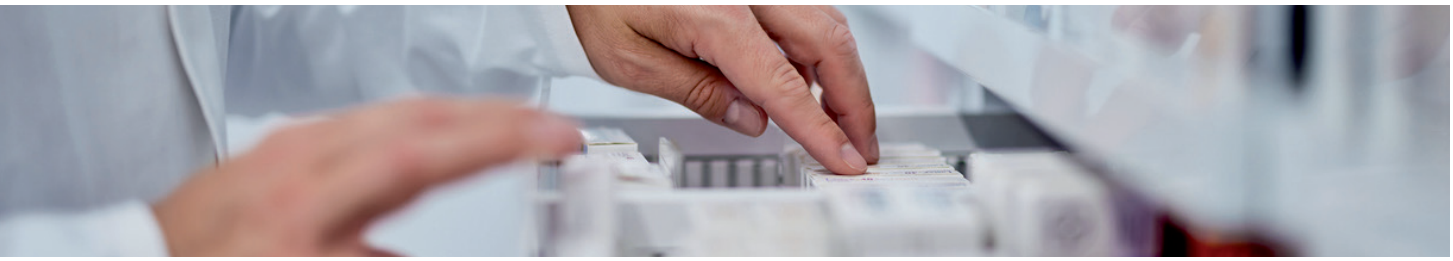

The Drug Shortage Crisis

Causes, Impacts and European Solutions

Maurizio Battistini
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En este artículo el autor pretende, a partir de la definición de escasez de medicamentos, identificar y analizar sus principales causas, considerando su impacto y, en consecuencia, proponiendo posibles soluciones, incluyendo la postura del Grupo Europeo de Farmacéuticos Industriales (EIPG), al que pertenece. Es reciente la noticia de la disponibilidad de una base de datos (C-CODE) que apoya la búsqueda de alternativas terapéuticas para la sustitución en todos los casos de escasez caracterizados por un efecto dominó que afecta a todos los medicamentos equivalentes disponibles. El artículo también describe brevemente las iniciativas más recientes adoptadas a nivel europeo (Critical Medicines Alliance) para abordar el problema, comenzando por los medicamentos considerados más críticos para el paciente, que siguen siendo el foco de atención. El contenido constituye un importante llamamiento a los representantes de la Unión Europea para que recuperen en Europa la producción de principios activos estratégicos para la salud (reshoring) mediante medidas de apoyo que permitan reducir el impacto actual de la significativa dependencia de suministros de países no pertenecientes a la UE. Esta iniciativa debe asociarse a otras medidas de intervención y mitigación que se abordan en el artículo.

Palabras clave: Desabastecimiento; EIPG; Alternativas terapéuticas; Reubicación.

In this article, the author aims, starting from the definition of medicine shortage, to identify and analyze its main causes considering their impact and consequently proposing possible solutions, including the position of the European Industrial Pharmacists Group (EIPG) to which the author belongs. It is recent news about the availability of a database (C-CODE) that supports the therapeutical alternatives search for substitution in alle cases of shortages characterized by a domino effect affecting all the available equivalent medicines. The article also briefly outlines the most recent initiatives taken at European level (Critical Medicines Alliance) to address the problem, starting with the medicines considered most critical to the patient, who remain the focus of the attention. The content constitutes an important appeal to the representatives of the European Union to bring back to Europe the production of active strategic ingredients for health (reshoring) through support measures that allow us to reduce the current impact of the significant dependence of supplies from non-EU countries. This initiative must then be associated with other intervention and mitigation measures that are given voice in the article.

Keywords: Medicine Shortage; EIPG; Therapeutical Alternatives; Reshoring

INTRODUCTION

Medicine shortages have become an increasingly pressing issue in Europe, significantly affecting healthcare systems, supply chains, and patient care. The crisis has been exacerbated by global economic instability, geopolitical tensions, production issues, and regulatory challenges. This article delves into the causes of these shortages, their impact on healthcare, and the measures being implemented at the European level to mitigate the crisis. Furthermore, it serves as an urgent appeal to the civil servants of the European Union to take decisive legal actions and mobilize efforts towards reshoring key medicines, reducing dependence on China and India, and ensuring European pharmaceutical sovereignty.

Medicine shortages have become an increasingly pressing issue in Europe, significantly affecting healthcare systems, supply chains, and patient care

"A shortage of a medicinal product for human or veterinary use occurs when supply does not meet demand at a national level". Some comment about:

- Shortage as defined, allows for identification of current, impeding or anticipated disruption of supply of a medicinal product.

Comment: definition consider only disruption not therapeutic alternatives.

- 'Medicinal product' as described in Article 1(2) of Directive 2001/83/EC and Article 1(2) of Directive 2001/82/EC. Medicinal products which contain the same active substance presented in different pharmaceutical forms and/or strengths and, when required by the national competent authority, pack sizes, are seen as individual unique medicinal products. The above definition applies to marketed human and veterinary medicines (not inclusive of medicines supplied on named patient basis or medicines supplied for compassionate use).

Comment: definition consider shortage of individual unique medicinal products. It does not consider the availability of therapeutically equivalents and alternatives with the same API (different pharmaceutical forms and/or dosage strengths) or other APIs having similar pharmaceutical activity. However, the availability of therapeutic alternatives can temporarily mitigate the disruption effects at clinical level (Figure 1).

- Supply refers to the total volume of stock of the individual medicinal product that is placed on the market by the Marketing Authorisation Holder. 'Supply' means the total volume of stock of a given medicinal product that is placed on the market by a marketing authorization holder or a manufacturer.

Comment: definition looks difficult to put in place because require the stock of all individual medicinal products that meet the definition (equivalents and not) in order to have the clear and full picture of the supply.

For determining the supply at national level, the sum of the stocks of all the therapeutically equivalents and alternatives, including also all the medicinal products containing the same API in different forms and/or dosage strengths. Obtaining such data can be difficult for single MAHs.

- Demand relates to the request for a medicinal product by a healthcare professional, veterinarian or patient in response to a clinical need. The medicinal product will need to be acquired in time and sufficient quantity to allow continuity of best care of patients/animals. *'demand' means the request for a medicinal product by healthcare professionals or patients in response to a clinical need; the demand is satisfactorily met when the medicinal product is acquired in appropriate time and in sufficient quantity to allow continuity of provision of the best care to patients;

Comment: the sentence "time and sufficient quantity to allow con-

FIGURE 1. Generic medicine substitution: a potential solution to mitigate impact of medicines' shortages. Source: Medicines' Shortages and Critical Medicines Alliance – State of the Art and proposal for problem mitigation – EIPG webinar 26.06.2024

	AUT	BEL	DEU	DNK	ESP	FRA	FIN	ITA	IRL
Generic medicine substitution is legally allowed?	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Medicines for Europe - Market Review – European Generic Medicine Markets 2020

"A potential solution to mitigate the impact of shortages, is to enable pharmacists to independently decide on appropriate substitutions for a medicine in shortage and dispense this directly to the patient without mandating consultation with a prescriber."

tinuity of best care" is not adequately measured and can be differently interpreted by end users. Demand is limited to a national level and do not consider the impact of the same issue in different countries; this could seriously amplify the trouble.

