Structured dialogue: work stream 1 robust supply chains

Final: 19 July 2021

Date of Submission: 20 July 2021

Working Group: Workstream 1: Robust Supply Chains

Rapporteurs/Co-Rapporteurs: Adrian van den Hoven, Marco Farinelli, Jürgen Roos

List of abbreviations:

ADS: Automated delivery system
AMR: Anti-microbial resistance
API: active pharmaceutical ingredient
BEUC: Bureau of European Consumer Unions
BFARM: German Medicines Agency
CEP: Certification of European Suitability
COGs: Cost of goods
CP: Centralised approval procedure
DCP: Decentralised approval procedure
ECDC: European Centre for Disease Control
EDQM: European Directorate for the Quality of Medicines and Healthcare (Council of Europe)
EEA: European Economic Area
EFCG: European fine chemicals group
EFPIA: European federation of pharmaceutical industrial associations
EHS: Environment, health, and safety
EMA: European Medicines Agency
EMVS: European medicines verification system
e-PI: Electronic product information
EU: European Union
Eudra: European Drug Regulatory Authorities
EXC: excipient
FDF: finished dosage form
FMD: Falsified medicines directive
GMP: Good manufacturing practice
GDP: Good distribution practice
HCP: Health care practitioner
HMA: Heads of Medicines Agency
ICH: International Conference on Harmonisation
ICU: Intensive care unit
IED: Industrial emissions directive
IM: intermediate
i-SPOC: Industry Single point of contact
MA: Marketing authorisation
MAH: Marketing authorisation holder
MEAT: Most economically advantage tender
MRA: Mutual Recognition Agreement
MRP: Mutual recognition procedure
NBCD: Non biologic complex drugs
NCA: National competent authority
NCD: Non-communicable disease
NGO: Non-governmental organisation
NMVS: National medicines verification system
NP: Nationally approved product
OSD: Oral solid dose
OTC: Over the counter (drug)
PIC/S: Pharmaceutical Inspection Cooperation Scheme
PiE: Pharmaceuticals in the Environment
REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals
RM: raw material
RSM: registered starting material
SC: Supply chain
SPOC: Single point of contact
WHO: World Health Organisation
WTO: World Trade Organisation
USFDA: United States Food and Drug Administration

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 and agreed by high level stakeholder representatives. 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.

Robust Supply Chains:

The workstream broke the issue down into different steps to improve shared understanding and advance toward coherent, consistent, and cohesive policy responses that could make a difference to the supply of medicines to patients. Hence, the dialogue and related document was structured along four important themes.

- First, the paper describes the **criteria for robust pharmaceutical supply chains**, the enablers, and the outcomes that they should deliver to patients.
- Second, the paper applies **the criteria, enablers, and outcomes across different production steps** (key registered starting materials and intermediates, upstream chemistry, excipients, APIs, medicines production), **different production segments** (oral solids, sterile and complex drug delivery) recognising that these segments operate in very

different settings or environments (single vs multisource; high vs low volume) and might require different solutions.[1]

- Third, the paper explores the **options for enablers of robust supply chains according to the different production steps and to the pharmaceutical segments and settings (volumes, single/multisource, technologies)**. The paper recognises that providing options, rather than additional requirements, is important because some solutions may increase robustness in some segments or settings and decrease robustness (or access to medicines) in other segments or settings.
- Fourth, the paper sets out **policy recommendations related to the EU Pharmaceutical Strategy and the EU Industrial Policy Strategy** (and other strategies such as the EU Trade Strategy) to provide a pathway to improve the conditions to enable robust and competitive pharmaceutical supply chains. The recommendations are classified under:

  1. The important contribution of stakeholders.
  2. Making the invisible, visible (or at least predictable).
  3. A robust, enabling and strongly enforced regulatory framework.
  4. Sustainability as a driver.
  5. Open trade flows and globally competitive industry

C. Table of Contents

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.

In terms of scope, this paper seeks to answer the questions addressed to work stream 1 by the European Commission.[2] However, there was an overarching perspective that the purpose of robust supply chains is to ensure the secure and timely supply of medicines to patients and consumers under normal market conditions and in times of crisis.

Regarding information/supporting evidence, the workstream relied on reports and evidence submitted by the participants. Most of the information compiled in the paper relies on expert opinions, often based on evidence from reports or studies available (often cited), of the stakeholders that brought different perspectives and worked to bridge those perspectives across the supply chain. The stakeholders felt there was a genuine effort to bring constructive solutions to the discussion and to work toward an alignment of views wherever possible. The Commission should take note that stakeholders may represent very different interests and that consensus was not possible on all points in the report. This is noted where applicable.

[1] While the focus is on pharmaceutical manufacturing, stakeholders acknowledge the interconnection between therapeutic need or *demand* and pharmaceutical manufacturing or *supply* and that patients are prescribed, dispensed and/or administered medicines by healthcare providers. In addition, key intermediaries such as wholesalers, pharmacies and hospitals distribute medicines and hold stocks to meet patient demand; payers and procurers purchase or reimburse prescription medicines for patients; regulatory agencies oversee the safety, quality and efficacy of medicines – and enforce important quality standards[1] such as good manufacturing practice or good distribution practice (GMP/GDP).

[2] The dialogue operates under the leadership of Commission Vice-President Schinas and Commissioners Kyriakides (Health) and Breton (Grow) with the support of the Health and the Grow Directorates.

To reduce knowledge gaps, the initial meetings were devoted to aligning on the definition of robust supply chains, enablers, and outcomes. Then, these criteria were applied across different production steps and segments:

- *The EFCG provided detailed information on the production of critical raw materials, intermediates, and active pharmaceutical ingredients.*
- *Medicines for Europe provided detailed information on the off-patent segment production (large volume, multisource solid oral production, sterile production, and follow-on specialty medicines (complex drug delivery) like biosimilar medicines.*
- *EFPIA provided detailed information on innovative medicines, including lower volume, often single source, specialty and complex drug and vaccine production.*
- *Stakeholders across the spectrum (HCPs, full-service healthcare distributors (wholesalers), payers, regulators, patients, consumers) provided additional detailed information on the necessity of robust supply chains, concerns over inadequate supply hospital supply management, or regulatory oversight (i.e., GMP enforcement).*

The dialogue provided an opportunity for stakeholders to increase their shared understanding of important issues such as the visibility/predictability of supply chains, demand, and long-term sustainability, and how this visibility/predictability is interconnected and essential to robust supply chains.

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, in particular data/information gathered (e.g., matrix definition of a robust supply chain depending on the product; enablers of robust supply chains; determination of a critical mass of production capacities in the EU, necessary to ensure robustness of the supply chains at all times…).

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

2.1 What are the main causes of problematic/ the most challenging disruptions? How do you classify the associated risks?

The dialogue explored supply chain disruptions under normal circumstances and under crisis situations. The reliability of the supply chain is a critical factor under normal circumstances. The responsiveness of the supply chain is a critical factor in a crisis.

A lack of visibility of supply/demand, regulatory constraints or for consumer organisations, the lack of clarity in the enforcement of supply obligations in national markets a, and an absence of sustainability of some manufacturing processes/technologies or a lack of specialised human resources were described as risk factors. Improving visibility of supply and demand via information sharing and innovative technological solutions, efficiency, flexibility, and openness to innovation of the regulatory system, encouraging sustainability throughout the supply chain, and leveraging global value chains are routes to increasing reliability and responsiveness. In addition, consumer organisations (BEUC), highlighted the need for better enforcement of supply obligations in national markets and reinforced industry obligations.

2.2 How do robust supply chains mitigate the risks associated with potential supply disruptions?

Supply chains are designed to mitigate potential supply disruptions, and this may vary across production steps or segments. From the production side, manufacturers typically have inventory polices with safety stock at the critical nodes to absorb demand variation, specialisation policies, business continuity plans, use digital tools such as tracing sensors for monitoring their logistics networks and may also apply multi-sourcing strategies as well as supplier rating schemes where relevant. From the demand side, manufacturers adapt the supply chain to the forecasted demand for the products which can be highly variable at times and may require automated digital technologies to monitor and process demand data to improve supply decisions. In a crisis characterised by demand surges, there is a more urgent necessity for responsive production supply chains and for more clarity on the demand. Increased availability of quality data and reliable information systems could provide this by feeding into risk simulation technology and automated statistical scanning of order flows.

Inherently, there is a certain degree of risk associated with all supply chains regardless of whether they are global or regional. While global supply chains must integrate trade risk, regional supply chains must integrate 'single point of failure' risk.

2.3 Is increased complexity of supply chains a risk factor? Are the critical points identifiable?

The dialogue acknowledged the complexity of pharmaceutical supply chains where hundreds of inputs are used in production. In addition, as production becomes more specialised, the number of reliable suppliers as well as the technologies, human resource skills and manufacturing facilities of those inputs declines.

On the other hand, significant efforts have been put in place over the past years to digitalise and strengthen the robustness of supply chains, allowing them to better respond to the increasing complexity and needs, particularly using digital tools to improve information analysis and thus resilience. The globalisation of production chains has played a key role in strengthening the supply chain resilience and ensured agility, to quickly address unforeseen challenges, enabling manufacturers to adjust as needed along production sources to avoid potential shortages and disruptions. It has also however underlined the importance of ensuring open trade flows and the risk for supply when this is not the case, such as for example the disruptions caused by export restrictions introduced by many governments during the pandemic.

Patient, consumer groups, and healthcare professional groups as well as healthcare distributors have highlighted that the problem of drug shortages is long-lasting and serious, as evidence in many surveys and reports.[3][4][5][6][7] Drug shortages can result in harm to patients and create major distress.[8] At the same time, drug shortage management takes up time from pharmacists that could be spent in other patient-centred tasks and to improve the quality of care.

Poor overview of available stocks and demand predictability due to the lack of information sharing practices and infrastructure amongst stakeholders, complexity due to outdated regulation in the digital age, poorly adapted procurement, and poor sustainability and according to consumers the need for better enforcement of national supply and a more robust regulatory/policy framework, were identified as risk factors for supply chains and areas for potential improvement. Stakeholders agree that regulation should be respected and enforced.

[3] https://www.france-assos-sante.org/wp-content/uploads/2019/01/Penuries-medicaments-Resultats-BVA-dec2018.pdf
[4] https://www.test-achats.be/sante/maladies-et-medicaments/medicaments/dossier/penurie-medicaments
[5] https://www.ocu.org/salud/medicamentos/noticias/encuesta-desabastecimiento
[6] https://www.eahp.eu/practice-and-policy/medicines-shortages
[7] https://www.pgeu.eu/wp-content/uploads/2019/03/2020-PGEU-Medicine-Shortages-Survey-Results-v2.pdf
[8] [1] http://girp.eu/sites/default/files/documents/girp_medicine_shortages_reflection_paper.pdf

2.4 Is the robustness of current supply chains threatened by long term industrial and health policies of countries our supply chains are the most integrated with (USA, China, India, Japan)? What specific vulnerabilities are already predictable/ can be foreseen or anticipated?

The dialogue acknowledged the global dimension of pharmaceutical production as both a benefit and a risk. Global and diversified supply chains helped in the response to the COVID-19 crisis as they were able to quickly adjust and address unforeseen challenges although reliance on a single geographic location for some production was affected by export restrictions. This global supply chain together with efforts by the EU (facilitating cooperation with manufacturers, Member States, and stakeholders) has enabled EU manufacturers to be leading exporters[9] of medicines and medicinal components (APIs, excipients, RSMs, precursors, etc) – contributing to security, economic growth, and innovative technologies as the EU27. The innovative pharmaceutical industry's limited international dependency for the supply of innovative APIs and its strong export performance are based on a strong R&D infrastructure in Europe, which is currently losing ground to other economies such as the US and China. Europe should build on its strengths and protect its innovation potential, including through strong research funding, as well as partnerships in areas where new technologies are needed. Ccollaboration with strategic raw material suppliers and external service partners is vital; and so are strong relationships with contract manufacturers and global third-party logistics (3PLs). But globalisation can also be a risk when the EU relies heavily on a single geographical source for an important share of its pharmaceutical production needs and open trade flows cannot be ensured – especially when the EU has lost the technical capabilities (in infrastructure or human skills) to manufacture some goods.

There is a general issue regarding the competitiveness of EU pharmaceutical manufacturing. For upstream production (raw materials, intermediates, some APIs), the EU lacks a competitive position due to higher cost factors in Europe – including those associated with the environment, health, and safety (EHS). The stakeholders do not call to lower EU EHS standards or sectoral regulations like REACH for chemicals. Rather, we acknowledge that any reshoring of manufacturing of EHS high risk production would likely need new technologies enabling more modern, greener, and safer chemistry processes in line with the objectives of the EU Green Deal and the Chemicals Strategy for Sustainability. We also acknowledge that stricter EHS rules in countries like China are necessary and positive to improve the local situation and that this evolution may provide an opportunity for EU manufacturers to compete more effectively on a level playing field. This issue is more amply discussed in the context of Workstream 3 (Supply Chain Vulnerabilities).

For generic medicine and API, the EU is still an important manufacturer, but Chinese and Indian production is growing much faster – a sign of higher competitiveness. For complex drug delivery systems, the EU is still a competitive manufacturing region[10], but it is not clear that the EU environment is conducive to maintaining that competitive position.[11] To do this, Europe should build on its strengths and protect its innovation potential, including through appropriate incentives and research funding, as well as partnerships in areas where new technologies are

[9] Contributing significantly to a positive balance of trade.

[10] The Pharma Letter: "Europe to surpass US in biologic manufacturing capacity by 2023" https://www.thepharmaletter.com/article/europe-to-surpass-the-usa-in-biologic-manufacturing-capacity-by-2023

[11] Politico, 24 June 2021 **Eli Lilly CEO: EU needs to look across the pond to keep up: "***With the EMA, I'm always a little cautious about commenting on regulatory reform until I see the writing. There's certainly an opportunity to bolster the scientific prowess of the EMA. It's one of the better experiments that has come out of the whole EU project and it's time for renewal. Technologies are moving at a much faster pace." "So do we want to focus on domestically balancing the budget or do we want to try to promote an industry? There's lots of good reasons to take a much more front-footed approach, whether it be on translational science — that is, taking ideas from laboratories to products, the real advantage of the U.S. — or looking at modernizing the industrial base to the latest technologies: the cell, gene, and RNA technologies, which are mostly being built outside of Europe." "We have a debate in front of us. Europe needs to decide what it wants, whether to make it easier to do business, or to focus on pure affordability at the expense of the industry. That will lead to a different outcome. And the migration of the industry out of Europe will continue, which is already a 20-year trend. "*

needed. Similarly, the EU may be a challenging environment to scale up complex drug production from small volume to large volume rapidly in a crisis.

2.5 What is the assessment of the evolution of the supply chains and their robustness in the last decade? Has it increased? Decreased? Are there any pivotal points that resulted in meaningful improvements?

The 2009 financial crisis led to an important reform of pharmaceutical markets across the EU as all payers shifted their focus to cost-containment. For multisource, off-patent markets, this translated into more consolidated procurement and to price reductions in reimbursement. In turn, this encouraged the pharmaceutical industry to reduce production costs – driving consolidation and globalisation across the whole production chain. For single source, on-patent markets, this translated into more restricted access to new medicines[12] and to lower volumes overall.

Despite this economic pressure, the EU remains an important manufacturer of medicine, vaccines, excipients, and APIs, especially for higher value-added and for innovative products. Investment in innovation and using digital technology has allowed manufacturers to digitalise their supply chains over the past decades which made them more robust. Advanced data analytics and machine learning are now fully integrated to ensure better security, agility and flexibility of supply chains making them more resilient also in times of crisis.

In terms of regulation, the EU has advanced regulation on quality (updated GMP guidelines) and security (FMD implementation, SEVESO directive, etc.), on Product Stewardship (REACH), the environment (EU-ETS, IED, PiE, etc…) and the use of digital tools at least temporarily during the Covid-19 pandemic.[13] Progress has been more limited regarding a greater use of digital regulatory tools and data to address visibility issues, more harmonised shortage reporting and more harmonised packaging and labelling requirements.

Meanwhile, China and India have increased their manufacturing competitiveness in API and FDF production and the US has maintained its leading role in drug development.

The policy recommendations of this paper take account of these dynamics and look to improve medicine availability, among other by restoring and strengthening Europe's competitive position in off-patent API and medicine manufacturing while recognising the importance of global supply chains.

2.7 How well does the existing regulatory framework support the robustness of the supply chains? What critical aspects are present/missing?

The Workstream will make many recommendations to ensure that the regulatory system encourages robust supply chains. The high standards for quality and for security of the EU system are an important starting point for resilient supply chains. The positive experience with regulatory flexibility during the Covid-19 pandemic also showed that the EU can maintain high regulatory standards combined with effective enforcement and a more practical implementation of those standards (for example the Variations Regulation or post-approval changes for vaccines), and where justified, the use of flexibilities provided they do not compromise quality, safety, or

[12] https://www.efpia.eu/news-events/the-efpia-view/statements-press-releases/access-to-medicines-inequalities-persist-but-solutions-must-be-found-in-partnership/

[13] Informa Pharma Intelligence/Cambrex (June 2021) Digital Transformation in regulatory : Achieving Virtual Excellence: https://img06.en25.com/Web/InformaUKLimited/%7B9930de5b-23ad-4328-a45c-555607744775%7D_JN4508_Cambrex_-_Digital_Transformation_-_Research_Report_Final_HR_no_crops.pdf?elqTrackId=6cc6edf542ec48409259f5e3482e8c2c&elqaid=9086&elqat=2; EFPIA Alternative GMP/GDP inspections in a pandemic (Covid-19) and Beyond, https://www.efpia.eu/media/547487/alternative-gmp-gdp-inspection-practices-in-a-pandemic-situation-covid-19-and-beyond.pdf

efficacy. EU leadership is expected to encourage more global standards for environmental health and safety to progress in this area while ensuring a global level playing field.

The EU must also target the long-standing challenges related limited harmonisation of packaging/labelling and other requirements across the internal market (including the EEA) as well as the UK and Switzerland, which creates sub-optimal stock allocation conditions – especially for smaller countries. This should be done in full consideration of the impact that such changes could have on patient safety and the need to ensure that patients or their caregivers have easy access to information on medicines.

There is a critical role for the EU to invest in interconnected digital regulatory systems that make better use of data and new digital technologies to improve supply and demand predictability/visibility for increase supply chain agility, to harmonise requirements to facilitate stock allocation across EU markets, when this is strictly necessary, and to improve the efficiency of implementation of regulation. The EU must also ensure that national supply chain measures are proportionate and do not undermine solidarity in access to medicines for patients. The more detailed proposals are in the paper.

Key deliverables

On a basis of the above analysis, please propose:

Check list for a robust supply chain.

The workstream defines robust supply chains, the enablers and the outcomes which is a more elaborate than a check list but fulfils a similar function.

List of enablers of a robust supply chain.

The workstream defines the enablers but also matches those to different production steps (critical raw materials, excipients, API, FDF) and to different segments (ranging from multisource generic to single source specialty) for clarity.

Determination of a critical mass of production capacities in the EU, necessary to ensure robustness of the supply chains to the EU market

The workstream makes recommendations to encourage production capacities in the EU for robust supply – especially for raw materials, intermediates, API, and generic medicines. This should be based on a Commission assessment/study that identifies the public health and industrial policy priorities for increasing production capacity in the EU along supply chain steps (raw materials, API, finished products), segments or therapeutic areas in line with the Pharmaceutical and the Industrial Strategies for Europe.[14] It also recognises the importance of global supply chains for diversity, agility, and robustness of the supply chain. Identification of the necessary technologies and their availability in the EU or through open trade flows to ensure optimal responsiveness of the supply chain.

