Workstream 4 Report

Workstream 4 Innovation

The purpose of this workstream is to identify the modernisation needs, including identification of priority R&D areas, to ensure supply chains are adequately robust and resilient to meet EU public health need. This includes innovation needed to address challenges in deployment of new measures and maintain competitive production capacity in the EU. This reflection should integrate considerations of green and digital transition requirements, as well as modernisation of manufacturing processes.

Date of Submission:	20 July 2021
Working Group:	Workstream 4
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A. 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.

B. Executive summary

The EU is a leading manufacturing location for innovative, patented active ingredients and medicines, generic medicines and biosimilars, and synthetic chemical active ingredients. Innovation in manufacturing and supply operations is a critical requirement for Europe to maintain its competitiveness and leading position as a supplier of medicines to the world, and to support the digital and green transitions. Innovation in manufacturing and supply can also provide solutions that will help to address the vulnerabilities and challenges in the supply chain identified by WS1 and WS3, and thereby secure the supply of medicines for European patients.

The innovation in manufacturing and supply must span all aspects of medicines lifecycle, from discovery and design, production processes to end-of-life management. Long term resilience of supply chains will be strengthened through innovation throughout the product lifecycle and from all actors involved with the supply chain. The innovations considered in this report include technologies, supply chain visibility, procurement practice, regulation and patient access modalities.

The conclusions and recommendations from WS4 are as follows:

- The EU should ensure its ongoing development of competitiveness as a location for manufacturing and supply operations through an integrated, holistic strategy considering the full ICH Q10 product lifecycle of Pharmaceutical Development, Technology Transfer, Commercial Manufacturing, and Product Discontinuation, both for innovator and generic medicines, that comprises: a supportive business environment that has competitive tax rates, procurement and reimbursement policies, and open trading without export restrictions; an intellectual property framework that rewards innovation and encourages risk-taking; a skilled workforce that is nurtured and developed through collaborations between industry, academia and government; an agile pharmaceutical regulatory framework, and a regulatory framework where initiatives in the food, chemical, environmental, etc. legislation are fully assessed and understood for their impact on pharmaceutical supply chains to inform benefit/risk-based decision-making. This must be considered within the context of fast changing global competitive development and not for Europe in isolation.
- Prioritise innovative technologies that can help to address supply chain vulnerabilities and increase the agility and capacity of manufacturing and supply operations. These include continuous manufacturing (for both active ingredients and medicinal products), portable, modular manufacturing facilities, and single-use-systems that enable faster development and expansion of supply. This should also include the opportunity to re-invent or innovate old API synthesis processes that were developed 20-30 years ago. Through innovative, new or improved manufacturing processes, the manufacturing continuity of many medicines can be achieved competitively, and with a better green footprint and efficiency proposition. Technology innovation priorities should be identified and integrated into the academic and industrial research communities to create critical mass of aligned progress rather than fragmented and sub-optimal advances that fail to progress through Technology Readiness Level stages through lack of visibility, unsuitability for industrial application or lack of investment for development to Proof of Concept.
- Digital technologies are necessary to implement the innovative manufacturing technologies described above. They are also key enablers for increasing the visibility of inventory in the supply chain (helping to prevent or mitigate shortages), and enhancing the agility, quality, reliability and efficiency of manufacturing and supply processes
- Innovations within the EU regulatory framework that remove barriers, facilitate changes, and improve processes and engagement/dialogue between stakeholders should be implemented as a matter of priority to avoid becoming rate limiting. Efficiencies can be realised by digitalisation of regulatory processes, and this includes measures such as providing patient information electronically (ePILs) rather than through paper leaflets, although patient/HCP representatives' concerns for all patients to have access to information must be addressed.

Because the manufacture and supply of medicines is highly regulated, and introducing changes can be a protracted effort, it is important that the impact on the medicines sector is fully considered when, for example, changes are proposed in food or chemicals legislation, and especially when restrictions may be placed on the use of materials in the development and manufacture of medicines.

