Addressing the root causes of medicines shortages

Supply chain Stakeholders' views on root causes and solutions

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Summary

Medicines shortages[1] are a multi-factorial issue that can have multiple root causes such as manufacturing and quality issues, economic related issues and supply chain issues. *Supply chain stakeholders, having patient's health as the primary objective, are committed to avoid and mitigate the issue of medicines shortages and believe that the root causes of shortages can be addressed by:*

- *Harmonizing and monitoring medicines shortages at EU level*
- *Create regulatory incentives for essential low-priced medicines*
- *Allow regulatory flexibility and improve regulatory efficiency to mitigate shortages*
- *Ensure market stability and sustainability*

Identifying the root causes of medicines shortages

Supply chain stakeholders worked together to identify the root causes of medicines shortages. Table 1 summarizes a non-exhaustive list of root causes of medicines shortages, classified according to their nature.

Table 1 - Summary of root causes of medicines shortages

		Regulatory	Manufacturing and quality	Economic	Supply chain
Products not authorized		Regulatory time lag	NA	NA	NA
Products authorized but not launched		National requirements	Manufacturing capacity Natural disasters	Market conditions	NA
Products authorized and marketed but unavailable due to shortages	**Temporary**	NA	Manufacturing lag times GMP issues Surges in demand API and excipient supply	Pricing mechanisms Tender practices Cost-containment measures	Supply quotas and parallel export Logistical inefficiency
	Permanent	NA	Manufacturing capacity	Commercial withdrawals	NA

Regulatory related root causes

The pharmaceutical regulation ensures the quality, safety and efficacy of medicines in Europe. For this purpose, every medicinal product must be the subject of a valid Marketing Authorisation (MA) within the European Union

[1] 'A shortage of a medicinal product for human or veterinary use occurs when supply does not meet demand at a national level.'[11]

before it can be placed on a market for sale and supply. The Marketing Authorisation Holder (MAH) has to market the product in compliance with the terms of the authorisation.

MAs issued only allow the product in question to be marketed by the MAH in that EU Member State, unless the product has been authorised via the centralised procedure in which case a single MA is granted by the European Commission and is considered valid in all EU Member States.

Either of these two regulatory **systems** can create delays in the approval of new MAs or variations to existing MAs, indivertibly creating access issues.

Two concrete examples were identified where shortages can be tied to the time necessary to fulfil the regulatory requirements:

- **Regulatory time lag:**
  - A medicine that was previously approved on a market and its MA was invalidated for administrative reasons, waits for MA approval from the Competent Authority or a medicine previously approved must wait for MA renewal
- **National requirements:**
  - A certain national Competent Authority requires the MAH to fulfil a specific requirement from that country (e.g. different pack size in the context of the decentralised procedure)

Manufacturing and quality related root causes

Manufacturing medicinal products is challenging and requires highly sophisticated facilities, procedures and highly trained staff to ensure quality, safety and efficacy of said medicines. In particular, the quality of medicinal products must conform to strict EU regulatory standards, which are amongst the highest of existing standards worldwide. Having consideration to the complexity of the manufacturing processes and the high-quality standards required for the safety of patients, any detected issue with any of the components used to produce a medicinal product may be the root cause of a shortage. There are several examples of how manufacturing and quality issues can cause shortages:

- **Manufacturing capacity:**
  - Due to limitations of the production output of a certain manufacturer, the supply cannot meet the need for a medicinal product
- **Natural disasters:**
  - Due to unforeseen manufacturing disruption caused by natural disasters, the supply of medicinal products depending on the production of the affected facilities are severely hampered
- **Manufacturing lag times**
  - Due to manufacturing scheduling issues and inherent complexities related to the production of medicines products, the supply of a medicinal product is delayed
- **GMP issues**
  - Due to manufacturing issues related to GMP, the supplies of medicinal products at the affected facility are severely hampered
- **Surges in demand**
  - Due to inaccurate forecasting or unexpected increases in the prescription and use of a certain medicinal product, the supply of the said product cannot meet the need either due to insufficient manufacturing capacity or manufacturing lag times
- **API and excipient supply:**
  - Due to quality issues detected in the active pharmaceutical ingredient (API) or excipient of a given medicinal product, and due to the limited availability of alternative suppliers considering both API market concentration and challenges in licensing alternative sources of raw material, production of the said product is halted until quality defects can be corrected or compliant alternative compound sources can be found