The workstream explored this issue from a qualitative perspective – outlining the realities across different production steps and segments. Notably, it has underlined the need to invest in certain technologies for production in Europe and to build on the existing manufacturing footprint of the sector for a robust manufacturing ecosystem. Recognising that rebuilding this capacity in Europe requires new technology, there is a link to Workstream 4 efforts on technology investments. The workstream also linked this to the overall competitiveness of European manufacturing to understand why Europe remains competitive (or not) in some aspects of production. The

[14] https://ec.europa.eu/info/strategy/priorities-2019-2024/europe-fit-digital-age/european-industrial-strategy_en. In this context, a study on API dependencies has already been conducted by the Commission. https://ec.europa.eu/info/strategy/priorities-2019-2024/europe-fit-digital-age/european-industrial-strategy/depth-reviews-strategic-areas-europes-interests_en

workstream has also identified human resource skill gaps/shortages for both manufacturers and regulatory agencies – notably in relation to quality and the need to consider greater investments in training and education.

Conclusion

What are the main findings of your workstream?

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

Most of the solutions proposed by the workstream are medium to long term reforms and objectives. Building a framework for a competitive manufacturing ecosystem requires investment and takes time.

We will 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. We will identify short, medium and longer term reforms to support robust 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.

1. Workstream 2 will identify critical products and is linked to our reflections on risk mitigation plans and related activity.
2. Workstream 3 identifies supply chain vulnerabilities. Robust supply chains should be designed to mitigate those vulnerabilities.
3. Workstream 4 identifies the technologies need for robust 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 thoughtfully consider the policy recommendations of this paper through a constructive dialogue with the stakeholders as many will need to adapt to a changed environment.

What are the potential solutions?

The policy reforms set out by the workstream aim to create an enabling environment for investments in robust supply chains for Europe covering:

1. The important contribution of stakeholders.
2. Greater predictability of manufacturing supply and patient demand.
3. A robust and enabling pharmaceutical regulatory framework.
4. Sustainability as a driver of robust supply chains.
5. Open trade flows and globally competitive industry

List of relevant documents, reports, statistics

Studies/data

International EU27 pharmaceutical production, trade, dependencies and vulnerabilities: a factual analysis, European Centre for International Political Economy (ECIPE) 2021 https://ecipe.org/wp-content/uploads/2021/06/Production-Import-dependencies-and-Export-vulnerabilities-of-pharmaceuticals-for-the-EU27-final.pdf

Mundicare, 2020, Where do APIs come from? For an English language summary: https://progenerika.de/app/uploads/2020/11/API-Study_short-version_EN.pdf

Soaeres et al.; Nanomedicine: Principles, Properties, and Regulatory Issues, Front Chem 2018 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6109690/

https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-medicines-use-in-2020.

https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/the-role-of-generic-medicines-in-sustaining-healthcare-systems.pdf

KPMG NV 2019, Improving healthcare delivery in hospitals by optimized utilization of medicines A study into 8 European countries, p. 88, https://www.medicinesforeurope.com/wp-content/uploads/2019/10/20190903_Hospital-Reform-Study_final.pdf

George P. Balla, Rachna Shahb, Kaitlin D. Wowak, 2018, Product competition, managerial discretion, and manufacturing recalls in the U.S. pharmaceutical industry, Journal of Operations management

Cap Gemini (2017) The Cost of the Falsified Medicines Directive: Impact on generic manufacturers in the Netherlands, https://www.politico.eu/wp-content/uploads/2019/01/FMD-cost-evaluation-Bogin-.pdf;
Klein et al. The EU regulatory landscape of non-biological complex drugs, European Journal of Pharmaceutical Sciences, 2019, https://www.sciencedirect.com/science/article/pii/S0928098719301381
Bouvy, F. and Rotaru, M. (2021) "Medicine Shortages: From Assumption to Evidence to Action - A Proposal for Using the FMD Data Repositories for Shortages Monitoring", Frontiers in Medicine, https://pubmed.ncbi.nlm.nih.gov/33614679/
EU Fine Chemical Commercial KPI; December 11, 2020 (commissioned by EFCG). https://efcg.cefic.org/wp-content/uploads/2021/06/20201211_IQVIA-for-EFCG_Executive-summary.pdf

News reports
Financial times 19 April 2021, "Brexit Red Tape threatens drug supplies in Northern Ireland", https://www.ft.com/content/40c52efc-17d8-4ac7-8a03-762df46adc9f
The Pharma Letter: "Europe to surpass US in biologic manufacturing capacity by 2023" https://www.thepharmaletter.com/article/europe-to-surpass-the-usa-in-biologic-manufacturing-capacity-by-2023
Informa Pharma Intelligence/Cambrex (June 2021) Digital Transformation in regulatory: Achieving Virtual Excellence: https://img06.en25.com/Web/InformaUKLimited/%7B9930de5b-23ad-4328-a45c-555607744775%7D_JN4508_Cambrex_-_Digital_Transformation_-_Research_Report_Final_HR_no_crops.pdf?elqTrackId=6cc6edf542ec48409259f5e3482e8c2c&elqaid=9086&elqat=2;

EU legislation/regulation/policy
Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA) https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-detection-notification-shortages-medicinal-products-marketing-authorisation-holders-mahs_en.pdf
https://ec.europa.eu/health/sites/default/files/human-use/docs/vaccinesstrategy_labellingpackaging_en.pdf.
For medicines in general, see the Notice from the Commission, EMA and HMA, specifically p.16
https://ec.europa.eu/health/sites/default/files/human-use/docs/guidance_regulatory_covid19_en.pdf
https://ec.europa.eu/health/sites/default/files/human-use/docs/pharmastrategy_consultationreport_en.pdf
https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52020DC0761&from=EN;
Description of MS shortage reporting https://ec.europa.eu/health/sites/health/files/files/committee/ev_20180525_summary_en.pdf
https://ec.europa.eu/health/human-use/strategy_en
https://ec.europa.eu/info/strategy/priorities-2019-2024/europe-fit-digital-age/european-industrial-strategy_en#strengthening-eus-open-strategic-autonomy
https://www.ema.europa.eu/en/human-regulatory/post-authorisation/availability-medicines/shortages-catalogue#national-registers-section
Commission study on strategic dependencies https://ec.europa.eu/info/sites/default/files/swd-strategic-dependencies-capacities_en.pdf
https://ec.europa.eu/eurostat/statistics-explained/index.php?title=File:People_who_used_the_internet_on_a_daily_basis,_2019_(%25)_BYIE20.png

US policy/regulation
Office of the White House, 2021, BUILDING RESILIENT SUPPLY CHAINS, REVITALIZING AMERICAN MANUFACTURING, AND FOSTERING BROAD-BASED GROWTH 100-Day Reviews under Executive Order 14017 June 2021 https://www.whitehouse.gov/wp-content/uploads/2021/06/100-day-supply-chain-review-report.pdf
FDA (2019, updated 2020): Drug Shortages – Root causes and potential Solutions, https://www.fda.gov/media/131130/download
https://www.fda.gov/drugs/drug-shortages/report-drug-shortages-root-causes-and-potential-solutions

Stakeholder contributions
https://www.efpia.eu/news-events/the-efpia-view/statements-press-releases/access-to-medicines-inequalities-persist-but-solutions-must-be-found-in-partnership/
EFPIA Alternative GMP/GDP inspections in a pandemic (Covid-19) and Beyond, https://www.efpia.eu/media/547487/alternative-gmp-gdp-inspection-practices-in-a-pandemic-situation-covid-19-and-beyond.pdf
https://www.efpia.eu/media/602699/production-import-dependencies-and-export-vulnerabilities-of-pharmaceuticals-for-the-eu27-final.pdf
Quality and Manufacturing Driven Supply Disruptions: Industry Communication Principles to Authorities, AESGP-EFPIA-EGA-PPTA, December 2014.
Joint Supply Chain Actors Statement on Information and Medicinal Products Shortages, AESGP, EAHP, EAEPC, EFPIA, EIPG, GIRP, Medicines for Europe, PGEU, January 2017; Joint Supply Chain Actors Statement on 'Addressing the root causes of medicines shortages, AESGP, EAEPC, EFPIA, EIPG, GIRP, Medicines for Europe, Vaccines Europe, 6 December 2019
BEUC 2020, "Addressing medicine shortages during the Covid-19 pandemic and beyond: the consumer check list", www.beuc.eu/publications/beuc-x-2020-034_addressing_medicine_shortages_during_the_covid-19_pandemic.pdf
https://www.medicinesforeurope.com/wp-content/uploads/2016/03/infographic-generics.pdf
https://www.medicinesforeurope.com/wp-content/uploads/2021/02/2020-Generic-Market-Review-Final.pdf
https://www.medicinesforeurope.com/wp-content/uploads/2020/01/ESE_2019_Medicine-for-Europe_AESGP_Variation_WEB.pdf
Medicines for Europe, 2019, Best procurement practices position paper. https://www.medicinesforeurope.com/wp-content/uploads/2019/04/M-Best-procurement-practices-position-paper_final-version.pdf.
https://www.eahp.eu/sites/default/files/eahp_position_paper_on_procurement_1.pdf
http://girp.eu/sites/default/files/documents/girp_position_on_use_of_emvs_for_monitoring_of_shortages_-_updatedfeb21.pdf
http://girp.eu/sites/default/files/documents/shortages_monitoring_in_case_of_public_health_emergencies-final.pdf
http://girp.eu/sites/default/files/documents/girp_medicine_shortages_reflection_paper.pdf
http://girp.eu/sites/default/files/documents/causes_of_supply_disruptions_across_europe_april_2020_-_read-only.pdf
https://www.amrindustryalliance.org/wp-content/uploads/2018/02/AMR_Industry_Alliance_Manufacturing_Framework.pdf

https://www.pgeu.eu/wp-content/uploads/2020/08/PGEU-Statement-on-the-potential-use-of-the-EMVS-to-monitor-shortages.pdf
https://www.pgeu.eu/wp-content/uploads/2021/05/PGEU-PP-on-ePI-WEB.pdf
https://www.pgeu.eu/wp-content/uploads/2019/03/2020-PGEU-Medicine-Shortages-Survey-Results-v2.pdf
https://www.pgeu.eu/wp-content/uploads/2019/03/2019-PGEU-Position-Paper-on-Medicine-Shortages-1.pdf

The following section is a more **detailed bibliography on hospital** and procurement related **supply chain issues** graciously put together by a contributing stakeholder, José-Louis Gomez:
https://www2.deloitte.com/content/dam/Deloitte/nl/Documents/public-sector/deloitte-nl-shaping-the-future-of-european-healthcare.pdf
Report on digital technologies among clinicians in EU: low level of automation and prescription systems still far to be optimal.
https://kitcheck.com/wp-content/uploads/2021/03/2020-HPOR-final.pdf
US survey among hospital pharmacists show the low level of stocks visibility and the importance of supply chain visibility in the hospitals.
https://ejhp.bmj.com/content/19/5/460.short
EAHP survey in Europe in 2010 showing the low level of automation and digitalisation in EU Hospitals.
https://www.scirp.org/pdf/JSSM20080200009_98414774.pdf
Examination of risks in the pharmaceutical chain in NHS: second rated risk in the list is lack of visibility of stocks.
https://ig.solutions/news_items/hospital-procurement-tips-for-optimizing-pharmacy-inventory/
Hospital Procurement: Tips for Optimizing Pharmacy Inventory. Manual workflows and processes in medication inventory management are not only cumbersome and slow but are also inadequate when it comes to gathering intelligent data. When staff is tasked with tracking, logging, and replenishing inventory manually, the resulting reporting is one or all of the below: Inaccurate because human errors are naturally bound to occur; Incomplete because processes were not followed, or only certain items were logged/tracked; Out-of-date because manual tracking is not real-time. In contrast, true real-time automation systems such as the Intelliguard® RFID solutions platform, not only simplify workflow processes for medication inventory management, but also provide historical reporting that is complete, accurate and real-time. https://healthcareglobal.com/procurement-and-supply-chain/top-10-myths-about-hospital-inventory-management-debunked
The main problem in hospital is inventory management. There is no way to see inventory that is stored all over the hospital.
https://www.pharmaceuticalcommerce.com/view/hospital-pharmacy-survey-finds-a-lack-of-visibility-to-internal-inventories
Hospital pharmacy survey finds a lack of visibility to internal inventories. https://apps.who.int/iris/bitstream/handle/10665/331028/DI302-180-185-eng.pdf
In supply chain unreliable data continue to be a major problem hindering coordinated stock management and effective forecasting.
https://joppp.biomedcentral.com/articles/10.1186/s40545-019-0188-8
Eliminating medicine waste in a Finnish university hospital — a qualitative study. The medicine supply process is characterised by many shortcomings in terms of IT systems usability and availability of consistent information. For example, information on stock levels and expiry dates in wards are maintained manually and the information is rarely accurate. As the IT systems are not integrated, staff need to manually crosscheck information from various applications when estimating medicines demand and placing orders. Staff often avoid this manual task and base their estimations on rules of thumb. The medicine inventory in wards is maintained manually and there is no accurate information on expiry dates. The expiry information on the wholesaler's ordering system can be incorrect.
https://www.supplychainquarterly.com/articles/4417-covid-19-and-the-health-care-supply-chain-impacts-and-lessons-learned.
COVID-19 and the health care supply chain impacts and lessons learned. By employing better cooperation, information sharing, and alignment among its members, health care supply chains could create a holistic view of essential medical supplies.
https://journals.sagepub.com/doi/pdf/10.1177/1460458219832056
Enablers and barriers for hospital pharmacy information systems. Our findings suggests that there is a need for pharmacy ISs. For example, central access to medicine machine to support the availability of medicine in wards would be beneficial especially for high-risk medicines which should be available 24/7 as needed, requiring the introduction of robotic technologies for dispensing medicines. Our research confirms that there is a need for such technology to facilitate greater flexibility, with a need for more central access for high-risk drugs. In addition, this research highlights the potential waste of medicines, costs associated with waste (millions of euros) due to poor stock control management strategies and tools and the impact of poor-quality medicine products on patients' healthcare.
https://www.nucleodoconhecimento.com.br/health/hospital-pharmacy: The study found that in most of the hospitals presented there is a difficulty in maintaining an adequate inventory control……such as difficulties to quantify actual consumption, specificity of stocked material.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4723708/
Conclusion: Improving communication systems within the hospital with vendor database management and reaching out to clinicians is important. Automation of inventory management requires to be simple and user- friendly, utilizing existing hardware. Physical stores monitoring is indispensable, especially due to the scattered nature of stores. Staff training and standardized documentation protocols are the other keystones for optimal medical store management. https://ecamet.eu/wp-content/uploads/Automated%20storage%20and%20electro/Batson%202020.pdf
Automation of in-hospital pharmacy dispensing: a systematic review. The studies demonstrate that both pharmacy and ward based ADSs offer benefits over traditional manual dispensing methods in terms of clinical and economic outcomes. The primary benefits following implementation of an ADS include reductions in medication errors, medication administration time and costs. Studies examining optimisation/inventory management strategies/refill programmes for these systems suggest that optimal implementation of the ADS is required to ensure that clinical success and economic benefits are maximised. https://ecamet.eu/wp-content/uploads/Automated%20storage%20and%20electro/Rodriguez-Gonzalez%202018.pdf
Robotic dispensing improves patient safety, inventory management, and staff satisfaction in an outpatient hospital pharmacy. The implementation of a robotic original pack dispensing system substantially decreased the rate of dispensing errors and optimized stock management. https://pharmaceutical-journal.com/article/research/managing-risks-arising-from-medicine-shortages-in-nhs-hospitals
Managing risks arising from medicine shortages in NHS hospitals. Medicine shortages also occur in hospitals (UK) due to failures in stock control and procurement, and a breakdown in the internal supply chain. Second failure with the highest criticality are failure to order medicines due to incorrect computer stock level or ordering parameters and alternative products not recognised or stored in a different location and not found and required.https://bmchealthservres.biomedcentral.com/track/pdf/10.1186/s12913-020-05080-1.pdf
Medicine shortages and challenges with the procurement process among public sector hospitals in South Africa; findings and implications. Results: The 'Procurement process' emerged from the data as the overarching theme, rooted in three main themes: (i) The buy-out process that was used to procure medicines from suppliers other than the contracted ones; (ii) Suppliers not performing thereby contributing to medicine shortages in the hospitals; and (iii) Challenges such as the inaccuracy of the electronic inventory management system used in the

hospitals Stock was not received and issued correctly, and the consumption data produced by RxSolution was not reliable. This made it difficult to quantify orders. Quantities ordered based on these unreliable consumption data by some hospitals subsequently led to medicine shortages because insufficient quantities that were ordered did not meet the needs of their patients. In some hospitals, staff also lacked confidence in the use of RxSolution. As a result, its use was minimal. Counting and verifying stock physically was also undertaken by storeroom staff since the quantities produced by the software were not always reliable.
https://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC6485132&blobtype=pdf

Availability of essential medicines and pharmaceutical inventory management practice at health centers of Adama town, Ethiopia. The availability of EMs and the accuracy of record keeping in the HCs were low. The major problem common for all HCs in the procurement process were PFSA stock status and transportation. The absence of computer software system and lack of enough pharmacy professionals are some of the challenges to perform inventory management practice in the HCs properly, which further decrease the availability of EMs in the facility. We recommend health professionals working at respective health centers to improve inventory management practice. The regional health bureau should provide capacity building to HCs with provision of computers and trainings.
https://aquas.gencat.cat/web/.content/minisite/aquas/publicacions/2019/Dispensacion_Robotizada_Hospitales_RedETS_AQuAS_2019.pdf

Economic, organization and safety impact of drug robotic dispensing in Spanish hospitals. The main result in organizational changes for hospitalized patients was that there is a reduction in nursing human resources as well as in time for stock selection and the annual value of the inventory. Moreover, automated robotic drugs dispensing systems for outpatients decrease the needs of pharmacy technicians, nursing assistants, administration staff and warehouse professionals. Improvements in managing stocks and inventory are observed too. In summary, reorganizing and optimizing circuits around the huge load and complexity that implies drugs storage, dispensation and control in hospitals seems to be a positive system. https://www.pharmacytimes.com/view/how-hospitals-can-keep-track-of-medications-drug-shortages-during-the-ongoing-covid-19-pandemic

It is imperative for hospital pharmacists to have full visibility into their medication inventory.
https://www.researchgate.net/publication/316245745_Medicines_Management_in_Hospitals_A_Supply_Chain_Perspective_

Pharmacy inventory management is a complex but critical process within the health care delivery system. Without adequate pharmacy inventory management practices, health care facilities run the risk of not being able to provide patients with the most appropriate medication when it is most needed. Addressing pharmacy inventory management and the revenue cycle effectively can enable organizations to improve financial performance, adhere to regulatory requirements, reduce risks relating to patient safety, and ensure availability of drugs without frequent stock outs. Effective and transparent tracking systems that allow pharmacies to accurately record inventory components, such as medication expiration dates and physical quantities, also have the potential to reduce adverse patient outcomes.
https://ahia.org/assets/Uploads/pdfUpload/WhitePapers/EvaluatingHospitalPharmacyInventoryManagementandRevenueCycleProcesses.pdf

