, Estonia, Finland, Germany, Iceland, Latvia, the Netherlands, Portugal, Spain, Sweden
At time of occurrence	14 (78%)	Austria, Denmark, Estonia, Finland, Germany, Iceland, Ireland, Latvia, Portugal, Slovenia, Spain, Sweden
After occurrence	5 (28%)	Estonia, Finland, Latvia, Spain, Sweden

Figure 36 Please indicate the number of months in advance shortages are effectively reported in your country (n=10)



[280] The answer for Austria does not match its legislation (Medicines Act, in Section 21(2)): "(2) The marketing authorisation holder or the holder of a registration of a traditional herbal or pharmacy proprietary medicinal product shall notify the Federal Office for Safety in Health Care of any temporary or permanent discontinuation of the marketing of the medicinal product in Austria. Unless there are special circumstances, this notification must be made at least two months before the cessation of marketing"

Figure 37 Who provides information and data on medicine shortages in your country to national authorities?

Country of respondent	MAH	Wholesalers	Manufacturer	Ministry of Health	Medicines agency	Pharmacy organisations	Other
Austria	1						
Belgium	2						
Denmark	1	1		1	1	1	1
Estonia	1	1					
Finland	1						
Germany	2			1			
Iceland	1						
Ireland	1	1		1	1	1	1
Latvia	1					1	1
The Netherlands	1						
Portugal	1						
Slovenia	2	2	2				
Spain	1					1	1
Sweden	1						

Figure 38 Who reports the cause of a medicine shortage in your country?

Country	MAH	Wholesaler-distributors	Manufacturer	Ministry of Health	Other
Austria	1				
Belgium	2				
Denmark	1				
Estonia	1				
Finland	1				
Germany	2			1	
Iceland	1				
Ireland	1	1			
Latvia	1				
Netherlands	1				
Portugal	1				
Slovenia	2	2	2		
Spain	1				

Sweden					1

Figure 39 Does your organisation have staff responsible for verifying and enforcing the timely notification of a shortage?

Answer	Countries
Yes	Austria, Belgium, Denmark, Estonia, Finland, Germany, Iceland, Ireland, Latvia, the Netherlands, Portugal, Spain, Sweden
No	Slovenia

Figure 40 Can you give an estimation of the number of staff involved in this (in full time equivalents)?

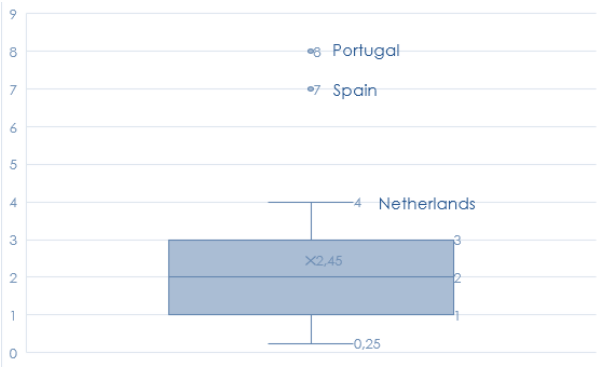


Figure 41 Does your organisation have staff responsible for monitoring/enforcing any public service obligation by MAHs or distributors?

Answer	Countries
Yes	Austria, Belgium, Estonia, Finland, Germany, Iceland, Ireland, Latvia, Portugal, Spain, Sweden
No	Denmark, the Netherlands, Slovenia

Figure 42 Can you give an estimation of the number of staff involved in this (in full time equivalents)

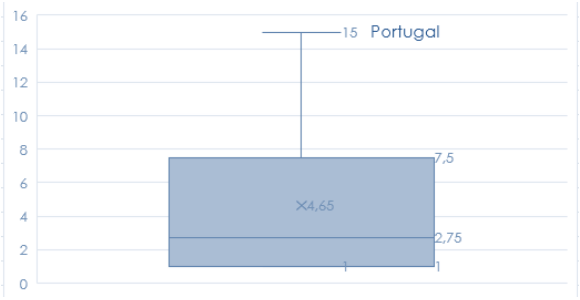
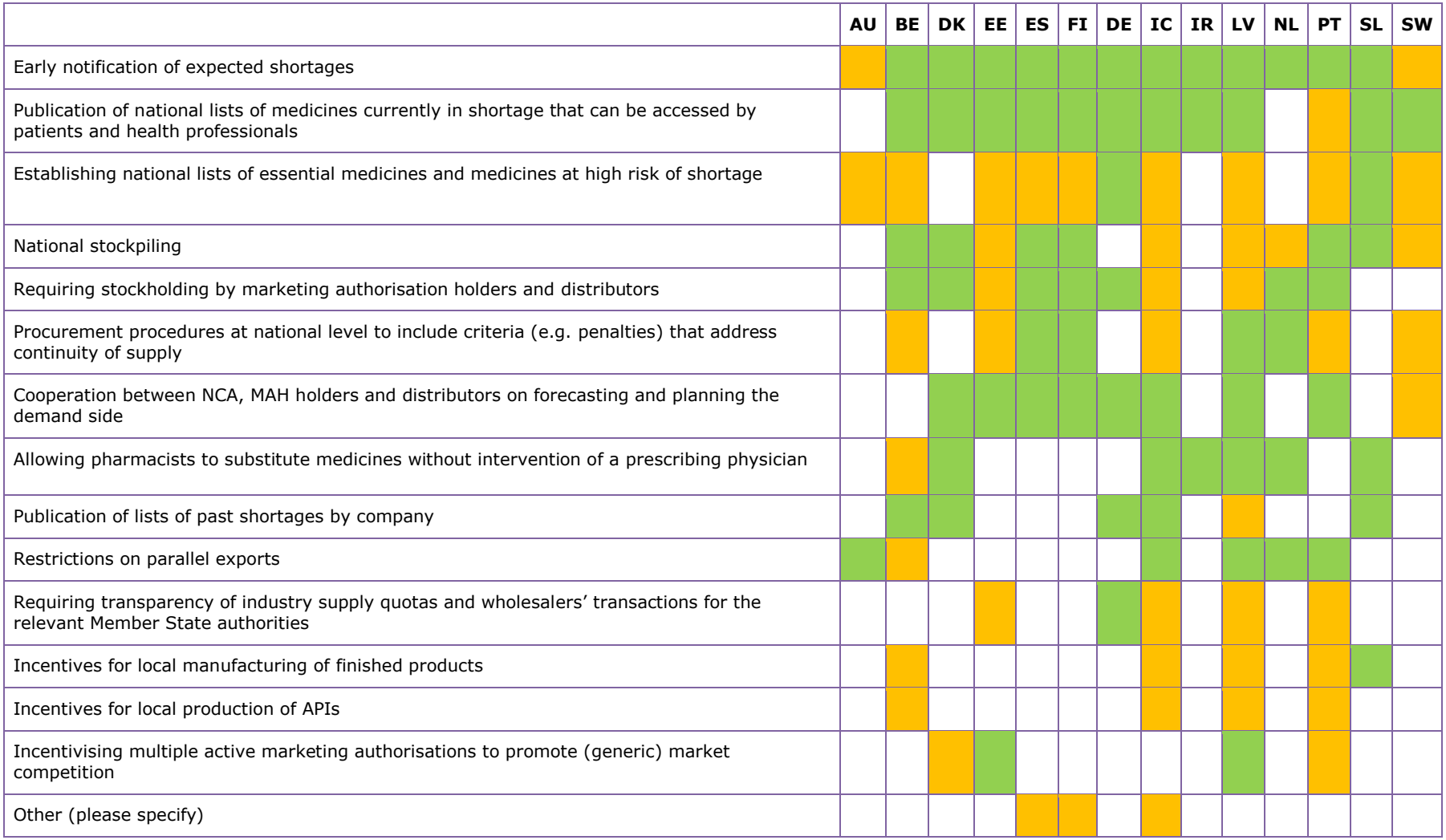


Figure 43 Please indicate which of the following measures have been implemented or are under consideration in your country:



Note: green = 100% of respondents from the same country selected the measure ; yellow = a portion of respondents from the same country, but not all, selected the measure

Figure 44 Which policies do you think would be relevant solutions to address medicine shortages at the EU/international level?

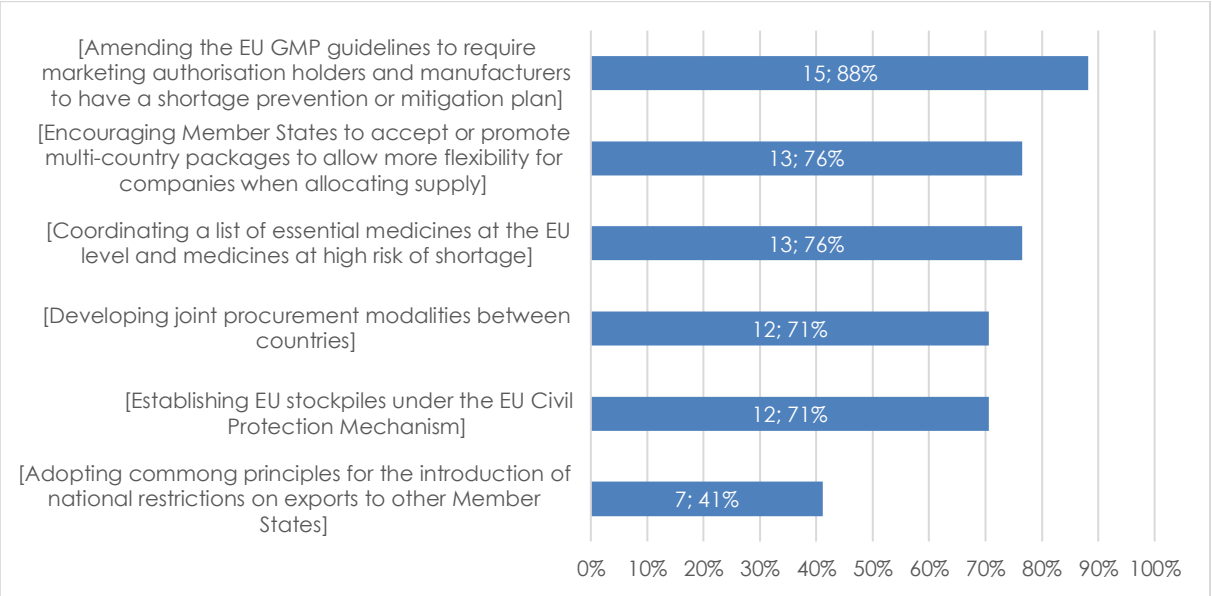


Figure 45 How effective have the measures implemented in your country been in reducing the frequency of shortages?

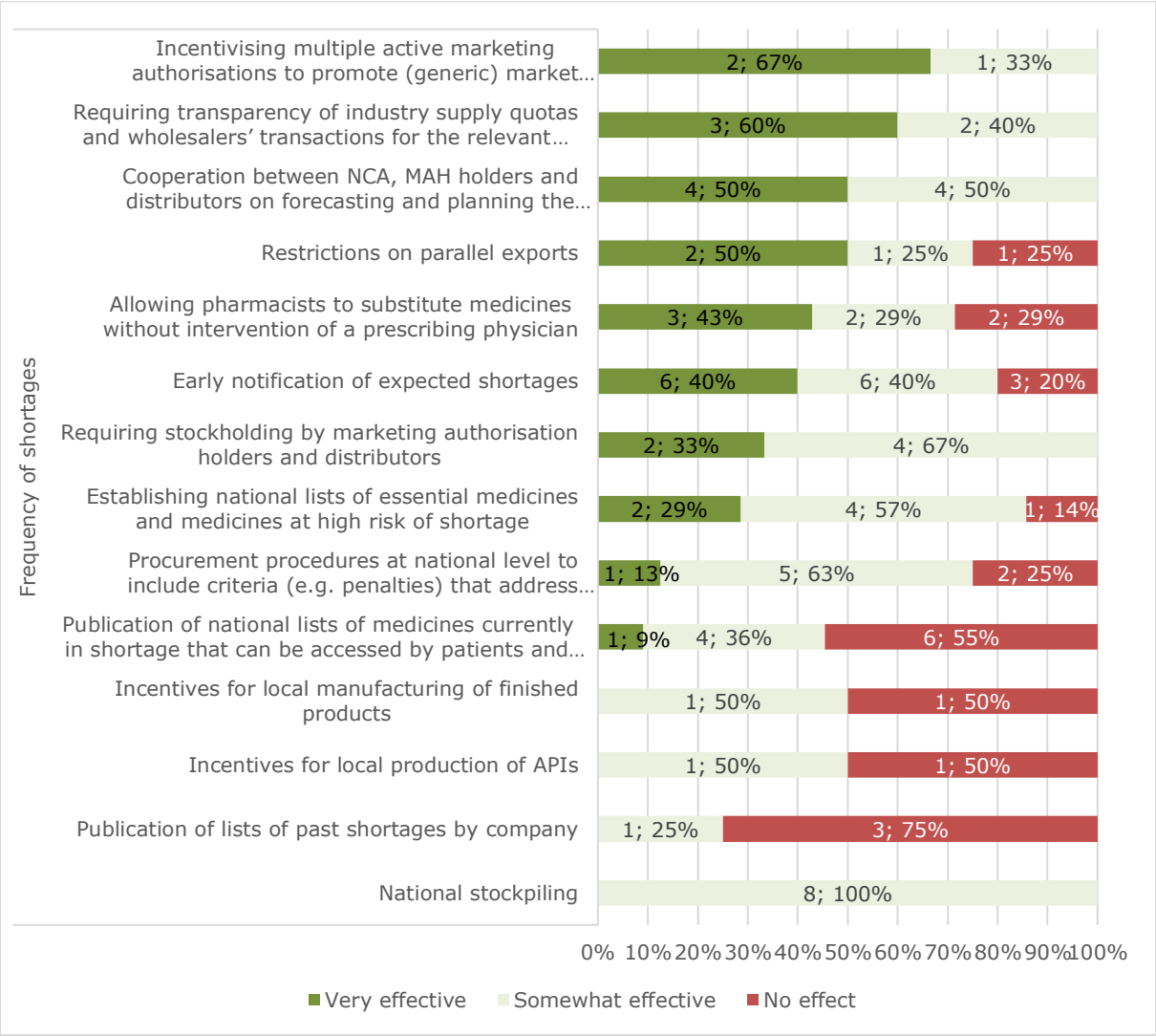


Figure 46 How effective have the measures implemented in your country been in reducing the duration of shortages:

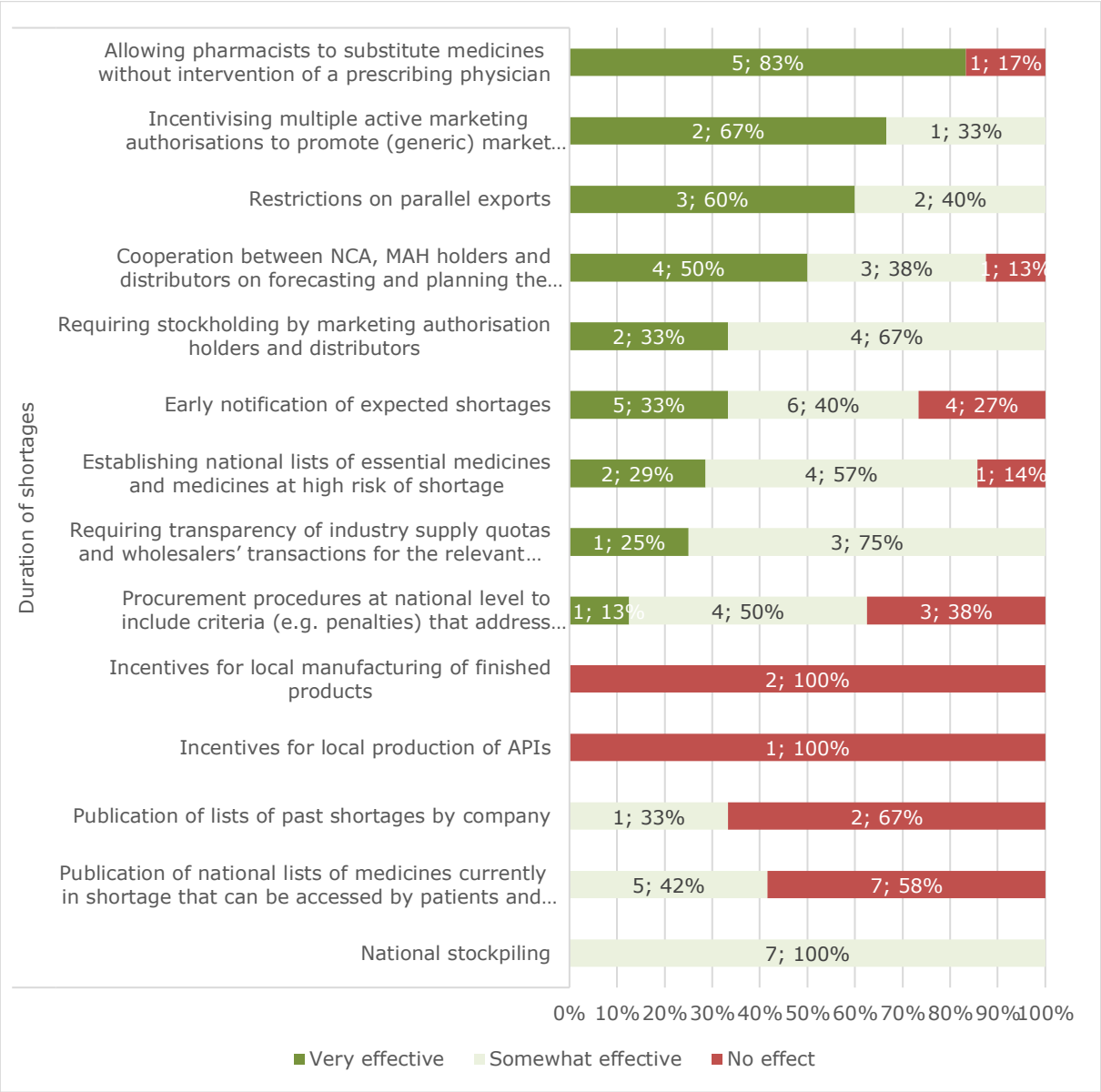
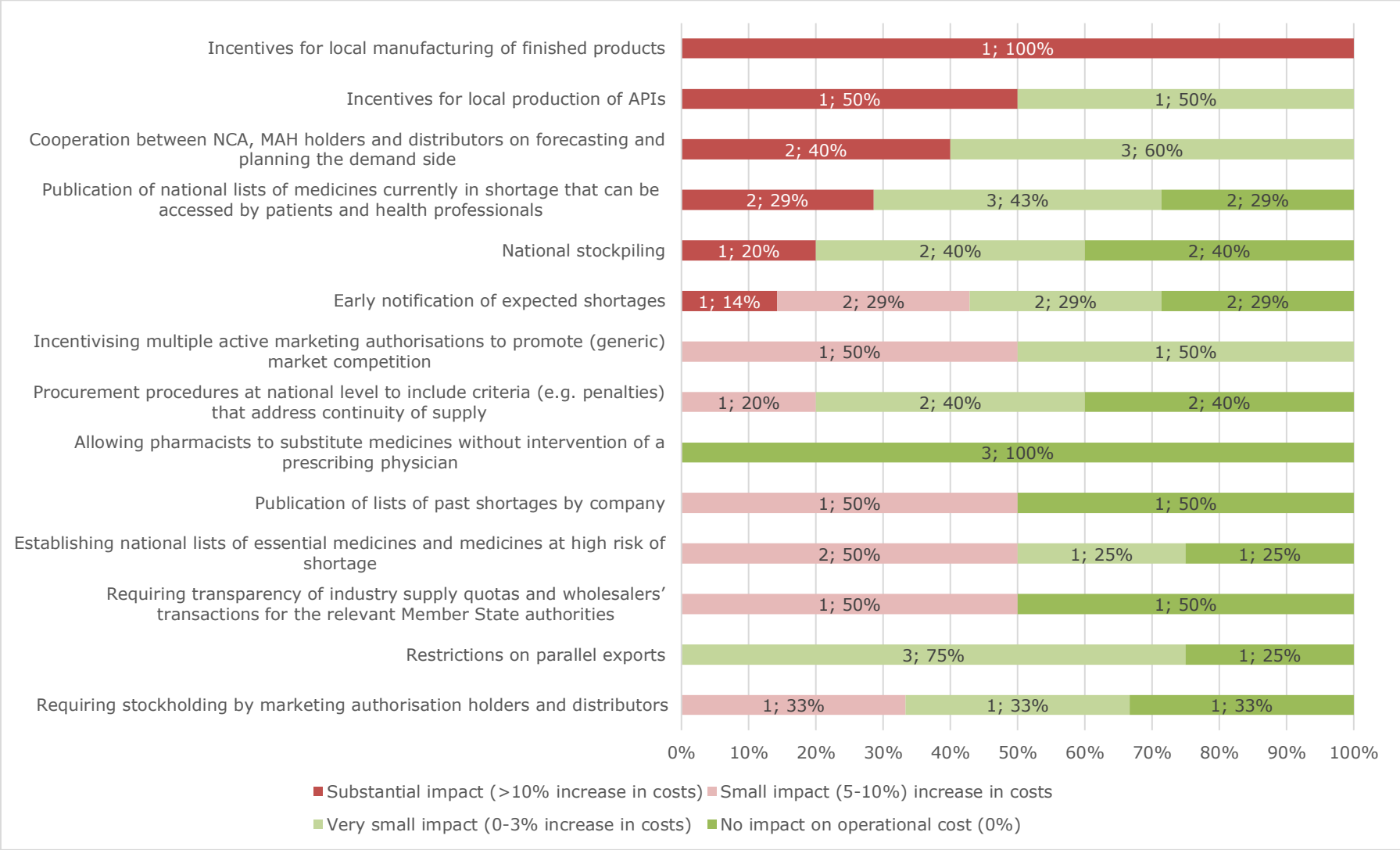


Figure 47 To what extent have the measures implemented in your country increased the operational costs (including compliance, monitoring, enforcement…) of the national authority?



G.2 Pharmacists and pharmacy organisations

Figure 48 What group of health professionals do you belong to/does your organisation represent?

Type	Respondents (n, %)
Retail pharmacist	23 (23%)
Hospital pharmacist	78 (77%)

Figure 49 In what country(ies) are you/is your organisation active?

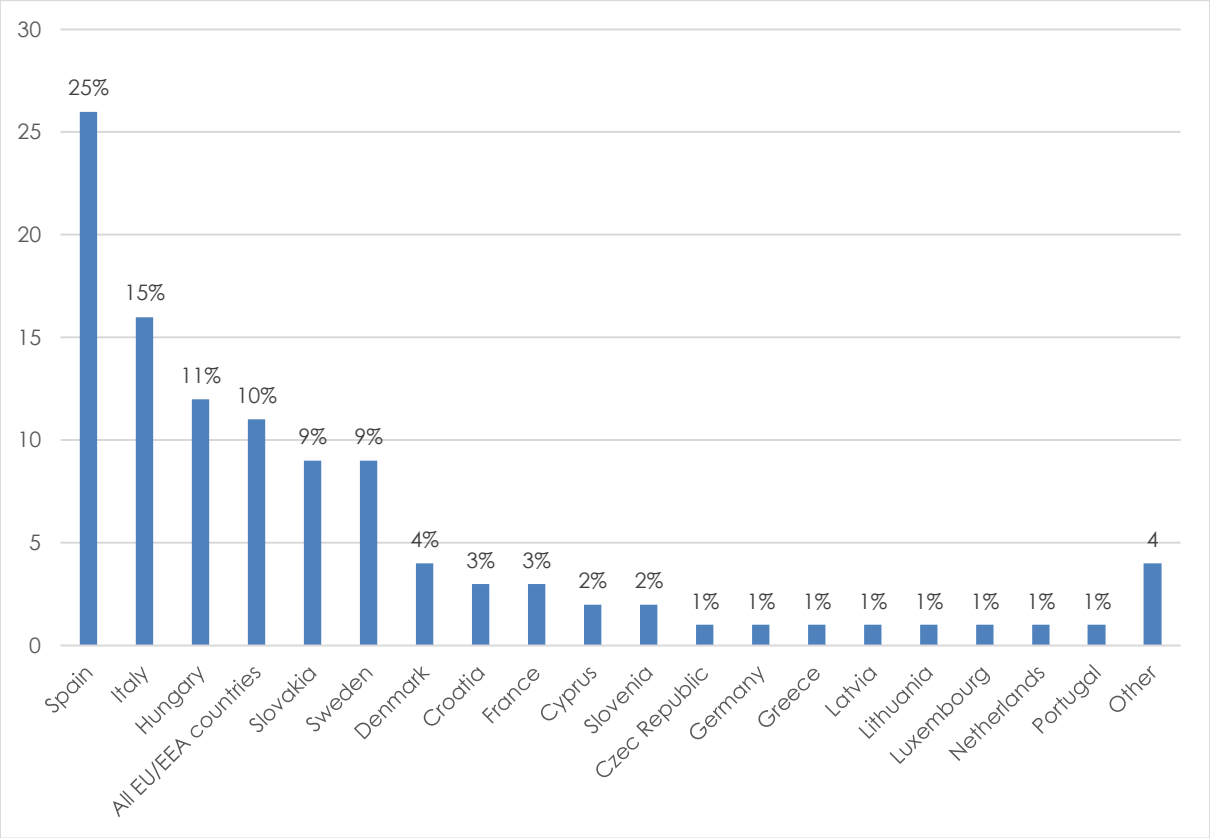


Figure 50 What definition of a medicine shortage is used in the country(ies) where you are/your organisation is active? EMA's definition: "A shortage of a medicinal product for human or veterinary use occurs when supply does not meet demand at a national level?

Definition	Respondents (%)
EMA	37 (55%)
No standard definition	15 (23%)
Other	15 (23%)

Figure 51 For the pharmacists using EMA's definition, in your opinion, is this definition adequate to identify medicine shortages?

Definition	Respondents (%)
Yes	30 (81%)
No	7 (19%)

Figure 52 What elements do you consider to be necessary in the reporting of a medicine shortage?(N=73)

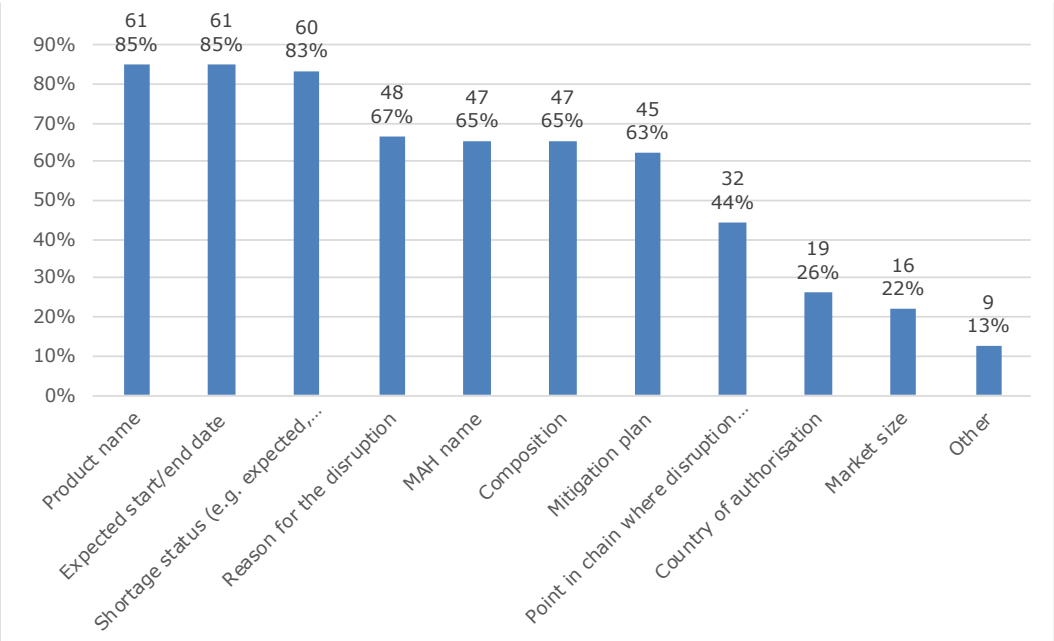


Figure 53 In what proportion of unfilled prescriptions is there an alternative treatment available (generic or therapeutic substitution)?

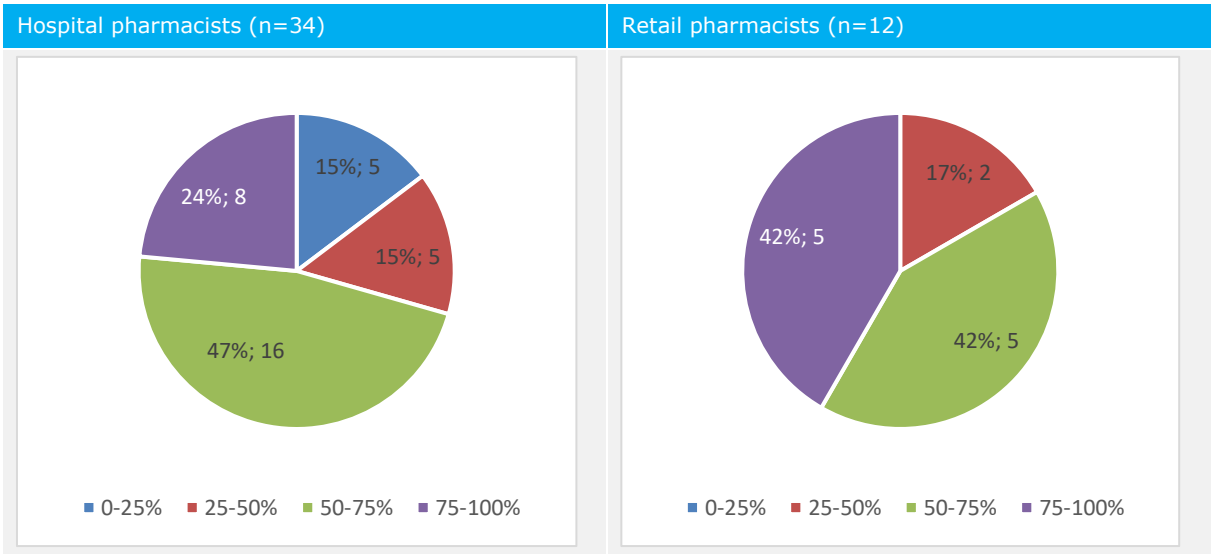


Figure 54 To what extent has the COVID-19 pandemic thus far impacted the national availability of the following types of medicines due to a surge in demand (not taking into account potential future impacts)? (n = 54)[281]

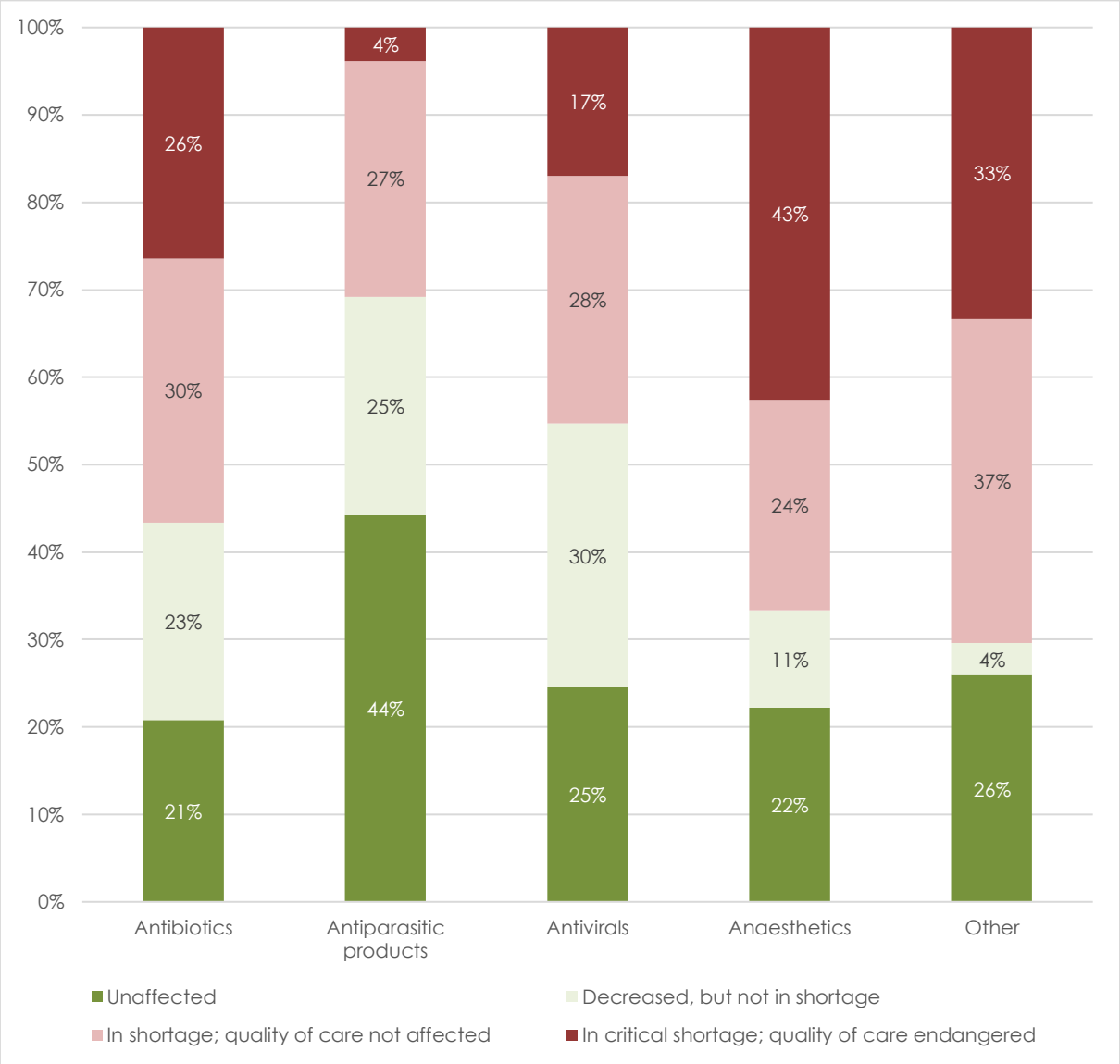


Figure 55 To what extent has the COVID-19 pandemic thus far impacted the national availability of medicines due to factors other than a surge in demand?

Impact on availability	Respondents (%)
Decreased > 10%	13 (23%)
Decreased 0-10%	15 (26%)
Remained unchanged	9 (16%)
Not known/no information available	20 (35%)

[281] The respondents that selected "Other" mentioned the following medicines: muscular relaxants, haemofiltration fluid, chlorhexidine, sterile water, anti-inflammatory, anticoagulants, oxygen, heparin, flu vaccines, asthma inhalers, tenders, paracetamol, steroids, benzodiazepine, opioids, and antipyretics.

Figure 56 On average, how much time per week do the health professionals from the group that you represent spend on managing shortages and the effects of such (e.g. finding alternative means of treatment and patient care): (as percentage by type of pharmacists)

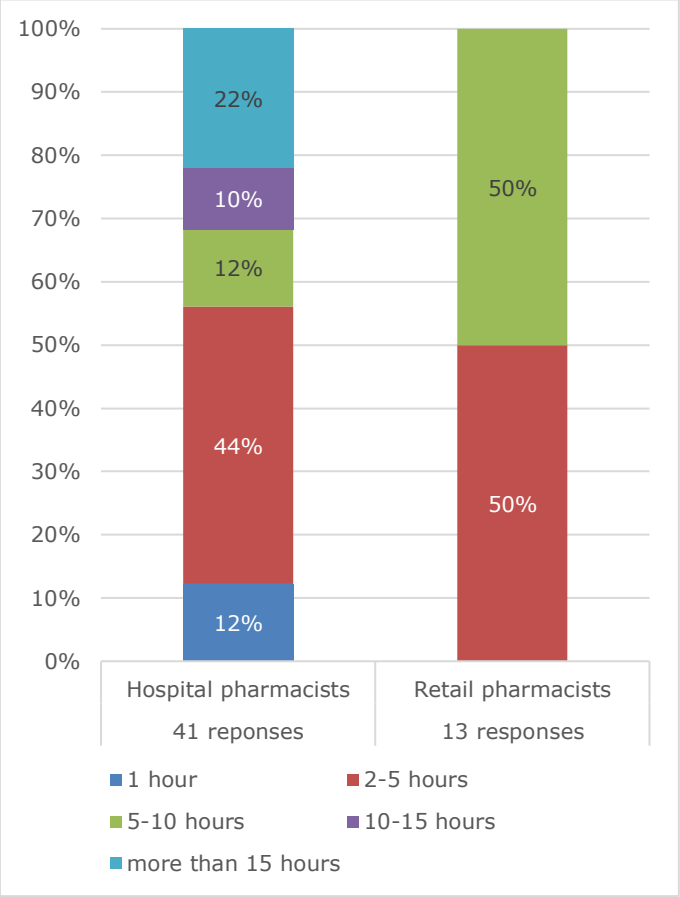


Figure 57 Please indicate which of the following financial consequences you/the health professionals that your organisation represents have experienced as a result of medicine shortages?

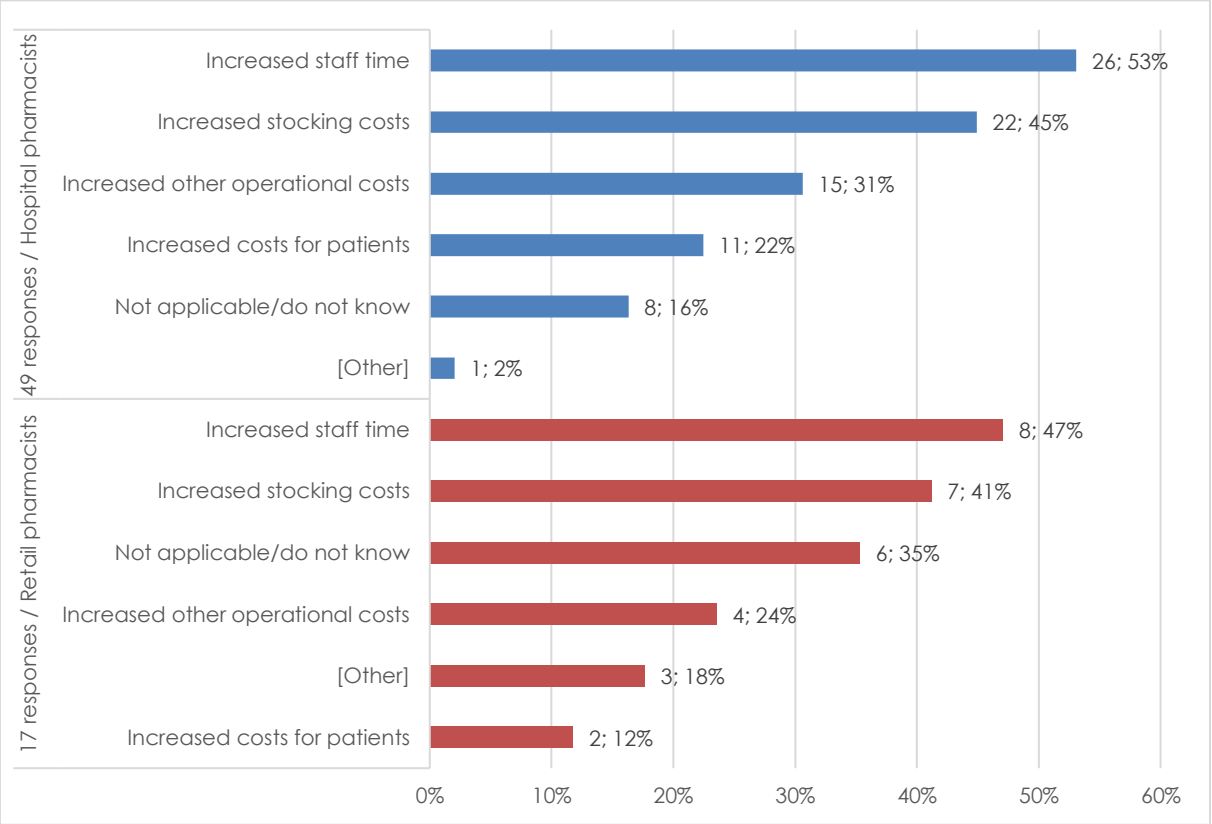


Figure 58 What was the extent of these financial consequences?

