Workstream 3 Report

Workstream 3 Vulnerabilities. The purpose of this workstream is to assess the existence of vulnerabilities, to reflect on the causes of vulnerabilities, considering at what stage in the supply chain they occur and if they differ for different types of medicines. The discussion should include consideration of disruption challenges most frequently observed that pose the greatest threat to supply, to identify the drivers of these vulnerabilities, including dependencies. This workstream will also assess the financial impact associated with addressing the challenges and drivers

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Working Group:	3	
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Background

This workstream report is the main deliverable following the operational phase of the Structured Dialogue on the security of medicines supply, announced in the Pharmaceutical Strategy and officially launched on 26 February 2021 by Vice-President Schinas, Commissioner Breton and Commissioner Kyriakides.

The main objective of the Structured Dialogue initiative is to ensure the security of supply and the availability of critical medicines, active pharmaceutical ingredients and raw pharmaceutical materials. It contributes to the objective of building the EU's open strategic autonomy.

The operational phase of the Structured Dialogue has been launched on 25 March 2021 with participation of representatives from industry, public authorities, patient organisations and the research community.

Between March and July 2021, participants self-organised their collaboration in four workstreams focused on defining robust supply chains and assessing associated vulnerabilities, identifying critical medicines, and considering innovation in the context of supply chains, in order to answer the questions put forward by the European Commission. Rapporteurs and co-rapporteurs coordinated the work within each workstream and ensured the rules of procedure were adhered to.

Additional meetings with each workstream and the Commission in April and June, as well as a stocktaking meeting in May with workstream representatives and the Commission, were held to exchange experiences, take stock and identify interlinks and synergies between the workstreams.

The four workstream reports, submitted by 20 July, present the product of these meetings, answering the questions posed and constitute the basis of the Commission reflection on possible solutions that ensure robust and sustainable medicines supply in the EU. They shall contribute to a better understanding of the issues relating to pharmaceutical supply chains.

On the basis of knowledge gathered and analysis performed, the Commission will propose potential solutions to the problems and challenges identified. The outcomes and possible policy actions to address issues identified will be discussed with the participants of the structured dialogue initiative meeting in September.

The reports will also inform the revision of pharmaceutical legislation, alongside a study and stakeholders' consultations.

Executive Summary

Please provide a short summary of the key findings and main messages of your workstream.

Important disclaimer: *The group notes the extensive documentation and great diversity of comments and positions communicated by the various participants, which play a direct role in the structured dialogue exercise. The group acknowledges that the content of this report does not reflect a consensus opinion of the group on the various questions asked by the Commission, nor does it contain all feedback provided. It is rather a collection of views which in many instances were still diverging at the time of finalizing this report.*

Workstream 3 was asked to (1) define what constitutes the vulnerability of the supply chain, (2) to examine the vulnerabilities of the medicines supply and identify their causes and drivers and (3) to identify the aspects of supply chains that need transparency. Participants agreed to look at each respective stage of the supply chain, starting with raw materials, through to active pharmaceutical ingredients, finished dosage forms, distribution, and patients.

On the vulnerability definition, there were intense discussions among the stakeholders involved and the group reached a compromise definition as follows: a vulnerability in the supply of medicines is a risk that might **cause challenges in access to medicines**. These risks in the supply of medicines can be different for different types of medicines.

On the vulnerability assessment (Section 2.2), the group looked into the following 4 aspects that could lead to vulnerabilities, the extent of which varies depending on the pharmaceutical segments/category of medicines:

1. Consolidation of the supply chain and investments in manufacturing capacity linked to cost pressures.
2. The degree of geographical diversification for certain pharmaceuticals, raw materials or technologies.
3. Regulatory complexity and degree of regulatory convergence.
4. Degree of visibility on supply and demand.

Consolidation of the supply chain and investments in manufacturing capacity
The first aspect appears of particular relevance for the off-patent generic medicines where the cost pressure has been high. Industry representatives argued that some healthcare systems have too often focused exclusively on price, ignoring supplier reliability, the sustainability of their operations, or compliance with environmental standards. Public sector representatives highlighted the importance of managing healthcare costs in an attempt to balance cost containment and the sustainability of healthcare systems.

Related to this is the fact that tender practices can also make it economically unsustainable for producers to invest in measures that would reduce vulnerabilities. Member states often use a "winner-take-all" model, with price as the only criteria. For some products there may even be several tenders per year, leaving producers unable to do even short-term production planning. Stakeholders agreed that tenders should include several criteria, such as the economic sustainability of supply chain actors, security of supply, or compliance with environmental standards, that support a level playing field. There was in this context a call for the use of tenders that make it attractive and feasible for several suppliers to remain active, rather than a call for healthcare systems to directly measure economic sustainability of private companies.

Geographical diversification for certain pharmaceuticals, raw materials or technologies
Cost pressures have also extended to the suppliers of generic medicines manufacturers, creating a situation where production is moved outside the EU and there is sometimes one or a limited number of suppliers for some raw materials and Active Pharmaceutical Ingredients (APIs). In some cases, this has created a strong dependence of the off-patent generic segment on few suppliers or even only one, with these located in China or India in particular for some raw materials. For the innovative industry this dependence is much lower with 77% of APIs sourced in Europe. For the plasma sector, the EU collects only 70% of its plasma needs, while being dependent on US plasma imports up to 30%, with a growing tendency.

Regulatory complexity and degree of regulatory convergence.
With relevance for all products, there is the need to improve the regulatory efficiency associated with Post Approval Changes (PACs). PACs are inevitable and necessary throughout the life of a drug product to implement new knowledge, maintain a state of control, and drive continual improvement which serves to enhance product quality and ultimately benefit patients. To better serve patients, PACs should be managed in a timely manner. However, today many PACs (including low risk changes) require prior regulatory approval that can take up to five years before full implementation worldwide. Standardizing regulatory procedures across the EU and globally, and leveraging a risk-based approach to post-approval changes, would decrease supply chain vulnerabilities. Regulators and the industry, working together at the ICH, have already adopted guidelines for this purpose.

Degree of visibility on supply and demand.
The lack of visibility on the supply and demand appears as an issue for actors across the entire supply chain – beginning with suppliers of raw materials for production. Lack of data on existing stocks (at national, regional, hospital level) and patient needs limits the ability of actors to better plan production and react to sudden changes in demand.

On the transparency aspects (Section 2.3), the workstream agreed that the lack of transparency across the complex medicines supply chain greatly reduces the ability to anticipate and reduce vulnerabilities. This is particularly important for medicines with longer production timelines. Upstream in the supply chain, the availability of information on consolidation, dependencies and key technologies would help to determine vulnerabilities occurring at this stage. Downstream of the supply chain, a greater visibility on projected demand needs and the amount and duration of supply disruptions would facilitate the work of distributors and health care professionals.

Looking at the various aspects, it appears critical to take measures to reduced vulnerabilities and dependencies based on a risk-benefit approach, adapted to each category of medicines or stage in the production cycle. There are significant differences in terms of risks and costs not only for different stages of medicines production, but also across supply chains from raw materials to final products for different categories of medicines. Measures to favour diversification should also take into account that for specific raw materials, some technologies and production capacities are only available in China or India.

Private sector stakeholders stressed that additional regulation that could be considered, such as requiring greater level of information provided by marketing authorization holders in their regulatory filings, would not be a solution. There was instead an emphasis on creating a framework to increase resilience and innovation.

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- **Introduction**

Please provide a general introduction to your workstream, specifying:

- *The scope of the problem analysis (what workstream participants agreed needed to be addressed).*
- *The main challenges to respond to the questions posed by the Commission e.g., in terms of identifying information or supporting evidence? Were there any specific barriers?*
- *Summarise how this workstream has closed knowledge gaps to respond to the objective of the structured dialogue.*

Challenges to respond to the questions and caveats concerning the content of this report

In light of the wide range of stakeholders represented and in the absence of clear rules of procedure, the self-organised group tried different methods to collect information, structure the discussion and proportionally weigh the various views in responding to the Commission's questions. This report is the result of this iterative process which has been evolving until the end of the first phase, collecting but not aligning on inputs and not leaving enough time for all participants to review the final version.

Workstream approach

Workstream 3 participants featured a wide range of stakeholders, and included healthcare professionals, suppliers to and manufacturers of medicines, full-service healthcare distributors (wholesalers), regulators and health ministry officials, academic experts, hospital procurers (List of participants in **ANNEXE A**). Participants agreed to cooperate in collecting information and drafting this paper on the basis of openness and focused debate on the issues at hand and recognized the critical importance of evidence- based work. The workstream agreed to work on a clear and shared understanding of supply chains for experts and non-experts alike, covering the several stages of supply chains, beginning with raw materials through to patients. Our aim was to identify vulnerabilities of each supply chain, including different stages, and to identify commonalities between medicines categories where relevant (e.g. off-patent/generic medicines, on-patent medicines, and biologics (which includes vaccines and wide range of treatments), in order to address variations in vulnerabilities where these exist.

Scope of the problem

In terms of scope, this paper seeks to answer the questions addressed to work stream 3 by the European Commission.

Commission Questions for Workstream 3:

- *What constitutes the vulnerability of the supply chain (dependency / number of suppliers / complexity of the supply chain).*
- *Are the supply chains sufficiently transparent to allow the assessment of risks and vulnerabilities? What aspects of supply chains must be transparent?*
- *Are the supply chains of the products identified as critically vulnerable? What specific aspects causes / lead to vulnerabilities? What are the drivers of these vulnerabilities?*
- *How do we link issue of supply chain security with other challenges as sustainability of health systems?*

Stakeholders agreed to have a staged approach and address one question per week in plenary sessions. Slides guided the discussions were provided before each meeting, and a summary of the discussions for additional comments was also circulated. In order to allow for greater participation by all participants, breakout sessions were used when discussing the links between supply chain security and the challenges associated with the sustainability of health systems. These were followed by a plenary session with a report provided by each of breakout groups.

In order to allow for more focused discussions and the identification of vulnerabilities at each stage, WS 3 participants proceeded on the basis of the following supply chain stages. These stages also provide the overall structure of the report:

A. Raw material production and collection
B. API manufacturing
C. Finished Dosage Form (FDF) manufacturing
D. Wholesale and distribution
E. Pharmacies and hospitals + patient input

In addition to the use of supply chain stages, the group agreed to look at each stage from the 3 following perspectives:

- **Industrial/economic perspective:** To what extent are economic factors in the operating environment of supply chain operators responsible for vulnerabilities?
- **Geopolitical perspective:** To what extent can geopolitical developments or changes in policy (which can be at the national or regional level) generate supply chain vulnerability?
- **Regulatory perspective:** What is the influence of the regulatory system on supply chain, and to what extent does this lead to supply chain vulnerabilities?

In order to capture vulnerability indicators that may be unique to different product categories, WS3 participants also considered differences and similarities across different product "categories."

(I) off-patent medicinal products refer to medicines on which the patent has expired and that can potentially be produced by an unlimited number of companies. These products can be generic medicines or branded medicines.
(II) patented medicinal products refer to proprietary products (in-patent), produced and marketed exclusively by the innovator pharmaceutical company,
(III) Biological Medicinal products refer to complex biological products, which have specific needs other than (I) and (II). Examples include vaccines, therapeutic biologics, and plasma derived medicinal products (PMDP)[1].

Depending on the supply chain stage and perspective, some vulnerabilities identified may have relevance for all three categories. Not all participants were of the view that this breakdown was best suited to answer the questions put forth in the Commission's mandate.

[1] Although the choice to look at these three categories was made early in the workstream, there was also a recognition that these categories are not as distinct as was initially considered. This includes for example the fact that biological products may no longer be patented and that biosimilars can be available. There can also be competing vaccines to prevent a given illness.

This approach resulted in a matrix-like structure to map out the vulnerabilities across the whole supply chain.

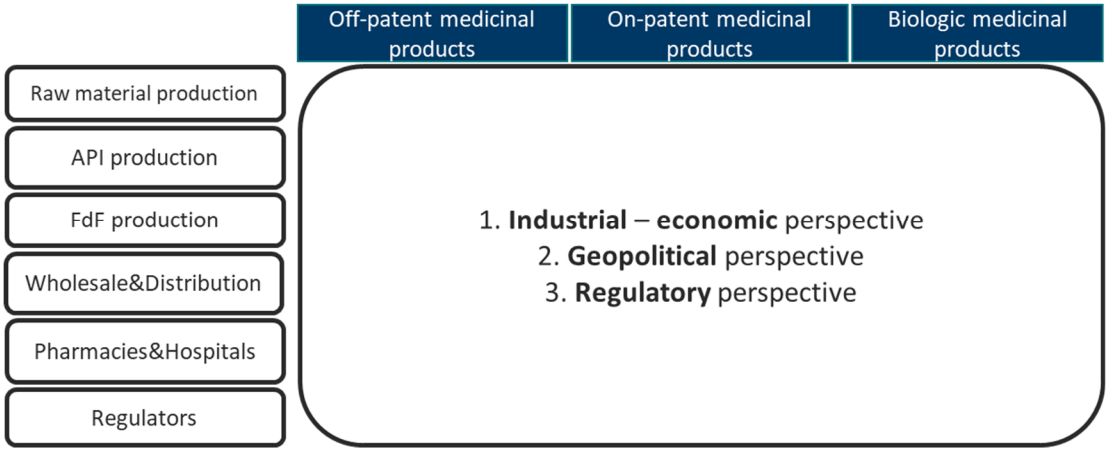


Figure 1. WS3's matrix approach.

A complex supply chain

Stakeholders first agreed on the high level of complexity of the medicinal products supply chain. In order to ease the reader in the understanding of the detailed report a short description of medicinal product (non-vaccine) is provided here.

Pharmaceutical supply chains can have a very complex structure with a global footprint with secondary manufacturing locations geographically separated from primary manufacturing locations.

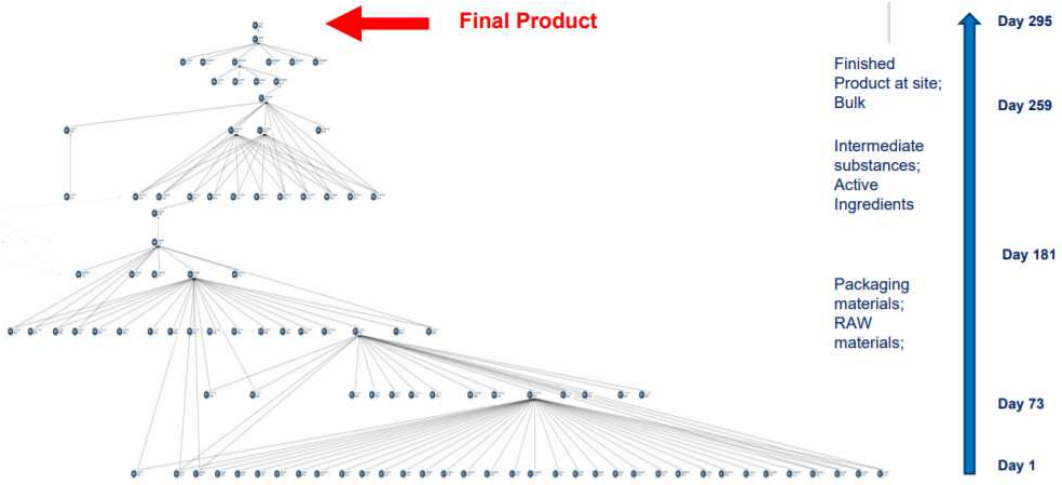


Figure 2. Illustrating scheme of the complex supply chain from raw materials up to finished dosage form.

The production process for all medicines requires a level of complexity based in part on the large number of "components:" For example, the production of some vaccine requires several hundred components. The very first of those components are the raw materials. There is a difference between a **raw material** and a **registered starting material (RSM)**. We call raw material any component or intermediate that is upstream the RSM in the value chain. The RSM is registered in the Active Pharmaceutical Ingredient File. Any change of the RSM requires a regulatory variation and a modification of the API regulatory file. Any step downstream RSM is subject to production under pharma Good Manufacturing Practices (GMP).