Evaluating Hospital Pharmacy Inventory Management and Revenue Cycle Processes. Effective and transparent tracking systems that allow pharmacies to accurately record inventory components, such as medication expiration dates and physical quantities, also have the potential to reduce adverse patient outcomes. In a national survey performed by the Institute for Safe Medication. The “real-time” tracking ability offered through these systems includes recommending items and quantities to be ordered based on par levels set by the pharmacy in the system, providing limits on excessive orders, and electronically placing orders after a manual authorization. When setting the par levels for the automated ordering, it is important to set appropriate levels to maximize the ordering process and minimize excessive supplies.https://www.supplychaindive.com/news/hospital-inventory-automation-case-study-Cardinal-White-Memorial/520004/

Facing inventory problems, hospitals automate their supply chains.https://www.ashp.org/-/media/assets/policy-guidelines/docs/guidelines/managing-drug-product-shortages.ashx

ASHP Guidelines on Managing Drug Product Shortages. Poor ordering practices, stockpiling before announced price increases, hoarding caused by rumours of an impending shortage, and unexpected delivery delays may also affect inventory levels in individual healthcare organizations. Once a shortage is identified, pharmacy staff should assess the inventory on hand and estimate the time it will cover. Available inventory includes all supplies of the drug product within the healthcare organization, including the pharmacies, inpatient units, ambulatory care clinics, automated medication storage and distribution devices, floor stock, code carts, and prepared trays. Therapeutic alternatives should be inventoried, and availability assessed to ensure adequate supplies to meet new demand. In many cases, supplies of the best alternative agent may be affected by the response to the shortage. Http

Pharmaceutical Inventory Management Issues in Hospital Supply Chains. To address this issue, this study aims to examine inventory management practice in one of Indonesian public hospital and focus on the role of inventory to drive hospital supply chain performance. Three major issues regarding inventory management practice have been identified such as overstock, unjustified forecasting technique and lack of IT support. https://informatics.bmj.com/content/bmjhci/26/1/e100016.full.pdf

Technologies that transform digital solutions for optimising medicines use in the NHS. This article will explore the transformative potential of technologies relating to medicines and pharmacy in the NHS, focusing specifically on: (1) electronic prescribing (EP) and medicines administration, (2) robotics/automated dispensing and supply and (3) community pharmacy electronic referral systems. The article describes how the transformation these technologies enable has the potential to improve medicines optimisation in the NHS.https://hbr.org/2020/04/how-hospitals-can-manage-supply-shortages-as-demand-surges

How Hospitals can manage supply shortages as demand surges by Harvard Business Review. A critical part of pooling is not just sharing physical inventory but also sharing information about inventory: What is available, in which quantities, and where it is located? Good information cannot magically make shortages of physical materials go away, but bad information can certainly make shortages worse. Lack of information creates uncertainty, and uncertainty can lead to “just in case” hoarding.
https://www.who.int/medicines/areas/access/Medicines_Shortages.pdf?ua=1

TECHNICAL CONSULTATION ON PREVENTING AND MANAGING GLOBAL STOCK OUTS OF MEDICINES WHO. Supply chains can contribute to preventing and managing stock outs and it was noted that IT systems that facilitate both upstream and downstream collection of information need additional support. That is, systems that allow early prediction of shortages as well as management information systems, electronic tracking of products through supply chains, accurate forecasting, and quantification of need. Rapidly advancing the use of standardized bar coding was acknowledged as important and feasible. The shortage of reliable data from peripheral levels of the supply chain was noted as a persistent problem.

Participant list

	Rapporteur: Adrian van den Hoven – Medicines for Europe Co-rapporteur: Marco Farinelli – Astra Zeneca Jurgen Roos – Siegfried	Manufacturers christopher.e.schmidt@merckgroup.com allen_barbara_mary@lilly.com	

Manufacturers Koen Laenen – Medicines for Europe Camille Andries – Medicines for Europe François Bouvy - EFPIA Jana Nackberg - EFPIA François Lamérant - EFPIA Sandoz - Luca Febbraio Mihai Rotaru – EFPIA Accord -Healthcare - Brandon Turk Polpharma - Dorota Chec Stada - Jesus Corchero Leisha Daly, Johnson & Johnson Viatris - Juergen Mahling **Regulators/MOH/institutions** mibarra@aemps.es elina.asola@stm.fi biljana.temova@jazmp.si virve.reiman-suijkerbuijk@lakemedelsverket.se Eva.Karaskova@mzcr.cz karin.froidbise@fagg-afmps.be jrodrigues@who.int nuno.simoes@infarmed.pt AVEZOU Jean-Marie (Commission) andreas.sundgren@legemiddelverket.no santeri.hietanen@aalto.fi Dirk Mergan (FAGG - AFMPS) **Distributors & related** Monika Derecque-Pois (m.derecque@girp.eu) Martin Fitzgerald (m.fitzgerald@girp.eu) Bernd Grabner (b.grabner@girp.eu) ke@affordablemedicines.eu TBauroth@kohlpharma.com **Public health NGOs** yannis@epha.org mike.isles@eaasm.eu **Academia** D.Cotta@maastrichtuniversity.nl	**Manufacturers** Gisela P Payeras, GSK Leonie Völker, Johnson & Johnson Barbara.solow@amriglobal.com Lucas.Wiarda@innogenerics.com noelte@bah-bonn.de AESGP - Christelle Anquez jlgs@novonordisk.com lgomes@hovione.com MSA@cefic.be marc.weissenfeld@bayer.com anders.liljegren@roquette.com jrumsch@bpi.de claudio.lorck@abbvie.com koen.berden.ext@efpia.eu Jadran JGL - Mate POROPAT Viatris - James Cubero B.Grimm@europabio.org patrick.costello@abbvie.com Efpia - Par Tellner AGranado@ITS.JNJ.com moya@eucope.org Association GR - PEF - Katerina Patavou Timothee de Chevron Villette Thomas Nothegger Rodriguez, Jose Luis Stephen Callanan Gang Shlomo Tsoutsa Vicky Heidari, Behnam /GB Mariagrazia Sturniolo Maheas, Arnaud Anna Wehage – BAH e.V. Centrient - Alba Tiley **Consumers** ancel.la.Santos@beuc.eu **Pharmacists** i.passarani@pgeu.eu **Doctors** Klaus.H.Meier@gmx.net

Reflection on the process

What was your overall experience with the process? Many experts contributed time and effort for a constructive dialogue and a strong paper. Some participants (BEUC) highlighted the fact that there is an unbalanced representation of stakeholders in the group. The participants list identifies each participating stakeholder group. On most issues, there was an effort to reach consensus. On some issues mainly related to the policy recommendations, there is still work needed to achieve a consensus. This will be clarified in the document.

Were all stakeholder views included in the discussions? There was an attempt to give all stakeholders the opportunity to comment and to contribute actively to this work. First, views and opinions were shared at meetings to scope out the work for the future paper. Then the draft paper was shared to enable comments and adaptations. The fruitful discussions enabled alignment and better understanding on many issues and a strong effort to understand different perspectives.

Were there particular (organizational) challenges concerning the collaboration within the workstream? The timeframe was short, but the stakeholders worked hard to align this recognising different resources and capacity of stakeholders to engage in the process.

SUMMARY OF POLICY OPTIONS FOR ROBUST SUPPLY CHAINS: *This table summarises the policy options in the paper which derived from stakeholder dialogue but is not a policy paper of any of the participating stakeholder associations nor the direct expression of the people that contributed to it. Where there is specific opposition from a participating stakeholder on an issue, this is identified in the table.*

PROBLEM AREA	POLICY OPTION	CHANGES REQUIRED	STAKEHOLDER OPPOSITION	POLICY LEVEL	TIMELINE
VISBIILITY/ PREDICTA-BILITY	DIGITAL SHORTAGE REPORTING	ALIGN ON COMMON DIGITAL TEMPLATE & FIELDS FOR MANUFACTURER SHORTAGE REPORTING ENABLE AGGREGATION OF RELEVANT DATA TO EU LEVEL (REPLACES SPOC/ISPOC)		EU LAW & NATIONAL IMPLEMENTA-TION	COMMON TEMPLATE 1 YEAR. PILOT 6 MONTHS: TOTAL: 1.5 YEARS
	SHORTAGE PREVENTION PLANS (SPP)	AGREE TO IMPLEMENT ISPE/PDA REPORTS, ALIGNING ON COMMON EU SPP TEMPLATE DEFINE AND AGREE CRITERIA FOR SPPS ENABLE DIGITALISATION OF SPPS FOR DATA CONSISTENCY AND EASE OF USE		EU & NATIONAL IMPLEMENTA-TION	COMMON TEMPLATE 1 YEAR. PILOT 6 MONTHS ROLL OUT 1-2 YEARS
	DIGITAL HOSPITAL INVENTORY MANAGEMENT	INVEST IN DIGITAL MANAGEMENT IN HOSPITALS		NATIONAL	UNKNOWN
	TELEMATICS	ENACT TELEMATICS ROADMAP AGREE STANDARDS FOR PRODUCT IDENTIFICATION FOR SUPPLY PURPOSE (LIKE GS1) INVEST IN DIGITAL SYSTEMS IN NCAS		EU LAW & NATIONAL IMPLEMENTA-TION	1 YEAR FOR STANDARDS 2 YEARS FOR DIGITAL INVESTMENTS
	INTEROPERABLE DATA SYSTEMS	INTERCONNECT SHORTAGE REPORTING, TELEMATICS, EMVS & OTHER RELEVANT DATA TO IMPROVE SHORTAGE PREVENTION/MITIGATION ALIGN ON CONFIDENTIAL/NON-CONFIDENTIAL DATA	FULL-SERVICE HEALTHCARE DISTRIBUTORS (WHOLESALERS) & PHARMACIES OPPOSE FOR EMVS DATA (SEE FULL DETAIL IN PAPER)	EU & NATIONAL IMPLEMENTA-TION	4 YEARS (CUMULATION OF 2 ABOVE)
A ROBUST AND ENABLING REGULATORY FRAMEWORK	REGULATION OF MANUFACTURING SITES	EXPEDITED REGULATORY FRAMEWORK FOR MANUFACTURING INNOVATION CHANGES, SITE TRANSFERS & OTHER INDUSTRIAL INVESTMENTS		EU LAW & EU/NATIONAL IMPLEMENTA-TION	UNKNOWN
	REDUCE MAINTENANCE COST/ COMPLEXITY	UPDATE OF VARIATIONS REGULATION: ICH & BETTER REGULATION & API INFORMATION REDUCE REGULATORY COST OF DUAL SOURCING WHERE APPLICABLE		EU PHARMA STRATEGY/ COMMISSION REGULATION	1.5 YEARS
	INTERNAL MARKET HARMONISATION	HARMONISE PACKAGING/LABELLING – INCLUDING EPI TO IMPROVE STOCK ALLOCATION ACROSS EU	PGEU/ BEUC/ESOP DISAGREE ON REMOVAL OF PAPER LEAFLET	EU REGULATION	2 YEARS
	SHORTAGE PREVENTION & MITIGATION	RISK MANAGEMENT PLANS/ FOLLOW WK 2 GUIDANCE: PILOT RELATED TO LIST OF CRITICAL MEDICINES PLANNED REGULATORY AGILITY AND FLEXIBILITY MEASURES TO ENABLE RAPID RESPONSES TO SHORTAGE MITIGATION	WK 2 VALIDATION REQUIRED	EU REGULATION	REFER TO WK 2 REPORT IMMEDIATE
SUSTAINA-BILITY	ENVIRONMENTAL SUSTAINABILITY	INTEGRATE ENVIRONMENTAL LEGISLATION FITNESS CHECKS (REACH, PIE, ETC)		EU REGULATION RRF	ONGOING ONGOING

		INVEST IN GREENER PRODUCTION WITH STRUCTURAL FUND SUPPORT ENSURE GLOBAL SUPPLY CHAINS COMMIT TO ENVIRONMENTAL PROGRESS		GLOBAL STANDARDS (AMR COMMON FRAMEWORK)	ONGOING
	ECONOMIC SUSTAINABILITY	REFORM PROCUREMENT RULES TO INTEGRATE SECURITY OF SUPPLY (MULTI-WINNER TENDERS, SUPPLY CRITERIA, LEAD TIMES) LIMIT COST-CONTAINMENT MEASURES ON OLDER, LOW-COST, GENERIC MEDICINES SUPPORT MEDICINES MANUFACTURING IN EUROPE NON-PROFIT MANUFACTURING DIALOGUE		EU DIALOGUE ON HEALTH PRODUCTS PROCUREMENT TRANSPARENCY COMMITTEE RRF --	1 YEAR 1 YEAR ONGOING --
OPEN TRADE FLOWS AND GLOBALLY COMPETITIVE INDUSTRY	STRENGHTEN GLOBAL VALUE CHAINS AND EU INDUSTRY GLOBAL COMPETITIVENESS	EU RULES TO ENSURE OPEN GLOBAL TRADE FLOWS AVOID EXPORT RESTRICTIONS, FORCED LOCALISAITON AND TARIFFS PUT IN PLACE MARKET INCENTIVES FOR STRENGTHENING R&D AND PRODUCTION LONG-TERM POLICIES THAT ENHANCE EU INDUSTRY COMPETITIVENESS GOVERNMENT AND INDUSTRY COLLABORATION ON UPSKILLING THE MANUFACTURING WORKFORCE MAINTAIN AND ENSURE REGULATORY FLEXIBILITY WHERE JUSTIFIED	IF IN THE PUBLIC INTEREST	EU / NATIONAL EU/NATIONAL NATIONAL (POSSIBLY EU STATE AID RULES) EU/NATIONAL EU	IMMEDIATE
	GLOBAL REGULATORY HARMONIZATION	EU LEADERSHIP IN IMPORTANT SUPPLY CHAIN CONVERGENCE DISCUSSIONS GMP INSPECTORATES PLAN TO ENSURE ADEQUATE RESOURCES ENCOURAGE VOLUNTARY REGULATORY COOPERATION ELEMENT (LED BY REGULATORS) IN EU TRADE AGREEMENTS SECURE MRAS ON GMP WITH THIRD COUNTRIES ON MANUFACTURING QUALITY AND ALIGNMENT/MUTUAL RECOGNITION OF STANDARDS		INTERNA-TIONAL/EU EU/NATIONAL INTERNA-TIONAL/EU INTERNA-TIONAL/ EU/	IMMEDIATE

Final version: 18 July 2021

The paper was drafted based on input from participating stakeholders and the rapporteurs (Adrian van den Hoven, Marco Farinelli and Jürgen Roos) take responsibility for the overall paper.

This document strives to give an account and draw some conclusions from discussions during the working meetings known as "Structured Dialogue on security of medicines supply" organised by the European Commission and taking place between 26 February 2021 and 15 July 2021. These meetings were organised by stakeholders and by the Commission. This document, while mentioning possible policy options in its conclusions, does not want to be a policy paper of any of the participating stakeholder associations nor the direct expression of the individual opinions of the people that contributed to it. The terms used in the paper to identify a plurality of individuals (i.e.: we identified, we believe, etc.) should be intended as the account of the discussions happening during this exercise, with such contributions made on a voluntary basis and according to each participating member's knowledge and interest on the specific topic.

The paper builds on a series of power point-led exchanges of information in a virtual setting as well as Commission brainstorming/break-out seminars. This paper hopes to inform the Commission's development of pharmaceutical and industrial policy initiatives related to this topic. This paper will be shared with the rapporteurs of work streams 2, 3 and 4 for policy coherence. Opinions expressed in this paper are based on the debate among the participants during the exercise and reflect the conclusions reached on the different points. While an effort to reach general consensus on the various topics was made during this process, where there is specific opposition from a participating stakeholder on an issue, this will be stated in the document.

1. Process & Scope

The wide range of stakeholders (including healthcare professionals, patient and consumer associations and health policy NGOs, manufacturers of medicines and chemistry, medicine regulators and health ministry officials, academic experts, hospital procurers, parallel distributors, and full-service healthcare distributors(wholesalers)) agreed to cooperate in the drafting of this paper based on openness, focused debate on the issue at hand and input/evidence-driven work. We agreed to develop a clear and shared understanding for supply chain experts and non-experts of robust supply chains across pharmaceutical production steps and segments operating in single or multi-source market settings and to look for opportunities to strengthen robustness.

This dialogue took place in the context of the Covid-19 pandemic whose experience and lessons were used in our discussions. There was consensus that robust supply chains should be agile to facilitate response to crisis situations. While the pandemic influenced discussions, it was acknowledged that supply disruptions also occur in more normal environments. Members were aware that EU citizens (patients & their healthcare providers) are expecting supply chain stakeholders and governments to do all in their power to prevent and mitigate medicinal product shortages and meaningful supply disruptions.

Stakeholders also discussed the extent of pharmaceutical production in Europe and the risk associated with reliance on imported medicines, their components, or raw materials in situations where there is limited supply chain diversification and there are distortions to open trade flows. While there is value and support for encouraging pharmaceutical manufacturing in Europe and strengthening the global competitiveness of the European industry, the EU is not able to be self-sufficient in terms of manufacturing. Supply chains are global and geographic diversification facilitates the adjustment of production and supply as demonstrated during Covid-19 when the industry had to react to an unprecedented increase in demand. The term *open strategic autonomy* (and how we balance autonomy and openness) will be a point for further elaboration in this paper.

In terms of scope, this paper seeks to answer the questions addressed to work stream 1 by the European Commission.[15] However, there was an overarching perspective that the purpose of robust supply chains is to ensure the secure supply of medicines to patients under normal market conditions and in times of crisis.

Commission Questions for Workstream 1

What are the main causes of problematic/ the most challenging disruptions? How do you classify the associated risks? Answer under definition of robustness *How do robust supply chains mitigate the risks associated with potential supply disruptions? Answer according to pharma segment* *Is increased complexity of supply chains a risk factor? Are the critical points identifiable? Answer according to pharma segment and drivers/constraints* *Is the robustness of current supply chains threatened by long term industrial and health policies of countries our supply chains are the most integrated with (USA, China, India, Japan)? What specific vulnerabilities are already predictable/ can be foreseen or anticipated? Answer according to different segments and drivers/constraints* *What is the assessment of the evolution of the supply chains and their robustness in the last decade? Has it increased? Decreased? Are there any pivotal points that resulted in meaningful improvements? Answer under drivers/constraints* *What is the cost implication for increasing the robustness of the supply chain? Where is the greatest investment required? Answer under drivers/constraints* *How well does the existing regulatory framework support the robustness of the supply chains? What critical aspects are present/ missing? Answer under drivers/constraints*

In line with those objectives, the stakeholders agreed to break the issue down into different steps to improve shared understanding and to advance toward coherent, consistent, and cohesive policy responses that could make a difference to the supply of medicines to patients. Hence, the paper is structured along four important themes.

1) First, the paper describes **the criteria for robust pharmaceutical supply chains**, the enablers, and the outcomes that they should deliver to patients (through healthcare practitioners).
2) Second, the paper applies the criteria, enablers, and outcomes across **different production steps (upstream chemistry, API, medicines production), different production segments (oral solid, sterile, and complex biologic or vaccine) recognising that these segments operate in very different settings or environments (single vs multisource; high vs low volume)**.[16]
3) Third, the paper explores **the options for enablers of robust supply chains** according to the different production steps and to the pharmaceutical segments and settings (volumes, single/multisource, technologies). The paper recognises that options are important because some solutions may increase robustness in some segments or settings and decrease robustness (or access to medicines) in other segments or settings.
4) Fourth, the paper sets out **policy options** related to the EU Pharmaceutical Strategy and the EU Industrial Policy Strategy (and possibly other strategies) to provide a pathway to improve the conditions to enable robust pharmaceutical supply chains.