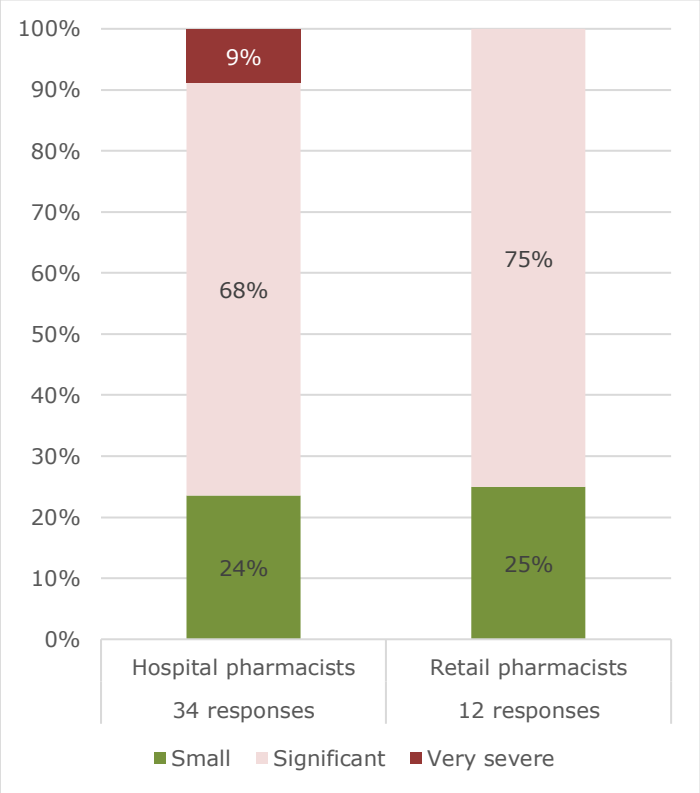
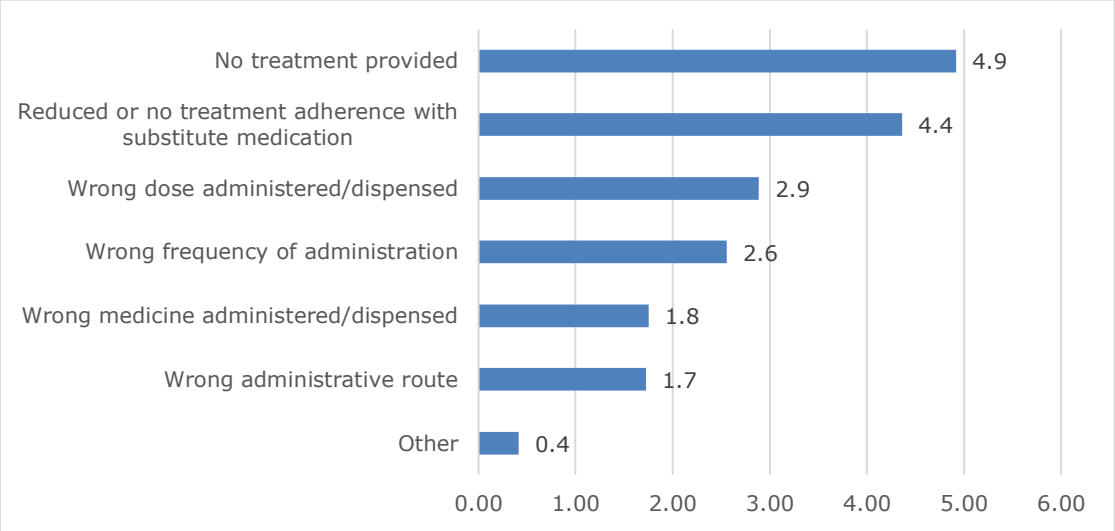


Figure 59 Please indicate if you are personally aware of any of the following consequences of a medicine shortage? Rank them according to their frequency (from most to least frequent)

Ranking score (7=1st rank; 0=not ranked)

Hospital pharmacists:



Retail pharmacists:

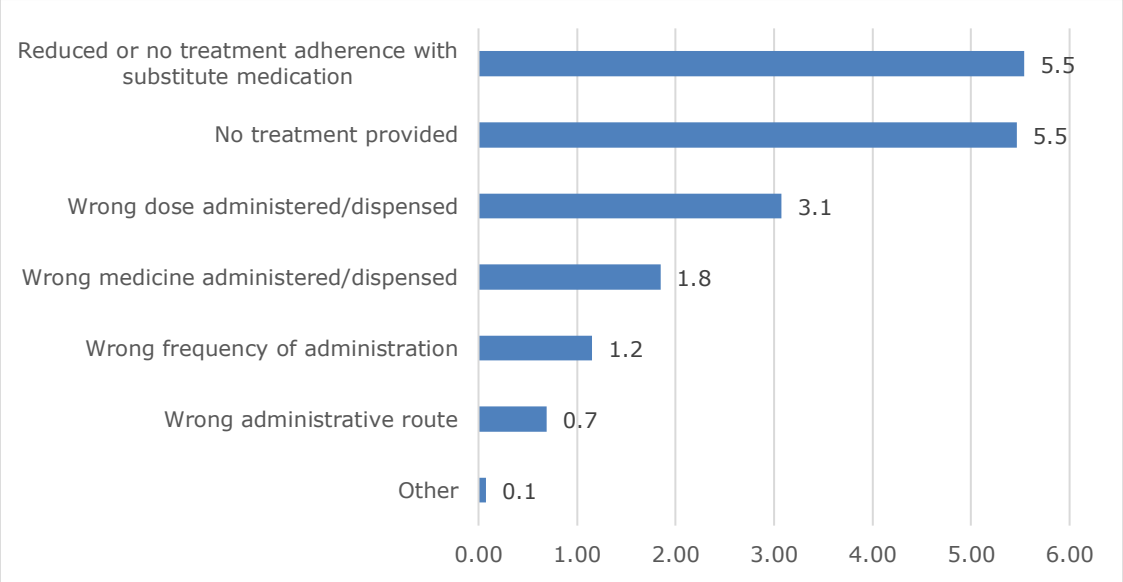
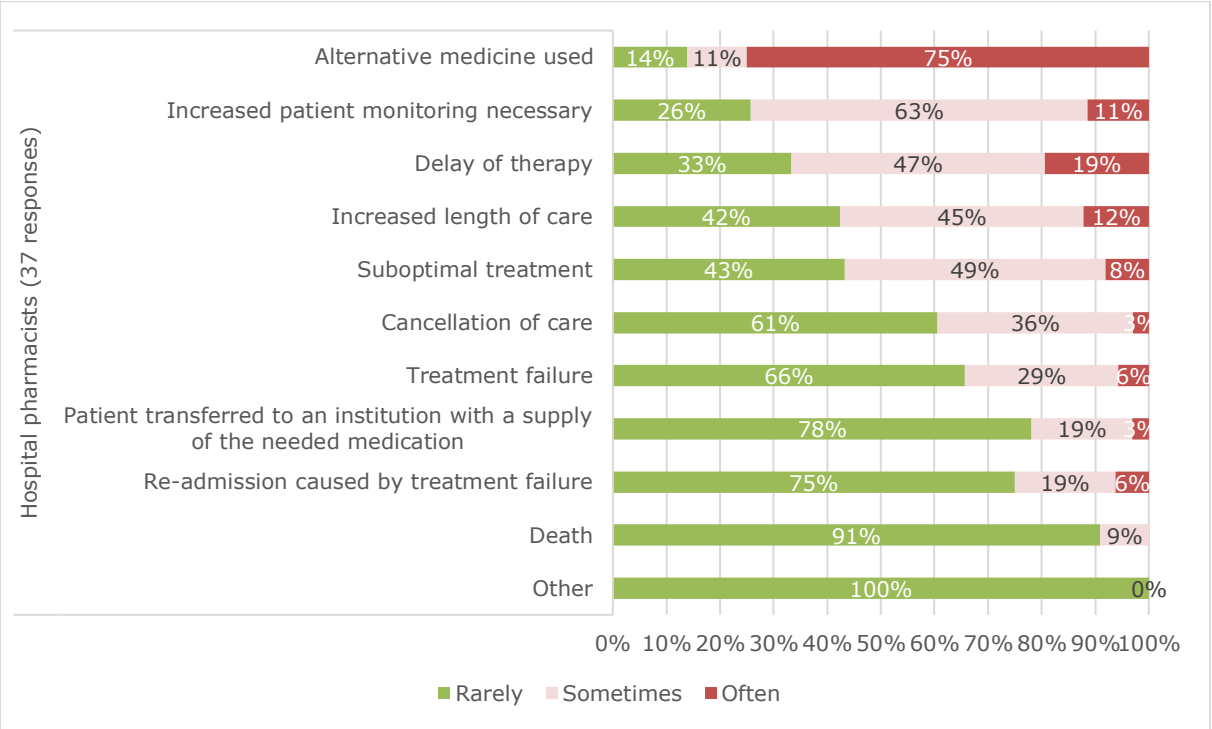


Figure 60 Please indicate how often the following patient outcomes occur as a consequence of a medicine shortage?



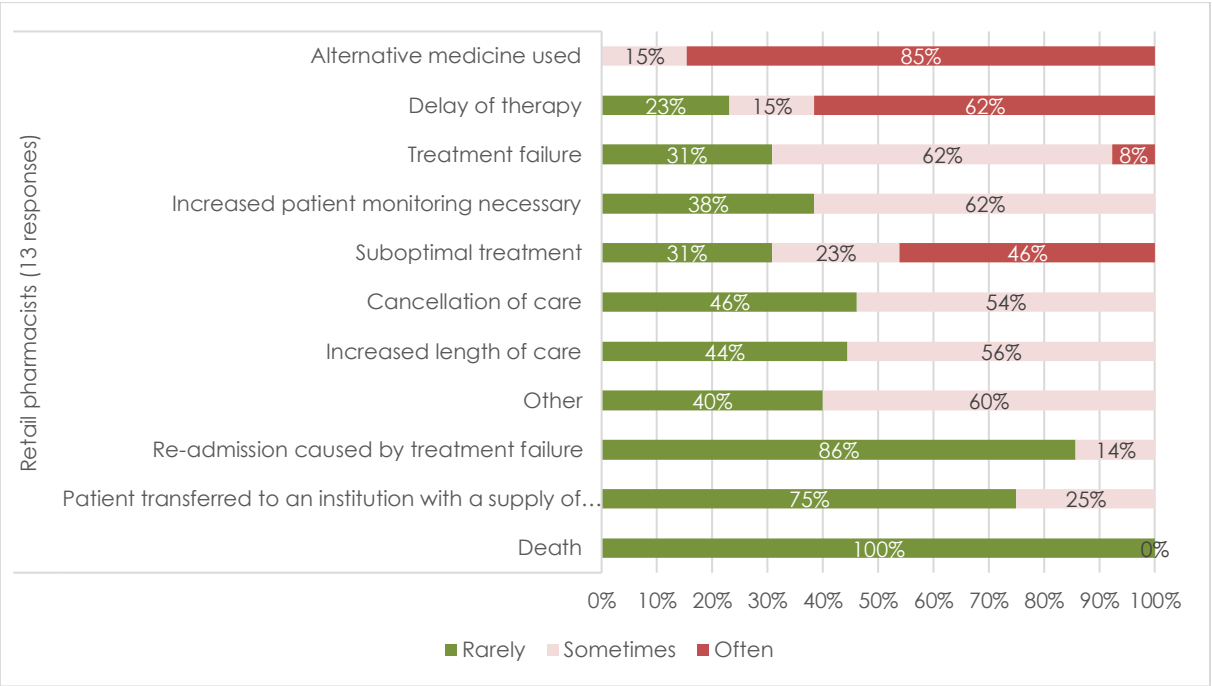


Figure 61 In the case of medicine shortages related to sudden changes in demand, what are the main causes of these demand-side changes?

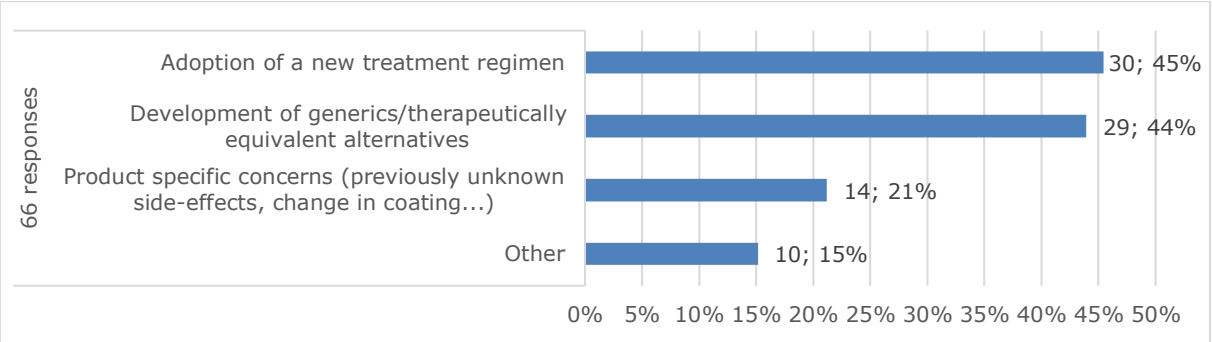


Figure 62 Does your country/countries of operation have a reporting system for shortages?

Country of operation	Yes	No
All EU/EEA	2	
Croatia	3	
Cypus	1	
Denmark	2	
Greece	1	
Hungary	5	1
Italy	5	
Latvia	1	
Luxembourg		1
The Netherlands	1	
Portugal	1	
Slovakia	3	3
Slovenia	1	1
Spain	8	2
Sweden	5	
Other	3	

Note: In countries were some respondents indicated 'yes' and others 'no', it is not known whether the difference is caused by the respondents belonging to different groups (hospital vs retail pharmacists) or because of different levels of awareness about existing systems.

Figure 63 To whom can healthcare professionals turn for professional advice and information how to deal with a medicine shortage?

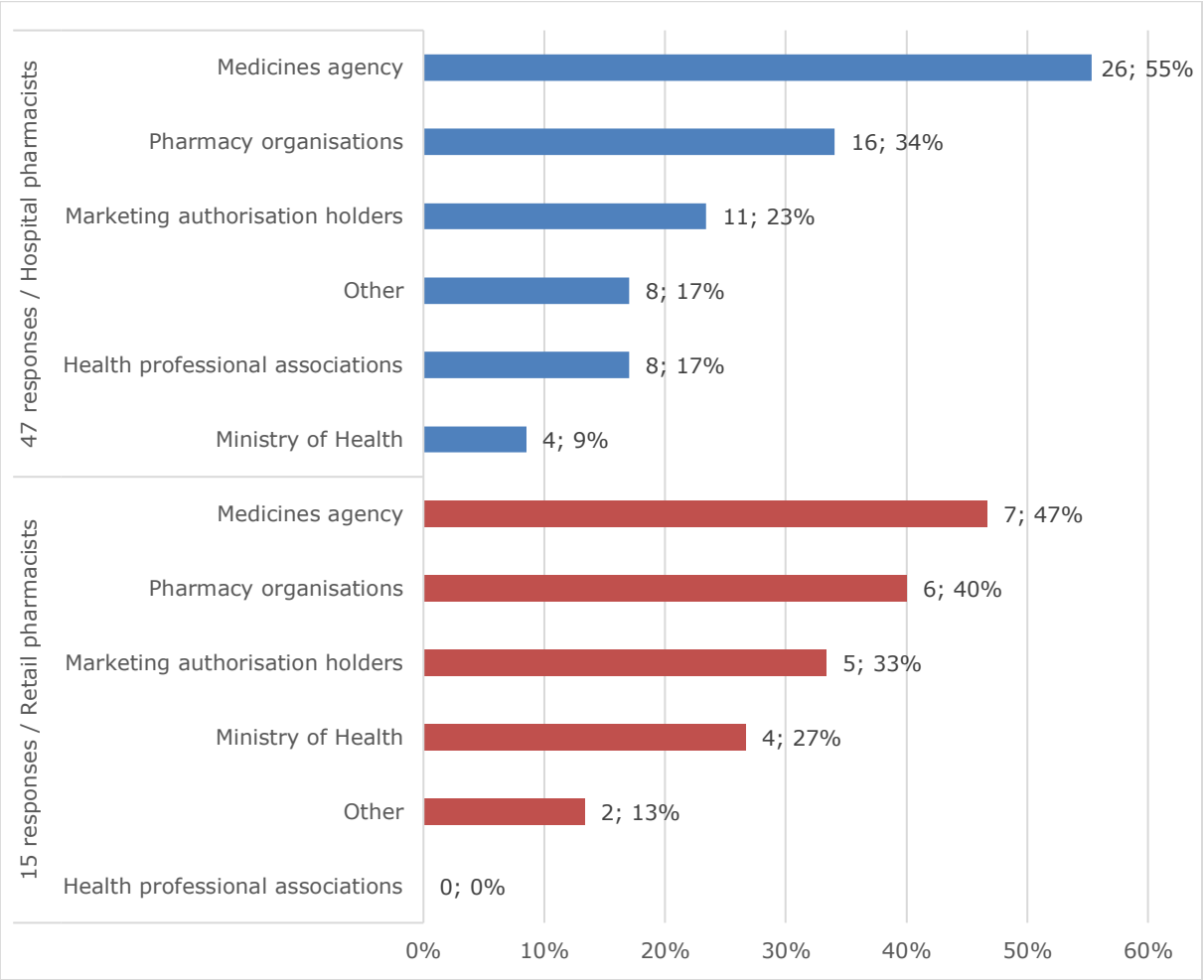


Figure 64 To what extent do you consider the criteria for notifying a shortage used in your country appropriate?

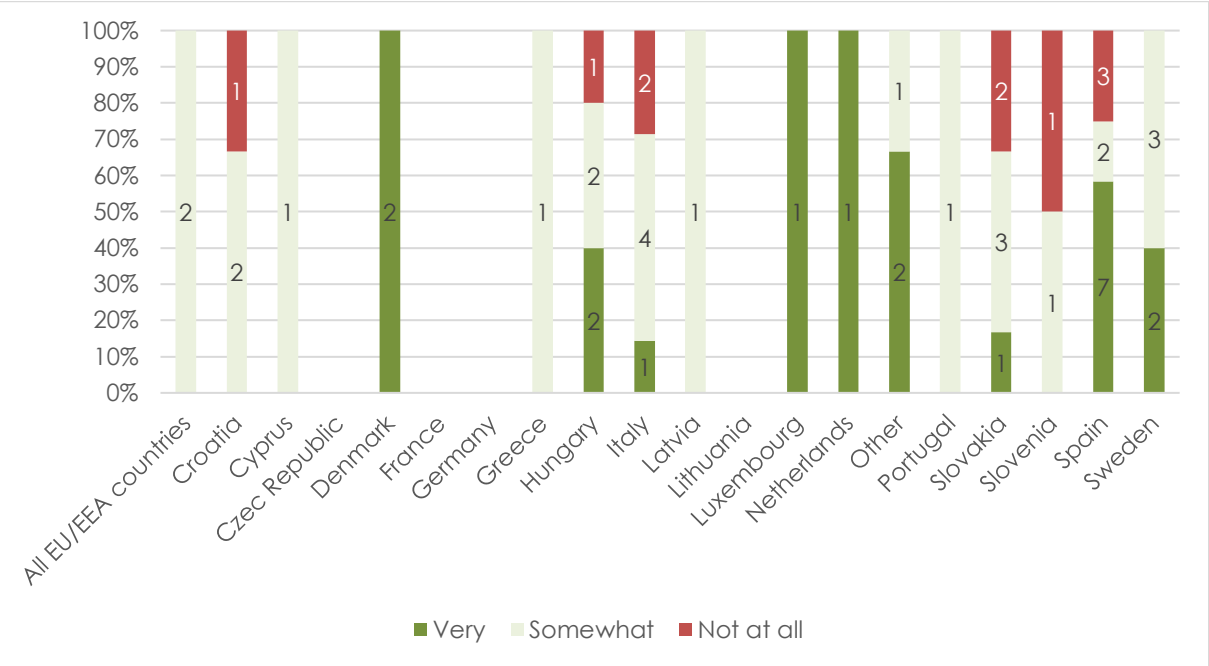


Figure 65 To what extent do you consider pharmacists to be in a position to address medicine shortages?

Extent	Responses
Very large	30 (60%)
Large	8 (16%)
Some	11 (22%)
Not at all	1 (2%)

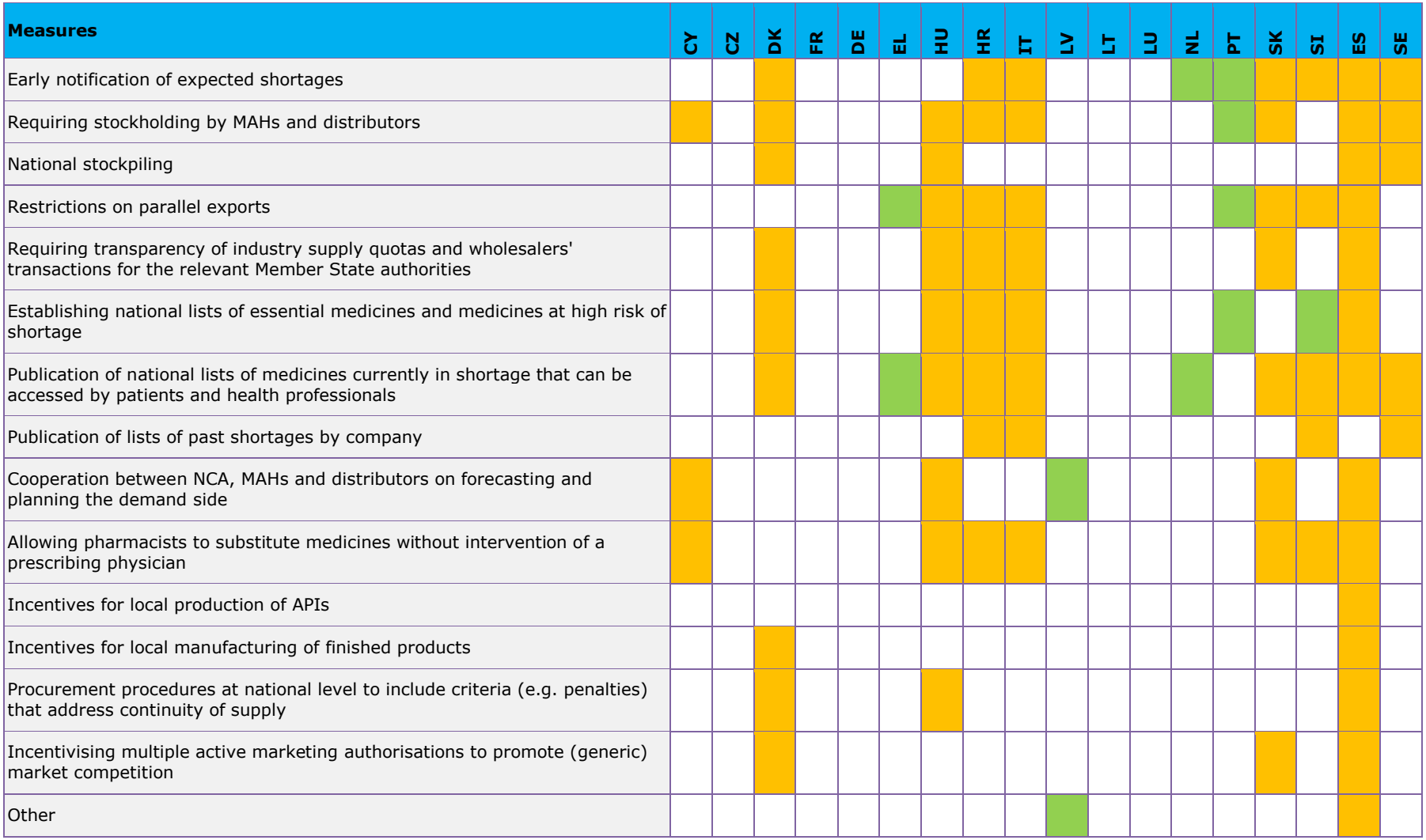
Figure 66 To your knowledge, have pharmacists or their representing organisations implemented any measures to prevent or mitigate shortages in their operations?

Pharmacist group	Yes	No
Hospital (N=33)	21 (61%)	12 (36%)
Retail (N=7)	6 (86%)	1 (14%)

Figure 67 To your knowledge, do the health professionals that you represent receive advance notices of shortages?

Country	Always	Frequently	Rarely	Never	Unknown / does not apply
All EU/EEA			1		1
Croatia		1	2		
Cyprus			1		
Denmark	1		1		
Greece			1		
Hungary			4	1	
Italy		3	4		
Latvia			1		
Luxembourg			1		
The Netherlands			1		
Portugal			1		
Slovakia			6		
Slovenia			2		
Spain		6	5	1	
Sweden		2	3		
Other		3			
Total	1	15	34	2	1

Figure 68 Please indicate which of the following measures have been implemented in the country/countries where you operate?



Note: green = 100% of respondents from the same country selected the measure ; yellow = a portion of respondents from the same country, but not all, selected the measure

Figure 69 Which policies do you think would be relevant solutions to address medicine shortages at the EU level

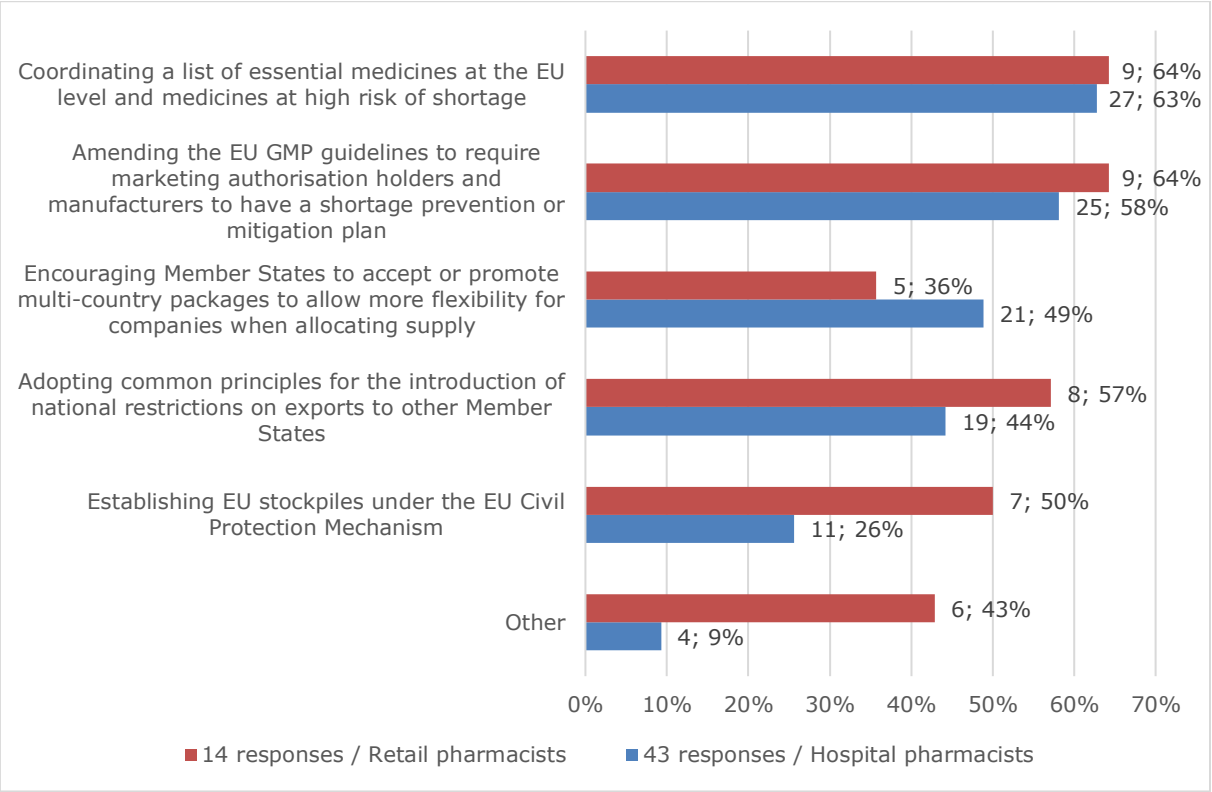
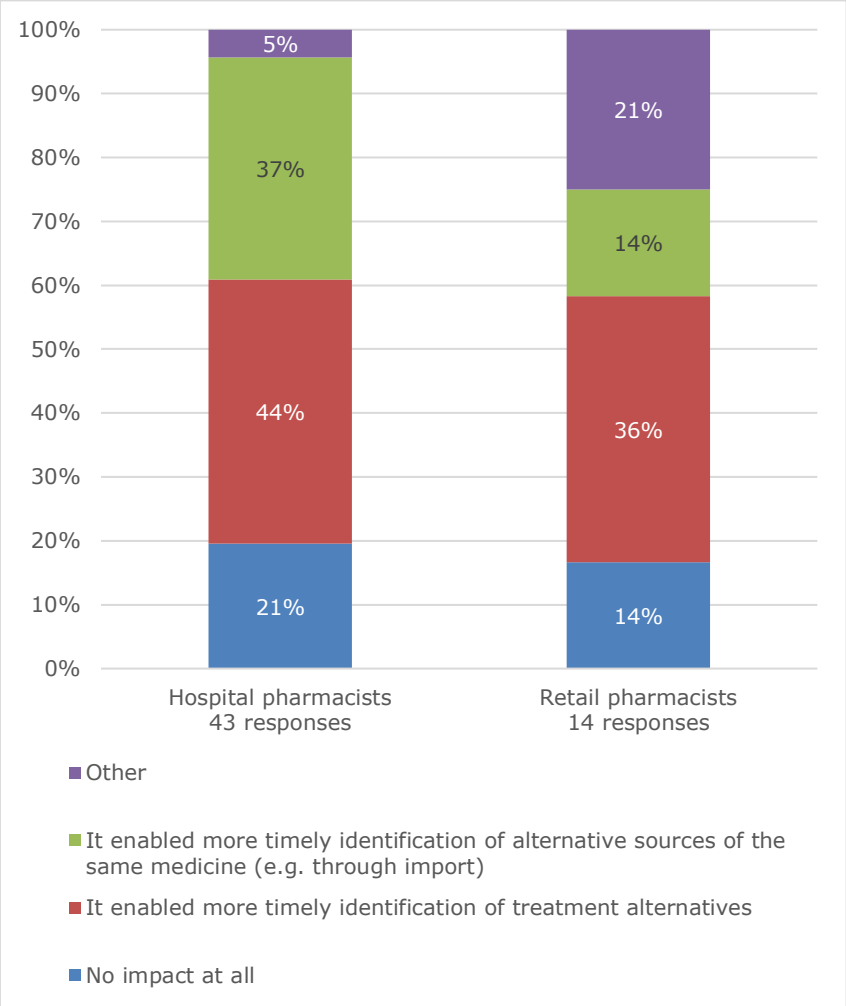


Figure 70 Did the implementation of the European requirement on MAHs to provide notification when a product ceases to be placed on the market (temporarily or permanently) at least 2 months in advance have any of the following impacts?



c

G.3 Supply chain actors

From supply chain actors, 205 responses were received. Where relevant, responses were disaggregated by specific stakeholder groups.

Figure 71 In what type of industry does your organisation operate? (N=256)

Wholesale-distribution	Manufacturers (API and/or finished products)	Innovative industry	Generics industry	Parallel trade	Other
76 (30%)	55 (21%)	47 (18%)	44 (17%)	24 (9%)	10 (4%)

Figure 72 Number of countries where the organisation is active (N=205)

All EU/EEA	1 country	2 countries	3-10 countries	11-25 countries
74 (36%)	104 (51%)	7 (3%)	9 (4%)	11 (5%)

Figure 73 What definition of a medicine shortage is used within your organisation?

Definition	Respondents (%)
EMA	136 (68%)
Other	43 (22%)
No standard	20 (10%)

Figure 74 If you use EMA's definition, in your opinion, is this definition adequate to identify medicine shortages?

Answer	Wholesalers-distributors	Manufacturers	Innovative	Generics	Parallel trade	Other	Total (%)
Yes	62	20	11	17	20	2	132 (92%)
No	2	2	4	3	0	1	12 (8%)

Figure 75 What elements do you consider to be necessary in the reporting of medicine shortages?

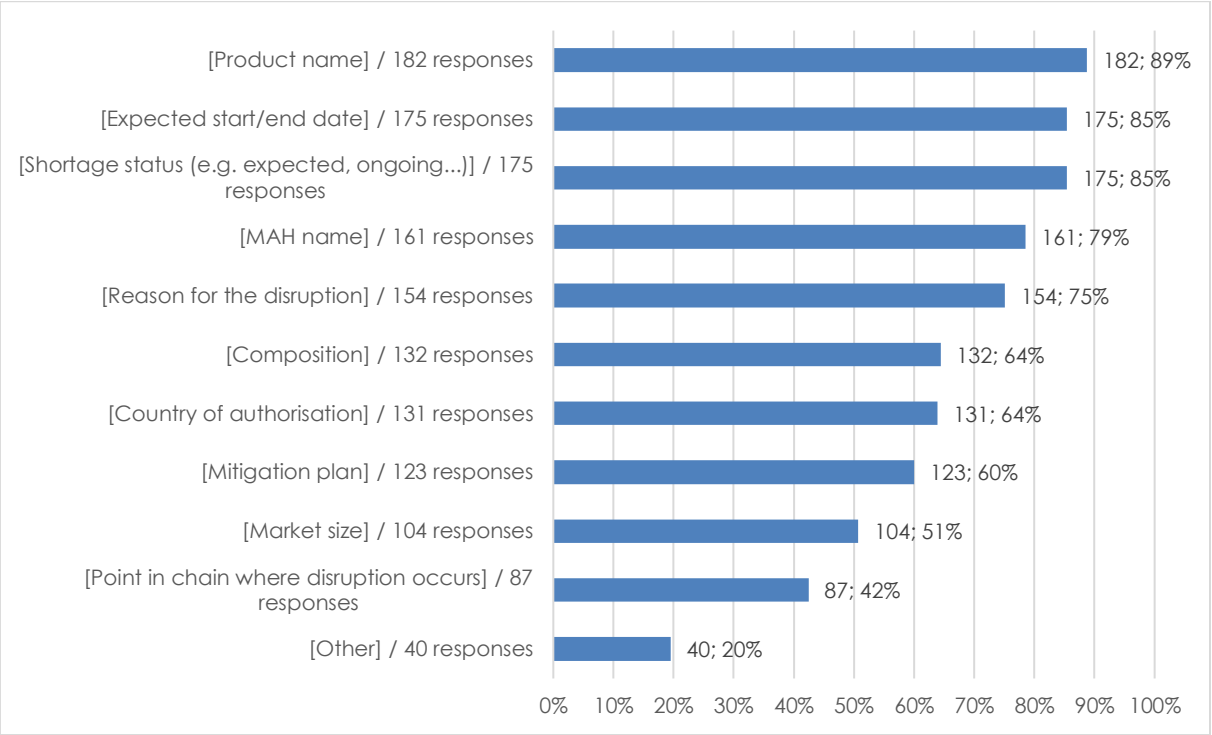
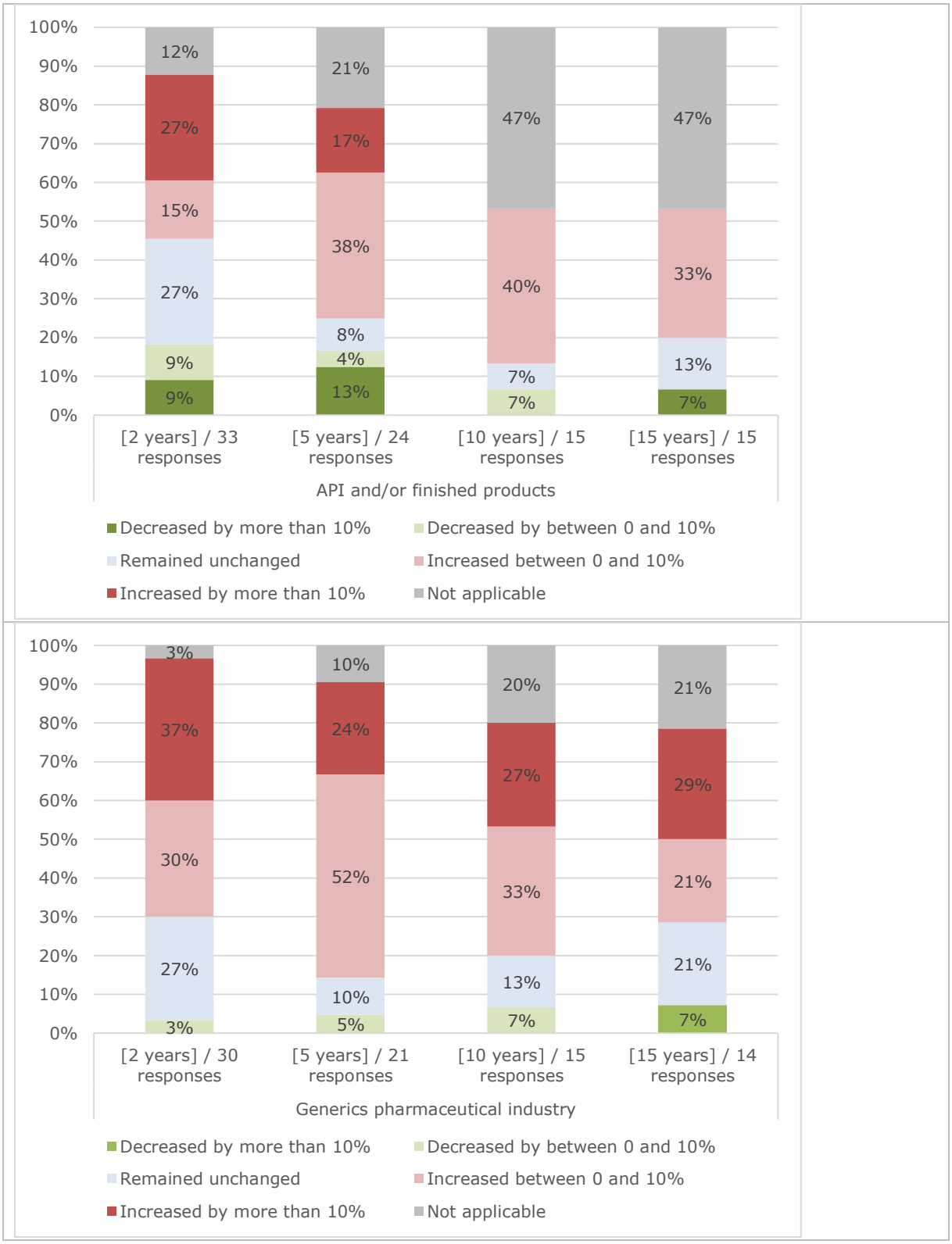
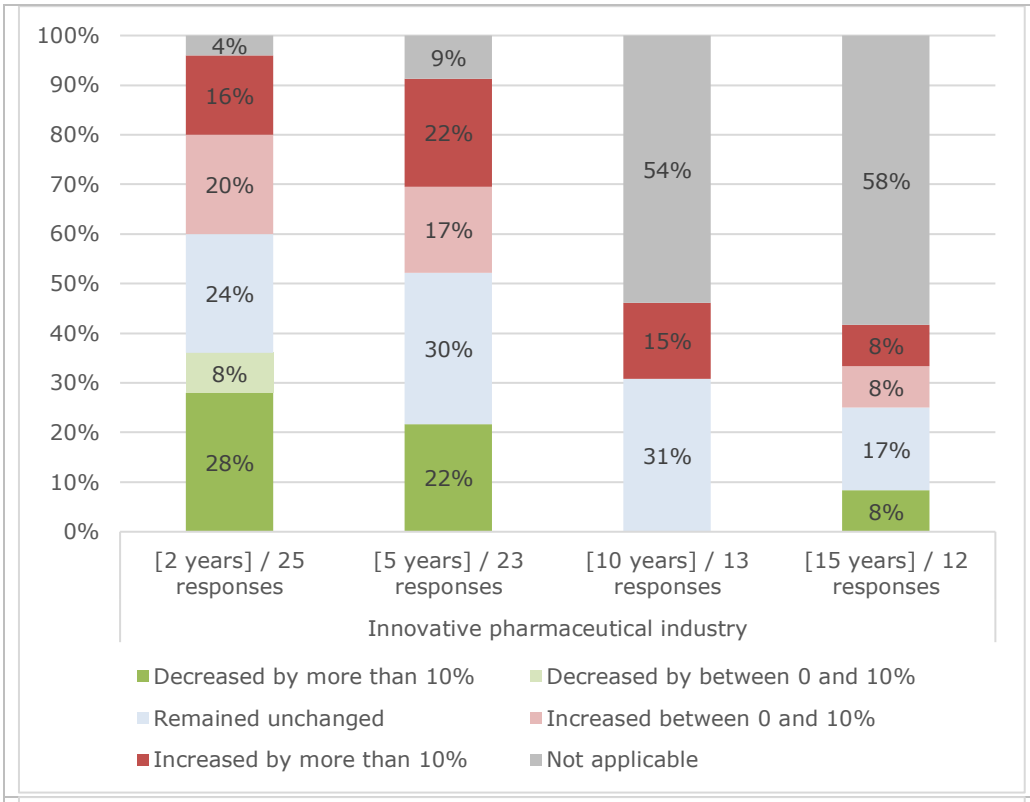
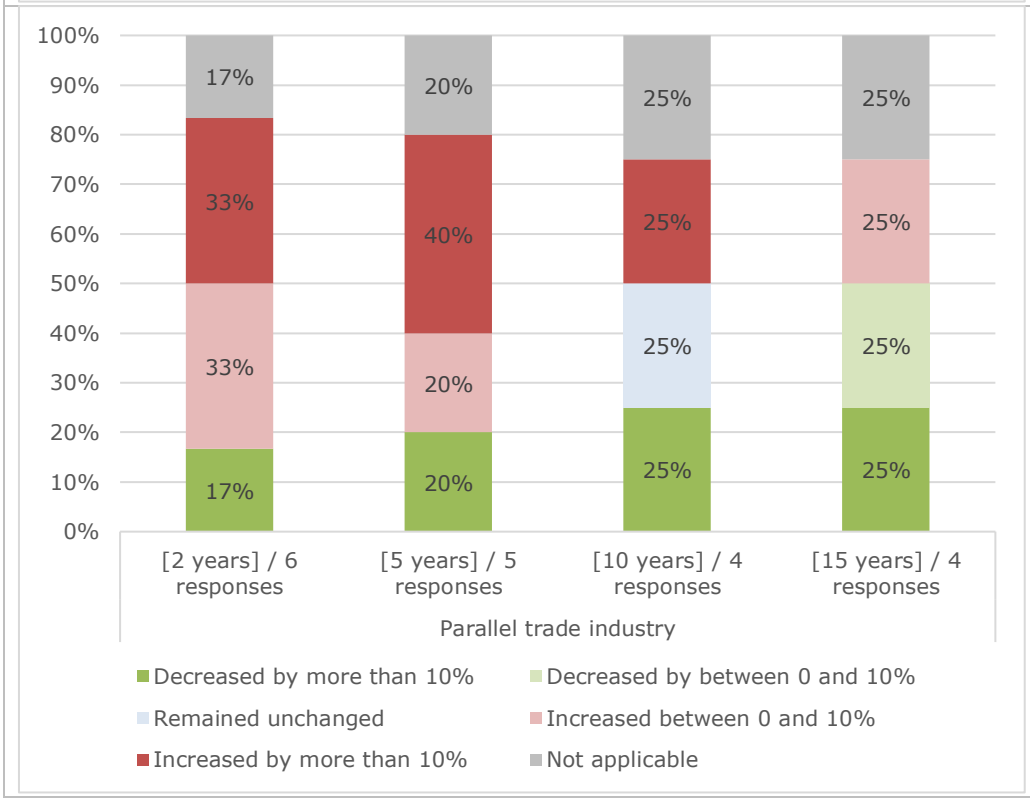


Figure 76 How has the frequency with which medicine shortages occur changed in the country/countries in which your organisation/your member organisations are active in the past […] years?