Raw materials are part of the structure of the final product or a specific reagent that enables functionality of the active principle. The production of the active pharmaceutical ingredient of a medicine is as follows:

A first raw material is functionalized with a specific reagent or reacts with another raw material to create an intermediate that becomes the raw material of a second step, and so on. After a number of steps, a Regulatory Starting Material is obtained that is finally transformed into an Active Pharmaceutical Ingredient (API). Next to the active ingredient, there are many other materials that are crucial to eventually produce a fully functional finished dosage form (FdF): excipients, devices (critical components), solvents, reagents, primary packaging materials etc.

The majority of medicinal products reaches patients across the EU through the healthcare distribution pathway, via manufacturer (pre-wholesaler), pharmaceutical full-line wholesaler, retail/hospital pharmacy/other health care facilities, pharmacy, to the patient. In some cases, a pre-wholesaler or third-party logistic provider (3PL) is part of the supply chain, linking the manufacturer to the pharmaceutical full-line wholesaler or, delivering directly on behalf of the manufacturer to hospitals and pharmacies.

While there are many actors in the supply chain, in the EU almost 60% of all medicinal products sold are distributed to pharmacies through pharmaceutical full-line wholesalers, whilst 33% are distributed by the manufacturer directly to hospitals and 8% directly to pharmacies (Figure 3).

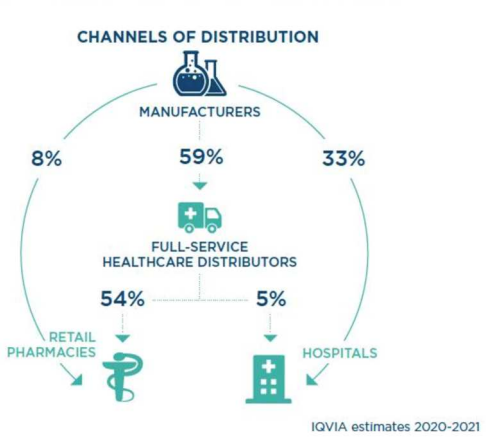


Figure 3. Channels of distribution for EU medicinal products.

- **Detailed reporting**

In the discussion, please highlight and elaborate on:

- *the most important aspects pertaining to each question that you identified in your workstream;*
- *the issues where divergences among stakeholders occurred. Present these by stakeholder group where consensus could not be reached;*
- *interlinks or synergies with other workstreams.*

Please specify/define the terms that you use as concretely as possible.

Please provide evidence to document your statements, such as sound examples of where transparency does to prevent vulnerabilities or does not exist resulting in supply chain vulnerabilities or where drivers of vulnerabilities have been identified and mitigated, tools used to support these activities.

Where useful, please structure your answers using sub-questions/sub-paragraphs.

***2.1** What constitutes the **vulnerability** of the supply chain (dependency/ number of suppliers/ complexity of the supply chain).*
Different stakeholders provided insights on their definition of a vulnerability based on their place in the supply chain. The following points were captured prior to concluding a uniform adopted definition. - The definition of vulnerabilities should, just like for shortages, look at the root causes of the problem. A vulnerability in the supply of medicines is a risk that might **cause challenges in access to medicines**. These risks in the supply of medicines can be different for different types of medicines. - Supply chain vulnerability is the exposure of the supply chain system to adverse events and changes, which could **compromise its robustness and efficacy**. - Vulnerability may lead to structural or temporary inability to consistently provide access to medicines to meet patient needs, bearing in mind that patient need is not consistent over time and necessary buffer stocks should be available in the supply chain. - Vulnerability in the context of the medicines supply chain can be defined as **the diminished capacity to anticipate, cope with, resist and recover** from external shocks to the supply chain. - Supply chain vulnerability can be defined as 'an exposure to serious disturbance, arising from risks within the supply chain as well as risks external to the supply chain. Consequently, supply chain risk management and mitigation aims at **identifying areas of hazards and implementing appropriate control to reduce risks**. Supply chain risk management is therefore best seen as the identification and management of risks within the supply chain and risks external to it through a co-ordinated approach amongst supply chain members and health authorities to reduce supply chain vulnerability as a whole. If the different elements of the contributions above are combined, we end up with the following definition:

"Supply chain vulnerabilities are those factors (internal or external to the supply chain) that could lead to structural or temporary inability to consistently provide access to medicines to meet patients' needs[2]. Vulnerable supply chains have a diminished capacity to assess, control and review the risk from changes compromising its robustness and efficacy. Vulnerabilities can exist within the end-to-end supply chain or can arise from external factors. These vulnerabilities need to be identified to allow for risk mitigations measures to be implemented, and structural actions in a coordinated and inclusive approach to be taken as appropriate."

***2.2** Are the supply chains of the products identified as critically vulnerable? What specific aspects cause/ lead to vulnerabilities? What are the drivers of these vulnerabilities?*

2.2.1. Industrial-economic perspective

Impact of tender practices

Tender practices using lowest price as the only criteria and poor lead time management destabilize manufacturing and disincentivise industry investments to mitigate vulnerabilities in the supply chain. Additional costs for API and FdF manufacturers, such as investments to further improve site reliability, e.g., additional manufacturing capacity, inventory policies, operational excellence programs, economical and EHS sustainability programs or safety stocks are disincentivised economically.

Generic markets are not designed to absorb these costs – they are designed specifically to reduce prices (i.e. in Germany average generic prices have been divided by 3 over the last 10 years from 17 cents Defined Daily Dose (DDD) to 7 cents DDD, accelerating further consolidation. In addition, tender practices in some countries (e.g., The Netherlands) do not take distribution costs into account. Instead of the often used 'winner-take-all' model, with price the only criterion, stakeholders are advocating for tenders that include several criteria, such as MEAT[3] criteria. However, this is not the only solution to solve all vulnerabilities. In the Netherlands according to hospital pharmacists, the hospital tender groups introduced multi-criteria tenders 4 years ago. That means that price is one criterion, but there are several others, such as safety for workers (e.g. stoppered vials score more points than glass ampoules that need to be broken), ease of administration to severely ill patients (e.g. ready-to-administer scores more points than formulations that require multiple compounding or diluting steps), hazards for the (aquatic) environment, etc. The tenders are for a minimum of 2 years. Since we these tender criteria were initiated however, hospital pharmacists argued that shortages increased every year. This example shows that a multi-facetted approach is needed to address the vulnerabilities in the European pharmaceutical supply chain.

Adapting the lead times for tenders to enable manufacturers to build up stock levels for generic medicines and implementing multiple tender winners instead of "winner take all" tenders would encourage the abovementioned investments. Some stakeholders indicated that there are

[2] There was an intense discussion among the stakeholders on whether 'in the absence of an appropriate buffer' should be included in the definition. In general, there were two views: one group argued that it should be mentioned because buffers can be a way to remedy vulnerabilities. Others argued that a definition of vulnerability should not arbitrarily include one measure (among many options) intended to deal with or prevent vulnerabilities. There were no other disagreements about the definition.

[3] The most economically advantageous tender (MEAT) criterion enables the contracting authority to take account of criteria that reflect qualitative, technical and sustainable aspects of the tender submission as well as price when reaching an award decision.

other countries (e.g., France and Denmark) that currently run tenders that include a wider set of criteria rather than a sole focus on price.

The off-patent prescription medicines value chain is more affected by cost pressure that generates a consolidation of the offer and increases dependences and vulnerabilities.

The off-patent sector represents the majority of prescription medicines by volume (close to 70%), is characterised by multisource competition, and reimbursement practices are designed to achieve low prices (for example through single winner tenders or reference pricing). This makes the off-patent segment a very price-sensitive procurer of raw materials that meet pharmaceutical industry standards. Therefore, it is important to consider the macro-level changes in raw materials supply for pharmaceuticals that may impact volume supplies or the cost of goods.

For off-patent medicines, the first vulnerability identified is the market-driven consolidation across the supply chain, in particular on raw materials and APIs. Due to cost-containment measures in reimbursement and poor tender practices, supply chain actors have been pushed to reduce costs further and have adopted outsourcing as one of the main strategic decisions for the primary (and secondary) manufacturing stage. As a result, the pharmaceutical industry has become dependent for some raw materials or APIs on only a few suppliers/countries (for some APIs for generic medicines there are only one or two manufacturers available worldwide). Although this strategy has reduced costs for healthcare systems, it has also created a vulnerability for the availability of medicines. With only a limited number of manufacturers available, there is more risk of shortages of medicinal products. Without a framework for incentives and a change in EU Members State policies, this situation will not improve. There is also "hidden" consolidation in the supply chain, e.g., several manufacturers may rely on the same supplier for an API or raw material. There may be greater consolidation affecting some raw materials (including raw materials before RSM). Addressing this is not necessarily/inherently a pharmaceutical strategy issue as such but would require input from DG GROW/European manufacturing base/industrial strategy.

Many raw materials are produced for a wide range of industrial uses and pharmaceutical manufacturing may be just a small share of the total volumes consumed. This means that large-scale suppliers of raw materials may prioritise supplies to other industries than pharmaceuticals or that active pharmaceutical ingredient manufacturers may need to rely on smaller, less responsive manufacturers. An illustrative example is the one of acetonitrile that is currently used in the pharmaceutical industry but that represents only small volumes compared to very high volumes consumed by the automotive industry. The latter industry is therefore often prioritize in case of tension.

On patent Medicinal products also experience a consolidation of the offer with less/limited effects

As for off-patent products there is also an effect of consolidation of the raw materials offer for on-patent medicines – even though volumes are much lower and quality is the primary driver for sourcing. While there is some visibility on sources for raw materials (especially until registered starting materials – RSM), there is more limited visibility between the companies on pre-RSM level of raw materials. The EFPIA survey suggests that there may be some levels of dependence, but members estimate it to be low. This issue cannot be fully solved by the private sector due to anti-trust rules. More clarity could potentially be addressed by implementing the already existing ICH provisions and with support from national/EU level and by regulators.

In addition, some on-patent medicines use very new processes and may be needed in very little volumes. Inherent to this sector is the presence of a single supplier for a particular

product. In addition, innovative medicines are more likely to require advanced technical equipment and a highly educated workforce for manufacturing of complex molecules. This can in turn constrain the possibility to make quick manufacturing adjustments. Depending on the complexity or novelty of the manufacturing process, there may also be a limited number of suppliers for some inputs for manufacturing, such as in cases where some of these inputs are patented as well.

The existing sources are not always EU sources, as we have a globally organized supply chain model. As for off-patent products, vendors do not supply exclusively to the pharmaceutical industry. Due to the low volumes, the attractiveness for said vendors to supply to pharmaceutical industry is also quite low.

Biologics pursue a risk mitigation approach to address the limited diversification possible.

Vaccines are highly technical biological products with complex and lengthy manufacturing, control and release processes. The outcome of an analysis of production lead time data at four major manufacturers shows that the majority of vaccines have production lead times (from the start of the production of the antigen until the release of the finished product by the manufacturer) ranging from 18 to 24 months. Complex multivalent vaccines (e.g., pertussis-containing vaccines, meningococcal and pneumococcal conjugated vaccines) have production lead times up to more than 36 months. Only very few vaccines have slightly shorter production lead times ranging from 12 to 18 months (e.g., monovalent hepatitis B vaccines). The production of some vaccines requires hundreds of raw materials, some of which are produced by only one supplier.

Vaccines Europe member companies argue that dual sourcing of all raw materials used for the production of vaccines is disproportionate and unfeasible due to the high number of raw materials needed, typically in the hundreds for a single vaccine, so that a single manufacturer may source thousands of raw materials across its product portfolio. To mitigate the risk of shortages, all vaccine manufacturers have internal business continuity plans designed to mitigate the risks related to the availability of raw materials. The continuity of supply for routine vaccines during the COVID-19 crisis (as reported on a weekly basis by EFPIA/VE to EMA and EC) has demonstrated the robustness of these business continuity plans. Typically, vaccine manufacturers produce the APIs (antigens) contained in their vaccines.

Today, 75% of Vaccines Europe (association of 14 vaccine companies operating in Europe) members production is taking place in EU, which represents 1.7 billion of vaccine doses annually used to immunize populations worldwide. Moreover, the ECIPE (2020) study shows that 86% of all global vaccine exports originated in the EU in 2019.

The worldwide demand for routine vaccines is extremely unpredictable, and rapid modulations can be required in response to multiple factors[4]. Volatility in global demand may be due to changes in epidemiology (e.g. outbreaks, pandemics) or changes in national immunization programs (e.g., large catch-up programs). The demand at the level of one manufacturer is also impacted by the capacity management of other manufacturers, for instance when another manufacturer enters the market, increases or decreases its capacity, or reallocates its capacity outside Europe (e.g., due to unsustainable conditions related to demand, price). Also, when one manufacturer experiences a stock out situation other

[4] Juvin P. Complexity of vaccine manufacture and supply. In: Michel JP., Maggi S. (eds) Adult Vaccinations. Practical Issues in Geriatrics. Springer, Cham. DOI: https://doi.org/10.1007/978-3-030-05159-4_1

manufacturers producing a vaccine that prevents the same disease(s) will face an unexpected increase in demand. Procurement practices also have an impact on demand (on/off effect of tenders), as discussed below.

Long-term and accurate forecasting of vaccine worldwide demand is a critical factor to achieve success when launching new vaccines or sustaining supply of established vaccines, especially in a complex and highly regulated environment. Increasing capacity is often a challenge. Facilities are usually custom-built for a specific product because many vaccines require unique manufacturing processes and techniques. In order to obtain accreditation of a new building by the various regulatory bodies, the steps taking the most time are validation of new equipment and launching activities to demonstrate the product quality. The total time to design, build, validate, get regulatory approvals and start commercial manufacturing and distribution in a new facility is between 5 to 10 years[5].

CASE STUDY: Plasma and Plasma Derived Medicinal Products (PDMPs)

1. Introduction and overview

Plasma-Derived Medicinal Products (PDMPs) are a unique class of biological therapies used to treat patients with rare, often genetic and severe, potentially life-threatening conditions. These include primary immunodeficiencies (PID) and certain secondary immunodeficiencies (SID), bleeding disorders such as haemophilia A and haemophilia B, alpha-1 antitrypsin deficiency (AATD), and other orphan diseases associated with the absence or malfunction of specific proteins.

PDMPs are the only therapies solely derived from human plasma, a scarcely available starting material. The entire process from plasma donation to patient is complex, labour-intensive, time-consuming and costly. The manufacturing process takes 7 to 12 months from the collection of plasma until the administration of the final product to the patient, and the manufacturing costs which include growing plasma costs, are the largest share (ca. 60%) in the plasma value chain, leaving no room for cost reductions[6]. Furthermore, given the starting material is human plasma, the processes for plasma donation and PDMP manufacturing are separately regulated to ensure patient and donor safety. All these elements make PDMPs thus unique. Yet these treatments face numerous vulnerabilities, to include economics with reimbursement constraints, as well as regulatory and geopolitical perspectives.

As to the EU policymakers' desire to bring back critical medicines manufacturing to Europe, the PDMP sector has already a strong manufacturing footprint in the EU with 17 commercial and three not-for-profit facilities (see below link)[7].

However, according to PPTA, insufficient plasma collection in Europe is the key vulnerability issue: 70 percent of plasma needed in the EU is collected in the EU, despite an increase in clinical need for PDMPs, there being thus a clear trend towards a growing reliance on plasma imports from the US. In the absence of policy changes, this trend is expected to continue, given the growing clinical need of PDMPs of about 8% per year. The insufficient European plasma collection as well as the dependency on US plasma have been identified as an important concern by the EU Commission in its Evaluation Report on the functioning of the EU Blood

[5] Preiss S, Garçon N, Cunningham AL, Strugnell R, Friedland LR. Vaccine provision: Delivering sustained & widespread use. Vaccine. 2016 Dec 20;34(52):6665-6671. doi: 10.1016/j.vaccine.2016.10.079.

