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**COMMISSION STAFF WORKING DOCUMENT**

**Vulnerabilities of the global supply chains of medicines - Structured Dialogue on the security of medicines supply**

## INTRODUCTION

**The availability of medicines has been a longstanding concern in the EU.**<sup>1</sup> Throughout the last decade, the issue of medicines shortages has become systemic.<sup>2</sup> Shortages of medicines affect treatment regimens. They may also affect the health of EU citizens and, ultimately, the resilience of health systems in Member States.

The root causes of shortages are multifactorial with challenges identified along the entire pharmaceutical<sup>3</sup> value chain, from quality and manufacturing problems to industry's competitiveness.<sup>4</sup> In particular, shortages of medicines can result from supply chain disruptions and vulnerabilities affecting the supply of key ingredients and components.

The COVID-19 pandemic has further highlighted the importance of ensuring continued supply of medicines, which is often taken for granted across Europe. 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.

The COVID-19 pandemic, Russia's unprovoked and unjustified military aggression against Ukraine and the current consequential energy crisis have also brought to the fore questions regarding the impact of the EU's dependency on third countries for medicines, raw materials and ingredients used in pharmaceutical manufacturing. These developments have brought additional pressures which could result in further vulnerabilities in pharmaceutical supply chains.

**The European Council highlighted the need to reinforce the security and continuity of supply of medicines and to address the causes of systemic shortages** and disruptions to supply chains, also beyond the specific crisis context. It invited the Commission and Member States to collaborate on "*timely solutions, in particular regarding [...] critical medicines*".<sup>5</sup> **The European Parliament** considered it is "*imperative to prevent medicine shortages and to mitigate their effects should they occur*".<sup>6</sup>

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<sup>1</sup> See, for instance, European Parliament, Committee on the Environment, Public Health and Food Safety, Report of 22 July 2020, *Shortage of medicines – how to address an emerging problem*, 2020/2071(INI).

<sup>2</sup> To respond to related shortage concerns, the Heads of Medicines Agencies ('HMA') and the European Medicines Agency ('EMA') created in 2016 a joint Task Force on Availability of Authorised Medicines for Human and Veterinary Use; this Task Force works on developing and coordinating actions that are necessary to facilitate a better prevention, identification, management and communication of shortages to ultimately ensure continuity of supply of authorised medicines.

<sup>3</sup> "Pharmaceutical", "medicine" and "medicinal product" are used interchangeably.

<sup>4</sup> See the Study commissioned by the European Commission on medicine shortages: final report (2021) accessible at: <https://op.europa.eu/en/publication-detail/-/publication/1f8185d5-5325-11ec-91ac-01aa75ed71a1/language-en/format-PDF/source-245338952>

<sup>5</sup> Council Conclusions on Access to medicines and medical devices for a Stronger and Resilient EU (2021/C 269 I/02), recital 5.

<sup>6</sup> European Parliament Resolution of 17 September 2020 on the shortages of medicines – how to address emerging problem (2020/2071(INI)), recital G.

The security of supply was also identified as a central objective<sup>7</sup> of the **Pharmaceutical Strategy for Europe (“Pharmaceutical Strategy”)** of November 2020. The Commission announced several actions aimed at improving the availability of medicines, in particular the Pharmaceutical Strategy initiated the **Structured Dialogue on security of medicines supply**.<sup>8</sup>

This initiative is also closely related to the Commission’s **New Industrial Strategy for Europe<sup>9</sup> (‘Industrial Strategy’)**, as updated in 2021,<sup>10</sup> and its objective to ensure secured supply chains in strategic areas, including health. The European Council Conclusions<sup>11</sup> invited the Commission to “*identify strategic dependencies, particularly in the most sensitive industrial ecosystems such as for health, and to propose measures to reduce these dependencies, including by diversifying production and supply chains, ensuring strategic stockpiling, as well as fostering production and investment in Europe.*” The Structured Dialogue is also contributing to this purpose. In parallel to the Structured Dialogue, based on lessons learnt from the COVID-19 pandemic, the Commission created a new service, the Health Emergency Preparedness and Response Authority (HERA), with a mission to ensure availability of medical countermeasures i.e., including medicines, to prepare for and respond to health crises. Furthermore, the mandate of the European Medicines Agency (EMA) has been extended to cover monitoring and reporting of shortages of medicines during public health emergencies and major events.<sup>12</sup>

### **The Structured Dialogue mandate**

The mandate<sup>13</sup> given by the Pharmaceutical Strategy was to initiate a Structured Dialogue with the actors in the pharmaceuticals manufacturing value chain, public authorities, patient and health non-governmental organisations and the research community. It aimed to gain a better understanding of the functioning of global pharmaceutical supply chains through the input of stakeholders; to identify the causes and drivers of different potential vulnerabilities, including dependencies, threatening the supply of critical medicines, active pharmaceutical ingredients (APIs) and raw materials.

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<sup>7</sup> Communication of 25 November 2020 from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions, *Pharmaceutical Strategy for Europe*, COM(20)761 final.

<sup>8</sup> [https://ec.europa.eu/health/human-use/strategy/dialogue\\_medicines-supply\\_en](https://ec.europa.eu/health/human-use/strategy/dialogue_medicines-supply_en)

<sup>9</sup> Communication of 10 March 2020 from the Commission to the European Parliament, the European Council, the Council, the European Economic and Social Committee and the Committee of the Regions, *A New Industrial Strategy for Europe*, COM/2020/102 final.

<sup>10</sup> Communication of 5 May 2021 from the Commission to the European Parliament, the European Council, the Council, the European Economic and Social Committee and the Committee of the Regions, *Updating the 2020 New Industrial Strategy: Building a stronger Single Market for Europe’s recovery* COM(2021)350 final and Commission Staff working document of 5 May 2021, *Strategic dependencies and capacities*, SWD (2021)352 final.

<sup>11</sup> Council Conclusions of 2 October 2020 (EUCO 13/20), point 5, available at: <https://www.consilium.europa.eu/media/45910/021020-euco-final-conclusions.pdf>

<sup>12</sup> Regulation (EU) 2022/123 of the European Parliament and of the Council of 25 January 2022 on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices, OJ L 20, 31.1.2022, p. 1–37.

<sup>13</sup> [pharma-strategy\\_report\\_en\\_0.pdf \(europa.eu\)](#)

Further, the ambition is for the Structured Dialogue to put forward a set of possible measures to address the identified vulnerabilities and formulate policy options to be considered by the Commission and other authorities in the EU to ensure the security of supply and the availability of critical medicines, APIs and raw materials.

The Structured Dialogue operational work started with a scoping meeting in March 2021.

The participants (Annex I), including a wide range of actors in the pharmaceutical manufacturing value chain, healthcare professionals, patients' representatives, experts from Member State authorities and academia **worked in four distinct groups or workstreams and discussed topics relating to the functioning of global supply chains:**

- robust supply chains,
- critical medicines,
- vulnerabilities and dependencies, and
- innovation (including the green and digital transition of the pharmaceutical manufacturing value chain).

A high-level closing meeting was held in September 2021 to reflect on the information provided in the Structured Dialogue.

