28 February 2023
EMA/760980/2022

# Good practices for industry for the prevention of human medicinal product shortages

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# 1. Introduction

Medicine shortages are recognised as a global problem by the European Medicines Regulatory Network (EMRN) and other international organisations such as the World Health Organization. Shortages have been a global issue for some time, increasingly affecting European countries with a significant impact on patient care. Improving the availability of medicines authorised in the European Union (EU) is a key priority for the EMRN. Since 2016, a task force set up by the European Medicines Agency (EMA) and the Heads of Medicines Agencies (HMA), the HMA / EMA Task Force on the Availability of Authorised Medicines for Human and Veterinary Use, has been looking at availability issues, including medicines that are authorised but not marketed and supply chain disruptions, to improve the continuity of supply of human and veterinary medicines across Europe. This builds on the network's efforts since 2012 to improve processes for handling shortages caused by good manufacturing practice (GMP) non-compliance and the experiences gained during the Covid-19 pandemic.

Prevention is an essential aspect of shortage management. This document provides recommendations on best practices that marketing authorisation holders, wholesalers, distributors and manufacturerscan consider adopting to ensure continuity of medicinal product supply and reduce the impact of shortages. The recommendations are based on data obtained from stakeholders' experience in coordinating the management of shortages and identified causes of shortages.

# 2. Scope

This document recommends good practices to marketing authorisation holders, wholesalers, distributors and manufacturerson shortage prevention for human medicines, i.e. to reduce the likelihood of shortages occurring in the first instance. Recommendations on how to mitigate a shortage event are also included. This paper describes some of the most common reasons for shortages and is not intended to be exhaustive. It is intended for guidance only. In addition, this paper is not intended to provide any conclusive interpretation of the obligations imposed on stakeholders by the relevant EU legislation and is without prejudice to the application of such provisions. This document has been developed in the context of the HMA/EMA Task Force on the Availability of Authorised Medicines for Human and Veterinary Use, which was set up in December 2016 to provide strategic support and advice to tackle disruptions in supply of human and veterinary medicines and to ensure their continued availability.

The document describes all actors of the supply chain however focuses on actions to be be taken by marketing authorisation holders, wholesalers, distributors and manufacturers. A separate document provides guidance for patients and healthcare professional organisations. Commercial activities, such as the pricing of medicines and the clinical specifics of patient treatment in the event of a shortage are not in the scope of the present document.

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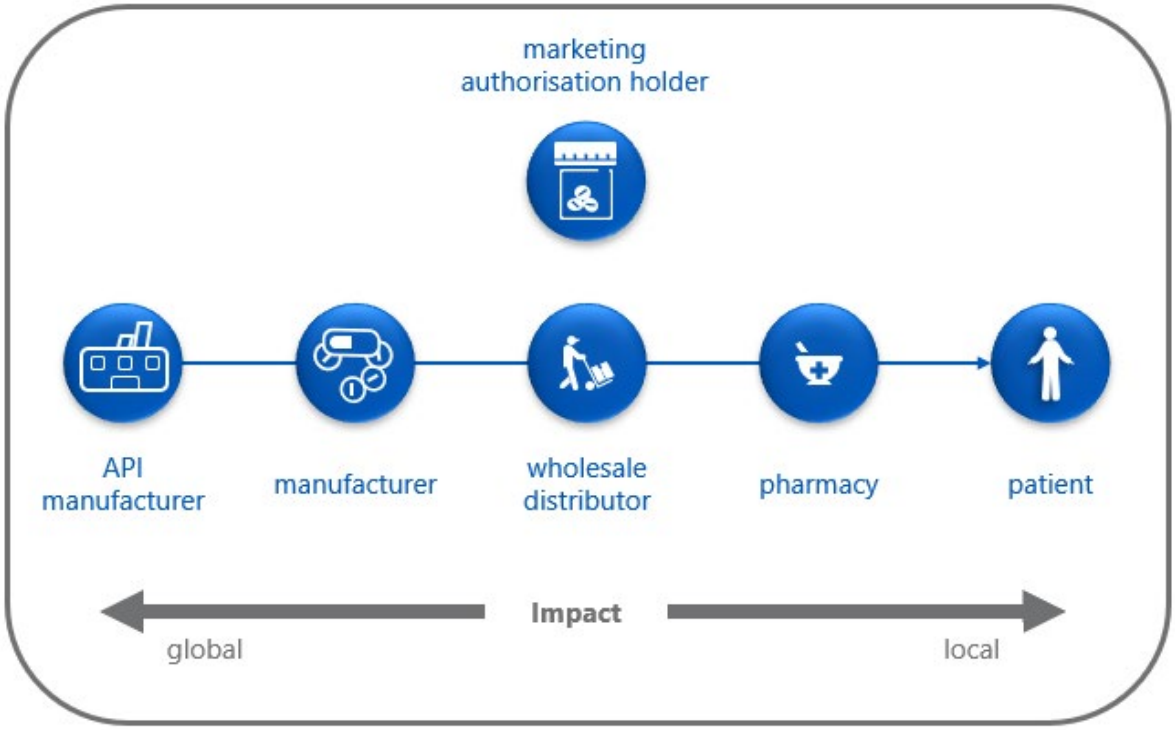
# 3. Players and their role in the supply chain