[15] The dialogue operates under the leadership of Commission Vice-President Schinas and Commissioners Kyriakides (Health) and Breton (Internal Market) with the support of the SANTE and GROW Directorates-General.

[16] While the focus is on pharmaceutical manufacturing, stakeholders acknowledge the interconnection between therapeutic need or *demand* and pharmaceutical manufacturing or *supply* and that patients are prescribed, dispensed and/or administered medicines by healthcare providers. In addition, key intermediaries such as wholesalers, pharmacies and hospitals distribute medicines and hold stocks to meet patient demand; payers and procurers purchase or reimburse prescription medicines for patients; regulatory agencies oversee the safety, quality, and efficacy of medicines – and enforce important quality standards[16] such as good manufacturing practice or good distribution practice (GMP/GDP).

Section 1: The Criteria for robustness – Reliability and Responsiveness

The stakeholders discussed the criteria for robust pharmaceutical supply chains and agreed on two overarching criteria - **reliability and responsiveness** - to ensure the supply of medicine to patients.

Reliability refers to the degree to which a pharmaceutical supply chain consistently achieves performance in delivering supply. In the pharmaceutical industry, companies will often measure their service levels to validate this reliability. Reliability may be challenged by different factors such as the complexity of production chains or a lack of visibility on future demand or keeping insufficient inventories.

Pharmaceutical production chains are long and complex: A typical pharmaceutical product may contain over 200 different sourced components and the production process requires consumables such as filters, bags, and other equipment. The supply of these components and consumables must be available and procured (by the manufacturer) for a reliable supply chain.

Visibility of demand may be unclear for different reasons: For example, changes to public vaccination policies will alter the demand for vaccine producers that typically have long production lead times. Procurement practices may lack volume commitments or have insufficient lead times. National tender processes where one provider wins the entire national supply for a product for a defined timeframe means losing competitors pivot manufacture to countries in which they still have a market. A production shortage of one product or a product withdrawal may lead physicians to prescribe another product in its place without the knowledge of the other producer. An unexpected increase in a disease may drive demand surges for products or panic in the market.

During Covid-19, the pharmaceutical industry was confronted simultaneously with demand surges for medicines used to treat or to prevent Covid-19 and with disruptions in global supply chains due to the shift of production to meet Covid-19 demand, lockdowns, logistics challenges and trade restrictions.

Table 1: Examples of supply/demand factors that affect the reliability of supply chains

	In normal market conditions…	In a crisis situation…
Production supply chain related…	**Production disruption**: If one producer has a production stoppage (for whatever reason) that disrupts supply to patients, there will be a need to switch to alternative suppliers (another generic or another molecule for a single source product), This can create stress on the supply chains for the other producers. This a challenge with injectable antibiotics. **Regulation changes**: A new environmental regulation in China (the Blue Sky, Blue Water policy) led to the closure of key RSM manufacturing plants that could not meet the required standards. This caused disruptions in the availability of RSMs as there were limited capacities available globally from other production sites. Stronger enforcement of environmental policy in China is positive but the rather abrupt implementation made it difficult to predict for supply chains. In some cases, the EU industry started to re-manufacture these RSM. In other cases, there were production bottlenecks. **Hidden consolidation**: The discovery of above specification nitrosamine impurities in certain sartan-based medicines led to regulatory action (temporary withdrawals) but it also showed high reliance on one big API supplier (even though there were others). This made it difficult to reorganise supply quickly. Also, if a product is withdrawn, there may be unforeseen demand for another product because there is no communication between companies on this. **Information on stock situation**: Some hospital procurers expressed frustration about receiving limited information about shortages from manufacturers and regulators. In some companies, supply chains are managed centrally at EU level – not in the commercial affiliates of each Member State. Hence there could be better information	**Production disruption**: When the Covid-19 pandemic struck China, many chemical factories and logistic centres were shut down, leading to stress on global production chains. On the other hand, global supply chains reacted quickly to this disruption. The EU, then India and the US agreed to maintain pharmaceutical production open (under strict hygiene rules) throughout the pandemic avoid shortages of medicine. Global and diversified supply chains also allowed companies to quickly adjust production and supply where needed to secure supply in Europe and at global level. **Border closures**: The closure of EU internal borders in March/April 2020 severed the EU pharmaceutical supply chain between API and FdF producers. The "green lanes" of the Commission prevented a complete breakdown (and near certain shortage of nearly all medicines). **Export restrictions**: India imposed export restrictions on some medicines and API needed for Covid-19 – notably paracetamol and the experimental use drug hydroxychloroquine. Although there was enough inventory to scale up production in Europe, some governments diverted stocks to hospitals and limited pharmacy purchases to stop hoarding by individual consumers.

	flow between EU and national level or between national regulators and market operators.[17]	
Demand visibility related…	**Procurement problems**: Many hospital tenders do not include volume commitments and apply very short lead times which increases the risk of stock outs. Many hospital tenders only rely on lowest price criteria, single winner policies with no analysis of the robustness /sustainability /reliability /responsiveness of the selected supplier. In Southern Europe, many hospital tenders receive no bids due to the problematic risk/reward ratio (penalties higher than the value), so companies do not build up stock for this demand creating a problem for hospitals to source the medicines through contracting. In the northern countries hospitals attempts to include stockpiling as a requirement for tender participation also acted as a barrier for companies to join leading to the opposite effect and limiting supply available. **Public health policies**: Vaccination recommending policies do not include dialogue with producers, hence difficult to plan production.	**Demand assessment**: During Covid-19, demand for ICU medicines surged. Neither Member States nor the ECDC could make any demand or inventory assessments. Industry then did its own epidemiological calculations. **Public health policies**: To reduce the risk of combined flu and 2nd wave Covid-19 pandemic, governments that had not ordered flu vaccination decided to encourage flu vaccination – increasing demand where production struggled to follow because of long production cycles. A dialogue between authorities and industry would have been important to make the best used of delivered vaccines **Public health policies**: Covid-19 has led to a dramatic decline in diagnosis and treatment for NCDs with historically high growth rates (cancers, diabetes…), when diagnosis/treatment resumes, there will likely be a surge in demand for these medicines.

Supply chain visibility in a shortage situation

The definition of shortages is an important issue that has two facets. First, it serves to define the supply obligations of manufacturers and the public service obligations of wholesalers. There is a need to align stakeholder views on this facet. Second, it can improve the harmonised collection of shortage reporting data across the EU. This is not controversial but requires better alignment across EU countries.

i) For the purpose of obligation to supply/Public service obligation: There have been several attempts to engage with all relevant industry[18] and supply-chain stakeholders[19] [20] to address medicinal product shortages and seek common solutions. However, there are different perspectives between manufacturers and wholesalers. In line with their supply obligations under Article 81 of Directive 2001/83/EU[21], **manufacturers** would define a shortage of a medicinal product for human use "*when supply does not meet patient need at a national level for a period of more than two weeks*"[22]. On the other hand, wholesalers consider the definition in the EMA notification as the most relevant.[23] Ideally, there could be an alignment of views between manufacturers and wholesalers while ensuring the input and views of other stakeholders.

[17] https://apps.who.int/iris/bitstream/handle/10665/331028/DI302-180-185-eng.pdf
In supply chain unreliable data continue to be a major problem hindering coordinated stock management and effective forecasting.; https://www.supplychainquarterly.com/articles/4417-covid-19-and-the-health-care-supply-chain-impacts-and-lessons-learned.
COVID-19 and the health care supply chain: impacts and lessons learned. By employing better cooperation, information sharing, and alignment among its members, health care supply chains could create a holistic view of essential medical supplies.

[18] Quality and Manufacturing Driven Supply Disruptions: Industry Communication Principles to Authorities, AESGP-EFPIA-EGA-PPTA, December 2014

[19] Joint Supply Chain Actors Statement on Information and Medicinal Products Shortages, AESGP, EAHP, EAEPC, EFPIA, EIPG, GIRP, Medicines for Europe, PGEU, January 2017

[20] Joint Supply Chain Actors Statement on 'Addressing the root causes of medicines shortages, AESGP, EAEPC, EFPIA, EIPG, GIRP, Medicines for Europe, Vaccines Europe, 6 December 2019

[21] Article 81 states that: The holder of a marketing authorisation for a medicinal product and 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. The arrangements for implementing this Article should, moreover, be justified on grounds of public health protection and be proportionate in relation to the objective of such protection, in compliance with the Treaty rules, particularly those concerning the free movement of goods and competition.

[22] See comments by EFPIA, Medicines for Europe and EASGP on EMA/HMA Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders in the Union: the definition included in the EMA/HMA Guidance refers to national demand rather than patients needs and therefore implies that it is the supply chain (e.g. wholesalers) that defines the existence of manufacturers' shortages irrespective of patient needs. The EMA/HMA definition goes beyond the responsibilities of a marketing authorisation holder and the scope as identified in Article 81 of Directive 2001/83/EU.

[23] Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA)

Recognising that API production problems may be a cause of shortages[24], this should be duly considered by regulatory agencies in the event of a shortage report by a MAH or a wholesaler in accordance with their supply obligations in national markets.

ii) For the purpose of shortage reporting: Improving the availability of useable data is important to better detect where and when a drug shortage will happen and to quickly adopt supply chain countermeasures to mitigate or avoid a shortage for patients. Although the EMA has adopted a guideline[25] on shortage reporting, this does not require Member States to align shortage reporting requirements. In practice, the definition of a shortage is not aligned[26] across national shortage reporting systems regarding what would be a meaningful disruption in the supply of medicines[27]. Furthermore, most reporting systems do not distinguish between 'suspected medicine shortage' and 'actual medicine shortage' that capture what is a meaningful supply disruption with patient impact. If the problem is to be effectively tackled, there needs to be a commonly agreed definition of what constitutes a material medicinal product disruption so that the detection of shortages is consistent across the supply chain and countries. In this regard, it is important to link this discussion on a shortage definition with the considerations of Workstream 2's list of critical products.[28] We reference here the work undertaken by Work Stream 2 "Critical Medicines" to clarify this matter.

A common approach would enable the authorities and supply chains to proactively prevent or mitigate shortages. This could be achieved through a proactive management system that actively assures and monitors quality standards, inventory levels and market signals for successful supply management to be achieved. Stakeholders recognise the importance of working towards preventing drug shortages and effectively managing supply before a shortage actually occurs. A management system itself can minimise the risks of drug product supply disruptions from arising.

Reliable, up-to-date, and comprehensive information systems are essential to identify, communicate and resolve potential and actual shortages. They help to:

- Ensure that assessment of likely shortages is based on actual data;
- Implement contingency plans to minimise any adverse impact on patients;
- Implement a rapid alert and resolution process between different supply chain actors in urgent cases to avoid severe adverse impacts on patients;
- Provide patients with appropriate information (for example why their treatment needs to be disrupted, delayed or changed). This should be based on a common shortage definition;
- Facilitate manufacturing mitigation actions (i.e., switching production lines, changing work organization to increase output, etc.) to increase production and meet demand.
- Ensure the optimal management and distribution of remaining stock; and consider ways to harmonise packaging and labelling requirements to facilitate manufacturing inventory management across (internal EU) borders.
- Facilitate substitution and/or provide therapeutic alternatives.

iii) Hospital data complexities: Reliable data is critical to make good decisions. The medicines supply chain in hospitals is a very complex process, including ordering, reception, storing, distribution among wards and departments and dispensing/administration to patients. Since the level of digital technology (including automation) in most of EU hospitals is relatively low, medicines supply in EU

[24] The interim report of the study on the root cause of shortages by Technopolis indicates that 9% of MAH reported shortages list API production as the declared cause of a shortage. Please note that these are interim results and therefore cannot be verified or confirmed at this moment.

[25] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-detection-notification-shortages-medicinal-products-marketing-authorisation-holders-mahs_en.pdf

[26] Also confirmed in this survey of Member States: https://ec.europa.eu/health/sites/default/files/files/committee/ev_20180525_summary_en.pdf

[27] Not all products have the same criticality and impact with regards to patient needs and supply. The fact that a medicine is not available in a specific presentation but is available in other presentations cannot be put on the same footing with a shortage of a life supporting or life sustaining medicine. At the same time, however, using alternative treatments may lead to medication errors and/or adverse drug reactions.

[28] The paper of WS 2 notably defines criticality according to timelines and patient risk factors.

hospitals is a manual process. There is a lack of visibility and accuracy of medicines inventory records. In most of cases, inventory records only reflect the inventory in the pharmacy warehouse, not the whole inventory in the hospital. And since it is managed manually, even the pharmacy warehouse inventory data may not be up to date. Therefore, in conjunction with a proactive management system to monitor shortages and stock levels, there should be an EU project to digitise and automate medicines management in EU hospitals for reliable data to make the right decisions.[29]

Responsiveness is the ability of supply chains to respond quickly and purposefully to sudden changes in supply or demand. From a production point of view, pharmaceutical manufacturers have been confronted with disruptions caused by unforeseeable events such as: volcanoes in Iceland disrupting air cargo, hurricanes in Puerto Rico affecting production and logistics, the first Covid-19 lockdown in China disrupting chemical production and logistics, or the closure of EU internal borders during the first Covid-19 lockdown in Europe. From a demand point of view, the pharmaceutical industry has also been confronted with unpredictability, the Covid-19 pandemic creating demand surges for ICU medicines, steroids, pain treatments and vaccines. Consequently, pharmaceutical companies use contingency planning for business disruption risks and the flexibility to pivot supply chains to adapt to new supply or demand circumstances. For example, many multipurpose pharmaceutical production sites in Europe were able to use inventories and/or to shift their production to Covid-19 priority medicines or vaccines. The corollary to this is that the production of other medicines declined (luckily from a supply constraint perspective only, so did demand due to the dramatic decline in diagnosis and treatment of most NCDs in Europe). The geographical diversity of supply chains and open trade flows also played a key role to allow companies to adjust supply and manufacturing during the pandemic and it remains a key factor to secure resilience of the supply chain beyond COVID19.

At the same time, national level hospital and healthcare provider (HCP) stakeholders highlighted concerns with pharmaceutical industry responsiveness to normal market conditions where no major disruptive event was occurring. They posited that pharmaceutical companies were not maintaining sufficient buffer stock to manage normal variations in demand such as a higher infective season and that "just in time"[30] delivery had become too lean. As this focused on tender markets, there was some debate over the flexibility or lack thereof in tender markets regarding criteria (usually price only) and visibility on demand (lead times, volume commitments). The same HCP stakeholders highlighted a perceived information gap between the centralised supply chain/production departments of companies and the commercial teams operating in Member States leading to limited information about supply chain problems, the potential duration of a disruption or shortage and, most critically, when the country or hospital would receive its allocation. Manufacturers clarified that the implementation of EU regulation (packaging, leaflets, sometimes different presentations) hinders a rapid response by manufacturers as they need to produce packaging (sometimes presentations) separately for each Member State – significantly delaying response times. Admittedly, much greater flexibility was afforded during the Covid-19 Pandemic on such matters.[31] These exchanges between HCPs and industry showed that there are pathways for deeper understanding of supply and demand dynamics and that there are also ways to improve communication and to solve these issues in the future.

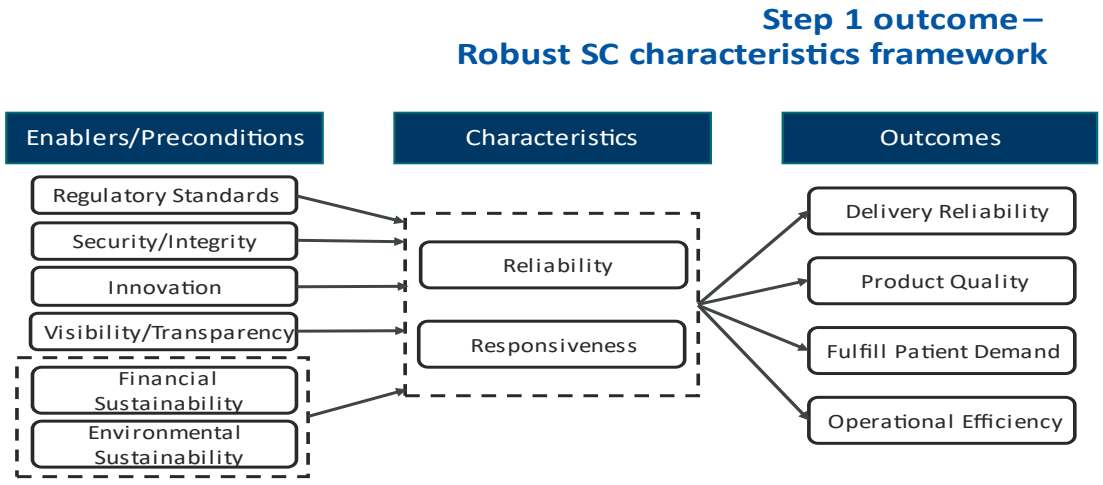
[29] This section is referenced by dozens of academic articles in the references section of this document which is a bibliography devoted to these hospital management issues. See pages 13-15 of this document.

[30] It is not clear that "just in time" supply chains are widely used in the pharmaceutical sector as most companies maintain inventories of components as these are not difficult to store – unlike other industries like the car industry which cannot hold comparable inventories. This may reflect the operation of some markets such as the Netherlands where most volume medicines are procured through tender systems or de facto tender systems (the 'preference' model). These procedures typically do not include coherent lead time transitions giving the perception of a "just in time" delivery.

[31] For Covid -19 vaccine packaging see: https://ec.europa.eu/health/sites/default/files/human-use/docs/vaccinesstrategy_labellingpackaging_en.pdf. For medicines in general, see the Notice from the Commission, EMA and HMA, specifically p.16 https://ec.europa.eu/health/sites/default/files/human-use/docs/guidance_regulatory_covid19_en.pdf

In some ways, the discussion indirectly tackled this with a reflection on the enablers or the preconditions of reliable and responsive supply chains.

- *Regulatory standards* are an important enabler because they establish clear requirements for manufacturers regarding the quality of products (an important outcome). For example, the manufacturing of a of medicines and many of their components must comply with good manufacturing practice (GMP) and their distribution must comply with good distribution practice (GDP). Regulatory agility can contribute to robust supply chains when, for example, changes of API, raw materials, or primary packaging are required urgently.
- *Security and integrity* are needed to ensure that products are safe and that the supply of medicines is not harmed by, for example, falsified medicinal products.
- *Innovation is important* to develop novel manufacturing (i.e., gene therapies), for innovative manufacturing and development in robust and sustainable processes and to leverage digital information to improve visibility of supply and demand. There is a great opportunity to increase supply chain resilience and robustness by optimising existing technologies and make them more agile thanks to the power of data. But Europe also needs to build its resilience on future medicines by being at the forefront globally of innovation in strategic therapy areas, modalities (advanced therapies, mRNA, new vaccines) and bioproduction. Financial sustainability is critical to encourage investment in manufacturing and robust supply chains. Multisource market policies aiming at lowest price discourage these investments.
- *Environmental sustainability* is a growing dimension of pharmaceutical policy related to the greening of production and to avoiding waste in the system such as producing large unused stocks. The pharmaceutical industry argued that environmental sustainability should be rewarded in market policies as this can increase the cost of production for those companies that invest in improvements. This requires an adaptive environment that focuses on value rather than cost to incentivize and offset the cost of investing in greener and more flexible manufacturing technologies.