**The purpose of this Staff Working Document is:**

- **to present the main findings of the Structured Dialogue that should be considered in the analysis of supply security (Section I).**
- **to map areas of focus at EU level, including both new and ongoing actions, for consideration and to inform further actions** to improve the security of supply and the availability of critical medicines, APIs and raw materials **(Section II).**

## I. VULNERABILITIES OF PHARMACEUTICAL SUPPLY CHAINS: MAIN FINDINGS OF THE STRUCTURED DIALOGUE ON THE SECURITY OF MEDICINES SUPPLY

Participants defined supply chain vulnerability as the diminished capacity to anticipate, cope with, resist and recover from external shocks to the supply chain. All segments of the supply chain of pharmaceutical production (i.e. from starting and raw materials, intermediates and APIs to the finished medicinal product) were considered in the discussions.

A summary is presented of the information provided by the four workstreams, is provided below. This included reflections on:

- Increasing complexity and specialisation of pharmaceutical supply chains
- Challenges linked to the production process and technologies
- Dependencies, including lack of geographical diversification,
- Unlock the potential of data for better supply and demand predictability
- Perceived regulatory complexity

### 1. Increasing complexity and specialisation of pharmaceutical supply chains

The increasing complexity or globalisation of pharmaceutical supply chains, considering also the specialisation of manufacturing, can be a potential source of vulnerabilities.

The **increasing complexity of pharmaceutical supply chains**, according to participants, is on the one hand due to the complexity of new medicines, including for example their manufacturing and authorisation.

On the other hand, there is a **growing trend of specialisation**, reflected in increased outsourcing of manufacturing operations<sup>14</sup> and an increase in the numbers of suppliers across the entire supply chain. To produce a single medicine many components are needed along the supply chain, including raw chemical materials, intermediates and solvents or reagents necessary to manufacture APIs. Moreover, packaging materials, other consumables and equipment are required to deliver and administer the medicines. The production of each of these components may require sophisticated processes and special technical expertise, with a need for sufficient economies of scale.

Greater consolidation affects some raw materials, which in addition, are often primarily used in other industries in much bigger volumes. In situation of tensions, there is a possibility that supply to these other industries is prioritised over pharmaceutical supply.

Participants considered that **pharmaceutical supply chains are heterogeneous**. The participants pointed to the variability in criteria that needs to be considered to assess "robustness" and its enablers, considering different production steps (key registered starting materials and intermediates, upstream chemistry, excipients, APIs, medicines production) and different production segments (oral solids, sterile and complex drug delivery), recognising that these segments operate in very different settings or environments (single *versus* multisource; high *versus* low volume) and might require different solutions. For instance, supply chains for generic

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<sup>14</sup> European Pharmaceutical Review, 8 October 2018.

medicines are different from those of innovative medicines, and supply chains for sterile production are different from solid dosage form production or complex biologicals.<sup>15</sup>

Supply chains for innovative, biological medicines tend to be more integrated (in many instances the same company manufactures the API and finished dosage form), whereas chemical medicines will very often have supply chains involving several manufacturers. Certain production processes (e.g. sterile or biological processes) are more challenging and, therefore, have to comply with additional quality and regulatory requirements.

Differences in supply chains also create different challenges for security of supply. For instance, for innovative medicines that are produced in the very first scaled-up production facility (based on processes to be improved) or that rely on novel, highly sophisticated manufacturing processes (that cannot be easily duplicated), dual-sourcing<sup>16</sup> may not be possible, at least not initially. For niche medicines (namely orphan medicines), dual-sourcing may be particularly costly, considering the small scale of production. By contrast, for large volume generic medicines, dual-sourcing seems mostly possible, even though alternative suppliers may have disappeared for various economic reasons.

## 2. Challenges linked to the production process and technologies

Challenges linked to production processes or technologies, or consolidation can be a further source of potential vulnerabilities. In this respect, participants acknowledged that resilience of supply chains could be strengthened through an investment in certain production technologies in Europe, building on the existing manufacturing footprint of the sector. A study<sup>17</sup> referred to by the participants, indicated that there is no EU production capacity for 17% (93) of the APIs analysed in the study. That study also pointed out that European manufacturers focus on specific APIs (e.g. low production volumes, complex production processes), but technical know-how and capacities to increase European API production are still available. Participants highlighted some technologies, used upstream in the manufacturing chain of medicines, which may no longer be available in Europe.<sup>18</sup> Those reporting on vulnerabilities and dependencies provided examples of these, such as nitration, cyanation, fluorination or iodination, although this list of technologies was neither exhaustive, nor indicative of what is essential to strengthen supply chains. From an environmental perspective, contributors proposed that manufacturers should be encouraged to re-invent or adopt innovate alternatives to old API synthesis processes that were developed 20 to 30 years ago, which are highly polluting and energy intensive. Those vulnerabilities do not seem to affect the innovative medicines sector, or at least not to the same degree as the generic medicines sector.

In case of innovative medicines that require complex and novel manufacturing processes and, in principle, rely on single sourcing, it was reported to be **more difficult to make quick**

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<sup>15</sup> [https://ec.europa.eu/health/documents/eudralex/vol-4\\_en](https://ec.europa.eu/health/documents/eudralex/vol-4_en), Annex I and II.

<sup>16</sup> Dual sourcing is the supply chain management practice of using two suppliers for a given ingredient or component.

<sup>17</sup> *Where do our Active Pharmaceutical Ingredients come from? – A World Map of API Production (2020)*, Study by Progenerika, accessible at: <https://www.progenerika.de/studies/where-do-our-active-ingredients-come-from/?lang=en>.

<sup>18</sup> Compare [https://efcg.cefic.org/wp-content/uploads/2021/06/20201211\\_IQVIA-for-EFCG\\_Executive-summary.pdf](https://efcg.cefic.org/wp-content/uploads/2021/06/20201211_IQVIA-for-EFCG_Executive-summary.pdf), slide 30.

**manufacturing adjustments.** The participants pointed out that even when there are a number of alternative suppliers, an absence of sufficient EU manufacturing capacities and capabilities (e.g. lack of technologies or skills) may constitute in itself a vulnerability. It was also noted that technology innovation priorities should be identified and integrated into the academic and industrial research communities to create critical mass of aligned progress.

To address the green and digital transitions and greater complexity in production technologies, the industry needs to consider and consolidate key skills needed for the modernisation of manufacturing, to ensure that it has **access to a qualified and skilled workforce needed** for both manufacturing and healthcare technologies. In this respect, participants highlighted that collaboration between the academic sector, industry and regulators needs to be strengthened and supported to develop a common understanding of digital technologies and support their further development and implementation.

### **3. Dependencies, including lack of geographical diversification**

Dependencies, in particular, when combined with the lack of geographical diversification of certain product and technologies and consolidation of the supply chain<sup>19</sup> can be another potential source of vulnerabilities.

The participants considered that the main threat to supply security in this context is reliance on a sole supply source or reliance on only one geographical region, especially if the technical capabilities to manufacture the products in question are not readily available in the EU.

**Vulnerabilities, due to dependencies, may exist at the level of finished medicinal product, or earlier in the supply chain.** A supply chain vulnerability may exist when there is a dependency on a supplier that is the only source of that raw material, intermediate or API globally.<sup>20</sup> Such vulnerabilities can also include dependencies on the supply of raw materials such as plasma, where the EU is highly dependent on the US.<sup>21</sup> Moreover, a vulnerability could exist when there is dependency on a number of suppliers located in only one geographical location. A vulnerability may also exist, but not be apparent, when many manufacturers are unknowingly dependent on a single supply source.