The medicine supply chain does not only refer to the distribution of products to healthcare providers such as pharmacies and hospitals. The journey of a medicine starts with the manufacture of the active ingredients and related materials that will be then incorporated into the finished product dosage and continues through the release and distribution of the medicine to those stakeholders, who then will interface with the end-user.

The medicine supply chain therefore involves several stakeholders with legal obligations within their responsibilities to ensure appropriate and continued supply of their medicines to patients. All stakeholders of the supply chain, therefore, play a vital role in the prevention and management of shortages.




## *3.1. Marketing Authorisation Holder*

Given the fact that they hold marketing authorisations, Marketing Authorisation Holders (MAHs) should have national and global oversight of the supply of their medicines from the start (manufacturing) to the end (end-user) of the supply chain. MAHs also have obligations to ensure continued supply to patients, within the limits of their responsibilities[1]. A good oversight enables them to continually align demand with supply to obtain a general understanding of the impact of a given shortage on patients and evaluate possible mitigating actions to prevent or mitigate the shortage from occurring. In accordance with their responsibilities and legal obligations, MAHs should require their stakeholders to have certain standards to achieve shortage prevention as much as possible. As recommended in "ISPE Drug shortages prevention plan – Holistic view from root cause to prevention"[2] it is important for a company to consider the quality culture as an absolute necessity, a tool to utilise to make decisions to benefit patients best. Therefore, shortage prevention is reached not only with a compliant system but through a quality culture integrated into the product's lifecycle. Having a system compliant with the

[1] Article 81 Directive 2001/83 of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use CL2001L0083EN0130010.0001.3bi_cp 1..1 (europa.eu)
[2] https://ispe.org/sites/default/files/initiatives/drug-shortages/drug-shortages-prevention-plan.pdf

principles outlined in ICH Q10 Pharmaceutical Quality System[3] facilitates the identification of all weaknesses and points of strengths internal to the company.

## 3.2. Manufacturers

Being the actual producers of the medicinal product or its active ingredients (API), manufacturers should have in depth knowledge of their manufacturing processes and related manufacturing issues that could be inherent to the process and not specific to any product, but which could result in potential or actual shortages. This also includes contract manufacturers, who produce products and APIs on behalf of several MAHs. An impact on their manufacturing capability could have a broader effect on the medicine supply.

In addition, manufacturers can also have oversight of demand fluctuation, enabling strategic planning of the activities.

## 3.3. Wholesale distributors

Wholesale distributors act as the interface between the MAH or manufacturer and persons entitled to supply medicines to the public. Subject to national provisions, wholesale distributors have obligations to ensure continued supply to patients, within the limits of their responsibilities, which is independent of the MAH's obligation. This position enables them to have general visibility of stock levels and product flow and identify early signals of a potential medicine shortage.