Economic related root causes

Accumulating evidence[1–10] points towards economic root causes of medicines shortages. Several economic agents are involved in the supply chain of medicinal products. European markets are frequently a monopsony

where the buyer is also the price setter. The factors driving economic related shortages are varied in nature and have complex interplays amongst themselves and with other root causes:

- **Market conditions**
  - The decision of an economic actor to operate in a certain market is a complex process, depending, among other factors, on the existing competition, market size, pricing and reimbursement policies and pharmaceutical policy. Due to these factors, it is possible that a medicinal product is not launched in a certain market.
- **Pricing policies**
  - Pharmaceutical pricing policies that are solely aimed at containing pharmaceutical expenditure (e.g. reference pricing or mandatory price reductions), do not allow for price adjustments to reflect changes in the cost of goods, manufacturing, regulatory procedures and/or distribution (e.g. increased cost of ingredients) and do not secure adequate volumes, have a negative effect on the supply reliability of medicinal products. All economic actors involved in the supply chain are directly or indirectly affected by the price setting mechanisms in place. The viability of those actors is essential for business and supply continuity.
- **Tender practices**
  - Single-winner, price-only tenders that cause severe price erosion, reduce the number of suppliers on the market, offer short lead times and apply harsh penalties on companies severely increase the risk of shortage of medicinal products.
- **Cost-containment measures**
  - Cost-containment measures only focused on reducing the expense such as payback mechanisms, payment delays, etc. offer no incentive for industry actors to continue operating in some markets. In fact, mechanisms such as the clawback offer little incentive for policy makers to enact structural changes allowing for more efficient use of the available budgets.
- **Commercial withdrawals**
  - The result of the combined action of the aforementioned economic causes where a medicinal product ceases to be available in a certain country due to the withdrawal of its Marketing Authorization, either by one or all the Market Authorization Holders.

Supply chain related root causes

Medicines' supply chains involve various actors with a common interest, to ensure the right medicine reaches the right patient. Given the complexity of the supply chain, the economic relations of the different actors involved and the complexity of manufacturing, storage, distribution and dispensing medicines, it is possible that medicine shortages arise due to issues related to these factors

- **Supply quotas and parallel export**
  - Discrepancy between the volume manufacturers release on a given market (i.e. Annex 16), the volume of exports and imports and the actual patients' needs from the said market, can give rise to shortage of a medicinal product. Supply quotas applied by some MAH on healthcare products distributors are set on several parameters including estimates of national patient needs. If the national demand fluctuates and exceeds estimated patient needs, problems for healthcare distributors to source stock may arise.
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- **Logistical inefficiency**
  - The medicinal product is available in the supply chain, but patients are unable to get it at their point of dispensing, providing a false signal of medicine shortage. It could be the case that there are sufficient stocks available in the particular market to cover the entire market (national demand) but they are simply not in the right location.

Finding collaborative solutions for medicines shortages

Harmonization, monitoring and cooperation

Harmonization at EU level

The centralized and harmonized definition of shortage[1] for reporting and monitoring purposes should facilitate communication of shortages among member states and is a necessary requirement of an EU level monitoring of

shortages. Additionally, clearly defining what is a 'risk of shortage' for an essential medicinal product would support the notification process to Competent Authorities. Finally, the reporting process should avoid duplication of reporting and be concise and consistent in the data required.

Monitoring of shortage at EU level

Monitoring shortages at EU level is essential to streamline efforts to collaboratively tackle the issue of medicines shortages. Information should be shared among Member States, regardless of the type of product registration procedure (CP, DCP, MRP or NP). "High-risk" medicinal products[2] should be established and given priority when addressing shortages and ensure a tailored approach with reasonable and appropriate security measures, incentives and proportionate penalties in case of failure to supply.