**Studies performed by pharmaceutical industry associations suggest that Asian producers of APIs hold a strong position in the large volume generic API market.** Some of these APIs

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<sup>19</sup> Consolidation of supply chains occurs when there is a reduction in the number of suppliers for a given API or raw material.

<sup>20</sup> The preparation of a European *Critical Raw Materials Act* has been announced in September 2022. It will cover a wide range of critical raw materials that are key to the green and digital transitions and also crucial to the defence, aerospace and health industries.

<sup>21</sup> [https://ec.europa.eu/health/sites/default/files/blood\\_tissues\\_organs/docs/swd\\_2019\\_376\\_en.pdf](https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/swd_2019_376_en.pdf)

are no longer produced in the EU.<sup>22</sup> Industry reports that the EU has dependencies upstream in the supply chains, for medicine precursors and intermediates.<sup>23</sup>

**Industry reports economic factors to be the main driver of these dependencies.** Participants argued that the price pressure or certain tendering or public procurement practices (such as very short procurement periods, focus on price only or “winner takes it all” approaches) would lead to consolidations (hidden wherever several medicine producers depend on the same (API) supplier) or other cost saving measures that may affect security of supply. The cost of APIs sourced in Asia would be 20 to 40% lower than those produced in the EU.<sup>24</sup> For APIs but also precursors and intermediates, Asian suppliers benefit from significant economies of scale as they are producing large volumes for the entire world market, as production moves to Asia due to lower labour and regulatory compliance costs, as well as environmental controls.<sup>25</sup> To assess the impact of these dependencies on the security of supply and to determine their strategic importance, a granular analysis at the product level would be required. Participants reported that while in the short term the **green transition** has a more limited role for immediate vulnerabilities in supply chains, it will be integral to all innovations enabling long-term medicines supply. When considering how to strengthen supply chains, participants considered that the environmental impacts as well as the potential impact of environmental legislation on supply, should be considered.

#### **4. Unlock the potential of data for better supply and demand predictability**

Participating stakeholders across workstreams agreed that **more transparency on supply chains and shortages** could help to address supply issues. Marketing authorisation holders repeated their desire for more clarity on **actual demand from healthcare systems**, in particular on anticipated changes or **possible surges of demand for critical medicines**, noting that such information would inform adjustments to production and supply in due time to avoid supply disruption. Representatives of wholesalers and patients argued in favour of **more transparency on the supply side**, focusing on downstream elements to mitigate and prevent medicines shortages.

Participants also reported that low-level transparency on the supply chains of raw materials prior to being a registered starting material<sup>26</sup> limits the ability of manufacturers and marketing authorisation holders to identify and report on potential vulnerabilities.

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<sup>22</sup> See the study referred to in footnote 21 (as well as the explanations above) and SICOS, GEEM and LEEM (Associations of French Health industries) (hereinafter “SICOS Study”), available at:

[https://chimiefine-biochimie.fr/IMG/pdf/20210730\\_-\\_sicos\\_leem\\_gemme\\_-\\_study\\_of\\_api\\_supply\\_vulnerabilities\\_for\\_the\\_european\\_pharmaceutical\\_industry\\_-\\_final\\_report\\_en\\_20210907.pdf](https://chimiefine-biochimie.fr/IMG/pdf/20210730_-_sicos_leem_gemme_-_study_of_api_supply_vulnerabilities_for_the_european_pharmaceutical_industry_-_final_report_en_20210907.pdf)

<sup>23</sup> See EU Fine Commercial KPI (2020), IQVIA study conducted for the European Fine Chemicals Group (EFCG), available at [https://efcg.cefic.org/wp-content/uploads/2021/06/20201211\\_IQVIA-for-EFCG\\_Executive-summary.pdf](https://efcg.cefic.org/wp-content/uploads/2021/06/20201211_IQVIA-for-EFCG_Executive-summary.pdf)

<sup>24</sup> See SICOS Study (referenced in footnote 22).

<sup>25</sup> For instance, the SICOS Study (referenced in footnote **Error! Bookmark not defined.**) alleges on slide 7 that in France, there is an additional cost or operating expenditure of 20-30% for compliance with health and safety regulation due to European environmental regulations compared to Asia. This allegation could not be verified.

<sup>26</sup> A material that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API (reference information, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Quality Guidelines, ICH Q11, accessible at: <https://www.ich.org/page/quality-guidelines>).



Additionally, industry participants highlighted that the data on API production sites, submitted in the regulatory dossier, is not fully used. However, there was also a recognition that this data is not necessarily available in a format that would enable automated processing and in some instances, e.g. where more than one API supplier is identified, there is insufficient information to properly analyse the supply chain resilience. Participants also stressed that information on supply chain design is available to regulators in marketing authorisation dossiers, flagging insufficient information exchange as the limiting factor to allow for detection of consolidations and supply risks.

## 5. Perceived regulatory complexity

**The pharmaceutical sector is highly and often differently regulated around the world. Participants noted that** differences in regulatory requirements between different regions impact the flexibility of supply chains.

**Industry representatives highlighted that the lack of international regulatory convergence,** (e.g. for environmental legislation or for post approval changes in different pharmaceutical frameworks) **combined with the complexity of legal frameworks across jurisdictions globally negatively affects the ability to respond in a flexible, effective and timely manner to supply chain challenges.** The industry representatives called for a more risk-based approach to post-approval changes to authorisations, noting that the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on this subject have already been adopted. According to industry, lack of convergence across international regulatory frameworks presents greater challenges, in particular during crises, when swift adaptations to supply chains are needed to ensure that increased demand can be met.

For the off-patent sector, participants suggested that the **cost of regulatory compliance increases pressure** to reduce costs and contributes to the consolidations. The feedback received points, in particular, to the burden of variations related to API changes.

Participants considered that **digital technologies** and process innovations, as well as optimised systems and processes used by manufacturers and marketing authorisation holders, could help to make use of the available information for the purpose of supply security, thereby enhancing Europe's competitiveness by contributing to reducing production costs. Regulatory frameworks, including stakeholder guidelines, should facilitate the introduction of digital technologies in manufacturing, as well as support novel manufacturing approaches and efficient post-approval change management throughout the medicinal product lifecycle.

## II. IMPROVING SECURITY OF MEDICINES SUPPLY: MAPPING OF EU-LEVEL AREAS OF FOCUS

To build on the work done by the Structured Dialogue and improve the security of medicines supply, the following actions could be contemplated:

## 1. Identify critical medicines

**The complexity and diversity of the sector, the large number of authorised medicines in the EU and the even larger number of key components required throughout the manufacturing process of medicines make it challenging to define an exhaustive list of dependencies, vulnerabilities and manufacturing capacities.** There are over 530.000 marketing authorisations granted for medicines in the EU market,<sup>27</sup> with an excess of 13.000 “active substances” (including combinations).<sup>28</sup> It was therefore decided to narrow the scope and the assessment to medicines that are considered to be most critical, due to their importance for the resilience of health care systems, public health and patient care at all times (‘Critical Medicines’).