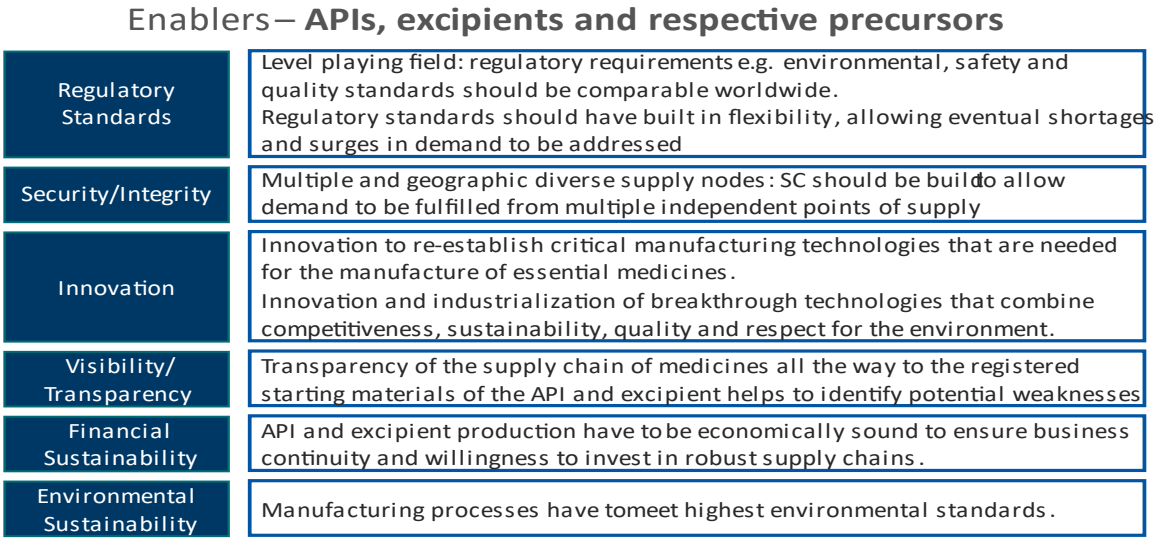


Section 2: Applying the criteria to different production segments/types

The stakeholders assessed supply chains across production steps, pharmaceutical segments, and settings. More specifically, there were presentations by EFCG on upstream chemistry, and the two rapporteurs (coming from EFPIA on single source specialty medicines and Medicines for Europe on multisource community and specialty medicines).

a. Upstream chemistry

The dialogue afforded a rare opportunity to look *below the iceberg* to better understand the role of raw materials, precursors, and intermediates in API production. API provide the therapeutic effects and are therefore an essential part of the pharmaceutical supply chain. The enablers of the upstream supply chains are described below.



The presentation also highlighted a concern over reliance on imported precursors, intermediates and APIs that are critical for production which has been driven by consolidation of the supply chain to lower the cost of goods (COGs). An IQVIA study[32] highlighted that whilst APIs for innovative drugs are mainly sourced from Europe, around two-thirds of APIs for generic drugs are sourced from Asia. Other studies confirm this data. A study by Mundicare and a study by the US Office of the White House show that while the EU is still a major manufacturer of generic API (also as a supplier to the US), India and China have grown much faster than EU manufacturers.[33] For all types of drugs, it is estimated that three-quarters of starting materials or critical process chemicals are sourced from Asia. In some instances, there is no technical infrastructure capability in Europe to produce those precursors, which means that the EU is dependent or reliant on external suppliers. The presentation by EFCG emphasised that this is not a molecule specific issue but rather a technological process issue covering some important chemistry processes necessary to produce most (chemically synthesised) medicines such as fluorination or nitration.

The presentation also outlined the multiple causes of this dependence on external sources – primarily China and to a lesser extent India.

- A focus on lowest cost medicines in pharmaceutical policies, incentivises pharmaceutical and API manufacturers to look for lower cost suppliers often located in China or India.[34]
- Stricter EHS rules for production in Europe have created an opportunity for Chinese or Indian suppliers, where until recently there has been lax enforcement of EHS rules, to step into the market.

[32] EU Fine Chemical Commercial KPI; December 11, 2020 (commissioned by EFCG). https://efcg.cefic.org/wp-content/uploads/2021/06/20201211_IQVIA-for-EFCG_Executive-summary.pdf

[33] Mundicare, 2020, Where do APIs come from? For an English language summary: https://progenerika.de/app/uploads/2020/11/API-Study_short-version_EN.pdf; https://www.whitehouse.gov/wp-content/uploads/2021/06/100-day-supply-chain-review-report.pdf

[34] This is also confirmed by the study of the US Office of the Whitehouse, citing: FDA's 2011 report, "Pathway to Global Product Safety and Quality," noted that both China and India have a labor cost advantage and that API manufacturing in India can reduce costs for U.S. and European companies by an estimated 30–40 percent", p. 215. Office of the White House, 2021, BUILDING RESILIENT SUPPLY CHAINS, REVITALIZING AMERICAN MANUFACTURING, AND FOSTERING BROAD-BASED GROWTH 100-Day Reviews under Executive Order 14017 June 2021

Recognising these important challenges, the EFCG is exploring industrial policy tools to encourage technological innovation and investment in Europe for cleaner and/or safer chemistry processes. However, this could have a cost and a "lowest cost pharmaceutical policy" framework would undermine the sustainability of those investments in new process technology.

Another study produced by ECIPE based on Eurostat data, provided however a different perspective outlining the limited EU dependencies and the vulnerability of EU exports if all countries around the world would reduce their import dependencies. According to this study, 64% of all global final pharmaceutical product exports come from the EU and 77% of Active Pharmaceutical Ingredients (APIs) used for producing innovative medicines in Europe are manufactured in Europe. The study finds that 81% of pharmaceutical imports in the EU27 come from Europe itself.[35] In this context, EFPIA pointed out the need to ensure open trade flows rather than resorting to protectionist policies as a sustainable solution to support EU competitiveness and European and global patient needs.

b. Single source specialty medicines

Our co-rapporteur presented the supply chain specificities of single source specialty medicines by reminding stakeholders of the lifecycle of an innovator drug from discovery and development, to launch and supply, then to growth and maturity of the medicine and finally to decline when generic or biosimilar competition occurs at patent expiry. As illustrative examples of these medicines we can take biologics, orphan drugs and non-biological complex drugs.

Biological products, including vaccines, have specific manufacturing and storage conditions. They are typically more complex than chemical products and their manufacturing is made possible thanks to the close interconnection of production sites. They require several hundred raw materials and components for a single product, specific infrastructure, long lead times and can be less stable than chemical forms. They require sensitive and sophisticated manufacturing processes often only available in a single manufacturing site, which may have a unique infrastructure and know-how. Moreover, the process will typically scale up from the clinical research phase and thus often rely on a single source which was involved from the early phases of process development. Therefore, process development is done in synergy with R&D as a key factor in shaping the supply chain of the future commercial product.

To ensure supply is not affected, manufacturers will rely on an interconnected global supply chain and uninterrupted open trade flows to receive supplies sourced from different continents, together with good visibility of demand so they can anticipate production considering the longer lead times that biomanufacturing processes require (often >1 year). To ensure the reliability of supply, manufacturers will also select providers based on their reliability reputation, including their capacity to deliver the highest quality standards in a systematic way.

Orphan Medicinal Products (covering diseases affecting at most 5 in 10,000 people) have very limited manufacturing volumes and are brought to the market thanks to specific incentives meant to counterbalance the lack of scale. Due to their limited patient population and high unmet medical need, they usually go through an expedited regulatory approval process. This adds additional challenges in setting up a functioning supply chain in compressed timelines, where relying on single sources of supply allows to maximise both the scale and speed of process development. Also, low volume manufacturing requires specialised sites that have the unique know-how for the production. Multiple sourcing for these products would result in delayed access to medicines and potentially even withdrawal from the market of existing products, also jeopardising the investments in new medicines.

[35] https://www.efpia.eu/media/602699/production-import-dependencies-and-export-vulnerabilities-of-pharmaceuticals-for-the-eu27-final.pdf

Non-Biological Complex Drugs (NBCD) and nanomedicines are highly manufacturing dependent where a consistent manufacturing process is key to guarantee a consistent therapeutic profile of the final product. From a supply chain perspective this means that it is not easy to subcontract the manufacturing of these products to third parties in case of emergencies. In addition, the process of scaling up often generates problems as some of the physicochemical characteristics of nanomaterials can change in the process of scaling up possibly compromising the quality and safety of the final nanomedicine.[36]

Open global supply chains remain key to ensure a robust supply chain for innovative drugs and vaccines, where access to specific technologies or capabilities (often developed with the discovery itself of the new medicine) is paramount and is difficult to plan before discovery. In these cases, dual and/or local sourcing would not be a workable strategy, e.g., some vaccines include over 1000 components, and it is not viable nor advisable to go for dual sourcing as a contingency plan. For some drugs and vaccines, local APIs are not available or not competitive and it is in the interest of patients that companies are able to work with high-quality and competitive sources allowing them to meet patient needs.

Whereas dual sourcing can be a feasible option for medicines where volumes are high and production alternatives exist, this is not the case for many low-volume innovative medicines. Implementing dual-sourcing requirements would impact innovation, delay launches and decrease competition in the health eco-system. More specifically, for single source specialty medicines, an EFPIA survey (aggregated below due to confidentiality) shows that dual sourcing would not be possible or due to:

Technical barriers

- For some materials there is only one supplier who can produce them with the required quality. Non-biological complex drugs (NBCD) have very specific quality standards and cannot be manufactured or transferred to other suppliers.
- Dual sourcing is a risk mitigation measure and is only truly effective when both production sites are actively used. Therefore, dual sourcing would not deliver a faster reaction in a crisis as back-up sites cannot be activated on short notice when shortages arise.

Regulatory barriers

- The registration of multiple sites is possible in the EU but not in all third countries. Since pharmaceutical supply chains operate globally, mandatory dual-sourcing would jeopardize access to medicines elsewhere.
- Usually, contractual terms require the partner company to serve as sole manufacturer for a defined period. For example: Innovative product with a unique dosing and delivery device.

IP barriers

- For some products, dual sourcing is not possible due to IP requirements (e.g.: innovative medicines, cell and gene therapies, new acquisitions for which the agreement specifically stipulates the use of one supplier for IP reasons).
- Dual sourcing is impossible for some products that have key components (e.g., device) that can only be sourced from a single supplier (e.g.: product where one of the key components is co-developed with the supplier)

Economic and resource barriers

- New products are initially single sourced to channel resources (people, material, time, spend) through submission and launch. Supply redundancy may be added later where relevant and when volumes have grown. For example: Innovative product with a unique dosing and delivery device, with single sources for aseptic filling and device manufacturing. An innovative product in the late phase of development with a complex API synthesis requires up to two years and high upfront investment. Priority will be given to launch, and a second source will therefore not be considered at that stage.
- The implementation and maintenance costs of dual sourcing are significant and could push some products out of the market, especially mature brands. A second source would be particularly expensive for some products, e.g., animal-based drugs/components requiring extensive studies including comparability and bioequivalence studies, products with animal-derived enzymes or hormones.

[36] Soaeres et al.; Nanomedicine: Principles, Properties, and Regulatory Issues, Front Chem 2018 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6109690/

Characteristics – Low volume Innovative medicine

Reliability	• Supply chain management predicts and monitors supply chain, and has strategy that balances forecasted demand with inventory and supply chain participants, thereby avoiding shortages
Responsiveness	• Ability to respond to emerging demand quickly through use of global supply chains[X] and through the use of continuity plans at every stage of the supply chain

X= OECD 'Building resilience in global supply chain for all' 3 Nov 2020 TAD/TC(2020)7

'In particular, it is clear that shortages of medical goods were not caused by the collapse of supply chains but by the unprecedented surge in demand. I global supply chains have been part of the solution to global shortages.'

- *'Strategies that allowed firms to mitigate the impact of actual disruptions included the use of safety stocks and different prod increases in demand in sectors producing essential goods (pharmaceuticals and medical goods or food and agriculture).'*
- *Firms emphasised that having a global supply network is what helped them to deal with spikes in demand. Companies that could shift produ countries depending on the timing of the shock appeared to be in a better position to deliver products when and where they were needed.*

Conclusions

35 METRO modelling scenarios, in-depth examination of specific supply chains, and the qualitative experience of business federa underline the importance of open markets in times of crisis and the crucial role value chains have played in adjusting to a sudden specific set of health-related goods.

Enablers – Low volume Innovative medicine

Regulatory Standards	• Streamlined, efficient and predictable timing for regulatory approval of submissions and changes in the supply chain and process, both at local, regional and global level. • Customization of facilities, testing, labelling, GMPs to meet individual countries or regions standards or interpretations of, mean supply chain planning, operation and flexibility is diminished, and may discourage investment, operations and supply optimization • Complex regulatory structures (e.g. use of certain chemicals [1], drug device combination products across DGs) can add a barrier or delay to market availability, and robustness & resilience of supply over lifecycle
Security/Integrity	• Innovative medicines have large footprint in EU based on attractiveness of EU as a manufacturing hub. Policies to maintain and enhance attractiveness can assist long term security. • Full enforcement of EU FMD at Member State level
Innovation	• Ability to implement manufacturing and testing quickly increases robustness and resilience • Innovation in clinical research means medicines are developed faster but less time to stabilise and optimize manufacturing processes – need ability to change manufacturing quickly to respond to clinical demand
Visibility/ Transparency	• The demand curve for innovative medicines at start of lifecycle depends on clinical uptake, label, listing, and approval times, competitor products timing. A robust Supply chain has to consider Shelf life information, inventory risk and global supply chain flexibility. Likewise at end of innovator lifecycle, entry of other producers changes demand patterns. Visibility is enabler [2] • Use of digital technology to better understand patient need and support SC visibility
Financial Sustainability Environmental Sustainability	• Niche technology is typically needed for some part of process. With low volume only one facility may be available (self or contract) to deliver and cannot duplicate. Eg fine particle milling of highly potent material. Financial investment in high tech is significant and can be encouraged. • Strengthening Europe's competitiveness as a global SC player, needing global supply to respond quickly to changes and an open flow of materials and processes

1: regulatory structures include quality and environmental e.g. chemicals of special interest used in small quantities in pharma e.g, Triton
2: policy-proposals-to-minimise-medicine-supply-shortages-in-europe.pdf (efpia.eu)

c. Multisource community and specialty medicines

The rapporteur presented supply chains for the off-patent multisource sector (generic and biosimilar medicines) which account for around 70% of the volume of prescription medicines (but around 20% of the value).[37] They are therefore typically a volume driven segment of the market that is

[37] https://www.medicinesforeurope.com/wp-content/uploads/2016/03/infographic-generics.pdf By 2020, 18% of traditional product volumes in developed markets will be for original brands, compared to 8% in pharmerging markets according to IQVIA. It also states that for Europe: the adoption of specialty medicines will drive higher spending growth to 2020, and whereas 81% of the increase will be driven by specialty medicines, that is in part due to a recovery in traditional medicine spending. In 2011-2015, spending on traditional medicines declined in Europe with only specialty medicines increasing within the time period. https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-medicines-use-in-2020. In another report, IQVIA states: In the European Union (EU), where strained healthcare systems are facing ever greater demands from an ageing population, generic medicines have played a significant part in controlling costs. Off-patent medicines now account for 92% of the treatment volume in the region. And competition from generic medicines drives the cost of off-patent products down 61% from their cost during market exclusivity. This saved payers an estimated €100Bn in 2014 and has contributed to significantly higher access for patients in many countries, across many therapeutic areas. It also states that generic competition drives

characterised by head-to-head competition between companies supplying the same (therapeutically equivalent) molecule.[38] This competition may be stimulated at prescriber level, at dispenser level or through procurement.

Off patent medicines have their own lifecycle. Their development and market formation phases occur during the maturity/decline phase of the reference product. During the market formation period, multiple generic or biosimilar manufacturers may enter the market to compete with the originator company. As generic or biosimilar market penetration grows, competition sharpens between generic and biosimilar manufacturers that compete for market share which is critical to sustainability. Although many older medicines continue to be prescribed on the EU market, there may also be a decline of the product when prescribers have better alternative molecules to choose for a treatment. At some point, the product may lose its commercial attractiveness and be withdrawn from the market. This may be exacerbated in Europe due to the phenomenon of small markets (as most of these medicines would have a national licence).

There are some important distinctions to be made across the off-patent segment. Oral solid dose (OSD) medicines typically have a higher number of competitors in the market – especially at launch. Over time, the production chains tend to consolidate as cost pressures increase. More complex to manufacture sterile products (or high potency OSDs) have fewer competitors on the market – especially as European hospital markets have evolved toward more consolidated buying at a national, regional or hospital group buying level.[39] More complex follow-on medicines like biosimilar medicines or respiratory medicines (drug-device combinations) are much more costly and complex to develop and approve. Consequently, there are fewer competitors on the market at launch – in some cases there may be only one competitor to the reference product.

i. OSD generic medicines

The EU regulatory system is a global *gold standard* scientifically for generic medicines. However, the practical implementation of regulatory procedures is very complex and unnecessarily burdensome. For example, a large generic portfolio companies will conduct 20000 to 60000 variations every year. Based on data gathered from 2010-2018, the number of variations per MA and per year has increased by 75% since 2010.[40] One area where a direct improvement to supply chain security could be considered would be how API used in multiple generic dossiers is regulated. Similarly, the EU adopted useful regulatory flexibility guidance (provided the flexibility did not affect quality) during Covid-19 to tackle demand surges, acting in many ways like the USFDA.[41] The EU should continue this role for all EU-wide (and therefore major) shortage situations.

Generic companies invest a lot in manufacturing innovation to improve the efficiency and the scale of their production to be cost competitive and to maintain compliance with constantly evolving quality/GMP or environmental standards. However, the EU does not incentivise innovation in molecule formulation for off-patent medicines (in contrast with the US). This limits the possibility to invest in more modern chemistry to improve on existing molecules.

Generic medicine markets in Europe are shaped by cost-containment tools to reduce prices which encourages manufacturers to be very efficient in cost of goods and supply chains. This reduces the

down the price of off-patent medicines by 61% on average. https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/the-role-of-generic-medicines-in-sustaining-healthcare-systems.pdf

[38] For a description of generic markets, see: https://www.medicinesforeurope.com/wp-content/uploads/2021/02/2020-Generic-Market-Review-Final.pdf

[39] See KPMG NV 2019, Improving healthcare delivery in hospitals by optimized utilization of medicines A study into 8 European countries, p. 88, https://www.medicinesforeurope.com/wp-content/uploads/2019/10/20190903_Hospital-Reform-Study_final.pdf

[40] https://www.medicinesforeurope.com/wp-content/uploads/2020/01/ESE_2019_Medicine-for-Europe_AESGP_Variation_WEB.pdf

[41] https://ec.europa.eu/health/sites/default/files/human-use/docs/guidance_regulatory_covid19_en.pdf

contingency options for manufacturers. Expensive options such as multiple API sourcing[42] (due to much higher regulatory maintenance cost and complexity) are not economically viable. The generic industry is investing in greening its industrial footprint both for wastewater and energy consumption/climate emissions. However, there are almost no rewards or incentives on EU markets for such investments.