[6] Vintura EU White Paper on plasma and PDMPs 2020

[7] Global European Interactive Map: https://prezi.com/view/hXBhxDEIo8R2cavcduIk/

Directive[8]; This was also addressed in the Commissions Targeted stakeholder consultation on the Blood Directive revision for inclusion in EU's strive for an "open strategic autonomy" on starting materials for medicines.

2. Raw material collection side: The vulnerabilities of plasma collection

The root causes driving the vulnerability of insufficient plasma collection lay in the following barriers:

- Lacking recognition of the specific nature of plasma and PDMPs and their ecosystem by EU and Member states with appropriate legal frameworks and policies.
- very limited establishment of dedicated plasma collection (plasmapheresis) programs in EU Member States. Only four EU countries (Austria, Czech Republic, Germany, Hungary) allow both public and private centres, featuring dedicated plasma collection (plasmapheresis) programs.

Further to this, there is overall an unnecessary regulatory burden as to plasma collection that do not take into account technological and scientific developments having occurred since 2002 when the EU Blood Directive was adopted. Also, trade agreements have failed to consider plasma as starting material for PDMPs, leading to insufficient regulatory cooperation and harmonisation with the US, such as EU-US MRA (Mutual Recognition Agreement) not covering GMP inspections. Plasma and PDMPs are currently not eligible for being included in the MRA, due to EU-US prioritization issues but also because the US and the EU do not have a common or similar definition as to plasma for manufacturing.

3. Finished product side: Vulnerabilities of PDMPs

Continued cost-containment measures and reimbursement constraints applied to PDMPs which do not recognize the intrinsic specificities of the PDMP sector and thus apply a "one size fits all" approach, threaten the ecosystem of the PDMP industry structure. This increases the supply chain vulnerabilities which ultimately limits even more patient access which is already now under pressure.

Further to this overview on vulnerabilities as to PDMP and plasma collection, more details are attached in the **ANNEXE C**.

[8] EU Commission Evaluation Report on EU Blood Directive swd_2019_376_en.pdf (europa.eu)

2.2.2 Geopolitical perspective

A dependence for some raw materials for some sectors with limited possibilities of diversification

A recent Commission study for the Industrial Strategy for Europe indicates that producers in India and especially China[9] have progressively taken over raw materials production for off-patent medicines due to cost pressure in pharmaceutical procurement and reimbursement. These countries also benefit from lower wage and lower manufacturing cost, as well as lower standards for social and environmental regulations, giving them a competitive advantage in terms of cost. Cost pressure is also pushing further consolidation of suppliers of raw materials and the overall dependency of Europe has increased as a result. There are serious concerns that this consolidation and increased reliance on a number of Asian suppliers exposes European supply chains to vulnerabilities. EFCG members argued that achieving a level playing field for any supplier of any region would positively balance the situation and. increase the reliability and sustainability of supplies. economic sustainability of suppliers. This could be achieved in part by requiring suppliers to meet European EHS standards.

There was agreement among the different stakeholders for a call for diversification of sources to ensure security of supply. However, diversification creates additional costs and administrative burden. A blanket call for dual sourcing was not supported by stakeholders, who pointed to a number of problems. These include the fact that some materials will only be available from a single supplier, or that certifying an additional supplier as required by law leads to additional complexity and costs. There was instead support for manufacturers to pursue a risk-based approach to identify components for which dual sourcing may be advisable. Participants also stressed the importance of ensuring that sustainability of suppliers be taken into account, incorporating both environmental and economic factors, although there was a lack of clarity about how to ascertain the economic sustainability of companies.

EFCG members argued that in addition to manufacturing capacity having been relocated from Europe to Asia, another consequence of the tender and purchasing practices focusing on price, is the disappearance of some technologies and processes in Europe. The potential of diversification is then limited due to the lack of available capabilities of some process and technologies in different regions. For raw materials production, technologies missing in whole or in part in Europe are listed below:

- Nitration[10]
- Cyanation[11]
- Fluorination[12]
- Iodination[13]
- Basic steroids
- Functionalized steroids

[9] COM 2021/1 Peptide supply chain

[10] COM 2021/2 Nitration case study

[11] COM 2021/3 Cyanation case study

[12] COM 2021/4 Fluorination case study

[13] COM 2021/5 Iodination case study

The list of missing technologies is not exhaustive and needs further investigation by an appropriate market mapping.

Most of these technologies are hazardous or require handling of harmful reagents or have a significant environmental impact. Due to cost pressure, they have over time relocated to regions with lower EHS standards, which has given them a competitive advantage versus Europe. For example, a key building block used in the production of multiple medicines and resulting of fluorination is only available in China.

In some cases, the technology exists in the European Economic Area (EEA) but capacities are not dedicated to pharmaceutical industry needs, so that they do not meet the very high standards required in terms of production range, costs and quality. Nitration illustrates this situation well, with capacity available in Europe but only China has capacities dedicated to pharma.

Where Europe depends on other countries for a large share of imports of raw materials, its policies should consider the macro-level policies changes in those countries that could impact the supply of those raw materials to European producers. These include:

- The risk that other countries could prioritize their own API and medicines suppliers in a crisis situation (e.g., through export restrictions) (such as the examples of India or the USA during the COVID-19 pandemic).
- The unwillingness of suppliers to submit relevant data to EU regulatory authorities to protect their intellectual property although EU regulators keep such information confidential.
- The stricter enforcement of environmental, health and safety rules that may lead to a sudden closure of manufacturing sites supplying European API or medicine manufacturers, as experienced recently in China with the implementation of the "Blue Sky/Blue Water" policy.

EFPIA highlighted that European policies should also consider the potential consequences for European producers who export to those countries. These include:

- The need for EU economic diplomacy to sign international agreements for cooperation as one of the international solutions to increase security of supply – like the EU has done in June 2021 when it signed a 'raw materials agreement' with Canada.
- The need for the EU to take pro-active pro-trade measures at the WTO through the Trade and Health Initiative (TAHI) to remove barriers to trade in (inputs for) medicines, medical equipment and personal & protective equipment.
- The risk that other countries could take import restrictive measures (the EU is at risk of taking under the guise of 'strategic autonomy') fundamentally hurting EU exports. Because the EU is the largest exporter of medicines and vaccines, other country's import restrictions will hurt the EU most of all countries in the world (ECIPE, 2021).

These macro-level changes are already impacting EU supplies of raw materials and the EU should consider the risks and opportunities afforded by these changes. The most important challenge is that there are fewer suppliers of some raw materials needed for API manufacturing for off-patent medicines, which in turn increases their cost. This creates an opportunity for the EU to sign global bilateral and multilateral agreements to secure supply and to encourage more production of raw materials (more chemical production) in Europe through an appropriate and sustainable industrial policy (i.e., technology support for green production processes in Europe that could be cost competitive), through revising tender procedures to focus not only on price, through creating a stronger set of incentives for R&D and production in Europe, and to acknowledge that higher raw material costs will inevitably increase the cost of goods for medicines. This can be a threat to medicines supply if there is a

consolidation of manufacturing or a risk of marketing authorization withdrawals due to loss of commercial attractiveness. There could be policies to either offset these cost increases through more efficient regulation of medicines (for example implementing standards such as ICH Q10 and Q12 or via signing international supply agreements like the raw materials agreement with Canada) or to factor these higher costs in medicines procurement and reimbursement. In doing so, the EU could increase its attractiveness for more production in Europe and ensure a level playing field so as to prevent further supply chain consolidation.

Another factor to consider is the risk of natural disasters that may impact large chemical production centres (often located near oil producing regions like Texas or seaports where oil is imported) with knock-on effects on the supply of raw materials or primary packaging materials to API or medicine manufacturers. In these circumstances, manufacturers may need to rapidly switch to alternative suppliers.

Off patent active principles and dosage forms also exposed to dependencies to China and India and requesting diversification

The off-patent market, as detailed in section 2.2.1: industrial-economic perspective, suffers from continued consolidation of manufacturing operations (in the EU and globally). As a measure to cope with this, many pharmaceutical operators have adopted outsourcing as one of the main strategic decisions for the primary and secondary manufacturing stage. As a result, a number of are currently produced in only a few countries (e.g., China, India) by a very small number of suppliers. A study conducted by Mundicare showed there is no European production for 94 APIs.

Depending on the level of consolidation of the supply; export bans or other limitations to imports or exports of pharmaceutical elements or finished products, or prior authorization/notification of exports can leave European supply vulnerable. One of the possible risk mitigation options is geographical diversification of suppliers which, depending on the level of consolidation and associated risk, would decrease vulnerabilities in the supply chains.

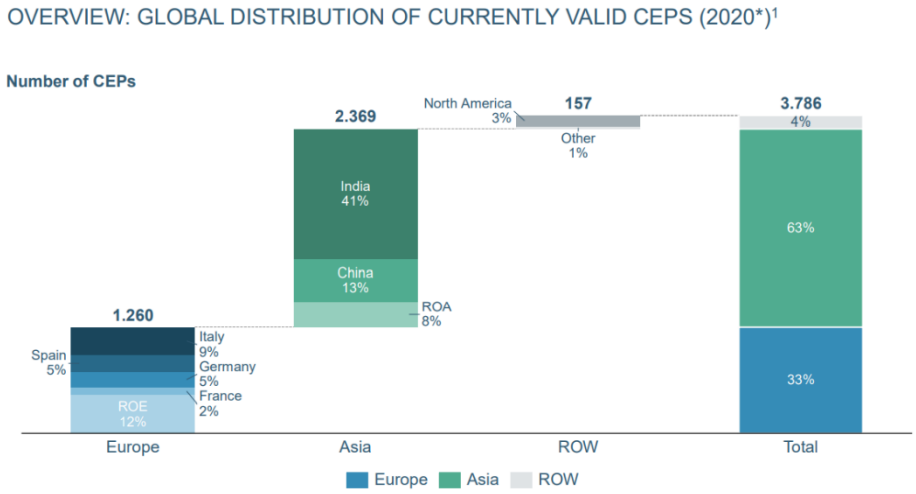
This high degree of consolidation was clearly visible for some specific molecules in two events occurring in the past years:

- The sartan referral caused by nitrosamines indicated the high consolidation of the supply chain based on very few Asian API manufacturers for some Angiotensin-II-receptor antagonists (sartan) intermediates and active substances.
- During COVID-19, the supply of ICU products required to treat mechanically ventilated patients came under pressure with few suppliers able to meet the demands for EU patients. Regulatory flexibility was required to rapidly upscale the production and to allow the importation of ICU medicinal products to countries where marketing authorisations by some manufacturers had been withdrawn in the past.

China and India are increasingly competitive in API and FdF manufacturing globally. Looking at new approvals of CEPs between 2000 and 2020, Asia significantly outperformed Europe: Asian manufacturers increased the number of their CEPs from 183 to 2,369, while European manufacturers grew from 348 to 1,260 CEPs. Also the share of China in supplying Europe with APIs in volume terms has gone from 12% in 2010 to 17% in 2015 and 23% in 2019 (ECIPE, 2021).

However, the data on the dependencies of the manufacturing chain for European medicinal products indicates that this is limited and shows that **our industry is still a major producer**

of medicines in Europe. Today, European manufacturers focus on specific APIs (e.g. low production volumes, complex production processes).



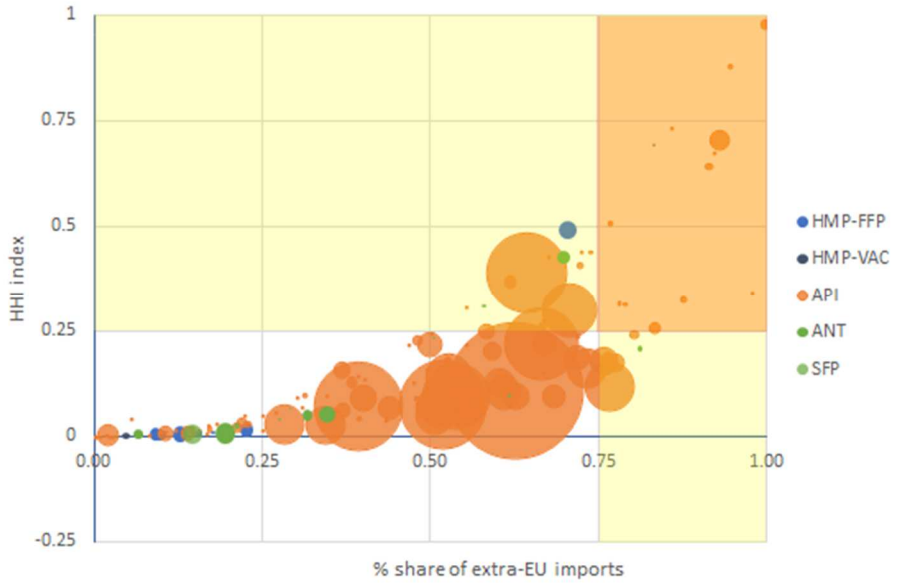
An in-house survey from Medicines for Europe members (completed in 2020) related to in house API manufacturing operations indicate that its members have 58% API production still in EU, 26% in Asia, 5% in USA and 11% in the rest of the world. An additional in-house survey on FdF manufacturing, showed that on average, 67% of FdF is manufactured in Europe, 16% in China, 13% in India and 6% in ROW.

The ECIPE (2020, 2021) studies show a similar pattern for the pharmaceutical industry as a whole, based on Eurostat (2019) statistics: 59% of APIs in volume terms come from Europe, 23% from China, 6% from the US and 3% from China. In value terms and for finished pharmaceutical products the EU share is much higher (ECIPE, 2021).

On patent and innovative medicines mainly relies on European sources of APIs

As for off-patent products, concentration in a particular region or country can have a negative impact on production for some materials. Regional concentration opens the door to the strategic use of exports and export controls (such as in response to a health crisis).

Nevertheless for the on-patent medicines the situation is different. Cost pressures have not led to relocations to Asia, and the EU has remained very resilient. The EU produces 51% of all APIs needed for production itself and imports materials for 53% of what is imported from Europe. The US, not China or India, is the most important non-EU supplier for APIs needed for EU finished medicines production as part of a deeply integrated transatlantic supply chain that creates strong bilateral leverage (ECIPE, 2020 and 2021). The study - further supported by EFPIA survey evidence – shows that only 6.1% of EU imports in value terms and 0.8% in volume terms for the entire industry (generic and innovative) has a high level of dependency (determined as the combination of a high level of extra-EU imports and low level of supplier concentration). See Figure 4. From Figure 4 is also becomes clear that diversifying supply (i.e. reducing the Herfindahl-Hirsch Index of supplier market concentration) is more relevant than reducing imports.



Source: ECIPE (2021) based on Eurostat (2019)

Figure 4: Degree of EU dependency in medicines (volumes, 2019)

This means that the EU innovative medicines supply chains remain highly resilient also regarding in raw materials and API inputs (EFPIA, 2021).

Based on Eurostat data, the overwhelming majority of APIs used in the production of patented medicines are produced in Europe, as is the majority of medicines. The EU imported pharmaceutical products with a total value of EUR 286 billion in 2019; 81% came from the EU itself. The majority of APIs used in the production of medicines also originates from Europe; based again on Eurostat data, the figure for volume is 59%. While aggregate figures do not reflect the level of variation across specific APIs or medicines (some products might be highly dependent on one region or a few suppliers, while others are not), they do highlight the fact that Europe's position as a producer and exporter of medicines remains particularly strong. The EU accounts for 63.8 percent of all medicinal products exported worldwide (WTO, 2019), although as noted there would be value in identifying those cases where there is a high level of dependency on very few suppliers remains.

Vaccines are also Euro-centric for principles and finished dosage form production.