## 3.4. National Competent Authority

The national competent authority's (NCA) role in medicine shortages is to coordinate the response to a shortage across stakeholders so that the impact is mitigated as much as possible through regulatory tools and strategies. The NCA's regulatory remit might not extend to certain areas, for example, pricing, sourcing medicines, and clinical practice, nor can it require a company to produce a medicine or may not determine the supply route by which to distribute it as long as it satisfies good distribution practice requirements.

Regulatory flexibilities and discretion already exist and may be employed by NCAs (e.g. accelerated reviews, temporary importation of medicine from another country) to mitigate any significant risk to patients. The NCA provides information on particular medicine shortages through its website and via other media where appropriate. To this extent, the EMA and HMA published guidance for NCAs and EMA on good practices in communicating medicine availability issues to the public.[4]

## 3.5. EMA

EMA's role in medicines shortages of centrally authorised products is to coordinate the response to a shortage so that the impact is mitigated as much as possible through regulatory tools and strategies.

EMA plays a key role in coordinating the EU response to medicine supply issues caused by crises such as major events or public health emergencies. This includes monitoring medicine shortages that might lead to such a crisis situation and reporting shortages of critical medicines during a crisis.

EMA publishes a public catalogue for shortages assessed by the Committee for Medicinal Products for Human Use (CHMP) and/or the Pharmacovigilance Risk Assessment Committee (PRAC), providing clear information and recommendations, if relevant, to patients, healthcare professionals and other

[3] https://database.ich.org/sites/default/files/Q10%20Guideline.pdf
[4] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/good-practice-guidance-communication-public-medicines-availability-issues_en.pdf

stakeholders. In addition, EMA also publishes information on critical shortages that are monitored at EU level by the Medicine Shortages Single Point of Contact (SPOC) Working Party.

### *3.6. National health service provider*

The national health service provider is responsible for policy and operational aspects of timely access to medicines through reimbursement schemes, purchasing arrangements for certain medicines and clinical guidelines. The health service provider may also identify alternative medicines or therapies for patients if a medicine is unavailable due to a shortage. Through supply and pricing agreements, the health service provider also provides a reasonable level of certainty so that there is a predictable environment for MAHs to supply their products and prevent shortages. The agreements also facilitate prevention and mitigation measures which include an expectation that suppliers will source alternatives to shortages and procedures to be followed when medicines are transferred from one MAH to another.

In case of shortages with a significant public health impact, the provider can issue clinical guidance to healthcare professionals, where appropriate.

### *3.7. Ministry of health*

The national Ministry of Health has an overarching policy and direction role in achieving a sustainable and accountable health system and in promoting and protecting the health of patients in the country. It provides leadership for the health sector to improve health outcomes. This includes developing and reviewing legislation, representing stakeholder interests in an international context and contributing to initiatives to mitigate the risk and disruption caused by medicine shortages. In some Member States, the Ministry has a leading role in coordinating the management and mitigation of medicinal product shortages.

### *3.8. Healthcare professionals*

Healthcare professionals (e.g. prescribers, pharmacists and nurses) use their professional expertise to identify alternative medicines or therapies for their patients if a medicine is unavailable due to a shortage. Healthcare professionals can be involved in clinical guidance on appropriate treatment alternatives during a medicine shortage. Healthcare professionals also play an important role in promoting appropriate prescribing and use of a medicine and their ethical and fair distribution to meet the needs of patients. Healthcare professiaonls can also play a role in the stockpiling of medicines whichhas been reported to precipitate a shortage.

### *3.9. Patient representative groups*

Patients need timely access to medicines. In the case of some medicine shortages, patient representative groups, particularly for specific diseases, may need to be involved in supporting patients with information on the shortage and alternative medicines. Patient representative groups also play an important part in providing feedback on the impact of a shortage.

## 4. Proposed best practices recommendations for shortage prevention

This guidance refers to medicines for human use only. Shortages referred to in this guidance are to be understood in the context of the harmonised definition agreed by EMA-HMA in the "Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA)":

"A shortage of a medicinal product for human or veterinary use occurs when supply does not meet demand at a national level".
The reasons behind the failure to meet the demand are diverse and can be linked to each supply chain step. Below are recommendations to enable shortage prevention and/or mitigation.

