efpia
European Federation of Pharmaceutical Industries and Associations

Reflection Paper on Regulatory Mitigation Measures for Shortages of Medicinal Products

1 Executive Summary

The COVID-19 pandemic highlighted some challenges in securing supply of crucial medicines in Europe and reinforced the need for a flexible, agile system in the European Union that can respond quickly when a crisis occurs.

EU-wide, harmonised definitions of reportable "drug shortages" at the manufacturing and at Member State/patient level and a single, EU-wide, harmonised notification and reporting procedure are needed to allow early coordinated intervention on potential shortages. Early implementation of IDMP/SPOR, with its Target Operating Model, and linking the system to EMVS would provide a way to alert Member States of potential shortages and simultaneously provide a mechanism for finding alternative supplies of medicines.

Heads of Medicines Agencies/Member States have mapped regulatory mitigation measures that can be used in a crisis: these should be harmonised, transparent and kept up to date. Being able to rapidly relocate medicines from one Member State to another is key to managing shortages in a single or small number of Member States: capitalising on digital capabilities and moving to electronic Product Information are measures that can facilitate these processes.

Simplification of post-approval procedures by implementation of Heads of Medicines Agencies-Regulatory Optimisation Group recommendations on post-approval procedures, halting regulatory drift and simplifying change management processes for Certificates of Suitability are key steps that could be taken to encourage Marketing Authorisation Holders to maintain alternative supply routes.

Finally, the harmonised International Council on Harmonisation Q12 guideline is an important tool for providing flexibility and reducing post-approval change burden associated with the continual improvement of manufacturing and supply and the introduction of innovative manufacturing technologies. It should be implemented in EU as soon as possible.

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3 Problem statement

The Marketing Authorisation Holder (MAH) is required to market the product in compliance with the terms of the Marketing Authorisation (MA). During the life-cycle of a medicinal product, life-cycle management processes involve the constant review and updating of the MA and the physical presentation of the product via submission of variations and other documentation to update the quality, safety and labelling sections of the dossier. These processes are mandated and specified by European Union (EU) legislation as set out in the Variations Legislation (Commission Regulation (EC) No 1234/2008) and associated classification guidance (C-2013-2804-EN).

As outlined in the *Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA)*[1], early notification to competent authorities of a potential shortage in supply is a key aspect in the prevention/mitigation of shortages by allowing MAH sufficient time to organize contingency arrangements where necessary. Further possible mitigation measures (or best practices) have been shared by each individual Member State (MS)[2]. The proposed measures differ by country and range from allowing use of foreign packaging and languages, without the need to update the dossier, to the importation of non-authorised products.

There are increasing concerns regarding shortages, both in the EU and globally, and facilitating post-approval changes globally is one preventive approach to help mitigate shortages[3]. If shortages are to be reduced in the future, there is a need to have a harmonized and coordinated response by European Medicines Agency (EMA)/MS. The aim would be to allow for regulatory flexibilities and fast-track procedures that facilitate restoration and/or avoid interruptions of supply of medicines. The key principle underlying these activities remains enabling the continued supply of high-quality medicines to patients and protection of public health.

The COVID-19 pandemic has highlighted some of the challenges in securing supply of crucial medicines and reinforces the need for a more flexible, agile system in Europe that can respond to the needs of its people quickly, in a coordinated way. Regulators and MAH have worked hard to ensure that patient needs have been met, implementing emergency measures as needed. Introducing the changes outlined below would better prepare the network in Europe for future challenges, by improving the robustness of supply chains and providing all stakeholders with better oversight of medicines supply in the region.

This paper highlights some of the changes that could be made to the system to reduce shortages in the longer-term, with a view to securing the uninterrupted supply of medicines within the EU in the future, and reviews some of the measures that could be introduced to mitigate the worst effects of those shortages when they occur. This paper does not cover deliberate cessation of supply of a medicinal product once marketed or decision not to launch an authorised medicinal product in an EU MS for whatever reason.

4 Detection and notifications of shortages

4.1 Identification and monitoring of drug shortages

MAH take the responsibility of supplying MS with marketed products seriously and have planning and logistical systems as well as procedures in place to ensure that they supply the correct quantities of

[1] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-detection-notification-shortages-medicinal-products-marketing-authorisation-holders-mahs_en.pdf
[2] https://www.hma.eu/598.html
[3] https://www.efpia.eu/media/413670/efpia-ve-ebe-reflection-paper-on-a-revision-of-the-eu-variations-regulatory-framework.pdf

medicines to each market according to patient need. They monitor their stock levels constantly and are required to notify competent authorities of a temporary or more extensive shortage of supply.