- The EU should lead the establishment of globally harmonised Quality-GMP pharmaceutical and environmental standards to support supply chain resilience and the green transition.
- Regulatory agencies need to advance in line with technology and process innovations, with skills development and strong aligned learning with applicants and governments to make these enhancements to avoid becoming rate-limiting for the modernisation of EU manufacturing capability and capacity. Adequate funding for agencies is needed to support these enhancements.
- Skills development is integral to innovation delivery across all actors. Skills in advanced technologies should be prioritised across all areas to ensure that the research pipeline in industry and academia develops transferable intellectual property. Digital skills are critical and in demand across industry in multiple applications and these should be addressed through national and EU research and education programmes. These skills should be aligned into regulators and authorities, in addition to industrial uptake.
- Innovation is also needed in procurement and reimbursement policies, such as multi-winner tenders and pricing that considers both the value of green improvements, and benefits to patient health. The cost frameworks for generics medicines inhibit investment in measures that could address supply vulnerabilities or support the green transition. Similar economic challenges have been highlighted by the EU fine chemicals industry where EU capacity and capability to manufacture mainly off-patent small molecule active ingredients has been lost to low-cost countries and investment in capacity or greener synthetic processes in the EU is not rewarded in the cost frameworks.
- The Green transition is integral to all innovations within long term medicines supply. In the short term, for the immediate vulnerabilities in supply chains, green transition has a more limited role. Apart from the reduction in waste-paper associated with the replacement of paper leaflets by the introduction of electronic Product Information (ePI), WS4 did not immediately identify opportunities from the green transition that would increase the resilience of supply chains.
- A long-term, integrated programme of policies and initiatives along the value chain is a priority to ensure resilient medicines supply within a green transition pathway for Europe. Innovation should include consideration of the full lifecycle, from design to end-of-life management, for contribution towards environmentally sustainable practise. Part of the management of the green transition is the identification of risk to supply through more restrictive environmental legislation and increased cost.
- The EU should align and deploy the appropriate R&D funding tools to support innovation in manufacturing and capacity building - including all instruments of Horizon Europe (collaborative research, EIC, Marie Curie, Joint Undertakings, etc.). Collaboration across the research ecosystem (public and private) should be strongly encouraged.

Next steps in the structured dialogue around innovation in manufacturing and supply should include securing further input from groups representing target research areas, patients and health-care professionals, and the manufacturers and suppliers of excipients, packaging materials/components, ancillary materials testing materials, equipment and facilities. It would also be valuable to consider innovations that might support resilient supply of critical medicines identified by the methodology proposed by WS2.

The report was generated after a significant number of meetings and discussions on the various questions asked by the Commission in the Structured Dialogue process. The content does not necessarily reflect a consensus on different topics and includes diverging opinions from some

participants. Some participants declined to be listed as contributors to the final report (see Appendix 9). The report does not contain all feedback provided during the process and it should be noted that certain stakeholders were unable to fully contribute due to workload/time pressures, and that some stakeholders were under-represented or missing from the WS4 team.

C. Table of Contents

1. Introduction

In the first operational meeting of the Structured Dialogue the following points were included in the Commission's presentation materials on innovation:

- Identify the modernisation needs, including priority R&D areas, to ensure supply chains are adequately robust and resilient to meet the EU public health need
- This includes the innovation needed to address challenges in deployment of new measures and maintain competitive production capacity in the EU
- Consider green and digital transition requirements, as well as modernisation of manufacturing processes

Workstream 4 began by considering the scope for its analysis and agreed not to define what was meant by 'innovation', but to consider discussing any type of innovation provided that it was relevant to supporting robustness/resilience in the supply chain and/or competitiveness of the EU pharmaceutical manufacturing sector.

It should be noted that some participants from the academic sector disagreed with the terms 'green transition': stating that "green' is not *per se* 'sustainable', even worse, it can be contra-productive and due to, e.g., rebound effects the opposite of sustainable." It seemed that 'sustainability' was preferred but that "having in focus the supply chain only is by far not enough becoming sustainable". Suggestions were made to expand the scope of WS4: "please include also environmentally better degradable future active ingredients, adjuvants and expedients/drugs themselves to protect water resources and soil and to avoid increasing resistance in the environment too". The report has generally stayed within the original parameters set within the European Commission template.