**The initial phase of the Structured Dialogue developed a draft methodology to identify critical medicines.**

The draft methodology takes into consideration two complimentary criteria, the therapeutic indication of the medicine and the availability of adequate alternatives. For each criterion, three risk levels (low, medium and high) are assigned to a medicine of interest. For example, a high risk level medicine from the perspective of its other therapeutic indication is a medicine which is indicated for the treatment of a life-threatening acute condition. On the other hand, a medicine will be considered to be high risk from the perspective of the availability of alternatives if no appropriate alternative treatment (generic or other therapeutic alternative) exists. Based on the two criteria, a **risk matrix** (Annex II, figure 1) is applied which allows the categorisation of medicines under three different groups: critical medicines (high risk or a combination of medium/ high risk), medicines at risk (medium risk or a combination of low/high risk) and other medicines (low risk or a combination of low/medium risk).

According to the proposed methodology, once the risk category is established, an additional element needs to be considered, i.e. the **impact of the vulnerabilities** in the supply chains of the products that are assigned to the medium risk category, the so called “**medicines at risk**”. For medicines that are categorised as ‘medicines at risk’ the vulnerabilities in their supply chain will need to be assessed, and if high vulnerability risks exist in the supply chain, the medicines will be categorised as **Critical Medicines** (Annex II, figure 2).

While the methodology was not completely finalised before the end of the process, a pilot exercise was carried out to validate or amend the risk matrix, taking into account both the number and name of the categories in the criteria (Annex II) and risk-level mapping. The six active substances, propofol, heparin (excluding LMWH<sup>29</sup>), 5-Fluorouracil, avelumab, diazepam and colistin, were selected by participants. The intention was not to determine if these medicines are ‘Critical Medicines’. They were selected because they represent a range of different classes of medicines, and also because of the expertise available in the group, but not based on their

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<sup>27</sup> According to the Article 57 database, accessible at: <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/data-medicines-iso-idmp-standards/public-data-article-57-database>. The number of marketing authorisations does not equate to the number of medicines, because it may include multiple records for a medicine to take into account multiple pack sizes or separate medicinal product entities (“EV code”).

<sup>28</sup> See the Article 57 database.

<sup>29</sup> Low Molecular Weight Heparin.

perceived criticality. The vulnerability analysis of the supply chains of these medicines was not completed.

All participants were asked to test the criteria and the matrix independently and provide feedback. Some divergent views among stakeholders were not resolved, even after completion of the pilot. These views included, but were not limited to, the number of levels of criticality (critical medicine, medicines at risk and other medicines) as some stakeholders preferred only two levels (critical (to include ‘critical’ and ‘at risk’) and non-critical medicines), the potential for different interpretations of the criteria and the role of industry in compiling a list of critical medicines.

For these reasons, the draft methodology **requires further refinement before it allows for the identification of Critical Medicines. The main aspects that still need to be addressed include:**

- having a defined process, with appropriate governance and necessary expertise needed to validate the approach (from ‘learned societies’, including doctors, patients and hospital and community pharmacists, as well as regulators and some considered the pharmaceutical industry),
- having a defined process to update the list, covering frequency of updates, governance, roles and responsibilities of those involved in the process,
- access to information on marketing status of medicines (needs to be collected from national competent authorities or industry),
- criterion 2 is highly dependent on marketed appropriate alternative medicines at national level and, therefore, the pilot would need to be expanded to determine how this could be addressed to reach agreement on one list.

**The methodology could be finalised, based on a collective approach and further piloting, before using it to identify Critical Medicines.** A group of experts, such as Pharmaceutical Committee *Ad hoc group on vulnerabilities, including dependencies, of the global supply chains*, co-ordinated by the Commission and supported by EMA, could be convened to finalise this methodology and use it to identify Critical Medicines. It would require **collective work across and between Member States on developing a list of critical medicines**, using and building on this methodology which sets out “criticality” criteria. Input of relevant stakeholders would be sought, when required.

It should be noted that, in some Member States, similar reflections have also been carried out at national level to define of an identification method of critical health products. The Commission’s *Future-proofing pharmaceutical legislation: Study on medicine shortages* stated that, amongst others, representatives of the national authorities of Germany, Slovakia and Spain reported having implemented a national list of essential medicines and medicines at high risk of shortage.<sup>30</sup> At the time of consultation, eight other countries reported this was under consideration at national level.<sup>31</sup>

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<sup>30</sup> [Future-proofing pharmaceutical legislation - Publications Office of the EU \(europa.eu\)](#)

<sup>31</sup> Austria, Belgium, Estonia, Finland, Iceland, Latvia, Poland and Sweden.

## 2. Identify strategic dependencies and EU level manufacturing capacity (for critical medicines)

### - *Assessing strategic dependencies*

Once the Critical Medicines are identified, a granular analysis at the medicinal product level, per marketing authorisation holder, is needed to determine the level of significance of dependencies associated with the supply of raw materials, intermediates and APIs for those Critical Medicines.

Discussions among stakeholders during the initial phase of the Structured Dialogue identified various forms of vulnerabilities and associated dependencies, as described above. On a medicinal product level, one analytical tool to identify the level of significance of dependencies would be to conduct a **mapping of basic production methods and technologies** used in pharmaceutical manufacturing that are relevant for security of supply of those identified Critical Medicines, but are no longer available in the EU.

Further analysis could also explore the level of diversification of suppliers, where dependencies exist, for raw materials, APIs and excipients used in the manufacture of such medicines.

In the context of the update of the Industrial Strategy, the Commission analysed the dependencies existing in strategic ecosystems, including the health ecosystem. The specific preliminary analysis on APIs was based on trade data (the six-digit 'World Customs Organisation Harmonised System' – WCO HS) and looked at the value of imports and **identified products categories with limited scope of substitution with products manufactured in the EU**. This led to the identification of broad *categories* of products, potentially encompassing several medicines, for which the EU is considered to be dependent on a small number of non-EU suppliers.<sup>32</sup> In particular, an increasing trend was noted in the concentration of generic APIs being produced in India and China. A second stage of in-depth review analysing dependencies has been carried out for supply chain chemical products which are also relevant for medicines' manufacturing.<sup>33</sup>

The **customs statistics** on trade flows based on the six-digit WCO HS do not allow a sufficient level of granularity to identify and isolate products or ingredients of interest. Therefore, this approach does not allow the determination of the level of dependency for a specific product of interest. It is, therefore, worth exploring, whether EU customs data could be collected for a limited subset of products using more granular and specific codes and, if so, whether a legal base would be required to do so.

In the context of the COVID-19 pandemic, joint efforts have been made by the EU and US to strengthen global supply chains and manufacturing and address strategic dependencies. The need to ensure vaccine and therapeutic dose supply and administration in the face of supply chain constraints led to the launch of the joint EU-U.S. COVID-19 manufacturing and supply chain task force in September 2021. The two parties have agreed on a selected list of key inputs which are subject to monitoring. Both sides will rely on the instruments at their respective disposal. The

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<sup>32</sup> Commission Staff Working Document on Strategic dependencies and capacities, SWD(2021) 350.

<sup>33</sup> Commission Staff Working Document on EU strategic dependencies and capacities: second stage of in-depth reviews, SWD(2022) 41 final.

insights into the supply situation will be shared and provide necessary information to have an overview on potential supply chain bottlenecks. The task force will extend its activities to provide early warning of supply chain bottlenecks that could hamper global availability of vaccines and treatments.