The preventative strategies outlined here are aimed at addressing the underlying causes of shortages (e.g. quality & manufacturing issues, unexpected increased demand, regulatory issues and distribution issues) as referenced in the European Commission's study on shortages[5]. They would ensure that shortage prevention is actively considered part of the medicine's lifecycle management. Additionally, shortages and their causes are interlinked lending themselves to being addressed by more than one preventative strategy. One example would be the 'unexpected increased demand' category, where often, an unexpected increased demand is linked to the unavailability of another medicine (spill over-effect). Although the underlying factors for the unexpected increased demand is the shortage of the other medicine it is important to target the root cause of the first shortage which could be any of the other categories mentioned in the Commission's study such as quality and manufacturing issues, distribution issues, regulatory issues and commercial reasons to fully address the unexpected increased demand.

Complementary to the recommendations outlined below is the European Commission's Pharmaceutical Strategy[6], which includes a specific intention to address medicine shortages as part of its four main pillars. The global nature of the medicine supply chain will require more international collaboration and alignment to ensure the security of medicine supplies and shortage prevention. The Commission aims to put forward legislative and non-legislative proposals to address medicine shortages, including preventative and mitigation strategies.

In presenting the preventative and mitigation strategies, the general intention is to optimise and harness the use of all information sources and intelligence available in a pre-emptive rather than a reactive way. Appropriate implementation of preventative strategies benefits patients and health systems by ensuring continued supply or being prepared to mitigate the impact of a shortage should it occur. For industry, the preventative strategies will have benefits, including concerning certainties of outcomes.

## *4.1. Recommendation 1*

**MAHs, manufacturers and wholesalers, should notify the National Competent Authority of a potential or actual shortage as soon as possible in advance of any shortage.**

The average timing of a shortage notification is suboptimal. The difficulty that this presents is that there is very little time to react and prepare for increased demands for alternative product suppliers. Contrast this to a situation where there is sufficient time for actors in the supply chain and the health system to prepare and have adequate stock of alternative products to mitigate the patient impact. MAHs and wholesale distributors, in particular, are key stakeholders in the supply chain that have more visibility of current stock and planned supply levels than others. These stakeholders must report potential shortages at an early stage. If action is successfully taken at an early stage to avoid the shortage or any impact on patients and healthcare professionals, then there is little impact on patients. Any shortage update (such as extension/reduction of the period of shortage, or change of the impacted channels of distribution) should be reported in a timely manner to allow for a re-evaluation of the shortage impact. Notification of the resumption of supply should also be reported to the NCA.

[5] European Commission, Directorate-General for Health and Food Safety, Jongh, T., Becker, D., Boulestreau, M., et al., *Future-proofing pharmaceutical legislation : study on medicine shortages : final report (revised)*, 2021, **https://data.europa.eu/doi/10.2875/211485**
[6] Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions. Pharmaceutical Strategy for Europe https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52020DC0761&from=EN

## 4.2. Recommendation 2

**Increase transparency relating to shortage information.**

A strategy to facilitate increased transparency is increased communication and knowledge sharing across different stakeholders, with due regard to competition law, which helps mitigate and prevent shortages. Healthcare professionals need additional time to identify and source alternative medicines. Additionally, in an information vacuum, confusion and concern can lead to stockpiling of medicines and unnecessary duplication of efforts to determine a product's availability and the reason for a shortage. While the regulatory network is not responsible for sourcing medicines, it can facilitate identification of available products and alternatives by increasing transparency.

An additional aspect is that, given the global nature of the supply chain, there is a need to collectively engage and develop closer relationships with European and international partners to facilitate coordinated actions about medicines' supply.

## 4.3. Recommendation 3

**MAHs should increase the accuracy of notification detail provided.**

An essential step in preventing a shortage or reducing its impact is receiving key information about a potential shortage. It is important that notifications provide all currently available information requested in the form, with follow-up communications as needed, to enable the understanding of the current situation, assessment of the impact and consideration of prevention or mitigation measures.