Figures for vaccines reflect even more strongly Europe's strength as a producer. 84% of vaccines used in Europe in 2019 originated from Europe; the US (11.2%) and the UK (2.8%) were the next two largest suppliers.

2.2.3 Regulatory perspective

No additional regulation requested for raw materials.

Neither regulators nor industry saw value in extending regulatory requirements for raw materials beyond the current requirements - meaning that unregistered starting materials should remain so.

However, manufacturers and suppliers agreed that it is critical to work on regulatory convergence and to decrease regulatory complexity. Any change of supplier or technology requires seeking approval for the variation. The treatment of such a change by the authorities is time-consuming and costly, and makes it financially challenging for manufacturers to diversify their suppliers. Modernising the EU variations system and leverage the use of

telematics could strengthen supply chains.

When talking about the regulatory complexity, private sector stakeholders stressed that one should take into account that it is not just health and medicines regulatory pathways but also environmental (e.g. REACH for materials used in pharmaceutical manufacturing), which each have their own requirements, increasing the regulatory complexity. In addition, national regulations (or their interpretations) add complexity to supply chain management and reduce flexibility to adjust to normal and crisis demand changes.

In addition, some products like biologics require time to allow adjustments in the manufacturing process or the volumes produced. These manufacturing processes are based on highly technical equipment and need highly educated manpower to operate. Scale up or batch size changes also require regulatory approvals. It is proposed to have regulatory flexibilities especially in time of crisis. Some products require 60K variations, 3K paper based. Adjustments may be technically possible but cannot be implemented due to needed regulatory approvals. When looking at the vulnerabilities of pharmaceutical supply chains, it is important to keep this complexity in mind.

From the perspective of 50 years of pharmaceutical legislation, enormous progress has been made to achieve better quality, safety and efficacy of medicinal products. Significant effort has been made to build a strong European regulatory structure and harmonized European standards. However, the current regulatory systems are an administrative and financial weight for companies, and their implementation does not always support the objectives of timely access and operational efficiency. Although participants from pharmaceutical industry stressed that regulatory bodies are not responsible for shortages, they argue that the framework does not sufficiently allow for innovation, diversification and standardization.

In section 2.2.1 (industrial – economic perspective) the problem of consolidation and extreme cost pressure was highlighted. The ever-increasing cost of EU regulation adds on to that pressure. Low-cost medicines markets are not designed to absorb these costs (the cost of manufacturing and compliance is at odds with constant reduction in prices). Some pharmaceutical manufacturers argued that the current system of financing variations does not encourage the adoption of improved cost-effective mechanisms as long as NCAs are paid by number of variations processed. by Marketing Authorisations. Some regulators disagreed, stressing that the need for them to abide by strict timelines provides a strong incentive to seek further efficiency, and that such efforts are underway in a number of countries. Only a few authorities have introduced flat or annual fees to reduce the administrative cost. Some stakeholders argued that the Dutch model with annual fees covering all variations, could be replicated elsewhere.

Supplier and pharmaceutical industry representatives stressed that the current regulatory system, while providing a high-quality standard, tends to be a rigid one. Changes cannot be introduced quickly, and there is little room for flexibility when needed. In their view, regulators need a more efficient system to process the information in the regulatory dossier in such a way that preserves the high European quality standards, but also can prevent and act on vulnerabilities in the supply chain by creating more agility.

Variations

As identified in the Regulatory Efficiency Report prepared by Medicines for Europe in 2015, there is an increase in the number variations filed by MAH which concern solely API information. Based on member companies' feedback, up to 60% of variations (related to quality) submitted by Marketing Authorisation Holders (MAHs) are related to changes to the API. The report show that Marketing Authorisation Holders are dedicating a large amount of their resources to API life-cycle management (submission of API related variations). For outsourced APIs, nearly 2 out of 3 quality variations relate to the API. In addition, given the high level of API outsourcing in the generic medicines industry, most of these changes will be filed multiple times through each and every 'user' of the concerned API. Based on data gathered from 2010-2018, the number of variations per MA and per year has increased about 75% since 2010 (see figure 5).

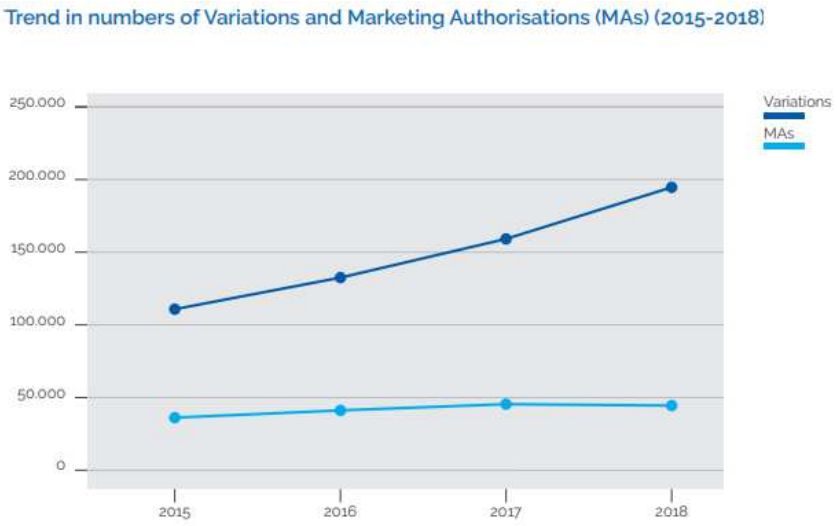


Figure 5. Increase in variations compared to increase in MAs between 2015 and 2018.

This puts significant pressure on the efficiency of regulatory operations and adherence to timelines in view of limited resources of both authorities and industry. It is urgent to look at a new approach to manage post-approval changes without compromising on the appropriate regulatory oversight or impacting the quality of the product. Particularly optimizing the process and reducing the average time spent on processing variations (mainly Type IA) could **deliver a real efficiency gain for both regulators and industry.** By reducing the average time spent on the Type IA notification process as well as lowering the volume by changing the way of reporting, approximately 65% of current efforts could be saved according to vaccines manufacturers. This same conclusion is made by other sectors of the industry[14]

Vaccines manufacturers stressed that vaccines are biological medicinal products with a long lifespan, during which many CMC changes are made to the marketing authorisation dossier, with many of these changes categorized as Type IB or II variations. Additional complexity arises from the fact that i) a single change may impact several vaccines (e.g. if an antigen is shared in different combination vaccines or if a raw material is used in the manufacturing process of several vaccines), and ii) the same vaccine may be impacted simultaneously by several changes. Considering the high degree of complexity and time needed for manufacturing, controlling and releasing vaccines, it can reasonably be assumed that vaccines

[14] https://aesgp.eu/content/uploads/2020/09/ESE_2019_Medicine-for-Europe_AESGP_Variation_WEB.pdf

represent the category of medicinal products which would benefit the most from a revision of the EU variations system. Such a revision would help securing the supply of vaccines in the EU and worldwide.

The COVID-19 pandemic posed unprecedented challenges to the continuity of medicines supplies. Therefore, targeted regulatory flexibility measures were needed to minimise shortages risks**,** by for example permitting companies to swiftly source starting materials, reagents, intermediates or active substances from alternative suppliers, or add new manufacturing sites for scale-up. Regulatory flexibility in manufacturing, GMP/GDP and labelling, as allowed during COVID-19, could be assessed and introduced for medicinal products even outside a crisis event to enable industry to move medicines to the effective patient demand in Europe. Related to pharmaceutical supply chains, COVID-19 crisis showed the need to:

- Introduce more flexibility on medicinal product labelling and use of e-Leaflet
- Adopt a notification process instead of traditional variation process for some registration files changes,
- Allow for more electronic reporting/ digital tools for regulatory activities. It is proposed that the digitalisation of the regulatory system in Europe should be progressed

CASE STUDY: Nitrosamines review

Important regulatory reviews have had a big impact on regulatory compliance costs for older medicines. One growing challenge in regulation concerns the general approach to risk. For example, the discovery of out of specification nitrosamine impurities in sartan and other products led to a full-scale review of all medicines across the EU Examples are for nitrosamines risk assessments related to chemical medicinal products affected about >79.000 marketing authorisations leading to >12.500 API manufacturers and >37.000 'other' sources to be assessed by the members of Medicines for Europe and for the members of Medicines for Europe an expected manpower cost of +500.000 man-hours. While it is justified to assess the risk of nitrosamines in these circumstances, the EU could have explored other avenues – notably international cooperation in the context of the ICH to align on risk impurity thresholds and on the most efficient process to assess this in medicinal products.

Other regulatory requirements leading to supply vulnerabilities

Annexe B provides detailed information, including evidence, on three sets of regulatory requirements leading to supply vulnerabilities in the EU:

1. global regulatory requirements for post-approval changes,
2. EU labelling/packaging requirements,
3. vaccine batch release by Official Medicines Control Laboratories, which represent.

It should be noted that regulators themselves recognises the role of impact of global regulatory requirements on supply in a recent communication of the International Coalition of Medicines Regulatory Authorities: *"ICMRA recognizes that regulatory authorities can gain efficiencies by developing common procedures, guidelines, requirements, and interoperable infrastructure that would facilitate the timely sharing of information among regulators on changes occurring within the supply chain. This may include reliance on the assessments of other regulators*

reviewing those changes. ICMRA considers that this could lead to more timely availability of medicinal products for patients by shortening approval timelines"[15].

2.2.4 Wholesale and distribution vulnerabilities

The landscape of medicines distribution in the EU

Pharmaceutical full-line wholesaling activity consists of the purchase, warehousing, storage, order preparation and delivery of medicines. Pharmaceutical full-line wholesalers carry and distribute the complete assortment of products in range and depth within the framework set by the authorities and the market to meet the needs of those with whom they have normal business relations and deliver all medicines in their geographical area of activity on the same day or within 24 hours. Pharmaceutical full-line wholesalers provide working capital and extended financing services, funding of stock and receivables of pharmacies and health care professionals.

In most EU Member States, pharmaceutical full-line wholesalers must also comply with Public Service Obligations (PSO) or carry a Public Service Function as foreseen by Article 81 of Directive 2001/83/EC, as amended in 2004 by Directive 2004/27/EC, introducing an obligation for the Member States to implement the following measures:

The holder of a marketing authorisation for a medicinal product and the distributors of the said medicinal product actually placed on the market in a Member State shall, within the limits of their responsibilities, ensure appropriate and continued supplies of that medicinal product to pharmacies and persons authorised to supply medicinal products so that the needs of patients in the Member State in question are covered.

Apart from the provision of Art. 81 2 of Directive 2001/83 EC, many Member States have enshrined a separate PSO on wholesale distributors (i.e., Belgium, France, Germany, Greece, Italy, Slovenia, Spain, Portugal etc.). This obligation aims to guarantee that through a permanently available, adequate range of medicinal products, referred to as buffer stocks, the requirements of any specific geographical area are met and requested medicinal products can be delivered in a timely manner across the territory.

GIRP argued that there exists a significant mismatch between the current legal framework and the correct legal interpretation [16] in most EU Member States. The different interpretations have been analysed in a study commissioned by the European Commission and carried out by the consultancy Matrix Insight 2012[17]which states that "generally the public service obligations relate to the obligation on wholesalers and distributors to supply the domestic market. In many cases they do not apply to manufacturers supplying distributors."

The European Commission "Paper on the obligation of continuous supply to tackle the problem of shortages of medicines" furthermore presents measures adopted in the Member States for the implementation of Article 81 Directive 2001/83/EC.

[16] http://icmra.info/drupal/strategicinitatives/pqkms/statement

[17] https://ec.europa.eu/health/sites/default/files/files/committee/73meeting/73plus/study_report.pdf

According to the aforementioned paper, the legislation requires EU Member States to:

- impose Public Service Obligations
- place them separately on manufacturers and distributors within the limits of their respective responsibilities

By imposing PSOs on both levels of the distribution chain, GIRP argued that the directive creates in turn an obligation for manufacturers to supply medicines to the distributors (who are bound by PSOs). Manufacturers, on the other hand, argued that they supply in line with patient need for Member States. Although pharmaceutical full-line wholesalers in EU Member States have the right to be supplied, manufacturers can choose to directly supply persons authorised to dispense medicinal products to the public.

EFPIA and its member companies stressed that quota systems which can be implemented by MAHs are meant to improve patient access to treatments. In their absence, orders of wholesalers would be fulfilled on a first-come, first-served basis. This in turn could increase the risk of the MAH being unable to supply other wholesalers in accordance with their share of the market, which they argued would jeopardise a fair and non-discriminatory supply of all wholesalers. Furthermore, EFPIA pointed to the fact that quotas are compliant with EU Treaty provisions.

Supply chain vulnerabilities at the national level

GIRP argued that the discrepancies in implementation of Article 81 at EU MS level have proven to create certain vulnerabilities impacting the supply of medicines on national level. MAHs hold the exclusive capacity to increase the supply of medicines in EU markets (apart from compounding, which also requires the necessary APIs and is of negligible quantity). Therefore, it is essential that future patient needs (epidemiology data, public health programmes) are calculated by authorities and communicated ahead of time, in coherence with manufacturing cycle-times (e.g. up to 3 years for vaccines) to allow manufacturers to forecast demand for medicinal products.

It is important to keep in mind that upstream shortages can only be solved at EU-level, not at national level.

According to an analysis conducted by GIRP[18] and based on public shortages databases where they are available in the different EU MS, shortages at the national level occur in larger and higher priced countries due to production/quality problems and in smaller, lower priced countries mainly due to discontinued marketing/market withdrawals, but also due to resale from countries where prices for medicines are lower to those where prices are higher.

An EFPIA survey indicates that the most commonly declared root causes of shortages across countries are:

- Insufficient production capacity or high demand
- Unforeseen market fluctuations, e.g. unexpected surge in demand
- Manufacturing and production issues
- API or other raw material supply issue

Regarding vaccines specifically, a survey conducted by Vaccines Europe found that the main root causes of vaccine shortages result from factors **which are largely beyond the control of vaccines manufacturers**. Among the following six main causes of vaccine shortages

[18]http://girp.eu/sites/default/files/documents/causes_of_supply_disruptions_across_europe_april_2020_-_read-only.pdf

identified, three are related to regulations:

- Long and complex vaccine manufacturing
- Complex regulatory life-cycle management worldwide
- Diversity of presentations, packs and labels in Europe
- Inefficiencies of testing by national control laboratories worldwide
- Unpredictable and increasing global demand
- Suboptimal procurement practices and funding of immunization programs

Both root causes 3 and 6 are linked to vulnerability of the supply chain at the national level. The suggested ways to address these root causes, as per the joint views of AESGP, EAEPC, EFPIA, GIRP Medicines for Europe and Vaccines Europe are:

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

Lack of timely information of anticipated shortages

There are no shortages-warning systems in place to connect authorities to all supply chain stakeholders, including doctors, to warn about upcoming shortages and to rationalise supplies before the shortage actually occurs. Some new tools were recently put in place in a few MS to bridge this information gap. In Europe this is only applicable for centralized procedures. In some countries (Portugal, Italy (for MAH's with penalties when no notification has been done or too late), the Netherlands (without penalties)) the suppliers are required to warn of shortages. Penalties might create a risk for MAHs and manufacturers to discontinue manufacturing when there are low margins (risk of penalty vs benefit). Every country has different regulations on warnings, but information should be reported in a harmonized way in order to allow consolidation at European level.

Right-to-be-supplied by manufacturers in some MS

Only in Belgium, France, Germany, and Portugal do pharmaceutical full-line wholesalers (full-service healthcare distributors) have the right-to-be-supplied. These countries distinguish the activities of full-line wholesalers from the ones of other distributors (short-line wholesalers), by ensuring that full-line wholesalers serve as a one-stop shop for pharmacies and other healthcare professionals.