100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
4%
16%
20%
24%
8%
28%
9%
22%
17%
30%
22%
54%
15%
31%
58%
8%
8%
17%
8%
[2 years] / 25 responses
[5 years] / 23 responses
[10 years] / 13 responses
[15 years] / 12 responses
Innovative pharmaceutical industry
Decreased by more than 10%
Decreased by between 0 and 10%
Remained unchanged
Increased between 0 and 10%
Increased by more than 10%
Not applicable


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
17%
33%
33%
17%
20%
40%
20%
20%
25%
25%
25%
25%
25%
25%
25%
[2 years] / 6 responses
[5 years] / 5 responses
[10 years] / 4 responses
[15 years] / 4 responses
Parallel trade industry
Decreased by more than 10%
Decreased by between 0 and 10%
Remained unchanged
Increased between 0 and 10%
Increased by more than 10%
Not applicable

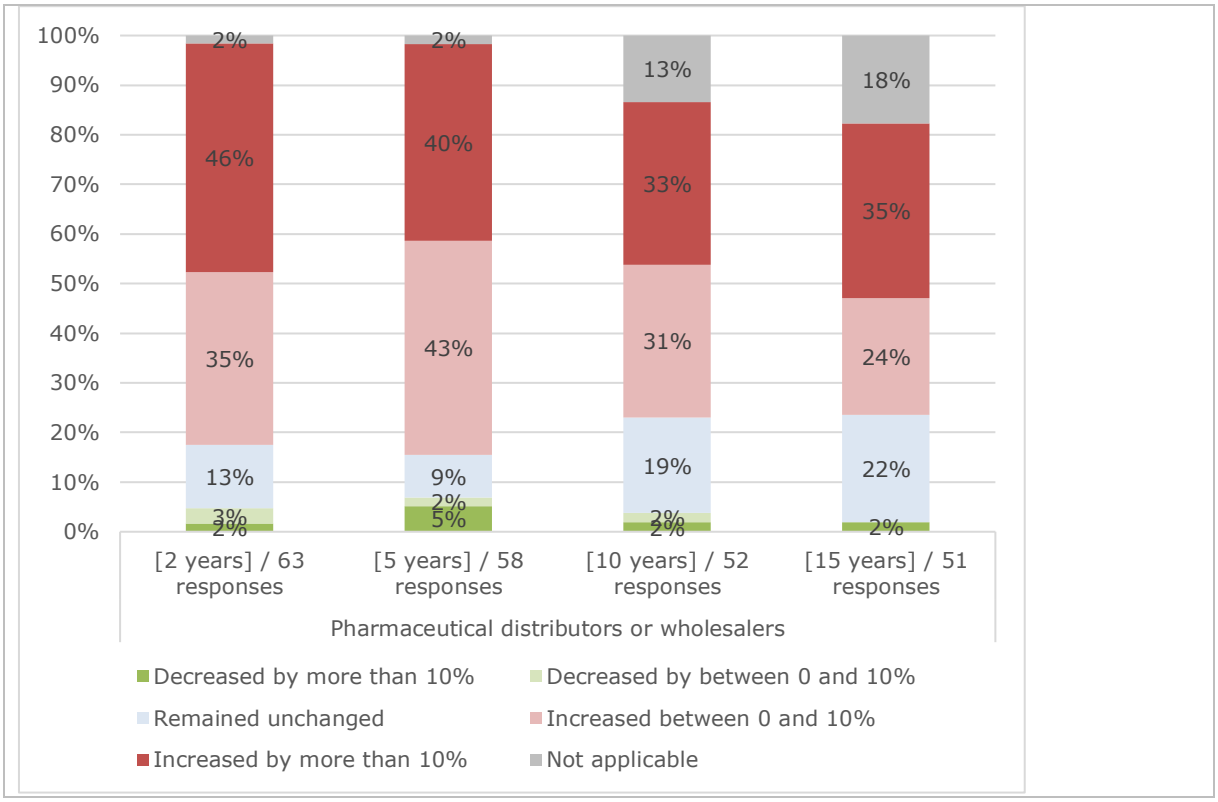
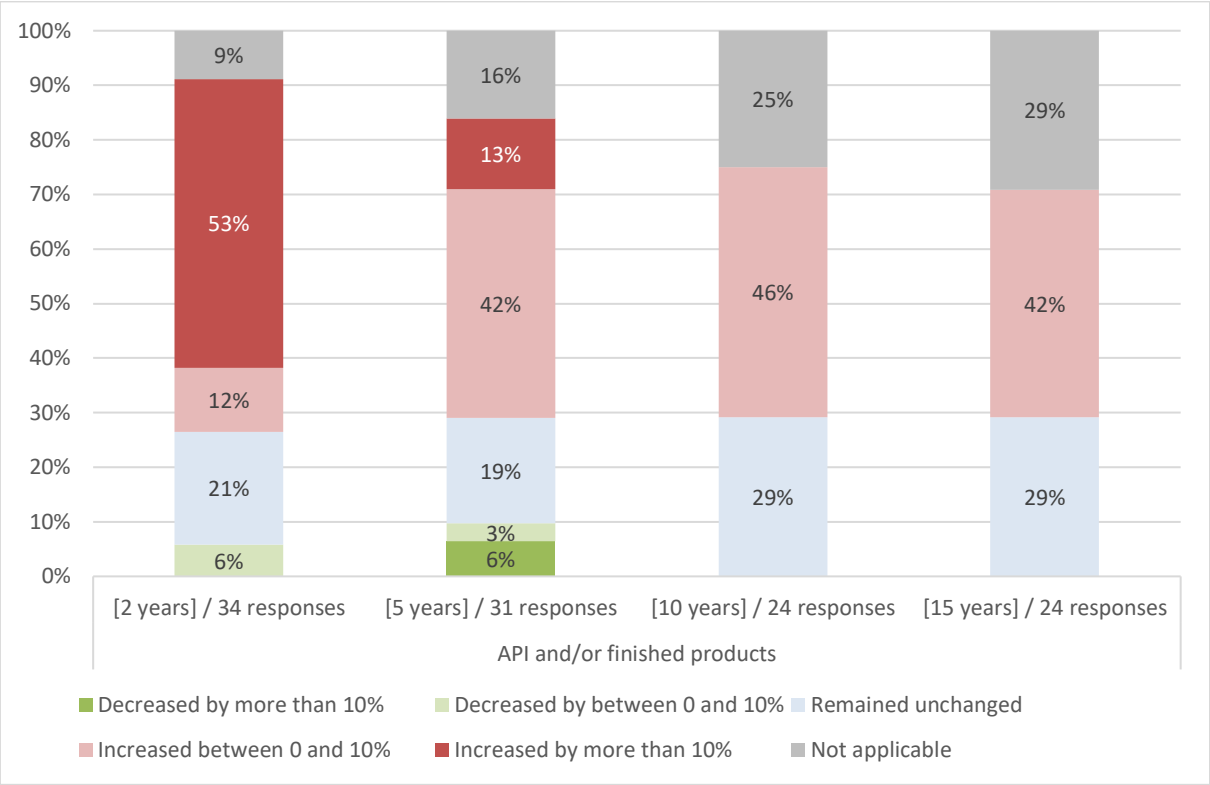
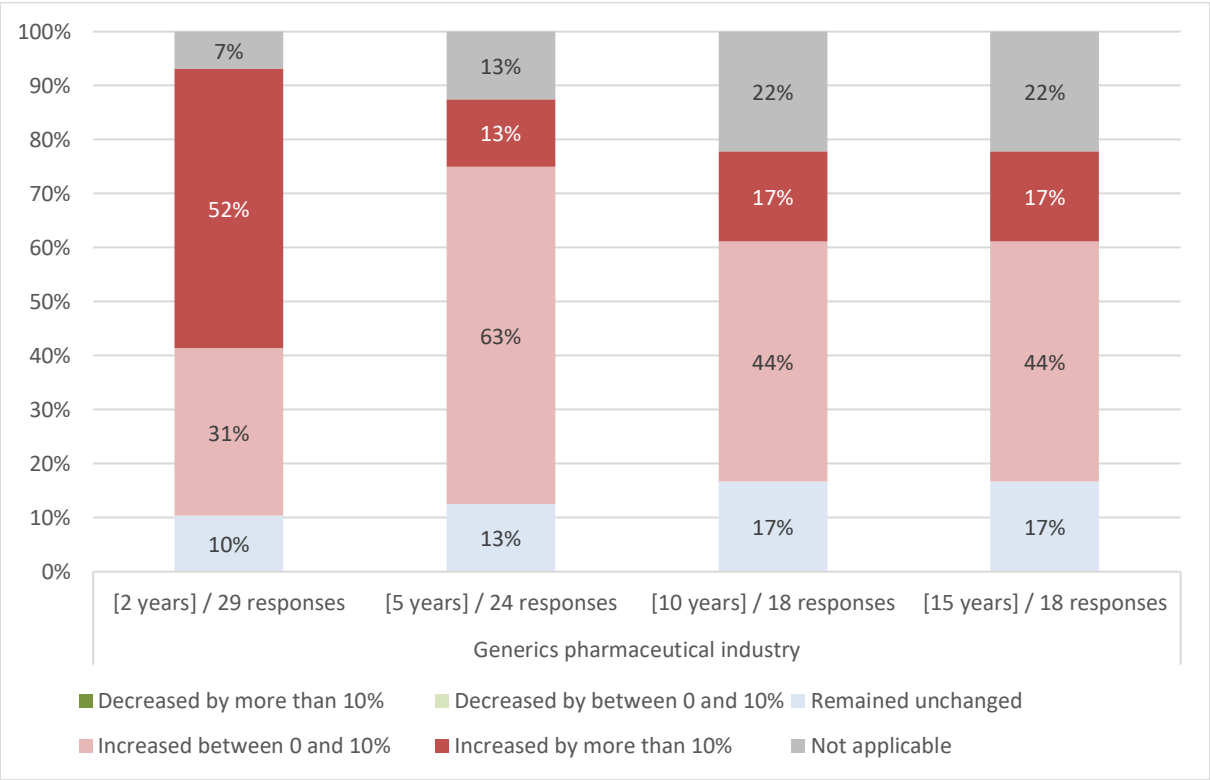
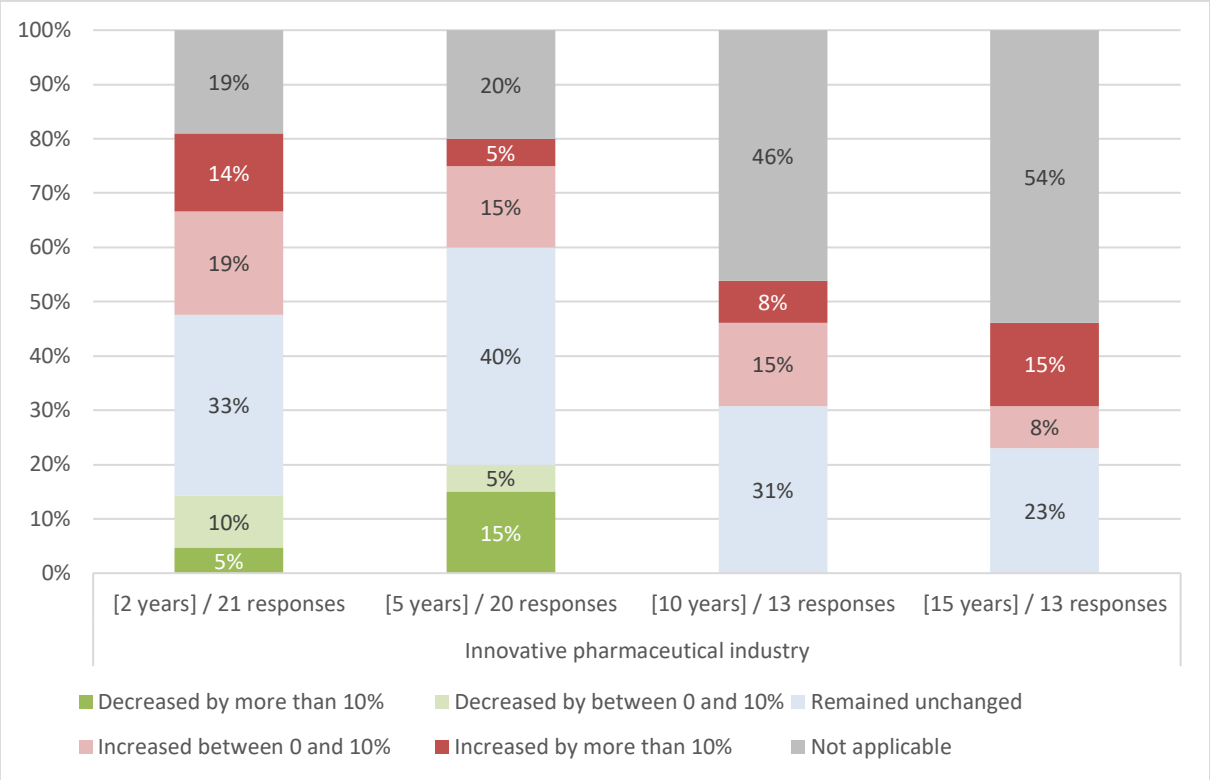
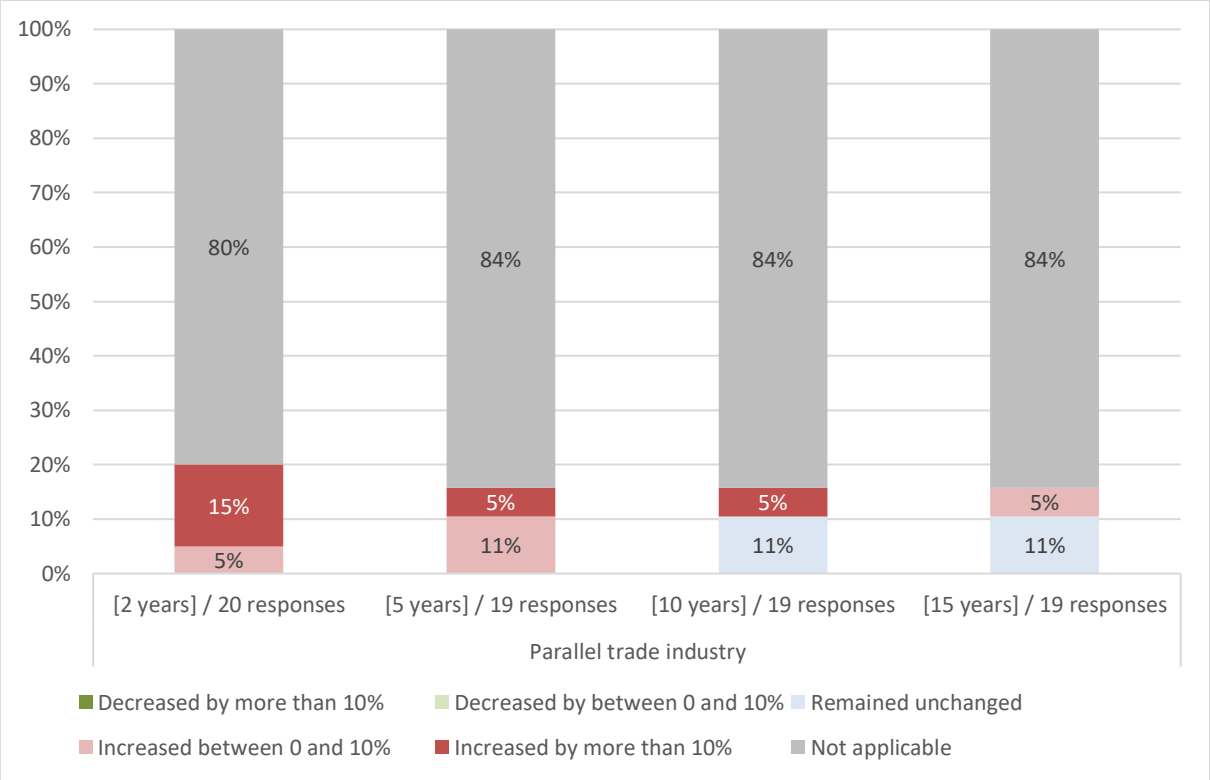

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
2%
46%
35%
13%
3%
2%
2%
40%
43%
9%
2%
5%
13%
33%
31%
19%
2%
2%
18%
35%
24%
22%
2%
[2 years] / 63 responses
[5 years] / 58 responses
[10 years] / 52 responses
[15 years] / 51 responses
Pharmaceutical distributors or wholesalers
Decreased by more than 10%
Decreased by between 0 and 10%
Remained unchanged
Increased between 0 and 10%
Increased by more than 10%
Not applicable

Figure 77 How has the frequency with which shortages of active pharmaceutical ingredients occur changed for your organisation/your member organisations in the past:






100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
19%
14%
19%
33%
10%
5%
20%
5%
15%
40%
5%
15%
46%
8%
15%
31%
54%
15%
8%
23%
[2 years] / 21 responses
[5 years] / 20 responses
[10 years] / 13 responses
[15 years] / 13 responses
Innovative pharmaceutical industry
Decreased by more than 10%
Decreased by between 0 and 10%
Remained unchanged
Increased between 0 and 10%
Increased by more than 10%
Not applicable


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
80%
15%
5%
84%
5%
11%
84%
5%
11%
84%
5%
11%
[2 years] / 20 responses
[5 years] / 19 responses
[10 years] / 19 responses
[15 years] / 19 responses
Parallel trade industry
Decreased by more than 10%
Decreased by between 0 and 10%
Remained unchanged
Increased between 0 and 10%
Increased by more than 10%
Not applicable

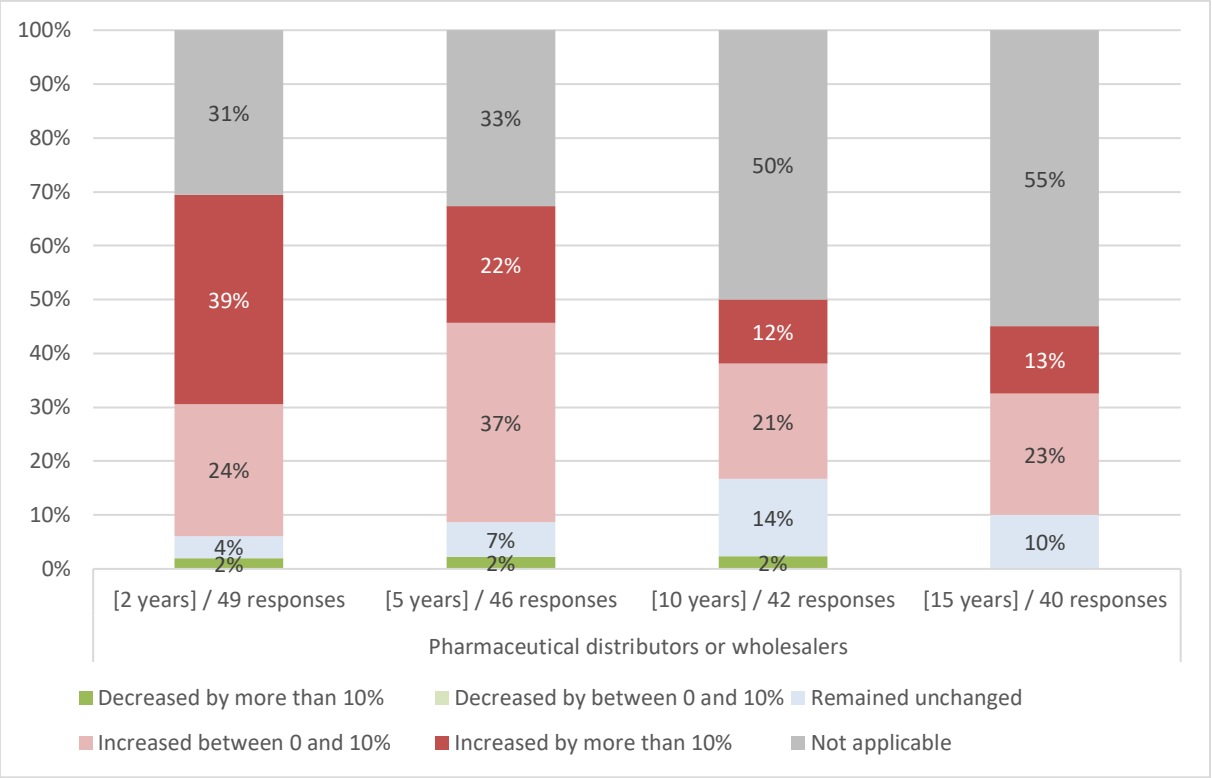
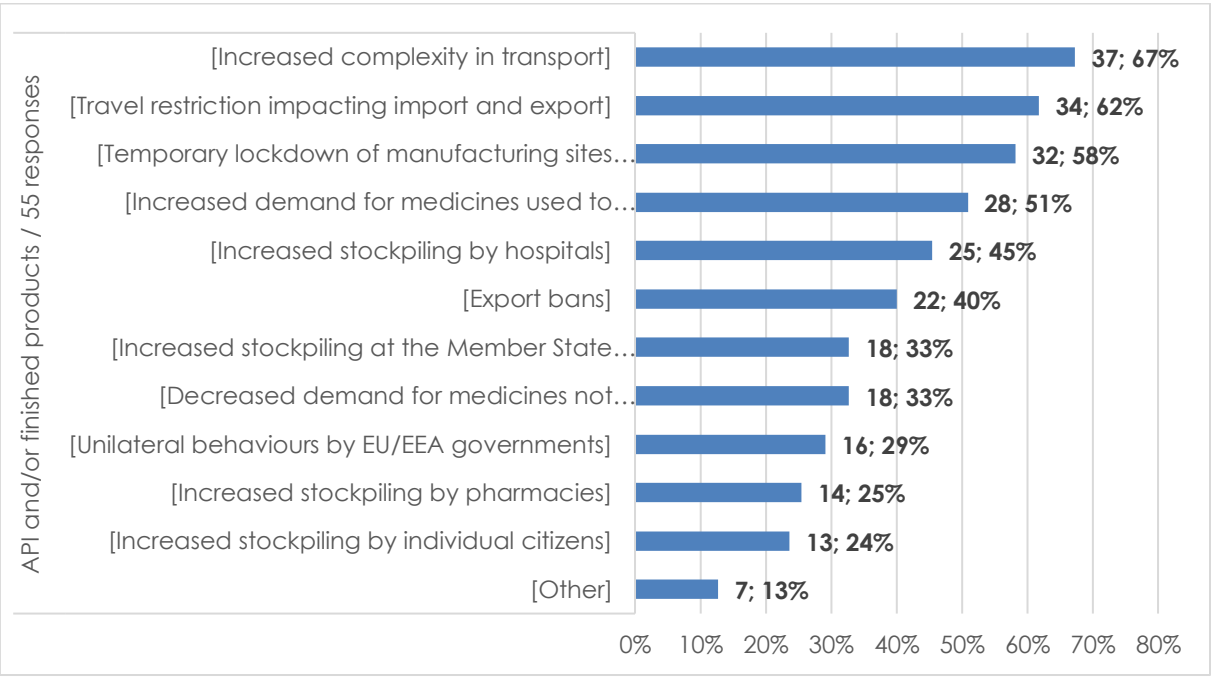
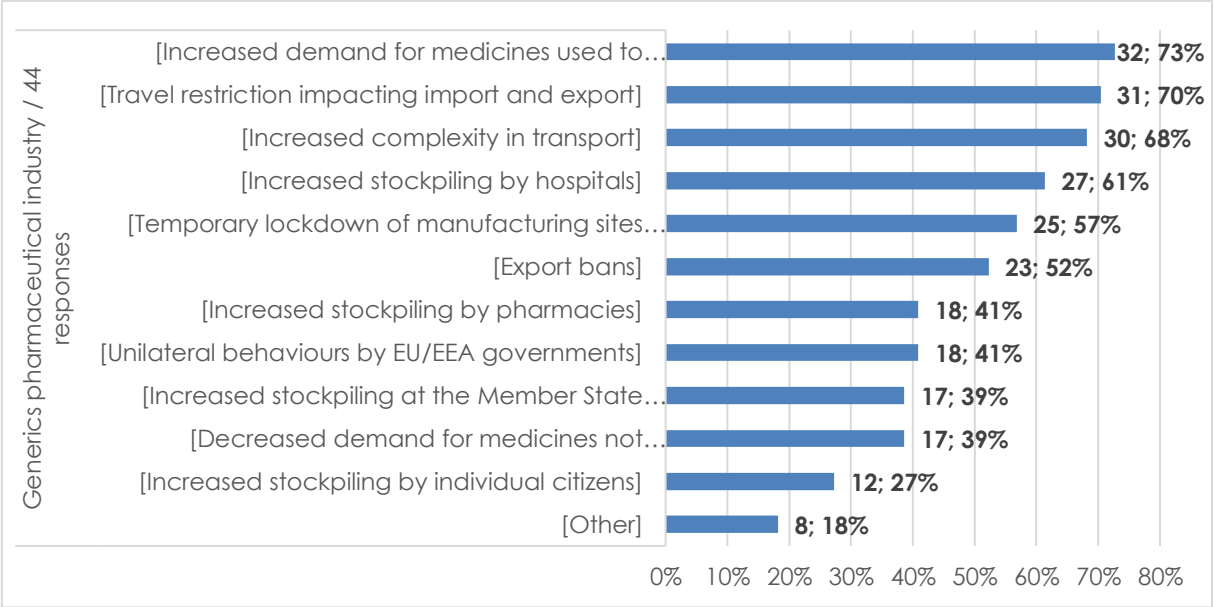
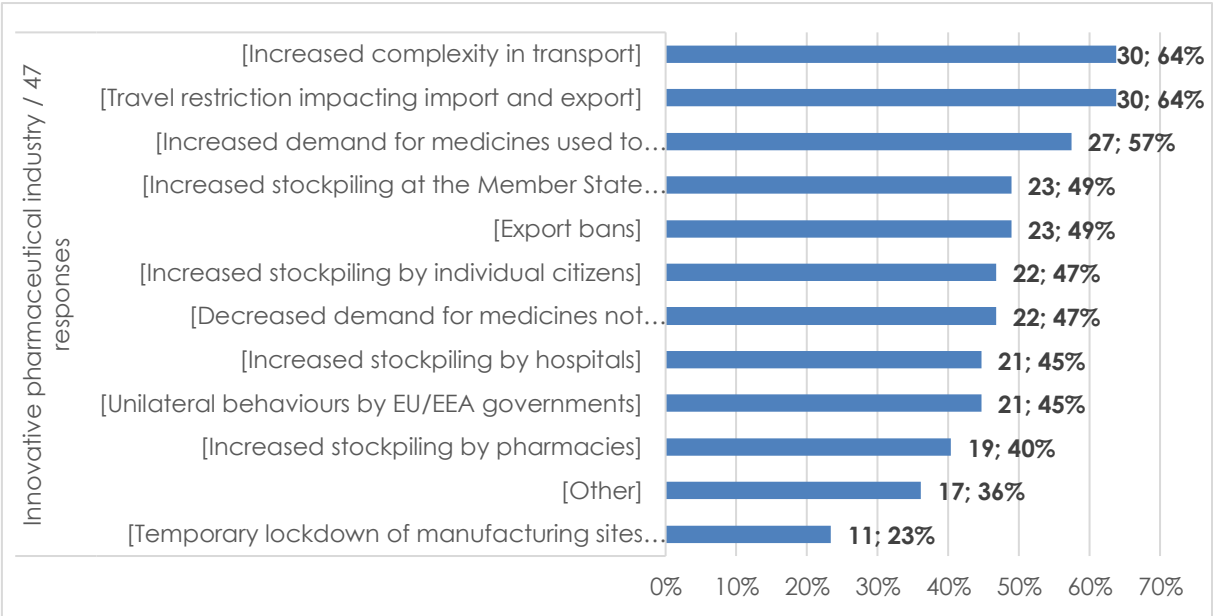
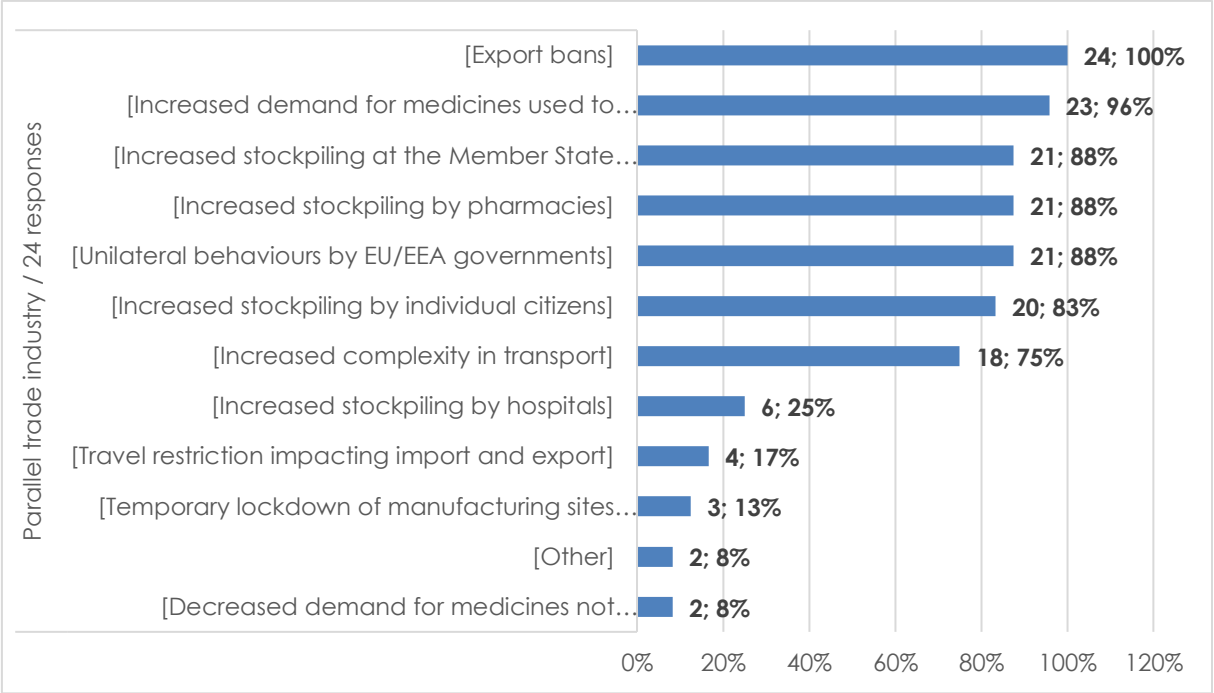


Figure 78 Please indicate which of the following events have affected your supply chain/the supply chain of your member organisations in the course of the COVID-19 pandemic?




Generics pharmaceutical industry / 44 responses
[Increased demand for medicines used to…
[Travel restriction impacting import and export]
[Increased complexity in transport]
[Increased stockpiling by hospitals]
[Temporary lockdown of manufacturing sites…
[Export bans]
[Increased stockpiling by pharmacies]
[Unilateral behaviours by EU/EEA governments]
[Increased stockpiling at the Member State…
[Decreased demand for medicines not…
[Increased stockpiling by individual citizens]
[Other]
32; 73%
31; 70%
30; 68%
27; 61%
25; 57%
23; 52%
18; 41%
18; 41%
17; 39%
17; 39%
12; 27%
8; 18%
0% 10% 20% 30% 40% 50% 60% 70% 80%


Innovative pharmaceutical industry / 47 responses
[Increased complexity in transport]
[Travel restriction impacting import and export]
[Increased demand for medicines used to…
[Increased stockpiling at the Member State…
[Export bans]
[Increased stockpiling by individual citizens]
[Decreased demand for medicines not…
[Increased stockpiling by hospitals]
[Unilateral behaviours by EU/EEA governments]
[Increased stockpiling by pharmacies]
[Other]
[Temporary lockdown of manufacturing sites…
30; 64%
30; 64%
27; 57%
23; 49%
23; 49%
22; 47%
22; 47%
21; 45%
21; 45%
19; 40%
17; 36%
11; 23%
0% 10% 20% 30% 40% 50% 60% 70%


Parallel trade industry / 24 responses
[Export bans]
[Increased demand for medicines used to…
[Increased stockpiling at the Member State…
[Increased stockpiling by pharmacies]
[Unilateral behaviours by EU/EEA governments]
[Increased stockpiling by individual citizens]
[Increased complexity in transport]
[Increased stockpiling by hospitals]
[Travel restriction impacting import and export]
[Temporary lockdown of manufacturing sites…
[Other]
[Decreased demand for medicines not…
24; 100%
23; 96%
21; 88%
21; 88%
21; 88%
20; 83%
18; 75%
6; 25%
4; 17%
3; 13%
2; 8%
2; 8%
0%
20%
40%
60%
80%
100%
120%

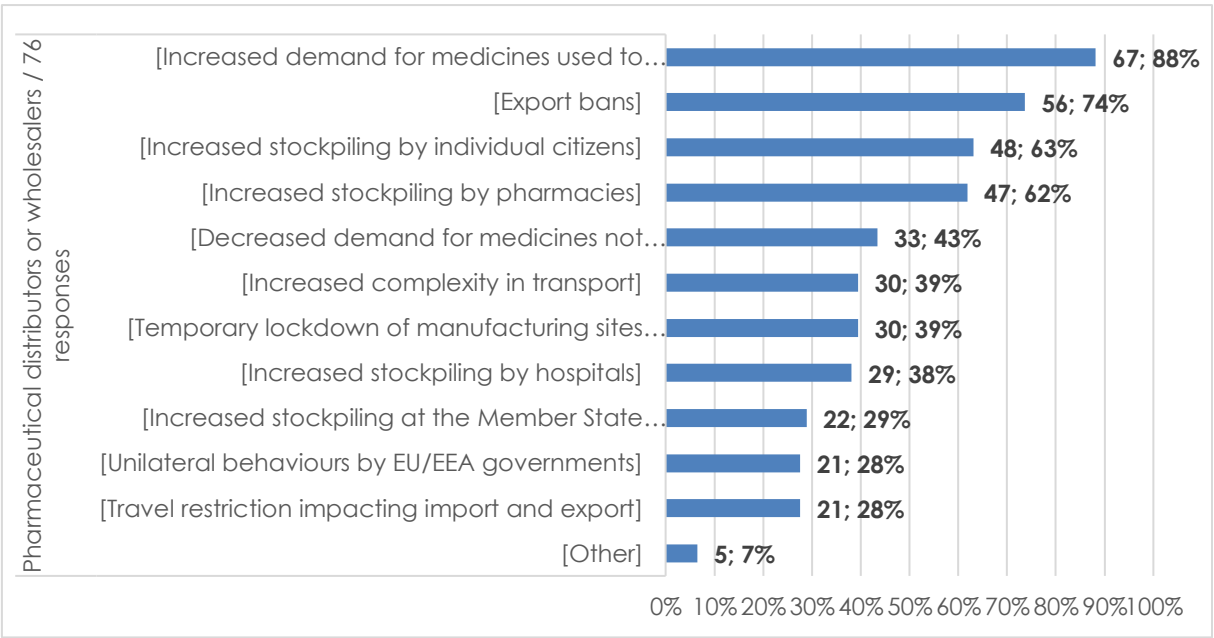
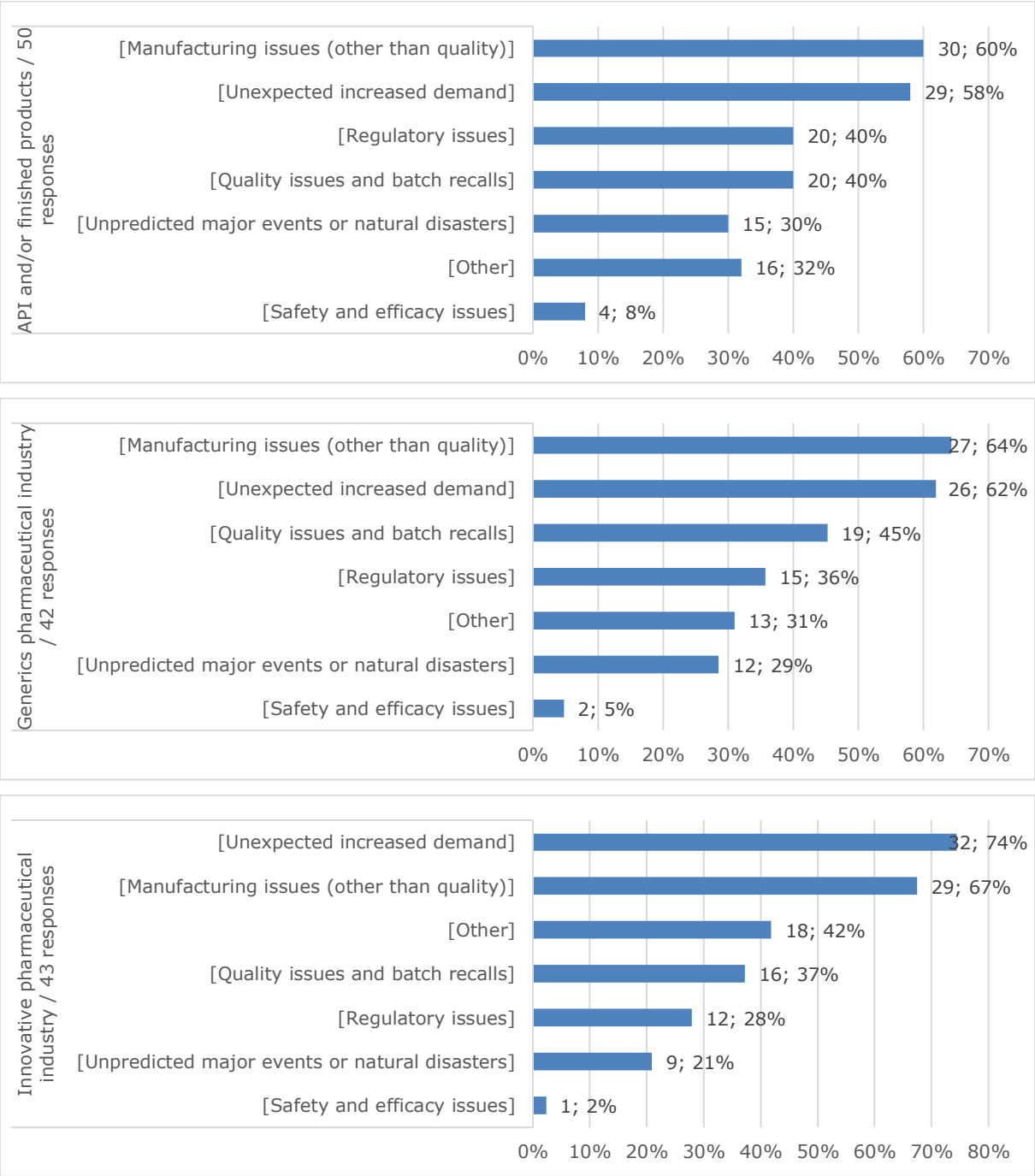
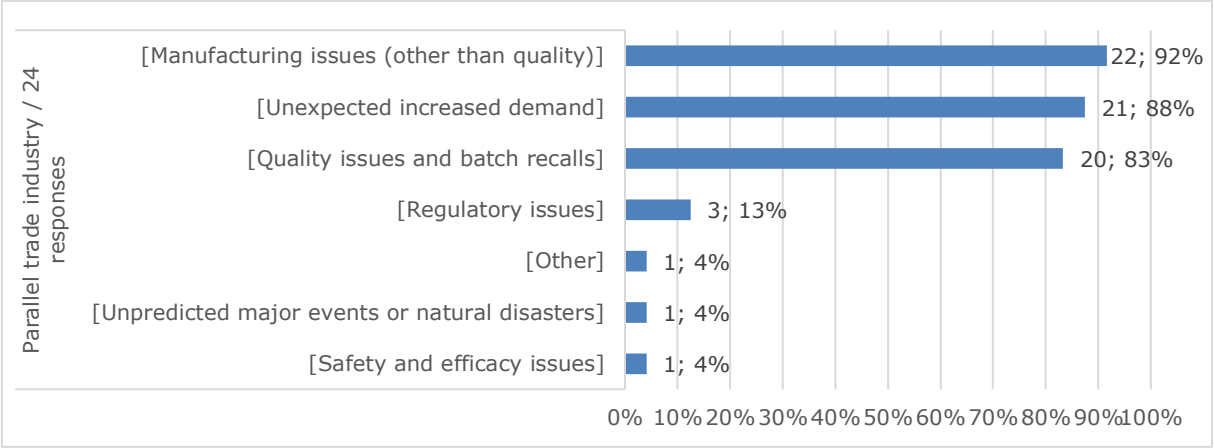

Pharmaceutical distributors or wholesalers / 76 responses
[Increased demand for medicines used to…
[Export bans]
[Increased stockpiling by individual citizens]
[Increased stockpiling by pharmacies]
[Decreased demand for medicines not…
[Increased complexity in transport]
[Temporary lockdown of manufacturing sites…
[Increased stockpiling by hospitals]
[Increased stockpiling at the Member State…
[Unilateral behaviours by EU/EEA governments]
[Travel restriction impacting import and export]
[Other]
67; 88%
56; 74%
48; 63%
47; 62%
33; 43%
30; 39%
30; 39%
29; 38%
22; 29%
21; 28%
21; 28%
5; 7%
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%

Figure 79 Please select the 3 most common causes of medicine shortages that your organisation/your member organisations experienced in the past 5 years:




Parallel trade industry / 24 responses
[Manufacturing issues (other than quality)]
[Unexpected increased demand]
[Quality issues and batch recalls]
[Regulatory issues]
[Other]
[Unpredicted major events or natural disasters]
[Safety and efficacy issues]
22; 92%
21; 88%
20; 83%
3; 13%
1; 4%
1; 4%
1; 4%
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