Based on the information from some Member States, some critical pieces of information are often missing from notifications or not fully completed. To illustrate, not elucidating the specific manufacturing delays means that it is difficult to understand the impact and evaluate the likely timeframe for the resumption of supply. Additionally, understanding if a shortage will affect one or multiple countries is important, as are details about affected API manufacturing sites, if appropriate (e.g. active versus dormant sites,) as this would assist in accurately determining the impact (including possible implications for the supply of other similar medicines) and understanding the options available to mitigate or prevent the shortage.

## 4.4. Recommendation 4

**MAHs, manufacturers and wholesalers, should each have a shortage prevention plan specific to their role.**

Manufacturing issues are the most common cause of shortages. A shortage prevention plan, focussing on product-specific parameters, provides a more structured framework within the pharmaceutical quality system for the industry to focus on shortage prevention. In essence, a shortage prevention plan is a risk management process.

MAHs have overall oversight of the supply of their medicines nationally and globally. Therefore, the prevention plan should encompass aspects from the sourcing of active ingredients through to wholesale distributors. Assumptions about the availability of alternative medicines should not influence a company’s prevention plan, or notification of a shortage (subject to national provisions).

Shortage prevention plans for manufacturers will focus on their manufacturing capabilities, sourcing raw materials, market trends, marketing activities and the supply of medicines manufactured by them.

Wholesale distributor prevention plans will identify and mitigate identified vulnerabilities from receipt of the medicine, its storage and through to delivery.

The overarching aspects to consider in developing a medicinal product shortage prevention plan are:

- To identify any vulnerabilities in the entire supply chain or risks of an interruption in supply for patients. This could include that the MAH ensures its manufacturers have effective prevention plans
- To assess the robustness of the total supply chain arrangements and any controls that are in place to prevent a lack of availability of the product for patients and evaluate the risks of the product going out of supply.
- Develop a medicine shortage risk register, including regular review, in particular, to identify products of clinical importance by therapeutic use and availability of alternatives, as is the case on a country-by-country basis. In this regard, attention is drawn to the EMA's 'Criteria for classification of critical medicinal products for human and veterinary use'[7].
- An assessment as to whether corrective and preventive action or any revalidation should be undertaken, based on information available to the company, such as root cause analysis of shortages.
- Once established, regularly review the effectiveness of the controls in place to prevent shortagesfor patients.

## *4.5. Recommendation 5*

**MAHs, manufacturers and wholesalers should each have a shortage management plan to respond to issues resulting in shortages.**

Whereas a shortage prevention plan aims to identify particular existing vulnerabilities in the supply chain and address these risks (i.e. before an issue arises), a shortage management plan is a tool to determine how a company reacts to an issue that has arisen to mitigate the effect of a shortage at the patient level (i.e. after a quality issue has arisen). Neither plan is mutually exclusive; there should be a reciprocal flow of information to identify and address vulnerabilities identified.

Delivery of medicines from the active substance manufacturer to patients involves a complex and often fragmented supply chain. Many steps occur before medicines reach patients, which means there are many possible sources of quality issues that could affect supply. The increasing utilisation of contract manufacturing organisations (CMOs) adds further complexity and vulnerability to the supply chain if not adequately controlled. The capacity of manufacturing sites, including CMOs, is limited and may not be agile enough to adapt quickly to react to an issue. This results in a reduced capability to recover supply quickly. MAHs should take measures to make CMOs aware of shortages and for the CMOs to increase their involvement in this issue. These kinds of actions could be added in writing in the agreements.

Given these challenges, MAHs, manufacturers and wholesale distributors that have identified and implemented systems to react to issues that could result in supply disruption are more likely to be in a position to mitigate the impact. Potential and actual shortages can follow the same internal process as quality issues to minimise patient impact in a timely and proportionate manner.

A shortage management plan for each stakeholder formally identifies signals and risks for the continued availability of the product. It implements a procedure for their prevention or at a minimum, their mitigation. The effectiveness of such mitigation plans and the controls intended to prevent supply interruptions should be formally and periodically evaluated for effectiveness.