EFPIA was one of the stakeholders who stressed there can be numerous causes for shortages resulting from a range of vulnerabilities, and that these in turn can be driven by actors all along the supply chain. These stakeholders pointed to a join paper released[19] in 2019 that found that shortages could be driven by regulatory, manufacturing & quality, economic, and supply chain considerations. In this context, EFPIA called for use of data generated by the network of national repositories set up in the context of the Falsified Medicines Directive to provide additional intelligence for monitoring shortages. EFPIA argued that this data could supplement information already provided by MAHs on manufacturing and quality related supply disruption to National Competent Authorities.

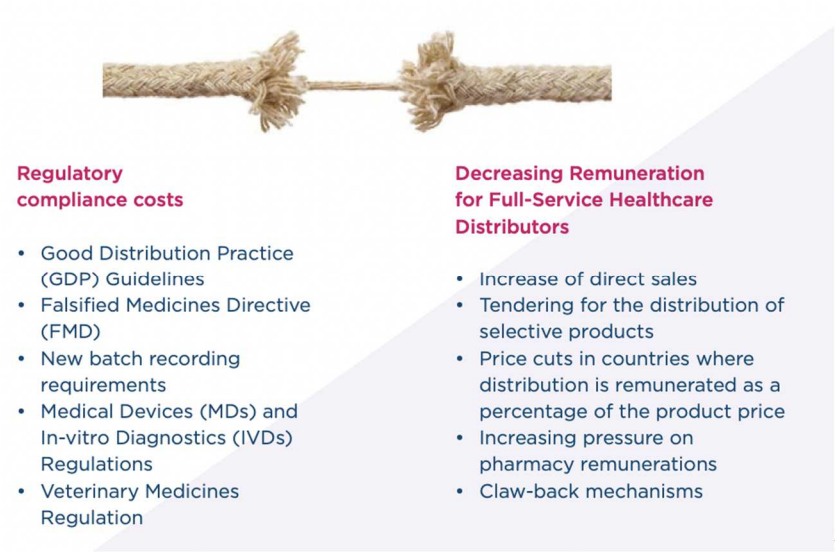
[19] https://www.efpia.eu/media/413378/addressing-the-root-causes-of-medicines-shortages-final-051219.pdf [Joint paper from AEGSP, EAEPC, EIPG, EFPIA, GIRP, Medicines for Europe, and Vaccines Europe.]

Others, including GIRP[20], EAHP and ESOP, however maintained that data generated by the system should not be expanded beyond its initial intended use of preventing falsified medicines from entering the legal supply chain. In particular, GIRP argued that data uploaded in the EMVS would overestimate available supply of medicines and underestimate demand at the national level.

Constant squeeze on margins and remuneration for distribution endangers the timely distribution of all medicinal products.

In most EU MS, margins for medicines' distribution are regulated by law and remuneration can according to GIRP often be extremely low. GIRP further argued that these low margins do not cover the costs of current service levels and could compromise the continuous availability of all medicines for patients into the future.

GIRP further argued that unlike MAHs, full-service healthcare distributors (full-line wholesalers) have a legal obligation to carry the full range of medicines according PSOs and cannot de-list or discontinue distribution of loss-making medicines for their portfolio. It is therefore important that all needed medicinal products are kept within the distribution structure of full-service healthcare distributors. This would ensure according to GIRP that even very low-priced medicines are distributed in exactly the same quality and speed as high-priced medicinal products.



[21]

National buffer stock on wholesale level (expressed in days/weeks of usual demand, in several EU MS. determined by PSOs).

GIRP also stated their belief that full effective implementation and enforcement of Article 81, paragraph 2 of the Directive 2001/83/EC could be a way to ensure that appropriate levels of buffer stocks are maintained at both national and EU level in order to help mitigate critical medicines shortages and effectively prepare for health emergencies. GIRP further argued that such measures should provide for adequate financial protection in the event of unnecessary stock. For the holding of buffer stocks, the principle of FEFO (first expired first out) should be applied.

[20] http://girp.eu/sites/default/files/documents/girp_position_on_use_of_emvs_for_monitoring_of_shortages_-_updatedfeb21.pdf

[21] http://girp.eu/sites/default/files/documents/200069_girp_annual_report_2019-2020-v6.pdf

2.2.5 At the end of the chain: Pharmacies, hospitals and patient input

Insufficient buffers stocks to absorb disruptions

According to the hospital pharmacists' associations (EAHP and ESOP) and French authorities, there are insufficient buffer stocks[22] at the level of manufacturers or wholesalers to absorb disruptions in the supply chain when they occur. EAHP and ESOP also argued that there should always be buffer stocks to allow enough time to take measures to mitigate a shortage (e.g. extra production by an alternative manufacturer, or set up parallel import from a country where there is no shortage, or switch patients to another drug, etc.).

Lack of transparency at dispensing level increases the burden

Hospital pharmacists reported that they are often not informed in advance of a shortage occurring, so that they cannot look for alternatives (such as the availability of other treatments) and adequately inform patients and their physicians. In addition, they stressed that such situations also lead to an increased workload as they seek ways to mitigate shortages. Furthermore, they reported typically not having information about the extent and duration of the shortage. Such information, they argued, would for example allow manufacturers of alternative drugs to increase their production to meet patient needs. By introducing more transparency via tracing packages of medicines and via EU-level measures to coordinate procurement, this could be alleviated.

Digitalization, automation and harmonization of the systems would decrease vulnerabilities

Some countries have automated systems to check the stock of a wholesaler, this is extremely helpful (benefit of digitalization). Countries lacking such systems have an increased vulnerability in the SC. If the wholesaler is out of stock, the duration and extent is not known and countries without automated systems cannot check the stock at the wholesaler. In some countries, pharmacies and hospital pharmacists face the impossibility or lack of flexibility when there is a scarcity of a critical product, to be able to substitute with a product from another EU country. All National authorities should have in place mechanisms (similar to the one that exists in Portugal) to allow the use of medicines from another EU country in case of a shortages that can endanger the patients.

EAHP mentioned that shortages are often regional, and price differences between countries actually drive these regional effects. There could be the temptation to make use of the menace of a potential shortage to obtain an increased price - some examples of this practice are available but are considered sensitive information and will be provided to the Commission on the terms agreed.

[22] There were significant debates around the terms "buffer stocks" and "stockpiling" throughout the structured dialogue. Generally, the view was that "buffer stocks" referred to a "normal" or "typical" quantity of a product stored as part of normal business operations by a supply chain actor. Stockpiling was most often understood to mean keeping larger quantities of a product well beyond "normal" or "typical" demand in order to allow for the continued supply of products in extreme circumstances.

2.3 *Are the supply chains sufficiently transparent to allow the assessment of risks and vulnerabilities? What aspects of supply chains must be transparent?*

Transparency prerequisites

Among the stakeholders, there was a clear consensus that transparency is not a simple and universal solution to remedy supply chain vulnerabilities, and that it should be considered only when it is justified for risk management purposes, i.e., when it can provide means to prevent, identify and/or remedy supply chain vulnerabilities. Participants also stressed that releasing sensitive data should be avoided (applicable to all actors across the supply chain).

The group identified requirements that transparency measures would have to meet to be considered necessary for achieving the supply chain resilience objective:

- Transparency should serve a clear **public interest purpose,** such as informing regulators of a high level of supply chain consolidation. This could in turn be used to identify market-based incentives that would allow supply chain actors to implement corrective action as appropriate.
- Transparency measures must be proportionate to the objective pursued and avoid becoming an additional source of vulnerabilities. This could be the case when, e.g., increasing transparency translates into a greater regulatory complexity and burden.
- The group identified the following aspects of supply chains as potentially requiring proportionate transparency measures:
- Transparency of market supply and demand can help authorities and industry allocate medicines based on patient need, bearing in mind that patient need is not consistent over time and that buffer stocks in the supply chain have an important role to play. This takes on even greater importance during a crisis.
- Some level of transparency on **supply chain timelines** could also be useful to determine when and if remedial actions should be considered. The COVID-19 pandemic has shown that there will be circumstances where supply needs increase suddenly and significantly. The ability to respond to such spikes in demand can be affected by complex, non-harmonized, non-flexible regulations with difficult to predict approval timelines.
- Greater transparency on **supply tensions and shortages**[23] could also enable other manufacturers who may have needed additional anticipation and/or capacity to fill gaps.
- Early and increased communication and transparency with all supply chain stakeholders. If the regulators have accurate information provided in a timely manner it allows the authority to collaborate with the MAHs and relevant stakeholders (manufacturers, wholesale distributors, pharmacies, hospitals, retailers, healthcare professionals and patient groups) in order to minimise the impact of a shortage. Some regulators reported that they have already made changes to national shortages notification system to include the obligation to submit a date to restore supply.

[23] While not discussed in detail and raising numerous questions on the feasibility and efficiency of the options, some stressed the importance of ensuring that EU Member States have a common understanding and definition of what constitutes a shortage.

Transparency limitations

Limits on the extent to which greater transparency can be achieved, and by whom, were also raised:

- Competition law prevents competitors from discussing their supply chains with one another as this could serve anti-competitive ends. Greater transparency is only achievable through regulators or other government actors.
- Business confidentiality may constrain transparency. Companies may put themselves at a competitive disadvantage or provide competitors with information they can use to their benefit should confidential information become public knowledge.
- Increased transparency is a means to an end and enhances the ability to perform risk management but does not in and of itself lead to an increase in supply capacity.
- Transparency should not be translated into an increase of administrative declarations and regulatory burden. Health authorities should prioritize optimisation and use of existing sources of information regarding supply (suppliers and manufacturers names, address and location as part of Drug master files for API or medicine license (EMA and national), material Compliance as part of Certificates of suitability (CEP) managed by EDQM, material sources names addresses and some volumes as part of annual site master file (ANSM France), volumes forecasted and produced each year per product for vaccines and products derived from blood (European Official Medicines Control laboratories OMCL).

2.3.1. Transparency of raw material production/collection

Lack of transparency of raw materials prior Registered Starting Material (RSM) limits the identification of vulnerabilities for chemically synthesised products.

Information on raw material production is only known by the company of this segment up until the upstream Registered Starting Material (RSM). All information downstream of the RSM is shared with regulators but not accessible in a central database. This lack of transparency mostly creates vulnerabilities regarding dependencies (no information on the geographical diversification of precursors, technologies used, no transparency on changes in the production process etc.) and environment, health and safety (EHS) performance. The Blue Sky program with the closure or necessary relocation of multiple manufacturing facilities in China is illustrative of such major risk and generated a number of potential shortages of raw materials and, as a matter of consequence, of medicinal products.

Considerations for biological products:

For biological products, such as therapeutic proteins and vaccines, the details of critical raw materials and starting materials such as cell banks and seed stocks are included in the regulatory dossier. The details of other critical raw materials, such as those materials with potential risk of Transmissible Spongiform Encephalopathies (TSE), are also included in the dossier and are additionally regulated via mechanisms such as plasma master files in the case of blood products or Certificate of Suitability for materials of animal origin and updates are required to filed via regulatory variations.

Transparency of raw materials prior to Registered Starting Material (RSM) could help to identify vulnerabilities

However, the desire of regulatory bodies to have transparency on processes before RSM is growing. The pharmaceutical industry in some cases accounts for only a small part of the demand for suppliers of some pre-RSM raw materials, and these producers may as a result be unable or unwilling to comply with transparency requirements. This results in significant

difficulties to find suppliers for the RSM, which in turn creates a vulnerability to the uninterrupted supply of affected medicines.

Increased visibility to map available capacities/capabilities and identify missing technologies.

Additionally, stakeholders believe more visibility and knowledge of the availability of key technologies in Europe would provide information needed to decrease supply chain vulnerabilities. This will create transparency on local manufacturing capabilities and diversity of technologies available (EFCG/IQVIA report), it will create a better view on the reliability of the processes involved in pharmaceutical manufacturing. One example is nitration technology, which is more or less only possible in Switzerland, where the first purpose of this technology is not dedicated to pharma industry.

2.3.2. Transparency of active pharmaceutical ingredient (API) production

Information already available to regulators on API production to allow for an assessment of consolidation

The transparency of API production towards the regulators is already high through the information captured in the regulatory dossiers (Active Substance Master File, DMF, Medicine license). Although participants stressed that available data contained in manufacturers' regulatory filings are currently underused, there was also a recognition of the fact that this data is not necessarily available in a format that would enable automated processing, instead requiring significant manual efforts to be compiled.

However, in cases where more than one API supplier is identified in a DMF, regulators will not be in a position to assess the full extent of supply chain consolidation without information about the relative weight of these suppliers. In these cases, registering a second source may therefore paradoxically both increase supply chain resiliency while also making it more challenging for NCAs to assess supply chain consolidation[24].

Heparin is illustrative of how regulators with appropriate data consolidation could have a good overview of suppliers and manufacturer and be used to avoid current consolidations and dependences.

As is the case for raw material production (section 2.2.1), an overview of key technologies present in European companies can give an indication of consolidated, so vulnerable technologies. For example: 65% of the APIs have a nitration somewhere in their route of synthesis whereas only 27% of the EU companies have this technology capacity[25] In that way, knowledge of technology capacity can help decrease supply chain vulnerabilities.

[24] A stakeholder argued that greater information on the "actual" API manufacturer is already required by the Commission Delegated Regulation (EU) No 1252/2014, though this is not enforced.

[25] EFCG/IQVIA report

2.3.3 Transparency of finished dosage form (FDF) production

Information that would make better understanding of resources available if used

As is true for API production, FDF manufacturers are required to provide a wealth of information to regulators through the regulatory dossier. As covered in section 2.3.2, greater information on FDF sources should be made available to and evaluated by regulators without additional burden for industry. This will require a more harmonized and digitalized system than is currently the case.

However, information on declining service levels or stockouts from wholesalers, pharmacies and hospitals should be provided as early warning signals for upcoming shortages.

A better transparency and harmonization to ease anticipation and management of shortages.

Unpredictability of national supply and stocks

There exist no clear delivery schedules for national medicines supplies, and no information either on existing national stock levels is available to the supply chain partners.

Information on available medicines supply on national markets would be key to help anticipate an upcoming shortage.

In addition, the following vulnerabilities/risks for national supply chains can be identified:

- Operational risks: general blackouts and power cuts, strikes
- Financial and economic risks
- Market system disruption: Payment delays (in some countries excessive delays in payment risks supply), Margin erosion (downward pressure results loss of commercial attractiveness to participate in distribution)
- Cybersecurity risks: cyberattacks
- Risks related to weather and environment conditions: bad weather conditions, natural/man-made disasters
- Legislative risks: additional regulatory burdens, imports/exports prohibitions, government-imposed costs containment measures
- Pandemics.

Stakeholders also called for a harmonized shortage definition (e.g. the EMA definition should focus on shortages linked to patient need) and harmonized European report template and system, accepted by all member states based on common data fields. The requests for different definitions, different templates and different timelines lead to a lot of duplications and extra work. During the COVID-19 crisis, the European Medicines Agency (EMA) set up the 'industry single point of contact' (i-SPOC), allowing pharmaceutical companies to report any issues related to the availability of crucial medicines used in the context of COVID-19 directly to the Agency. In the future, this could be continued as a 2-way centralised communication system between industry and other supply chain stakeholders at time of crisis. This should replace other reporting systems (example: national) and not come in addition to them.

Regulators stressed that critical information, such as when a product will be back on the market, is often not released. Regulators do not have visibility on the **allocation of the products** down to the hospital or pharmacies. On recommendation of the WHO, Denmark implemented a shared platform to see the allocation and the change in demand.

2.3.4 Transparency of wholesale and distribution

There exists no transparency about the supply situation at the national level, and manufacturers' stock levels or delivery timelines are not known to wholesale distributors and other downstream supply chain actors, nor are MAHs aware of the stock levels of distributors. Wholesale distributors have no visibility of the actual supply situation and are not informed about eventual upcoming shortages in order to rationalise supplies, until a shortage is confirmed. Denmark benefits of a system that gives an early warning of upcoming shortages to switch from one source to the other.