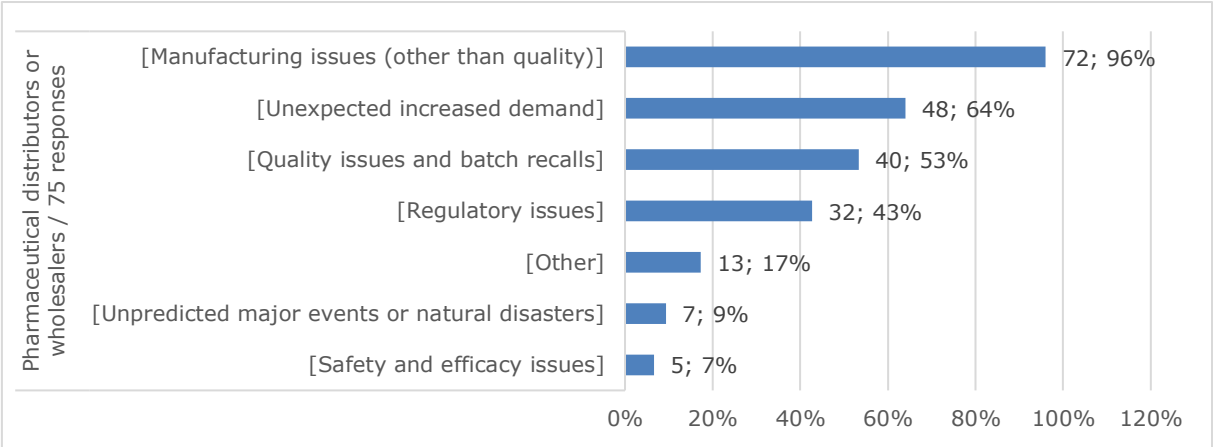
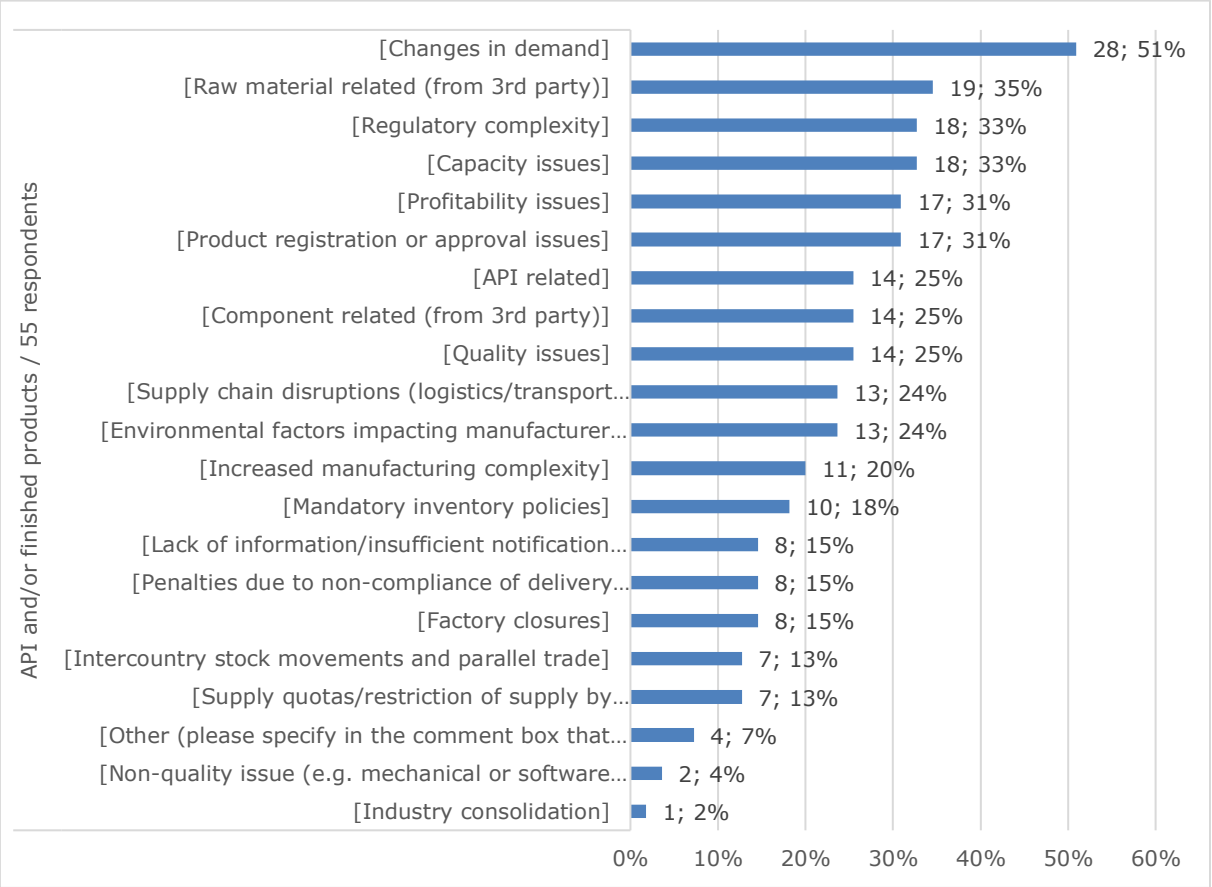
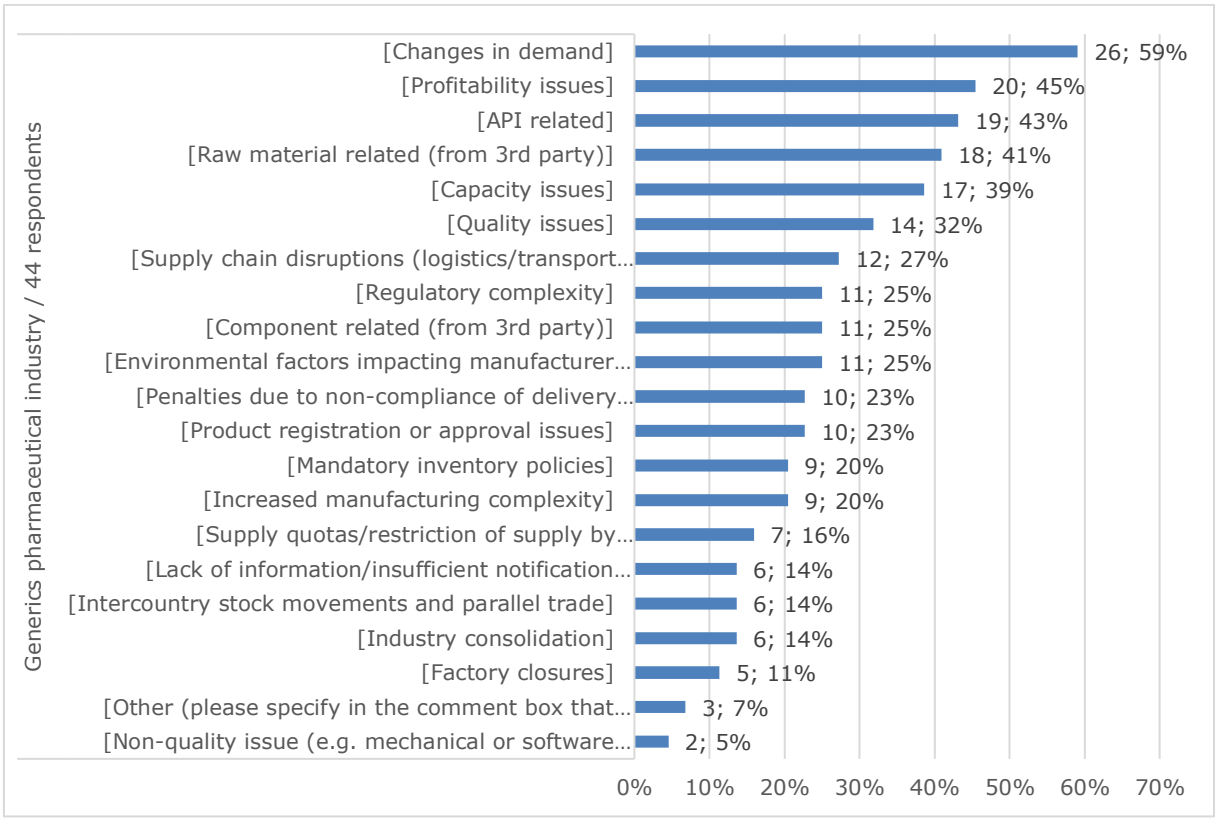
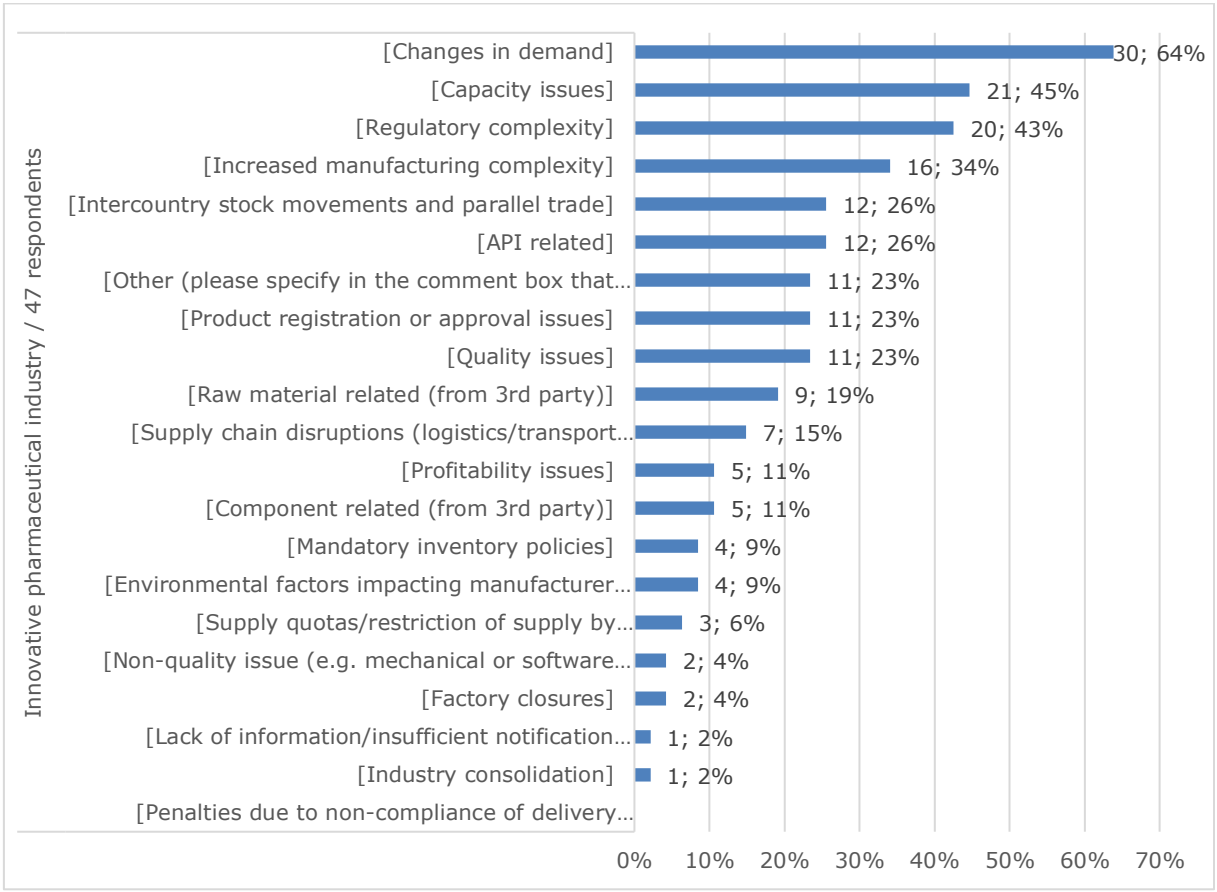
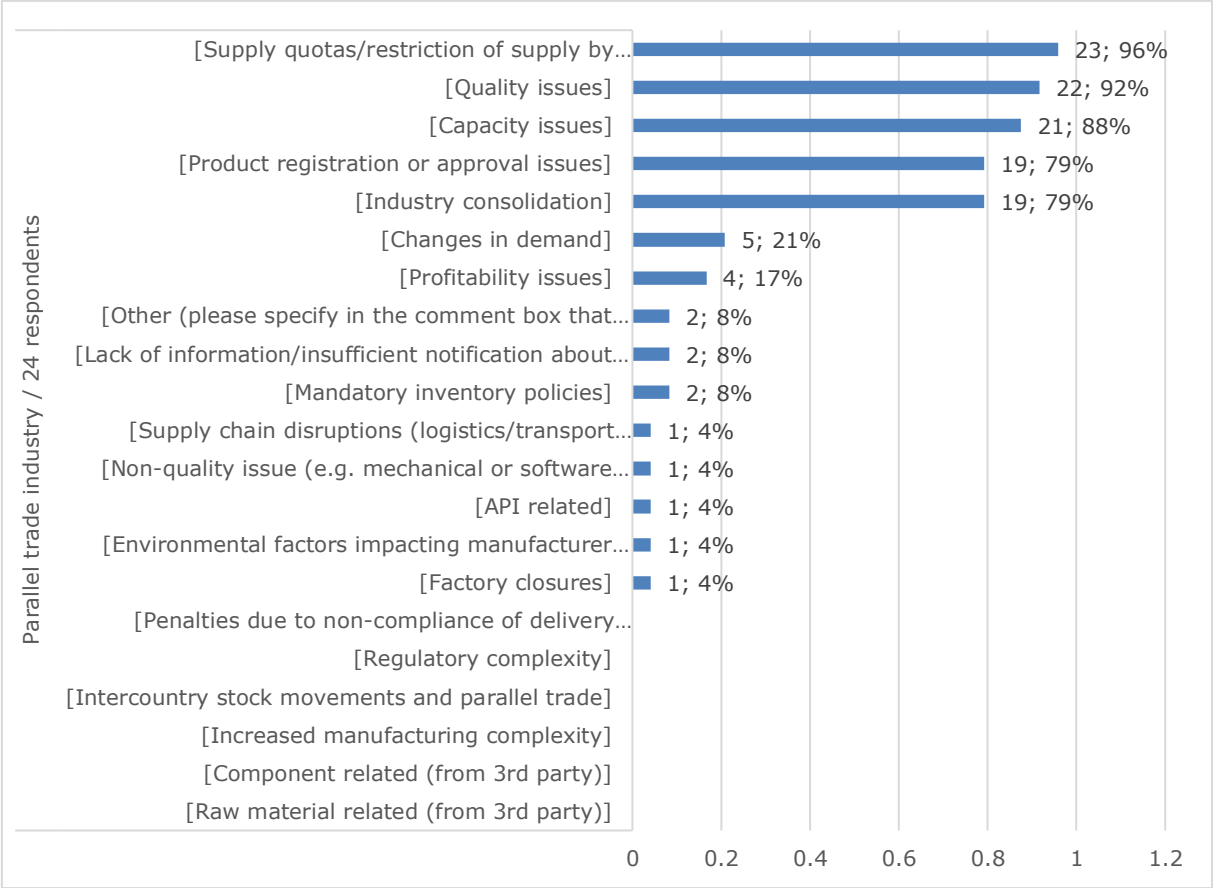

Pharmaceutical distributors or wholesalers / 75 responses
[Manufacturing issues (other than quality)]
[Unexpected increased demand]
[Quality issues and batch recalls]
[Regulatory issues]
[Other]
[Unpredicted major events or natural disasters]
[Safety and efficacy issues]
72; 96%
48; 64%
40; 53%
32; 43%
13; 17%
7; 9%
5; 7%
0% 20% 40% 60% 80% 100% 120%

Figure 80 Which of the following factors have most affected the ability of your organisation/your member organisations to ensure appropriate and continued supply of medicines? Select up to 5 answers




Generics pharmaceutical industry / 44 respondents
[Changes in demand] 26; 59%
[Profitability issues] 20; 45%
[API related] 19; 43%
[Raw material related (from 3rd party)] 18; 41%
[Capacity issues] 17; 39%
[Quality issues] 14; 32%
[Supply chain disruptions (logistics/transport… 12; 27%
[Regulatory complexity] 11; 25%
[Component related (from 3rd party)] 11; 25%
[Environmental factors impacting manufacturer… 11; 25%
[Penalties due to non-compliance of delivery… 10; 23%
[Product registration or approval issues] 10; 23%
[Mandatory inventory policies] 9; 20%
[Increased manufacturing complexity] 9; 20%
[Supply quotas/restriction of supply by… 7; 16%
[Lack of information/insufficient notification… 6; 14%
[Intercountry stock movements and parallel trade] 6; 14%
[Industry consolidation] 6; 14%
[Factory closures] 5; 11%
[Other (please specify in the comment box that… 3; 7%
[Non-quality issue (e.g. mechanical or software… 2; 5%
0% 10% 20% 30% 40% 50% 60% 70%


Innovative pharmaceutical industry / 47 respondents
[Changes in demand] 30; 64%
[Capacity issues] 21; 45%
[Regulatory complexity] 20; 43%
[Increased manufacturing complexity] 16; 34%
[Intercountry stock movements and parallel trade] 12; 26%
[API related] 12; 26%
[Other (please specify in the comment box that… 11; 23%
[Product registration or approval issues] 11; 23%
[Quality issues] 11; 23%
[Raw material related (from 3rd party)] 9; 19%
[Supply chain disruptions (logistics/transport… 7; 15%
[Profitability issues] 5; 11%
[Component related (from 3rd party)] 5; 11%
[Mandatory inventory policies] 4; 9%
[Environmental factors impacting manufacturer… 4; 9%
[Supply quotas/restriction of supply by… 3; 6%
[Non-quality issue (e.g. mechanical or software… 2; 4%
[Factory closures] 2; 4%
[Lack of information/insufficient notification… 1; 2%
[Industry consolidation] 1; 2%
[Penalties due to non-compliance of delivery…
0% 10% 20% 30% 40% 50% 60% 70%


Parallel trade industry / 24 respondents
[Supply quotas/restriction of supply by...
[Quality issues]
[Capacity issues]
[Product registration or approval issues]
[Industry consolidation]
[Changes in demand]
[Profitability issues]
[Other (please specify in the comment box that...
[Lack of information/insufficient notification about...
[Mandatory inventory policies]
[Supply chain disruptions (logistics/transport...
[Non-quality issue (e.g. mechanical or software...
[API related]
[Environmental factors impacting manufacturer...
[Factory closures]
[Penalties due to non-compliance of delivery...
[Regulatory complexity]
[Intercountry stock movements and parallel trade]
[Increased manufacturing complexity]
[Component related (from 3rd party)]
[Raw material related (from 3rd party)]
23; 96%
22; 92%
21; 88%
19; 79%
19; 79%
5; 21%
4; 17%
2; 8%
2; 8%
2; 8%
1; 4%
1; 4%
1; 4%
1; 4%
1; 4%
0
0.2
0.4
0.6
0.8
1
1.2

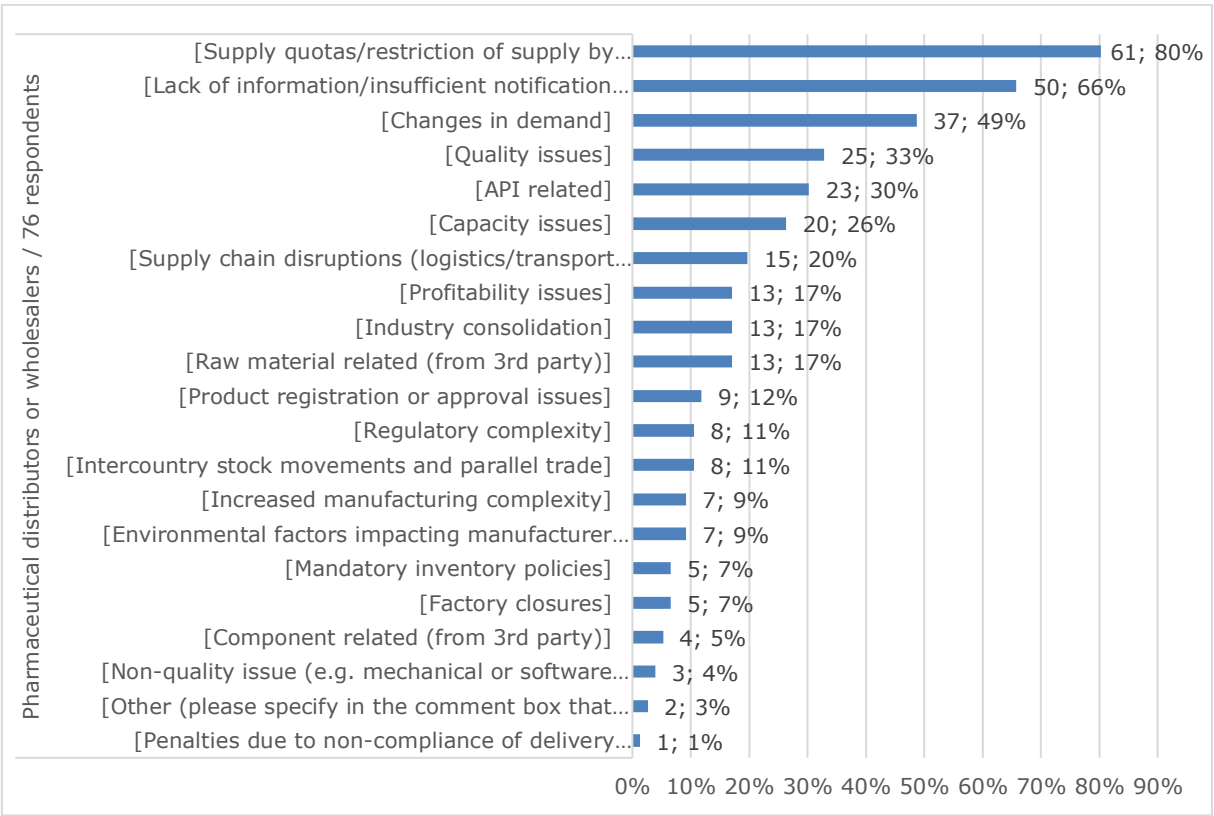
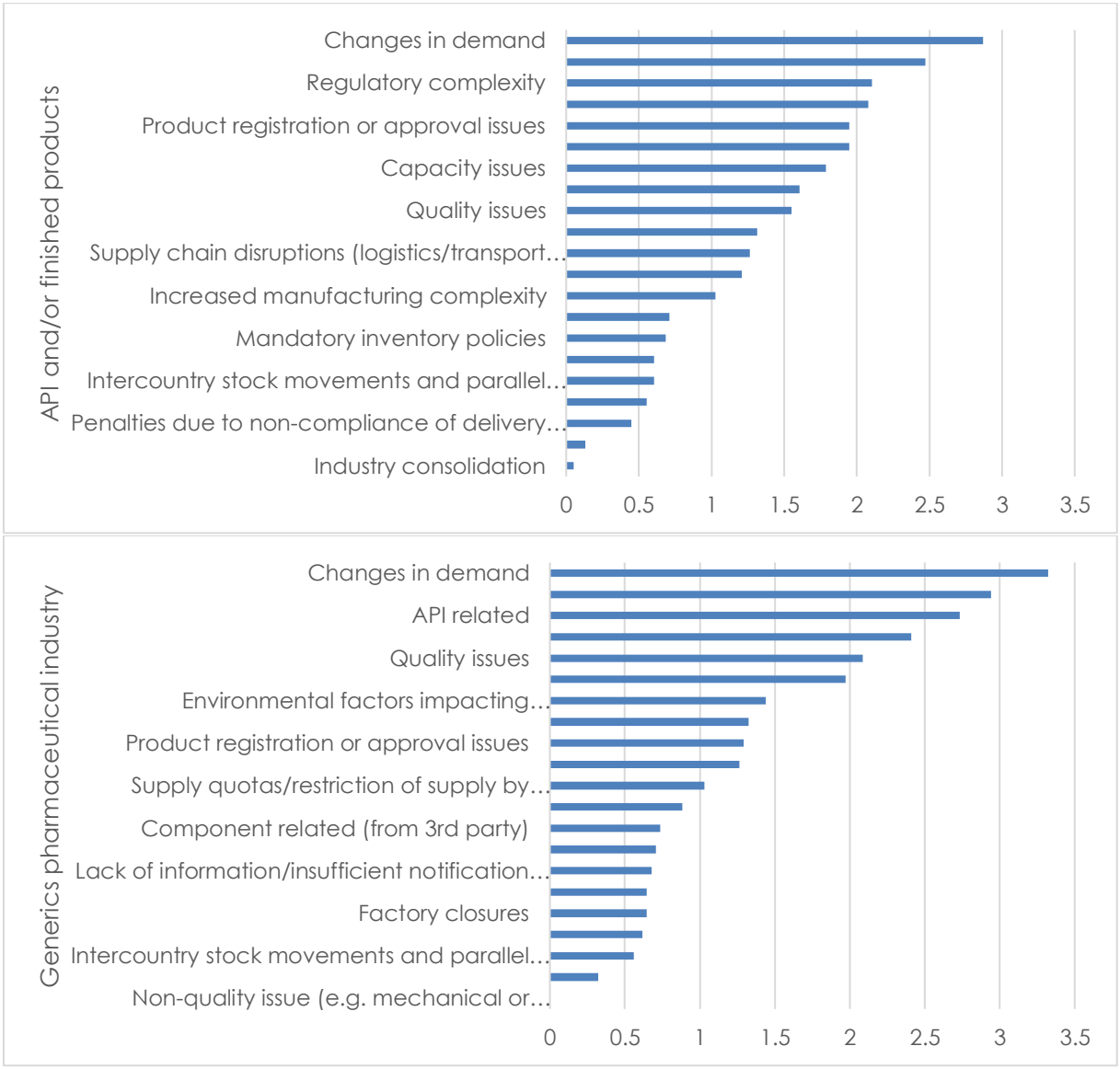
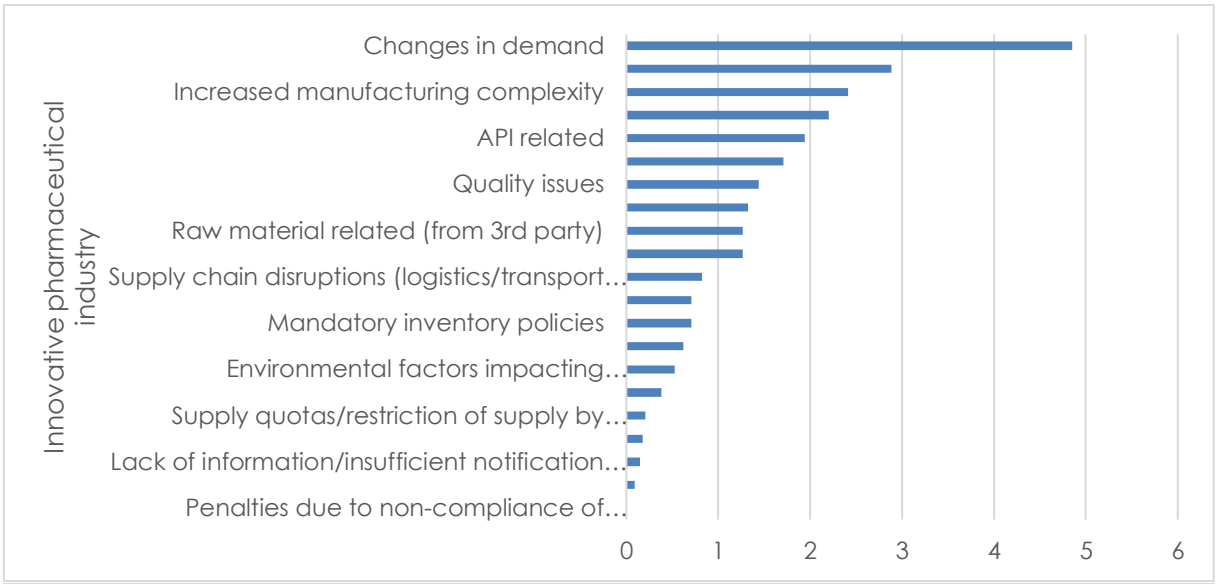
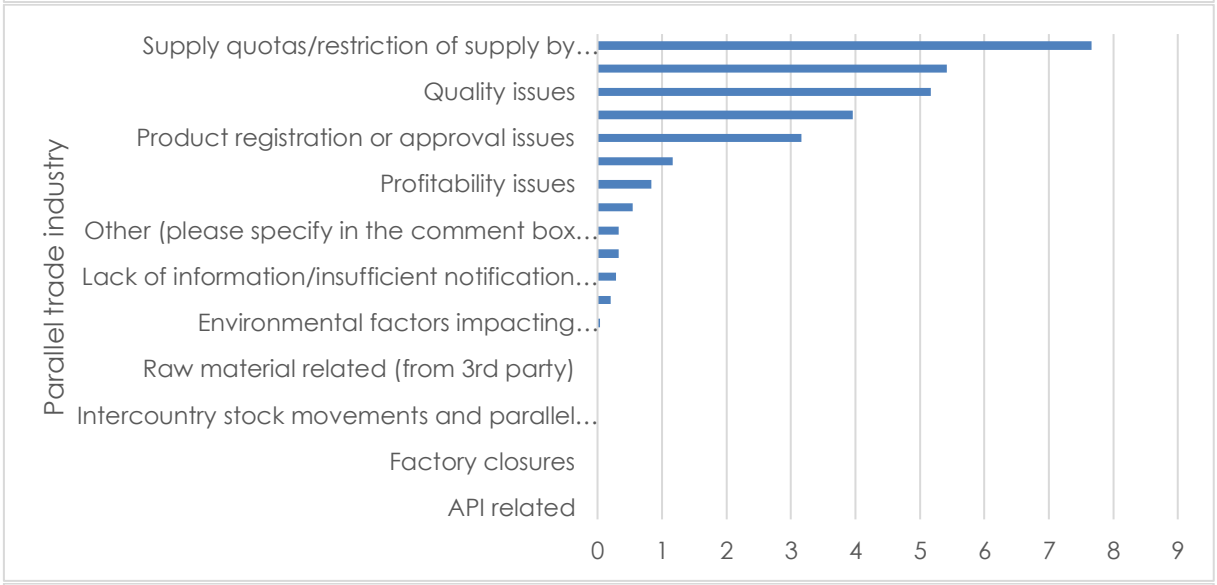

Pharmaceutical distributors or wholesalers / 76 respondents
[Supply quotas/restriction of supply by...
[Lack of information/insufficient notification...
[Changes in demand]
[Quality issues]
[API related]
[Capacity issues]
[Supply chain disruptions (logistics/transport...
[Profitability issues]
[Industry consolidation]
[Raw material related (from 3rd party)]
[Product registration or approval issues]
[Regulatory complexity]
[Intercountry stock movements and parallel trade]
[Increased manufacturing complexity]
[Environmental factors impacting manufacturer...
[Mandatory inventory policies]
[Factory closures]
[Component related (from 3rd party)]
[Non-quality issue (e.g. mechanical or software...
[Other (please specify in the comment box that...
[Penalties due to non-compliance of delivery...
61; 80%
50; 66%
37; 49%
25; 33%
23; 30%
20; 26%
15; 20%
13; 17%
13; 17%
13; 17%
9; 12%
8; 11%
8; 11%
7; 9%
7; 9%
5; 7%
5; 7%
4; 5%
3; 4%
2; 3%
1; 1%
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%

Figure 81 Out of the selected factors, which had the strongest impact on your operations? (compounded ranking score)




Innovative pharmaceutical industry
Changes in demand
Increased manufacturing complexity
API related
Quality issues
Raw material related (from 3rd party)
Supply chain disruptions (logistics/transport…
Mandatory inventory policies
Environmental factors impacting…
Supply quotas/restriction of supply by…
Lack of information/insufficient notification…
Penalties due to non-compliance of…
0 1 2 3 4 5 6


Parallel trade industry
Supply quotas/restriction of supply by…
Quality issues
Product registration or approval issues
Profitability issues
Other (please specify in the comment box…
Lack of information/insufficient notification…
Environmental factors impacting…
Raw material related (from 3rd party)
Intercountry stock movements and parallel…
Factory closures
API related
0 1 2 3 4 5 6 7 8 9

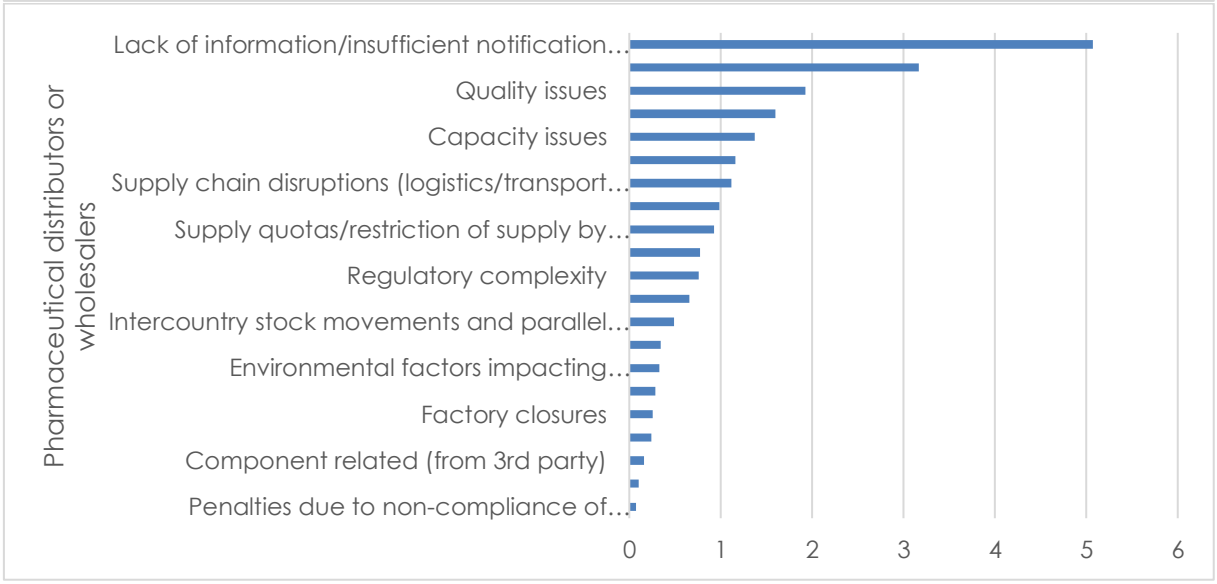

Pharmaceutical distributors or wholesalers
Lack of information/insufficient notification…
Quality issues
Capacity issues
Supply chain disruptions (logistics/transport…
Supply quotas/restriction of supply by…
Regulatory complexity
Intercountry stock movements and parallel…
Environmental factors impacting…
Factory closures
Component related (from 3rd party)
Penalties due to non-compliance of…
0 1 2 3 4 5 6

Figure 82 Which production methods and/or types of products are most associated with shortages?

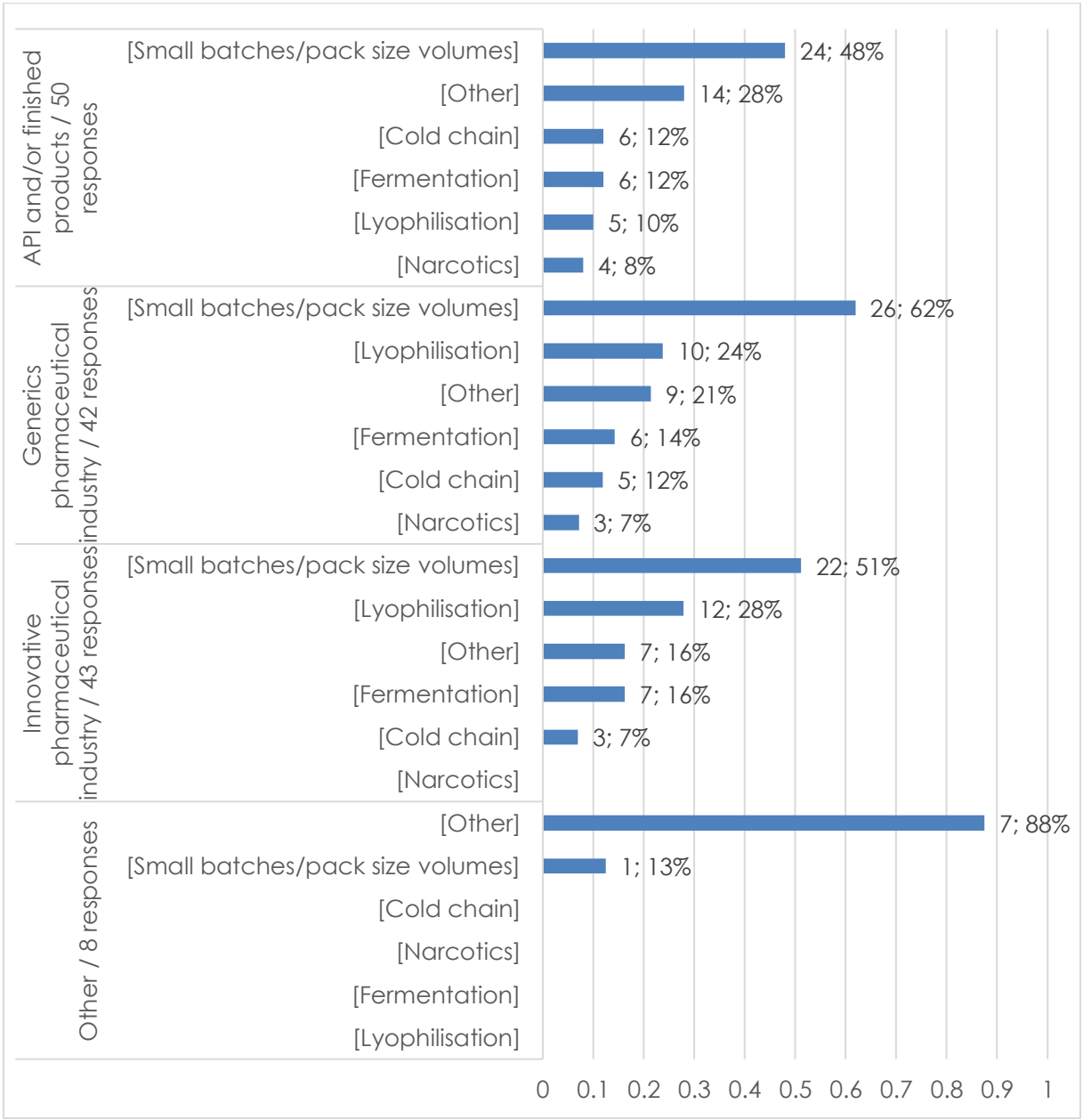


Figure 83 To what extent are shortages of medicines produced, marketed and/or traded by your organisation / your member organisations influenced by external shocks and international trends?

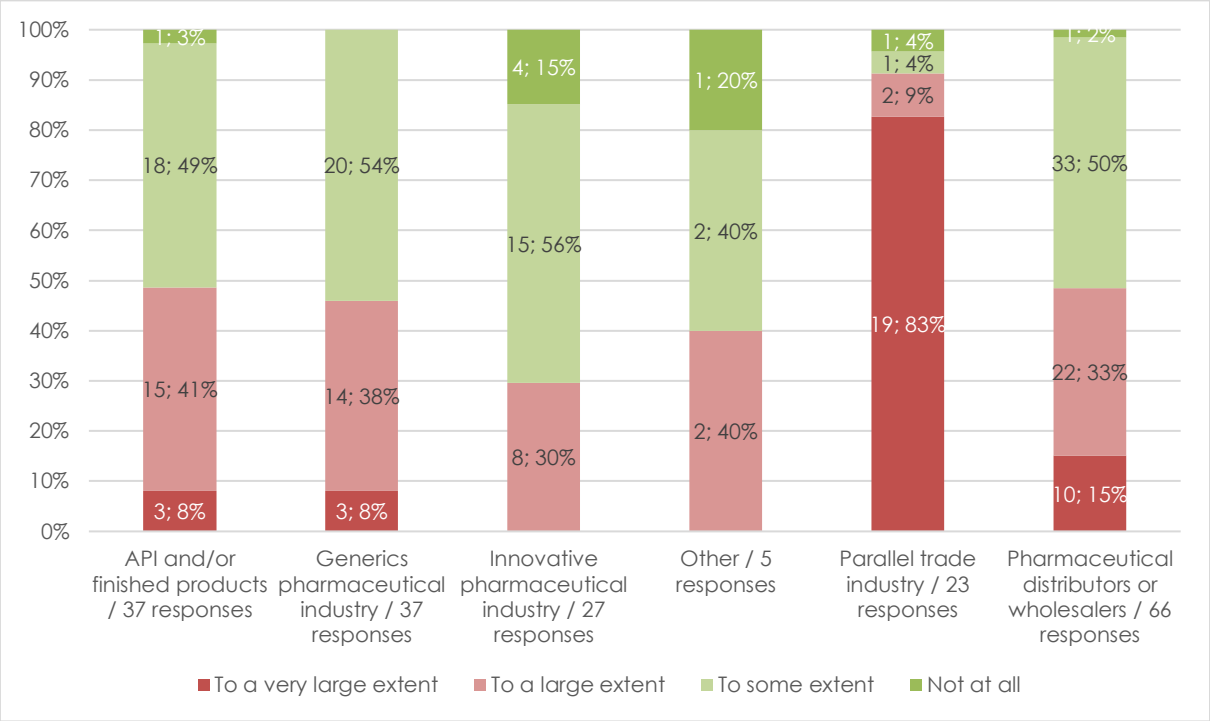


Figure 84 To what extent do you consider manufacturers and business associations to be in a position to address causes of medicine/API shortages?