Usually, the MAH will compensate for peaks in normal demand variations from a MS through demand and supply planning, however, when a difficulty arises unexpectedly, there are some changes to the existing system that could be considered to assist in mitigating the effects of supply issues as they occur.

4.1.1 Monitoring of EU supply levels

There is a need for a pan-EU agreement on the definition of a shortage based on patient need (rather than national demand) and a single, harmonized system for monitoring stock levels a) at the manufacturing level (availability) and b) at the MS/patient level (shortage) across the EU to predict future shortages and to notify other suppliers of the potential need for action so mitigation activity can begin earlier to avoid an out of stock situation occurring at the patient level.

The representative of the MAH in a MS may become aware of a short lived, unusually high increase in demand in one market that could result in a temporary out of stock situation at the wholesale level, that can be mitigated by diverting stock originally intended for another market, such that there is never a shortage at the patient level; whereas a Good Manufacturing Practice (GMP) issue that shuts down a manufacturing plant may result in patient level shortage of stock for some months later on. MAH need clarity on what types of shortage really need to be reported, to whom, and by when, using a single harmonized pan-EU system with a common portal.

> EU-wide, harmonised definitions of reportable “drug shortages” at the manufacturing and at MS/patient level and a single, EU-wide, harmonised notification and reporting procedure are needed to allow early coordinated intervention on potential shortages.

4.1.2 Implementing IDMP (SPOR) and linking to EMVS

In Europe, the use of IDMP standards is a regulatory requirement as they are mandated by the EU legislation (Commission Implementing Regulation (EU) No 520/2012 [articles 25 and 26]). EMA will implement IDMP through a set of projects known as the SPOR data management services. These services will establish central management of data in each of the four main areas: Substances, Products, Organisations and Referentials

With the implementation of SPOR, unique identifiers are provided for active substances, pharmaceutical dose forms, units of presentation, routes of administration and packaging. These identifiers could be linked to other databases in Europe (e.g. the interoperable network of national repositories being set up in the context of the Falsified Medicines Directive[4]) in order to identify issues and bottlenecks in supply across countries, regions and products.

Once implemented, the detailed product data available in SPOR would be available to all stakeholders in the Healthcare Systems of each MS and would function as an aid to finding alternative medicines that are identical to the product at risk of shortage. In addition, the detailed information of the registration status in each country, would allow regulators, customs officials or Healthcare Professionals (HCP) to better assess the risk of replacing one medicine with another when moving product between MS.

[4] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32011L0062&from=EN

Implementing IDMP and linking to EMVS would provide stakeholders with detailed information on supply issues and bottlenecks and would give them options for finding alternative medicines.

4.1.3 Early notification of shortages to MS

The SPOR plan calls for the proactive communication of supply risks to EMA by MAH via the IDMP submission. This feature has been postponed to after implementation of the first iteration of the system, but if implemented earlier this mechanism could be used to alert MS on potential shortage situations.

Implementing SPOR after first iteration of the system could be used as the mechanism to alert MS to potential shortages.

5 Regulatory mitigation measures

Applying effective mitigation measures should reduce timelines for addressing potential shortages, through minimizing regulatory administrative burden and facilitating flexible supply chains without compromising quality of medicinal products and public health. This section will provide a reflection of established national regulatory mitigation measures and proposes a harmonized approach across MS for the future.

5.1 Overview of MS mapping of regulatory mitigation options

Currently, the Heads of Medicines Agencies (HMA) have published on their website[5] a mapping across all MS of different solutions or best practices to manage shortages. As stated above, in most cases shortages can be addressed at a national level, depending on the type of medicines and the type of shortages. However, further discussion is needed with MS on how to develop a common framework of regulatory solutions to drug shortages (taking into account the national legislative framework).

HMA (and MS) should agree on a harmonized approach towards flexibilities and increase transparency by regularly updating HMA's mapping of existing regulatory mitigation measures.

5.2 Product information

Current legislation provides flexibility in situations of severe problems with the availability of medicinal products (Directive 2001/83/EC, Article 63 (3)[6]). In these situations, MS may i) grant exemptions to certain particulars that should appear on the labelling and in the Patient Information Leaflets (PIL) and/or ii) grant a full or partial language(s) exemption.

These foreseen flexibilities are aimed at allowing the supply chain to rapidly re-allocate finished medicinal products already released on one market to another, by eliminating the resource intensive step of re-packaging, which in some cases could take a matter of weeks to complete.