Distributors argued that supply quota systems imposed on them by MAHs can further blur transparency of confirmed or eventually future shortages as quotas can also be imposed outside of shortage situations. Distributors also argued that quotas are only justified in a shortage or upcoming shortage situation and, if allocated quantities are not communicated to wholesale distributors, can hinder wholesale distribution planning.

Distributors further argued that information on behalf of full-service healthcare distributors (wholesalers) about declining service-levels from MAHs could help to signal early warnings on upcoming shortages. If then, on individual warehouse level, the stock-out of a product is confirmed, the situation may already become more critical. The final and most critical warning signal could come from persons authorised to supply medicines to the public whilst reporting that they cannot order the medicine in question from their usual pharmaceutical full-line wholesalers. Spanish and German authorities are working with wholesale distributors on service level monitoring systems for early identification of potential medicines shortage and also the EMVS could be used to get more transparency of where medicines are.

2.3.5 Transparency of pharmacies and hospitals (including demand)

Limited or no anticipation of shortages

As noted earlier, the lack of transparency about shortages is particularly problematic for hospitals and pharmacies. This inevitably leads to anxiety and trust issues in the end of the supply chain (directly after the pharmacy), which is the patient. It also leads to an increased burden on a daily base work of pharmacists to solve the shortage. Most shortages are not forewarned to the hospitals and pharmacies, which leaves no time to look for alternatives and adequately inform the patients and their physicians. If there is a shortage, there is usually no notification of the extend and the duration of the shortage, this then in turn drives shortages of alternative drugs, and also hampers the ability of the manufacturers of alternative drugs to upscale their production to meet the patients' needs. More transparency is urgently needed. A regulator commented that in Portugal, whenever a shortage has a medium or high impact in public health, MAH's are requested to issue a DDL to prescribers (which include hospitals). However, this system doesn't always work: In the Netherlands, for example, hospitals do not receive DDLs. The following paragraph is testimony from two hospital pharmacists:

Hospital pharmacists pointed to a current example to illustrate the challenges they face. Their attempts to order a particular product (Cernevit) were unsuccessful, with the only notification from the supplier that the product was on backorder. They only learned that the shortage would most likely last somewhere around 9 months after calling the manufacturer. Furthermore, there is still no DDL.

Stock and supply management

According to BD, a medical-technological company, most of the hospital's supply chain systems, including EU hospitals, are not automated and digitalized, and therefore not optimally efficient (e.g. manual, time-consuming and inaccurate process of ordering, manual replenishing and storing inventory). This drives stock outs, waste from expired medicines, low transparency of inventory (no real time and inaccurate inventory data) and patient demand, since the ordering process is not always accurate, and very often does not reflect the right level of patient demand vs real time stocks[26]. When automation or digitalization is not present, there is an inherent lack of transparency of the stocks of pharmacies and hospitals.

According to hospital pharmacists' associations EAHP and ESOP, most of the hospitals have at least a simple software of stock management, and even the smallest hospitals have at least a rudimentary software to manage the inventory. Hospital pharmacists know at every timepoint exactly how many pills /capsules/vials they have of each drug, and they know exactly how many patients in the hospital are on that drug. Community pharmacies also know exactly how much stock they have. However, lack of information on patient adherence means that they may need medicines on a schedule that differs from what is expected.

EAHP and ESOP stressed that there is full support for the advancement of digitised and automated order systems, as it reduces inefficient manual labour in a sector where in many regions there is a lack of staff. They also argued that the statement that this is a vulnerability in terms of a potential to cause shortages is not proven. For example, both the Netherlands and Germany have fully digitised order systems, yet there were 17 shortages in Germany in 2018, compared to 769 in the Netherlands.

In addition, some countries have automated systems to check the stock of a wholesaler. However, this automated system is not implemented in most European countries, thus the stock at wholesale level cannot be confirmed in order to understand availability of alternative medicinal products during a shortage.

In order to resolve this a European database to consolidate EU data would be beneficial: Currently, France is in the process of setting up a database, based on annual inventories, including all production sites for medicines of major therapeutic interest. This database will make it possible to identify weak links such as consolidation of suppliers where for a given product several or all companies may rely on the same supplier, but this process is difficult due to quality data issues. The adoption of a standardized format at European level was seen as worth pursuing. According to regulators, processing the annual inventories is currently hampered by poorly formatted documents and challenges in correctly identifying that e.g., two addresses in China are in fact the same.

Lack of Transparency on Demand

For industry participants, the **lack of transparency on demand sufficiently in advance is a significant area of concern.** This is an issue for actors across the entire supply chain – beginning with suppliers of raw materials for production. Lack of data on existing stocks (at national, regional, hospital level) and patient needs limits the ability of actors to better plan production and react to sudden changes in demand. Industry participants stressed the problems

[26] For evidence: see appendix with overview of references (14)

associated with the decision by actors to suddenly increase stock at times (e.g., anticipated peaks in demand that could be due to a pandemic), so that demand may outpace actual patient needs. This in turn prevents suppliers from allocating products where they are most needed. This lack of transparency on existing stocks may in turn contribute to shortages due to a misallocation of available medicines, and difficulties in the management of alternative medicines. If there would be aggregated data available on epidemiology to identify where the clinical needs are for specific APIs, their allocation could perhaps be more efficient.

Visibility on demand is particularly important for products with long lead times of manufacturing such as vaccines and PDMP. The production of seasonal influenza vaccines is a good example illustrating the impact of the pre-booking of raw material. Millions of eggs are needed to produce the egg-derived seasonal influenza vaccines that are distributed annually in the EU. The lead time for production is close to 12 months. The total vaccine capacity depends on the number of eggs which is fixed 12 months before the start of the production (i.e., approximately 24 months before the start of the flu season).

***2.4** How do we link issue of supply chain security with other challenges as sustainability of health systems?*

How to ensure financial sustainability of the health care system without excessively increasing costs? On the one hand, profitability is a prerequisite for sustainability, and hence for supply chain resilience. On the other hand, products should remain affordable for patients and the healthcare system. Keeping the balance between affordability of products and a sustainable supply chain is a critical challenge.

Stakeholders generally recognized that ensuring supply chain security inevitably will be associated with some costs. To maintain a proper balance, several stakeholders called for risk-benefit calculations to be done and to ensure that a framework allowing continued investments in innovation is in place. Implementation of the green agenda and ensuring production sustainability will also entail additional costs. Some private sector stakeholders argued however that "budget management" through constant price pressure is ultimately counterproductive, as this will lead to greater consolidation, and result in more vulnerable supply chains with fewer suppliers. Moreover, new treatments more than ever lead to reductions in healthcare costs further down the line, a development that should taken into account more strongly.

There should instead be a push for investments and innovation throughout the supply chains. The security of supply should be integrated in cost thinking of the member states. The current market structure does not allow for true competition (the procurement caps limit competition as price cannot go up). Promoting security of supply in procurement criteria would enable industry to invest in increasing supply chain resiliency. But very importantly, there should be **EU-wide solutions** to address these problems: only a handful of countries changing tender rules would have very limited impact.

The shortages report of the FDA[27] underlines that markets should recognize efforts made by manufacturers to invest in mature quality systems and strengthen the resilience of their supply chains. In addition to patient impact, shortages also have an economic cost (additional treatments, medical consultations, identification of alternatives identification by pharmacists, etc). Incentives to manufacturers reduce the health care cost long term. The FDA has implemented an increased quality maturity program API and FdF manufacturers and

[27] USFDA 2019, REPORT | DRUG SHORTAGES: ROOT CAUSES AND POTENTIAL SOLUTIONS, HTTPS://WWW.FDA.GOV/DRUGS/DRUG-SHORTAGES/REPORT-DRUG-SHORTAGES-ROOT-CAUSES-AND-POTENTIAL-SOLUTIONS

recognizes this in procurement/tenders (MEAT criteria).

One benefit of improving geographic diversification would be the reduction of vulnerabilities resulting from export restrictions. Most stakeholders also stressed that improving sustainable supply chains should also entail reducing waste in supply chains and optimizing the use of medicines. Furthermore, production outside of the EU should be subject to similarly high EHS standards. EAHP and ESOP also argued that additional costs that may result from addressing supply chain vulnerabilities should not only be borne by health systems or patients.

- **Conclusion**

- *What are the main findings of your workstream?*
- *Which aspects need to be addressed in the short/medium/long-term?*
- *Are there outstanding gaps that were not in scope of the workstream that you would recommend pursuing?*
- *What do you see as the next steps?*
- *What are the potential solutions?*

Important note: *The group acknowledges that the content of this report does not reflect a consensus opinion of the group on the various questions asked by the Commission but rather a collection of views which in many instances were still diverging at the time of finalizing this report and which have not taken all inputs on board.*

What are the main findings of your workstream?

Which aspects need to be addressed in the short/medium/long-term?

Most of the options identified and discussed by the workstream require further assessment and are medium to long term options. Building a framework for a resilient supply chain takes investment and time.

The group will now need to discuss, explore and assess the impact of the possible options and look at possible time frames for policy reforms in line with the important policy agendas linked to the structured dialogue such as the Pharmaceutical Strategy for Europe or the Industrial Strategy for Europe. As such the group will at points have to go back to this report and adjust elements to remain consistent, especially when discussing policy options that are based on further evidence or insights into root causes of vulnerabilities. We will identify short-, medium- and longer-term reforms to support resilient supply chains.

Are there outstanding gaps that were not in scope of the workstream that you would recommend pursuing?

Some aspects of our work are covered by the other workstreams and synergies in the discussion should be explored.

1. Workstream 2 will identify critical products and is linked to our reflections on risk mitigation plans and related activity. Here it is important to acknowledge that if there is a critical product and the supply chain is not vulnerable, the risk for that product and need for action are also downgraded.
2. Workstream 1 identifies criteria for robust pharmaceutical supply chains. Robust supply chains should be designed to mitigate the vulnerabilities identified in our group.
3. Workstream 4 identifies the technologies need for resilient supply chains including digital and green investments which are key areas of our work.

What do you see as the next steps?

We would encourage the European Commission to continue its engagement and constructive dialogue with the stakeholders involved in the drafting of this paper as many discussions need to be continued to carefully consider and properly assess the impact of the related policy recommendations to be considered as many will need to adapt to a changed environment. This group could continue the discussions beyond statements of their views and integrate some into joint positions.

List of abbreviations

3PL: Third-Party Logistic Provider

AATD: Alpha-1 Antitrypsin Deficiency

AESGP: Association of the European Self-Care Industry

ANSM: L'Agence nationale de sécurité du médicament et des produits de santé

API: Active Pharmaceutical Ingredient

BD: Becton Dickinson

CEP: Certificates of suitability

CHMP: Committee for Medicinal Products for Human Use

CQOs: Chief Quality Officers

DDD: Defined Daily Dose

DDL: Dear Doctor Letter

DG GROW: Directorate General for Internal Market, Industry, Entrepreneurship and SMEs

DMF: Drug Master File

EC: European Commission

eCTD: Electronic Common Technical Document

EMA: European Medicines Agency

EDQM: European Directorate for the Quality of Medicines & HealthCare

EEA: European Economic Area

EFCG: European fine chemicals group

EFPIA: European federation of pharmaceutical industrial associations

EAHP: European Association of Hospital Pharmacists

ESOP: European Society of Oncology Pharmacy

EHS: Environmental Health and Safety

EMVO: European Medicines Verification Organisation

EMVS: European medicines verification system

EU: European Union

EUR: Euro

FDA: Food and Drug Administration

FDF: Finished Dosage Form

FMD: Falsified Medicines Directive

GEON: General European OMCL Network

GIRP: Groupement International de la Répartition Pharmaceutique (European Healthcare Distribution Association)

GDP: Good Distribution Practices

GMP: Good Manufacturing Practices

ICH: International Conference on Harmonisation

ICU: Intensive Care Unit

ICMRA: International Coalition of Medicines Regulatory Authorities

i-SPOC: industry single point of contact

IQVIA: Quintiles and IMS Health, Inc

ISO: International Standards Organisation

IDMP: Identification of Medicinal Products

IT: Information Technology

IVDs: In Vitro Diagnostics

K: Thousand

MA: Marketing Authorisation

MAH: Marketing Authorisation Holder

MEAT: Most Economically Advantageous Tender

MD: Medical Device

MS: Member State

NCA: National Competent Authorities

NCL: National Control Laboratory

OCABR: Official Control Authority Batch Release

OMCL: European Official Medicines Control laboratories

PACs: Post Approval Changes

PID: Primary Immunodeficiencies

PDA: Parenteral Drug Association

PMDP: Plasma Derived Medicinal Products PMDP

PPTA: Plasma Protein Therapeutics Association

PQS: Pharmaceutical Quality System

PSO: Public Service Obligations

REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals

RMS: Registered Starting Material

ROW: Rest of World

SKU: Stock Keeping Unit

SIC: Secondary Immunodeficiencies

SC: Supply Chain

SPOR: Substance, Product, Organisation and Referential

TSE: Transmissible Spongiform Encephalopathies

UK: United Kingdom

USA: United States of America

WHO: World Health Organisation

WS: Workstream

ANNEXE A Participants list
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ANNEXE B – Other regulatory requirements leading to supply vulnerabilities

1. Global regulatory requirements for post-approval changes

It is suggested that a practical and standardized solution to reduce the regulatory complexity can be explored by leveraging the principles laid down in various regulatory guidance documents: ICH Q9, Q10 and Q12; World Health Organization (WHO) recommendations. The WHO document *"Good reliance practices in regulatory decision-making: high level principles and recommendations"* states *"The WHO supports the implementation of reliance on other regulators' work as a general principle in order to make the best use of available resources and expertise[28]."* The guidance describes increasing levels of reliance from accepting standard processes and the practice of work-sharing between Regulatory Agencies to full reliance and recognition of other Regulatory Agencies work. WHO also has detailed guidance documents for managing specific types of post approval changes (PACs) including recommending a maximum 6 months prior approval timeline. These documents have been developed through collaboration with the 194 WHO member states. Some countries have chosen to follow the WHO guidance documents for PACs, but many have developed their own national or regional guidance. However, increased reliance on other Regulatory Agencies and the WHO guidance documents would help reduce the overall regulatory complexity[29]. In 2002, FDA introduced the "*Pharmaceutical Quality for the 21st Century Initiative[30]"* to encourage the adoption of new technologies and risk-based management approaches as well as to facilitate the application of modern quality management practices. FDA's stated vision desired, *"A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight."* Three years later, in 2005, the ICH Q10 Concept Paper stated that *"Delays in the implementation of innovation and continual improvement for existing products may occur due to different expectations in the three regions (Japan, EU, USA)."* In support, many governmental and non-governmental organizations have written Position Papers on the PAC complexity topic as well and the attendant need to simplify the regulatory process. Leveraging the principles of the ICH guidance documents the One-Voice-Of-Quality industry group has issued a proposal on managing Post-Approval Changes which is sponsored by the Chief Quality Officers (CQOs) of the world's 25 largest pharmaceutical companies. The solution proposes that lower risk post approval changes can be managed using risk-based principles as laid down in ICH Q10 Annex 1. The current post approval change process requires that each country (or region) has its own reporting requirements (or levels) for prior approval of a PAC, distinct documentation requirements for the change, and different review/approval timelines. Each country completes their own individual scientific and technical assessment of the PAC. It typically takes 3-5 years (or more) from the first to the last regulatory agency approval of the same PAC even when circumstances would warrant a more rapid response.

The figure below shows a real example of a single change involving a vaccine approved in 138

[28] See: ICH Q9, Quality Risk Management, 2005, ICH Q10, Pharmaceutical Quality System, 2008, ICH Q12, Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management, 2019, QAS/20.851, WHO draft, Good reliance practices in regulatory decision-making for medical products: 6 high-level principles and considerations, 2020.