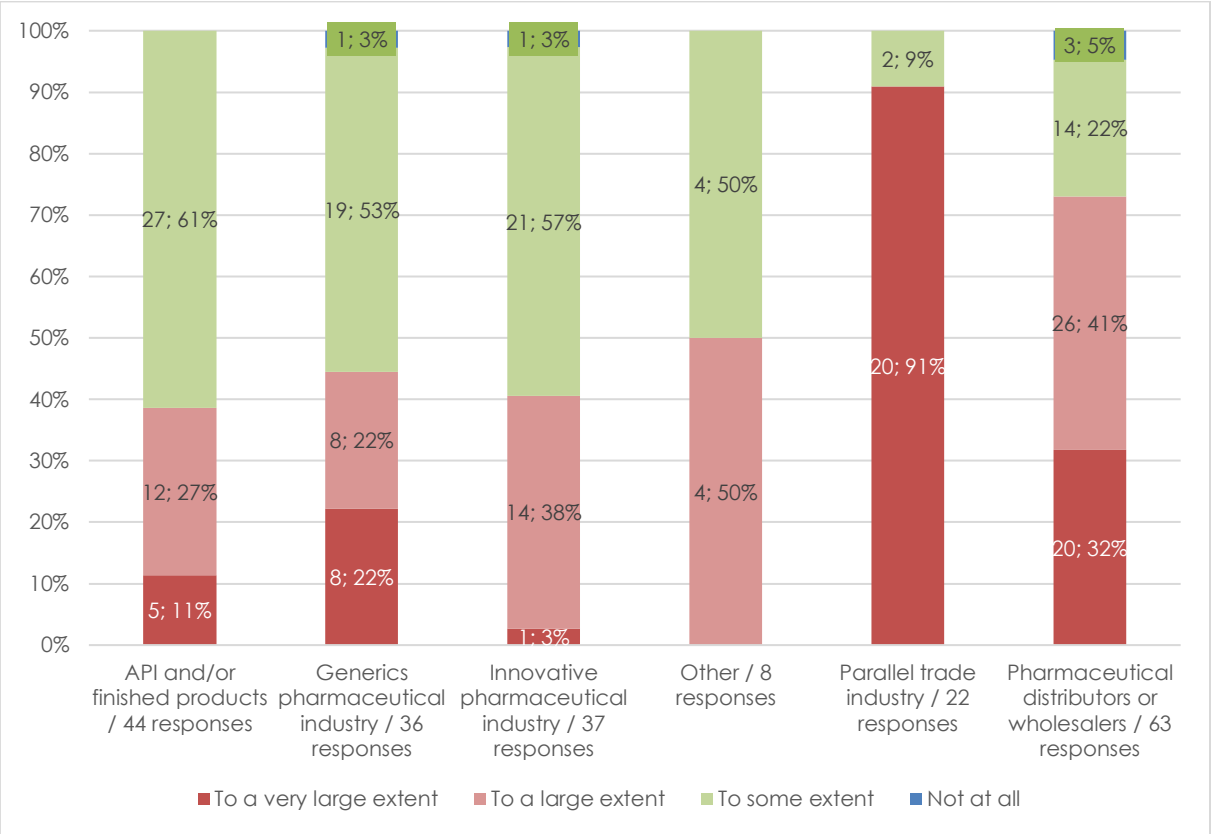
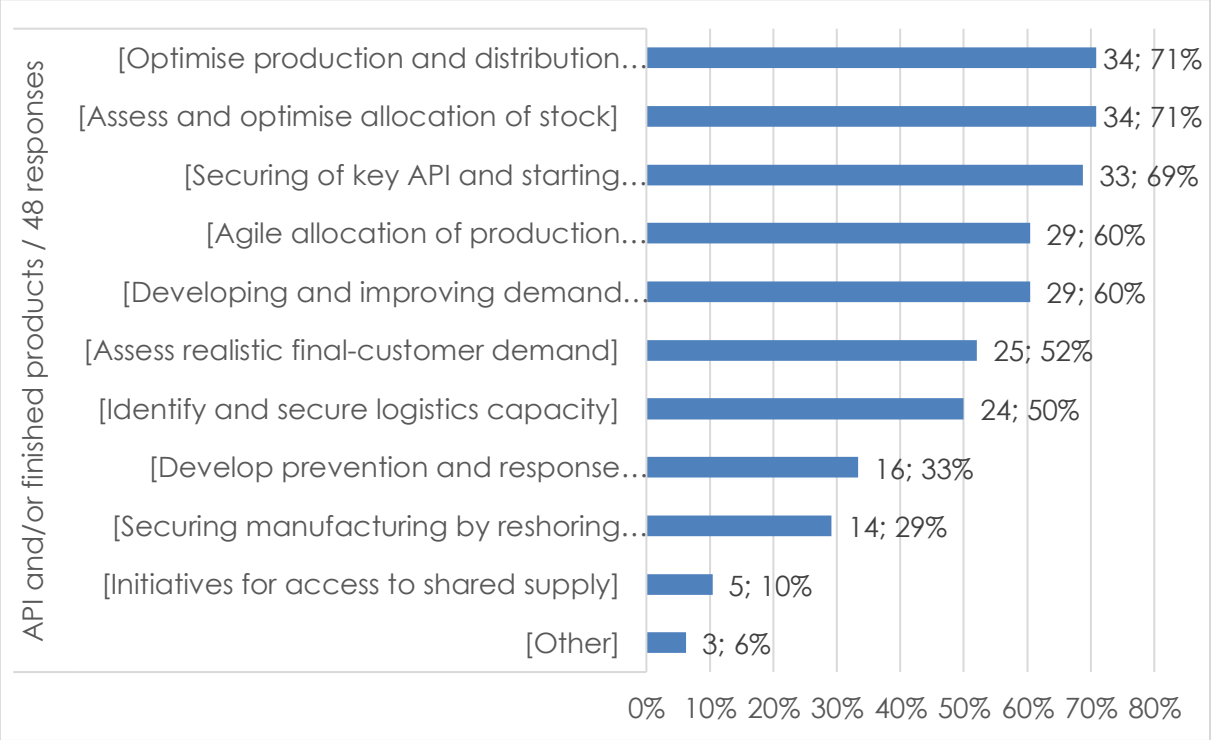
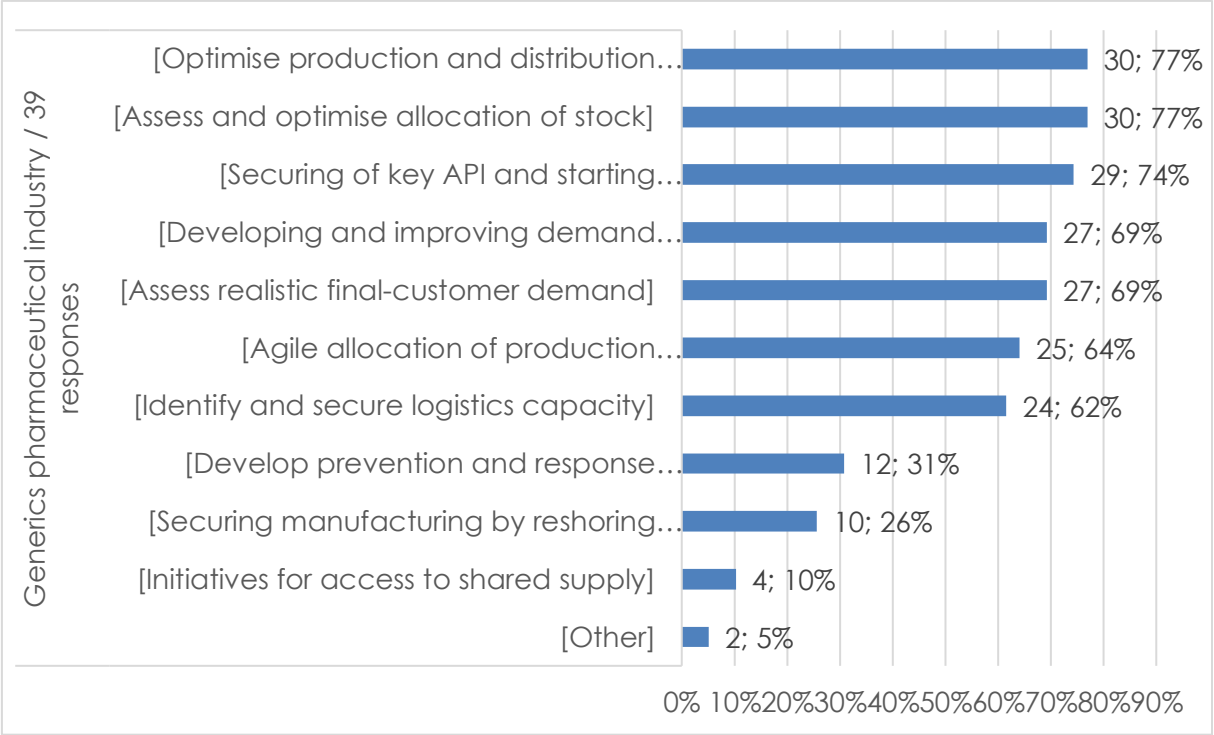
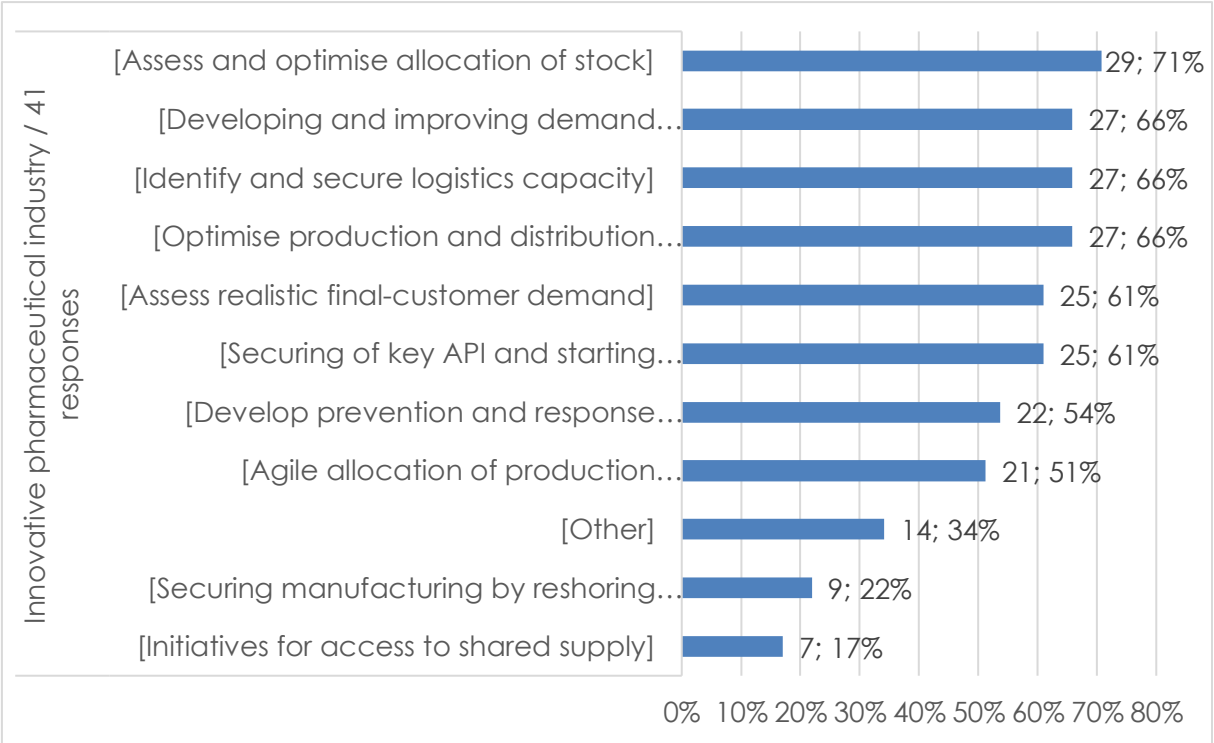
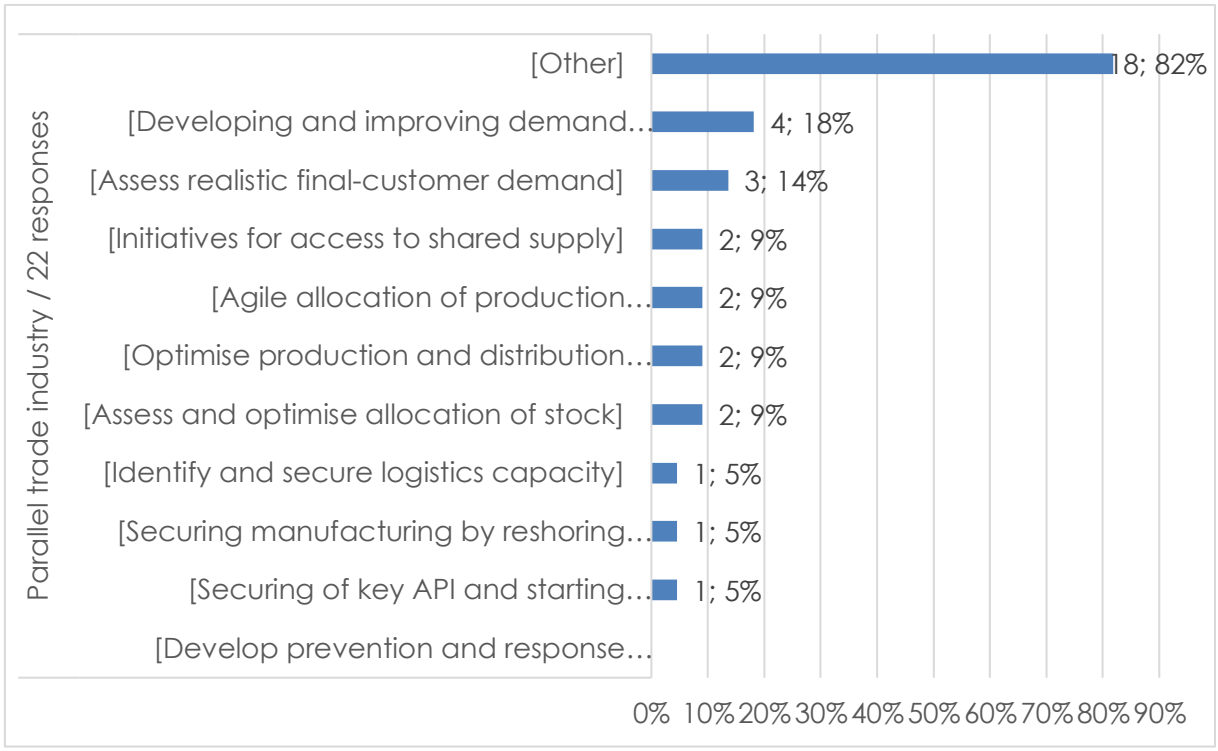


Figure 85 Has your organisation implemented any of the following measures to address medicine/API shortages in your operations?




Generics pharmaceutical industry / 39 responses
[Optimise production and distribution…
[Assess and optimise allocation of stock]
[Securing of key API and starting…
[Developing and improving demand…
[Assess realistic final-customer demand]
[Agile allocation of production…
[Identify and secure logistics capacity]
[Develop prevention and response…
[Securing manufacturing by reshoring…
[Initiatives for access to shared supply]
[Other]
30; 77%
30; 77%
29; 74%
27; 69%
27; 69%
25; 64%
24; 62%
12; 31%
10; 26%
4; 10%
2; 5%
0% 10%20%30%40%50%60%70%80%90%


Innovative pharmaceutical industry / 41 responses
[Assess and optimise allocation of stock]
[Developing and improving demand…
[Identify and secure logistics capacity]
[Optimise production and distribution…
[Assess realistic final-customer demand]
[Securing of key API and starting…
[Develop prevention and response…
[Agile allocation of production…
[Other]
[Securing manufacturing by reshoring…
[Initiatives for access to shared supply]
29; 71%
27; 66%
27; 66%
27; 66%
25; 61%
25; 61%
22; 54%
21; 51%
14; 34%
9; 22%
7; 17%
0% 10% 20% 30% 40% 50% 60% 70% 80%


Parallel trade industry / 22 responses
[Other]
[Developing and improving demand…
[Assess realistic final-customer demand]
[Initiatives for access to shared supply]
[Agile allocation of production…
[Optimise production and distribution…
[Assess and optimise allocation of stock]
[Identify and secure logistics capacity]
[Securing manufacturing by reshoring…
[Securing of key API and starting…
[Develop prevention and response…
18; 82%
4; 18%
3; 14%
2; 9%
2; 9%
2; 9%
2; 9%
1; 5%
1; 5%
1; 5%
0% 10% 20% 30% 40% 50% 60% 70% 80% 90%

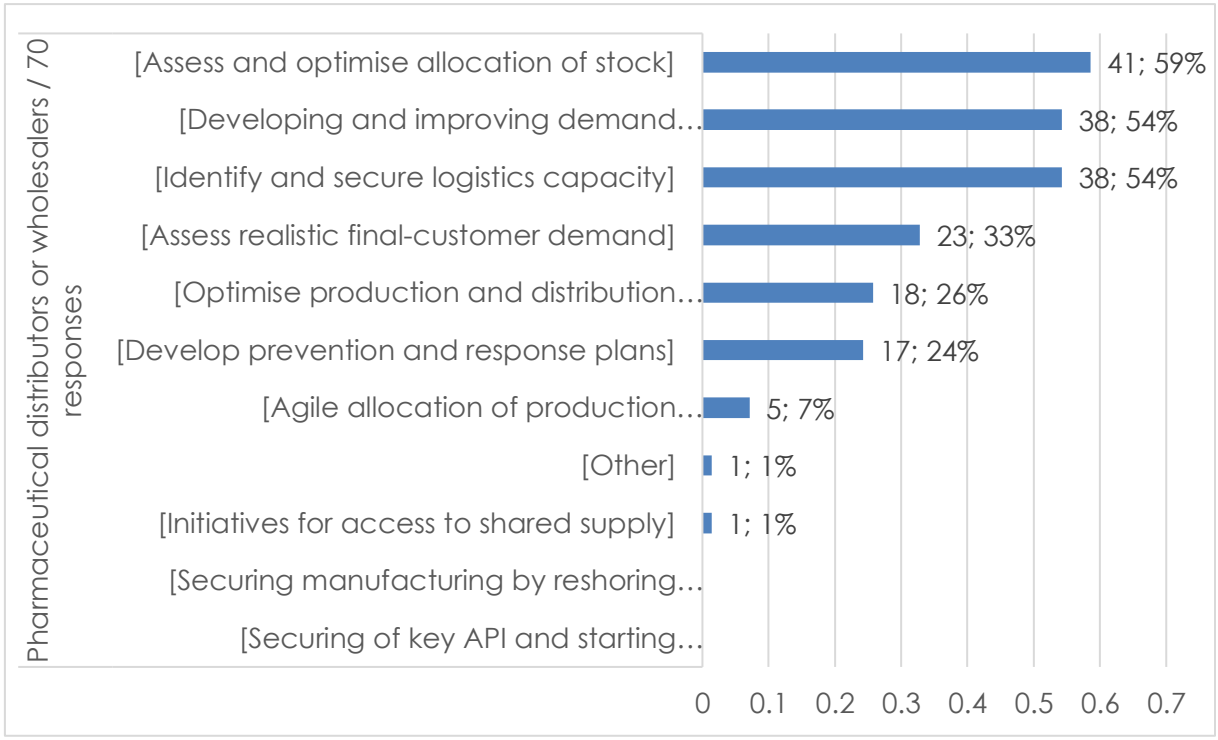

Pharmaceutical distributors or wholesalers / 70 responses
[Assess and optimise allocation of stock]
[Developing and improving demand…
[Identify and secure logistics capacity]
[Assess realistic final-customer demand]
[Optimise production and distribution…
[Develop prevention and response plans]
[Agile allocation of production…
[Other]
[Initiatives for access to shared supply]
[Securing manufacturing by reshoring…
[Securing of key API and starting…
41; 59%
38; 54%
38; 54%
23; 33%
18; 26%
17; 24%
5; 7%
1; 1%
1; 1%
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7

Figure 86 At the level of the EU, which of the following measures do you consider necessary in addressing medicine shortages? Please select up to 5 answers

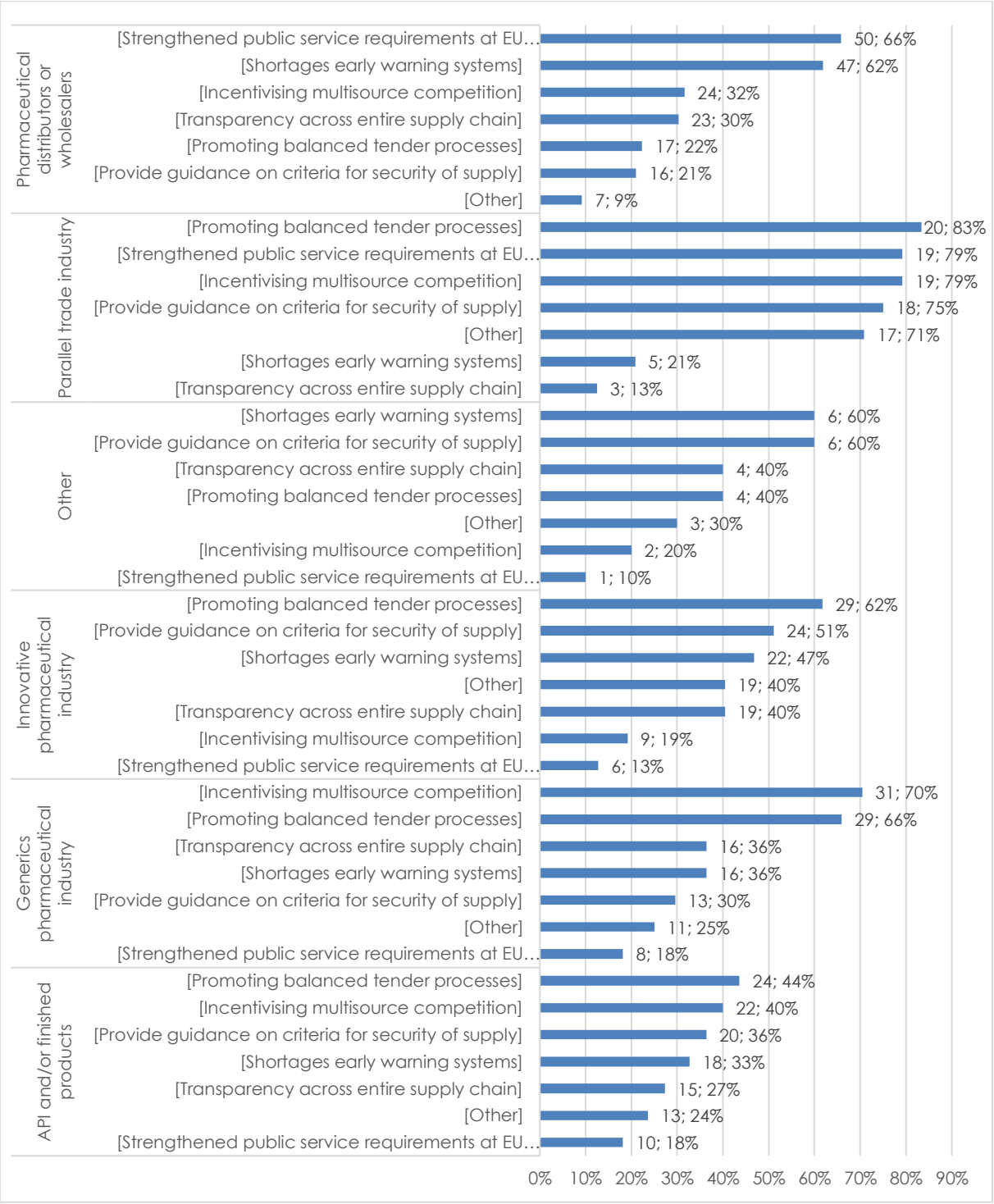
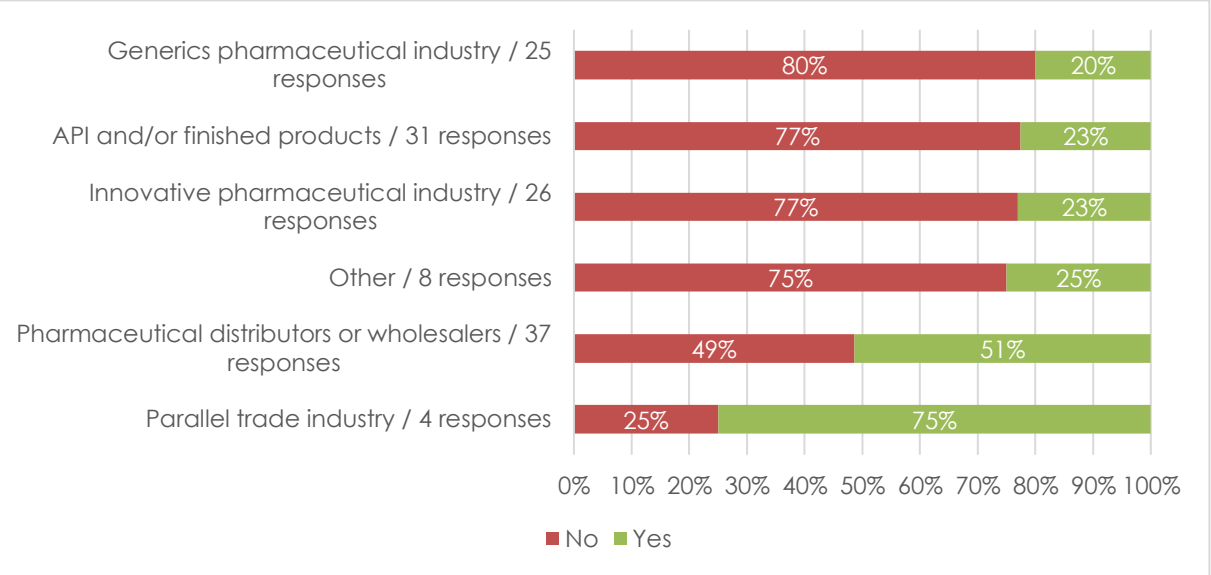


Figure 87 Did the implementation of the European obligation for market authorisation holders to notify competent authorities if a product ceases to be placed on the market (temporarily or permanently) have an impact on your operations?



Annex I. PRODUCT CASE STUDIES

This Annex contains the full product case studies. Summaries of these have been incorporated into Chapter 0 of the main report. Selection of the case studies was based on the criteria described in Section 2.7.

I.1. EpiPen

Product description

One of the most public cases of a shortage of a medicinal product in recent years has been that of the so-called 'EpiPen'. Epipens are epinephrine (adrenaline) filled auto-injectors that are used as an emergency treatment for people at risk of anaphylaxis from a severe allergic reaction.[282] The benefits of epinephrine in treatment of anaphylactic shock have been known for over 150 years.[283] Because of its importance as a potentially life-saving medicine, epinephrine is also included on the WHO Essential Medicines List. However, it wasn't until the 1970s that it became available in a formulation for self-administration, via a device known as the EpiPen. The auto-injector design originated in the United States as a device to treat soldiers exposed to nerve gas. It is a spring-loaded syringe pre-filled with a fixed dose of epinephrine.[284] It is designed to be carried by those at risk of anaphylaxis and can be used without medical expertise. The device technology has been patented by Survival Technology Inc.

The EpiPen was first approved by the USFDA in 1987. A marketing authorisation was granted to Meridian Medical Technologies, currently a subsidiary company of Pfizer.[285] Since then, the rights to market the EpiPen have changed multiple times. It is currently owned by Mylan, which acquired it from Merck KGaA in 2007. Mylan markets two versions of the EpiPen: a 300 microgram formulation (EpiPen®) and a 150 microgram formulation specifically for young children, the EpiPen Jr®. Both versions have been approved through national procedures in all EU Member States.[282] The EpiPen is what is known as a combination product: it combines a medicine (epinephrine) with an injection device. The epinephrine is produced by Pfizer, whilst the device is manufactured by Pfizer's subsidiary Meridian Medical Technologies.[286] All devices are manufactured at a single plant in the United States.[287] The assembled product is then sold and marketed by Mylan.

When Mylan acquired the rights to the EpiPen, the product had annual sales of around USD 200 million.[288] Mylan has since managed to further grow the market: in 2019 the company was reported to share 65% of the total market which is estimated around $750 million per year.[289,290] In 2012 Mylan launched the EpiPen4Schools programme to advocate for the availability of epinephrine auto-injectors in elementary, middle and high schools in the US. Under this programme, Mylan offers

[282] Committee for Medicinal Products for Human Use. (2015) CHMP Assessment report. Available at: www.ema.europa.eu/contact. Accessed 16 June 2021.
[283] Arthur G. (2015) Epinephrine: A short history. The Lancet Respiratory Medicine. 3:350-1. Available at: www.thelancet.com/respiratory
[284] Rimler R. (Updated 9 April 2020) The Long, Strange History of the EpiPen. Available at: https://www.healthline.com/health-news/strange-history-of-epipen#Discovery-of-adrenaline. Accessed 16 June 2021.
[285] Ramsey L. (17 August 2018) The strange history of the EpiPen, the device developed by the military that turned into a billion-dollar business that now faces generic competition between Mylan and Teva. Available at: https://www.businessinsider.nl/the-history-of-the-epipen-and-epinephrine-2016-8?international=true&r=US. Accessed 17 June 2021.
[286] Clopton J. (10 May 2019) Frustration Mounts as EpiPen Shortage Hits 1 Year. Available at: https://www.webmd.com/allergies/news/20190510/frustration-mounts-as-epipen-shortage-hits-1-year. Accessed 16 June 2021.
[287] Hirschler B. (10 May 2018) In Europe, Mylan's rivals try to plug EpiPen shortages | Reuters. Available at: https://www.reuters.com/article/us-mylan-epipen-idUSKBN1IB26Z. Accessed 16 June 2021.
[288] Raymond N. (17 August 2017) Mylan, U.S. finalize $465 million EpiPen settlement | Reuters. Available at: https://www.reuters.com/article/us-mylan-epipen-idUSKCN1AX1RW. Accessed 17 June 2021.
[289] HEAT (28 March 2019) EpiPen's Evolving Market Share. Available at: https://heatinformatics.com/posts/epipens-evolving-market-share. Accessed 17 June 2021.
[290] Keown A. (19 February 2019) Teva Eyes 25 Percent of the $750 Million EpiPen Market by Year's End. BioSpace. Available at: https://www.biospace.com/article/teva-eyes-25-percent-of-the-750-million-epipen-market-by-year-s-end/. Accessed 17 June 2021.

schools discounts[291] and donations on EpiPens. Mylan has also been instrumental in the adoption of the 2013 School Access to Emergency Epinephrine Act, which allows US states to give funding preference to schools that maintain a supply of epinephrine auto-injectors and train staff to administer these.[292] Whilst this law does not specifically refer to the brand EpiPen, Mylan's market position makes it the largest commercial beneficiary of the programme.

In 2016, Mylan announced it would market its own generic version[293] but the company has long managed to hold off generic competition by others. In 2019, Teva launched the first generic competitor to the EpiPen. Although other epinephrine auto-injectors are marketed both in the US and in Europe, thus far none have achieved the brand recognition of the EpiPen.[294]

Supply and shortage status

In March 2018, Mylan warned of supply problems for the EpiPen in Britain.[287] By then, shortages had already been signalled in Canada and the United States as well. In May 2018, the USFDA confirmed that the US was experiencing a severe shortage of EpiPens.[286] The shortages in the US affected both the branded and Mylan's own generic version of the 300 microgram EpiPen but not the EpiPen Jr.295 Mylan acknowledged the supply problems and attributed these to otherwise unspecified "production delays" at a Meridian production site. The site had previously been shut down for maintenance and upgrades. Along with an unplanned equipment downtime, this meant that the production was insufficient to meet demand and build up reserves. The production problems followed a warning issued in September 2017 by the FDA to Meridian of numerous violations of good manufacturing practices. However, Mylan and Pfizer denied any causal link between this warning and the sites' ability to manufacture and supply products.[286,296] Mylan did not offer further insight into what had caused the manufacturing problems.297

Data from the national shortage registries show shortages reported throughout 2018 and 2019 in Belgium, Croatia, France, Germany, Hungary, Ireland, the Netherlands, Norway, Portugal, Slovakia, Slovenia, Spain and Sweden. Nearly all notifications involved the pens produced by Mylan and included both the EpiPen and the EpiPen Jr.[298] For notifications for which a root cause was provided, around half of notifications (44%) listed manufacturing issues and a further 35% cited distribution issues.

The supply problems for Mylan lasted for over a year.[286] In the meantime, various other suppliers of epinephrine auto-injectors (such as ALK-Abello AS, Bausch Health Companies) ramped up production to fill some of the market gaps left by Mylan. A 2018 report in the Lancet suggested that stocks of these alternative were also threatening to run low as a result of the increased demand.[297] Although the worst of the EpiPen shortage appears to be over, several countries have continued reporting new

[291] Mylan N.V. (27 October 2017) Mylan's EpiPen4Schools® Program Surpasses One Million Free Epinephrine Auto-Injector Donations to U.S. Schools. Available at: https://www.prnewswire.com/news-releases/mylans-epipen4schools-program-surpasses-one-million-free-epinephrine-auto-injector-donations-to-us-schools-300545086.html. Accessed 16 June 2021.

[292] Jarrett V. (13 November 2013) President Obama Signs New EpiPen Law To Protect Children with Asthma and Severe Allergies, And Help Their Families To Breathe Easier. The White House. Available at: https://obamawhitehouse.archives.gov/blog/2013/11/13/president-obama-signs-new-epipen-law-protect-children-asthma-and-severe-allergies-an. Accessed 16 June 2021.

[293] Simon S. (29 August 2016) Mylan to launch generic version of EpiPen, at half the cost. Available at: https://www.statnews.com/2016/08/29/generic-epipen-mylan/. Accessed 17 June 2021.

[294] Whooley S. (20 August 2019) Teva launches generic EpiPen Jr. Drug Delivery Business. Available at: https://www.drugdeliverybusiness.com/teva-launches-generic-epipen-jr/. Accessed 17 June 2021.

[295] LaMotta L. (9 May 2018) EpiPen shortage tied to Pfizer manufacturing issues | BioPharma Dive. Available at: https://www.biopharmadive.com/news/epipen-shortage-tied-to-pfizer-manufacturing-issues/523183/. Accessed 17 June 2021.

[296] Scutti S. (8 May 2018) EpiPen shortage reports unfounded, Mylan says - CNN. Available at: https://edition.cnn.com/2018/05/08/health/epipen-shortage-us-bn/index.html. Accessed 17 June 2021.

[297] The Lancet Child & Adolescent Health: editorial. (31 October 2018) The EpiPen shortage: how has it come to this? The Lancet Child and Adolescent Health 2:839. Elsevier B.V. Available at: https://doi.org/10.1016/S2352-4642(18)30344-4. Accessed 16 June 2021

[298] Portugal, Spain, France, Germany and Ireland during this time also reported a shortage of Allergopharma's adrenaline autoinjector.

shortages. As of the time of data collection, Belgium, Ireland, Norway, Portugal and Spain all list current shortages of EpiPens.

Impact and solutions

The long shortage of EpiPens has had a severe impact on patients, parents, pharmacists and clinicians who all have had to deal with finding remaining supplies or suitable alternatives.[299] Because of Mylan's dominant market share, the gap left by its inability to meet demand was very substantial and could not easily be filled by competitor brands or generic alternatives. To mitigate the impact of the EpiPen shortage, in August 2018 the USFDA released a statement announcing that it had decided to allow EpiPen (but not the EpiPen Jr) devices to remain on the market for four months after their labelled expiration date.[300] The UK's Medicines and Healthcare products Regulatory Agency (MHRA) similarly allowed extension of the expiration date for not only the EpiPen but also for one of the EpiPen's competitor products, the Jext pen.[301] It is unclear if any of the affected EU Member States took similar measures or to what extent patients have had to use EpiPens beyond their expiration date. Because of critical shortages for the EpiPen Jr, UK community pharmacists were furthermore instructed to prioritise supplies for smaller children.[302]

The EpiPen shortage highlights the vulnerability of the supply chain in situations where there is a particularly dominant supplier and where the production capacity is highly concentrated. Because in this case the manufacturing issues do not appear to have been caused by underlying shortages of raw materials or device components, the impact could have been less severe if either Mylan's production had not been tied to a single production site or if there had been more manufacturers with sufficient production capacity to ramp up supply to meet demand. The lack of generic competition is not uncommon for complex drug-device combination products, which are harder to replicate than typical small-molecule medicines. Some analysts expect that with the launch of the generic EpiPen by Teva and other auto-injectors, the position of Mylan could weaken and that the market will become more diverse.[303] This could also help to prevent, or at least mitigate the impact, of future supply disruptions.

[299] Ward M. (10 July 2019) How to Get EpiPen: US Shortage Enters Second Year - Bloomberg. Available at: https://www.bloomberg.com/news/articles/2019-07-10/-there-s-nothing-to-give-them-the-hunt-for-lifesaving-epipens. Accessed 17 June 2021.

[300] FDA, CDER (5 June 2019). Important Update on EpiPen® (epinephrine injection, USP) 0.3 mg Auto-Injectors from Mylan and Pfizer Extended Expiration Dates for Select Lots of EpiPen® 0.3 mg Auto-Injectors and its Authorized Generic. Available at: https://www.fda.gov/media/127690/download. Accessed 25 August 2021.

[301] Palmer E. (17 October 2018) U.K. fights EpiPen shortage by extending injector expiry dates | FiercePharma. Available at: https://www.fiercepharma.com/manufacturing/uk-fights-epipen-shortage-by-extending-injector-expiry-dates. Accessed 16 June 2021.

[302] The Pharmaceutical Journal. (18 October 2018) Small children prioritised under emergency protocol to tackle "critical" EpiPen shortage. Available at: https://pharmaceutical-journal.com/article/news/small-children-prioritised-under-emergency-protocol-to-tackle-critical-epipen-shortage. Accessed 25 August 2021.

[303] Edwards C. (April 2019) Epipen: from monopoly to multiplicity. Medical Technology 14. Available at: https://medical-technology.nridigital.com/medical_technology_apr19/epipen_from_monopoly_to_multiplicity. Accessed 16 June 2021.

I.2 5-Fluorouracil

Product description

5-Fluorouracil (5FU) is used in the treatment of many adult and paediatric cancers, including topically for skin cancer.[304] It is one of the most commonly used cancer therapeutics and can be used by itself or, more commonly, in combination with other medicines. It inhibits DNA synthesis by blocking the incorporation of the thymidine nucleotide into DNA.[305] In addition, it blocks an enzyme which converts the cytosine nucleotide into the deoxy derivative.

5FU was developed and patented in 1957 by Dr Charles Heidelberger and came into medical use in 1962.[306] It was first added to the WHO essential medicines list in 1977, where it was indicated for unspecified malignant neoplasms. In 2015, this indication was replaced with several more specific indications, namely malignant neoplasms of breast, colon, nasopharynx, and rectum as well as neoplasm metastasis in large intestine.[307] As a cancer treatment, 5FU is administered intravenously. By now, it is predominantly sold as a generic drug.

In the EU, 5FU is a component of the standard therapy for a variety of malignancies, including colorectal, pancreatic, gastric, breast and head and neck cancers.[308] It can be administered via bolus infusion[309] or as a continuous infusion over several days. It is most frequently administered with the modulator leucovorin as the standard combination chemotherapy for colon cancer. Two prodrugs of 5FU are also in use in the EU: 1) Tegafur (available as part of the combined product Teysuno) which is approved for treatment of rectal, colon gastric, and breast cancer, as well as some types of brain tumours; and 2) capecitabine (brand name, Xeloda) currently authorised for the treatment of colorectal, gastric and breast cancers. In 2018, in the EEA, about 600,000 patients were treated with 5FU and its prodrugs in oncological indications and about 1,500,000 patients were treated with topical 5FU products.[310] 5FU is authorised in all EU countries with the main manufacturers being Accord Healthcare, Teva Pharmaceuticals, Sandoz, Pfizer, Hospira UK, Hexal and Ebewe Pharma.[311]

Supply and shortage status

Between 2010 and 2021 there have been multiple 5FU shortages, of varying severity, across about half of EU Member States. The first major shortage was recorded in 2012 in Germany when Teva Pharmaceuticals discontinued sales of 5FU because the company no longer deemed the supply of the product to be economically viable.[312] This left the country with only a sole (German) supplier, who struggled to meet the increased demand.[313] The resulting knock-on effect was said to have been felt

[304] World Health Organization. (no date) Fluorouracil. Electronic essential medicines list. Available at: https://list.essentialmeds.org/medicines/91. Accessed 12 June 2021.

[305] Drugbank Online (no date). Fluorouracil. Available at: https://go.drugbank.com/drugs/DB00544. Accessed 12 June 2021.

[306] Chu, E. (2007) 'Clinical Colorectal Cancer: "Ode to 5-Fluorouracil"', *Clinical Colorectal Cancer*, 6(9), p. 609. Available at: https://doi.org/10.3816/CCC.2007.n.029.

[307] World Health Organization. (2019) World Health Organization Model List of Essential Medicines 21st list 2019. Available at: http://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?sequence=1&isAllowed=y. Accessed 25 August 2021.

[308] EMA Pharmacovigilance Risk Assessment Committee (2020) Fluorouracil and fluorouracil related substances (capecitabine, tegafur and flucytosine) containing medicinal products. Assessment report.

[309] Bolus administration is the administration of a fixed dose of medicine within a specific, usually relatively short, space of time.

[310] Boshnakova, A. et al. (2017) 'Cancer medicines shortages in Europe - Policy recommendations to prevent and manage shortages', The economist intelligence unit, European Society for Medical Oncology. Available at: https://www.eiu.com/graphics/marketing/pdf/ESMO-Cancer-medicines-shortages.pdf.

[311] EMA (2018) List of nationally authorised medicinal products. Active substance: 5 fluorouracil (i.v. application). Procedure no.: PSUSA/00000007/201712.

[312] Brazil, R. (30 May 2019) 'Shortages of generic cancer medicines are harming patients. So why can't we fix it?'. Cancerworld. Available at: https://archive.cancerworld.net/spotlight-on/shortages-of-generic-cancer-medicines-are-harming-patients-so-why-cant-we-fix-it/.

[313] The Economist. (2019). Country profile: cancer medicines shortages. Germany. The Economist Intelligence Unit Limited, supported by the European Society for Medical Oncology. Available at: https://www.esmo.org/content/download/197312/3552896/1/ESMO-Country-profile-Germany.pdf. Accessed 19 August 2021.

across eastern and central Europe as Germany resorted to parallel import of 5FU from lower-price countries.

Data from the national shortage registries confirms that, in 2013 and 2014, there were several more instances of shortages of 5FU due to permanent market withdrawals: in 2013 Sandoz withdrew from Slovakia and in 2014 TEVA withdrew from Italy. Shortages meanwhile have continued in Belgium, France, Ireland, Portugal, Slovenia and Spain. For most of these notifications, either manufacturing (63%) or distribution issues (21%) were reported as the root cause. Portugal has been particularly heavily affected by 5FU shortages: between 2017 and 2020, the country has reported shortages of 5FU from various suppliers in nearly every quarter. Along with Italy and Spain, it continued to list current shortages of 5FU at the time of data collection.

Impact and solutions

The 2012 5FU shortage in Germany meant that about 170,000 patients with colon cancer could not be treated properly.[313] Such delays and interruptions to chemotherapy can be highly distressing for patients, families, carers and healthcare professionals given its importance for positive patient outcomes. Recent publications suggest that shortages of several essential, generic oncology medicines, among them 5FU, continue to recur periodically affecting the availability of treatments for patients.[312, 310,314] For some indications, such as colorectal, gastric and breast cancers, capecitabine could be used as a substitute for 5FU in which case the consequences may be less severe. [315,316]

A 2018 survey by the European Society for Paediatric Oncology showed that over 80% of the countries had authorised 5FU use in children and 5FU had been available in around 94% of these countries in 24 months prior to the survey.[317] This suggests that, despite notified shortages of 5FU in several member States between 2016 and 2018, the product remained in high availability for use in paediatric treatment during this time.

[314] European Cancer Organisation. (2020) Response of the European Cancer Organisation to the Roadmap consultation on a new EU Pharmaceutical Strategy.

[315] EMA Pharmacovigilance Risk Assessment Committee. (2020) Fluorouracil and fluorouracil related substances (capecitabine, tegafur and flucytosine) containing medicinal products. Assessment report.

[316] Alpert, A. and Jacobson, M. (2019) 'Impact of Oncology Drug Shortages on Chemotherapy Treatment', *Clinical Pharmacology & Therapeutics*, 106(2), pp. 415–421. doi: 10.1002/cpt.1390.

[317] Vassal, G. et al. (2021) 'Access to essential anticancer medicines for children and adolescents in Europe', Annals of Oncology, 32(4), pp. 560–568. Available at: https://doi.org/10.1016/j.annonc.2020.12.015.