National level refers to the situation in a specific country, i.e. if there is insufficient supply of a medicine to meet the demands of the country overall. Logistic -related issues leading to regional supply disruption of a medicinal product e.g. delivery difficulties, national redistribution of stock, are a short term and localised problem and should not be taken into account.

DRUG SHORTAGE AND UNAVAILABILITY. SUBSTANTIAL DIFFERENCES

Before delving into the causes and solutions, it is essential to distinguish between drug shortages and unavailability (Tabla 1).

The European Medicines Agency (EMA) and national regulatory bodies distinguish between these terms to ensure effective monitoring and resolution strategies.

OVERALL COMMENT

It is important to decide whether the proposed definition of Medicines' shortages in the "Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA)" is what practitioners believe are in the interest of patients and healthcare professionals as well as those responsible for supply; at the same time the revision of the definition would avoid to consider as shortage only a temporary disruption of the supply of a specific medicine when a therapeutical alternative is available as equivalent medicine or by a therapeutic indication coming from a qualified advisory medical body at National or European Level.

DEFINITION REVIEW: MAIN GOAL 1

Define what is a shortage, at least from a healthcare professionals' viewpoint. The definition of shortage should be based on what practitioners believe to be in the best interest of patients.

Shortages' definition should include a minimum duration for a shortage; this also would help prevent Regulatory Agencies from being overloaded with irrelevant notifications. In industry there is obviously concern over the reporting of all "impending and anticipated" as well as confirmed shortages since many "potential" shortages will not lead to a supply disruption for patients, leaving Agencies inundated with a vast amount of data, much of which could be irrelevant.

DEFINITION REVIEW: MAIN GOAL 2

Definition of medicines' shortage has to land to a realistic list with meaningful timescales and levels of certainty of shortage.

Essential medicine concept, and related criteria, should be harmonized and included in the definition in order to realistically address the issue and avoid overload of the system. Most of the shortage reported may have a low or negligible impact on public health for the availability of therapeutic alternatives (87 % of shortages are solved by the substitution carried out by pharmacist or MD according to Farmanco® results reported in PGEU report). Using this approach, each country can concentrate mitigation actions on the most critical medicinal products, adopting the most appropriate problem-solving strategies for its peculiar situation without wasting time and human resources in low-impact shortages.

Differences between ongoing shortages and potential shortages should be also taken in consideration in order to define the best mitigation strategies and communication.

DEFINITION REVIEW: MAIN GOALS - 3

The use of the risk assessment and the related prevention/mitigation plan tools should be considered in the definition to highlight how to commonly approach the shortages in order to have a harmonized evaluation criteria and understand the impact of the issue. Please refer to PDA Technical Report No 68 for a better understanding of a risk-based approach in the shortages field

The unavailability of medicine at a hospital/community-pharmacies level is not only affected by the reduction of MAH supply but also distribution-related issues, distortion and inefficiencies.

TABLE 1.

COMPARISON BETWEEN MEDICINE SHORTAGES AND UNAVAILABILITY: DEFINITION, CAUSES AND IMPACT

Aspect	Medicine Shortage	Unavailability
Definition	A situation where a medicinal product is not sufficiently supplied to meet demand	The absence of a drug in a specific pharmacy or distribution point, despite its availability in the market
Causes	Supply chain disruptions, manufacturing issues, raw material shortages	Logistic inefficiencies, stock mismanagement, commercial strategies.
Impact	Affects multiple countries or regions, leading to critical treatment gaps	Affects local access but does not indicate systemic failure

HOW APPROACH TO FIND THERAPEUTICAL ALTERNATIVE: C-CODE DATABASE

To meet the challenges to find therapeutical alternative when originator and equivalents having the same API's and dosage are not available, I am been recently informed about the existence of an extensive database recently created (C-CODE), a patented system that introduces a new model for classifying and grouping

medicines, medical devices and food supplements on the basis of the equivalence of their clinical therapeutic effect.

The C-CODE makes possible to see products that, despite having different compositions, offer the same therapeutic benefit related to each other.

In addition to comparing solutions that are comparable in terms of clinical effect, there is also the possibility to obtain the relevant dosage correspondences and comparison information on the economic impact of the treatment options.

The writer has been insisting for several years on the need to be able to have recourse to therapeutic alternatives where there is an extensive shortage almost always characterized by a domino effect affecting all equivalent medicines. To date, this strategic solution has been scarcely pursued, probably mainly because there is no useful tool at national, and above all supranational, level that can assist health professionals in identifying solutions in the event of shortages or even just disruption (equally critical when it comes to medicines that are essential for the continuation of therapy without interruption of any sort).

THE RISE OF MEDICINE SHORTAGES IN EUROPE (2018-2023)

Over the past five years, the frequency and severity of drug shortages have increased dramatically across Europe. Below is a graphical representation of the trend (Figure 2).

This steady rise can be attributed to several factors, including manufacturing disruptions, increasing global demand, and geopolitical instability.

ROOT CAUSES OF DRUG SHORTAGES

PRODUCTION AND SUPPLY CHAIN ISSUES

• Dependence on Non-EU Active Pharmaceutical Ingredient (API) Suppliers: The pharmaceutical industry relies heavily on raw materials from India and China. Any disruption in these supply chains (e.g., COVID-19 lockdowns, geopolitical tensions) can halt production.

• Manufacturing Problems: Regulatory compliance failures, contamination issues, and factory closures often lead to prolonged shortages.

• Quality Control Issues: Stricter quality controls imposed by EMA and national agencies sometimes lead to product recalls, further exacerbating shortages.

• Limited API Production Facilities in Europe: With cost-driven outsourcing of API manufacturing, Europe faces a lack of sufficient local production capacity (Figure 3).

ECONOMIC AND REGULATORY FACTORS

• Low Profitability of Essential Drugs: Many older but essential drugs, such as antibiotics, are produced at minimal profit margins, discouraging manufacturers from continuing production.

• Regulatory Delays: The approval process for alternative suppliers or manufacturing sites can be lengthy, slowing down the response to shortages.

• Parallel Trade within the EU: Different pricing policies across European countries incentivize parallel

FIGURE 2. Increase in Medicines Shortages in Europe (2018-2023). Source: Author of this article

