GIRP recommendations on ways to deal with medicines shortages

The continuous availability of medicines for patients whenever and wherever needed is one of the fundamental pillars of any healthcare system. Full-service healthcare distributors (licensed as 'wholesale distribution authorisation holders' and also referred to as pharmaceutical full-line wholesalers) are indispensable to help ensure availability of medicines through their role at the centre of the medicines supply chain.

Full-service healthcare distributors, recognised at EU level as critical entities, commit to:

- **carrying and distributing the complete assortment of medicines, medical products and devices** in both range and depth within the framework set by the authorities and the market;
- continuously **ensuring product availability** for patients within a matter of hours;
- setting and delivering **quality standards** that safeguard, above all, the **safety and integrity of medicines, medical products and devices** delivered to pharmacists and other healthcare professionals;
- performing a **public service function** by maintaining access to vital products**.**

The EU Member States are currently experiencing a spate of production-related shortages of critical medicinal products including analgesics and antibiotics. A proportionate response to the issue of shortages is therefore more urgent than ever.

GIRP would like to share specific solutions based on their members' longstanding expertise and extensive supply chain experience.

Executive summary – dealing with medicines shortages

The revision of the EU General Pharmaceutical Legislation in 2023 should enable pharmaceutical full-line wholesalers to fulfil their public service role, notably through providing them with the "right to be adequately and continuously supplied" by pharmaceutical manufacturers.

Managing the issue of medicines shortages relies on well-structured communication and coordination among the different stakeholders of the supply chain and with the competent authorities at national and EU levels, involving:

- Implementing the definition of medicines shortages in Regulation (EU) 2022/123 into national law for all medicines;
- Introducing an EU-wide harmonised categorisation of root causes of shortages;
- Conducting an exhaustive mapping of the global supply chains for medicines, including raw materials, Active Pharmaceutical Ingredients (APIs), auxiliary products, etc;
- Requesting shortages prevention plans by manufacturers as well as shortages management plans by all supply chain stakeholders;
- Establishing a legal basis for an EU-wide early warning system for anticipated/potential and verified/confirmed shortages for critical medicines, involving all supply chain stakeholders;
- Facilitating the movement of stocks managed by full-service healthcare distributors across Europe in case of a critical shortage in a Member State.

1. Enabling pharmaceutical full-line wholesalers to fulfil their public service role of ensuring equitable, efficient, and safe medicines access to all EU patients

Directive 2001/83/EC only foresees one distribution license granted to any and every operator claiming to distribute medicines.

Rue de la Loi 26, Box 14
1040 Brussels, Belgium
T +32 (0)2 777 99 77
F +32 (0)2 770 36 01
E girp@girp.eu
W www.girp.eu

Pharmaceutical full-line wholesalers fulfilling Public Service Obligations (PSOs) or Public Service functions should be distinguished by law from other actors, who are by choice storing and distributing only a selective/limited range of products, while pharmaceutical full-line wholesalers (bound by their PSOs):

- continuously ensure the availability of the full range of medicines and healthcare products,
- regardless of the price and subsequent distribution margin and
- irrespective of the quantity procured to retail pharmacies, hospitals, and dispensing doctors, to
- wherever the dispenser may be located or the size of their operations.

GIRP therefore calls for a revision of the wholesale distribution licensing system, differentiating pharmaceutical full-line wholesalers from other operators by law.

Distinguishing pharmaceutical full-line wholesalers from other distributors would confer them with the frame to comply with their Public Service Obligations and give them the legitimacy to ensure equitable, efficient, and safe medicines access to all EU patients.[1]

Pharmaceutical full-line wholesalers can properly carry out their public service function only if the legal framework provides them in all EU Member States with the right to be appropriately and continuously supplied by MAHs with the full range of products.

This is a pre-requisite for pharmaceutical full-line wholesalers to:
- Fulfil the needs of patients in an appropriate and timely manner;
- Act as a one-stop shop for healthcare professionals who, otherwise, must spend valuable time and resources trying to obtain the required product from the different manufacturers, rather than focusing on patient care.

The current legal framework provides EU Member States with the possibility of addressing system failures in medicines availability, when implementing Article 81, paragraph 2 and 3 of the Directive in national legislation in a way that places separate obligations on both Marketing Authorisation Holders (MAHs) and full-line wholesale distributors (recognised as such as per the above pre-conditions) including the "right to be supplied").