[29] "Industry One-Voice of Quality (1QV) Solutions: Effective Management of Post-Approval Changes in the Pharmaceutical Quality System (PQS) through Enhanced Science and Risk Based Approached: Emma Ramnarine, Anders Vinther, Kimberly Bruhin, et al. PDA J Pharm Sci & Tech 2020, 74 456-467.

[30] Pharmaceutical CGMP Initiative for the 21st Century – a Risk Based Approach, FDA, 2002.

countries. The change was a simple scale up of an early process step. It was concluded by the company that there were no safety, efficacy or quality impact to patients. 62 countries classified the change as a major change requiring prior approval, 37 countries classified it as a minor change not requiring prior approval, and 39 countries did not require reporting. In response to the proposed change the company received 177 questions from 22 countries following the individual assessments, there were only 19 different questions as many were asked by multiple countries (see figure 3).

Due to the complexity of manufacturing and control of vaccines and the limited number of manufacturing facilities, vaccine manufacturers cannot manage at the same time 2 different versions of a manufacturing and control process. As a consequence, vaccine manufacturers are obliged to organise a very sophisticated stockpile mechanism which enables to supply each country with the current nationally approved vaccine, pending the approvals of the submitted change. Between downscaling production of the initial vaccine version and full approval and distribution of a new version, there is the potential for a shortfall in supply, especially when during this period an abrupt increase in demand occurs. Obtaining PAC approvals remains a complex process for global manufacturers, despite global regulatory harmonization efforts. This complexity leads to increased risk to global vaccine supply (including in Europe) and delays the implementation of technical changes allowing increase of manufacturing capacity.

In a recently published communication, the International Coalition of Medicines Regulatory Authorities (ICMRA) *"recognizes that regulatory authorities can gain efficiencies by developing common procedures, guidelines, requirements, and interoperable infrastructure that would facilitate the timely sharing of information among regulators on changes occurring within the supply chain. This may include reliance on the assessments of other regulators reviewing those changes. ICMRA considers that this could lead to more timely availability of medicinal products for patients by shortening approval timelines*" [31].

The proposed solution is to leverage published guidance documents to reduce the complexity (particularly for low-risk changes) with industry and regulatory authorities working in partnership and in full transparency to reduce risk to supply. The solution proposed however is not intended to compromise on the production of high-quality medicinal product, impact regulatory compliance or patient safety. Conversely, by leveraging ICHQ10, it is warranted that industry must *demonstrate an effective pharmaceutical quality system and product and process understanding, including the use of quality risk management principles* and once this is demonstrated the opportunity arises to *optimise science and risk based post-approval change processes to maximise benefits from innovation and continual improvement.* The intended enhanced science and risk-based approach cannot be used to justify noncompliance with GMP

[31] http://icmra.info/drupal/strategicinitatives/pqkms/statement

requirements. Companies should remain compliant with GMP requirements while using this approach to determine regulatory strategy and manage conformance to global registrations. Regulatory filings should be kept current on a regular basis.

2. Packaging and labelling requirements in the EU

The burdensome packaging and labelling national requirements across the EU may have an impact on the supply of small markets as well as on the flexibility of supply (this is especially true for products with long manufacturing cycles). For inexpensive and older medicines, specifically, it can be economically too burdensome for MAHs to continue marketing products in small markets for which they have to separately produce very small batches due to national packaging and labelling requirements. The European Commission should allow for flexibilities for medicinal products dedicated to small markets by setting a framework for regulatory flexibility in licencing and labelling rules for small markets.

For vaccines, the use of multilingual packs/package leaflets is strongly limited by logistical constraints. Given that the vast majority of vaccines have to be stored in refrigerated conditions, reducing as much as possible the size of the packs to facilitate storage is critical to. For this reason, multilingual packs for vaccines are limited to a maximum of three different languages. Four Vaccines Europe companies independently evaluated the number of shared packs needed to cover all EU/EEA countries for a single presentation of a centrally approved vaccine. They reached the conclusion that 14 to 16 different packs are needed even with the optimal use of multi-lingual packs due to different reasons (including pack size, serialization constraints, logistical considerations). The diversity in vaccine presentations and languages for pack and leaflet in EU/EEA contrasts with countries such as the United States for which large amounts of doses can be supplied using the same packaging[32].

Taking into account the vaccine specificity, including the fact that vaccines are not self-administered, Vaccines Europe's recommendation is 1) to move to a common EU pack accepted by all EU/EEA countries and 2) to replace the paper leaflet by an electronic leaflet to address the problem of shortages in the EU.

3. Vaccine batch release by Official Medicines Control Laboratories

As part of the regulation of medicinal products for human use, article 114 of Directive 2001/83/EC states that a Member State is allowed, but is not required, to test a batch of an

[32] For example, a large company with 14 vaccines distributed in the US and 27 in the EU reports that approximately 20 times more stock keeping units (SKUs) are needed to cover the EU market compared to the US. The need to produce different vaccine packs and leaflets in different languages significantly reduces supply chain efficiency. Due to a combination of factors such as the size of the market (18 countries in EEA have a population of less than 10 million inhabitants), limited shelf life or conditions imposed by tenders, vaccines may have to be delivered in small volumes (sometimes a few thousand doses) of country-specific packs. As a result, packaging lines have to be stopped to allow the changes of label (text on the immediate or outer packaging), leaflet and carton, and quality controls have to be performed. Frequent changes significantly reduce the capacity of packaging lines. Vaccine packs and leaflets in different languages can also prevent that a shortage situation in one country to be immediately solved by the use of vaccines produced for another country. Although some countries accept the transfer of doses in a foreign pack in case of shortage or in emergency situations, this remains an exception granted on a case-by-case basis. A number of measures (presented in Annex X / Table Y) to reduce the number of country-specific packs and leaflets across the EU/EEA and to facilitate the transfer of vaccines between EU/EEA countries in order to avoid supply disruptions.

immunological medicinal product by an Official Medicines Control Laboratory (OMCL) before it is placed on the market. In practice, every vaccine batch is tested by an OMCL before being distributed in the EU. The Official Control Authority Batch Release (OCABR) consists of analytical testing and document review. The testing to be performed as well as the content of the documents to be reviewed by the OMCLs are defined in the product guidelines published by the European Directorate for the Quality of Medicines & HealthCare (EDQM). OCABR performed by any given Member State is recognised by all other Member States. As mandated by the European Commission, the EDQM acts as the Secretariat of the General European OMCL Network (GEON). During the GEON yearly plenary meeting, all the representatives are offered the opportunity to officially adopt the OCABR procedures and guidelines drafted by the Advisory Group (consisting of six representatives from different Member States). The approval process of guidelines and procedures for testing reduction schemes requires a unanimous vote which is a hurdle to fast and efficient evolution of OCABR guidelines. Independent batch release by a National Control Laboratory (NCL, referred to as OMCL in the EU) is one of the final steps before placing a vaccine on the market and is, regardless of its duration, a contributing factor to vaccine shortages and supply delays. The data collected by 3 manufacturers shows that an optimization of the EU vaccine batch release process would allow a more predictable and earlier supply and thus reduce the duration of shortages (see Figure 6). For vaccines manufactured outside of the EU and distributed in EU, each lot has to be tested and released by an EU OMCL even if it has been tested by the NCL of the country where it has been produced. Similarly, vaccines manufactured in the EU and exported to non-EU countries may be tested by an EU OMCL and retested by the NCL of the importing country. Therefore, the same vaccine lot may be tested several times by independent control laboratories.

Vaccines Europe strongly recommends mutual recognition agreements or reliance mechanisms between authorities in order to avoid the repetition of independent batch certification which leads to a reduction of the remaining shelf-life and may lead to vaccine shortages and supply delays. Vaccines Europe also recommends 1) that EDQM procedures and guidelines are adopted by a majority of the representatives (and not unanimity) as it is currently done for CHMP opinions for centrally approved products and 2) that EDQM guidelines are revised to avoid that OMCL testing is on the critical path of batch release, at least for well-established vaccines. For example, testing on purified antigen bulk rather than on drug product should be considered. Other opportunities such as reduced testing or testing of manufacturer' sera for in vivo assays should be more widely implemented.

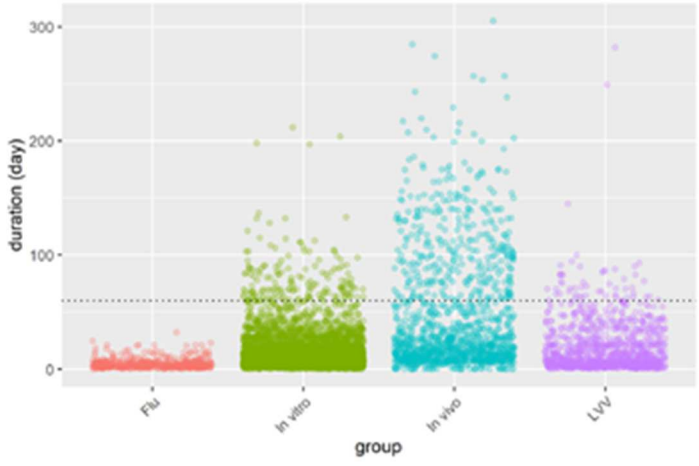

Figure 6: Review of timelines for OMCL batch release.

The graph illustrates the time between the release by the manufacturer (Day 0) and the OCABR certification. The timelines have been analysed for 7,420 batches from 3 manufacturers; each dot on the graph corresponds to a single batch. The analysis shows a large heterogeneity in the OCABR timelines for all categories of vaccines, except seasonal influenza vaccines. It also confirms that vaccines which are released based on in vivo assays have on average the longest timelines for OCABR certification. It has to be noted that at Day 0, each vaccine batch may already be allocated by the manufacturer to one or several markets. The heterogeneity of the OCABR timelines results in difficulties to predict when a batch will be available for distribution which may in some cases lead to shortages. Abbreviations: Flu: seasonal influenza vaccine (503 batches); In vitro: vaccines released based on in vitro testing only, excluding influenza vaccines and live virus vaccines (4,642 batches); In vivo: vaccines released based on an in vivo potency assay (1,260 batches); LVV: live virus vaccines (1,015 batches).

ANNEXE C - Plasma Derived Medicinal Products (PDMPs) and their vulnerabilities

1. Economical and geopolitical perspectives

Plasma-derived medicinal product made from human plasma given by healthy, committed donors, are essential for some 300,000 European patients who rely on these therapies day to treat a variety of rare, chronic, and potentially life-threatening conditions. Without these treatments, many patients may not survive or would have a substantially diminished quality of life.

The PDMP industry brings a strong European manufacturing sites footprint, unlike other pharma sectors. This global map below illustrates the PDMP manufacturing footprint in the EU with 17 commercial and three not-for-profit plasma fractionation facilities (many more than the US).

Global European Interactive Map: https://prezi.com/view/hXBhxDEIo8R2cavcduIk/

The key vulnerability lays in an in sufficient plasma collection in the EU and a significant dependency on US plasma imports which has been highlighted as a concern by the EU Commission in its 2019 Evaluation Report of the functioning of the EU Blood Directive: currently, only 70% of EU's plasma needs for manufacturing PDMPs to cover patients needs (growing by 8% every year) are collected in the EU, whilst around 30% of the plasma needed

is imported from the U.S.

In order to increase plasma collection in Europe for the manufacturing of PDMPs and ensure the availability of PDMPs for patients, an appropriate framework is needed that differentiates between whole blood and blood components for transfusion and plasma for manufacturing.

The root causes driving this vulnerability lay in the following barriers:

- The absence of insufficient dedicated plasma collection (plasmapheresis) programs in many EU Member States
- Restrictive policies to establish a stronger plasma collection infrastructure
- Co-existence of public sector and private sector plasma collection centres are only allowed in Austria, Czech Republic, Germany and Hungary.
- Unnecessary regulatory burden for plasma collection that do not take into account technological and scientific developments that have occurred since 2002
- "One size fits all" application to PDMPs of reimbursement system constraints such as clawback/payback taxes, despite the specificities of PDMPs

2. Regulatory framework perspective

1. There is overall an unnecessary regulatory burden as to plasma collection that do not take into account technological and scientific developments that have occurred since the EU Blood Directive was adopted.

Plasma for manufacturing is very different to whole blood (for transfusion purposes) from a pathogen safety and testing perspective, and should be subject to rules generated by a European technical body with sufficient expertise in plasma which must be subject to the strict EU rules on inclusive consultations and transparency. These rules should reflect current scientific evidence and remove outdated regulatory barriers to the collection of plasma for fractionation that are no longer supported by science.

The following regulatory barriers are no longer supported by science, and should be removed in a revised EU Blood Directive, to increase regulatory efficiency by[4]:

- Revising existing eligibility criteria for plasma donors based on the newest technological and scientific progress. Donor eligibility criteria should take into account the ability of the PDMP manufacturing process to remove known and emerging pathogens, thus ensuring highest quality and safety of PDMPs.
- There is a need to refine, improve and accelerate standard activities in inter-epidemic periods to increase preparedness, and, where a more efficient and effective approach is possible, adapt regulatory requirements to scientific and technological developments. This includes regulatory tools such as rolling reviews of data as they become available from ongoing studies.
- For PDMP manufacturers actions are needed including removal of the '2nd step approval process' for Plasma Master File (PMF) certification and relevant guidance, and change to process to accept and enter new plasma collection centres in the EMA PMF system.

On GMP inspections and EU-US MRAs (Mutual Recognition Agreements):

a) Modification of GMP inspection procedures is needed, including provisional certification of new manufacturing facilities, re-certification of existing manufacturing facilities, modification of GMP inspections to include remote or paper audits for the duration of COVID -19. PPTA calls for update and flexibility of inspection procedures, and operational support to national authorities which currently are not able to apply flexibility, such as remote GMP inspections. In order to tackle the (re-)emergence of communicable diseases/pandemics, an

adequate EU framework to facilitate production of hyperimmune immune globulins (HI-IGs) is needed

b) PPTA specifically advocates for the inclusion of U.S plasma collection centres in the current EU-US Mutual Recognition Agreement (MRA) on GMP inspections and EU inspectors' capacity building. The need for an MRA was particularly well highlighted during the pandemic, as physical EU inspections could not be performed and were delayed, impacting the availability of US-plasma derived medicines to be marketed in EU. Also, there is a shortage of EU authority inspectors who perform remote and/or 3rd country plasma centre inspections.

Trade agreements have failed to consider plasma as starting material for PDMPs, leading to insufficient regulatory cooperation and harmonisation with the US, such as EU-US MRA (Mutual Recognition Agreement): Plasma and PDMPs are currently not eligible for inclusion in the MRA, in large part due to the fact that the US and the EU do not have a common or similar definition as to plasma for manufacturing. A revised EU Blood Directive containing a definition of plasma for manufacturing would help address this gap and open the door to the inclusion of PMDPs in future EU-US MRAs. PPTA specifically advocates for the inclusion of U.S plasma collection centres in the current Mutual Recognition Agreement (MRA) on GMP inspections and EU inspectors' capacity building. Also, there is a shortage of EU authority inspectors who perform remote and/or 3rd country plasma centre inspections.

3. Reimbursement framework perspective

When PDMPs are reimbursed, they often face additional economic challenges, including reimbursement issues, the consequences of external reference pricing (ERP model), and/or cost-containment measures such as clawback or payback taxes. Although several countries have lifted, deferred or reduced application of these taxes, in recognition of PDMPs' unique value and nature and unique risks to availability, there remain many others that continue to apply them (see below visual), such as:

- Greece, with a 45 % clawback tax on PDMPs, Hungary with several clawback tax alike mechanisms, Bulgaria with a 10 % clawback;
- Italy with a 15.7 % payback tax applied selectively to PDMPs made with plasma collected outside of Italy (but not to PDMPs made with plasma collected in Italy);
- France applying a payback tax mechanism to PDMPs made with plasma collected outside of France from compensated donors (but applied to PDMPs made with plasma collected in France.