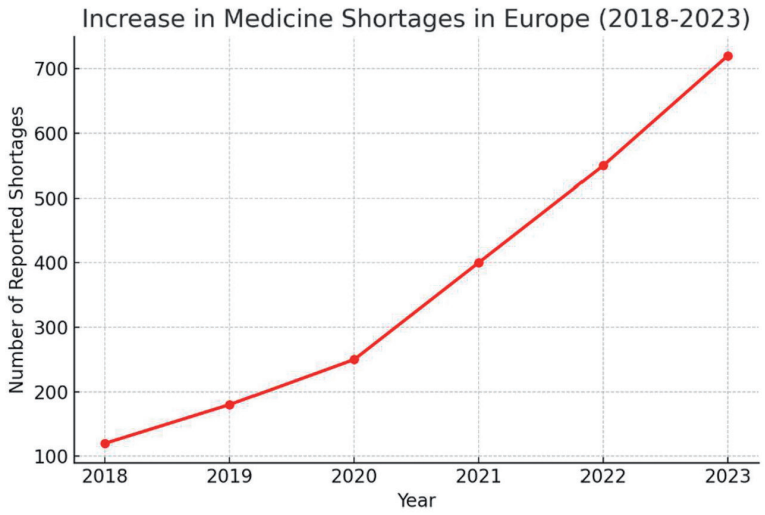
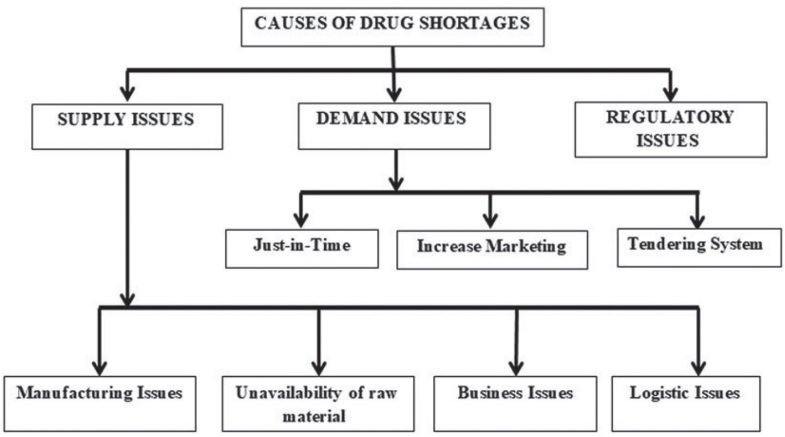


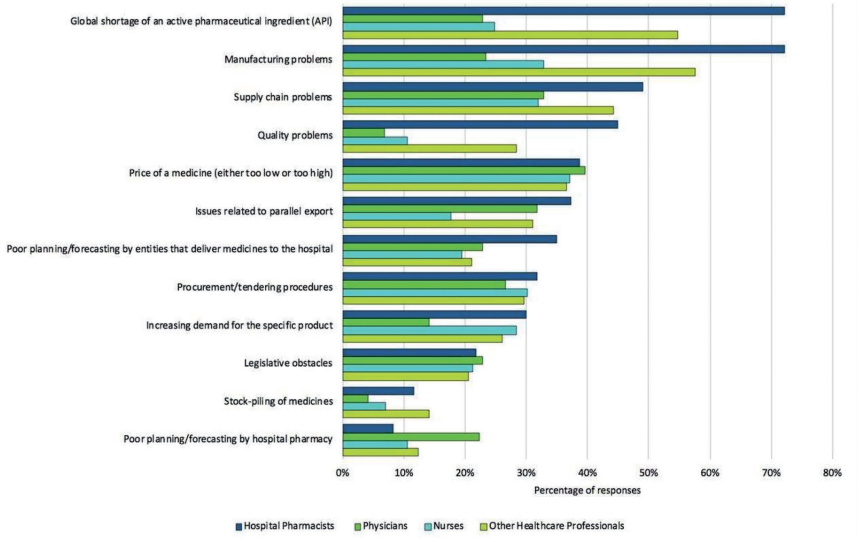
FIGURE 3. An Overview on The Main Root Causes Originating Medicines' Shortages. Source: Drug Shortages – Root Causes and Potential Solutions - US FDA 2019



A database that only collect medicines' shortages is not a proactive system!

FIGURE 4. Supply Chain Security Toolkit for Medical Products. Source: Supply Chain Security Toolkit (Food and Drugs Administration www.fda.gov/Drugs/DrugSafety/DrugIntegrityandSupplyChainSecurity and Asia Pacific Economic Cooperation - apec/SupplyChain/APEC_SupplyChainToolkit

FIGURE 5. Main origins of drug shortages experienced at final dispensers in the supply chain. Source: European Journal of Hospital Pharmacy - Results of EAHP's 2019 Medicines Shortages Survey



trade, leading to local shortages in lower-priced markets.

• Limited Strategic Stockpiling: Unlike other sectors, the pharmaceutical industry lacks a systematic approach to maintaining reserves for essential medicines.

MARKET DEMAND FLUCTUATIONS

• Sudden Spikes in Demand: The COVID-19 pandemic, seasonal flu outbreaks, and increasing chronic disease prevalence have significantly increased demand for certain medicines.

• Stockpiling Behavior: Both hospitals and pharmacies sometimes engage in stockpiling, worsening perceived shortages.

MEDICINES' SHORTAGES. A BRIEF FOCUS ON POTENTIAL MANUFACTURING AND QUALITY ISSUES

2017 - STARTING ASSUMPTIONS

A database that only collect medicines' shortages is not a proactive system! Is a surveillance system. It is simply a way to share/collect information but not a solution. A different approach in different countries also do not allow a real and effective sharing of information (Figure 4).

Collection of information of shortages are in any case an interesting starting point (data analysis):

- Active Ingredient.
- Brand Name.
- Dosage form and Strenght.
- Therapeutic Category.
- Identification number.
- Suppliers and Manufacturers.

Key words:
- Reason of shortage.
- Estimate duration.
- Availability of alternative Medicines/Therapies.
- Reoccurencies and related shortages (Figures 5, 6).

FROM DATA ANALYSIS TO MITIGATION STRATEGIES

Mitigation activities are directed at

preventing supply disruptions from turning into actual shortages. Long-term Prevention strategies are intended to address the underlying causes of shortages to prevent supply disruptions from occurring in the first place (Figures 7, 8).

BUT IN PARTICULAR … SOME DETAILS

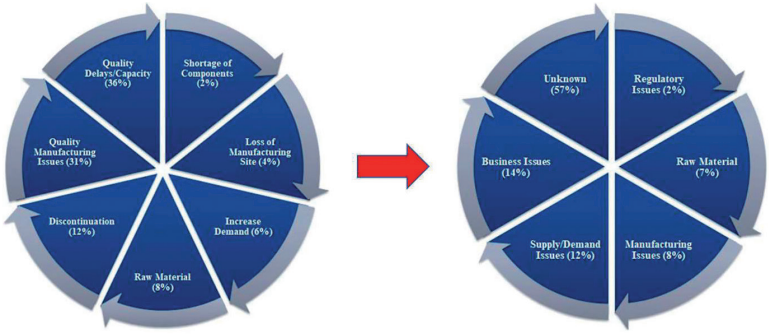
- Shortages of API.
- Noncompliance with GMP (i.e. deviations, investigations, …..)
- Equipments and related manufacturing issues
- Shipment delay
- Regulatory issue (i.e complaints)
- Discontinuation
- Increasing demand of the market

Many of them are Unexpected. Medicines'shortages risk reduction start from the analysis of the main manufacturing reasons.

A deep analysis of the entire manufacturing and control flow is requested to identify the critical steps in the production process that could lead to a shortage or disruption:

- Unexpected shortages of Starting Materials, Intermediates, Auxiliary Materials (including laboratories supply and spare parts)
- Starting materials (API, Excipients, Primary and Secondary Packaging Materials, Printed Packaging Materials) affected by unexpected defects of noncompliance.
- Intermediates produced far away from final product assembling.
- Contaminations and impurities happen, due to significant quality assurance issues during manufacturing steps.
- Occurrence of a quality defect despite all measures being taken according to quality standards.
- Unforeseen results of environmental monitoring in routine manufacturing (especially in the aseptic process manufacturing) but also in the periodic process simulation trials (media fill performed in the shutdown period).