[7] Criteria for classification of critical medicinal products for human and veterinary use (europa.eu)

An example of this would be developing a dashboard that continuously monitors signals for potential supply disruption. The potential impact can be readily identified, such as using a traffic light system based on risk management principles. The MAH, manufacturer or distributor will then follow a protocol to assess the effect on the supply and implement the mitigation measures identified in the shortage management plan, including appropriate communication with the NCAs and other stakeholders. During a shortage, the automated order system can sometimes create additional difficulties in identifying true shortages. For example, wholesalers may have placed orders with their suppliers, as will customers placing orders with their wholesalers. This may result in back-orders accumulating, even though customers may have obtained products from alternative sources. Stakeholders involved in the ordering and supply at MAH and wholesale should establish mechanisms to identify such circumstances and elucidate the true shortage points to ensure equitable distribution of medicines.

## *4.6. Recommendation 6*

**Optimise pharmaceutical quality systems to strengthen the reliability and resilience of supply chains throughout the lifecycle of a medicine**

It is apparent from the data gathered that failures associated with pharmaceutical quality systems (i.e. regulatory issues) contribute to many shortages. While the current Good Manufacturing and Distribution Practices (GxPs) set out practically a minimum standard for quality, there is a need to shift the paradigm and focus of the industry to achieve an effective quality system that reduces the burden of shortages. As the focus on the medicine regulatory system adapts to new demands, applying a robust quality system during the lifecycle of a medicine becomes more important. Delays in the submission of variations or in applying for appropriate licences (for example, controlled drugs export and import licences) have directly contributed to shortages. MAHs should give equal attention to all medicines they markets, regardless of the stage in the lifecycle of the medicine.

Chapter 1 of the GMPs describes the use of product quality reviews (PQRs) which is a mechanism to ensure that data captured by the quality system is reviewed for trends and can, in turn, support an environment of continuous improvement. For example, PQRs are designed to identify and implement recommendations for required continuous improvements.

MAHs and manufacturers should adapt the PQRs to include assessing the robustness of the supply chain arrangements and any controls that are in place to prevent a lack of availability of the product for patients.

ICH guideline Q10 on Pharmaceutical Quality System is intended to provide a framework to move beyond just adherence to the GxPs. It describes the use of knowledge management and quality risk management as enablers, outlining potential opportunities where companies more actively demonstrate the effectiveness of their quality systems and regulators can take a more risk-based approach to regulatory oversight. In addition, ICH Q12[8] provides a framework to facilitate the management of post-approval changes more predictably and efficiently, promoting continuous improvement, with the ultimate aim of ensuring a reliable supply of product.

Industry stakeholders should implement the principles from the guidelines to promote continual improvement of the GxP environment and post-authorisation changes to strengthen the reliability and resilience of supply chains, thereby enabling better prevention of shortages.

[8] ICH guideline Q12 on technical and regulatory considerations for pharmaceutical product lifecycle management

## 4.7. Recommendation 7

**Increase resilience in the supply chain, taking into account known vulnerabilities**

Pharmaceutical supply chains are complex and often fragmented and involve many hand-overs throughout the supply chain before dispensing to a patient in the pharmacy. While consolidated global supply chains offer efficiencies, some aspects are more vulnerable to disruption, leading to shortages. Based on data available, this has been demonstrated by the number of shortages related to shipping delays coupled with a lack of contingencies.

Companies should assess and document if the just-in-time supply model is justifiable (using risk management tools already contained in their quality management systems), particularly for medicines with limited alternatives, given the potential for high impact shortages.

In case of an unexpected disruption during the manufacture of medicines, it is often not possible to increase production to restore depleted stocks at short notice due to lead times or pre-determined production schedules, particularly at CMO facilities. If this happens in the supply chain for a medicine supplied using a 'just-in-time' model, there is little redundancy to cover the shortfall of product, and shortages are likely. Just-in-time delivery models have benefits for the industry. Still, the use of such models for medicines must be carefully considered and justified unless there are specific reasons why it is not possible to maintain contingency stocks (e.g. medicines with a very short shelf-life).