However, so far, separate supply obligations have been implemented in about half of the EU Member States and the "right to be supplied" only in Belgium, Czech Republic, France, Finland, Germany, Hungary and Portugal.

Therefore, GIRP strongly recommends that the revision of directive 2001/83/EC includes the "right to be adequately and continuously supplied", enforceable by national authorities to ensure the almost immediate availability of medicines to patients through retail pharmacies, hospitals, and dispensing doctors, while not impeding or limiting other distribution models such as direct sales.

Manufacturer-imposed supply quotas in general are highly problematic and should be abolished, or their use restricted to legally defined criteria, e.g., public health emergencies, shortages of critical medicines etc. The practice of supply quotas cannot be reconciled with Public Service Obligations (PSOs) or Public Service Functions and rather contribute to the occurrence of shortages instead of preventing them.

The revised legislation should set out the pre-conditions allowing for the establishment of supply quotas and their monitoring by National Competent Authorities (NCAs), should the shortage of an essential product justify the need for such measure. In that case, the allocation scheme for supply quotas must be transparent and

[1] Please see the GIRP position paper on a distinct system of wholesale distribution licenses for pharmaceutical full-line wholesalers

previously notified to the NCA and communicated to full-line wholesalers to allow optimised rationalisation of the available quantities of medicines.

2. Collaboration, coordination, and communication throughout the supply chain

GIRP believes that well-structured communication and coordination among the different stakeholders of the supply chain and with the competent authorities at national and EU levels are vital.

A. Implementing the definition of medicines shortages in Regulation (EU) 2022/123 into national law for all medicines

To better assess the root causes of shortages across EU Member States and to better monitor anticipated and verified medicines shortages, GIRP calls for the application of a common definition across Member States.

GIRP supports adopting the existing definition in Regulation (EU) 2022/123 on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices:

> *"'shortage' means a situation in which the supply of a medicinal product that is authorised and placed on the market in a Member State or of a CE-marked medical device does not meet demand for that medicinal product or medical device at a national level, whatever the cause;"*

Why patient demand is not a reliable indicator to forecast actual demand

Patient demand is dynamic and subject to many factors such as seasonality, disease outbreaks, public and media attention, political decisions, prescribing policy changes, etc. At the start of the COVID-19 pandemic, there was a sudden and drastic upsurge in patient demand for specific products, such as asthma inhalers, which had to be met, as well as rapid changes in the use of products in critical care units.

Although, pharmaceutical full-line wholesalers fulfil a stock-keeping function, and 'normal' swings in demand can be largely met and absorbed by buffer stocks, these can quickly be exhausted when there is a widespread health emergency. The most recent example is the acute shortage of antibiotics, cough, and cold medication as well as analgesics for which the unusually low consumption over the last 2 years led to dramatically underestimated demand.

Furthermore, certain products have little to no patient need over long periods. However, a sudden localised outbreak of a specific disease (e.g., meningitis) may lead to a sharp increase in patient demand. Due to the stock-keeping function of pharmaceutical full-line wholesalers, the product is always available, although there is generally little to no patient need and therefore, also no demand from healthcare professionals.

Lastly, the narrow approach to patient demand is no longer applicable due to movement of patients across the EU. As patients are now looking towards the possibility of purchasing their prescribed medicinal products outside of their own country (as is already the case between Finland, Estonia and Portugal), the notion of patient demand within a Member State is becoming irrelevant.

B. Introducing an EU-wide harmonised categorisation of root causes of shortages

A legislative basis should be established to harmonise the different approaches to shortages reporting and monitoring across the EU Member States. The implementation of agreed **EU-wide harmonised categories for root causes** of shortages in any published databases, would facilitate this, and should include a separate listing of the Active Pharmaceutical Ingredients (APIs) in any list of critical medicines.

Studies into root causes of medicines shortages

While the discrepancies in the reporting of root causes across the Member States do not allow for a clear read of the origin of the shortages, reports seem to converge on manufacturing issues and market withdrawals being the lead causes. The OECD, for example, produced a report[2] stating that '*Several analyses have noted that shortages, as reported by marketing authorisation holders, are predominantly due to (exogenous) manufacturing and quality issues (in about 60% of cases). Manufacturing and quality problems include, for example, production quality issues or defects in any component of a product; shortages of inputs; inventory and storage practices; temporary and permanent suspension of production due to e.g., technical issues with production or non-compliance with Good Manufacturing Practice (GMP), or manufacturing site closure or relocation.'*

While the scope of this report goes beyond the European level, another comparable study conducted by Technopolis and commissioned by the European Commission[3] concluded that '*By far the most often recorded cause relates to quality and manufacturing issues (51%). Commercial reasons, which have previously been noted as a prevalent root cause of shortages in Europe, were the second most common reported root cause (25%).* The study found however that 'distribution issues have steadily declined as a reported root cause of shortages since 2015.'