FIGURE 6. Drugs Shortages main reasons - comparison between different causes in 2012 and 2020. Source: Source: Different sources combined by the author – mainly from Front. Pharmacol., 09 July 2021 - Sec. Drugs Outcomes Research and Policies - Volume 12 – 2021; Drug Shortage: Causes, Impact, and Mitigation Strategies



Reasons of drugs in shortages in **2012** reported by University of Utah Drug Information Services (UUDIS) (Dill and Ahn, 2014)

Reasons of drugs in shortages in **2020** reported by University of Utah Drug Information Services (UUDIS) (Pharmacists, 2020)

FIGURE 7. Two different approach in managing medicines supply discontinuity. Source: Training School on "Pharmaceutical Supply Chains II" Portalegre - July 3, 2017 – Speach of Maurizio Battistini - Shortages of Medicines

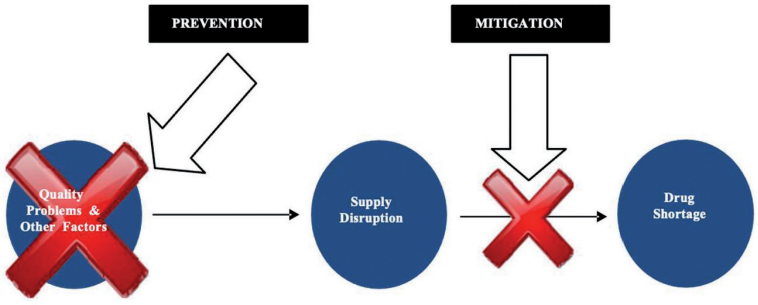
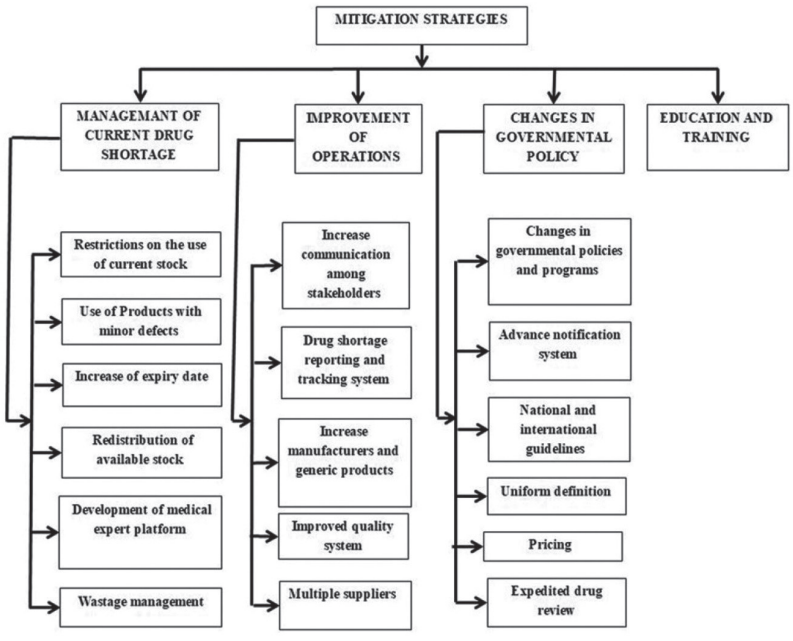


FIGURE 8. Medicines' Shortages – Mitigation Strategies. Source: Different sources combined by the author – mainly from Front. Pharmacol., 09 July 2021 - Sec. Drugs Outcomes Research and Policies - Volume 12 – 2021; Drug Shortage: Causes, Impact, and Mitigation Strategies



- Manufacturing capacity overload.
- Unexpected lack of staff.
- Sudden or unexpected failure of instruments or systems (time of reaction frequently linked with maintenance and repair interventions involving external supplier and spare parts procurement) .
- Delay in the time of release.
- Failure of control in process or cleaning checks.
- Delay of quality Procedures/Processes having an impact on the time of the release (Deviation management - root cause investigation and finding, CAPA/RAC implementation, risk assessment development, extraordinary analysis,... Change Control management; Complaints management; ...).
- Carriers delay affecting the shipment of the goods.
- Delays occurred in developing and transferring the analytical methods needed to support the transfer of a legacy product (a drug typically developed 10 to 20 years ago) to a new manufacturing site.
- Violations as a result of the company's final product contract manufacturing site did not follow certain cGMP regulations.

MEDICINES' SHORTAGES. A BRIEF FOCUS ON SUPPLY CHAIN RISK FACTOR EVALUATION

- There is only one single manufacturer of the API registered
- There is only one single manufacturer of Finished Product registered
- Location of the Manufacturing Site(s) cause any concern? This may be based on a general concern that there is a potential for future disruption in the supply due to the geographical location of the manufacturing facility, or source of plant or animal materials.
- One or more manufacturing sites have a marginal level of GMP compliance or are subject to increased inspection surveillance. (link to EudraGMDP and potentially risk-based classification).
- There is a high product concentration at the finished product manufacturing site.
- End to End Manufacturing process has long lead/holding times and/or extended supply chain.
- Manufacturing methods are complex, with capacity bottle necks in production.
- The manufacturer has had previous problems with quality defects and/or recalls.
- The manufacturer has had previous problems with supply.
- The medicinal product would meet the criteria of critical.

BUILDING REDUNDANCY, HOLDING SPARE CAPACITY, AND INCREASING INVENTORY LEVELS COULD LOWER THE RISKS OF SHORTAGES

- Supply Chain Management
- Safety stock of raw materials
- Business continuity planning
- Safety stock of intermediates and finished products
- Backup internal and external manufacturing facilities
- Dual-source suppliers
- Ability to add a shift to an existing manufacturing line
- Warm starts

Reviewed gaps across the supply chain management processes allow to identify areas for prevention of future shortages. There are some business continuity elements involved in protecting against a sudden and unexpected demand for a product (Figure 9).

FIGURE 9. Business continuity main strategies. Source: Business Continuity Elements identified by Companies for protecting against Shortages (Drugs Shortages - Report from the Pew Charitable Trust and the International Society for Pharmaceutical Engineering – January 2017)

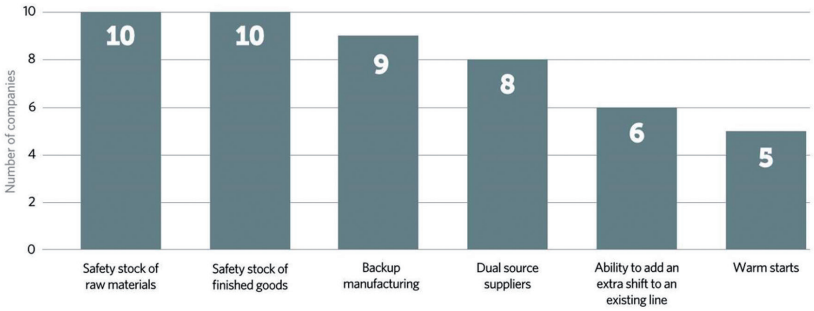


TABLE 2.