I.3 DTPP (Combinations of Diphtheria, tetanus, pertussis, and polio vaccines)

Product description

Childhood immunisation programmes, including vaccines against various infectious diseases, have greatly reduced the incidence of several life-threatening diseases and child mortality. These days, vaccines for diphtheria, tetanus, pertussis (whooping cough) and polio (DTPP) are commonly administered as a combination vaccine, to reduce the number of immunisations required in infancy. The combination diphtheria, tetanus, and pertussis (DTP) vaccine is most commonly administered (three doses in infancy) and has been used since the 1940s.[318] Because of their importance for global public health, polio and tetanus vaccines have been on the WHO essential medicines list since 1977 and diphtheria and pertussis vaccines since 1999.[319]

The diphtheria and tetanus vaccines contain toxoids while the pertussis and polio vaccines comprise inactivated antigens.[318] Initial preparations contained whole-cell pertussis antigens, but concern regarding minor yet common local reactions and less common severe reactions led to the development of acellular vaccines in the 1980s. However, whole-cell pertussis vaccine remains a safe, inexpensive and effective option as it can generate more antibodies which is associated with higher vaccine efficacy.

Various combination products, with trade names including Daptacel and Infanrix, have been authorised in EU Member States. The two main manufacturers are GlaxoSmithKline (GSK) and Sanofi/Sanofi-Pasteur.[320] The vaccines are delivered through injections and as such are supplied as suspensions, solutions, or pre-filled syringes.[321]

Supply and shortage status

In 2015, the ECDC reported a major shortage of acellular pertussis-containing vaccines. This was caused by a reduction of production capacity for the pertussis antigen.[322] A 2019 survey on vaccine shortages conducted among those in charge of national immunisation programmes or vaccine supply/procurement in EU/EEA, found that six EU countries had experienced vaccine shortages between 2016 and 2018.[323] DT-containing vaccines were among those most frequently affected.

The shortage situation that begun in 2015 was reflected in the data provided by the NCAs: most shortage notifications occurred between 2015 and 2019. Shortages of DTPP combination vaccines were recorded in 15 Member States, with nearly a fifth of notifications (19%) made in Spain, closely followed by Portugal (17%). Where information on root causes was provided, this most often concerned manufacturing issues. Only Italy and Spain reported current shortages at the time of data collection. All reported product withdrawals occurred before the second half of 2018.

[318] World Health Organization. (2014) Information sheet. Observed rate of vaccine reactions – Diphtheria, pertussis, tetanus vaccines. Available at: https://www.who.int/vaccine_safety/initiative/tools/DTP_vaccine_rates_information_sheet.pdf. Accessed 12 June 2021.

[319] World Health Organization (no date) Electronic essential medicines list. Available at: https://list.essentialmeds.org/?section=503 Accessed 12 June 2021.

[320] European Medicines Agency. (2021) List of nationally authorised medicinal products. Active substance: diphtheria / tetanus / pertussis (acellular, component) and poliomyelitis (inactivated) vaccine (adsorbed), diphtheria / tetanus / pertussis (acellular, component) and poliomyelitis (inactivated)vaccine (adsorbed) reduce antigens content. Procedure no.: PSUSA/00001126/202007.

[321] Drugbank Online. (no date) Bordetella pertussis pertactin antigen. Available at: https://go.drugbank.com/drugs/DB10789. Accessed 12 June 2021.

[322] European Centre for Disease prevention and Control. (2015) Shortage of acellular pertussis-containing vaccines and impact on immunisation programmes in the EU/EEA. Available at: https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/vaccine-shortage-rapid-risk-assessment-october-2015.pdf Accessed 12 June 2021.

[323] Filia, et al. (2020) Are vaccine shortages a relevant public health issue in Europe?, European Journal of Public Health, 30 (Supplement 5), pp. ckaa165.670. Available at: https://doi.org/10.1016/j.ijid.2020.09.1261.

Vaccine shortages are not limited to Europe but rather are a global problem. Underlying issues include increasing global demand owing to large immunisation programmes in Africa and Asia, and concentration of production in a handful of large pharmaceutical companies.[324,325]

Impact and solutions

Non-availability of vaccines for immunisation presents a major threat to public health. In the EU diphtheria and tetanus are no longer a risk for young, vaccinated infants thanks to high vaccination coverage rates, whilst polio has been largely eliminated from the WHO European Region.[323] Nevertheless, these diseases are severe, and any disruptions in the usual vaccination schedule could have major consequences. Pertussis still causes child deaths worldwide and vaccination is important to prevent severe disease or death.[322]

Shortages in combination vaccines can be mitigated by use of individual vaccines or other combinations supplemented by individual vaccines, where available. However, the 'monovalent' vaccines are hardly manufactured anymore: for instance, pertussis vaccines are no longer available as standalone vaccines.[322,324] Other mitigation strategies could include adjustments to the timing of doses, stockpiling, importing from non-EU countries, and centralised vaccine imports.

The shortage of acellular pertussis-containing combination vaccines in 2015 prompted some countries to adjust their immunisation policy as follows:[322]

- Temporary suspension of the primary immunisation scheme (e.g. Bulgaria)
- Changes to the primary immunisation schedule age of dose administration (e.g. Romania, Hungary)
- Modification of the vaccine formulation used as pre-school booster (e.g. Belgium, France)
- Delayed introduction of a new antigen in the primary immunisation scheme (e.g. Norway)
- Prioritisation of vaccine formulation for the primary immunisation scheme (e.g. Spain, Sweden)

[324] SWI (2017) What's behind Switzerland's vaccine shortage? Available at: https://www.swissinfo.ch/eng/drug-dilemma_what-s-behind-switzerland-s-vaccine-shortage/43412750 Accessed 12 June 2021.

[325] Filia, et al. (2021) 'Report on previous experiences with vaccine shortages in EU countries (and non-EU consortium member countries), and responses at national and European levels', European Joint Action on Vaccination report

I.4 Midazolam

Product description

Midazolam is a short-acting muscle relaxant, sedative medicine used to create drowsiness and relieve anxiety before surgeries or cause a state of decreased consciousness in seriously ill people in intensive care units (ICUs). It belongs to the class of benzodiazepines[326], which inhibit neuron activity in the brain and nervous system. Midazolam is a fast-acting medicine used in children, adults and elderly persons. As one of the few water-soluble benzodiazepines, it suitable for injection but can also be used in tablet form. The onset of action is rapid (within 1 minute) when used intravenously. The patient does not become unconscious but loses the ability to remember things. Midazolam is used regularly as a pre-anaesthetic after which anaesthesia is deepened with another intravenous anaesthetics.[326] The tablet form of midazolam is used mainly for sleep disorders but also for sedation (calming) and anxiolysis (reducing anxiety). Like other medicines in the benzodiazepine group, midazolam is suitable for countering prolonged, acute, convulsive epileptic seizures[327]. Terminally ill patients are sometimes administered midazolam to give rest in the last stages of life. As of 2010, it is the most used benzodiazepine in anaesthetic medicine[328].

Midazolam hydrochloride was first synthesised in 1976 by Fryer and Walser and patented in 1974. It came into medical use in 1982.[329] The synthesis of Midazolam is a fairly complicated process which involves conversion of tricyclic acid to Midazolam at scale.[330]. Isolation techniques such as dehydrogenation have proven to result in low yields with limited purity. Therefore, production processes have been optimised to minimise by-product formation and to increase yield and purity.

Amongst others, Midazolam is branded as Dormicum and marketed by Roche as tablets and is available in different dosages depending on the application. In addition, injection ampoules are sold in a concentration of 5 mg/ml. Midazolam is available as a generic medication.[331] Manufacturers include Novell Pharmaceutical Laboratories (for injection) and Roxane Laboratories (oral syrup). In 2011, the European Medicines Agency (EMA) granted a marketing authorisation to Shire Pharmaceuticals (now Takeda) for a buccal application form[332] of Midazolam, sold under the trade name Buccolam[333]. Buccolam was approved for the treatment of prolonged, acute, convulsive seizures in children from three months to 18 years of age. This was the first application of a paediatric-use marketing authorisation.

---

[326] The American Society of Health-System Pharmacists. (no date) Midazolam. Drugs.com. Available at: https://www.drugs.com/monograph/midazolam.html. Accessed July 2021.

[327] Brigo F., Nardone R., Tezzon F., Trinka E. (August 2015). "Nonintravenous midazolam versus intravenous or rectal diazepam for the treatment of early status epilepticus: A systematic review with meta-analysis". Epilepsy & Behavior. 49: 325–36. doi:10.1016/j.yebeh.2015.02.030. PMID 25817929. S2CID 33207030.

[328] Oparil S, Weber M (22 April 2005). Hypertension: a companion to Brenner and Rector's the kidney (2 ed.). Philadelphia: Elsevier Mosby. p. 816. ISBN 978-0-7216-0258-5.

[329] Fischer J., Ganellin C.R. (2006). Analogue-based Drug Discovery. John Wiley & Sons. p. 539. ISBN 9783527607495.

[330] Madhup K., DhaonGrant L., EsserDeborah A., DavisAshok V., Bhatia, Abbott Laboratories, 1999, patent no. US6512114B1.

[331] Hamilton R (2015). Tarascon Pocket Pharmacopoeia 2015 Deluxe Lab-Coat Edition. Jones & Bartlett Learning. p. 21. ISBN 9781284057560.

[332] In buccal administration, a medicine is absorbed into the bloodstream after being held in the mouth to allow for diffusion through the cheek tissue.

[333] European Medicines Agency. (2011) European public assessment report (EPAR) for Buccolam. EMA/522148/2011. Available at: https://www.ema.europa.eu/en/documents/overview/buccolam-epar-summary-public_en.pdf.

Midazolam is included in the World Health Organization's List of Essential Medicines.[334] It is listed as a Schedule IV drug under the Convention on Psychotropic Substances[335] as is registered as a controlled substance in many countries.[326]

Supply and shortage status

Prior to 2020, there had been several instances of shortages of Midazolam. In April 2014, several Member States temporarily recalled Buccolam from the market following deficiencies in the manufacturing process due to potential contamination with another medicine produced at the same factory.[336] Supply disruptions occurred in Finland, France, Germany, Italy and Spain. The issue was resolved in March 2015. Data from the national shortage registries also show that between 2017 and 2019 shortages of Midazolam from different suppliers were reported in Belgium, France, Ireland, Italy, Portugal, Slovenia and Spain. Most were attributed to distribution issues.

In 2020, following the onset of the COVID-19 pandemic, demand for Midazolam suddenly sharply increased. Midazolam is used as a first-line sedative in the management of COVID-19 patients.[337] Sedatives play an integral role in treatment of patients with COVID-19 by inducing amnesia and facilitate intubation. They are also used post-intubation to improve pulmonary compliance and reduce discomfort during mechanical ventilation. Supply of Midazolam could not keep up with the rapidly increased demand. Shortages of Midazolam were recorded in the national shortage registries in Belgium, Estonia, Ireland, Italy, Portugal, Slovenia, Spain and Sweden, many of which attributed the shortage directly to increased demand. Six countries continued to list Midazolam as a current shortage at the time of data collection.[338] In the US, the FDA also reported a shortage of sedatives and updated listings for five manufacturers who note an increased demand for Midazolam.[339]

As an intensive therapy unit medicine, Midazolam is part of a relatively small supply chain and is produced in a limited number of factories. As such, it was warned to be subject to demand pressure due to COVID-19 and available stock is monitored daily.

Impact and solutions

In Brazil, the shortage of sedatives sparked by the COVID-19 crisis, in combination with high numbers of seriously ill patients, resulted in reports of patients being tied down in ICUs and intubated without effective sedatives.[340] No such reports were found for any of the EU Member States. Nonetheless, the shortage of sedatives was seen as a very serious issue. It not only put COVID-19 patients in ICUs at risk but also non-COVID-19 patients in need of surgery. It was feared that, as elective surgery and anaesthetic activity resume, allocation of sedatives could become an increased issue that would impact a larger audience.[341]

In response to the COVID-19 crisis, some governments have centralised management of procurement and stocking of critical medicines, including Midazolam. For example, the French

[334] World Health Organization. (2019) World Health Organization model list of essential medicines: 21st list 2019. Geneva: World Health Organization. hdl:10665/325771. WHO/MVP/EMP/IAU/2019.06. License: CC BY-NC-SA 3.0 IGO.

[335] International Narcotics Control Board. (August 2003). "List of psychotropic substances under international control" (PDF). incb.org. Available at: https://www.ema.europa.eu/en/documents/overview/buccolam-epar-summary-public_en.pdf.

[336] European Medicines Agency. (2015) Buccolam Midazolam Shortage – Europe. Available at: https://www.ema.europa.eu/en/documents/shortage/buccolam-midazolam-supply-shortage_en.pdf.

[337] Royal College of Anaesthetics, Association of Anaesthetics. (2020) Guidance on potential changes to anaesthetic drug usage and administration during pandemic emergency pressures. Available at: https://icmanaesthesiacovid-19.org/drug-demand-supply-anaesthetic-drug-usage-and-administration.

[338] Belgium, Italy, Portugal, Slovenia, Spain and Sweden.

[339] Brennan, Regulatory Focus (2020) FDA reports shortage of sedation drug used for putting COVID-19 patients on ventilators. Available at: https://www.raps.org/news-and-articles/news-articles/2020/4/fda-reports-shortage-of-sedation-drug-used-for-put.

[340]Reuters (2021). Brazil's hospitals running out of sedatives as COVID-19 rages. Available at: https://www.reuters.com/world/americas/brazils-covid-19-response-cost-thousands-lives-says-humanitarian-group-2021-04-15/.

[341] Montmeat et. al., (2020). Shortage of sedatives and neuromuscular blockers during COVID-19 pandemic: The result of an overstocking procedure in French hospitals?. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7326429/.

government issued a national platform for managing medicine shortages of five priority medicines including Midazolam in April 2020. A national requisition was placed on the stock of these medicines, and hospitals and pharmacies were not authorised to purchase them. The French government took complete responsibility for purchasing all stocks from the companies and ensured distribution to the hospitals on a weekly basis.[342] Prior to this, a strategic stock from Accord Healthcare (22,000 units) was distributed from France to meet the raised demand in the United Kingdom in March 2020.[343] In the same period, the European University Hospital Alliance called for concerted action between Member States and on European level. It noted that, next to personal protective equipment and ventilators, existing hospital stocks of muscle relaxants, sedatives and pain-killing medicines were being consumed rapidly and feared that insufficient or non-existing resupply would become the limiting factor in the care for COVID-19 patients. The EUHA thus called for intensifying collaboration and coordination of the supply of critical medicines for intensive care patients.

Besides stockpiling and (joint) procurement strategies on national and European level, strategies have been suggested that focus on reducing usage of sedatives in ICU patients to reduce (the risk of) shortages. [344] In case a patient requires light sedation, an escalation strategy could be used whereby alternative agents are promoted for patients with lower sedation needs and infusions are reserved for patients who need deeper sedation. Protocolised and targeted sedation could prevent over-sedation and unnecessary sedative usage and shorten the duration of mechanical ventilation.

[342] French Ministry of Health. Ministerial direction related to the procurement and supply of some priority drugs to health facilities, as part of the fight against the Covid-19 epidemic, 2020.

[343] Wickware C. (19 May 2020) Supplies of sedative used for COVID-19 patients diverted from France to avoid potential shortages. The Pharmaceutical Journal. Available at: https://pharmaceutical-journal.com/article/news/supplies-of-sedative-used-for-covid-19-patients-diverted-from-france-to-avoid-potential-shortages.

[344] Kanji, S., Burry, L., Williamson, D. et al. Therapeutic alternatives and strategies for drug conservation in the intensive care unit during times of drug shortage: a report of the Ontario COVID-19 ICU Drug Task Force. Can J Anesth/J Can Anesth 67, 1405–1416 (2020). Available at: https://doi-org.vu-nl.idm.oclc.org/10.1007/s12630-020-01713-5.

I.5 Amoxicillin(/clavulanic acid)

Product description

Amoxicillin/clavulanic acid, also known as co-amoxiclav, is a broad-spectrum antibiotic medicine, used to treat several common bacterial infections affecting, among others, the ear, throat, chest, urinary tract or skin. It is a combination of amoxicillin, a derivative of penicillin, developed by Beecham Group (part of GlaxoSmithKline Beecham today) in the 1960s; and clavulanic acid, a β-lactamase inhibitor, discovered in the 1970s also by Beecham scientists. The ratio of amoxicillin to clavulanic acid has varied over the years according to needs.[345]

It is used as first choice medication for adults and children for many indications. It can be taken orally as tablet, capsule or liquid (suspension), but may also be given as injection, usually in hospitals. However, use of broad-spectrum antibiotics, such as co-amoxiclav, has seen pushback and should be reserved for treating more serious infections as overuse of these antibiotics may contribute to antimicrobial resistance (AMR).[346] Amoxicillin/clavulanic acid has been on the WHO's List of Essential Medicines since 1997 where it is classified as a critically important human medicine. [347,348]

The oral formulations of the combination product have been available worldwide since 1981 and the intravenous formulation since 1984, under the brand name Augmentin. The product has been available as a generic medication since 2002 when the original patents protecting Augmentin expired. While GlaxoSmithKline moved to obtain additional patents on Augmentin in the USA before expiry in 2002, which would have extended its market protection until 2018, these were later invalidated due to "double patenting". Geneva Pharmaceuticals (the US generics unit of Novartis, currently Sandoz), followed by Teva and Ranbaxy (currently Sun Pharma), launched their generic version of the product in 2003 in the USA. The medicine is now marketed globally under numerous generic and trade names, including Augmentan, Augmentine, Clavamel, Clavamox, Clavepen, Clavulin, Clavumox, Clavurion, Neoduplamox, Noprilam, Pangamox, Penilan, and Spektramox. In Europe, marketing authorisation holders of generic versions also include Milpharm Limited (UK) and Pinewood Laboratories Ltd (Ireland).

In the European Union, until 2009, Augmentin had been authorised through national procedures. This led to divergences between Member States in the way the medicine could be used In 2009 the European Medicines Agency completed a review that concluded that there was a need for harmonisation of the therapeutic indications, of the recommended dosages and methods of administration information and of the information on contra-indications.[349] In 2009, the Commission issued a decision requiring Member States to update the information accordingly.

Supply and shortage status

The availability of amoxicillin and combination products containing amoxicillin has fluctuated in recent years, but shortages occur frequently. Co-amoxiclav was reported as one of the top 10 medicines in shortage in European hospitals by the EAHP's 2018 Survey on Medicines.[350] According to a report by Medicines for Europe in 2017, price pressure is one of the causes affecting the availability of

[345] European Medicines Agency. (2009) Review of Augmentin. Annex II. Available at: https://www.ema.europa.eu/en/documents/referral/augmentin-article-30-annex-ii_en.pdf Accessed 12 June 2021.

[346] National Institute for Health and Care Excellence (2018) NICEimpact antimicrobial resistance. Available at: https://www.nice.org.uk/media/default/about/what-we-do/into-practice/measuring-uptake/niceimpact-antimicrobial-resistance.pdf Accessed 11 August 2021).

[347] World Health Organization. Model list of essential medicines. Available at: https://list.essentialmeds.org/medicines/310. Accessed 12 June 2021.

[348] World Health Organization. (2019) Critically important antimicrobials for human medicine. Available at: http://apps.who.int/iris/handle/10665/312266 Accessed 12 June 2021.

[349] European Medicines Agency. (2009) Review of Augmentin. Available at: https://www.ema.europa.eu/en/medicines/human/referrals/augmentin Accessed 12 June 2021.

[350] Miljković et al. (2019) Results of EAHP's 2018 Survey on Medicines Shortages, European Journal of Hospital Pharmacy 2019;26:60-65. Available at: https://ejhp.bmj.com/content/26/2/60

medicines, including the injectable form of amoxiclav, and led to a "dramatic reduction in hospital suppliers" in Portugal.[351]

In a 2016 report, the French Agency for the Safety of Health Products investigating the situation related to the active substance amoxicillin for the French market.[352] It reported that in 2013, there was an inventory shortage of Panpharma's supply of amoxicillin for injectable solution due to quality issues at a manufacturing site. This required a massive switch to Clamoxyl. The report highlighted that there are only three manufacturers of the active substance worldwide, including two European sites (Austria and Spain) and a source in China. However, following a compliance check by the European Directorate for the Quality of Medicines & HealthCare (EDQM) and the Romanian authorities in 2015, the Chinese production site's Certificates of Suitability (CEP) was suspended, leaving only two GMP-compliant API production sites. It was concluded that, while the Chinese manufacturer is not one of the major suppliers of this active substance, given the small number of players, any quality/production problem encountered by a sodium amoxicillin manufacturer immediately affects the availability of injectable amoxicillin. According to EDQM's public certification database, currently additional manufacturers supplying sterile sodium amoxicillin include Italy and India, and the Chinese manufacturer holds a valid certificate since November 2020.[353]

In 2019, Sandoz Ltd recalled two batches of co-amoxiclav (various dosages) following a potential packaging issue relating to poor seal adherence.[354] Following the COVID-19 outbreak, shortages of antibiotics – including amoxicillin – were noted across the EU, due to a combination of increased demand and supply disruptions.[355] Antibiotics have also been included in the EMA's fast-track monitoring system to help member States prevent and mitigate supply issues with crucial medicines used to treat COVID-19 patients.[356] COVID-19 related shortages of antibiotics were also reported in the USA.[357] In March 2020, Great Britain included all forms of amoxicillin on its list of medicines that cannot be exported from the UK, meaning that it will not be possible for any Member State to obtain amoxicillin through importation from Great Britain.[358]

Data from the national shortages show notified shortages of amoxicillin/clavulanic acid, in different dosages, in Belgium, Estonia, France, Portugal and Romania, between 2015 and 2021. Most notifications (83%) originate from Portugal, which has recorded very frequent delivery delays,

[351] Medicines for Europe. (2017) Patient access to medicines: how to prevent medicine shortages? Available at: https://www.medicinesforeurope.com/docs/20171106_Overall_presentation_final.pdf Accessed 12 June 2021.

[352] The French Agency for the Safety of Health Products. (2016) Situation Report on the active substance amoxicillin. Available at: http://dev4-afssaps-marche2017.integra.fr/var/ansm_site/storage/original/application/cae8a3e3e3ec6ef704b2ff963d02d310.pdf Accessed 11 August 2021).

[353] Amoxicillin sodium - EDQM's public certification database. (no date) Available at: https://extranet.edqm.eu/4DLink1/4DCGI/Query_CEP?vSelectName=1&Case_TSE=none&vContains=1&vContainsDate=1&vtsubName=Amoxicillin+sodium&vtsubDateBegin=&vtsubDateBtwBegin=&vtsubDateBtwEnd=&SWTP=1&OK=Search

[354] See: Class 2 Medicines Recall: Co-amoxiclav 125 mg/31.25 mg/5 ml and 25 mg/62.5 mg/5 ml Powder for Oral Suspension (MDR 24-05/19). Available at: https://www.gov.uk/drug-device-alerts/class-2-medicines-recall-co-amoxiclav-125-mg-31-25-mg-5-ml-and-25-mg-62-5-mg-5-ml-powder-for-oral-suspension-mdr-24-05-19 Accessed 11 August 2021).

[355] Guarascio F. (8 July 2020) EU scrambles to buy intensive care drugs to tackle COVID shortages. Reuters. Available at: https://www.reuters.com/article/us-health-coronavirus-eu-patients-idINKBN2492D5. Accessed 19 August 2021.

[356] European medicines Agency. (no date) Availability of medicines during COVID-19 pandemic. Available at: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/availability-medicines-during-covid-19-pandemic. Accessed 19 August 2021.

[357] For example, in the US: CBS News (2020) Coronavirus outbreak causes first drug shortage in U.S., FDA says. Available at: https://www.cbsnews.com/news/coronavirus-human-drug-shortage-food-drug-administration/ Accessed 11 August 2021).

[358] Department of Health and Social Care and Medicines and Healthcare products Regulatory Agency. (3 October 2019, last updated 3 August 2021). List of medicines that cannot be exported from the UK or hoarded. Available at: https://www.gov.uk/government/publications/medicines-that-cannot-be-parallel-exported-from-the-uk. Accessed 11 August 2021).

ranging from just a few days to several months. At the time of data collection, current shortages were reported in Belgium, Estonia and Portugal.

Impact and solutions

When first-choice antibiotics are not available and patients are instead provided a suboptimal antibiotic with a different therapeutic spectrum, this can lead to poorer patient outcomes and an increased risk of side effects.[359] It can also contribute to a rise in AMR, particularly if the alternative has a broader spectrum, and increased healthcare costs.[360]

In May 2021, Sandoz, a global supplier of generic antibiotics and a key source of European antibiotics, including sterile amoxicillin - announced that it plans to invest EUR 150 million in the coming years to upgrade its antibiotics manufacturing technology and boost capacity.[361] In addition, the company stated that it will not increase the prices of priority antibiotics, including amoxicillin for the management of coronavirus respiratory infections, during the COVID-pandemic.[362]

[359] Beraud G. (12 February 2021). Shortages without Frontiers: Antimicrobial drug and vaccine shortages impact far beyondthe individual! Frontiers in Medicine. Available at: https://doi.org/10.3389/fmed.2021.593712.

[360] (March 2020). Shortages and AMR – why should we care? 4 consequences of antibiotic shortages. Available at: https://www.reactgroup.org/news-and-views/news-and-opinions/year-2020/shortages-and-amr-why-should-we-care-4-consequences-of-antibiotic-shortages/.

[361] Sandoz. (18 May 2021) Sandoz announces plans to further strengthen its antibiotics manufacturing setup in Europe. Available at: https://www.sandoz.com/news/media-releases/sandoz-announces-plans-further-strengthen-its-antibiotics-manufacturing-setup. Accessed 19 August 2021.

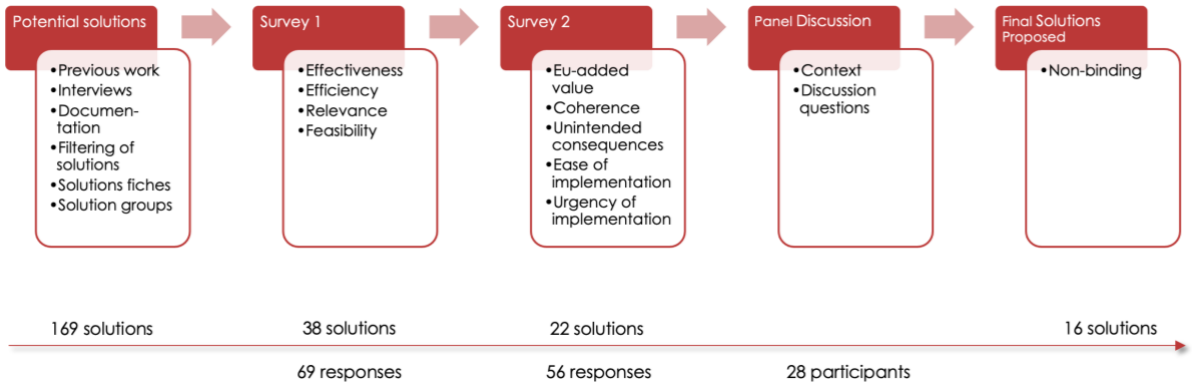
[362] https://www.raps.org/news-and-articles/news-articles/2020/2/generic-firms-brace-for-coronavirus-related-drug-s

Annex J. POTENTIAL SOLUTIONS TO SHORTAGES

Process of the Consultation

Figure 88 Solutions consultation process: overview

Technical Explanation



The following provides an explanation of how the indicators presented in Table 47 were calculated and what they represent.

Table 47 Technical Explanation of the calculations carried out on survey scores

Indicator	Explanation
Solution Group	Group the respective solution belongs to / Underlying root cause it addresses
Solution	Proposed solution
Total Average Score	The gathered responses were divided per 4 different stakeholder groups: i) Civil Society & Health Professionals; ii) Manufacturers; iii) Distributors & Parallel Traders; iv) NCAs. We calculated a total score per solution and stakeholder group. The average of these scores per solution and stakeholder group were then averaged (i.e. normalised) to calculate an overall, normalised total average score (TAS) per solution. We deemed it necessary to normalise per stakeholder group to make sure that no single stakeholder group's input will be overrepresented simply because they had more respondents to the respective surveys.
Difference in Sentiment between Stakeholder Groups	Here, we indicate how the respective solution scored per stakeholder group, where the difference between the normalised total score and the respective stakeholder group's score is displayed. For instance, the highest-ranking solution (Include information about available alternative medicines in shortage databases, with a total score of 4.40, is particularly supported by Distributors and Parallel Traders (stakeholder group score of close to 5), while being less supported by NCAs (group score of just above 4). To visualise the differences, the following colour codes were applied: Difference > 0.5: Dark Green (Proportionately strongly in favour) Difference 0.1 < 0.5: Light Green (Proportionately somewhat in favour) Difference - 0.1 < 0.1: Grey (Proportionately neutral) Difference -0.1 > - 0.5: Light Red (Proportionately somewhat opposed) Difference < - 0.5: Dark Red (Proportionately strongly opposed) This approach allowed us to identify which stakeholder groups are either relatively in favour of or opposed to a solution.

Consensus between Stakeholder Groups	Here, the standard deviation between the respective stakeholder groups on any single solution was calculated. In other words, we captured the degree of agreement / disagreement between the stakeholder groups on the solutions. The lower the score (standard deviation), the higher the agreement and vice versa.
Consensus within Stakeholder Groups	In addition to the consensus between stakeholder groups, we also captured the consensus within stakeholder groups, i.e. how much do respondents within a stakeholder groups agree on a solution. Once more, the lower the score (standard deviation), the higher the agreement and vice versa. This measure allows us to identify solutions that are controversial within stakeholder groups and serves as a control mechanism of the stakeholder grouping that the study team agreed on.
Consensus between Criteria	The four criteria used for the first survey (efficiency, effectiveness, relevance & feasibility) as well as the five criteria for the second survey (EU-added value, coherence, unintended consequences, ease of implementation & urgency of implementation) were also screened for consensus between each other. This helped us to see whether some criteria were more applicable for any single solution than others.

Assessment Criteria

The following provides an overview of the assessment criteria used in both surveys. Respondents were asked to assess each solution against defined statements corresponding to the assessment criteria, as presented in Table 48.

Table 48 Assessment Criteria for Potential Solutions

Survey	Criterion	Statements
1	Effectiveness	The proposed solution leads to a reduction in the occurrence and/or impact of shortages
1	Efficiency	The value that may be gained from this solution justifies the effort and resources needed for its implementation
1	Relevance	The proposed solution has a clear logical link to preventing and/or mitigating shortages
1	Feasibility	The proposed solution is realistic and can be implemented by relevant stakeholders
2	EU-added value	The proposed solution yields more value if implemented at EU level than at Member State level
2	Coherence	The proposed solution complements other solutions and does NOT create unnecessary duplication
2	Unintended Consequences[363]	The proposed solution does NOT pose major risks of unintended negative effects
2	Ease of Implementation	There are NO major obstacles to the implementation of the proposed solution
2	Urgency of Implementation	The proposed solution should be implemented as a matter of priority

Average scoring of solutions by assessment criteria

Figure 89 through 131 present the scores per solution by stakeholder group against the respective assessment criteria. These solutions were assessed by respondents and thereby filtered in two rounds. In the first round, four assessment criteria were applied to each solution, while in the second round, an additional five were employed. The figures representing those solutions that were excluded after the first round (Figure 89- Figure 104) therefore feature only four criteria, while those that proceeded to the second round (Figure 105 - Figure 126) feature nine in total.

[363] The assessment criterion *Unintended Consequences* implies a minimisation of consequences, meaning that the higher the score, the lower the risk of unintended consequences.

Figure 89 Establish and mainstream centralised and/or interoperable interfaces for monitoring shortages

Figure 90 Encourage pharmacists to increase the use of prospective risk assessments for the mitigation of medicines shortages

Figure 91 Support cooperation on national strategies for demand forecasting, planning, and shortage mitigation across the Member State

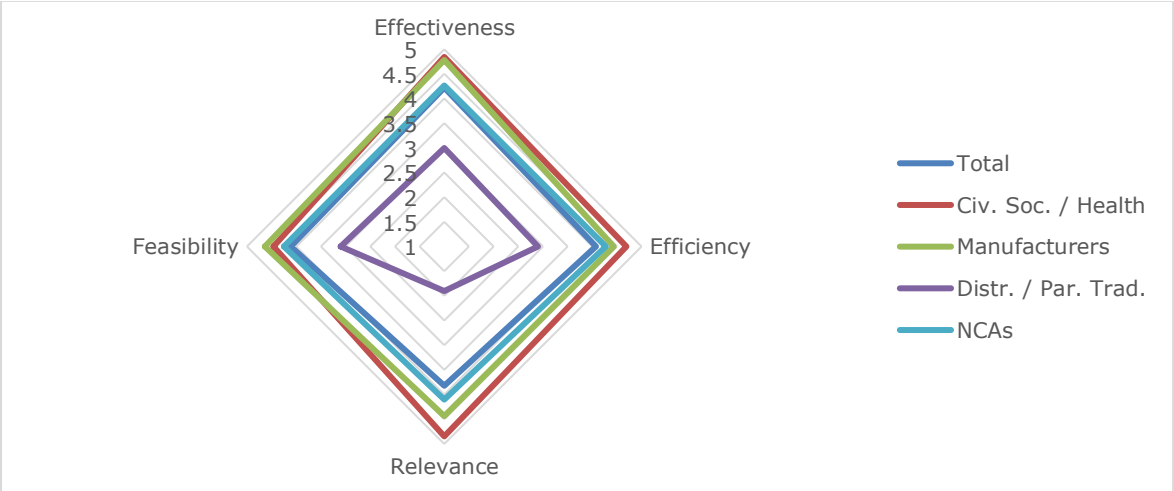


Figure 92 Create incentives for the local production of APIs

Figure 93 Wholesalers who are under a PSO obligation should have a right to be supplied

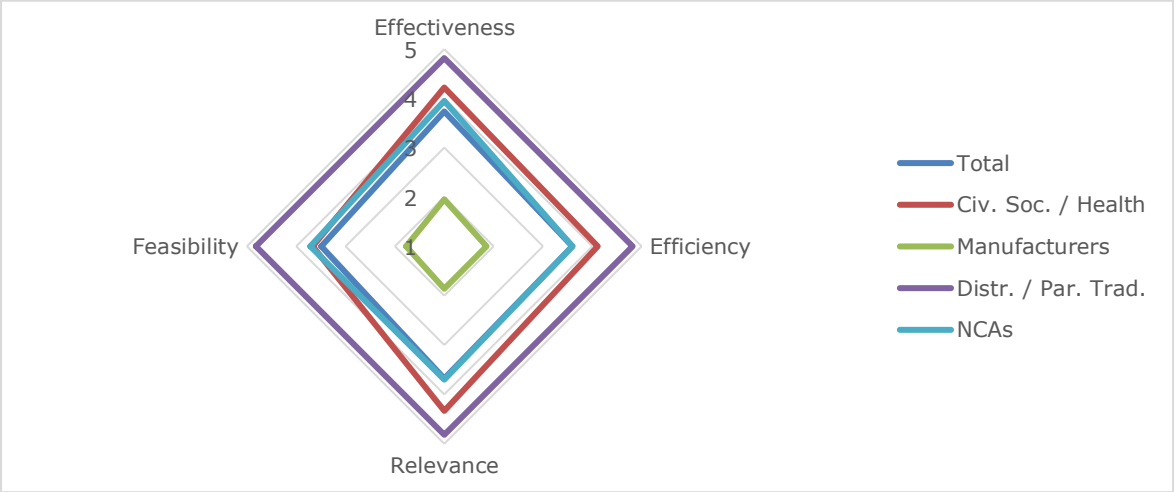


Figure 94 Enforcement of the commitment to supply by manufacturers / wholesale suppliers

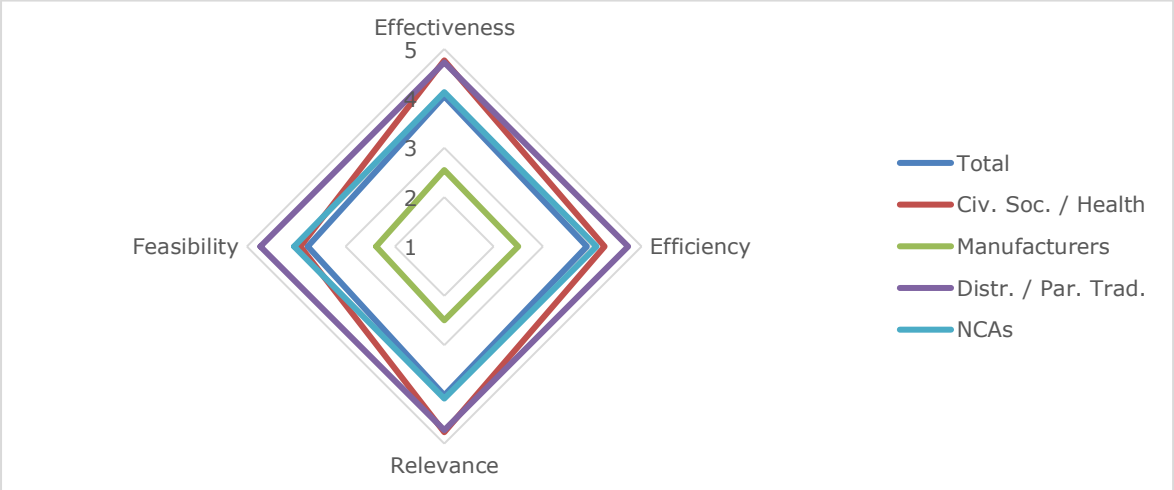


Figure 95 Restrict Direct-to-Pharmacy (DTP) Schemes

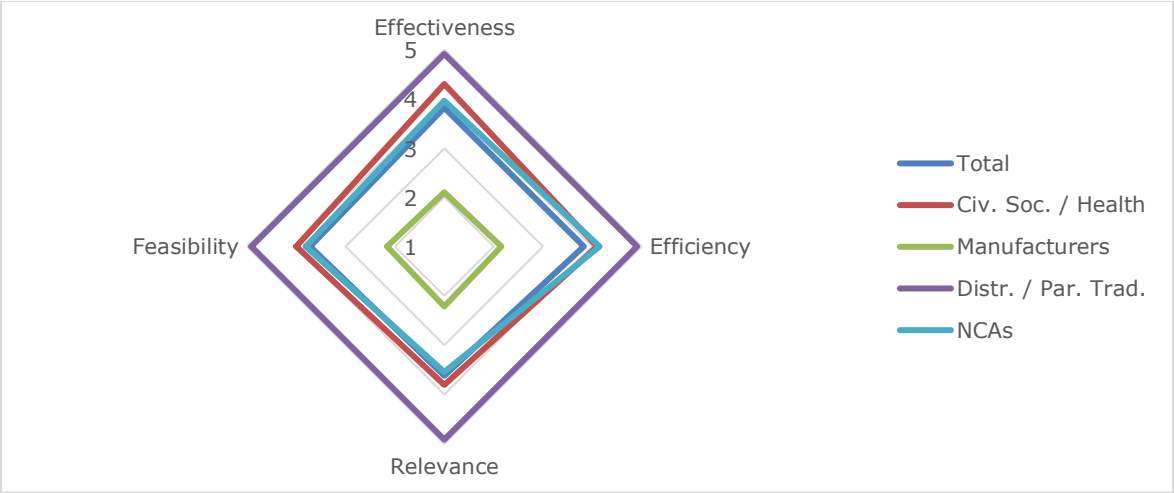


Figure 96 Set quotas for delivery to pharmacies in case of shortages

Figure 97 Introduce smaller and more frequent tenders aimed at maintaining healthy market competition

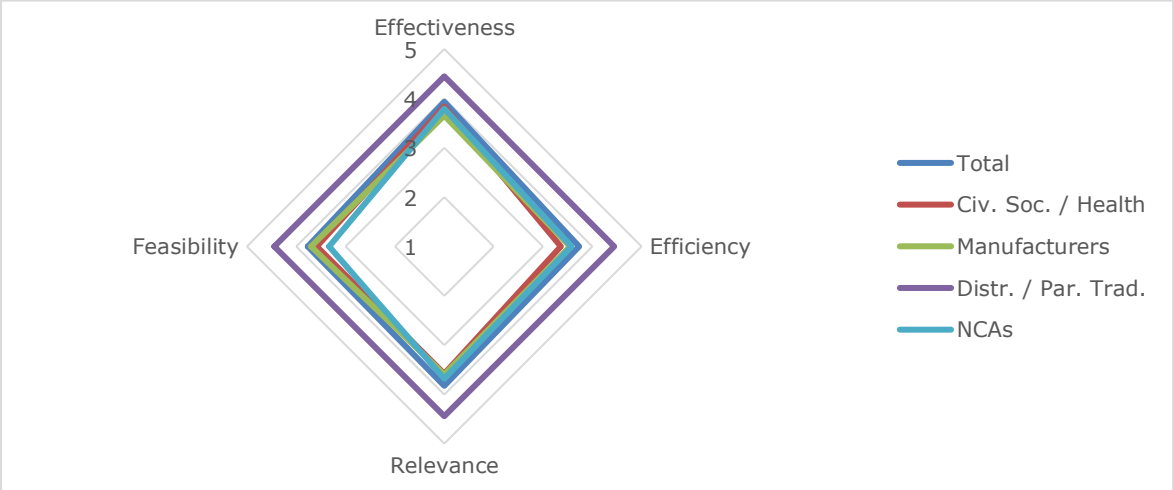


Figure 98 Anchor supply security provisions in procurement contracts

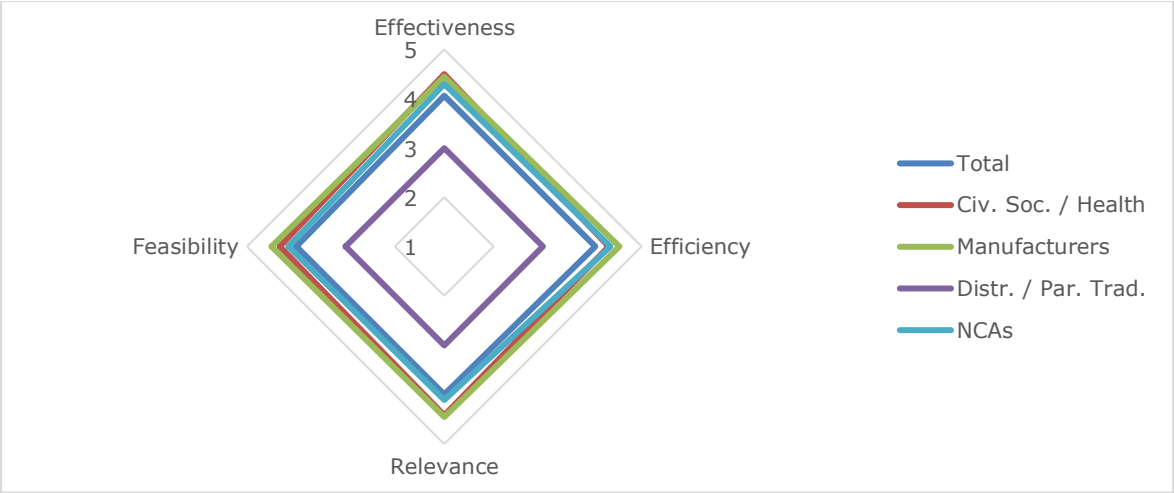


Figure 99 Adjust national tendering procedures so as to include criteria other than price