Other steps could be taken to optimize the utilization of medicines within EU, as described below.

[5] https://www.hma.eu/598.html
[6] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32001L0083&from=en

5.2.1 Exemption from use of official language(s) to allow greater flexibility in movement of medicines from one MS to another in times of medicines shortages

Supplies of medicines intended for the market can be delayed or destroyed if required changes to the packaging materials (labelling of immediate or outer container or change to the PIL) must be introduced before stocks of the previous versions of the marketed product are exhausted naturally. Usually, the medicine itself in its immediate packaging is not affected by the proposed changes; often the outcome is a need for redressing of existing stock to incorporate new labelling.

When drug shortages occur, they are not usually EU-wide, but limited to one or more MS. The current use of national labelling on cartons restricts the ability of MAH and MS to respond to such issues by moving supplies of medicines between MS to relieve local shortages in a timely manner: it necessitates national action from MS to wave the requirements of the legislation to alleviate potential shortages.

One way to eliminate these limitations on handling local shortages would be to allow for labelling of the carton to one common EU language and access to an on-line, electronic version of the full package labelling and/or patient information via a code on the pack. During the dispensing process, 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 a minority of patients that cannot access on-line labelling, the Pharmacist would be able to print off the needed material in the local language.

> Exemption from use of official language(s) with link to electronic labelling in local language would allow rapid redistribution of medicines between MS when local drug shortages occur.

5.2.2 Replacing paper PIL with electronic Product Information (ePIL)

The PIL is intended to provide patients with the information necessary for them to safely use a medicine that they have purchased, or which has been prescribed for them. A significant group of medicines (from contrast media to anaesthetics or vaccines) are administered by HCP directly, in circumstances where the patient does not in fact handle the medicine at all.

The inclusion of a PIL in the packs of medicines intended for such use is a waste of resources and this requirement should be eliminated from the requirements in the legislation. For other medicines, replacement of the paper PIL with a code that links to an ePIL would immediately obviate the need to redress medicines to take account of changes to the PIL. In addition, substitution of the physical PIL with an ePIL has the benefit of ensuring that the PIL in use by the patient is the most up to date version. Similarly, manufacturing processes mean that changes to PIL often take several months to be integrated into the physical pack, whereas online compendia are more routinely updated.

Finally, the use of an ePIL would provide additional options to improve patient understanding of their medicines and how they should be used. For example, ePIL could be provided in multiple languages in addition to those mandated per MS, to increase access to accurate information on a medicine. In addition, medicines that are complicated to use could have videos included in the ePIL which demonstrate their correct use (e.g. correct use of an inhaler).

EMA, MS and MAH share common aspirations and understanding of a need for electronic and structured labelling and MAH would hope that a fully operational ePI could be introduced that would rely on structured content, which is integrated with SPOR datasets resulting in the use of similar information and messaging standards (e.g. HL7 FHIR) by all stakeholders.

Obviating the need for a PIL for medicines administered by an HCP and moving to an ePIL would eliminate shortages and wastage caused by the need to redress packaging and would ensure patients always have up-to-date information.

5.3 Simplification of post-approval procedures

The administrative burden associated with life-cycle management of the quality of the medicines has increased significantly since the introduction of the Variations Regulation in 2008. Procedural simplification is needed allowing the management of more changes under the MAH internal Quality Management System under GMP without the need for regulatory submission. In addition to reducing the administrative burden in terms of numbers of variations required to be submitted per MA per year, other procedural simplifications could also be introduced, these could include:

- Managing more reporting of minor changes (Type IA changes) via databases (i.e. through use of SPOR) as proposed by Regulatory Optimisation Group (ROG), instead of the variation route.
- Moving towards structured data submission with the support of the Target Operating Model (TOM) for the future handling of supply chain information and its changes via digital tools.
- Adopting a fast track procedure to add/change Active Pharmaceutical Ingredient (API) suppliers.
- Increasing flexibility to reduce change management lag time for the supply chain.

HMA-ROG recommendations to simplify harmonized post-approval procedures, enabling adoption of digital alternatives to burdensome submissions though use of SPOR and TOM, need to be adopted.

5.3.1 Greater inclusion of API supply chain information in MA (so-called "Regulatory Drift") significantly contributes to increasing variation numbers

Greater inclusion of API supply chain information in the MA has resulted in many of the changes previously handled by the Qualified Person (QP) /MAH within the Quality Management System under GMP requirements to be translated into an increased need for variations – a process called "Regulatory Drift".