Drug	Primary Use	Average Shortage Duration
Amoxicillin	Antibiotic	6 months
Paracetamol	Pain relief	4 months
Insulin	Diabetes treatment	8 months
Oncology drugs	Cancer treatment	12 months

(Source: EMA Reports 2023)

CRITICAL SHORTAGES: THE MOST AFFECTED DRUGS

The Table 2 lists some of the most critical drugs affected by shortages in recent years.

STRATEGIES TO MITIGATE MEDICINES' SHORTAGES (FIGURE 10)

CRITICAL MEDICINES

Critical medicines are medicines for which no appropriate alternative is available and for which insufficient supply would result in serious harm or risk of harm to patients. These medicines are considered to be essen-

tial to ensure the continuity of care, the provision of quality healthcare and guarantee a high level of public health protection in Europe.

CRITICAL SHORTAGES

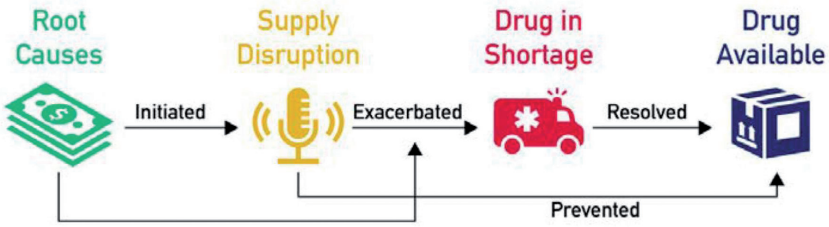
A shortage occurs when the supply of a medicine does not meet the demand for that medicine. Many shortages are managed and resolved at national level. However certain shortages require coordinated action at the European level, with close involvement of the European Medicines Agency (EMA) and Member States, to resolve the situation. These are called critical shortages.

Depending on national rules, the most common solutions offered by community pharmacists are the following:

- Sourcing the same medicine from alternative sources (e.g. other pharmacies where legally allowed or directly from manufacturers in case of contingency plans).
- Changing to the same medicine with a different strength when still available and adjusting therapy posology accordingly.
- Generic substitution.
- Therapeutic substitution.
- Preparing a compounded formulation.
- Importing medicine from a country where it is available.

The scope of pharmacy practice should be extended when medicines are in short supply, so pharmacists can use their skills and knowledge to better manage patient care and ensure continuity of treatment. When medicine is not available, pharmacists should be allowed to substitute with the most appropriate alternative as part of a shared decision-making process with prescribers and patients or in accordance with national protocols where appropriate. Shared electronic communication tools between pharmacists and prescribers (e.g., shared electronic health records) can enable this process effectively and safely.

FIGURE 10. Connection within Root Causes, Supply Disruption and Shortages



EUROPEAN INITIATIVES TO ADDRESS THE CRISIS

EUROPEAN SHORTAGES MONITORING PLATFORM (ESMP)

The EMA has launched the European Shortages Monitoring Platform (ESMP) to centralize real-time data on medicine supply and demand. This initiative aims to:

- Detect potential shortages early.
- Improve coordination between manufacturers, regulators, and healthcare providers.
- Reduce the time needed to react to critical shortages. (EMA - ESMP).

THE NEED FOR RESHORING: A STRATEGIC MOVE FOR EUROPE

A key aspect of solving medicine shortages is reshoring pharmaceutical production within Europe. To achieve this, the following measures are recommended:

- Financial Incentives: Provide subsidies and tax breaks for companies that manufacture essential drugs within the EU.
- Legislative Reforms: Enforce laws that prioritize European-made pharmaceuticals in hospitals and pharmacy procurement.
- Investment in Infrastructure: Encourage the creation of new production plants for APIs and finished drugs in strategic European locations.
- Public-Private Partnerships: Foster collaborations between governments, research institutions, and pharmaceutical companies to boost production capabilities.
- Stockpiling Mandates: Introduce legal requirements for minimum reserves of critical drugs within the EU.

THE EU MEDICINES ALLIANCE

The European Commission has initiated the Medicines Alliance, a collaborative effort among EU countries, regulators, and industry stakeholders to:

- Strengthen the production of essential medicines within the EU (reshoring).
- Foster innovation in pharmaceutical manufacturing.
- Reduce dependency on non-EU suppliers. (EC - Medicines Alliance)

STRENGTHENING EU COORDINATION

To ensure a sustainable pharmaceutical supply, Europe must:

- Establish a unified European response to shortages, avoiding country-specific measures that create market imbalances.
- Implement joint procurement policies for critical drugs.
- Set up emergency task forces to address supply chain disruptions in real-time.
- Promote green and sustainable pharmaceutical production to secure local supply chains.

EU'S PHARMACEUTICAL REFORM

Addressing Shortages of Medicines and ensuring Security of Supply (Figure 11).

The EU's pharmaceutical reform aims to mitigate and address shortages of medicines and enhance security of supply so that medicines are

FIGURE 11. Reform of the EU pharmaceutical legislation - Affordable, accessible, and innovative medicines. Source: European Union website

available for citizens across the EU at all times.

There is a clear need for greater EU-wide coordination, increased legal empowerment of authorities and appropriate measures to safeguard the supply and availability of medicines for EU citizens, not only during public crises but at all times. Continued coordinated action is also needed to address potential challenges in the supply of critical medicines and to make medicines supply chains in Europe more resilient in the long run.

THE PROPOSED MEASURES ARE FOCUSED ON TWO MAIN AREAS OF ACTION

- Monitoring and management of shortages and critical shortages (Shortage monitoring).

- Enhancing the security of supply of critical medicines (Security of supply).

MEDICINES' SHORTAGES MONITORING

Background

• Member States manage most shortages at the national level, but for critical shortages that cannot be resolved at national level, they work, through their Head of Agency (HMA), with the European Medicines Agency (EMA) and the Commission.

• The HMA-EMA Task Force was established in 2016 to develop joint policies and guidance for shortage management. In 2019, the Medicine Shortages Single Point of Contact Network (SPOC Network) was mandated and later formalised with the extension of the EMA's mandate in 2022, as the SPOC Working Party (SPOC WP).

• Today, the system consists of the SPOC WP and a high-level steering group called the Executive Steering Group on Shortages and Safety of Medicinal Products (MSSG). The SPOC WP is responsible for monitoring and reporting on critical shortages while the MSSG coordinates urgent actions within the EU.

Prevention

• Shortage prevention plans for all medicines. All companies will be obliged to establish a shortage prevention plan, to anticipate any potential future shortages. Shortage prevention plans provide essential information to quickly resolve notified medicine shortages. They also include key information to identify supply chain challenges of critical medicines. Harmonisation of definitions and the required data submissions for companies to notify shortages and withdrawals of medicines.

• Earlier notifications to allow Member States and the EMA to identify preventitive and mitigation measures

• Wholesale distributors and other entities (e.g. pharmacists) are not obliged, but may report a shortage to the relevant Member State's authority to avoid overburdening shortage monitoring systems.

Mitigation

• Reinforced coordination at EU level: Extending the scope of existing coordination mechanisms such as SPOC Working Party and MSSG outside crisis times, to offer prevention and mitigation measures, on-going monitoring and a set of recommendations on measures to resolve or to mitigate critical shortages.