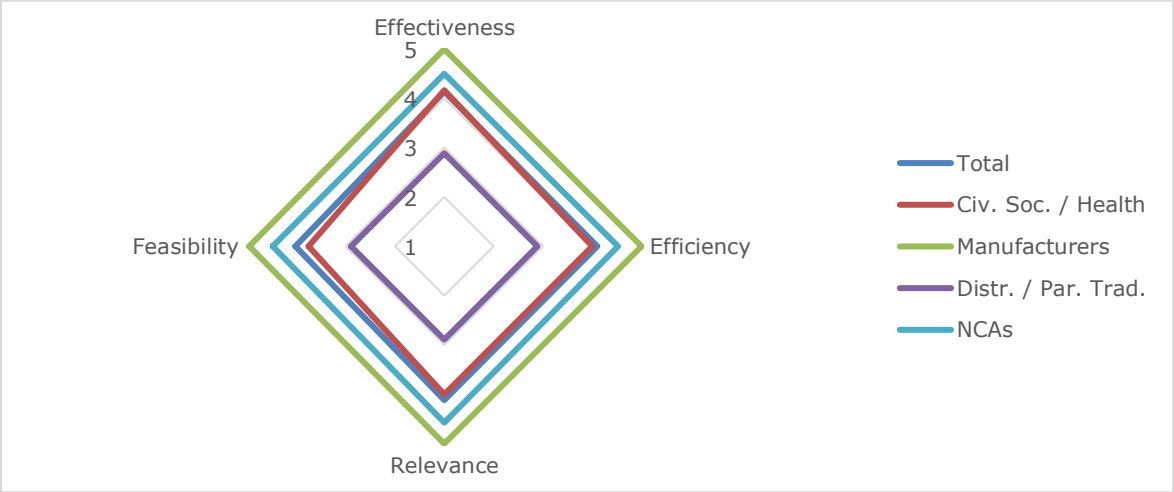


Figure 100 Make greater use of centralised and/or pooled procurement

Figure 101 Producers should avoid excessive national- and regional-level stockpiling and avoid procurement in excess of regular demand

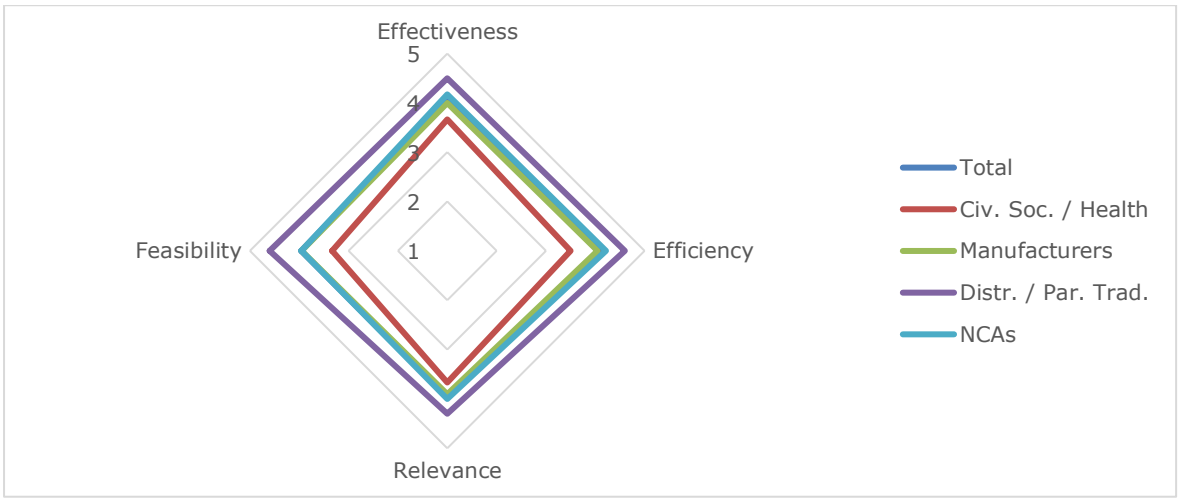


Figure 102 Introduce EU-coordinated strategic stockpiling

Figure 103 Allow the use of pharmacy preparations as alternatives

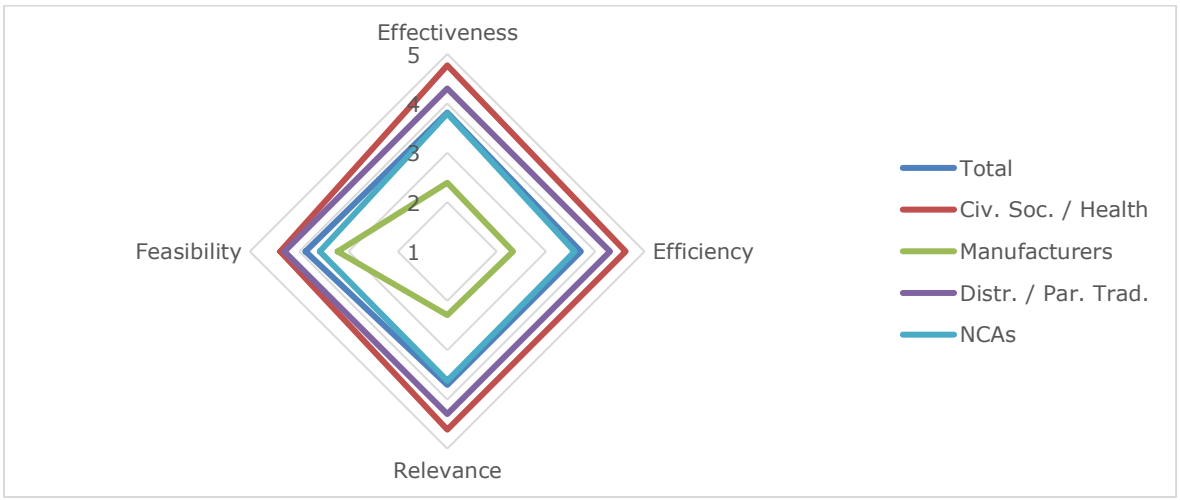


Figure 104 Greater flexibility of multi-country/-language packaging and labelling

Figure 105 Establish and follow a centralised and harmonised EU-wide definition of medicine shortages

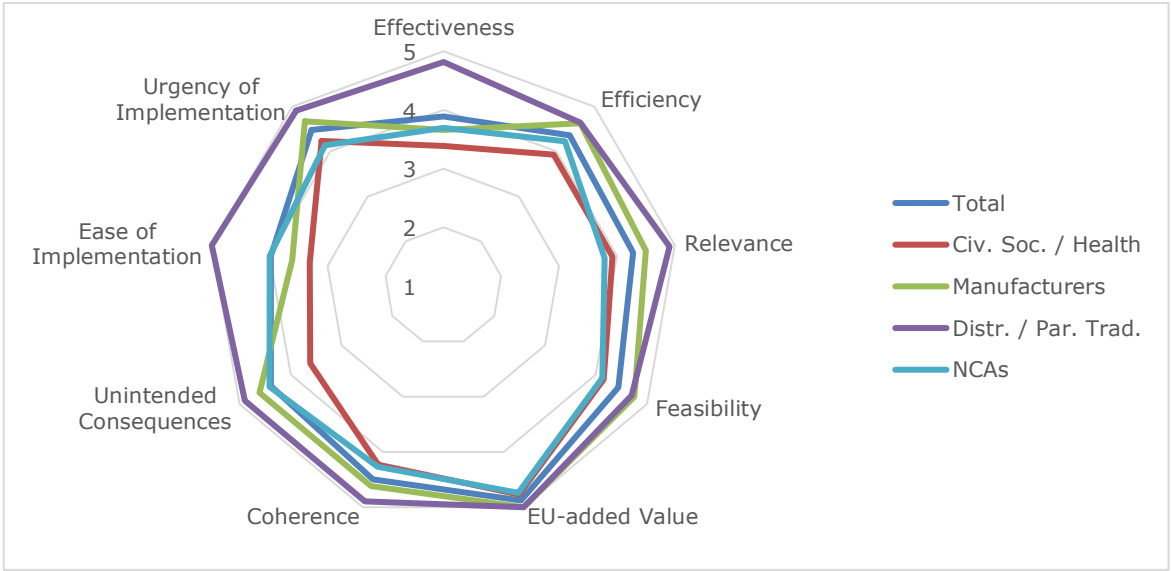


Figure 106 Establish and mainstream centralised reporting criteria for shortages

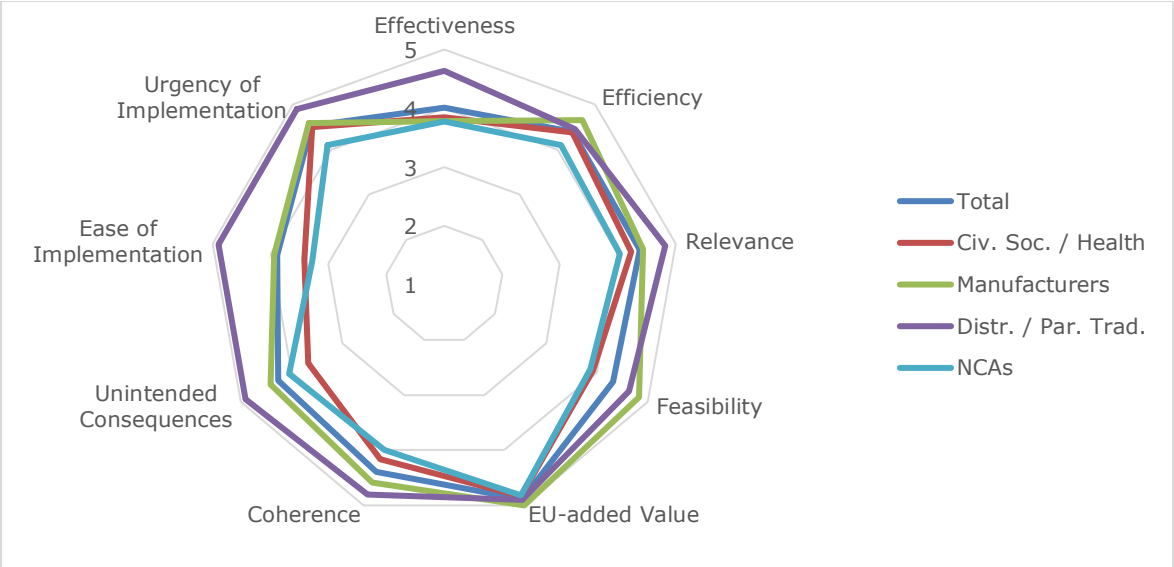


Figure 107 Increase the transparency of supply chains by use of appropriate systems and tools

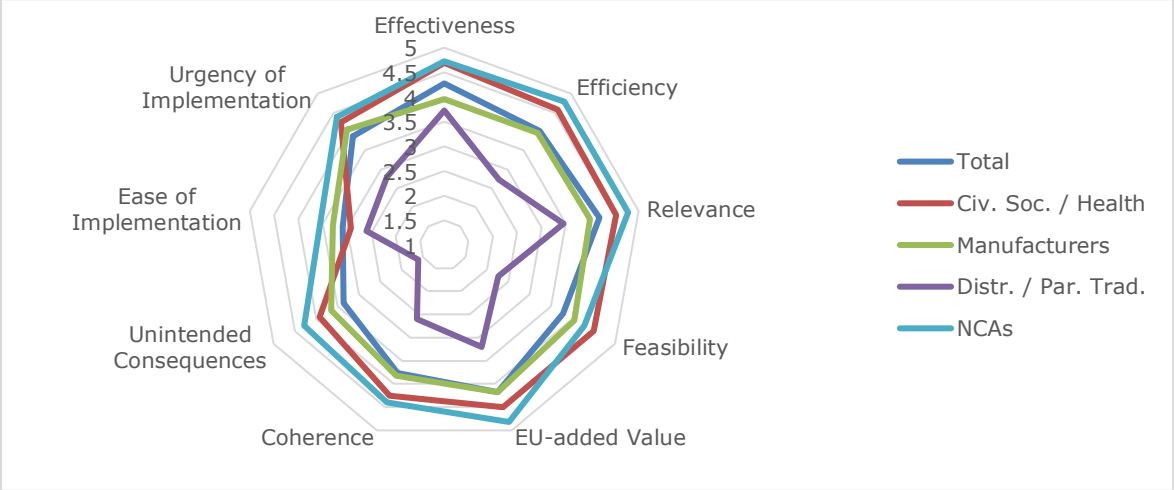


Figure 108 Strengthen and enforce notification obligations

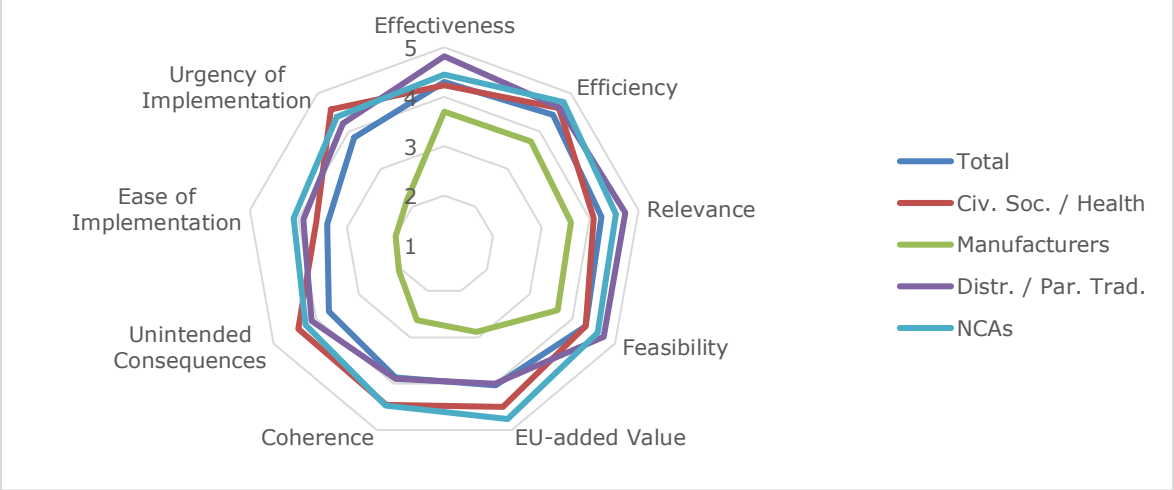


Figure 109 Develop an EU-wide list of medicines for which shortages are the most critical and develop policies and/or regulations to improve their availability

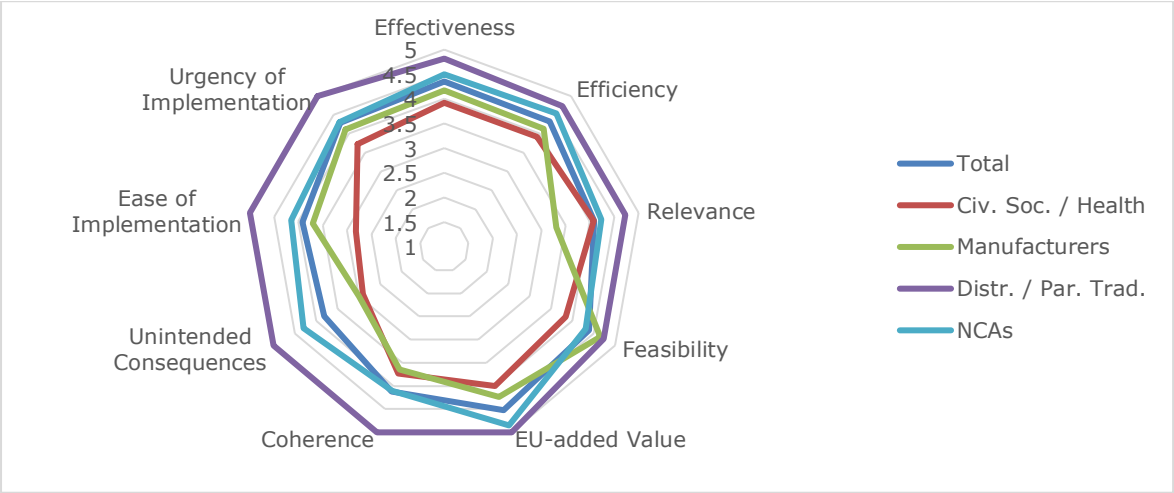


Figure 110 Require suppliers to have adequate shortage prevention or mitigation plans in places

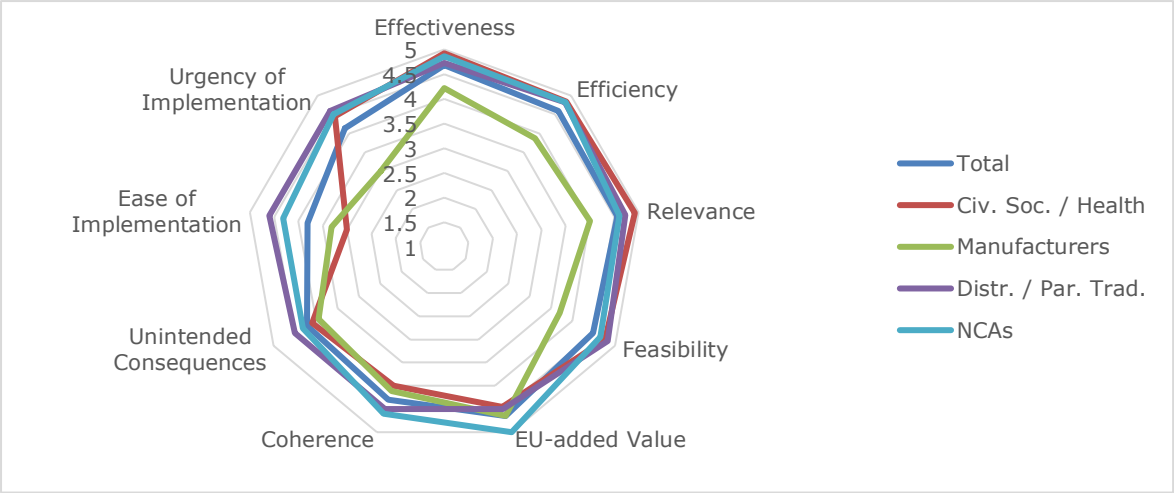


Figure 111 Introduce measures to create an economic and regulatory framework incentivising the diversification of production of APIs, raw materials and medicines

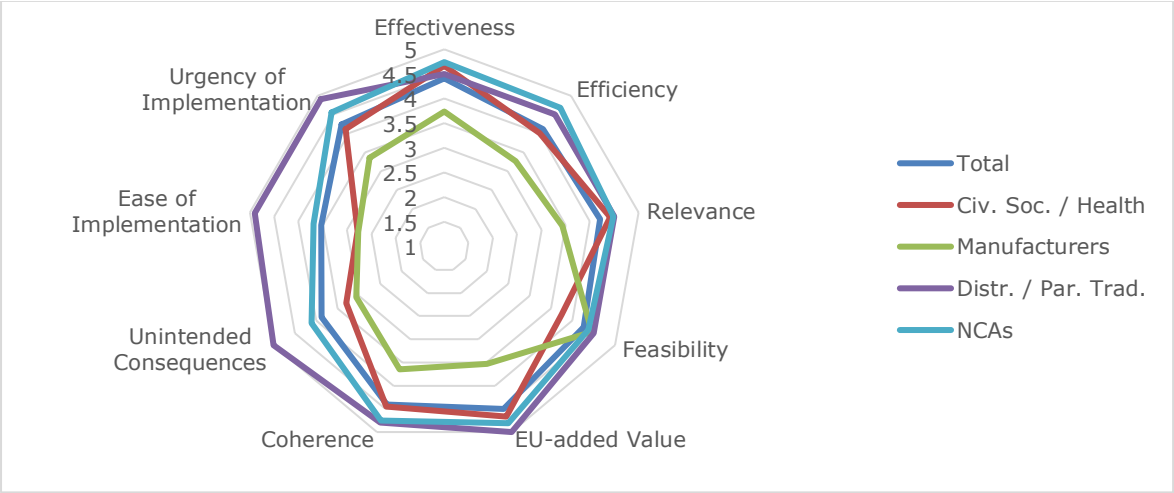


Figure 112 Introduce a 'PSO-responsible-pay' principle

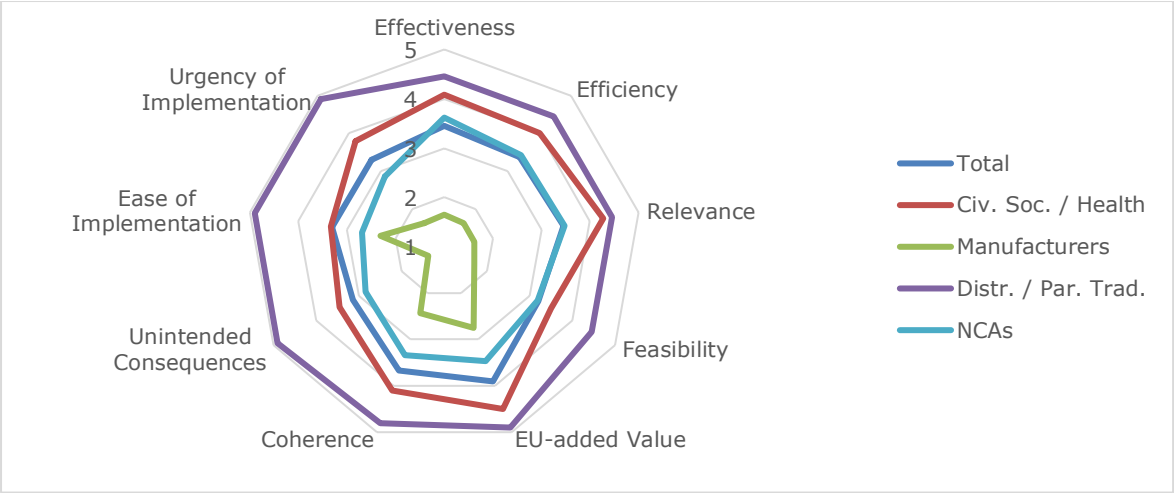


Figure 113 Require greater transparency of industry supply quotas as well as parallel traders' and wholesalers' transactions

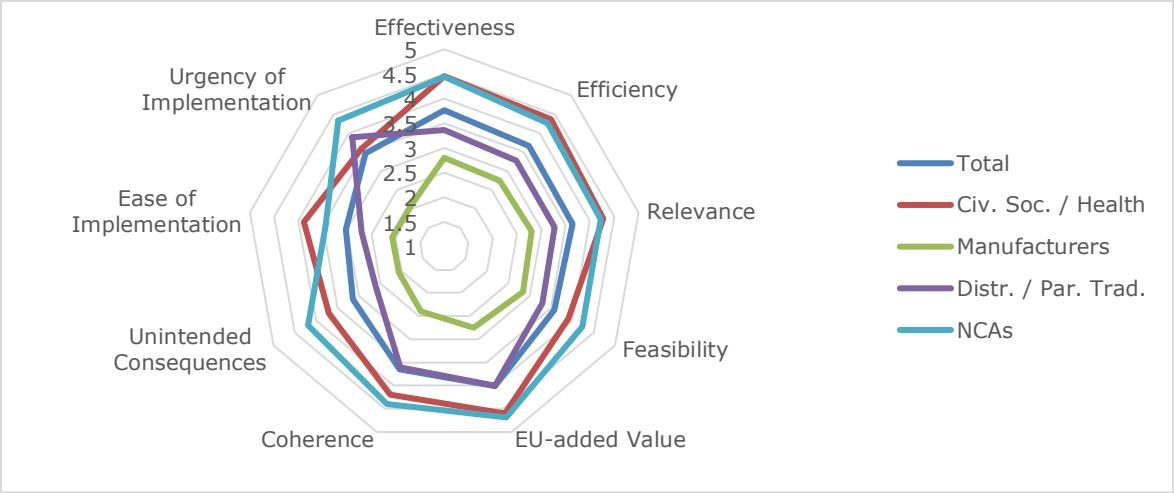


Figure 114 Allow for greater flexibilities for emergency imports of specific products in case of market withdrawals and other critical shortages

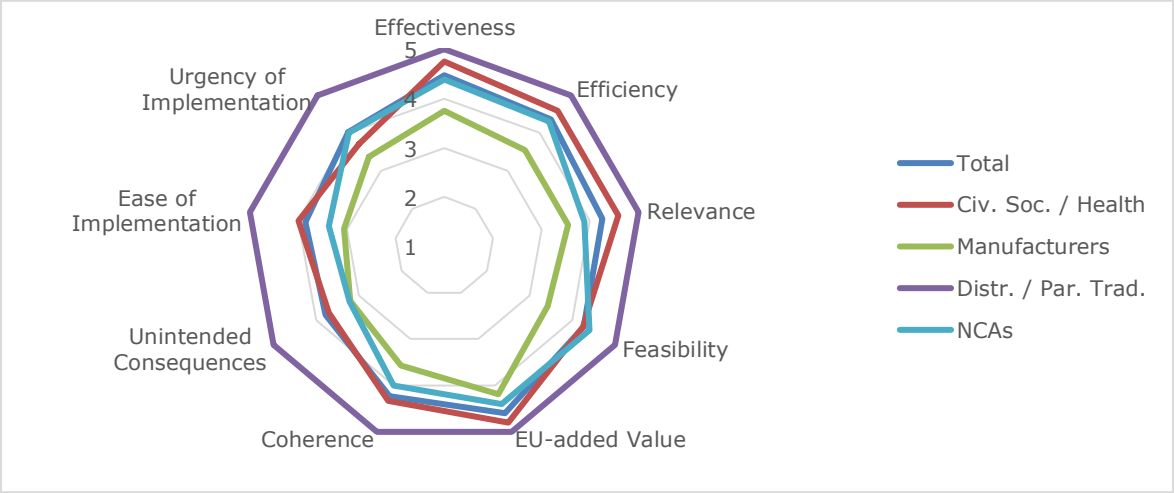


Figure 115 Adopt common principles for the introduction of national restrictions on export

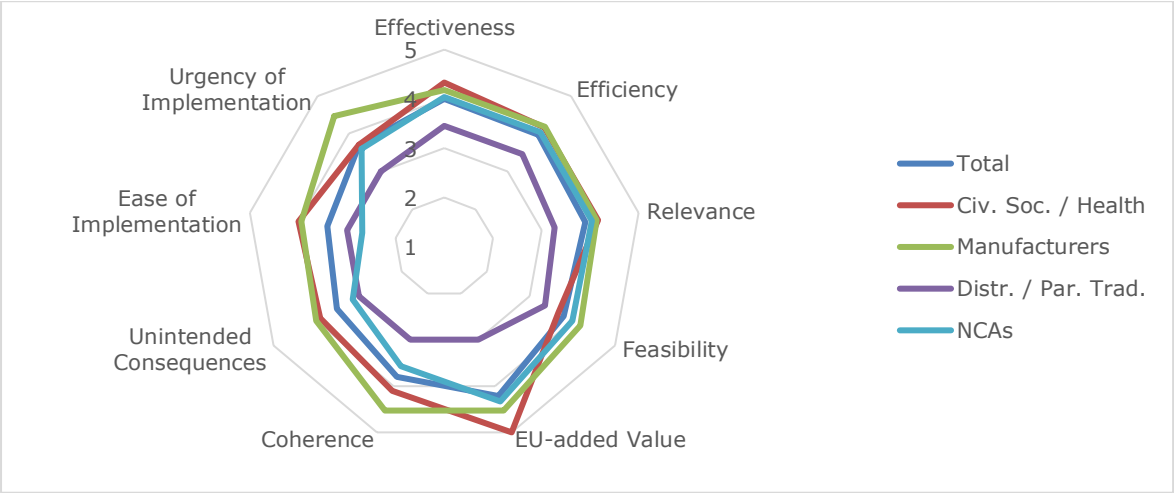


Figure 116 Develop EU legislation allowing for greater flexibility of Member States to impose financial sanctions if supply responsibilities are not met

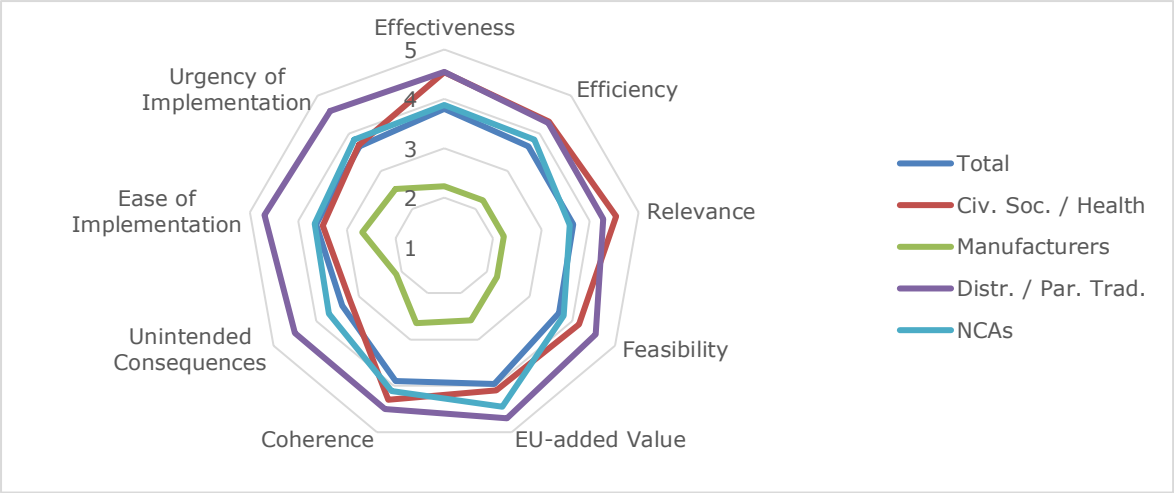


Figure 117 Develop EU legislation allowing for greater flexibility of Member States to impose financial sanctions if notification requirements are not met

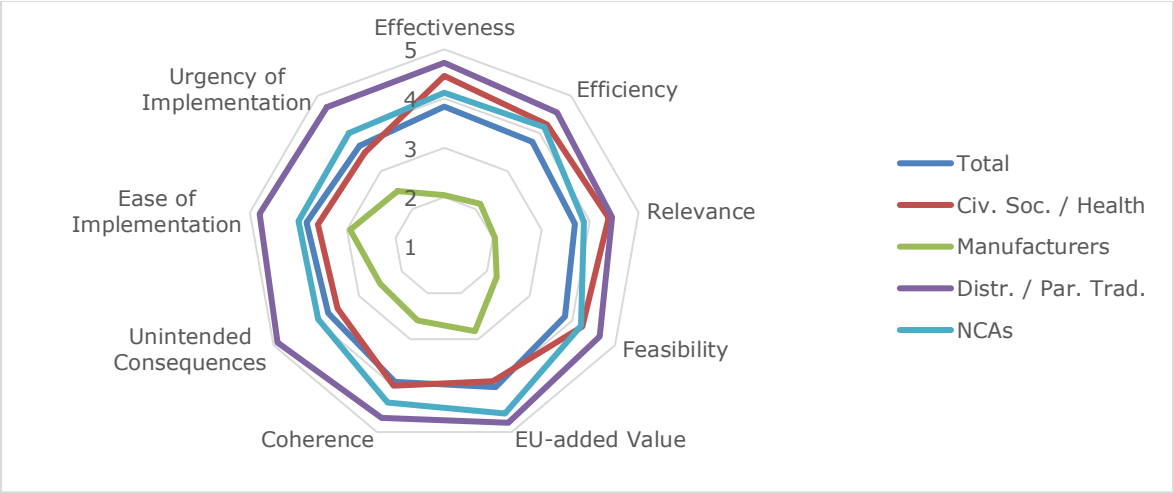


Figure 118 Incorporate requirements for having more diversified, multiple tenderers and thereby supply sources in public procurement tenders

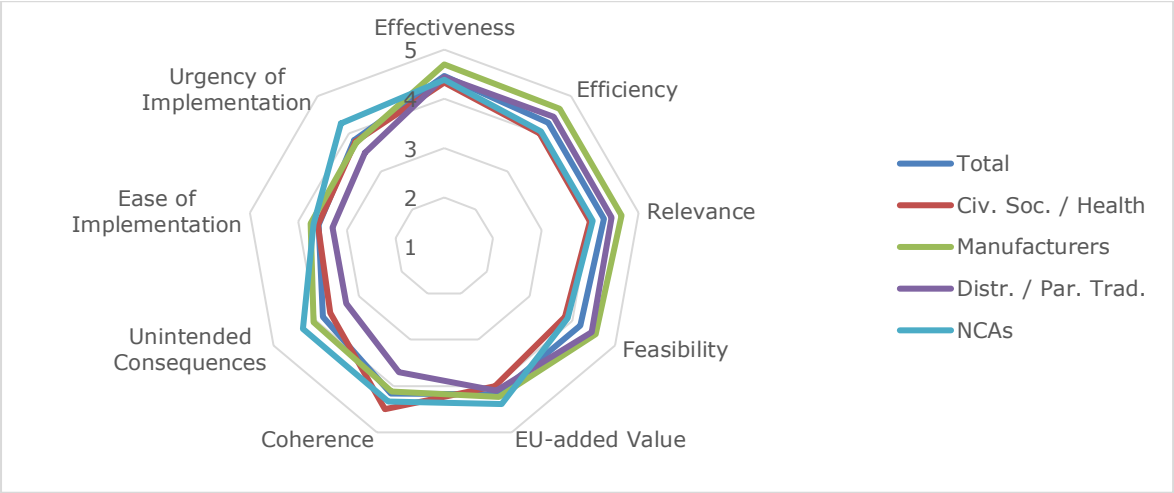


Figure 119 Introduce legal obligations for MAHs and wholesalers to maintain a safety stock for medicines of major therapeutic interest at EU-level

Figure 120 Allowing pharmacies to substitute medicines (generics or more expensive INNs) or supply a part of a unit pack to avoid waste in case of shortages

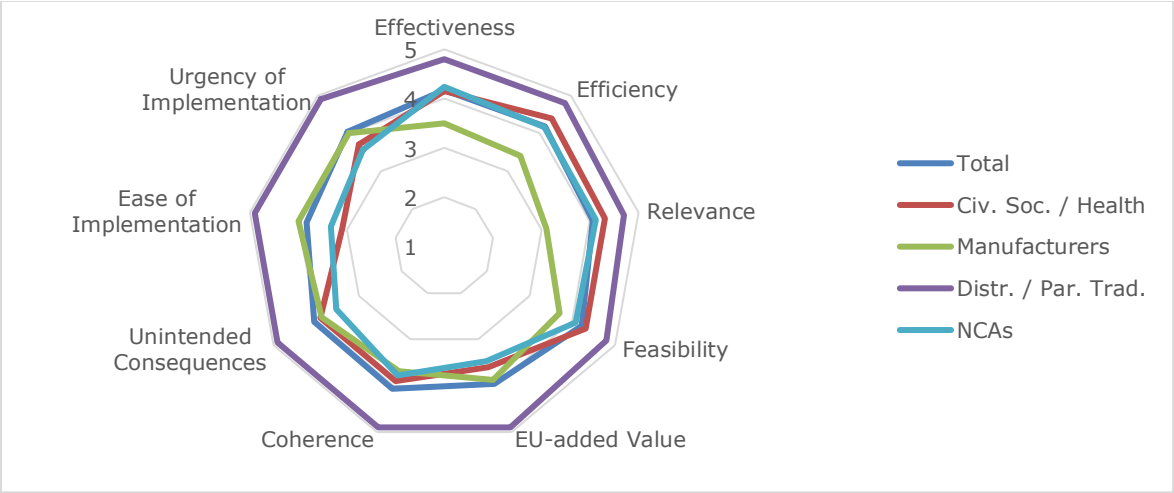


Figure 121 Include information about available alternative medicines in shortage databases

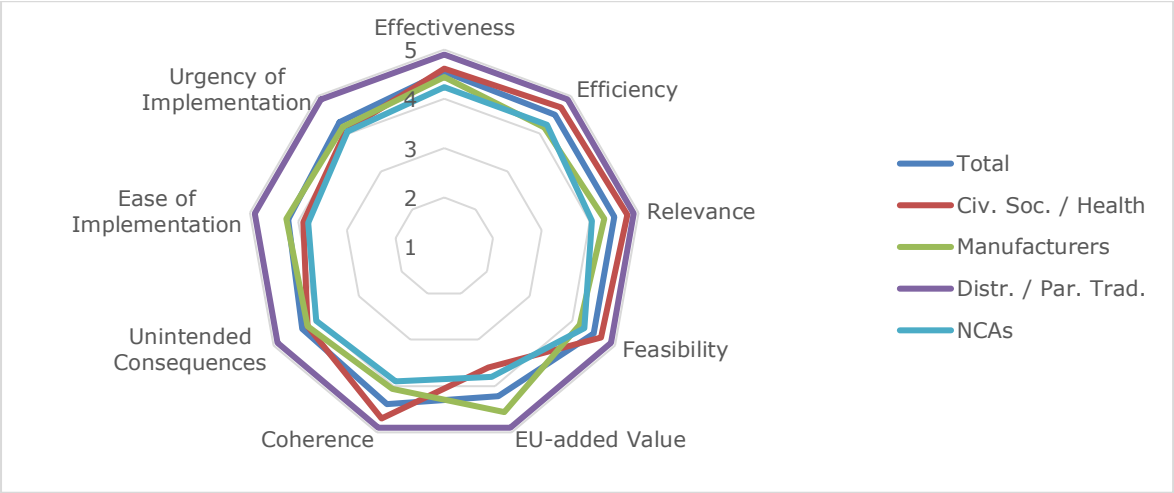


Figure 122 Enable a (more) efficient Repeat Use Procedure

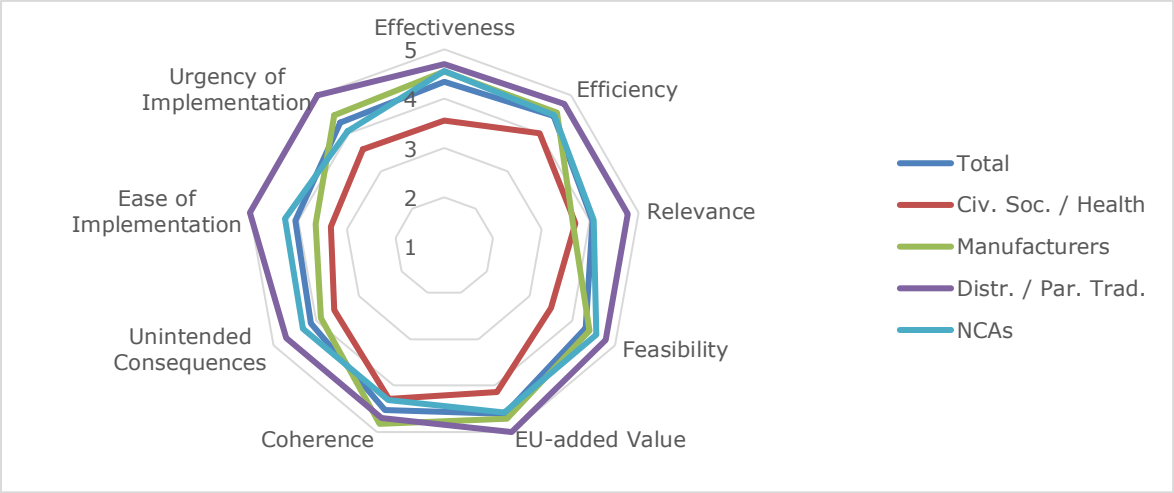


Figure 123 Enable an accelerated mutual recognition procedure within the EU

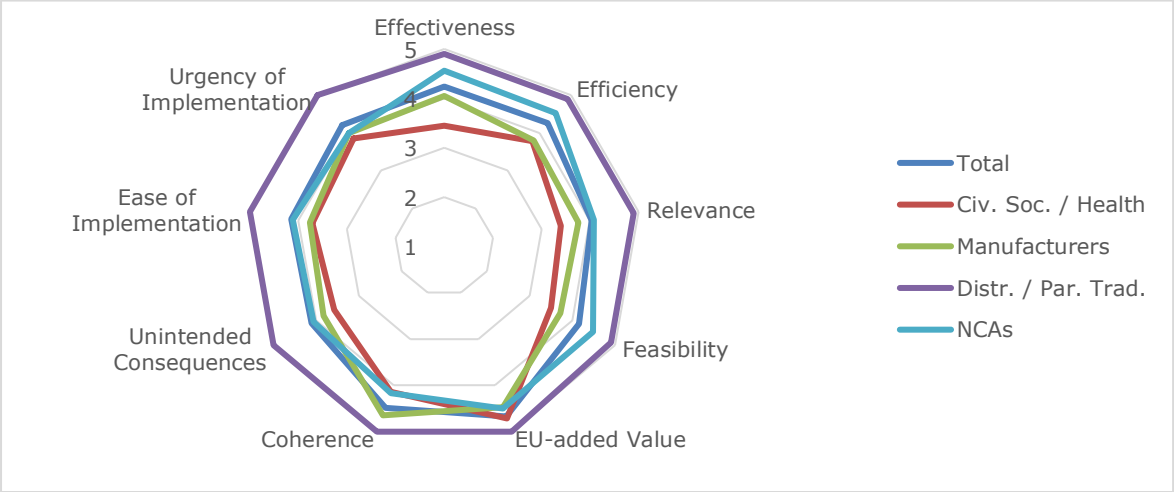


Figure 124 EU authorities reduce the administrative and cost burden submission of post-approval changes