- *Assessing the need to increase manufacturing capacity in the EU*

The COVID 19 pandemic demonstrated how supply security of medicines or health equipment can be jeopardised by global trade disruptions and by unanticipated demand surge triggering protectionist measures from key trade partners. The demand surge created a need to rapidly scale up industrial production. Global trade disruption can also be triggered by other causes such as military or diplomatic conflicts, natural disasters or other major events. Such disruptions are not always limited to medicines required to address or respond to a specific crisis.

**When trade disruptions or unanticipated demand surges threaten the supply of critical medicines and their raw materials or APIs, the existence of sufficient EU manufacturing capacity can contribute to reducing supply vulnerabilities and ensuring supply security in the EU.** It should also be determined if and how strategic stockpiling could be effective in reducing supply vulnerabilities, as currently done by DG HERA and DG ECHO, for medical countermeasures.

The EU has a strong pharmaceutical industry. However, the trend observed in the last two decades suggests that the production capacity in the EU is diminishing, in particular, for large volume, off-patent medicines and APIs. Some stakeholders argued that it would be important that the EU reinforces its manufacturing capacity for critical medicines and APIs to contribute to the diversification of global supply chains, thereby ensuring continuity and security of supply, not only in the EU, but also across the globe. One way to address this would be to assess whether certain manufacturing capacity in the EU, for those identified Critical Medicines and associated APIs, should be maintained or restored to address healthcare system needs, so that production can be quickly triggered when needed. Such an approach has been adopted by the Commission for vaccines, and a call was launched for tender for EU FAB, a network of vaccine manufacturing facilities to secure early availability of vaccines in case of a future public health emergency. However, it may not always be necessary to increase manufacturing capacity in the EU.

HERA is currently undertaking the development of a list of critical medical countermeasures in relation to the three identified health threat categories constituting potential serious cross-border health threats, which will feed into in the State of Preparedness Report, to be adopted in November 2022. Any relevant methodology to assess supply chain vulnerabilities developed by HERA should be considered.

For Critical Medicines<sup>34</sup> that are not covered by the HERA mandate (i.e. not identified as medical countermeasures), the Commission could consider assessing to what extent security of supply would require increasing the manufacturing capacity of, maintaining or establishing specific manufacturing sites in the EU.

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<sup>34</sup> Critical Medicines identified as outlined in section II 1. above.

It may also be necessary to **discuss, whether certain common approaches are necessary to ensure supply through strategic stockpiling** of key raw materials or APIs for Critical Medicines. The HERA preparatory action on “Feasibility Study on Stockpiling of Medical Countermeasures in the Area of AMR” as well as DG ECHO experience in creating rescEU stockpiles for medical countermeasures would inform the discussion on those approaches.

### **3. Enhanced security of supply: optimising the regulatory environment**

In the participants’ reports of the Structured Dialogue, **industry representatives presented challenges with respect to regulatory obligations in the EU pharmaceutical legislation.**<sup>35</sup> They claimed that practical compliance with regulatory procedures is very complex and burdensome and that the EU regulatory system could improve operational efficiency and is technically not up to date regarding the use of digital tools.

The Pharmaceutical Strategy announced that the Commission will propose to revise the EU pharmaceutical legislation to **improve overall regulatory efficiency**, e.g. by simplifying and streamlining the procedures, allowing for timely adaptation of technical and technological development, and improving the medicines lifecycle management.

**Improving the digital infrastructure or tools** in the regulatory context based on harmonised and interoperable approaches could also contribute to security of supply. **Enhanced digitalisation of regulatory submissions** would also **facilitate the cooperation between regulatory authorities** at the EU level and support more efficient product lifecycle change management, leading to more agility in supply chains.

In addition to the EU pharmaceutical legislation, **raw materials and other chemicals used in the pharmaceutical production are regulated under the chemicals legislation (REACH)**<sup>36</sup> and the applicable environmental legislation. The ongoing process of revision of the REACH framework has notably the objective of reflecting the ambitions of the Commission on innovation and a high level of protection of health and the environment, while preserving the internal market, as provided for in the Chemicals Strategy for Sustainability.<sup>37</sup> It will also aim to simplify processes, especially for essential uses, for which health and safety are considered to be among the criteria for an exemption. The impacts of the planned revision are being assessed in an ongoing impact assessment.

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<sup>35</sup> References to the ‘general pharmaceuticals legislation’ or ‘pharmaceutical legislation’ are to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67) and Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1).

<sup>36</sup> Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC.

<sup>37</sup> Chemicals Strategy for Sustainability - Towards a Toxic-Free Environment, COM(2020) 667 final of 14.10.2020

#### **4. Enhanced security of supply: promote green and digital innovation in manufacturing**

The ability of the pharmaceutical industry to deliver high-quality innovative products and manufacturing processes is a condition for supply security. The digital transition could enhance Europe's competitiveness by reducing production costs and cycle times. The benefits of this transition could also help to address the vulnerabilities identified in supply chains and gain efficiencies in operations that can help to support additional costs for the green transition. Digital technologies are also necessary to implement innovative technologies that are key enablers for increasing the visibility of inventory in the supply chain (helping to prevent or mitigate shortages), hence enhancing the agility, reliability and efficiency of manufacturing and supply processes. The development of more environmentally efficient manufacturing processes, using less fossil-based inputs, solvents and energy, is also contributing to improved security of supply and a reduced dependency on third countries' input, decreasing EU strategic dependency.

Some aspects of supply security are already integrated in Commission research programmes. Under Horizon Europe, a call on green pharmaceuticals<sup>38</sup> aims to support, among other objectives, the development of innovative manufacturing technologies that are greener, lower in energy consumption and emissions, and use less solvent or recycling solvents.

The development of innovative, economically and environmentally sustainable technologies going beyond the current state of the art in the sector, and where the existence of market failures have been identified, could be supported through an **Important Project of Common European Interest (IPCEI) initiated by Member States**. Initiative has been taken by 16 Member States<sup>39</sup> who are committed to '*deepen the work towards the deployment of "Important Projects of Common European Interest" (IPCEI) to further address potential market failures impeding innovation and improve quality of, and access to, healthcare of patients.*' Two Health IPCEIs are foreseen, and Member States are in the driving seat for defining their scope and timeline, with the Commission acting as facilitator in this process.

#### **5. Enhanced security of supply: promote pricing and procurement practices**

As outlined above, the Structured Dialogue did not provide sufficient evidence on the impact of pricing and procurement practices on security of supply including aspects related to the alleged lack of profitability and resulting consolidation. There is also a lack of knowledge on the side of public authorities as to the causal link between prices, profits and supply chain vulnerabilities.

While it is a national responsibility to define purchasing policies and strategies in the context of public procurement, the Commission has, following the publication of the Pharmaceutical Strategy, stepped up **co-operation in the group of national pricing and reimbursement authorities and healthcare payers** ('NCAPR') to support mutual learning through information and best-practice exchange on pricing, payment and procurement policies. The NCAPR cooperation could consider exchanges on how procurement and pricing practices could better include supply security considerations.

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<sup>38</sup> Horizon Europe Framework Programme, 2021 call on *A competitive health-related industry*, Green pharmaceuticals (HORIZON-HLTH-2021-IND-07-01).