Three broad areas were identified for consideration:

1. New technologies, processes and technological innovations, particularly including those related to the green and digital transitions
2. Regulatory frameworks including for pharmaceutical, environmental, chemical, food, agriculture etc. legislation
3. The industrial ecosystem, business processes, and government policies and academia, Aspects of manufacturing and supply innovation within these broad areas could include consideration of:

   a. Manufacturing and distribution/wholesaling of established and new medicines in the generic, patented/innovator, and self-medication sectors, including:

      - Medicines containing small molecule active ingredients, biological products including vaccines, Advanced Therapy Medicinal Products (cell/gene therapies), medicinal product/device combinations etc
      - Manufacturing and supply of input materials for the medicinal product including active substances and their raw and starting materials and intermediates; excipients; packaging materials/components; ancillary materials (e.g., filters…)
      - Testing materials/reagents etc.
      - Manufacturing and testing equipment and manufacturing, laboratory and storage facilities

   b. Small/Medium/Large enterprises, including contract development and manufacturing, packaging testing and product release organisations, research institutions
   c. Geography: Europe (EU/EEA and Member States) and global trade blocs

The analysis was structured following the question framework described in section 2 below. All inputs were captured, but only those specifically related to manufacturing and supply were

discussed in detail, because this was the scope identified by the Commission (e.g. the discussions in the digital and green transitions were focused on innovations in manufacturing and supply, rather than aspects such as the use of 'big data' in clinical science, or broader aspects relating to sustainability and/or pharmaceuticals in the environment were not considered to be within the WS4 remit).

During the development of this report consistent use of terminology emerged as an aspect for consideration in the next phase of the Structured Dialogue. For example, the term 'product lifecycle' can have different meanings in pharmaceutical guidance (e.g. ICH Q10 and Q12) and environmental standards (e.g. ISO 14001). In ICH Q10 the product lifecycle stages are Pharmaceutical Development, Technology Transfer, Commercial Manufacturing, and Product Discontinuation. In ISO 14001 life cycle is defined as 'Consecutive and interlinked stages of a product (or service) system, from raw material acquisition or generation from natural resources to final disposal. Life cycle stages include acquisition of raw materials, design, production, transportation/delivery, use, end-of-life treatment and final disposal.' As far as possible the particular usage has been clarified if is not clear from the context.

During the analysis, WS4 identified the need to confirm with WS1 and WS3 the weaknesses and vulnerabilities in supply chains that they had identified and agree where innovations identified by WS4 could address these issues.

Three themes from WS1 and related proposals (Visibility/Predictability of the supply chain; A robust and enabling regulatory framework; and Sustainability) appeared to have good congruence with WS4 innovation areas. WS3 identified four main areas of vulnerabilities: Consolidation of the supply chain and investments in manufacturing capacity linked to cost pressures; The degree of geographical diversification for certain pharmaceuticals, raw materials or technologies; Regulatory complexity and degree of regulatory convergence; and Degree of visibility on supply and demand. WS4 discussed innovations that could help address many of these vulnerabilities.

WS4 also engaged with WS2 to consider whether certain innovations might be associated with critical medicines identified by WS2. Reflections on the manufacturing technologies used for medicines suggested by WS2 for the pilot evaluation of the methodology proposed by WS2 for criticality evaluation are included as Appendix 2.

Patient and healthcare professional (HCP) groups did not include representatives in WS4 and therefore WS4 rapporteurs requested input from those groups involved in the Structured Dialogue via a separate discussion. This discussion involved exploration of some of the general themes emerging from WS4 analyses and was supported by specific questions to elicit perspectives from patient and HCP groups on certain innovations. Feedback was received from one group, EURORDIS, and is included as Appendix 1.

Concerns were expressed about the limited number of representatives in WS4 from the academic community, and from regulatory agencies; it was also noted that there were no representatives from the suppliers of excipients, ancillary materials, packaging components, equipment etc. The WS4 rapporteurs were unable to address these concerns, and note the open call for experts to participate in the Structured Dialogue posted by the European Commission . The structure and timetable of the Structured Dialogue did not allow the expansion of communities represented, particularly for technology innovation from the diverse and highly international research community and it is recommended that a next phase addresses technology research expertise to enable coherent and productive research priorities that can be transferred into national and international funding and education programmes.

2. Detailed reporting

2.1. What are the key innovation needs to preserve and enhance the EU manufacturing footprint?

2.1.1 Technologies

Critical Raw Materials and Active Pharmaceutical Ingredients Manufacturing

In the recent years, Europe's dependence on Asia for the supply of precursors and generic APIs has increased significantly.