Cooperation to address shortages at EU level

Establishing a cooperation mechanism to coordinate EU and national policies is essential to address medicines shortages. Medicines shortages are pan-European issues thus a strong cooperation among institutions and Member States is necessary to reduce the risk of shortages and to avoid spill over effects through which one country's policy could create supply issues in another country.

Regulatory aspects

Regulatory flexibility (ad-hoc)

Regulatory flexibility is key both to avoid and help mitigate shortages. A case-by-case approach is necessary in foreseen circumstances that can endanger the supply of medicinal products to patients (e.g. FMD, Brexit). It is equally important to facilitate post approval changes in a controlled but fast process to avoid shortages. Flexibility to accept different pack sizes at national level based on Marketing Authorization and multi-country packages in case of a confirmed shortage of a medicinal product can help mitigate the shortage and reduce the health risk for patients. The future use of eLeaflets would be useful in mitigating shortages.

Regulatory efficiency

An efficient use of the "Repeat Use" procedure would allow MAHs to get approval in a Member State facing a shortage of a medicinal product, thus contributing to mitigate said shortage.

Regulatory incentives

Incentives for medically essential low-price products (e.g. lower variation fees/flat fee) are necessary to ensure that lifesaving products remain on markets where sufficient revenue can no longer be obtained.

Economic aspects

Market stability and sustainability

A predictable and sustainable pricing & reimbursement environment is a desirable market condition for Market Authorization holders and provides an incentive for increasing the number of manufacturers willing to enter or remain on a certain market. The larger the number of manufacturers guaranteeing supply, the less likely that patients are exposed to medicines shortages. In case one of the manufacturers cannot supply patients with the necessary medicines, other manufacturers active in the market should be able to supply the medicine, thus avoiding or mitigating the impact.

[2] e.g. lifesaving medicinal products with no possible substitute or therapeutic alternative, lifesaving medicinal products with alternatives in different presentations, acute or chronical treatment with no possible substitute or therapeutic alternatives.

The use of short-term cost containment measures is a key factor of unpredictability in the markets and, therefore it can be a driver of medicines shortages. Pharmaceutical pricing policies limited to arbitrary price reductions and artificial price control mechanisms, namely external reference pricing, that do not consider the different competitive environments in the markets are important factors that contribute to unpredictability. In addition, payback mechanisms that put the responsibility of budgetary compliance on industry actors instead of governments and/or payers to create a sustainable pharmaceutical policy framework, are largely detrimental to a predictable and reliable supply chain. These measures should consist of a combination of policies aimed at ensuring the sustainability of the supply chain and healthcare systems by securing patients with their medicines, rather than blindly aiming at achieving budgetary targets.

In addition, different markets require tendering practices that ensure supply reliability for patients, such as inclusion of MEAT[3] principles, adjusting the number of tender winners according to the market, product and country characteristics and using lead times that guarantee a steady supply of medicines. That is achieved with tendering frameworks aiming at the long-term sustainability of both healthcare systems and all stakeholders**.**

Overall, all policies should put the right economic incentives in place, which reward medicine quality and supply as well as strengthening the overall supply chain resilience. This can only occur if the market conditions offer viability to all stakeholders**.**

Manufacturing and quality aspects

Rewarding supply reliability

The pharmaceutical industry has made and continues to make considerable investment in manufacturing and quality. These investments aim at compliance with the latest regulation (e.g. FMD) and strengthening the supply reliability of medicinal products. Policy and decision makers should acknowledge and reward actions that support improvements in supply reliability.

Communication aspects

Ensuring adequate information for all stakeholders

Market Authorisation Holders communicate to Authorities when anticipating or experiencing a shortage. It is therefore essential that Competent Authorities cascade relevant information to stakeholders in a way that allows for economic operators, healthcare professionals and patients to be sufficiently informed about the shortage. This requires Authorities to adjust information according to their target audience, and time the communication in such a fashion that allows for preparation but avoids panic and unnecessary stockpiling that can aggravate a situation of limited supply. Furthermore, when communicating, Authorities must be mindful of the possible implications for other MAHs on the market by communicating to alternative suppliers the probability of an increase in the demand for their products, thus avoiding a snowball effect.

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[3] Most Economically Advantageous Tender

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