Based on the information available, on average, there is usually a stockholding of many medicines within the wholesale supply chain. This, however, is not the case for all medicines. A disruption in a manufacturing activity for medicines with lower contingency stock levels, for example, could result in a delay in the replenishment of stocks that could quickly lead to the depletion of the available stock and shortages. Multiple confounding factors could also elevate the risk of shortages if coinciding, including a shortage of a similar medicine or unexpected increased ordering by the public and healthcare professionals. Based on the information available, some shortages could have been prevented if there had been adequate contingency stock to allow for possible transportation delays from manufacturers to wholesalers and ultimately to pharmacies.

Issues linked to transfers of manufacturing activities to different sites has been a common cause of shortages. In general, in these cases there was either not enough or no contingency stock available to prevent a shortage.

MAHs and manufacturers should ensure enough contingency stock to allow for unexpected delays during manufacturing site changes or ownership transfers through their management of change, particularly for clinically important medicines.

## 4.8. Recommendation 8

**Improve communication between stakeholders**

The single biggest issue that has resulted in difficulties during the management of shortages is sub-optimal communication (either inadequate or inaccurate) such as lack of timely communication of potential or actual shortages. Other examples relate to ordering delays and local delays in confirming an order resulted in shortages. Additionally, based on the data available, in some cases, weeks can pass before a problem identified at a manufacturer is communicated to the MAH. The introductory chapter to the GMP Guide implies the need for cooperation between the MAH and manufacturer and the need for two-way communication systems to be in place between them. This cooperation should be extended to communication relating to potential or actual shortages.

Several points in the supply chain could benefit from increased communication, particularly given the medicine supply chain's complex nature. Illustrative examples include:

- Intra-company communication between different departments, such as commercial and regulatory functions. Such communication allows the information gathered by those who have visibility on supply at the wholesale and pharmacy level to be shared with regulatory colleagues and vice-versa to identify potential issues early and take actions to prevent any impact on supply. It has been observed that where companies have increased internal communications, such as between commercial, logistics/supply and regulatory colleagues, this has resulted in better quality communication with the NCA and an increased ability to prevent and mitigate shortages.
- Communication between the local MAH representative in a member state and the manufacturer should be expedited where potential supply problems are identified. This could be done through software applications.
- Wholesale distributors can identify supply issues, for example, by observing low stock levels or identifying increased orders for products. In some cases that have arisen, shortages could have been prevented if the reduction in stock levels had been identified earlier and a system was in place to respond effectively by placing an order with the MAH or the primary wholesaler.
- Information about stock levels may be made available to entities entitled to supply medicines to the public via ordering portals. While this can be helpful, if the information is incorrect (e.g. a medicine is presented as being out of stock instead of on allocation), this can lead to confusion and unnecessary use of the shortages framework.

The benefits of communication, including notification to the NCA, enable all stakeholders to be better prepared to prevent the shortage from occurring or, at worst, mitigate its impact.

Each stakeholder should identify the key processes and supply chain maps for both individual products and overall quality systems, to establish effective and frequent communication between the different actors such as within the different teams or affiliates of the MAH as well as between the MAH, the relevant manufacturing sites and the wholesaler. The processes should establish timely and accurate communication to avoid shortages caused by issues such as local delays in ordering or failure to order.

Actors in the supply chain involved in the storage and distribution of medicines should develop a system based on criteria (e.g. stock reaches a defined level and delivery of replacement is not expected) to identify and communicate potential supply disruptions to their suppliers. Furthermore, should these affect the distribution of products with the potential to lead to shortages, these should be notified to the NCA independently of liaising with the MAH.

Stakeholders involved in developing clinical treatment or public health measures should consider the impact of any changes on the demand for some medicines. Where there is a potential for a significantly increased demand for individual medicines, arrangements should be made to communicate this to suppliers to enable them to adjust supply accordingly.