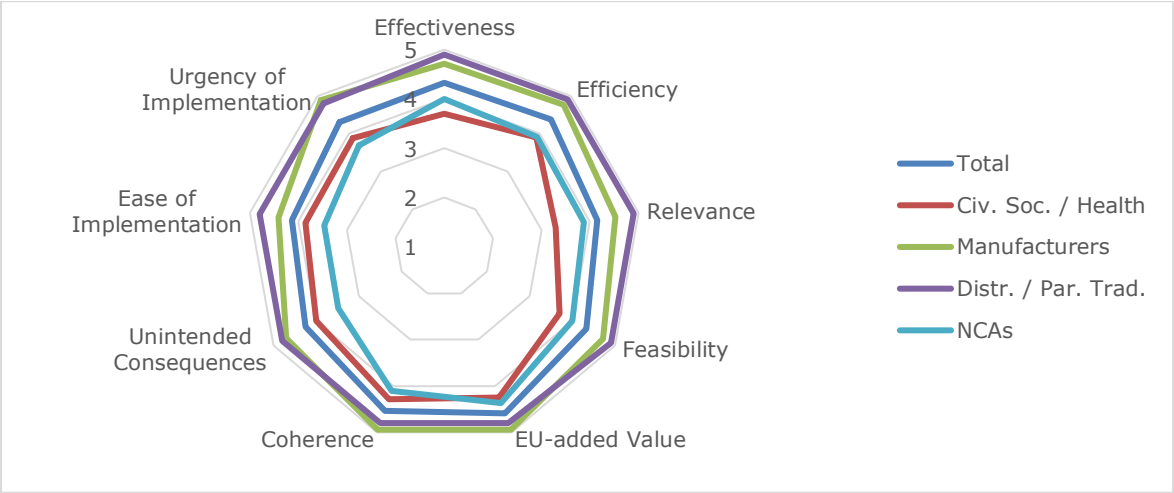


Figure 125 Develop EU-wide medicines packaging and labelling regulation, including flexibilities for digital leaflets

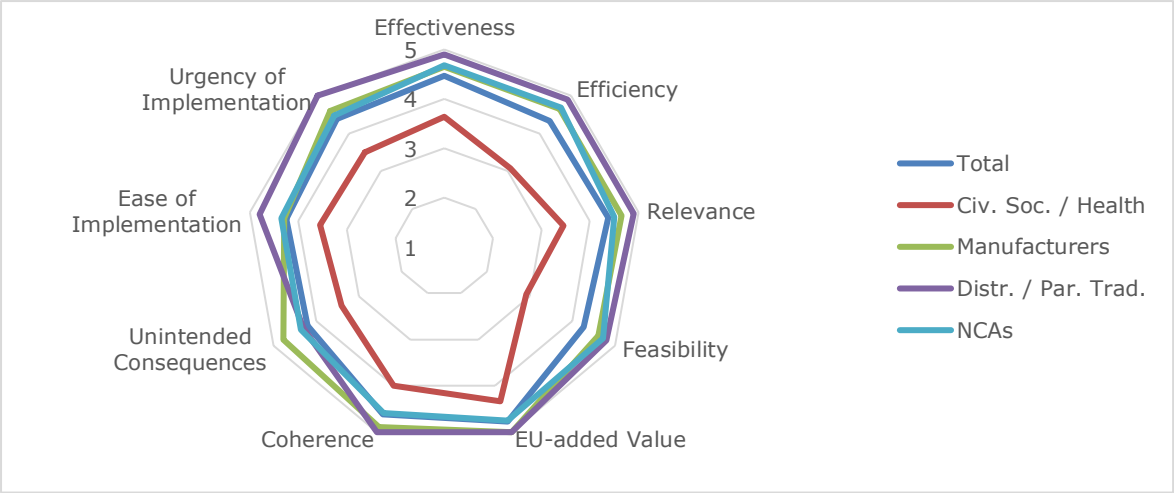
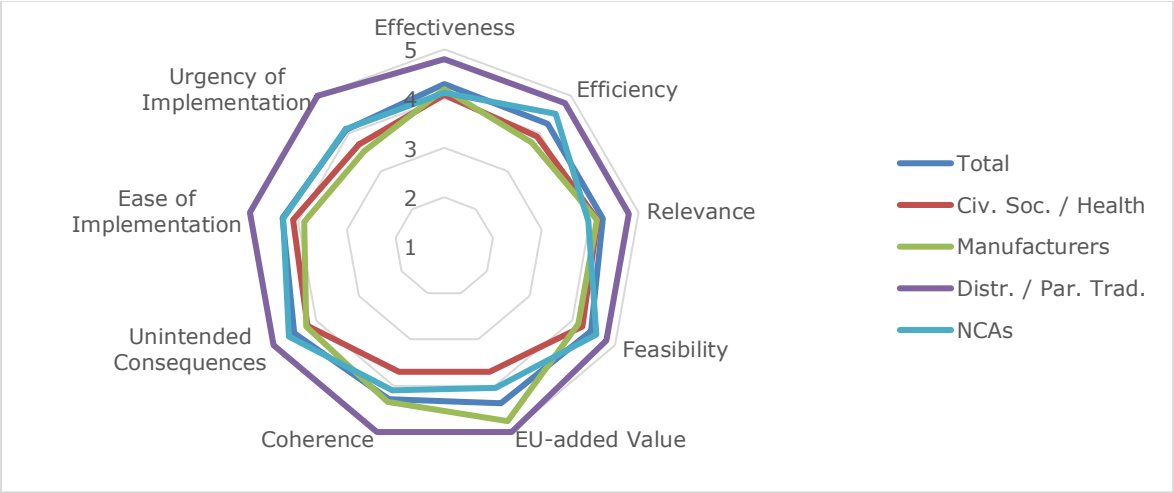


Figure 126 Set up stakeholder dialogue platforms for/between supply chain stakeholders, patients and healthcare providers, respectively at Member States level



I.6 EXCLUDED SOLUTIONS

Table 49 Overview of Excluded Solutions throughout the Consultation Process and their Scores

Solution Group	Solution	Total Average Score (TAS)	Difference in Sentiment between Stakeholder Groups				Consensus		
			Civil Society & Health Professionals	*Manufacturers*	*Distributors & Parallel Traders*	*NCAs*	*Between Stakeholder Groups*	*Within Stakeholder Groups*	*Between Criteria*
Survey 1									
Packaging & Labelling	Greater flexibility of multi-country/-language packaging and labelling	**4,36**	-1,08	0,28	0,52	0,29	**0,73**	0,70	0,13
Procurement & Tendering	Adjust national tendering procedures so as to include criteria other than price	**4,09**	-0,11	0,89	-1,20	0,42	**0,90**	0,88	0,06
Prevention / Mitigation Plan	Support cooperation on national strategies for demand forecasting, planning, and shortage mitigation across the Member State	**4,06**	0,65	0,51	-1,33	0,17	**0,91**	0,86	0,25
Procurement & Tendering	Anchor supply security provisions in procurement contracts	**4,03**	0,37	0,46	-1,03	0,20	**0,69**	1,15	0,06
Procurement & Tendering	Producers should avoid excessive national- and regional-level stockpiling and avoid procurement in excess of regular demand	**4,03**	-0,48	-0,05	0,47	0,06	**0,39**	0,95	0,12
Supply Obligation	Enforcement of the commitment to supply by manufacturers / wholesale suppliers	**3,93**	0,50	-1,45	0,80	0,16	**1,00**	0,94	0,13
Monitoring & Notification	Establish and mainstream centralised and/or interoperable interfaces for monitoring shortages	**3,89**	0,39	-0,02	-0,57	0,19	**0,41**	1,03	0,39
Procurement & Tendering	Introduce smaller and more frequent tenders aimed at maintaining healthy market competition	**3,81**	-0,22	-0,19	0,63	-0,22	**0,42**	1,10	0,11
Pharmacies' role	Allow the use of pharmacy preparations as alternatives	**3,78**	0,82	-1,22	0,52	-0,13	**0,90**	1,15	0,18
Supply Quota	Restrict Direct-to-Pharmacy (DTP) Schemes	**3,75**	0,30	-1,59	1,16	0,12	**1,15**	0,94	0,13
Supply Chain Resilience	Create incentives for the local production of APIs	**3,64**	-0,25	-0,42	0,31	0,36	**0,39**	1,16	0,26
Supply Obligation	Wholesalers who are under a PSO obligation should have a right to be supplied	**3,63**	0,46	-1,77	1,19	0,12	**1,26**	0,94	0,13
Procurement & Tendering	Introduce EU-coordinated strategic stockpiling	**3,59**	0,14	-0,25	-0,39	0,49	**0,40**	1,37	0,10
Supply Obligation	Introduce a 'PSO-responsible-pay' principle	**3,37**	0,59	-1,73	1,08	0,05	**1,22**	1,16	0,14
Supply Quota	Set quotas for delivery to pharmacies in case of shortages	**3,32**	-0,31	-0,94	0,70	0,55	**0,77**	1,05	0,24
Procurement & Tendering	Make greater use of centralised and/or pooled procurement	**3,17**	0,64	-0,86	-0,54	0,76	**0,82**	1,30	0,13
Survey 2									
Supply Chain Resilience	Introduce measures to create an economic and regulatory framework incentivising the diversification of production of APIs, raw materials and medicines	**4,18**	-0,14	-0,68	0,53	0,29	**0,55**	0,90	0,34
Pharmacies' role	Allowing pharmacies to substitute medicines (generics or more expensive INNs) or supply a part of a unit pack to avoid waste in case of shortages	**4,07**	-0,11	-0,42	0,76	-0,23	**0,59**	0,89	0,11
Monitoring & Notification	Strengthen and enforce notification obligations	**4,05**	0,27	-1,04	0,33	0,44	**0,71**	1,00	0,18
Monitoring & Notification	Increase the transparency of supply chains by use of appropriate systems and tools	**3,86**	0,41	0,04	-1,06	0,61	**0,75**	0,83	0,34

Solution Group	Solution	Total Average Score (TAS)	Difference in Sentiment between Stakeholder Groups				Consensus		
			Civil Society & Health Professionals	*Manufacturers*	*Distributors & Parallel Traders*	*NCAs*	*Between Stakeholder Groups*	*Within Stakeholder Groups*	*Between Criteria*
Sanctions	Develop EU legislation allowing for greater flexibility of Member States to impose financial sanctions if supply responsibilities are not met	**3,70**	0,37	-1,33	0,80	0,16	**0,95**	1,02	0,17
Supply Obligation	Introduce a 'PSO-responsible-pay' principle and grant a right to be supplied to wholesalers who are under a PSO	**3,42**	0,48	-1,54	1,25	-0,19	**1,20**	1,01	0,23

cliv

Table 50 Overview of Excluded Solutions throughout the Consultation Process and their Explanation for Exclusion

Solution Group	Solution	Explanation for Exclusion
Survey 1		
Packaging & Labelling	Greater flexibility of multi-country/-language packaging and labelling	Solution received high scores across the assessment criteria, however, a redundancy with another solution on packaging was identified. It was decided to merge solutions in one and removed the current one.
Procurement & Tendering	Adjust national tendering procedures so as to include criteria other than price	Solution received high scores across the assessment criteria, however the consensus was too low to proceed to further round of assessment.
Prevention / Mitigation Plan	Support cooperation on national strategies for demand forecasting, planning, and shortage mitigation across the Member State	Solution received relatively high scores across the assessment criteria, however the consensus was too low to proceed to further round of assessment.
Procurement & Tendering	Anchor supply security provisions in procurement contracts	Solution received medium high scores and medium level of consensus. Overall, the solution did not receive sufficient support from the panel across the assessment criteria.
Procurement & Tendering	Producers should avoid excessive national- and regional-level stockpiling and avoid procurement in excess of regular demand	Solution received medium high scores and medium level of consensus. Overall, the solution did not receive sufficient support from the panel across the assessment criteria.
Supply Obligation	Enforcement of the commitment to supply by manufacturers / wholesale suppliers	Solution received medium scores across the assessment criteria, however the consensus was too low to proceed to further round of assessment.
Monitoring & Notification	Establish and mainstream centralised and/or interoperable interfaces for monitoring shortages	Solution received medium scores and medium level of consensus. Overall, the solution did not receive sufficient support from the panel across the assessment criteria.
Procurement & Tendering	Introduce smaller and more frequent tenders aimed at maintaining healthy market competition	Solution received medium scores and medium level of consensus. Overall, the solution did not receive sufficient support from the panel across the assessment criteria.
Pharmacies' role	Allow the use of pharmacy preparations as alternatives	Solution received medium scores and low level of consensus. Overall, the solution did not receive sufficient support from the panel across the assessment criteria.
Supply Quota	Restrict Direct-to-Pharmacy (DTP) Schemes	Solution received medium scores and low level of consensus. Overall, the solution did not receive sufficient support from the panel across the assessment criteria.
Supply Chain Resilience	Create incentives for the local production of APIs	Solution received low scores and high level of consensus. Overall, the solution did not receive sufficient support from the panel across the assessment criteria.
Supply Obligation	Wholesalers who are under a PSO obligation should have a right to be supplied	Solution received medium scores and low level of consensus. Overall, the solution did not receive sufficient support from the panel across the assessment criteria.
Procurement & Tendering	Introduce EU-coordinated strategic stockpiling	Solution received low scores and high level of consensus. Overall, the solution did not receive sufficient support from the panel across the assessment criteria.
Supply Obligation	Introduce a 'PSO-responsible-pay' principle	Solution received low scores and low level of consensus. Overall, the solution did not receive sufficient support from the panel across the assessment criteria.
Supply Quota	Set quotas for delivery to pharmacies in case of shortages	Solution received low scores and low level of consensus. Overall, the solution did not receive sufficient support from the panel across the assessment criteria.
Procurement & Tendering	Make greater use of centralised and/or pooled procurement	Solution received low scores and low level of consensus. Overall, the solution did not receive sufficient support from the panel across the assessment criteria.
Survey 2		
Supply Chain Resilience	Introduce measures to create an economic and regulatory framework incentivising the diversification of production of APIs, raw materials and medicines	**Solution received relatively high scores across the assessment criteria. In the stakeholder panel meeting, a redundancy with another solution in the area of procurement and tendering was identified. It was decided to remove the current solution.**
Pharmacies' role	Allowing pharmacies to substitute medicines (generics or more expensive INNs) or supply a part of a unit pack to avoid waste in case of shortages	**Solution received relatively medium scores across the assessment criteria, with a medium level of consensus among the stakeholders. In the panel meeting, a potential conflict was identified with national legal frameworks.**
Monitoring & Notification	Strengthen and enforce notification obligations	**Solution received relatively medium scores across the assessment criteria, with a low level of consensus among the stakeholders. Overall, the solution did not receive sufficient support from the panel across the assessment criteria.**
Monitoring & Notification	Increase the transparency of supply chains by use of appropriate systems and tools	**Solution received relatively medium scores across the assessment criteria, with a low level of consensus among the stakeholders. Overall, the solution did not receive sufficient support from the panel across the assessment criteria.**
Sanctions	Develop EU legislation allowing for greater flexibility of Member States to impose financial sanctions if supply responsibilities are not met	**Solution received relatively low scores across the assessment criteria, with a low level of consensus among the stakeholders. Overall, the solution did not receive sufficient support from the panel across the assessment criteria.**
Supply Obligation	Introduce a 'PSO-responsible-pay' principle and grant a right to be supplied to wholesalers who are under a PSO	**Solution received low scores across the assessment criteria, with a low level of consensus among the stakeholders. Overall, the solution did not receive sufficient support from the panel across the assessment criteria.**

K.7 SOLUTION FICHES

As part of the development of a list of recommendations, a selected group of stakeholders was invited to participate in a multi-staged consultation process. The following fiches were presented to these stakeholders along with the assessment surveys.

K.7.1. Definition

Establish and follow a centralised and harmonised EU-wide definition of medicine shortages
Description Currently, definitions of a medicine shortage differ between Member States as well as between stakeholders. The lack of a unified definition hampers the coordination of a common approach across the EU, which is crucial for many of the solutions presented in the following. A centralised and harmonised definition of shortages across the EU could improve understanding of the scope and nature of shortages in the EU and provide a better basis for the development of policy solutions.
Objectives General objectives Create and follow a centralised and harmonised EU-wide definition of medicine shortages that enables a common understanding of the issue and facilitates the development of policy solutions. Value added Establishing and mainstreaming a standardised definition has the potential to improve the handling and mitigation of shortages. For instance, standardised definitions may enable standardised reporting and monitoring standards (see below), which can facilitate the communication and monitoring of shortages across the EU.

K.7.2. Monitoring & Notification

i) Establish and mainstream centralised reporting criteria for shortages
Description At present, the criteria for reporting shortages differ greatly between European Member States. This hinders the comprehensive understanding of the issue. It also creates inefficiencies in the national reporting systems. Whilst harmonised and centralised reporting will not prevent the occurrence of shortages per se, improved information sharing through timely and standardised reporting may improve understanding of the nature and causes of shortages. Standardised reporting requirements for shortages could thus be agreed on and implemented. Reporting criteria to consider could involve the (expected) duration of a shortage, the criticality of a medicine, availability of alternatives and the relation between supply and demand. The reporting process should ultimately avoid duplication of reporting and be concise and consistent in the data required.
Objectives <u>General Objectives</u> Better exchange of information and interoperability thereof through centralised and harmonised reporting criteria. National reporting systems may therefore be streamlined and fed into, bundled or centralised in an EU-wide interface. (see below). <u>Value added</u> Similar to a centralised definition of shortages addressed previously, agreed reporting criteria can foster communication, system reliability, functionality and resilience. Downstream benefits, such as higher predictability or better-informed decision making in case of a shortage, are further anticipated.

i) Increase the transparency of supply chains by use of appropriate systems and tools

Description

Currently, the systems and tools used by authorities in Member States differ greatly in their level of sophistication. The information contained in systems thus varies in both content and quality. As a result, it is difficult to get a good and full understanding of the issue of shortages at the level of the EU. To improve this understanding and facilitate greater collaboration between Member States in preventing and mitigating shortages, systems could be centralised or their interoperability improved. This requires development of standards for data reporting (e.g. what data to provide, in which formats) and a technical interface that allows systems to be connected. The system could further benefit from incorporation of analytical tools and platforms for communication between authorities.

Feeding into this technical interface is a supply chain monitoring and tracking system. This may include transparent supply registers or contracts, for instance. Attention needs to be paid to greatest possible transparency for all stakeholders, while respecting commercially confidential information and the General Data Protection Regulation (GDPR).

In addition to the infrastructure needed to implement such technical systems (both, hard- and software), staff maintaining these interfaces (e.g. databases) is necessary, and different stakeholders need to be trained on how to report information to ensure coherence and workability.

Objectives

General Objectives

The aim is to improve the quality and quantity of data available regarding shortages and improve information sharing between Member States, as well as between different groups of stakeholders. Through this, strategies to prevent and mitigate shortages can be improved and evaluated.

Value added

The timely adoption of measures and subsequent identification of disruptions along the supply chain is key for health authorities to mitigate the impact of shortages or prevent them altogether.

i) Strengthen and enforce notification obligations

Description

Member States typically have requirements in place for marketing authorisation holders and wholesaler-distributors to report any shortage at the national level. The advance warning of a shortage they are expected to give may vary. However, in most cases shortages are only notified at the time of their first occurrence or even after. Consequently, prescribers and pharmacists have not had time to prepare for mitigation of the impact of shortages. Existing notification requirements are typically not enforced in the sense that penalties are levied when notification is delayed. The information provided with the reported shortage may also be complete.

To improve information sharing and preparedness against shortages, additional notification obligations – both voluntary and compulsory – could be introduced and enforcement of existing obligations improved. These may include earlier notification requirements or standardised reporting mechanisms.

Objectives

General Objectives

Identify (prospective) shortages as early as possible to better prepare for their consequences. Create a better and more stringent reporting compliance by effectively enforcing obligations.

Value added

Monitoring, identifying, reacting to, and effectively mitigating or preventing prospective shortages is one of the key aspects in dealing with medicine shortages. Having reliable and timely information from relevant supply chain stakeholders is a prerequisite for effective monitoring. The sooner this information can be gathered, the greater the options for corrective measures.

i)	**Develop an EU-wide list of medicines for which shortages are the most critical and develop policies and/or regulations to improve their availability**

Description

Most shortages can usually be resolved at the level of the pharmacy, either by sourcing the medicine through other channels (such as parallel import) or by dispensing an alternative medicine. Whilst such shortages create a lot of work for pharmacists and physicians and substitutes may pose risks for reduced treatment adherence or decreased effectiveness, the consequences are usually not critical. Shortages of potentially life-saving medicines, particularly when there are no suitable alternatives, may have far greater impact. In this sense, not all shortages are equal. To prevent or mitigate the effects of shortages of such critical medicines, separate mechanisms could be introduced to safeguard their supply. Possible measures include strategic stockpiling, joint procurement or other legislative measures to improve availability.

As a first step, agreement is needed on which medicines should be included in such mechanisms. Therefore, a central list of most critical medicines could be developed for all EU Member States. Criteria to consider for determining criticality may include the size of the potentially affected patient population, the vulnerability of supply, the complexity of production, medical necessity, and the ability to substitute.

Objectives

General Objectives

Member States share information to identify and prioritise critical medicinal products. The resulting list or database would then serve as a basis for addressing shortages and ensuring a tailored approach with reasonable and appropriate mitigation measures.

Value added

Having a centralised list of critical medicines across all EU Member States enables better screening and oversight of medicine shortages that could have a particularly detrimental impact on the health of patients. Mitigatory efforts can be coordinated in a more comprehensive manner between Member States as a result.

K.7.3. Prevention / Mitigation Plan

i)	**Require suppliers to have adequate shortage prevention or mitigation plans in place**

Description

Marketing authorisation holders and wholesalers have a responsibility to ensure the continued supply of medicines to the best of their ability. As part of this responsibility, they could be required to submit shortage mitigation and prevention plans to the regulatory authorities. Such strategies could outline, for example, approaches to handling a shortage, steps to mitigate the core issue, prospective action-timelines or information on alternatives in case a shortage occurs. Furthermore, they could include clear communication guidelines and channels which can become activated in case of a shortage (e.g. how will NCAs, practitioners or other stakeholders be informed?). Legal obligations on MAHs to develop shortage mitigation or prevention plans already exist in several countries, e.g. France.

Pharmacists are the final link in the supply chain and connect directly to the patient. As such, they have a large role to play in mitigating the impact of a shortage at the patient level. To assist them in such efforts, they could be encouraged and equipped to develop prospective risk assessments, considering the potential impact of a shortage and any actions that could be taken to either obtain a product another way or offer appropriate substitutes. For this, they will require access to clear communication and notification channels through which they can signal (impending) shortages to responsible authorities and receive intelligence and insight for their own practices.

The development of appropriate shortage mitigation strategies, whether by pharmacists, manufacturers or national authorities, requires insight into expected and realised demand and supply throughout the supply chain. This insight would allow shortages to be observed – and potentially prevented – in real-time and potentially even show where a product could still be sourced. To achieve this, more use could be made of national and EU competent authorities' data repositories. One such data repository that has been suggested is the European Medicines Verification System, which was set up in the context of the EU Falsified Medicines Directive.

Objectives

General Objectives

A clear placement of responsibility is sought so that shortages can be anticipated and handled systematically, efficiently, and urgently.

Value added

With more mitigation and prevention mechanisms in place, the entire supply chain could become more robust. The mechanisms devised should follow streamlined principles, be interoperable and cascade into each other. Information from forecasts and assessments is crucial for all stakeholders along the supply chain to ensure supply and facilitate planning of aspects such as manufacturing capacity and distribution arrangements.

I.7.4. Supply Chain Resilience

i) Introduce measures to create an economic and regulatory framework incentivising the diversification of production of APIs, raw materials and medicines

Description

Even in a market where there are multiple suppliers of a (generic) medicinal product, these suppliers frequently rely on raw materials and active pharmaceutical ingredients from a very limited number of sources. Any disruptions to the operations of these upstream suppliers thus can have large scale domino effects on the manufacturers who rely on their products. Insufficiently diversified supply chains are thus much more vulnerable to disruption and may result in shortages.

Furthermore, at present a large part of all APIs and raw materials are produced in non-EU countries, which leads to limited oversight and control over supply chains. Non-EU based production also means that the supply of medicines to the EU is at increased risk from export restrictions or from events and policies that affect operations elsewhere. This was illustrated by the COVID-19 pandemic when API production in China was suspended due to local lock-downs.

A possible strategy to reduce the risk of shortages is thus to introduce measures that incentivise the diversification of the production of APIs, raw materials and medicines. These measures could be both economic and legislative nature. Economic measures may involve. subsidies, grants or tax breaks, whilst regulations could be introduced to mandate MAHs to source materials from multiple suppliers.

Objectives

General Objectives

The objective is to ensure the supply and supply chain resilience of APIs, raw materials and medicines to the greatest extent possible.

Value added

More diverse supply sources may enable greater shock resilience and flexibility in preventing and mitigating shortages. This effect could be boosted through increased local production of APIs, reducing the dependency on third markets, and minimising the length and complexity of supply chains.

K.7.5. Supply Obligation

i) Introduce a 'PSO-responsible-pay' principle and grant a right to be supplied to wholesalers who are under a PSO

Description

A Public Service Obligation (PSO) specifies that there should be an "obligation placed on wholesalers to guarantee permanently an adequate range of medicinal products to meet the requirements of a specific geographical area and to deliver the supplies requested within a very short time over the whole of the area in question." PSO-responsible pay defines an obligation for suppliers to pay the price difference (if positive) between emergency or parallel imports and the normal reimbursement price for products in shortage.

Whether suppliers are required to pay this difference may depend on the specifics of the situation that led to the shortage and on the efforts made by the supplier to prevent or mitigate the situation. A more measured approach may also help to prevent situations in which any potential risk margins and penalty fees will be included in the medicinal products' retail price and thereby be shifted onto the health insurers and patients.

Objectives

General Objectives

Ensure supply and strengthen supply chains through actionable and enforceable tools that hold Wholesalers and Manufacturers accountable within the limits of a Public Service Obligation

Value added

Greater responsibility and accountability are expected to trickle down throughout the supply chain. Preventive measures may be implemented more strategically by wholesalers and manufacturers to make sure PSO responsibilities are met and potential penalties avoided.

K.7.6. Supply Quota

i) Require greater transparency of industry supply quotas as well as parallel traders' and wholesalers' transactions

Description

Supply quotas are set by marketing authorisation holders to define the quantity of a certain medicine with which they supply a wholesaler or other relevant actor throughout the supply chain. Marketing authorisation holders state that supply quotas allow them to better regulate the distribution of medicines across countries to ensure that patient demands are met. In doing so, supply quotas have the effect of limiting parallel exportation from certain countries. Supply quotas are thus seen as contrary to the functioning of the internal EU market. They could be justified only if there is a clear and justified reason, such as production problems, that would warrant rationing. In such circumstances quotas should be sufficiently transparent and flexible to account for normal market fluctuations. However, in practice, wholesalers are not always informed of how much stock they will receive per week or month, so-called 'black-box quotas'.

Supply quotas have been linked to shortages, when wholesalers are not able to fulfil orders because their quotas have been reached. These types of shortages are usually resolved relatively quickly, as the manufacturer can resupply wholesalers-distributors at the start of the next supply period.

Objectives

General Objectives

When supply quotas are not transparently defined and communicated, wholesaler-distributors are not able to foresee supply problems or inform pharmacies and authorities of their inability to supply in a timely way. Greater transparency on quotas would enable wholesaler-distributors to predict shortages and inform pharmacies accordingly, so that they may take timely action to mitigate the impact of the expected shortage.

Value added

Greater transparency is expected to translate into better predictability and planning, which, in turn, is expected to prevent shortages more systematically.

K.7.7. Parallel Trade

i) Allow for greater flexibilities for emergency imports of specific products in case of market withdrawals and other critical shortages

ii) Adopt common principles for the introduction of national restrictions on export

Description

The parallel export of medicines from one Member State to another is often considered a contributor to the occurrence of shortages. However, under the right circumstances, emergency imports can also be used to mitigate shortages when medicines are moved from a country where they remain in surplus to one where there is an acute and critical shortage. Hence, policymakers may consider making use of the parallel import framework provided by the EU and national legislation. Practical evidence suggests that in case of shortages, excess stocks of the medicine in question are typically available elsewhere.

To prevent excessive stock held in some EU Member States while others are experiencing shortages, common principles may be adopted that lay the foundation for export restrictions or the reduction thereof. Member States may therefore be requested to abolish the distortive effects of national schemes incentivising parallel imports and instead promoting the application of the non-extraterritoriality principle.

Objectives

General Objectives

Reach better control over, and greater transparency of supply and stocks and the management thereof between Member States.

Value added

In the context of parallel trade, a functioning and efficient framework between EU Member States has the potential to alleviate shortages in a short timeframe or prevent them in the first place. The quantities of parallel traded medicines are usually not traceable; introducing shared liability could therefore serve as an effective control mechanism.

K.7.8. Sanctions

i) Develop EU legislation allowing for greater flexibility of Member States to impose financial sanctions if supply responsibilities are not met

ii) Develop EU legislation allowing for greater flexibility of Member States to impose financial sanctions if notification requirements are not met

Description

Procurement contracts can, and often do, include financial sanctions in case a supplier does not meet its stipulated supply obligations and/or does not notify authorities in time in case of inability to supply according to the terms of the contract. Whether sanctions are imposed depends on a range of "penalty steps". For instance, extenuating circumstances (e.g. the duration of a violation, culpability, etc.), aggravating circumstances (such as recidivism / repeated occurrence) and the size of the company may be taken into consideration. Purely commercially motivated decisions that result in a shortage (or permanent discontinuation) may be reflected in different sanctions than if the supplier has acted in good faith but experiences a disruption caused by events outside their responsibility.

With regard to notification requirements, suppliers often point out that there is frequently little advance warning for the occurrence of shortages. Pre-emptive notification could also create unnecessary unrest and costs as the supply disruption may be resolved before a shortage happens. As such, enforcing fines for not meeting notification requirements can be fraught with difficulties.

While several responsibilities and requirements are already specific and in place nowadays (see below), procurement agencies often do not enforce such sanctions at all or not to the full extent either because the tools to do so are missing or they fear a backlash (e.g. market withdrawal) that could be detrimental. Penalties could also have the undesirable effect of suppliers prioritising supply against contracts that include penalties over those without such penalties.

A more systematic and EU-wide approach to the imposition and enforcement of sanctions could enhance the bargaining power of procurers and minimise or avoid potential adverse effects.

Objectives

General Objectives

Similar to the previously introduced PSO, supply ought to be ensured and supply chains strengthened through actionable and enforceable tools that hold suppliers accountable within the limits defined under the relevant legislative measures

Value added

Greater responsibility and accountability is expected to trickle down throughout the supply chain. Suppliers could be expected to implement or strengthen preventive measures strategically to avoid penalty fees.

K.7.9. Procurement / Tender

i) Incorporate requirements for having more diversified, multiple tenderers and thereby supply sources in public procurement tenders

Description

Procurement practices can have a major impact on the medicines supply chain. Some current practices, aimed primarily at reducing healthcare expenditure on medicine, can directly affect market dynamics and the level of competition. For instance, tenders that are evaluated primarily on price, without due consideration for other issues such as multi-sourcing, may force prices down to the level where it is no longer attractive for potential bidders to remain in a market. This reduces the competition and leaves markets vulnerable when remaining suppliers experience disruptions.

A similar effect can be seen with "winner-takes-all" tenders, whereby the winning bidder becomes the sole supplier to a market for a given time period for a specific product. Losing tenderers may decide to stop production (and potentially not renew the marketing authorisation) for that medicine all together as their overall market has become too small to be economically attractive. This again has the effect of thinning out competition, leaving the market dependent on a single or only few suppliers and reduces the absorptive capacity in case of demand shocks or production problems.

Potential solutions thus lie in smaller and more frequent tenders and reduced use of 'winner-takes-all' tenders. Procurers could furthermore be encouraged or even obligated to evaluate tenders not only on price but also on criteria such as supply chain robustness. Procurement contracts could have built in security provisions, specifying how the provider intends to protect against the risk of shortages and how these would be mitigated should they occur.

Objectives

General Objectives

More holistic tendering practices, greater efficiency and supply reliability. Centralised/pooled procurement, is set to maximise the bargaining power which is expected to facilitate a more resilient supply chain and less frequent shortages.

Value added

More strategic and fair procurement is expected to translate into less dependency on single manufacturers and wholesalers and thereby greater supply chain resilience, which is complemented by a generally more strategic approach to tendering.

i)	**Introduce legal obligations for MAHs and wholesalers to maintain a safety stock for medicines of major therapeutic interest at EU-level**

Description

Efforts to prevent or respond to shortages in one country may have the unwanted by-effect of increasing (the risk of) shortages in another. Excessive stockpiling of medicines at national or sub-national levels represents perhaps the clearest example of how actions by individual Member States can impact on product availability elsewhere. Whilst a certain level of stockholding is a normal aspect of responsible supply chain management, countries also engage in building up greater stock of critical medicines to prepare for unexpected events, such as sudden supply chain disruptions or surge demand (e.g. as part of epidemic preparedness).

When there is a limited overall supply of such medicine, national stockpiling could mean that other countries, in particular those with lower purchasing and negotiation power, cannot be sufficiently supplied anymore. Products that are kept in national (or regional) stockpiles cannot easily be redistributed to other markets in need, due to country-specific packaging and labelling requirements. The normal relation between supply and demand can also be distorted when countries procure a product well in excess of estimated demand for other reasons, such as for parallel exportation. For equitable product availability between Member States, it is thus important that there is a clear and transparent relation between supply and demand and that individual Member States are discouraged from locking in critical supplies through excessive stockpiling.

Although excessive national or regional stockpiling is counter to equitable access, holding sufficient stock of medicines of major therapeutic interest can be an effective tool to protect against shortages, if done jointly (such as at EU-level) and when managed properly. Marketing authorisation holders and/or wholesalers could be obligated to hold sufficient stock, not only of finished products but potentially also of raw materials and of unfinished/unpackaged products that can be prepared to meet specific national requirements. Stockholding can also be centrally coordinated at the EU-level for particular products. In 2020, against the backdrop of COVID-19, the Commission introduced the first strategic EU-coordinated stockpile (rescEU) for medical equipment, vaccines and therapeutics. For other medicinal products thus far a coordinated approach to stockpiling at the EU-level does not exist.

Objectives

General Objectives

Build strategic stockpiles for medicines of major therapeutic interest that ensure sufficient product availability but without increasing unequitable distribution between Member States.

Value added

A coordinated stockpiling obligation for certain raw materials, active pharmaceutical ingredients and critical medicines may enhance the EU's preparedness for unexpected supply disruptions

K.7.10. Pharmacies' Role

i)	**Allowing pharmacies to substitute medicines (generics or more expensive INNs) or supply a part of a unit pack to avoid waste in case of shortages**
ii)	**Include information about available alternative medicines in shortage databases**

Description

Depending on the country, if a prescribed medicine is not available in the exact strength and formulation indicated on the prescription, pharmacists may not have the authorisation to instead dispense another version of the product. Moreover, they usually cannot dispense a therapeutic alternative (i.e. a medicine with the same or a similar therapeutic profile but containing a different active ingredient). In such cases, the pharmacist needs to contact the prescriber to discuss an appropriate alternative and a new prescription needs to be issued. This creates significant additional work for both the pharmacist and the prescriber and can result in delays in dispensing of the medicine to the patient.

A potential solution to mitigate the impact of shortages, is to enable pharmacists to independently decide on appropriate substitutions for a medicine in shortage and dispense this directly to the patient without further consultation with a prescriber. This would decrease the administrative and cost burden on the involved health professionals and decrease the impact on the patient. Competent authorities could thus consider extended the mandate for pharmacists to

independently issue substitutions, whilst clarifying the conditions under which such substitution would and would not be allowed.

To enable these mitigating measures, more systematic and better information is needed about the availability and suitability of substitutes. Therefore, shortage databases could also provide information about available alternative medicines that may be dispensed if a shortage occurs. These alternatives will be decided upon a-priori by competent authorities.

Besides dispensing available substitutes, it is also possible for pharmacists to produce medicines that are in shortage directly or to have these produced in compounding pharmacies. For patented medicines, this is allowed only under a prescribed set of conditions and only for the pharmacy's own patient population. Expanding the regulatory framework to increase the scope for use of pharmacy preparations could help reduce shortages provided raw materials are still available.

Objectives

General Objectives

The aim is to have a more efficient and resilient mitigation infrastructure in place at the very end of the supply chain, at the interface between pharmacies and patients.

Value added

Granting pharmacists greater flexibility in case of a shortage helps them address shortages more directly and mitigate them efficiently, thereby enhancing the capacity to respond to shortages.

K.7.11. Authorisation, Approval, Recognition

i) Enable a (more) efficient Repeat Use Procedure

ii) Enable an accelerated mutual recognition procedure within the EU

Description

The Repeat Use Procedure is defined as "the use of the Mutual Recognition Procedure (MRP) after the completion of a first MRP or Decentralised Procedure (DCP) for the recognition of a marketing authorisation by other Member States. This means that a marketing authorisation holder may use the MRP several times for the same marketing authorisation, once the first MRP is complete, to include additional Member States that were not involved in the initial MRP" (CMDh, 2020).

The MRP is a European marketing authorisation procedure based on the principle of recognition of the evaluation performed by the reference Member State. If a European Member State has already issued a marketing authorisation, other Member States may refer to, and rely on this authorization instead of having to run their own authorisation procedures.

Currently, approval is granted on a per-country-basis and, more often than not, results in double-testing between countries. This additional step may cause delayed batch releases, which, in turn, can be problematic particularly in emergency situations involving shortages of medicinal products of high therapeutic relevance or urgency (e.g. vaccines).

Objectives

General Objectives

Avoiding lengthy procedures and double testing through Repeat Use and / or Mutual Recognition Procedures

Value added

Greater efficiency in authorisation procedures, which may, for instance, facilitate emergency imports while reducing costs

i) EU authorities reduce the administrative and cost burden submission of post-approval changes

Description

Any time a manufacturer changes the production of a medicine, for instance because ingredients are sourced from new suppliers or because the production method has changed, they need to submit an application for a post-approval change (PAC). Delays in obtaining PAC approval have been linked to the occurrence of shortages. More efficient handling of PACs, such as through expedited review, is thus seen as a way to prevent shortages.

Objectives

General Objectives

Ensuring the supply of older molecules which may still have high therapeutic value but limited commercial relevance. In addition, to initiate further cost-reducing procedural adjustments that in turn serve as incentives for multiple stakeholders throughout the supply chain, particularly MAHs, wholesalers or manufacturers.

Value added

Greater commercial incentives for the abovementioned stakeholder groups may translate into greater supply reliability

K.7.12. Packaging & Labelling

i) Develop EU-wide medicines packaging and labelling regulation, including flexibilities for digital leaflets and multi country/-language packaging and labelling

Description

Medicine shortages rarely affect more than a few EU Member States at the same time. However, the current requirement of national labelling on packaging restricts the ability of marketing authorisation holders and Member States to respond to shortages by moving supplies of medicines between countries to relieve local shortages in a timely manner.

An approach allowing for multi-language packaging would be to implement labelling that refers to an online, electronic version of the full package labelling and/or patient information via a code on the pack. During dispense, the pharmacist provides details of the dose regimen that needs to be followed in the national language thereby ensuring that the medicine is taken correctly: the rest of the information could then be accessed electronically. For those patients that cannot access online labelling, the pharmacist would be able to print out the needed material in the local language.

The ultimate goal could be the mainstreaming of Electronic Product Information Leaflets (ePIL), which would provide additional options to improve patient understanding of their medicines and how they should be used, for instance in the form of videos included in the ePIL demonstrating their correct use (e.g. correct use of an inhaler).

Objectives

General Objectives

Efficiency gains and greater flexibility in preventing shortages in the first instance, as well as greater flexibility in mitigating them (e.g. through emergency imports) in the second instance

Value added

Smaller markets could particularly benefit from these solutions as their relative commercial viability and attractiveness towards MAHs, wholesalers and manufacturers may improve

K.7.13. Dialogue

i)	**Set up stakeholder dialogue platforms for/between supply chain stakeholders, patients and healthcare providers, respectively at Member States level**

Description

Information sharing is crucial in solving the problem of medicines shortages. This includes information sharing between Member States but also between regulators, supply chain actors, pharmacists and patients, both at national and EU level. These stakeholders need to continuously share information and perspectives on the issue to discuss and plan the response to national and European shortages. To do so, coordination platforms should be set up by the national/European health authorities responsible for shortage mitigation and response.

Objectives

General Objectives

To improve information sharing between the various actors in the supply chain as well as the national authorities, prescribers, and patients

Value added

Greater communication between the supply chain actors as well as national and healthcare stakeholders could help create a greater sense of shared responsibility, ultimately leading to improved understanding of mutual issues and challenges in relation to shortages. This in turn, will lead to a more coherent response to and mitigation of shortages.

Europe Direct is a service to help you find answers to your questions about the European Union.
Freephone number (*)**:**
00 800 6 7 8 9 10 11

(*) The information given is free, as are most calls (though some operators, phone boxes or hotels may charge you).

Luxembourg: Publications Office of the European Union, 2021
ISBN 978-92-76-43478-8

doi: 10.2875/211485

PRINTED IN LUXEMBOURG

PRINTED ON ELEMENTAL CHLORINE-FREE BLEACHED PAPER (ECF)

PRINTED ON TOTALLY CHLORINE-FREE BLEACHED PAPER (TCF)

PRINTED ON RECYCLED PAPER

PRINTED ON PROCESS CHLORINE-FREE RECYCLED PAPER (PCF)

HOW TO OBTAIN EU PUBLICATIONS

Free publications:

- one copy:
  via EU Bookshop (http://bookshop.europa.eu);
- more than one copy or posters/maps:
  from the European Union's representations (http://ec.europa.eu/represent_en.htm);
  from the delegations in non-EU countries
  (http://eeas.europa.eu/delegations/index_en.htm);
  by contacting the Europe Direct service (http://europa.eu/europedirect/index_en.htm)
  or calling 00 800 6 7 8 9 10 11 (freephone number from anywhere in the EU) (*).

  (*) The information given is free, as are most calls (though some operators, phone boxes or hotels may charge you).

Priced publications:

- via EU Bookshop (http://bookshop.europa.eu).

Priced subscriptions:

- via one of the sales agents of the Publications Office of the European Union
  (http://publications.europa.eu/others/agents/index_en.htm).

EW-01-21-416-EN-N

Publications Office
of the European Union

doi: 10.2875/211485

ISBN 978-92-76-43478-8