• Companies are obliged to draw up a Shortage Mitigation Plan that identifies actions to mitigate a given shortage.

• Clarification of roles and stronger obligations on companies and different actors, e.g. wholesale distributors and other entities must submit any information requested by the relevant authority.

Obligation

Companies will have to notify relevant authorities 12 months in advance if they plan to permanently withdraw a product from the market or permanently withdraw the marketing authorisation. For a temporary market suspension or a temporary supply disruption lasting more than 2 weeks, companies will have to notify relevant authorities 6 months in advance or, if justified (because the information

was not available previously), as soon as they become aware of the temporary supply disruption.

MEDICINES' SHORTAGES SECURITY OF SUPPLY

Background

The COVID-19 pandemic and the recent flu seasons have further highlighted the importance of ensuring the continued supply of medicines. This is especially true for the most critical medicines which are essential to ensure the continuity of care, the provision of quality healthcare and guarantee a high level of public health protection in Europe

Changes

Reform will establish a legal framework to address issues of security of supply for critical medicines. This includes a legal basis for the list of critical medicines, identifying supply chain vulnerabilities and measures to improve security of supply:

- Identifying Critical Medicines for EU health systems – Medicines that are considered most critical for EU health systems are identified in an EU list, to be adopted by the Commission. The first version of such list was adopted in December 2023.

1. Analyzing supply chain vulnerabilities – The supply chain of those critical medicines is analyzed to identify vulnerabilities.
2. Taking appropriate measures to ensure supply – MSSG provides recommendations to strengthen the security of supply of critical medicines with vulnerabilities in their supply chain. The Commission may adopt an implementing act imposing appropriate measures, including contingency stock requirements of active pharmaceutical ingredients or finished dosage forms on marketing authorization holders or other relevant entities.

While the extension of the mandate of the EMA's in 2022 focused on crisis preparedness and response, this Commission's proposals aim at extending this system to all times

THE EU INITIATIVES TO REDUCE MEDICINE SHORTAGES

Represents the estimated impact of various European strategies on mitigating drug shortages.

KEY INSIGHTS:

1. Reshoring Incentives (30 %)

- This initiative is projected to have the highest impact, significantly reducing shortages by promoting domestic production of medicines and active pharmaceutical ingredients (APIs).
- It reflects efforts to reduce dependence on non-EU suppliers (mainly from China and India).

2. Medicines Alliance (25 %)

- A collaborative effort among EU nations, regulators, and industries to boost local production and enhance supply chain resilience.
- Its effectiveness stems from improved coordination and strategic partnerships.

3. Joint Procurement (20 %)

- Centralized purchasing of critical medicines across EU countries helps prevent bidding wars and ensures equitable distribution.
- It mitigates local shortages by discouraging parallel trade and hoarding.

4. European Shortages Monitoring Platform (ESMP) (15 %)

- A real-time data tracking system designed to identify early warning signs of shortages.
- While crucial for transparency, its effectiveness depends on how quickly regulators and manufacturers act on the information.

5. Stockpiling Mandates (10 %)

- Requires minimum reserves of essential medicines to cushion supply disruptions.
- Less effective for long-term shortages but crucial for emergency preparedness.

No single solution is enough, a combination of reshoring, strategic coordination, and proactive monitoring is essential to tackling the crisis effectively.

THE DRUG SHORTAGE SITUATION. EUROPEAN INDUSTRIAL PHARMACISTS GROUP (EIPG) POINT OF VIEW

The shortage of medicines has been a major concern in the countries of the European Union, and elsewhere, for more than 10 years, so much so that the Economic Community has devoted a great deal of effort and increasing attention to this problem in an attempt to mitigate its impact on patient health.

Several factors can be identified as being at the root of the shortage of medicines, some of which intersect with each other, mainly concerning aspects with technical- qualitative, regulatory, forecasting, supply, speculative and economic implications.

EIPG has made its contribution to the various attempts to contain the phenomenon by participating in task forces, round tables and convenings dedicated to identifying the root causes of the issue and, through gap analysis, the consequent mitigation measures. Overall, strengthening the risk-assessment approach to assess and define the risk level of individual deficiencies or the causes to which they pertain in order to rationalize and focus mitigation interventions and identify their level of acceptance with a proactive approach.

Before defining the particularly deserving aspects to be emphasized and consequently acted upon, it is important to mention those that represent, in the opinion of EIPG, but not limited to, the elements on which priority action should be taken. In analyzing the problem, one cannot in fact fail to take proper account of the fact

that medicines are not such without their active ingredients and that, for diseases with the widest spread, there are equivalent medicines and alternative therapies. On the basis of the latter assumption, it is understandable that the definition of a shortage of medicines should be restricted to cases where no equivalent medicines or alternative therapies with different medicines are available, so as to concentrate efforts to solve the problem only on those conditions that are worthy of attention because they are not limited to the unavailability of a specific product or to situations for which it is possible to identify an alternative treatment (defining a list of critical medicines and defining risk assessment criteria for assessing whether a product should be on the list or not). The operation required to bring the production of active ingredients back to Europe, recognizing their strategic and central role in the composition of medicines for the entire community and patients, takes longer. The relocation of the manufacturing of active ingredients to third countries, which has been taking place for several years now for mainly economic reasons, has led to the dependence of many other countries, including mainly those of the Union, on supplies that today has the occasional impact that we know of but which could become much more serious if not systemic. We have been hearing about reshoring the production of active pharmaceutical ingredients for some time now, but so far there do not seem to be any concrete initiatives for its implementation.

As mentioned above, it is clear that EIPG identified the revision of the definition of drug shortages and the reallocation of strategic production of active pharmaceutical ingredients in Europe as a main key action to mitigate the impact of drug shortages.

As far as the technical quality aspects are concerned, given the vastness of such occasional events in the production cycle of a medicine, a separate, dedicated discussion should be devoted to them. In addition to a few examples, please refer to the chapter 'Shortages Originating from Manufacturing' in the text 'Pharmaceutical Supply Chains - Medicines Shortages' published by Springer and written by the same author as this article. The book, authored by experts in the field, provides an insight of relevant case studies and updated practices in Pharmaceutical Supply Chains (PharmSC) while addressing the most relevant topics within the COST Action Medicines Shortages (CA15105) and it covers uncertainty and risk aspects of supply chain management, carefully combining the scientific level with a pedagogical approach. In industry, proactive strategies such as the adoption of reserve stocks or back-up establishments can be adopted to make up for medicine shortages on an emergency basis, although the expense of sustaining these prudential approaches remains the main problem.

In a number of situations, shortages can occur due to underestimated sales forecasts or problems with the supply of raw materials, and in particular APIs.

A particular case in point is parallel trade, which by its very nature can have such contrasting effects that it has been dubbed 'The double face of the parallel trade'. While on the one hand, this method is useful in dealing with shortages in a relatively short time (import in the country where the shortage needs to be filled and export from the country where the availability exists), on the other hand, it has often encouraged the migration of products from countries where they are cheap to others where they guarantee a higher margin, in which case it could be the source of the problem and not its solution.

Last but not least, it should be pointed out that the phenomenon of shortages has an economic implication, as it is more likely to affect drugs with low profitability or movements of drugs from countries with low margins or sales volumes to those with high margins or higher market shares.