<sup>39</sup> Health IPCEI Manifesto of 3 March 2022: [https://www.entreprises.gouv.fr/files/files/secteurs-d-activite/industrie/industries-de-sante/manifesto\\_towards\\_a\\_health\\_ipcei.pdf](https://www.entreprises.gouv.fr/files/files/secteurs-d-activite/industrie/industries-de-sante/manifesto_towards_a_health_ipcei.pdf).

The Commission has also launched a **study to assess ways to optimise public procurement of medicines**, including to improve access and availability. This study analyses the impact of price levels and non-price criteria when applying procurement policies aimed at improving the security of supply. The Commission will publish the study final report in Q4 2022.

Within the health subgroup of the Expert Group on Public Procurement, a reflection will be launched on **how public procurement can contribute to addressing strategic dependencies in the pharmaceutical sector.**

## **6. Enhanced knowledge of supply chains: digital tools and data gathering mechanisms**

The Structured Dialogue showed that **public authorities do not have access to sufficient data to determine vulnerabilities.** However, it is not only about access to information which in any case should be facilitated but also about providing information in an accessible, usable and commonly agreed and digital format. **More information on supply chains and the industrial aspects of pharmaceutical manufacturing in the EU and in non-EU countries is also needed.**

The information marketing authorisation holders are required to submit when applying for a marketing authorisation is not currently collected with a view to ensuring supply chain transparency and resilience and security of supply of medicines. Therefore, this information is not easily accessible to national authorities, although it could enable authorities to accurately map the supply chain of a medicine, thereby contributing to security of supply. In addition, once it is possible to submit such information to EMA or national competent authorities in a commonly agreed and digital format, additional tools may be developed in order to allow for an appropriate and up-to-date analysis. For instance, it would be useful to assess to what extent companies (which are often competitors) rely on the same few (concentrated) sources of supply e.g. of raw materials or APIs, and where the greatest risk is in the supply chain of Critical Medicines.

The Commission, Member States and EMA could also consider what additional information marketing authorisation holders could provide, and in what format, to support achieving the objectives of supply chain transparency and resilience and security of supply of medicines. For instance, where the marketing authorisation holder sources a raw material, intermediate or API from several sources (dual sourcing), there is currently no indication in the dossier submitted by the marketing authorisation holder if there is a primary supplier and backup or if all sites supply actively, at all times. The dossier also does not specify the volumes supplied from listed sites, which may also vary over time. Based on the **cooperation already developed in the Pharmaceutical Committee** and the experience of the Task Force for Industrial Scale up of COVID-19 Vaccines, it could be considered to set up **a mechanism for national authorities to further exchange information.** This mechanism could then be used to determine what could be done, where required, for a specific Critical Medicine with a view to strengthen supply security. This cooperation could involve coordination of relevant ministries or competent authorities at national level (such as those responsible for industrial and competition policies and health).

The potential of using digital tools could also be explored with a view to structurally develop knowledge, generate data and deepen the analysis.



Approaches should be co-ordinated with HERA and EMA, to build on established structures and expertise for crisis situations, and avoid unnecessary duplication, streamline efforts and ensure a good interplay of different activities. In particular, HERA is currently developing an intelligence gathering tool to support its mission, with an objective of supporting detection vulnerabilities in supply chains and availability challenges.

## 7. Enhanced security of supply: promote global cooperation

- *Enhanced cooperation in international regulatory convergence fora and with regulators from other world regions.*

As manufacture and trade of pharmaceuticals are highly globalised, **the EU could consider continuing its supporting efforts to attain greater harmonisation and regulatory convergence at a global level.** In doing so, supply chains could be strengthened through the promotion of high quality and safety standards and streamlining of regulatory requirements for marketing authorisation holders. The Pharmaceutical Strategy for Europe highlights that the EU can achieve this through continued cooperation in international fora<sup>40</sup> as well as the ongoing WHO efforts to promote cooperation between regulators and reliance, whenever this is feasible. The Team Europe initiative on manufacturing and access to medicines in Africa, led by INTPA and in collaboration with the EMA, is funding WHO and African partners to advance harmonisation, reliance and regulatory convergence in this region.

- *Promoting high quality standards, equivalent to EU GMP*

According to a Commission study on shortages, manufacturing and quality issues were reported as the root cause of about half of shortages reported in the EU.<sup>41</sup> **Promoting EU Good Manufacturing Practice (GMP) and quality standards at a global level helps to mitigate supply vulnerabilities caused by quality-related incidents, in particular, as many medicines destined for the EU market are produced outside the EU.**

The Pharmaceutical Strategy for Europe aims to strengthen the oversight of GMP compliance to ensure the highest quality for products marketed in the EU. Taking into account the global dimension of supply chains, encouraging global implementation of EU-equivalent GMP standards, ensured through regulatory oversight, will not only ensure the highest quality of medicines worldwide, but could also contribute to preventing supply disruptions in the EU due to quality or manufacturing issues.

In its bilateral relations, the Commission encourages non-EU countries to join the multilateral cooperation mechanisms, such as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the Pharmaceutical Inspection Co-operation Scheme (PIC/S), as well as supporting the enforcement of these standards through the cooperation on inspections.

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<sup>40</sup> International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), the International Pharmaceutical Regulators Programme (IPRP), the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S), the International Coalition of Medicines Regulatory Authorities (ICMRA).

<sup>41</sup> Study on medicine shortages: final report published on 8 December 2021: <https://op.europa.eu/en/publication-detail/-/publication/1f8185d5-5325-11ec-91ac-01aa75ed71a1/language-en/format-PDF/source-24533895>

- *Reward compliance with green manufacturing standards outside the EU*

Production of APIs and precursors in the EU must comply with EU environmental, health and safety standards. However, when these products are imported from third countries, the environmental standards of those jurisdictions apply, in particular, for API production. Lower environmental standards or poor enforcement or compliance with environmental, health and safety standards are not only detrimental to the environment, security and occupational health, but they are also a predictor of lower security of supply. Many countries across the world are working to implement and enforce stronger environmental policies. This has resulted in the closure of manufacturing plants that are not environmentally sustainable. The **promotion of EU environmental standards should continue**, and relevant authorities could consider rewarding marketing authorisation holders or manufacturers that select third country suppliers based on their compliance with those standards.

- *Address export restrictions globally*

Highly globalised supply chains require free movement of key ingredients. Trade restrictions and barriers can disrupt those supply chains. The EU relies on imports of pharmaceutical ingredients and medicines. At the same time, the EU produces one third of the world's supply of APIs. It is important not only for the EU but also for the security of supply of third countries to tackle export restrictions to facilitate the trade flow in pharmaceutical products. Promoting geographic diversification of supply chains, while removing trade barriers helps to increase supply security. The Commission could consider **continuing to pursue this objective both through bilateral and multilateral cooperation, notably through the EU-led initiative on Trade and Health (TAHI) within the WTO.**

- *Promote manufacturing in other regions*

**The diversification of supply sources contributes to securing supply in the EU.** It is in the interest of the EU to promote conditions that would allow building up of manufacturing capacities in different regions of the world, in particular, taking into account the impact of unanticipated disruptions of logistics and trade in neighbouring regions.

The EU has initiated cooperation with strategic partners and regions. For instance, the €1 billion Team Europe Initiative on manufacturing in Africa, announced at the Global Health Summit in May 2021, aims at reinforcing African pharmaceutical systems and manufacturing capacity to facilitate access to safe, effective, quality and affordable essential medicines.