This taxation of PDMPs in a "one size fits all" approach" like all other pharmaceuticals adds a supplementary layer of cost pressure and vulnerability of the supply chain of PDMPs on their way to patients.

Several countries recognized the PDMP specifics and either lifted, deferred, or reduced the application of these taxes for PDMPs; this relieved the sector from burdens to contribute to vulnerabilities and resulting tensions as to patient access to those treatments, for instance (see below visual and Vintura EU White Paper, 2020):

- Belgium exempted in 2009 PDMPs from the application of a clawback like tax, Poland exempted immunoglobulins from a similar tax; Greece exempted also immunoglobulins;
- Romania exempted in 2020 definitively all PDMPs from the application of the clawback tax,
- Bulgaria exempted in 2021 immunoglobulins from the application of the supply growth tax,
- Portugal applied a reduced tax of 2.5 % to PDMPs versus 14.5 % for other

pharmaceuticals.

In PPTA's view, the examples of countries that have lifted cost-containment measures for PDMPs by recognizing their unique nature, ultimately to the patients benefit, could become a blueprint for other countries in their economic policies as to PDMPs.

The EU could thus envisage addressing a recommendation to EU Member States to apply cost containment measures in a differentiated manner to PDMPs, on basis of abovementioned rationale, and to either exempt them from or strongly reduce the burden.

Tender practices and procurement

The final set of economic practices and policies that affect patient access is the way in which PDMPs are procured. Tenders should be designed to include more (value-added) criteria instead of only being focused on price. In the heterogeneous European healthcare systems, varied procurement approaches are practised; from direct procurement, through the so-called "intelligent tenders" which aim to ensure availability of diverse medicines and brands, and "centralised, regional or hospital tenders" which typically result in availability of the "cheapest" single medicine or brand. Instead, procurement practices should ensure that the optimal treatment is available. Treated patients must be allowed to continue the optimal therapy, and for naïve patients, alternative brands must be made available.

European payers and policymakers may wish to revisit their procurement practices specific to PDMPs and take into account that they cannot be considered bioequivalent and interchangeable. It is worth considering a number of measures, such as tenders allowing for multiple brands to be procured or exemption of PDMPs from central tendering procedures.

National stockpiling

PDMPs should be exempted from national stockpiling due to its specifics, or be subject to stockpiling requirements limited to maximum a month or less. Longer stockpiling would severely distort patient supply, such as of products like immunoglobulins, since stockpiling, especially in big markets would deprive/limit supply in other middle/small countries and by that jeopardize the EU solidarity principle.

Additional Elements

- **API manufacturing – options to improve variations management**

Increasing quantity of GMP-related information in the regulatory dossier

Over the past years the trend by quality assessors to request more and more API supply chain data in the dossier has the potential to triple the number of variations per MA per year at first and then to lead to an increased number of variations due to maintenance of the newly introduced regulatory dossier information. While the outsourcing trend within the API manufacturing industry was already a reality, Marketing Authorisation (MA) dossiers submitted did not generally include information on API supply chain operators involved before the final API manufacturer (particularly not testing sites, in-process testing sites or intermediate manufacturers). These were, and still are, managed and controlled through GMP/GDP audit and API manufacturers' quality systems qualification. It should be noted that this is in line with Directive 2001/8313 which states that Manufacturing Authorisation Holders have the responsibility to only use APIs that have been manufactured in accordance with GMP.

Since 2013, several regulatory guidance documents or forms have undergone changes with regards to the description of what is meant by API manufacturing, bringing consistency to the already existing definitions in the pharmaceutical legislation and the EU GMP Guide Part II, and clarifying regulatory expectation for the information to be put in the dossier.

Often, drug product manufacturers rely on external laboratories for testing of e.g. microbial purity to deal with bottlenecks or for specific tests that cannot be performed internally. All subcontracted activities are covered by relevant quality and technical agreements. With the publication of the aforementioned guideline, all additional sites (even backup sites not in use) have to be covered in the regulatory dossier.

The authorities should have full access to the information and keep full visibility of the supply chain. However, a lean approach to transparency on relevant supply chain functions compared to the current submissions of variations to the health authorities should be considered.

- Changes of a purely administrative nature generate a disproportionate amount of work for the applicant and health authorities to process. There is a need to incorporate information flow from existing controlled respective quality systems, audits and inspections to facilitate transparency and better lifecycle management of medicinal products. As outlined previously in the section on *"Variations*" currently available guidance issued by ICH and WHO could be effectively utilised to manage low risk changes by applying risk-based regulatory strategies to allow more changes to be managed in the Pharmaceutical Quality System or via notification pathways rather than the conventional prior approval process[33].
- Information on some types of manufacturers in the supply chain or changes thereof should be provided via digital means to the databases accessible by each health authority (i.e. SPOR database), instead of via classical variation procedures.

[33] IVQ Reference: "Industry One-Voice of Quality (1QV) Solutions: Effective Management of Post-Approval Changes in the Pharmaceutical Quality System (PQS) through Enhanced Science and Risk Based Approached: Emma Ramnarine, Anders Vinther, Kimberly Bruhin, et al. PDA J Pharm Sci & Tech 2020, 74 456-467

- **Digitalization in the supply chain processes**

The crisis has exacerbated longstanding issues related to lack of digitalization in healthcare, including regulatory processes for the approval and maintenance of medicines. We know that robust and harmonized digital regulatory systems for addressing challenges such as shortages of medicines can make a tangible difference in handling health emergencies. This should be reflected in the European Medicines Agency legislation. Digital solutions in the regulatory field can bring us much needed agility, a rapid response to a fast-changing environment, and enable regulatory authorities to monitor and promptly react to major health events. The EU legislation concerning regulatory variations (human pharmaceutical products) is not aligned to the newly developed IT tools and Telematics system initiatives, such as eCTD, Art 57, SPOR/ISO IDMP and FMD. Consequently, the complex and invariably segregated EU Telematics environment fails to make an ideal fit with the submission and processing of regulatory variations linked to the supply chains. As a result, Industry and Authorities are forced to continue to undertake redundant tasks or adopt workarounds: investing resources and time to manage a huge and annually growing number of variations: notably administrative, often information-only variations such as changes or corrections of addresses.

Switching from a document-based processes towards the submission, management, and evaluation of structured data via a two-way common EU Regulatory submission gateway. Regulatory data submitted once, as structured data and in one format only and reused by the authorities for various purposes. Achieving greater digitalization and interoperability of systems will likely be an effort over a longer time span. Recent improvements, such as the use of a web portal instead of paper, required significant efforts and the task ahead will be significantly more challenging.

- **Shortage reporting optimization options**

In the current medicines shortages reporting system, Marketing Authorization Holders (MAHs) have the obligation to report potential shortages to National Competent Authorities (NCAs). Shortage does neither have the same definition nor the same timeline requirements across EU member states. They must be reported via different portals which are hosted by the National regulatory agencies, mostly under national language. This results in multiple channels to submit similar data, but with differences in specific information to be provided depending on different national requirements. These inconsistencies result in different interpretations and different questions by national agencies. The lack of a harmonized template for data collection or use of master data leads makes sharing information across National Competent Authorities and the EMA very burdensome.

Establishing the full implementation of the ongoing master data management (SPOR) by all stakeholders (e.g. SPOR currently doesn't cover wholesalers and distributors) in all processes and all products and with the connection between existing systems (e.g. SPOR and EMVO) would bring important benefits. National agencies would be in a position to better evaluate the impact on the supply chain (e.g. suppliers from specific regions/countries), evaluate the availability of medicinal products within Europe (e.g. potentially tracking volume changes) and identify and signal shortages for critical products.

While ensuring a connection between existing systems identified (SPOR and EMVO) is

desirable, this will not directly lead to the improvements listed[34]. It should be noted that the hospital pharmacists' association (EAHP), Affordable Medicines Europe, PGEU, and GIRP (the European Healthcare Distribution Association, representing full-service healthcare distributors (wholesalers)) do not support using EMVS data for shortages monitoring, as the EMVS was created to protect patients from falsified medicines. Data uploaded in the EMVS, they argue, will overestimate available supply of medicines and underestimate demand on national level[35]. These associations make up the majority of stakeholders associated to EMVO, the organisation in charge of the EMVS.

To conclude, there was agreement that all stakeholders would benefit from a shortage reporting system which enables **on-time and harmonized information on shortages** (see figure 8). For this to work efficiently, a collaborative approach and 2-way communication between regulators and manufacturers (and other SC stakeholders at time of crisis) is needed. Communication will not necessarily or "only" be required between regulators and manufacturers but directly include other actors across the supply chain ex-manufacturing.

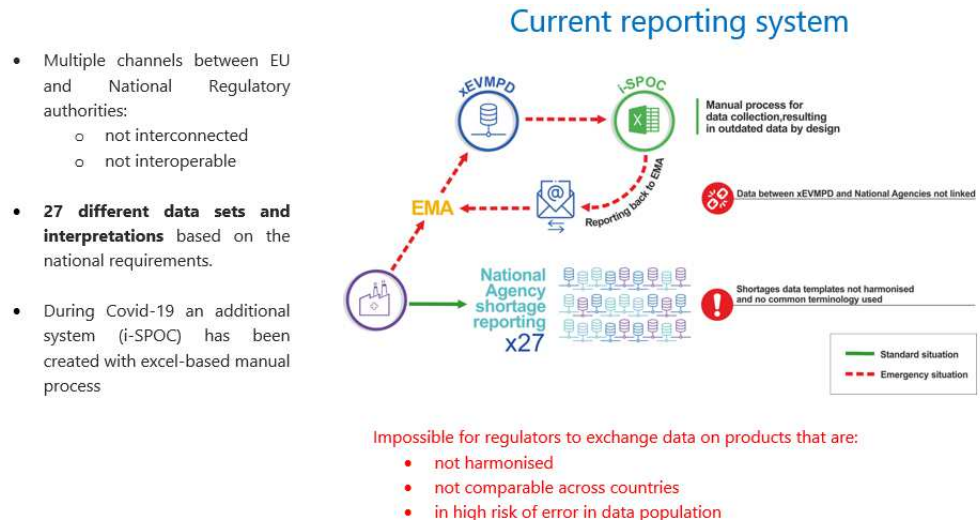

Figure 7. Current reporting system

[35]http://girp.eu/sites/default/files/documents/girp_position_on_use_of_emvs_for_monitoring_of_shortages_-_updatedfeb21.pdf

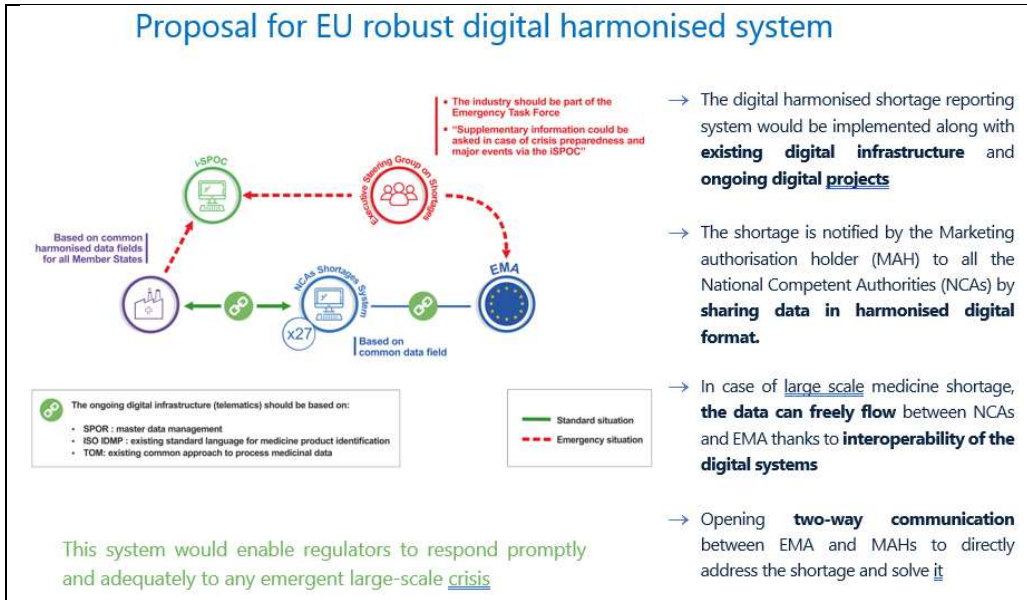

Figure 8. Proposal for a robust digital EU-harmonised system

- **Investments for R&D the key on-patent medicine vulnerability**

The medicinal product lifecycle starts with the introduction of a new in-patent, novel, drug to address patient need. The innovative pharmaceutical industry is focused on innovation and developing new drugs. This R&D process is characterised by:

1) The very high risk of failure (1 in 10.000 molecules ends up in a medicine for patients);

2. The very high costs of R&D (€2.1 bn on average (DiMasi et al., 2016);

3. The long time period needed to develop a new medicine – ranging from 8 to 13 years;

4) The highly regulated nature and process steps that need to be taken in the R&D process from a promising molecule to a finished dose product. Vulnerabilities in the in-patent medicine segment are those that undermine the necessary investments to fuel the R&D process. Ultimately all in-patent medicines go off-patent and become generically available.

Once the patent expires, the medicine goes off-patent and starts to be produced in large quantities. For this reason, the off-patent sector represents the majority of prescription medicines in volume terms (close to 70%). The off-patent sector is characterised by multisource competition, and reimbursement practices are designed to achieve low prices (for example through single winner tenders or reference pricing). This makes the off-patent segment a very price-sensitive procurer of raw materials that meet pharmaceutical industry standards.

This medicinal lifecycle is what is key to understanding the differences in how vulnerabilities matter for different medicines and these differences are essential to drive policies that will increase EU supply chain resilience without damaging more than a policy is trying to solve.

The on-patent products are the result of massive investments in R&D. Unlike the off-patent products (see below) s**upply chain vulnerabilities start with attracting investments to fund R&D that lead to the innovative medicines of today and generic medicines of tomorrow**. The supply chain for on-patent products is also very complex but managed very differently.

The global supply chain for on-patent medicines is not driven by cost-pressure considerations mainly, but rather by R&D and production optimising decisions from manufacturers, from

raw materials to final finished products. If the attractiveness for the EU in terms of investments for R&D is reduced, EU vulnerability in terms of access to the latest scientific developments and technologies to ward off a future pandemic will increase. This is the key element a pharmaceutical strategy should address for long-term resilience to address vulnerabilities.

Contrary to vulnerabilities that need to be addressed to maintain EU innovative capacity, the production part of supply chains for on-patent medicines is much less vulnerable; much lower than for the generic industry, for raw materials, APIs and for finished dose forms. A very detailed ECIPE study (2021) has shown – based on Eurostat (2019) data that imports of pharmaceutical for the combined on- and off-patent industries come for 81% from the EU itself in value terms (71% in volume terms). The large majority of EU imports are destined for production for re-exporting after adding significant value. An EFPIA Membership survey shows that 64% of APIs are manufactured in Europe, 15% in North-America and 11% in both India and China combined. The large majority of companies have also not moved production to lower-cost countries at the moment their products went off-patent. For on-patent medicines, the survey finds that 92% of shortage of medicines notifications result from a disruption of API supplies in the EU and UK. The most reliable API supplier countries are Switzerland (0% disruptions), Singapore (0%), North-America (1.1%) and China (1.7%).

Some on-patent medicines use very new processes and need very little volumes. Because of the patent-system, there is one final producer of an innovative medicine. This producer – via market pressure – ensures that supply continues and is resilient. The main criteria – shown by the EFPIA survey – for location and sourcing of APIs are (in order of importance): quality (1), sustainability (2), reliability of supply (3), costs (4), and location (5), a picture that is very different for generic medicines (see below). In addition, innovative medicines are more likely to require advanced technical equipment and a highly educated workforce for manufacturing of complex molecules which make adjustment more complex than just relocating supply chain activities.