Shown below is the action plan that EIPG submitted to the group at the meeting; an action plan that largely reflects what is the topic of this article.

1. Establish pro-active risk management plan.
2. Prepare list of medicinal products of clinical importance that lack therapeutic alternatives.
3. Criticality in the procurement of all starting materials with particular attention to APIs. How to mitigate?
4. Quality and manufacturing aspects that could have an impact on medicines' shortages How to manage them preventively?
5. Appropriate agreements on quality and capacity of CMOs.
6. Need to review quality management systems throughout life cycle (including those for older products).
7. Consideration of batch release and transportation impact on the time to deliver products to the market
8. Review impact on production planning of potential weaknesses in sales forecasting.

Although it is not an aspect of primary interest to the European in-

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dustrial pharmacist community, EIPG recognizes the economic aspects as playing an important role in the origin of shortages, particularly with regard to the low price paid for certain categories of medicines, which induces manufacturers to abandon the manufacture of low-profit products, and the discrepancies in the price of medicines that exist in the different countries of the Union, discrepancies that, coincidentally, "predominantly" make weak the countries where prices are the lowest or even where volumes are not so attractive as to devote production.

Having made this necessary digression on the aspects requiring corrective action at source, there are, however, other causes, mostly 'occasional', on which to intervene, where possible, proactively or with reaction instruments capable of reducing the impact of medicines' shortages (technical-qualitative, regulatory, predictive and speculative).

A PATIENT CENTRIC APPROACH IS STRONGLY REQUESTED

From this point of view the voice of health practitioners is essential being them the front off line of the entire supply chain

Regarding the technical aspects of quality, which are occasional events in the production cycle of a medicine, for details please refer to the chapter 'Shortages Originating from Manufacturing' in the text 'Pharmaceutical Supply Chains - Medicines Shortages' published by Springer. In the industry, proactive strategies such as the adoption of reserve stocks or back-up plants can be adopted to make up for drug shortages in the event of an emergency, although the main problem remains the cost to sustain these prudential approaches.

A particular case in point is parallel trade, which by its very nature can have such contrasting effects that it has been dubbed 'The double face of the parallel trade'. While on the one hand, this approach is useful in dealing with shortages in a relatively short time (import in the country where the shortage needs to be filled and export from the country where the availability exists), on the other hand, it has often encouraged the migration of products from countries where they are cheap to others where they guarantee a higher margin, in which case it could be the source of the problem and not its solution.

Until 2022 in the opinion of EIPG, but not limited to, the elements on which priority action should be taken to mitigate the shortage impact were based on the following two main assumptions:

1. Take proper account of the fact that medicines are not such without their active ingredients.
2. For diseases with the widest spread, there are equivalent medicines and alternative therapies.

Consequently

1. Bring the manufacturing of active ingredients back to Europe, recognising their strategic and central role in the composition of medicines for the entire community and patients. The relocation of the manufacturing of active ingredients to third countries, which has been taking place for several years now for mainly economic reasons, has led to the dependence of many other countries, including mainly those of the Union, on supplies that today has the occasional impact that we know of but which could become much more serious if not systemic. We have been hearing about reshoring the production of active pharmaceutical ingredients for some time now, but so far there do not seem to be any concrete initiatives for its implementation.
2. The definition of a shortage of medicines should be restricted to cases where no equivalent medicines or alternative therapies with different medicines are available, so as to concentrate efforts to solve the problem only on those conditions that are worthy of attention because they are not limited to the unavailability of a specific product or to situations for which it is possible to identify an alternative treatment (defining a list of critical medicines and related risk assessment criteria for assessing whether a product should be on the list or not).

Everyone in industry agrees that problems of shortages are complex with no quick solutions, and it was interesting to hear staff from Agencies agree that one of the main problems of shortages for older products is the impact of low pricing of products by national healthcare systems. Also, product dumping of medicines at an extremely low price was mentioned as occurring in some countries and everyone present agreed this must not be tolerated.

The work done by the European community is aimed at addressing the shortages of the most critical medicines by emphasizing the role of logistical aspects but overlooking certain critical elements that go beyond supply chain management and concern the upstream management of the concrete problems for which medicine shortages continue to occur (root causes). For the time being, the Commission seems to be oriented towards a predominantly top-down approach, even if there are spaces where opportunities for a multidisciplinary discussion involving all stakeholders in the supply chain are offered. However, it remains important to note that the Community is taking an active interest in the problem albeit adopting measures aimed at containing the problem rather than solving it at its root.

A MOST RECENT INITIATIVES TO ADRESS MEDICINES'SHORTAGES. PROPOSAL FOR A CRITICAL MEDICINES ACT

Even with the awareness that the underlying causes of shortages are multifactorial, there is a growing perception that supply chain vulnerability may be

In 2023, the European Commission, the EMA and the heads of the medicines agencies of the Member States published an initial Union List of Critical Medicinal Products

one of the riskiest elements, especially when related to dependence on a single supplier, especially of active ingredients (APIs) at a global level; the same is true if there is dependence on a number of suppliers concentrated in one geographical location.

In 2023, the European Commission, the EMA and the heads of the medicines agencies of the Member States published an initial Union List of Critical Medicinal Products; a list that was then updated at the end of 2024 covering more than 270 APIs. Most of the medicines from the critical list APIs are out of patent and often characterized by very low selling prices. But even for patent-protected drugs, the environment is becoming increasingly highly competitive, resulting in a focus on the lowest price as the main criterion for selecting suppliers. In this context, many companies have shifted production or outsourced the supply of key ingredients outside the EU, resulting in the EU becoming increasingly dependent on a limited number of suppliers or manufacturers for many essential medicines, many of which are located outside the EU, mainly in Asia. This heavy dependence has made the supply chains of several essential medicines particularly vulnerable to boundary conditions, such as:

- Increased demand.
- Supplier recalls.
- Production and quality issues.
- Supply disruptions.

This last factor, in addition to being a critical issue, can become even more risky if we imagine it can create supply dependency on others, which in today's geopolitical framework can be a serious threat.

This factor is compounded by the fact that for some critical medicines and other medicines of common interest, access may vary considerably from one Member State to another. Due to various factors, including the size of the markets but also different selling prices, companies market medicines where economic interest may sometimes prevail with the consequent consequences on accessibility in the different Union Member States.

In this context, in the content of the full text, to which the extract from the EU document that opens this article refers, under the heading Basis for EU action (legal basis and subsidiarity check) it is stated that *"The proposal is expected to be based on Articles 114(1) and 168(4), point (c), of the Treaty on the Functioning of the European Union (TFEU). This ensures a comprehensive approach that addresses both the internal market and public health aspects of the initiative. Article 114(1) TFEU serves as the legal basis for measures aiming to ensure the establishment and functioning of the internal market. Article 168(4), point (c) TFEU enables the EU to adopt measures to ensure high standards of quality and safety for medicinal products. Finally, the expected choice of the legal basis is consistent with the legal basis of existing EU pharmaceutical legislation"*.

The same document also expresses the recognition that *"Medicine shortages have hit every Member State in the EU over the last decade. While an individual Member State can act to improve its supply of certain medicines, these efforts are fragmented and insufficient to address the broader, cross-border supply chain problems, including dependency on certain non-EU countries. To address these challenges and to achieve a secure and reliable supply of critical medicines, a common effort at EU level is needed through this new initiative, i.e. the proposed act"*.