Discussions between EU and its international partners may explore how the EU could contribute, in a practical way, to promote local manufacturing and operation. Actions to diversify production centres and, consequently, enhance the security of global value chains, are already carried out in the context of the Global Gateway strategy by joining forces with EU Member States (through Team Europe Initiatives) and European Development Finance Institutions (EDFIs).

## CONCLUSION

The Pharmaceutical and the Industrial Strategies provide a strong base for action, to improve the security of supply of medicines.

This Staff Working Document has first summarised the main findings of the stakeholders' work, more generally on pharmaceutical supply chain challenges, as well as presenting the draft

methodology to identify Critical Medicines, and, once identified, approaches that could be adopted to identify vulnerabilities in the supply chain of those medicines to improve the security of supply. The document also reflects on the challenges that may be associated with certain vulnerabilities, including dependencies in the context of a highly globalised pharmaceutical industry, the regulatory framework, and the green and digital transitions.

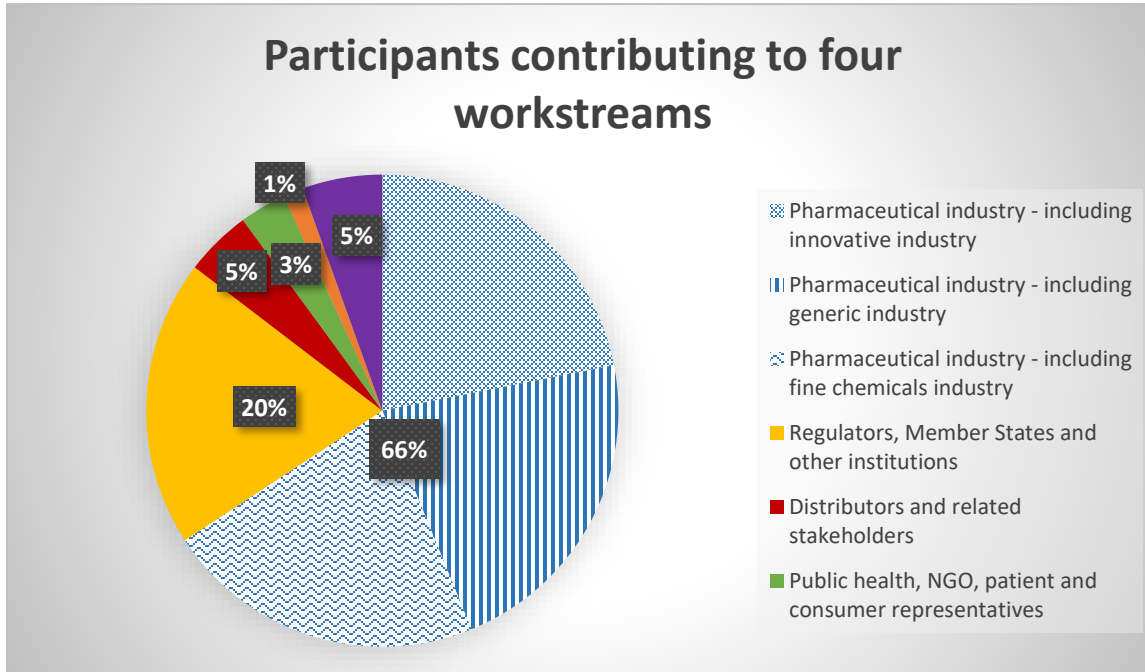
The Structured Dialogue has improved communication and information exchange among supply chain stakeholders. However, it is clear from the process that, while it is essential to keep open and well-functioning communication channels with stakeholders, including economic actors and industry players, public authorities would likely not be satisfied to rely on an informal and voluntary approach.

The process pointed to the lack of appropriate and modern tools and mechanisms that enable a robust, granular, uniform and consistent data and evidence gathering in support of policy making. Development of well-designed digital tools and related processes to collect pertinent information could provide significant contribution to support public authorities at all levels to structurally develop knowledge, generate data and deepen the analysis for policy making, also beyond the crisis situations.

The Commission will continue its reflection, notably in the context of the upcoming reform of the pharmaceutical legislation, in order to formulate policy options and put forward actions to strengthen the continuity and security of supply in the EU, in particular for those medicines considered to be most critical to health systems.

Any future actions or policy measures identified based on the information presented in this Staff Working Document would also take into account the remit of the work carried out by HERA and EMA. In particular, and where applicable, new processes should be established in coherence with relevant actions from HERA and EMA, and in synergy with other Union policies, programmes, funds and other initiatives, including the upcoming EU Global Health Strategy.

## ANNEX I PARTICIPANTS INVOLVED IN THE STRUCTURED DIALOGUE PROCESS

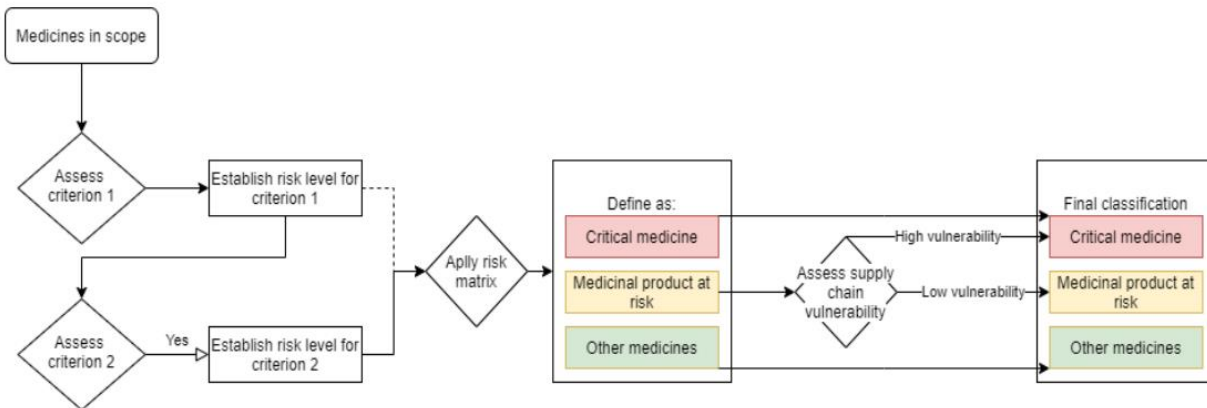


**ANNEX II PROPOSED METHODOLOGY AND MATRIX TO CATEGORISE CRITICAL MEDICINES DEVELOPED IN THE INITIAL PHASE OF THE STRUCTURED DIALOGUE**

**Figure 1: Risk matrix** (Details of criteria 1 and 2 are outlined below)

		Criterion 1: Therapeutic indication / therapeutic importance		
		High risk	Medium risk	Low risk
Criterion 2: Availability of appropriate alternatives	High risk	Critical medicine	Critical medicine	Medicinal products at risk
	Medium risk	Critical medicine	Medicinal products at risk	Other medicines
	Low risk	Medicinal products at risk	Other medicines	Other medicines