## *4.9. Recommendation 9*

**Promote fair and equitable distribution to meet the needs of patients**

The stockpiling of medicines results in a disrupted supply chain. Stockpiling can prolong the duration of a shortage, precipitate a shortage or result in an inequitable distribution to patients.

To illustrate, in one case observed, five months' worth of stock of one clinically important medicine was depleted from wholesale distributors in one month, leading to a shortage. This was despite the company's additional stock being made available in response to the increased demand. This meant that

available supply was not fairly distributed to all pharmacies and consequently to patients that needed it.

In another instance, where a potential shortage was anticipated but should have been prevented if all stakeholders ordered their normal quantities, a significant increase in orders was observed following communication of the possible shortage leading to quicker than expected depletion of the available stock and an actual shortage. As observed during the Covid-19 pandemic, where multiplestakeholders, such as MAHs, wholesalers, health systems, pharmacies, and NCAs coordinated actions, shortages were prevented by promoting equitable distribution of stock.

Stakeholders, such as healthcare professionals, should not order or dispense more stock than normal where there is a potential or actual shortage. This has the effect of creating a supply issue where there may not have been one. Additionally, in a shortage, MAH stock allocation practices between countries should take into account the clinical need of patients in the Member States, not just economic factors.

### *4.10. Recommendation 10*

**Take appropriate steps to minimise the risk of parallel trade or export exacerbating shortages**

Parallel trade[9] or export is the activity of companies such as MAHs and wholesale distributors of supplying medicines intended for patients in one country to another country. The free movement of medicines is a legitimate business practice. It depends on several factors, including arbitrage and, more recently, in the case of export, demand from non-EEA-based companies. When a shortage of medicine occurs, the medicine supply is insufficient to meet patients' needs. Although the export of medicines is unlikely alone to cause a shortage, it can contribute to worsening the extent of a shortage in the source country.

Decisions concerning restrictions on parallel trade in medicines by Member States' competent authorities would need to be duly justified and be proportionate, in accordance with the applicable EU laws governing free movement of goods. In situations of critical shortage, however, companies involved in parallel trade should monitor the situation, and, in cases of an identified risk to public health, should inform, and if required seek advice from, the relevant authorities of the exporting Member State in relation to their parallel trade activity.

## 5. Concluding remarks

This document has identified ten recommendations that can serve as the foundation for implementing preventative strategies. There is a need to optimise the notifications of potential and actual shortages, including earlier submission of notifications in advance of potential shortages and improving the accuracy of the detail provided to maximise the opportunities to prevent potential shortages from being realised or limiting their impact. There are also pathways to address the challenge of preventing shortages and further mitigating their impact, aiming to tackle the causes and exacerbating factors. These include developing shortage prevention and management plans, optimising the pharmaceutical quality system, increasing supply chain resilience and improving communications.

Recent major events such as the COVD-19 pandemic have further highlighted many international challenges in ensuring medicines supply. These challenges and the importance of addressing medicines shortages have been recognised across the EU and more globally and additional steps are being taken

[9] Parallel trade in this context is the term used to describe parallel distribution of both centrally and nationally authorised medicinal products. Parallel trade of centrally authorised medicinal products requires the involvement of parallel distribution notification holders and parallel trade of nationally authorised products requires the involvement of holders for those parallel product marketing authorisations, subject to national provisions.

to tackle shortages. Complementary to the strategies outlined in this good practice document, the international initiatives tackling the complexities of shortages include:

- the European Commission's Pharmaceutical Strategy,
- the strengthening under EMA's extended maandate of the European Single Point of Contact (SPOC) network (now renamed as SPOC working party), which has facilitated greater communication on shortages that may impact multiple countries,
- legislation to expand the remit of the EMA to enhance coordination of shortages from an EU perspective,
- the European Joint Action on shortages, CHESSMEN – Coordination and Harmonisation of the Existing Systems against Shortages of Medicines, European Network and
- the inclusion of medicine shortages in the European Medicines Agencies Network Strategy to 2025.

Stakeholders' actions in implementing prevention strategies and mitigation measures will enable a more significant chance of success in preventing shortages.