The IQVIA report suggests that currently 74% of the total volume of precursors and APIs for medicines consumed in the EU are imported, mainly from Asia (Reference 1: IQVIA Report for EFCG).

There are different perspectives on the manufacture of active pharmaceutical ingredients in Europe. Medicines for Europe noted that the EU is still a major producer and supplier of API to the EU and other regulated markets like the US. In practice, the EU, India and China have roughly equal market shares in the EU and the US markets. The reported market shares of EU based API manufacturing are in line with the reported locations in the US FDA GDUFA listing of the API manufacturing locations (Reference 2: GDUFA Paid facilities List), indicating a share of 31% of API sites for US market are in the EU and 47% of API sites located in India and China. However, it is clear that European manufacturers are losing competitiveness to India and China as Asian producers are accounting for much higher growth rates. Looking at new approvals of CEPs between 2000 and 2020, Asia significantly outperformed Europe: Asian manufacturers increased the number of their CEPs from 183 to 2,369, while European manufacturers only grew from 348 to 1,260 CEPs. (Reference 3: Progenerika report; Reference 4: Commission Staff Working Document Strategic dependencies and capacities). China and India are increasingly competitive in API and finished dosage form manufacturing globally. However, this dependency for European medicinal products is not as negative as reported in the media. The data show that European industry is still a major producer of medicines in Europe. An in-house survey from Medicines for Europe members (end 2020) related to in-house API manufacturing operations indicate that the members of Medicines for Europe have 58% API production still in EU, 26% in Asia, 5% in USA and 11% in Rest Of World. Data from EFPIA members suggests that approximately 77% of innovator company active ingredients are manufactured in Europe (Reference 5: EFPIA contribution to DG Trade consultation 2020), and the ECIPE reports suggest that 71% of imports by value are from Europe itself. (Reference 6: ECIPE reports 2020 and 2021)

The fine chemicals industry believes that restoring Europe's health strategic autonomy will depend on its ability to maintain and to develop its existing industrial base as well as invest in new technologies to selectively re-shore manufacturing of precursors and APIs to secure supply. Medicines for Europe suggests that, since most APIs are manufactured in multi-purpose facilities, selective approaches to re-shoring may not be appropriate as an industrial policy approach. Today, European manufacturers focus on specific APIs (e.g. low production volumes, complex production processes). The technical know-how and capacities to increase European API production are still available

Existing European intermediates and APIs manufacturers represent around 600 sites all across Europe. They provide critical molecules along the value chain of essential medicines and adapt their production to the needs of the Healthcare Industry, especially during medical crises.

For example, considering the top 10 drugs in EU5 markets (in volumes), namely Paracetamol, Salbutamol, Metformin, Levothyroxine Sodium, Acetylsalicylic Acid, Omeprazole, Atorvastatin, Ramipril, Diclofenac, Bisoprolol, the dependency from outside Europe is on average higher than 80% (Reference 1: IQVIA Report for EFCG).

Europe needs to maintain its global competitiveness and create a different economic framework that incentivises investment in the technologies required for the sustainable manufacturing of APIs needed for the production of essential medicines.

To be successful and compatible with the concept of global supply chains, respecting WTO principles, reshoring should be:

- Selective: regulatory, economic and financial incentives should be applicable to critical medicines, as defined by EU regulators
- Holistic: covering the supply chain end to end, to ensure robustness and real independence from overseas sources
- Non-exclusive: define the percentage of EU demand that should be covered by EU-based suppliers, allowing the balance to be supplied from overseas

The fine chemicals industry believes that the ultimate goal should be to reinforce the critical mass and technological autonomy of the EU-based pharmaceutical supply chain.

The existence of a solid European-based portfolio of technologies will allow the EU to successfully prevent and address current and future shortages, independently from their root causes.

Regarding the key technologies on which focus innovation, the IQVIA study indicated the following that have been partially lost from Europe, or are still present but critical:

- Nitration (partially lost in Europe
- Fermentation (partially lost in Europe)
- Fluorination (partially lost in Europe)
- Bromination, chlorination, sulfonation (partially lost in Europe)

During the WS4 sessions a significant convergence was reached on the list above. At the same time, some of the participants raised concerns regarding the reshoring of some technologies that have a potential impact on the environment (such as Fluorination; Reference 7: Chemical Aspects of Human and Environmental Overload with Fluorine), suggesting instead embracing step-change innovation programs that would avoid the adoption of "critical" technology from the onset. This is linked to the impact of the green transition on supply chain resilience. Phasing-out environmentally non-sustainable technologies is a part of broader, lifecycle approach (Q10), which will occur for specific materials and processes, some of which will impact current medicines supply directly or indirectly (where materials restriction from other sectors reduces supply for medicines). These considerations should be included in future innovation efforts.