The author of this article can boast of having anticipated several of the problems outlined here several years ago, highlighting the criticality and consequent fragility of various aspects and identifying and proposing a number of solutions that gradually seem to have opened a breach in the actions of those with the power to intervene; awareness must, however, necessarily be followed by action.

WHAT ARE THE OBJECTIVES AND HOW TO DO IT

It is stated in the above-mentioned document that *'the initiative will cover critical medicines' a step that is certainly important to start with but probably not sufficient even if it is a priority. It is however explicit in the document that "In addition, certain measures will also apply to other medicinal products of common interest, where the functioning of the market does not sufficiently ensure that these products are available and accessible to patients in the different Member States"*.

To this end, it should be remembered that critical medicines are identified as those whose insufficient supply leads to serious harm or risk of serious harm to patients. The main objective of the act will be to support the security of supply and availability of essential medicines, as well as the availability and accessibility of other medicines of common interest.

It is also made explicit in the document that, to achieve this objective, the act will propose a series of interventions whose aim is:

1) Facilitate investments to diversify production capacities for critical medicines, particularly investments that address supply chain vulnerability.

2) Reduce the risk of supply disrup-

tions by incentivizing and rewarding supply chain resilience in the procurement of critical medicines.

3) Harnessing the aggregate demand of interested Member States through collaborative procurement of essential medicines and certain other medicines of common interest.

It is clear that the proposed act aims to create a more favorable situation for the creation or expansion of production facilities for essential medicines in the EU, but above all the return to Europe of the production of APIs, which are the essential component to which the medicine owes its activity. However, with what measures and facilities this can be achieved it is, at least for now, unknown, as the same document speaks generically of strategic projects that will benefit from faster administrative procedures, rather than regulatory and scientific support and access to financial support to improve the resilience of the supply of essential medicines.

The proposed act would also introduce measures that incentivize the use of criteria other than the lowest price in the purchase of essential medicines; criteria related to safety and diversity of supply.

POSSIBLE IMPACTS

The proposed act should strengthen the resilience of the EU's medicines supply chains, helping to improve security of supply and help reduce shortages of essential medicines.

As a result, it is expected that:

- At the economic level, the proposal would strengthen the production base of essential medicines and make the pharmaceutical sector more competitive, including through diversification.
- On a social level, it should improve access to essential medicines and certain other medicines for EU patients.

In spite of the public health benefits, the proposal is expected to have an impact on the pharmaceutical industry, particularly those involved in the supply of essential medicines and related APIs, as the industry will be able to benefit from administrative and regulatory support and access to funding for certain strategic projects with inevitable repercussions for national administrative authorities and purchasers active in the public procurement of essential medicines.

FUTURE MONITORING

The implementation of the proposed act will be monitored using key indicators (KPIs) that relate to vulnerabilities in the supply chain of critical medicines; these include:

- The frequency and duration of shortages of critical medicines.
- Changes in public procurement practices for medicines.
- The increase in the production of critical medicines and their components in the EU.

The aforementioned of course includes data collection and analysis to monitor the availability and analyze the vulnerability of medicines on the Union's list of critical medicines.

Critical in this regard will be the way in which the results achieved (effectiveness of the measures) will be evaluated and the consequent corrective measures necessary to achieve the objectives within the set timeframe will be defined.

CONSULTATION STRATEGY

In the act, a heterogeneous group of stakeholders are invited to submit ideas and contributions in order to support the development of the draft law with the aim of integrating proposals from a wide range of perspectives and expertise. The main aim is to properly prepare and subsequently negotiate the contents of the bill together with the results of previous consultations.

The proposed approach is certainly correct and appropriate; however, it may be hindered by the difficulty of matching conflicting expressions of spokespersons with significant differences in views if not instead united by a patient-centric attitude.

CONCLUSION: A CALL TO ACTION

The medicine shortage crisis represents a critical threat to public health and European sovereignty. We urge EU policymakers, regulatory authorities, and industry leaders to take decisive action to reshore pharmaceutical production and reduce dependence on third countries. The European Union has taken some steps, such as the creation of the European Shortages Monitoring Platform (ESMP) and the Medicines Alliance, but these efforts need to be complemented by stronger regulatory and financial incentives.

ONGOING AND UPCOMING EU INITIATIVES

- Shortages of MEDICINES: HERA Critical Medicines Alliance - Consultation on the Strategic Report: The EU is evaluating strategies to secure pharmaceutical supply chains, focusing on critical medicines. This initiative will play a key role in ensuring long-term availability and reducing supply chain risks.
- Critical Medicines Act: A new legislative framework under discussion, aiming to strengthen the EU's manufacturing capacity and develop resilient procurement strategies. (EC - Critical Medicines Act).
- Second Forum of the Critical Medicines Alliance (CMA): This forum presented recommendations from two key working groups:

1. Strengthening Manufacturing Capacity in the EU: Encouraging investment in European pharmaceutical production.
2. International Partnership and Solidarity: Enhancing procurement strategies and global collaboration to secure medicine supplies.

While progress is being made, challenges remain. Some discussions at

the CMA Forum revealed concerns about clarity and the feasibility of short-term goals, but the overall strategic direction aligns with ensuring a secure and resilient pharmaceutical supply chain in Europe.

WHAT THE EU MUST DO NEXT

- Expand Reshoring Incentives: Introduce tax benefits and grants for pharmaceutical companies that establish production within Europe.
- Implement Joint Procurement Policies: Strengthen centralized purchasing mechanisms to ensure equitable distribution across member states.
- Enhance Stockpiling Regulations: Establish legally mandated reserves of critical medicines to avoid crisis scenarios.
- Fast-Track Regulatory Approvals: Streamline approval processes for alternative manufacturing sites and suppliers.
- Develop EU-Based API Production: Invest in infrastructure for the local manufacturing of active pharmaceutical ingredients (APIs).

THE COST OF INACTION

Without urgent legal and economic intervention, Europe risks continued supply chain vulnerabilities, patient safety concerns, and economic repercussions. The time to act is now: only through proactive and united European policy changes can we ensure a secure, resilient, and independent pharmaceutical supply for the future. We urge EU policymakers, regulatory authorities, and industry leaders to take decisive action to reshore pharmaceutical production and reduce dependence on third countries. The European Union has taken some steps, such as the creation of the European Shortages Monitoring Platform (ESMP) and the Medicines Alliance, but these efforts need to be complemented by stronger regulatory and financial incentives.

The above position is confirmed by the recent news about the recommendations from the Critical Medicines Alliance to the European Commission on the European Union's need for less dependency on foreign countries and more EU-made investment. At the end of a year of work and consultation, the Critical Medicines Alliance has published its full report with clear recommendations on what the EU strategy should contain to address shortages of strategic medicines and strengthen the European pharmaceutical supply chain. That is, essentially, measures to reduce foreign dependence and funds and investments to strengthen the value chain located in the Union, in line with the imperative to support the competitiveness of European companies at the heart of Mario Draghi's report.

> The proposed act would also introduce measures that incentivize the use of criteria other than the lowest price in the purchase of essential medicines

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