This trend towards increasing regulatory oversight has not been associated with a decrease in quality issues or shortages but is a major contributor to regulatory burden. It is also contrary to the spirit and direction of travel of the ICH which is working on global harmonisation of guidelines.

Regulatory Drift is a major contributor to procedural burden and should be stopped.

5.3.2 Alternative processing of CEP updates could result in very significant post-authorisation efficiency gains

A simple change to the Certificate of Suitability (CEP) update to an API used in multiple MA can result in a very significant administrative impact and represents one of the major areas of potential reduction in administrative burden for the MS and MAH.

The process for approval of changes to the CEP issued by the EDQM impacting multiple MAH could be modified to offer the possibility of a leaner, less administrative approach to maintenance, incentivising MAH to maintain an alternative EU source of API, taking into account the additional controls of outsourced activities, which have been implemented and enforced recently.

Post-approval procedures (e.g. for API) and processing (e.g. CEP) increase burden but do not result in a proportionate benefit to patients but can contribute to decisions on product viability.

5.4 Opportunity to implement the harmonised procedure on life cycle management of ICH Q12

One of the recent guidelines (ICH Q12[7]) which is intended to provide flexibility and reduce post-approval change burden associated with continual improvement of manufacturing and supply, and the introduction of innovative manufacturing technologies, requires revision of the EU Variations framework to be fully adopted in the EU.

The post-approval 'operational flexibility' envisioned from implementing ICH Q8 to Q11 has not been achieved and the Q12 Product Lifecycle Management guideline provides opportunities for a more science and risk-based approach for assessing changes across the lifecycle while all steps are under control and documented. Q12 aims to clearly distinguish between major to moderate changes that need to be notified to competent authorities and minor changes to the product that can be managed solely within the Pharmaceutical Quality System. Q12 also aims to accelerate the implementation of Chemistry, Manufacturing and Control (CMC) changes through Post-Approval Change Management Protocols (PACMPs), a tool that already exists within the EU system. Faster implementation of CMC changes and harmonization of the basic principles upon which the different regional variations systems are based should help to reduce potential disruptions in global supply chains, to the benefit of patients in EU and worldwide.

As noted above, the EU Variations framework already includes PACMPs. Although incorporating the 'Established Conditions' (EC) concept from Q12 into the EU framework requires legal changes, the EU system already relies on a risk-based categorization of post-approval CMC changes, which is necessary to gain the benefit of EC and PACMP Q12 tools. Implementation of the principles and tools described in the ICH Q12 guideline would promote continual improvement, the introduction of innovative manufacturing technologies, and proactive planning of supply chain adjustments. This would strengthen quality assurance and reliability of the supply chain. In addition, as the EU is seen as a reference authority internationally, implementing the principles described in ICH Q12 would give a clear signal and pave the way for further harmonization of regulatory requirements across countries worldwide, encouraging use of a science- and a risk-based approach to reduce lead times for life-cycle changes.

ICH12 is an important tool that will provide flexibility and reduce post-approval change burden associated with continual improvement of manufacturing and supply, and the introduction of innovative manufacturing technologies. It should be implemented as soon as possible.

[7] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-q12-technical-regulatory-considerations-pharmaceutical-product-lifecycle-management_en.pdf

6 Lessons Learned from COVID-19

The COVID-19 pandemic was an unprecedented and unexpected event that challenged the world's Healthcare systems' ability to respond quickly to medical emergencies on a global scale.

Within the EU, the way in which regulatory processes evolve through a process of consensus building, which in normal times is a model of how to cooperate internationally, hindered the ability of the system to react quickly. In the meantime, MS acted unilaterally to protect their citizens, by for example closing borders, stockpiling medicines to the detriment of patients that really needed them and restricting free movement of medicines.

From a drug supply perspective, the initial lag time necessary for coordination, and the parallel but differing national responses, compounded the difficulties faced by MAH when trying to secure and maintain drug supply to all MS in a period of time when demand was increasing exponentially due to stockpiling, without transparency on real patient need. At the same time, manufacturers were facing work force depletion through illness and the need to change normal working practices in response to the emerging health crisis.

Consolidating the learning and achievements from the COVID-19 pandemic and implementing mitigation strategies, will ensure that we have a fit-for-purpose mechanism in place that monitors drug shortages in real time and adjusts to changing needs quickly in a harmonized way throughout the EU to cope with whatever form a future crisis may take.