Considering the need to preserve access to medicines and particularly to existing drugs, the discussion led to the need to redefine the concept of premium to innovation itself.
There is an opportunity to apply new technologies and knowledge to re-invent or innovate old processes that were developed 20-30 years ago to produce APIs (or precursors) through improved or new processes that will positively impact their green footprint and efficiency. However, compliance with higher standards can lead to higher manufacturing costs and the current business model would not allow European manufacturers to compete on the same 'level playing field' in such cases.
To ensure investments leading to this desired outcome, two basic conditions need to be respected: strong and focused incentive programs that will trigger the process and an appropriate industrial economic system to make such investments sustainable.
Some of the key aspects that need to be ensured are:

- support manufacturers to invest in development of long-term green transition and sustainable processes for precursors and APIs. Such green and resilient innovation should be recognised and rewarded; for instance a price premium for innovation, currently applied only to new drugs, could be extended and applied to greener, more sustainable or improved versions of existing drugs, supporting investments by the private sector to upgrade existing sites or to build new sites recognising the additional investment costs associated with high European EHS standards. This public-private approach will enable the EU to leverage private investment while encouraging production in Europe. For example, some antibiotic

manufacturers in Europe have invested in facilities with support from governments – in these examples, Austria and Italy (Reference 8: Antibiotic manufacturing expansion);

- support R&D investments for re-inventing processes to manufacture existing compounds: EU incentive programs should be set ensuring the structured cooperation between Industry and Academia;
- support (and ensure that it is not prevented) the allocation and execution of investments for the selective reshoring of precursors and API manufacturing and making them Greener and more resilient. Regulatory agility and a limited set of exemptions (including all existing and emerging regulations) should be available; A WS4 team member emphasised that pharma manufacturing should, as a rule of thumb, not be exempted from e.g. environmental and chemicals legislation and suggested that "one substance, one assessment" approach (Reference 9: COM(2020) 667 final, p. 14–15) is desired;
- reach an adequate level of manufacturing in Europe for specific technologies, reducing the supply chain risks and strategic dependencies from Asia. An EU-coordinated program of Incentives is also needed. This central coordination would prevent redundancies of production capacity in some areas and shortfalls in others;
- obtain a significant shift towards supply robustness is also needed to innovate the Ecosystem supporting the manufacturing of precursors and APIs in Europe. The existing business model, based only on costs, is in fact one of the root causes of the existing vulnerabilities (Reference 10: FDA report on Drug shortages). A new ecosystem is required to better streamline and incentivize the Innovation for Green and more sustainable manufacturing of API, with specific focus on the existing (such as generics).

Medicinal Products Manufacturing

Several new or emerging technologies were identified by the WS4 team that could enhance EU manufacturing competitiveness and resilience. It is important to note that most of these technologies require the application of digital technologies to enable them and this aspect is discussed more fully in section 2.3 below.

There is a general consensus among industry and regulators that continuous manufacturing has potential for improving the efficiency, agility, and flexibility of drug substance (as noted above) and drug product manufacturing. This is currently the subject of a regulatory harmonisation initiative in ICH (Reference 11: ICH Q13 concept paper) and a voluntary consensus standard had been developed in 2014 (Reference 12: ASTM International E2968).

The agility of manufacturing in fixed facilities can be increased by creating innovative multipurpose facilities e.g. producing vaccines and biologics in the same facility, or multi-dose vials and single dose vials/syringes in the same fill-finish unit.