In terms of reliability, generic medicines should offer a supply advantage because of their multisource nature. If one manufacturer has a stock out, another manufacturer should be able to absorb the demand. However, this implies that generic markets are organised to encourage multiple players to compete in the market. In practice, more and more generic markets are organised to reduce prices for payers which consolidates the market. A related challenge can be the consolidation of the supply chain where generic companies source from the same manufacturer for the medicine or the API. In case of a production issue, all companies using that contract manufacturer face the same supply problem. For some older generic medicines with low prescription volumes and very low prices, there may be no commercial interest to maintain the production. Important regulatory processes like FMD serialisation or Brexit led to many withdrawals of such products as the additional regulatory complexity was not worth the investment.[43]

ii. Sterile injectable medicines

Sterile injectable products have typically more consolidated productions in Europe where additional GMP requirements may also be a supply chain risk factor. This can make supply chains less responsive if there is a production problem with one important manufacturer. However, these are often large manufacturers with important inventory policies to tackle demand surges. EU regulation is again of a high standard for these products and industry-regulator dialogue around upgrades to GMP is very important to ensure that implementation can be done without negative supply effects[44] (as some changes require a temporarily stop to production). The complexity of the implementation of EU regulations (labels, leaflets) is particularly acute in this sector which hinders the possibility to adjust stock allocation across Member States and raises barrier to the flexibility of supply. One may question the relevance of some of this regulation given that hospitals in Europe are well adapted to use digital tools like e-Leaflets. Some pilot project discussions between manufacturers, hospitals and procurers are underway in Spain and in Sweden to implement this in practice. The learnings from these pilots may serve the wider EU interest in this topic.

There is a lot of innovation in manufacturing processes in this sector in Europe, as many plants supply the global market – not just Europe. This is typically to increase the scale and efficiency of production. However, like for OSDs, the EU system does not incentivise investments in more modern chemistry formulations in this segment.[45] These medicines are usually purchased through hospital tendering which is increasingly consolidated and targeted by cost containment measures leading to consolidation on the market and in the supply chain. Most EU countries do not include security of

[42] It was highlighted during the meeting that multiple sourcing in supply chains can be a benefit or a risk depending on the type of production and the regulatory/market setting. An FDA study was cited underlining issues with product recalls in the US in the pre-GDUFA period (before an extension of FDA inspection activity to India & China). George P. Balla, Rachna Shahb, Kaitlin D. Wowak, 2018, Journal of Operations Management, Product competition, managerial discretion, and manufacturing recalls in the U.S. pharmaceutical industry

[43] In the Commission consultation on the Pharmaceutical strategy for Europe, "*almost all public authorities (…) cited the lack of profitability as a key reason for the withdrawal of medicines*." See page 13 https://ec.europa.eu/health/sites/default/files/human-use/docs/pharmastrategy_consultationreport_en.pdf
A study in the Netherlands calculated the impact of the cost of FMD on low margin generic medicines. Cap Gemini (2017)The Cost of the Falsified Medicines Directive: Impact on generic manufacturers in the Netherlands, https://www.politico.eu/wp-content/uploads/2019/01/FMD-cost-evaluation-Bogin-.pdf; The Financial times has reported often on the negative impact of Brexit related regulation on the supply of medicines including here. Financial times 19 April 2021, "Brexit Red Tape threatens drug supplies in Northern Ireland", https://www.ft.com/content/40c52efc-17d8-4ac7-8a03-762df46adc9f

[44] Industry and the EMA discussed extensively the impact of the updated Annex 1 of the EU GMP in relation to this challenge.

[45] In its study, IQVIA shows that most value added medicines are developed and marketed in the US due to the encouragements of the 505(b)2 system. IQVIA, 2019, White Paper: A Digital Future for Value Added Medicines: Supporting Positive Patient Behaviour, https://www.iqvia.com/library/white-papers/digital-future-for-value-added-medicines

supply in procurement[46] – although there have been some experiments with multi-winner tenders (UK, PT), clearer volume commitments (DK) and longer lead times (DE). For example, in Germany, the regulatory agency for pharmaceuticals BFARM recommends multi-winner tenders for high volume medicines and integrating more providers with more reliable supply chains in terms of supplies in hospital procurement contracts but this is not a legal obligation.[47] A report on the root causes of shortages of the USFDA also indicates that hospital tendering is an aggravating factor of the economic root cause of shortages.[48] The impact of tender policies on demand visibility and supply chain robustness should not be underestimated. As some of these medicines have an environmental risk (antibiotics, cancer medicines), there are efforts to improve production processes and to agree to international frameworks for wastewater treatment (AMR Industry Alliance Common Manufacturing Framework).[49]

iii. Biosimilar and other complex follow-on medicines

Europe invented both the technology and the regulatory framework for biosimilar medicines and is a leader in the development of complex follow-on medicines (hybrids, drug-device combinations) and in many ways, serves as the model for the rest of the world. The regulatory approval of these medicines is very complex and has an impact on the production supply chain. The regulatory approval process for NBCD/nanomedicines, for instance, requires complex clinical data and most follow-on NBCDs are approved through the article 10(3) hybrid application pathway.[50]

Notably, there is more vertical integration of biologics production and therefore, there are fewer possibilities for multi-sourcing ingredients or components.

There is a high degree of innovation in the manufacturing process around yields, purification and other important processes that can affect the volume or speed of production and that are important for security of supply. There has also been an increase in greenfield biologics manufacturing investment in Europe. There are fewer developers and manufacturers of complex products, so the market is more consolidated. Environmental issues are more limited for biologics production, but energy efficiency is important due to the energy intensive nature of the production process. There have been few shortages in the multisource biosimilar sector but high volume/short lead time tenders and higher than expected demand[51] have stressed the supply chain.

iv. Non-prescription medicines

Non-prescription medicines (also named 'OTC') contain molecules which are out of patent and are multisource products. Non-prescription medicines do usually have many alternatives either products with the same API or with different APIs but with the same indication. This is the reason why shortages of over the counter (OTC) products are normally only happening under extreme circumstances, as we have seen with the recent pandemic.

[46] As recognised in the Pharmaceutical Strategy for Europe where the Commission has initiated a dialogue with Member States on integrating factors such as security of supply into medicines procurement. https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52020DC0761&from=EN; the European Association of Hospital Pharmacists also highlights the importance of supply chain security in its position: https://www.eahp.eu/sites/default/files/eahp_position_paper_on_procurement_1.pdf

[47] https://www.bfarm.de/SharedDocs/Downloads/DE/Arzneimittel/Zulassung/amInformationen/Lieferengpaesse/Protokolle/Recommendations_on_delivery_and_supply_shortages_190711.pdf;jsessionid=3FF0DBBAF24523CEAF8C4316327FE3DE.1_cid354?__blob=publicationFile&v=2

[48] FDA (2019, updated 2020): Drug Shortages – Root causes and potential Solutions, https://www.fda.gov/media/131130/download

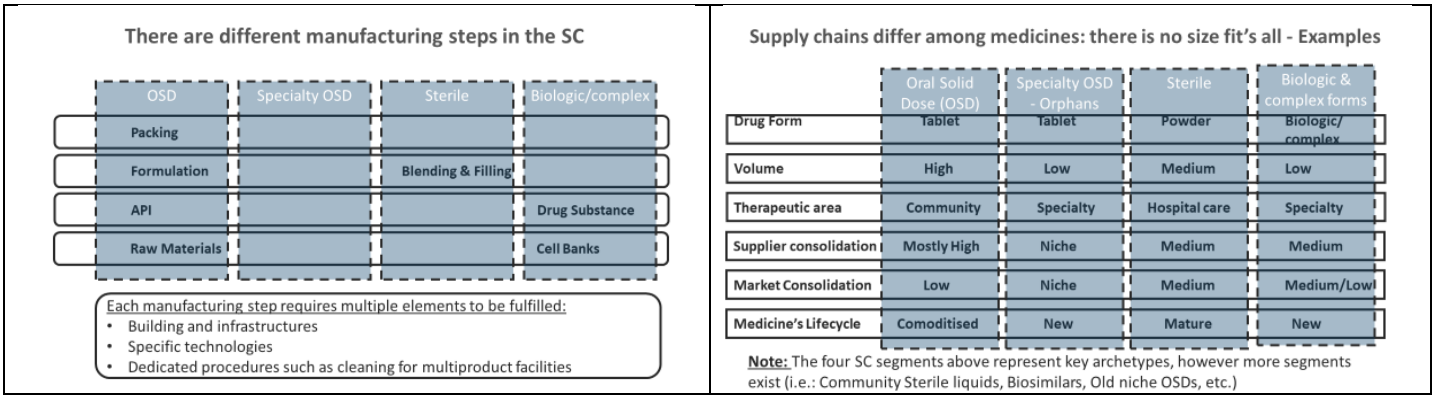
[49] https://www.amrindustryalliance.org/wp-content/uploads/2018/02/AMR_Industry_Alliance_Manufacturing_Framework.pdf

[50] Klein et al. The EU regulatory landscape of non-biological complex drugs, European Journal of Pharmaceutical Sciences, 2019 https://www.sciencedirect.com/science/article/pii/S0928098719301381

[51] The uptake of recent oncology biosimilar medicines was much faster than the uptake of rheumatology biosimilar medicines taking even the industry by surprise.

d. Summarising robustness by production step and segments

Supply chains need to be robust from beginning to end to supply patients. The different steps in the process can present different risks that need to be factored into contingency plans. In addition, different pharmaceutical segments operate in very different market environments that condition the demand in the demand/supply equation.



Section 3: Achieving the best possible robustness outcomes

Robust supply chains should deliver important outcomes for public health, namely fulfilling patient demand, product quality, delivery reliability and operational efficiency. This section will explore the regulatory, visibility/transparency and sustainability drivers and constraints to robust supply chains recognising that those constraints and drivers differ across steps and segments. Therefore, we will conclude with a matrix analysis to understand the common versus the differentiated drives and constraints.

a. Regulatory drivers and constraints

The EU regulatory system is driven by scientific principles to define critical parameters of medicines regulation such as risk/benefit analysis or quality, safety, and efficacy. This ensures a rational approach to overseeing the pharmaceutical sector including manufacturing and supply chains. However, the EU regulatory system also lacks operational efficiency and is technically out of date regarding the use of digital tools as has been often raised by stakeholders in Work stream 1. There is also a challenge with the implementation of EU regulation at national level which may exacerbate security of supply for some pharmaceutical segments (vaccines, hospital medicines). Finally, the system is conservative which makes it challenging to bring innovation in manufacturing development – a central theme in the Structured dialogue (work stream 4). This section will describe how the current regulatory system impacts supply chain robustness.

The EU regulatory system consists of a network of national medicines agencies (called National Competent Authorities – NCAs) and the European Medicines Agency (EMA) and the European Commission (in practice DG Santé). The functioning of the regulatory system is somehow fused together as EMA decisions are made by committees composed of NCA representatives and then issued by the Commission after a legal review and many national decisions are influenced by committees of NCAs (like the HMA) which, for practical purposes, are often hosted by the EMA. The EDQM (a body of the Council of Europe[52]) also plays a role in supply chain regulation through the governance of the European Pharmacopoeia monographs which set common standards for the quality of medicines and their components. The EDQM also issues Certificates of European Suitability (CEP) which are common for well-established API.

[52] EU pharmaceutical regulation recognises the role of the EDQM, which is not an EU institution, for this purpose.

The EMA and the Commission are responsible for the issuance and maintenance of licences for Centrally Approved Products (CPs) while NCAs issue and maintain nationally approved products which may take different forms (DCPs, MRPs or NPs) depending on the number of countries covered by the licence. Most new medicines and biologics (including biosimilars) are approved as CPs[53]. Most other medicines (including most generic medicines[54]) are approved by NCAs. The overwhelming (10 to 1) number of licences are approved nationally and most of them are generic medicine applications.

The regulatory system plays an important role in pharmaceutical supply chain oversight, notably:

- *Obligation to supply*: Pharmaceutical manufacturers and wholesaler distributors have specific obligations to supply markets under EU pharmaceutical legislation[55]. In practice for manufacturers and MAHs, this requires manufacturers or MAHs to report shortages to NCAs and/or the EMA (for CPs and voluntarily for a list of Covid-19 critical medicines[56]) if possible, in advance of the shortage to allow for mitigation measures. One concern raised was a possible gap in communication of shortages between the headquarters of companies to their national affiliates who are in dialogue with regulators and concerned stakeholders (i.e., hospitals). For wholesalers, this typically requires the holding of certain stocks to ensure continuous supply to pharmacies or hospitals within defined time limits according to public service obligations. WHERE DOES THIS APPLY: ALL PHARMA SEGMENTS
- *Quality oversight of the supply chain*: pharmaceutical companies submit information in their regulatory dossiers about the components of each medicine (API, regulated components, finished dosage forms) including quality audit information on their production sites or those of their suppliers. EMA[57] or the NCAs may conduct GMP inspections of these factories anywhere in the world. The EMA and Member State Inspectorates maintain a database of GMP inspections – EUDRAGMP – with information about compliant and non-compliant inspections of firms. Inspectors have access to this information and apply routine or risk-based decision-making to inspect for GMP compliance. An issue that has been raised is the quality of production from Asia – principally India and China. The EU is a highly regulated market with numerous checkpoints and safeguards to verify the quality of medicines such as import testing of API or medicines for EU specification and a series of audit requirements that MAHs must conduct for this purpose. One challenging point however may be the human resource capacities of inspectorates which play a critical role in the system and whether administrative efficiencies in other aspects of regulation could enable a shift in resources for this. The EU has increased GMP mutual recognition agreements (MRAs) with other countries to optimise the use of (limited) inspectorate resources. During Covid-19, digital inspections were used and may be an opportunity to further optimise resources. WHERE DOES THIS APPLY: ALL PHARMA SEGMENTS. ADDITIONAL INSPECTORATE RESOURCES COULD BE DEVOTED TO API PRODUCTION SITES.
- An important point to underline is that *the regulatory network has the supply chain information for all licensed medicines* in the EU. However, access to this information for security of supply analysis purposes (i.e., analysing consolidation in the multisource supply chain) may be challenging either because supply chain information is not fully digital or because the digital information is not interoperable or easily readable. Similarly, manufacturers cannot legally share this information with one another as it would clearly expose them to competition law compliance risks. There is also an inflation of repetitive quality information in different aspects of pharmaceutical regulation related to where pharmaceutical manufacturers source their API rather than produce it internally. In the generic sector, multiple medicine manufacturers may purchase API from the same source. Any regulatory changes to this API therefore generate a flood of regulatory processes across the network. There may be a reflection on a more centralised approach to API regulatory information that would simplify the

[53] 57% of the 117 new CP applications were originator or orphan drugs. 43% were generic or biosimilar applications.
[54] 87% of new DCP and 76% of new MRP applications were generic or hybrid medicines.
[55] As NCAs apply these obligations differently, there is a description here: https://ec.europa.eu/health/sites/health/files/files/committee/ev_20180525_summary_en.pdf
[56] Draft European Health Union legislation gives the EMA a formal role in shortage monitoring and mitigation for crisis situations (large scale shortages affecting multiple EU countries).
[57] NCA inspectors on behalf of the EMA.

work of manufacturers and NCAs and improve oversight of the supply chain. WHERE DOES THIS APPLY: MULTISOURCE GENERIC SEGMENT AND UPSTREAM CHEMISTRY

- Regulators in the dialogue raised a concern over poor *planning of technology transfers* leading to shortages. A technology transfer occurs when the licence holder of a medicine transfers the production from one site to another for example when an innovator drug moves from a small volume development to a bigger volume commercial product or due to a merger or acquisition where a portfolio of medicines comes under new ownership. Technology transfer is a challenging aspect for security of supply and there should be an opportunity to agree on clearer and more harmonised processes for regulatory flexibility to apply in the context of a technology or a site transfer WHERE DOES THIS APPLY: ALL PHARMA SEGMENTS
- The EU pharmaceutical strategy[58] has highlighted the importance of the *operational efficiency of the regulatory system for medicines supply* notably related to different labelling and packaging requirements. It seems obvious that digital solutions and a consistent effort to tackle some small market challenges (i.e., multimarket packs) that have been discussed for years but not acted upon should advance in future policy reforms. WHERE DOES THIS APPLY: ALL PRODUCTS BUT ESPECIALLY IMPORTANT FOR VOLUME PRODUCTS LIKE GENERIC MEDICINES AND VACCINES.
- Along similar lines, the Commission has recognised[59] the inefficiency of certain regulatory processes such as *administrative variations* that consume a lot of resources for both industry and NCAs – resources that could be used much more efficiently for patient benefit rather than administration. WHERE DOES THIS APPLY: ALL PHARMA SEGMENTS BUT ESPECIALLY FOR DCP/MRP PRODUCTS
- For vaccines, there are *specific challenges with EU requirements regarding vaccine batches* under article 114 of Directive 2001/83/EC and national legislation. In practice, every vaccine batch is tested by a National Control Laboratory (NCL, referred to as OMCL in the EU) before being distributed in the EU. Independent batch release by an OMCL 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. For vaccines manufactured outside of the EU, each lot must 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 to avoid the repetition of batch certification which reduces the remaining shelf-life and may trigger vaccine shortages and supply delays. Vaccines Europe also recommends that 1) the procedures and guidelines issued by the European Directorate for the Quality of Medicines and HealthCare (EDQM) are adopted by a majority decision (and not unanimity) like CHMP opinions for centrally approved products and 2) EDQM guidelines are revised to avoid that OMCL testing is on the critical path of batch release, at least for well-established vaccines.
- The EU Industrial Strategy[60] highlighted the importance of building an *Open Strategic Autonomy* for the manufacturing of API and raw materials that was also referenced in the Pharmaceutical Strategy and in the Trade Strategy. This could be achieved by building on the European industrial footprint, ensuring a level playing field for regulatory compliance and convergence and supporting innovation in robust, sustainable, and competitive manufacturing processes. This includes creating incentives for R&D and production in Europe to reduce dependencies on third countries in the long term and to increase EU competitiveness. There should be more global frameworks to lower the environmental footprint of API and precursor manufacturing. There are frameworks to achieve this such as the AMR Common Manufacturing Framework for antibiotic medicine. This has an impact on the cost production

[58] https://ec.europa.eu/health/human-use/strategy_en
[59] https://ec.europa.eu/health/human-use/strategy_en
[60] https://ec.europa.eu/info/strategy/priorities-2019-2024/europe-fit-digital-age/european-industrial-strategy_en#strengthening-eus-open-strategic-autonomy

and should be recognised in EU markets to reward companies that invest in this effort (i.e., in procurement or reimbursement criteria). The absence of frameworks can also affect supply chain reliability, as in certain cases a safety incident or the enforcement of environmental regulations could be the cause of a supply disruption. The EU Trade Strategy should also be leveraged to secure open trade flows that enable global supply chain networks to operate without disruption.