**Figure 2: Classification steps** – criticality category based on risk matrix and supply chain vulnerability assessment



**CRITERION 1: Therapeutic indication / therapeutic importance**

High risk	<ul style="list-style-type: none"> <li>• Indications with <b>very serious or serious implications</b> for the health of <b>individual patient or public health</b>: medicines or classes of medicines used to treat patients with <b>general life-threatening acute conditions, specific life-threatening acute conditions, or irreversibly progressive conditions*</b></li> <li>• The disease to be treated is potentially fatal, irreversibly progressive or, if left untreated, would pose an immediate threat, or cause severe impairment to the patient. This applies similarly to acute situations (emergencies), chronic situations or situations with potentially fatal outcome.</li> <li>• If the treatment is unavailable or interrupted, it will jeopardise the vital prognosis of patients in the short or medium term or represents a significant loss of opportunity for patients regarding the severity or potential evolution of the disease.</li> <li>• The treatment <b>must be taken within a short period of time (immediately) or within regular dosing intervals. **</b></li> <li>• The product is as part of a national disease control program (vaccination campaign)***</li> </ul>
Medium risk	<ul style="list-style-type: none"> <li>• If the disease is left untreated, it may induce reversible disease progression or hospitalisation or intensified treatment, but no fatality is expected or severe impairment.</li> <li>• A product which prevents relapses of a condition, if suspended, would not immediately expose relapses, maybe the relapse will only occur weeks or months after treatment interruption (e.g. multiple sclerosis), or the disease progression is slow (Duchenne muscular dystrophy, or cystic fibrosis)</li> <li>• <b>The treatment should be taken within <u>days</u>.</b></li> </ul>
Low risk	Other indications.

\* For the purpose of this sub-criteria to treat should be interpreted as to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action, in line with the EU definition of medicinal product.

\*\*This requirement originates from the recommendations of the Jour Fixe on Delivery and Supply shortages. The opinion of the WS2 is, that the requirement is appropriately defined without a specific time limit. However, if during the risk assessment for medicines, the need to define a specific time period is identified, it should be defined, but should not exceed 24 hours.

\*\*\* The ‘national disease control programme’ does not refer to lists of essential or critical medicines established by the WHO or available at national level.

With respect to Orphan Medicinal Products (OMPs), Criterion 1 when seen together with Criterion 2 would need to be more granular in order to ultimately secure the supply to very small patient populations.

## CRITERION 2: Availability of appropriate alternatives

The aim of this criteria is to identify **appropriate alternatives**, i.e. medicines that can be substituted without any negative impact on the patient's health.

<b>High risk</b>	<p>High risk treatments are those treatments, for which no appropriate alternative treatment exists or is not available or switching to the alternative treatment would require extensive clinical consultations not applicable for certain indications. Substitution of treatment is expected to affect patient safety or disease prognosis.</p> <p><b>Alternative treatment is not clinically possible:</b></p> <ul style="list-style-type: none"><li>• The active substance or combination of active substances (e.g., combination of ethambutol, rifampicin and isoniazid used to treat tuberculosis, combination treatment for HIV) has unique pharmacology and no alternative treatment options exist.</li></ul> <p><b>Alternative treatment would require extensive clinical consultations, not applicable for high-risk indications:</b></p> <ul style="list-style-type: none"><li>• The alternative treatment has a lower therapeutic index than the initial treatment.</li><li>• Switching to alternative treatment cannot be accomplished in short time due to clinical reasons related to degraded clinical outcomes, therapeutic failures, delayed onset of treatment, compromised disease control (e.g., psychiatric drugs), decreased efficacy (i.e. antibiotic resistance) or requires additional monitoring (e.g., renal or hepatic parameters).</li><li>• Switching to alternative treatment cannot be accomplished in short time due to organisation of care (e.g., to receive the alternative treatment the patient may require an appointment by a different specialist, only who can prescribe the alternative treatment) or requires switching from self-administration to in-patient / hospital administration (e.g. switch from subcutaneous to intravenous administration).</li><li>• The alternative treatment is only available as compassionate use.</li><li>• The alternative treatment does not meet the clinical needs of the entire target patient population: a group of patients, that is not the majority, cannot use the alternative treatment / the alternative treatment is contra-indicated (including patients with specific needs, target population normally served by off-label use, elderly, paediatric, disabled patients, etc.).</li><li>• The alternative treatment has additional serious, or irreversible or incurable adverse events compared to adverse effects associated with the initial treatment. Due to use of the alternative treatment, the target patient population may experience life threatening complications (e.g., greater toxicity).</li></ul> <p><b>Alternative treatment is not available:</b></p> <ul style="list-style-type: none"><li>• Alternative treatment is possible, but the alternative treatment is not available (the alternative treatment is not marketed, or the alternative product has been withdrawn from the market).</li><li>• Alternative treatment can only be obtained at great expense (e.g. the price of alternative treatment does not exceed highest allowed price of the initial treatment or does not exceed an increase in expenses with a trivial limit or the price for the patient does not change etc.). *</li><li>• The initial treatment is expected to have increased demand in time of crisis.</li></ul>
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	<ul style="list-style-type: none"> <li>• The alternative treatment is commonly in shortage**</li> </ul>
Medium risk	<p>Medium risk treatments are those treatments, for which alternative treatment exists or the availability of alternative treatment may be limited. However, the substitution of treatment requires additional input from medical personal but is not expected to affect patient safety or disease prognosis.</p> <p><b>Alternative treatment is clinically possible, but requires input from medical personnel:</b></p> <ul style="list-style-type: none"> <li>• Alternative treatment has the same or equal or similar therapeutic effect and may be achieved by using alternative active substances (from the same therapeutic or ATC or pharmacological group). The substitution with alternative treatment cannot be done by pharmacists without doctor's involvement.</li> <li>• Alternative treatment may be achieved by using alternative pharmaceutical forms or different routes of administration or extemporaneous preparations / in-house compounding or alternative strengths or alternative dosing regiments. Using the alternative pharmaceutical form does not require switching from self-administration to in-patient administration.</li> </ul> <p><b>Alternative treatment is available in limited quantities:</b> The alternative product is available, but in limited quantities and potential shortage is expected due to increased demand.</p>
Low risk	<p>Low risk treatments are those treatments, for which alternative treatment exists or the availability of alternative treatment is not problematic. Products can feely be substituted and little to no input from medical personnel is required.</p> <p><b>Alternative treatment is clinically possible and requires little to no input from medical personnel:</b></p> <ul style="list-style-type: none"> <li>• Alternative treatment is possible by using the same active substance the same strength in the same pharmaceutical form or different pharmaceutical form with equal administration route (e.g. generic substitution, substitution of formulations)</li> <li>• Alternative treatment is possible by using a well-established alternative active substance (e.g. OTC dispensing of pain medication). The substitution with alternative treatment can be done by pharmacists, without doctor involvement.</li> <li>• The use of alternative treatment does not affect patient safety.</li> </ul> <p><b>Alternative treatment is readily available, and no supply issues are expected due to increased demand.</b></p>

\*This requirement originates from the recommendations of the Jour Fixe on Delivery and Supply shortages. The opinion of the WS2 is that the requirement is relevant and should remain included. However, the group also agrees that a more precise quantification mechanism should be defined for elaboration of increased expenses.

\*\*Commonly in shortage needs to be defined once a definition of shortage is agreed under the legal proposal for the extended mandate of EMA.

NOTE: Divergent views on elements of criteria 1 and 2 were expressed by participants involved.