C. An exhaustive mapping of the global supply chains for medicines

An exhaustive mapping of the global supply chain for medicines access in the European Union should be drafted. The mapping should account for the suppliers of raw materials and producers of APIs in and out of the European Union, the European production capability and should identify risk mitigation measures (alternative suppliers, production sites, etc.)

For essential medicines, manufacturers should put in place solid shortages prevention plans to be shared with competent authorities for maximised, coordinated preparedness.

For essential medicines, all stakeholders should be required to put in place a shortage management plan to respond to the impact of that medicines shortage, including appropriate communication with the NCAs, other stakeholders and prescribers, through an interconnected monitoring system.

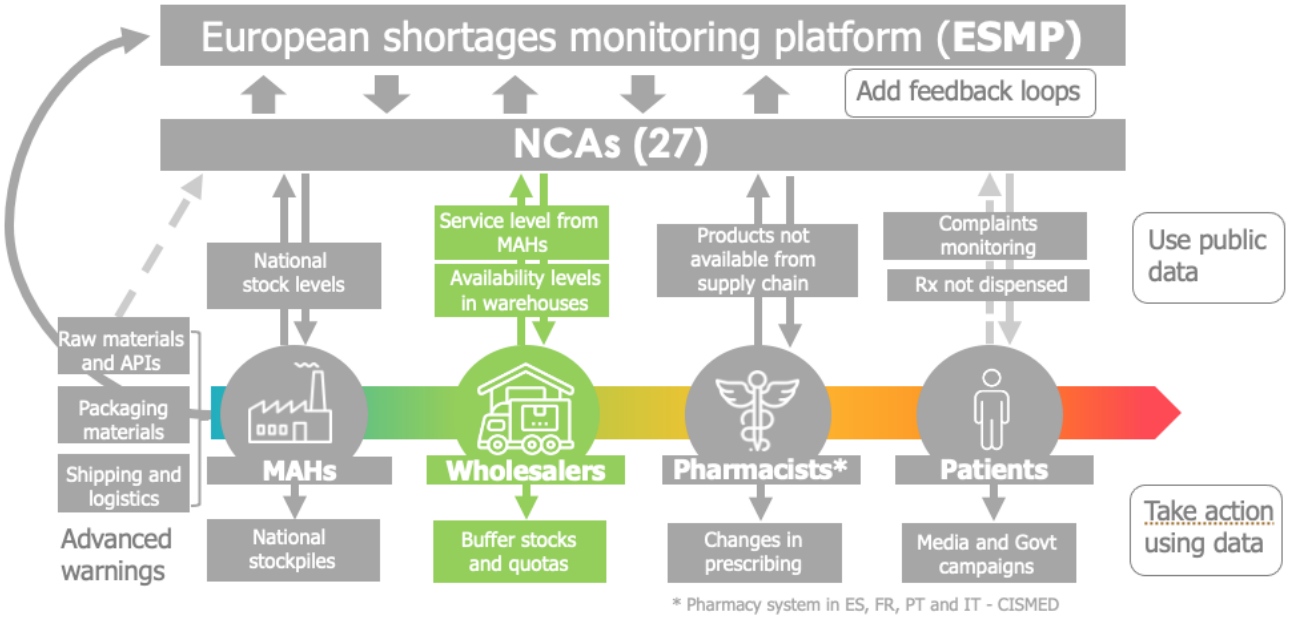
- The revision of the EU General Pharmaceutical Legislation should introduce a legal basis for an EU-wide early warning system for anticipated/potential and verified/confirmed shortages for critical medicines, involving all supply chain stakeholders, from manufacturers, pharmaceutical full-line wholesalers, hospitals, online and community pharmacists to prescribers, the national competent authorities and EMA for coordination at EU level. This system should include the obligation of early notification of shortages by MAHs to pharmaceutical full-line wholesalers (in addition to NCAs) and of anticipated shortages. To avoid duplication of reporting and to ensure readability of the situation at national and EU level, GIRP supports connecting available national shortages monitoring systems for aggregation of the data at EU level.