- In emergencies, there may be a need to *accelerate the registration of additional API sites* as the registration of new manufacturing sites requires a long lead time. This is a time critical step to expand the supply chain and output in an emergency.
- Finally, *reimbursement or procurement policies that put pressure to lower prices without considering supply criteria* (security of supply, robustness and sustainability of the supplier, respect for the environment, financial robustness, etc.) drive consolidation of manufacturing supply chains with hidden costs for European citizens (shortages, environmental issues, etc.). Supply chains have also moved out of the EU due to a push in procurement contracts for lowest price offerings. By including a significant weight to security of supply in the award criteria for public tenders, companies can be given room to find new solutions to increase security of supply and increase the EU's resilience.

b. Visibility drivers and constraints

i. Visibility of the production supply chain

Problem areas:

Shortage reporting data: The EU is divided into 27 national markets (plus EEA markets) so most shortage reporting by manufacturers takes place at the national level. The EU has taken some steps to improve access to this information held by NCAs[61]. The challenge however is that the information is not collected in a harmonised format which makes it challenging to rapidly assess the information and to compare it across the EU. The EU has also adopted a notice to encourage a more harmonised approach to shortage reporting by NCAs, but this guideline has not yet been implemented in practice. During Covid-19, the EMA introduced a voluntary shortage reporting system at EU level – the i-SPOC – to allow manufacturers to report EU-wide shortages for a list of critical medicines related to the pandemic. The EMA also has a SPOC process to collate national shortage reporting data – although this is not aligned data, so aggregation is challenge. Consequently, there is still an absence of standardised shortage reporting information at EU level. This is unfortunate because most shortages are localised in a national market rather than an EU-wide. More information would therefore provide an opportunity for manufacturers to allocate stock across countries to address these localised shortages. This information would also improve access to information for prescribers and dispensers that expressed concerns over the limited information available to them regarding the duration of a shortage.

Supply chain consolidation data: The extent of manufacturing supply chain consolidation may be difficult to assess as the pharmaceutical industry is still fragmented. However, there have been cases of regulatory action and different studies on API production suggesting that the production API or other components is increasingly consolidated.[62] The collection of digital information on supply chains could enable regulatory agencies to review the extent of such consolidation and to consider dialogue with manufacturers on how to address that.

Volumes placed on the market/dispensed: In the event of a shortage, NCAs should look at volumes placed on the market by manufacturers and dispensed to patients in the market by looking at relevant data sets such as reimbursement data and early warning shortages platforms/systems such as using

[61] https://www.ema.europa.eu/en/human-regulatory/post-authorisation/availability-medicines/shortages-catalogue#national-registers-section

[62] For an overview, see the Commission study on strategic dependencies which includes a chapter on API. https://ec.europa.eu/info/sites/default/files/swd-strategic-dependencies-capacities_en.pdf

NMVS data. However, it is noted here that GIRP representing the full-service wholesalers and parallel distributers do not agree that NMVS data provides an accurate picture of supply and demand on national level. Therefore, they believe that NCAs should receive national stock-level information from the MAH and use early warning signals from wholesale distributors and healthcare professionals about the service level.

Supply chain in trade agreements: The EU is an important negotiator of multilateral and bilateral trade agreements. This cooperation could be leveraged to support open trade flows to guarantee the integrity of global supply chains and to advance regulatory cooperation (i.e., for GMP mutual recognition and to facilitate global development and speed up approval times) in the pharmaceutical sector.

Predictability of demand

Supply chains are built around projected demand for products in each Member State market where the product is supplied. Therefore, demand visibility is an important element of supply chain security. Market volatility can be impacted by single winner tender policies that do not include supply security criteria or adaptations such as appropriate lead times or volume commitments. Sudden demand increases can be exacerbated by market panic that encourages either governments or market operators to hoard medicines (in exceptional cases patients such as with paracetamol during Covid-19) which may exacerbate shortages in different EU markets due to suboptimal allocation of stocks.

The use of digital technologies by manufacturers that can monitor sales patterns and order flow to understand fluctuations in customer demand would help minimize delivery disruptions but requires policies that promote data sharing and a digitally collaborative ecosystem infrastructure.

c. Sustainability drivers and constraints

The low profitability of certain value chains (antibiotics, mature small molecules) does not encourage manufacturers to invest in robust supply chains. EU generic markets are designed to obtain the lowest price which incentivises lower cost of goods and consolidation in the market or in supply chains. This is efficient to lower prices, but it increases supply risks. Most competitive (off-patent) reimbursement markets are regulated to decrease prices through a reference price. There is no flexibility to adapt these systems for higher cost of goods or regulatory costs. This creates hidden costs (environmental issues, shortages costs, etc.) in the system. Procurement markets are characterised by increasingly consolidated buying and price only criteria. This is conducive to lower prices but not to security of supply. Some stakeholders reported that companies no longer bid in some hospital tenders due to the high risk-low reward ratio.

For vaccines, a quick response to an under-capacity situation following an unexpected increase in demand is extremely challenging due to long production lead times (up to 36+ months for some complex multivalent vaccines) and the time needed to build and license a new facility. We recommend an early and continuous dialogue between manufacturers and health authorities (in compliance with competition law) to better anticipate the evolution of vaccine recommendations and programmes, and thus more accurately forecast vaccine demand. We also recommend adapted procurement mechanisms taking into consideration the length of vaccine manufacturing cycles.

API and excipient production must be economically sound to ensure business continuity and willingness to invest in robust supply chains. This includes investment in more efficient and sustainable manufacturing technologies.

Section 4: Conclusions and policy options

At the Commission organised meeting of Work Stream 1, stakeholders called for a *consistent, cohesive, and coherent* policy framework to encourage robust supply chains. The policy recommendations cover four themes

1. Stakeholder alignment and recognition
2. Making the invisible visible (or at least more predictable)
3. An enabling and robust regulatory framework
4. Sustainability as a driver
5. Ensure open trade flows and globally competitive industry

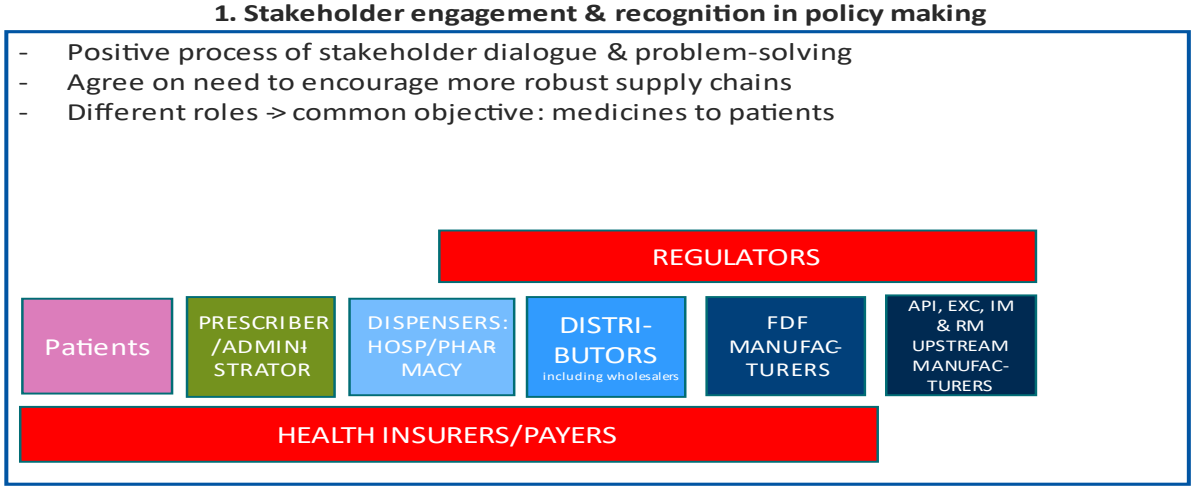
Policy option 1. Stakeholder alignment and recognition

This workstream enabled a positive process of stakeholder dialogue and problem-solving. Stakeholders agree on need to encourage more robust supply chains and although each stakeholder plays a different role, they share the common objective of wanting to secure medicines supply to patients.

1. Stakeholder roles/responsibility

Stakeholder	Role	Supply responsibility
Upstream manufacturers	Manufacture critical components & API, RM, EXC, ETC	Supply medicine manufacturers
Medicine manufacturers	Manufacture medicines & API	Obligation to supply market (regulatory)
Wholesalers	Deliver to hospital/pharmacy	Public service obligation to pharmacies/hospitals (regulatory)
Dispensers	Dispense correct medicine to patients	Supply patients medicine
Prescribers	Prescribe treatment	--
Patients	Follow treatment	--
Regulators	Oversee/enforce standards	Mitigate shortages (regulatory)
Insurers	Reimburse/procure	--

1. Stakeholder engagement & recognition in policy making



Stakeholders defined their original position in this dialogue based on their role in the system. However, through dialogue and exchange, alignment was found across a range of issues in this process and are identified below. There are also divergent views that are captured case-by-case in this document. For the future, this constructive dialogue offers a clear guidance to policymakers on the value of including stakeholders in policymaking. We therefore strongly recommend that the Commission continues this transparent consultation with stakeholders, ensuring that the process is inclusive, as the EU progresses toward the introduction of actual policy reforms for robust supply

chains over the next two years. This may include more focused discussions with concerned stakeholders on specific technical issues.

1. Examples of stakeholder alignment in the dialogue

Stakeholders divided	Problem	Stakeholder alignment
Wholesalers & Manufacturers	Definition of a shortage	Supply—Demand—clinical/therapeutic need
Hospitals, regulators & manufactures	Information about shortages	Improve information flow: MAH —NCA —Hospital; standardise shortage reporting across EU
Manufacturers & regulators	Pharma regulation too rigid/slow (cause of problems)	Maintain high standards; simplify implementation; progress digital regulation
Upstream & downstream	Invest in multi-sourcing for volume chemical products	Need adapt regulation and market recognition for complexity/cost
Stakeholders & manufacturers	Manufacturing supply chain transparency	Digitalisation of regulatory data a possibility
Manufacturers & regulators/payers	Demand predictability	Digitalisation for inventories; procurement reform
Stakeholders/manufacturers	Stockpiling/crisis production	Smart inventory management/Reg flex for manufacturing responsiveness
EU & manufacturers (FDF & API)	Invest in EU manufacturing & greening	Regulatory acceptance, technology support and sustainable markets needed

Policy Option 2. Making the invisible visible (or at least more predictable)

A substantive discussion enabled stakeholders to identify a lack of visibility or at least predictability of supply and demand as a major challenge for robust supply chains. There are legitimate reasons why certain information is held confidentially and why certain information should be made publicly available or available to concerned parties that can prevent or mitigate a supply disruption. In this regard, digital tools should enable a more effective use of aggregate large volume information to improve the predictability of supply and demand.

For manufacturing supply chains, the digitization of regulatory information (through telematics and the interoperability of relevant databases) and shortage reporting systems should be an opportunity to improve the analysis of supply chain risks for manufacturers and for regulators that are responsible for shortage mitigation. This data should also improve the ability of regulators to assess manufacturing consolidation risks in the supply chain – for example, if multiple generic manufacturers are relying on the same API source. The EU also has confidential information from GMP inspections and there are discussions to share more of this information with relevant stakeholders in the future. As this topic deals with sensitive commercial information, there would be a need to discuss this further. The EU should also learn from the USFDA policy on quality metrics and mature quality systems which has advantages and disadvantages.

Some of the challenges identified with more visibility of manufacturing supply chains include the need to protect legitimate confidential information, to avoid misusing this information for protectionism and to respect the right of manufacturers to qualify their suppliers as they ultimately hold responsibility for the quality and efficiency of their supply chains. At the same time information that is in the public interest should be disclosed either to the public or concerned parties that can prevent or mitigate a supply disruption. Given the size of the EU market and the vast number of medicines available, progress in this area can only be achieved through the more efficient use of digital tools to gather information – a weak point in the EU system until now.

In terms of solutions, we propose:

- An **interoperable telematics** system to digitalize supply chain information for regulators. Investment in a digital infrastructure that links manufacturing sites to products across the Union is needed, to assess the risk of over-reliance in the supply chain.

- Agree to **standardized shortage reporting** in a digital format at Member State level to provide better information for cross-border mitigation action when needed. BEUC recommends that making the invisible visible (or more visible) requires full transparency on the reasons for the shortage in a systematic way (including root causes) in the national (and EMA) public catalogues on drug shortages (BEUC recommendation)[63]. Other stakeholders such as manufacturers agree that it is important to tackle the root cause of drug shortages but question the value of this for shortage notification to regulatory agencies which might not be able to correct root causes. In contrast, relevant pharmaceutical policy reforms would likely tackle those root causes. For example, the USFDA has undertaken this analysis[64] and declared that the root cause of drug shortages is economic and more precisely that:
    - *There is a lack of Incentives to Produce Less Profitable Drugs.*
    - *The Market Does Not Recognize and Reward Manufacturers for Mature Quality Management Systems.*
    - *Logistical and Regulatory Challenges Make It Difficult for the Market to Recover After a Disruption.*

  The Commission has hired a consultancy to conduct a similar root cause analysis for Europe and its interim analysis, which is not yet confirmed, seems to indicate similar challenges in Europe.
- **Stock transparency** is recommended to be limited to finished product of critical medicinal products (with some divergent views on whether it should be limited or not to critical medicines). In that case, the term critical is to be defined by workstream 2. Stock transparency of API and starting materials is extremely complex and resource intensive, and due to multiple supply chain components, often product-specific, is expected to overburden regulator capabilities, capacities, and structures.
- **Timely, pro-active drug shortage reporting** is required if there is no possibility to mitigate drug shortages in line with the pharmaceutical legislation recognizing that some out-of-stock situations may occur with shorter notice than foreseen in the legislation (2 months). In such cases, the reporting should be done as rapidly as possible.
- An early notification of **withdrawals/market discontinuation** is required independent from drug shortage events in line with EU pharmaceutical law. BEUC calls for earlier notification of shortages and withdrawals in the revised EU pharmaceutical legislation, based on best practices identified in Member States.[65]
- According to manufacturers, a better **definition of shortage** is needed as the current definition requires a notification while the company still has options to mitigate and is not aligned across Europe. We take note of the efforts of Workstream 2 to define critical medicines in relation to patient therapy and time considerations.
- An industry-inspectorate dialogue on sharing more **information regarding GMP inspection** reports. This may consider multiple approaches: information for regulators-only, for manufacturers-only and for the public.
- Enabling **API producers to input supply chain data** directly to regulatory system to improve oversight and management of upstream supply chains, for example the same quality data that is submitted multiple times in regulatory dossiers.
- **In the context of procurement, stock accountability** may be ensured by requiring industry to demonstrate a track record to supply patients with product (with sufficient flexibility for new market entrants), with or without risk assessment procedures applied. An EU template for risk prevention plans may be useful in line with the proposals of Workstream 2 related to critical products.

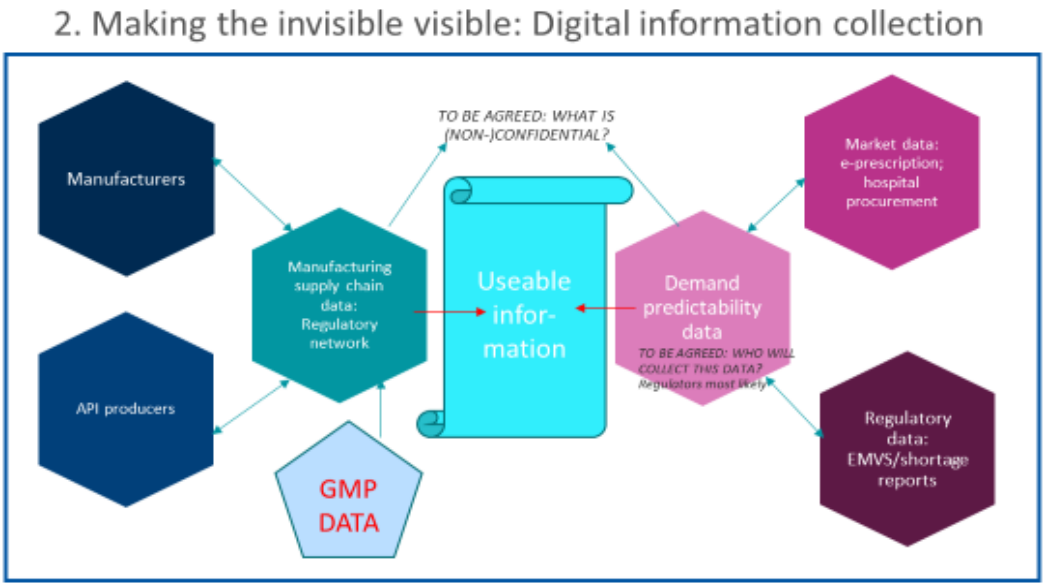
[63] BEUC member organisations report that information on the causes of shortages is not always available on the national databases, or is not reported comprehensively. Example https://www.ocu.org/salud/medicamentos/informe/razones-desabastecimiento-medicamentos/autoridades (accessed 14 July 2021)
[64] https://www.fda.gov/drugs/drug-shortages/report-drug-shortages-root-causes-and-potential-solutions
[65] https://www.beuc.eu/publications/beuc-x-2020-034_addressing_medicine_shortages_during_the_covid-19_pandemic.pdf

- BEUC considers that companies should be obliged to **submit prevention plans** to the competent authorities when they put on the market a new medicine – in line with their legal obligation to ensure the continued supply of *all* medicines. For medicines already on the market, BEUC proposes that companies submit prevention plans at least for some specific types of medicines (concrete criteria to be further defined in consultation with consumer and patient groups) and/or gradually following some deadlines. Information from such plans that is in the public interest should be proactively disclosed by the authorities. Indeed, the report on "Prevention of Drug Shortages" published in 2014 by the Inter-association TF already described the principles of ISPE and PDA Shortage Prevention Plans (SPP) and encouraged companies and Health Authorities to implement the solutions summarized in these reports. However, the reports described by the two professional associations (ISPRE and PDA) were developed to be used by companies in their internal processes and were not designed as reporting or communication tools. So, while manufacturers have been following the recommendations of these reports to strengthen the robustness of their supply chains, additional work is needed to develop a more systematic approach and agree adequate standards, ensuring these SPPs can be meaningfully used to serve the purpose of providing greater supply chain transparency. To reach this goal a suggested approach would be to develop a common EU template for SPPs and agree on the criteria in which an SPP is needed. Any development should also consider the opportunity to have this information also on a digital format rather than just paper/pdf. **This issue should be aligned in future with Work Stream 2 as regulators would need the resources and technical capabilities to manage this information.**
- The need for **common digital information standards** applied by all regulatory agencies and industry across Europe for the aggregation of product identification data into relevant products groups. This would require significant changes to current practice including: The need for the EU, agencies, and hospitals to invest in digitalization as promised under the EU4Health program to support "actions and interoperable IT tools to monitor, prevent, manage, report and notify shortages of medicinal products and medical devices, while contributing to their affordability".[66]
- The need to **align on confidential/non-confidential information** to balance various public policy interests: notably transparency/predictability, accountability, maintaining competition and ensuring product security. There should be a dialogue to define a clear policy on how to use such a wealth of information (available in regulatory networks) to support robust supply chains.
- The need to **invest in the digital upskilling of the workforce** by increasing educational assistance and high-quality, innovative, ongoing training models that tackle skills gaps and ensure professionals have the competencies required for the digitization of the supply chain.
- The need to ensure **compliance with the EU General Data Protection Regulation** when using digital tools where applicable.[67]
- With **demand predictability**, there is an opportunity to use digital information to improve supply chain forecasting, ensure an optimal use of resources and prevent waste (oversupply) or shortages (undersupply). In the event of a shortage, this could better identify where medicines are needed most and where alternative products (i.e., generic medicines) could mitigate the risks for patients. In addition, a more predictable market will contribute to sustaining investments in manufacturing plants and in supply chains. Manufacturers have proposed to use available data sets to assess demand changes such as prescription data, hospital procurement data and EMVS data.[68] Full line wholesale distributors underlined concerns over the legitimate protection of confidential business information

[66] Article 3.b. of the Regulation: https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32021R0522&from=EN ; see also references section devoted to hospital bibliography pages 13-15 of this document.
[67] Most regulatory data do not include the data of individuals (i.e., patient data) therefore, GDPR would not apply.
[68] Bouvy, F. and Rotaru, M. (2021) "Medicine Shortages: From Assumption to Evidence to Action - A Proposal for Using the FMD Data Repositories for Shortages Monitoring", Frontiers in Medicine, https://pubmed.ncbi.nlm.nih.gov/33614679/
[68]

and market competition in relation to this issue. They together with PGEU,[69][70] do not support the use of the EMVS or NMVS data because they overestimate national supply and do not provide accurate and reliable information on the availability of medicines on national markets (underestimation of demand).

- Recognize the specific **challenge for hospitals (often public institutions with limited digital capacities**) described in this paper and consider an EU project to support the digitization of data within the hospital medicines supply. This will enable hospitals to enact changes that can support better predictability (inventory analysis) in normal and crisis situations.[71]
- Build on existing initiatives such as **SPOC, i-SPOC, the EMA notice on shortage reporting to standardize shortage reporting data across Member States** to move toward a single aggregated database to better mitigate stock outs through an early warning system approach in the future.
- **Reinforce the early warning** through stock monitoring systems at the national level.
- Introduce an **advanced dialogue on health policy changes** with important demand effects (i.e., Vaccination policies). Early dialogue with manufacturers on foreseen changes in demand, including changes in vaccination calendars, would reduce supply risks.
- Adapt **off-patent procurement/reimbursement policies** to production supply chain realities.



Policy Option 3. A Robust, Agile and Enabling Regulatory Framework for Supply chains

Whilst recognizing the value of the high standard EU regulatory system, stakeholders suggested reforms to improve the overall efficiency of the system. The proposed solutions cover different themes and include:

[69] http://girp.eu/sites/default/files/documents/girp_position_on_use_of_emvs_for_monitoring_of_shortages_-_updatedfeb21.pdf
[70] https://www.pgeu.eu/wp-content/uploads/2020/08/PGEU-Statement-on-the-potential-use-of-the-EMVS-to-monitor-shortages.pdf
[71] Please refer to references in detailed bibliography devoted to this issue on hospitals pages 13-15 that provides dozens of academic references in support of this recommendation.

i. Regulation of manufacturing sites

- Creating an expedited regulatory framework for innovative manufacturing processes, site transfers and other industrial investment efforts.

ii. Reducing maintenance costs and complexity

- Updating the variations regulation (reduce administration/speed up assessments) in line with ICH Q12 guidance and better regulation principles.
- Providing API producers with the opportunity to submit supply chain information changes to regulators to improve oversight of the upstream supply chain recognizing the importance of MAH responsibility for their final product.
- Reducing the maintenance cost and complexity of dual sourcing of API to make this a viable option for large volume generic manufacturers.

iii. Internal Market harmonization

- Implementing an internal market harmonization policy to reduce national variability that makes manufacturing inefficient.
- Advance the harmonization of packaging and product information across the EU and ideally EEA and UK.
- Revise the Variations Regulation to simplify and modernise the post-approval framework, including simplification, efficient life-cycle management (addressing challenges relating to the interplay of medicines and devices and for novel and more complex therapies) anddigitalization. There is an opportunity for the EU to also drive international alignment across variation systems, thereby improving lifecycle management globally.
- For the safe handling of certain medicines (i.e., cytotoxic medicines in oncology) by HCPs in the hospital setting, there should be more effort to harmonise and align on warning pictograms for managing those substances. For example, HCP organisations in Germany have aligned on the use of the “yellow hand” pictogram (see enclosed picture courtesy of ADKA) to be placed on the outer packaging (cardboard box) of those medicines but it has only been formally acknowledged in one EU country (Austria). All involved stakeholders (from manufacturers to distributors to and in hospitals) would benefit from an aligned approach to ensuring the use of those pictograms for the benefit of HCPs and the care to be apportioned to the handling of those medicines.

iv. Shortage prevention and mitigation

- Develop and deploy IT infrastructure (telematics) to support regulatory pathways.
- Enable regulatory flexibility for stock allocation by manufacturers across the EU.
- Enable regulatory flexibility during site transfer where production risks are high notably to allow an extended grace period of 12 months (over the current 6 months) as the current timeline may be too short creating an unnecessary risk for supply interruptions.
- Enable digital and harmonized shortage reporting so that manufacturers can react more quickly to shortage or stock out situations. Including the supply chain actors in an early warning system about anticipated shortages will allow better rationalization of available supplies.
- Enact more use of digital regulatory processes to accelerate compliance activities as was done during Covid-19 (i.e., for narcotic import/export licenses at UN level).
- Grant the Commission clear “EU solidarity” powers in crisis situations to immediately intervene to prevent national hoarding activities that put in danger medicines’ availability in other countries.
- In crisis situations, establish structured dialogues with relevant manufacturers to remove barriers to manufacturing (competition law guidance, regulatory flexibility measures, etc.

- Enable rapid regulatory flexibility measures as used during Covid-19 such as temporary imports by manufacturers. The EU should align global development with important partners like the US or Japan in the future as this would also ensure that products are equivalent (facilitating this option). NB: we are only recommending this for emergency situations. Only EU licensed products should be available under normal circumstances.
- BEUC believes that consumer groups should also have a dialogue for the mitigation of drug shortages and BEUC and Affordable Medicines Europe recommends the enforcement of sanctions when companies fail to comply with legal requirements on drug shortage notification. The sanctions should be dissuasive enough to promote compliance (BEUC recommendation).[72] Manufacturers warn to consider this proposal very cautiously and focus on enforcing existing sanctions before reviewing the current framework for three reasons: The survey of Member States by the Commission indicate that they do have sanctions in place for non-compliance with supply obligations. These have not been applied because MAHs are fulfilling the obligation to notify authorities about shortages.[73] Please note that there are also fines potentially applicable to wholesale distributors detailed in this survey as they face similar requirements. Member States should also be aware that most commercial contracts such as hospital procurement contracts already include penalties for non-supply. In some cases, the penalty for one month of inability to supply might be as high as the value of the entire business per annum.[74] Therefore, additional regulatory sanctions would lead to double penalties and disincentivize companies from competing in tenders.

v. Dual sourcing in the supply chain

- The pros and cons of dual sourcing certain components of manufacturing supply (i.e., more than one API or FDF production site or supplier) was discussed. While this could be an option to encourage for some segments, it would not be suitable for others.
- Where conducive to security for some production segments or steps, there could be measures to promote the diversification of supply chains and include this in supply chain risk management plans. Measures could include economic incentives and lower regulatory maintenance costs to compensate the duplication of requirements and additional testing/qualification. Maintaining two manufacturing sites actively registered in the dossiers is very challenging for many products given the strict regulatory framework. To maintain two sites active the manufacturer needs to ensure that all specifications are the same and maintained fully consistent. Any minor difference across the specifications of the two sites typically prevents a continuous dual registration. More regulatory flexibility would allow

[72] Example of sanctions not being dissuasive enough https://www.france-assos-sante.org/bon_mauvais_point/penuries-de-medicaments-renforcer-et-rendre-publiques-les-sanctions-france-assos-sante-salue-les-propositions-dune-mission-de-lassemblee-nationale/ (accessed 14 July 2021)

[73] https://ec.europa.eu/health/sites/default/files/files/committee/ev_20180525_summary_en.pdf Penalties are applied for supply interruptions in this way in Member States:

11. Are there specific penalties for interruption of supply/shortages? (e.g. suspension of distribution authorisation or marketing authorisation, fines for export or shipment of medicines to other Member States in case of shortages)? If yes, did you impose sanctions during the last 10 years and have the penalties for shortage resulted in reluctance from the MAH to inform you about shortages, or in deregistration of the medicinal product? *The responses indicate that most authorities foresee sanctions (administrative or financial penalties); however, the majority of respondents have not applied them in the context of shortages in the last 10 years. No reluctance from the MAH to inform the authorities about shortages, or deregistration of the medicinal product as a consequence of specific sanctions in the context of supply interruption has been reported. In CY, the national legislation provides for the imposition of an administrative fine up to 34,000 € for the failure to comply with the obligation to notify any disruptions/shortages in supply. No fines however have been imposed the past 10 years with regard to this obligation. In CZ the MAHs can be fined up to the 20,000,000 CZK if they fail to fulfil their obligations; no sanctions in the context of Art. 23a of Directive 2001/83/EC were imposed in the past 10 years. CZ has imposed penalties on distributors in three cases of non-compliance with the prohibition of export in case of shortages (1.5 million CZK); one case is currently being reassessed (400,000 CZK) following an appeal filed by the company. EE can fine wholesalers for infringing an export ban under the Code of Misdemeanour Procedure. 18 EL has legal provisions for penalties for insufficient coverage of patients' needs. ES has established penalties for MAH that stop the distribution of a medicinal product since it can only be suspended under exceptional conditions adequately justified once the authorization of the Spanish agency is issued. There are also specific penalties for exporting medicines when this activity.*

[74] Medicines for Europe, 2019, Best procurement practices position paper. https://www.medicinesforeurope.com/wp-content/uploads/2019/04/M-Best-procurement-practices-position-paper_final-version.pdf. KPMG also identifies disproportionate penalties as major barriers for hospital procurement in France and Germany. *Improving healthcare delivery in hospitals by optimized utilization of medicines A study into 8 European countries https://www.medicinesforeurope.com/wp-content/uploads/2019/10/20190903_Hospital-Reform-Study_final.pdf*

manufacturers to build a more resilient supply network by a higher degree of dual sourcing / back-ups among sites.

- Where dual sourcing would not be appropriate such as for biologics, for complex to manufacture or for very small volume drugs, **risk management models** based on supply chain risk assessment of relevant products, well supported assurance of supply (by e.g., back-up sites, e.g., outsource or in-house MFG) could be used. Consideration for specific technology investment is warranted for vaccine manufacture and advanced therapies.

vi. International regulatory convergence

- Investing in inspectorate human resources, advancing mutual recognition agreements, and expanding overseas inspection activities.
- Take leadership in regulatory convergence in bilateral/multilateral fora (ICH, PIC/S) to advance cooperation on supply chains, to encourage more global development to increase availability, etc.

vii. Issue lacking consensus: Digital leaflets

- Progressively replace paper information leaflets with digital versions. (CONSENSUS NOT ACHIEVED ON THIS ISSUE SEE BELOW CLARIFICATION OF OPPOSING VIEWS ON THIS) For policymakers, it is important to consider that there is an absence of consensus on the proposal for digital leaflets.
- *Manufacturers are committed to this process* as it will provide up-to-date safety information to patients in all languages, massively improve manufacturing and allocation efficiency and package waste reduction and recall/repack related to updated safety information. Manufacturers also consider that digital formats will likely be more easily readable/accessible to patients than the current difficult to read paper version. Manufacturers also see that the current experiments with digital leaflets in Belgium, Italy, and Spain (for hospital administered products) confirm their value for all stakeholders. Manufacturers also note that citizens are used to switching to digital applications in many areas of daily life (i.e., QR code menus in restaurants due to Covid-19 rules) and close to 80% of the adult population accesses the internet daily (likely via smartphones)[75].
- *Pharmacists and BEUC[76] expressed their opposition to the replacement of the paper leaflet by digital versions* as they believe that product information should always accompany each pack and be easily accessible to all patients, consumers, and carers – also those with limited digital skills and limited access to digital tools and internet such as elderly patients and people with limited financial resources. Moreover, pharmacists are concerned that the printing requests for paper package leaflets in pharmacies would cause serious workflow disruptions and delays in the delivery of medicines to patients and would take away precious time from patient care.

Policy Option 4. Sustainability

Sustainability for robust supply chains focused on the environment, market reforms to encourage investment in robust supply chains for medicine and measures to harness the benefits of global supply chains.

a. Regarding **the environment**, discussions focused mainly on encouraging investment in a greener production footprint related to waste and energy use. BEUC added the importance of addressing the regulatory inefficiencies identified in the Fitness Check of the EU Water Legislation[77] and the actions

[75] https://ec.europa.eu/eurostat/statistics-explained/index.php?title=File:People_who_used_the_internet_on_a_daily_basis,_2019_(%25)_BYIE20.png
[76] https://www.beuc.eu/publications/beuc-x-2021-016_why_moving_essential_product_information_online_is_a_no-go.pdf
[77] https://ec.europa.eu/environment/water/fitness_check_of_the_eu_water_legislation/documents/Water%20Fitness%20Check%20-%20SWD(2019)439%20-%20web.pdf

outlined in the EU Strategic Approach to Pharmaceuticals in the Environment[78], which manufacturers are also actively engaged in. The proposed solutions include:

Provide technological support through EU funds and state aid reforms for:

- Investment in technologies for greener production processes, energy efficiency and renewable energy use.

Recognizing the global dimension of supply chains, the group proposed more global alignment on the environment notably:

- To support global initiatives such as the AMR common manufacturing framework to encourage investment in environment improvement.
- Recognize environmental investments in EU markets by introducing aligned EU criteria to recognize environmental performance in medicines procurement (avoid unharmonized criteria in MS). For high environmental impact productions, require Member State reimbursement rules to reward companies that investment in better performance. Wherever possible, there should be clear and aligned rules on how industry can justify environmental accountability to apply for incentives.
- To ensure that environmental progress goes hand in hand with access to medicines, target ERAs on high impact molecules and prevent the multiplication of study requirements on the same molecules.

b. For **sustainable markets** that encourage investments in robust supply chains, we recommend that procurers and payers be required to integrate robust supply chain criteria in their policies.

For multisource procurement:

- Apply multi-winner tenders to encourage more manufacturers to supply.
- Introduce MEAT criteria to reward investments in robust supply chains while maintaining financial sustainability with affordable medicine prices.
- Ensure procurement penalties are dissuasive but also proportionate to the value of the tender as increasingly companies are refusing to bid in certain tenders. For example, if certain bidders regularly fail to meet their supply obligations in tender markets, there should be procedures to reward other bidders with solid supply performance.

For multisource reimbursement:

- For mature products, reduce the impact of cost-containment measures (reference pricing, claw back, mandated price cuts) which are often cumulative and make generic medicines manufacturing unsustainable.
- For low margin products, enable a process to integrate cost inflation into reimbursement.

To encourage manufacturing in Europe:

- Encourage the use of EU RRF funds to support investment in pharmaceutical manufacturing across the production supply chain, with attached conditions in disbursed funding that contribute to maximise public return on public investment.
- BEUC proposes to use EU funds to support the creation of EU non-profit manufacturing undertakings which operate in the public interest, as proposed by the 2020 European Parliament's report of on medicine shortages.[79]

[78] https://ec.europa.eu/environment/water/water-dangersub/pdf/strategic_approach_pharmaceuticals_env.PDF
[79] https://www.europarl.europa.eu/doceo/document/TA-9-2020-0228_EN.pdf

Policy option 5. Ensure open trade flows and globally competitive industry

Medicine supply chains are global and international cooperation is crucial to ensuring that they are kept open and functioning. 64% of all global final pharmaceutical product exports come from the EU and 77% of Active Pharmaceutical Ingredients (APIs) used for producing innovative medicines in Europe are already manufactured in Europe. To **harness global supply chains** and ensure increased EU competitiveness and resilience for robust medicines supply, the EU should recognise supply chains are designed to deal with product diversity and manufacturing/distribution complexity with appropriate policies:

- Put in place appropriate market incentives for R&D and production and advanced manufacturing in Europe. This could be e.g., tax incentives and quality and security of supply criteria in public tenders. Increased R&D incentives for manufacturing could ensure that manufacturing in innovative products, has a reason to stay and grow in the EU.
- Maintain a strong innovation eco-system and incentives framework which is a core driver of investment and innovation in advanced manufacturing.
- BEUC underlines that market incentives should be balanced, should not unduly delay competition in pharmaceutical markets, and should include binding conditions to ensure public return on investment (BEUC recommendation).
- Increase educational assistance to eliminate skills gaps and ensure professionals have the competencies required for both current and next-generation manufacturing. High-quality, innovative, ongoing training models are essential to build, maintain, and expand manufacturing workforce capabilities.

In line with the EU strategies for industrial and trade policy, several stakeholders issued clear statements against protectionism. For example:

- BEUC recommends that any EU reshoring measures follow an independent assessment by the Commission which identifies the steps and segments of the supply chain would be of greater added value from a public health perspective, and they should be compliant with EU competition and WTO rules (BEUC recommendation). The EU should ensure that the 'strategic autonomy' discussion in the pharmaceutical sector, and the trade debate on 'open' strategic autonomy are aligned. BEUC emphasises the importance of globally diversified supply chains.
- EFPIA and Affordable Medicines Europe consider that protectionist policies will fail to serve European and global patient needs and advocates for more sustainable solutions relying on open trade flows, making the most use of integrated global supply chains, including leveraging regulatory cooperation and convergence and EU trade agreements to reach this objective.
- Strengthen global coordination e.g., with US through the Transatlantic Manufacturing Task force or the Trade and Technology Council as well as OECD work on supply chains. Multiple manufacturing, distribution and testing sites requires companies to maintain globally coordinated supply chains to reap the benefits of supply diversity (resilience, back-up capacity, learning, etc.). Therefore, global regulatory convergence is key (leveraging ICH and PIC/S platforms) to support streamlining regulatory processes, to facilitate operations and support supply chain agility.
- Create a global level playing field and EU taking the lead as a global standard-setter leveraging EU multilateral & bilateral trade negotiations and processes to support open trade flows and a more resilient supply chain at global level (e.g., Free Trade Agreements, Trade in Healthcare Initiative at the WTO, MRAs on GMP with third countries that focus on manufacturing quality and alignment/recognition of standards.
- Avoid unilateral Member State initiatives such as stockpiling or blocking exports that negatively impact patient access in other EU Member States and at global level. Ensure open global trade flows at all levels of supply chain (i.e., processes, materials, finished products),

and across borders, reject export restrictions, forced localisation, controls or bans, and remove tariffs on medicinal products or their ingredients.

- Recognise that every supply chain or manufacturing investment entails certain risk, and that the industry and the pharmaceutical policy framework should strive to minimise these risks. Long-term agility and resilience require long-term policies that enhance competitiveness. Europe is in a good position to be a world leader in life sciences. We have first-class science and a highly skilled workforce. However, Europe is currently losing ground to other economies such as the US and China. Today, 47% of new innovative treatments originate from the US compared with just 25% from Europe. This represents a complete reversal of the situation just 25 years ago. New cutting-edge research is being transferred out of Europe, mainly to the US and more recently to China. Europe needs to look beyond today and secure its strategic resilience on tomorrow's medicines by positioning itself at the forefront of innovation in strategic therapeutic areas and advanced technologies.
- We do not yet know where the next serious threat will emerge from, and what technologies will enable us to tackle the future health challenges we will face. For this reason, long-term supply chain resilience requires a robust life sciences eco-system in Europe. Such an eco-system should include a favourable and globally competitive R&D framework and an agile and flexible regulatory system to enable seamless adoption of new technologies.
- The Structured dialogue on supply is key and very timely, and it is key that we focus also on the need to maintain and increase European industry's overall competitiveness at a moment where we face increasing competition at global level to attract investments on what has now clearly been confirmed (even more with COVID) as a key strategic sector. **Only working together, instead of in silos, we can achieve this common goal.** In this context, it would be important to ensure consistency between different EU policies and strategies with manufacturing elements (Industrial Strategy, Pharma Strategy, Trade Strategy) and focusing on the *open* element of Open Strategic Autonomy to maintain a globally competitive EU industry while ensuring EU resilience.