- Detecting or predicting shortages of medicines and healthcare products should not be seen as an end itself. Information must be shared within healthcare systems so that changes to supply routes, ordering, prescribing and dispensing can be made in good time to avoid disruptions to patient care.

  Please see here the proposed structure for a EU-wide shortage monitoring system

[2] Shortages of medicines in OECD countries
[3] Future-proofing pharmaceutical legislation — study on medicine shortages

Medicines shortages reporting to NCAs & EMA



Why the EMVS cannot produce accurate predictions of upcoming shortages

Apart from the fact that the use of the EMVS system to monitor shortages would require a change of current FMD legislation and would need the support of all stakeholders, which is also currently not the case, the EMVS cannot produce accurate predictions of upcoming shortages.

Some supply chain actors have promoted the European Medicines Verification System (EMVS) as a solution for monitoring of medicines shortages. GIRP would like to briefly outline why the EMVS, built to protect patients from falsified medicines, cannot provide an overview of national stock levels and even less so, serve as an indicator of demand.

On the supply side, the deficiency of the EMVS lies in a huge overestimation of available products as the data contained therein will always be significantly higher than the number of packs actually available on national markets. This is due to multi-markets packs which are counted for every country where they are uploaded (overestimation of available supplies by 14%-15%, i.e., 2.5 billion packs per year), whereas they can only be physically present in a single country.

In addition, data uploaded to the EMVS (and subsequently redistributed to NMVSs) are supposed to happen once a batch has cleared its Quality Control (QC) sign-off at which point, it can be supplied to the market. However, data related to the pack such as the serial number will happen before batch release and there can be a long delay between data upload and the release of the physical pack. The data in the system is not exactly representative of the physical supply of product to the market (to wholesalers or pharmacies, nor indeed patients. This can lead to a further overestimation of supply.

Although the EMVS is nearing the end of its implementation phase, there are still certain supply chain actors who remain to be connected to the system. Two markets have yet to join (Italy and Greece) and there are still ongoing disruptions stemming from the departure of one of the largest markets (UK).

Rue de la Loi 26, Box 14
1040 Brussels, Belgium
T +32 (0)2 777 99 77
F +32 (0)2 770 36 01
E girp@girp.eu
W www.girp.eu

Most importantly, however, data about products decommissioned from the system in no way indicates national demand. Leaving aside the many cases where products are currently not decommissioned, due to non-compliance, the number of products decommissioned are in no way an indication of demand.

Therefore, numbers of decommissioned products would be highly misleading for demand estimations and could lead to wrong conclusions on demand with a detrimental impact on patients. In order to accurately estimate demand, e-prescribing systems, which have been swiftly advancing especially during the COVID-19 crisis can serve as basis for the most accurate estimation.

Lastly, the EMVS only accounts for prescription medicines and does not provide information about non-prescription medicines, medical devices and other healthcare products, all of which have experienced demand surges and/or product shortages in recent years.

For more information, please follow this link.

GIRP members report that patients in a specific Member State can suffer from a shortage when that same medicinal product is available in other, often neighbouring, European Union markets. As demonstrated by IQVIA in their 2020 white paper 'Reporting of Medicine Shortages in Europe', a very limited number of products have a general shortage issue across Europe.

GIRP recommends shortages of medicines in an EU Member State also to be made transparent at EU level, to allowing for solving or at least mitigating of said shortages by imports from other Member States. GIRP also calls for regulatory flexibility in licensing and labelling rules to facilitate the movement of stocks managed by full-service healthcare distributors across Europe in case of a critical shortage in a Member State.

Conclusion

Addressing the issue of medicines shortages demands a concerted effort involving all supply chain stakeholders, national competent authorities and European institutions for harmonised and coordinated communication and action. We believe a first step should consist in adjusting the European pharmaceutical legislation and subsequently, the auditing of the rightful implementation by NCAs.

GIRP also invites the European institutions to make full use of the full-service healthcare distributors' expertise, experience and infrastructure while ensuring the sustainability of their activity.

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Rue de la Loi 26, Box 14
1040 Brussels, Belgium
T +32 (0)2 777 99 77
F +32 (0)2 770 36 01
E girp@girp.eu
W www.girp.eu