As well as looking at new concepts for increasing manufacturing agility when using fixed facilities, the industry is also looking to introduce 'Autonomous & Portable' manufacturing facilities - prefabricated modular constructions that, through replication, could increase manufacturing agility, speed and consistency when moving from small to large scale production, including from clinical to commercial supply; or when replicating a unit across countries, allowing for faster response to patients' demand and emergency preparedness. (Reference 13: FDA Advanced Manufacturing). This approach to the creation of manufacturing facilities could also help to address the concerns about the geographic location of manufacturing facilities - portable, modular units would be faster and cheaper to construct and are potentially easier to locate where they are needed when compared to more conventional, fixed facilities (Reference 14: EFPIA paper Autonomous & Portable Manufacturing). It should be noted that these technologies are also applicable to manufacture of active ingredients. This mobile manufacturing approach could also be relevant as an innovative solution to the issue raised by patient group EURORDIS that support is needed to bring patients to specialist medicines if they cannot be produced directly in their own country (see Appendix 1).

With the manufacture of sterile products there is trend towards reducing direct human involvement in manufacturing processes via a variety of technologies and approaches to reduce the opportunities for contamination and hence supply interruptions through, for example, sterility failures. Another trend is for the use of single-use-systems in manufacturing, which essentially are disposable plastic bioreactors (rather than stainless steel vessels) that avoid the time and effort needed for cleaning validation etc., proving, streamlined and more flexible manufacturing processes. It will be noted that the disposable nature of the plastic equipment also brings environmental factors for consideration (e.g. potential to recycle the plastic equipment because of pharmaceutical residues, which may mean that incineration is required; reduction in wastewater etc. because cleaning isn't necessary). It is noteworthy that many of the COVID-19 vaccine manufacturing processes have used single-use-systems to enable the rapid development of manufacturing processes and the subsequent rapid increase in supply of vaccines to meet the global need for billions of doses.

Development of expertise in other emerging manufacturing technologies (e.g. 3-D printing (Reference 15: FDA approves Spritam; Additive manufacturing, Precision medicine (Reference 16: Top 10 Pharma Industry Trends & Innovations in 2021)) could be important for European manufacturing competitiveness but were not discussed in detail by WS4.

Excipients, Packaging and Ancillary Materials

The complexity of supply chains for medicines, and the opportunities for innovation by all actors involved, is illustrated by the example of vaccines developed against COVID-19: manufacturing the first vaccine to be authorised for emergency use requires 280 materials or components from suppliers in 19 countries, including specialised lipid excipients (Reference 17: Pfizer open letter).

Representatives from the excipients, packaging etc. sectors were not involved in WS4, so the innovation needs from these sectors were not discussed.

Electronic Product Information

Medicines are required to include paper product information leaflets in the packages and WS4 identified the opportunity to provide this information electronically, for example by scanning a bar code on the package (Reference 18: Inter-Association paper on ePI). This would offer the very latest information to patients in their language, be more environmentally friendly, and reduce complexity in the supply chain, thereby increasing resilience. It is acknowledged that patient groups have expressed concerns about the need to continue providing this information in a suitable format to patients who may not be able to access electronic information.

Medicinal Product Distribution

Opportunities for innovation in the distribution of medicines include the application of digital technologies and enhancing the use of data to increase visibility of inventories along the supply chain and thereby enhance supply chain resilience and mitigate shortages, as discussed in section 2.3 of this report. Other opportunities include, for example, the development of new or improved shipping technologies and processes to enable the supply of innovative medicines or reduce the environmental impact of operations (Reference 19: GIRP Annual Report 2020-2021)

The WS4 team also highlighted the necessity to harmonize the way serial numbers are generated for serialisation programmes across Europe to facilitate packaging harmonization.

Manufacturing and Supply of Advanced Therapies and other New Modalities

The manufacture and supply of 'traditional' biological medicinal products (e.g. monoclonal antibodies) has matured considerably over the last 20+ years but for Advanced Therapy Medicinal Products (cell/gene therapies) the analytical and manufacturing technologies are rapidly evolving.

Small patient populations, or, in the case of a personalized ATMP (e.g. autologous), where each batch has unique quality properties because it is produced for a specific patient, may represent a new paradigm for manufacture and supply. (Reference 20: EFPIA-PhRMA paper on EU-US Regulatory Co-operation activities) The European ecosystem needs to accommodate the increasing importance of ATMPs and their different modes of manufacturing (due to their inherent heterogeneity) to avoid losing competitiveness as a manufacturing location for this new, important class of medicines

The manufacture and supply of vaccines for COVID-19 has involved development of solutions for a range of new issues in manufacturing and supply, including the manufacture of plasmids for viral vector-based vaccines, ribonucleic acid and liposomes for mRNA vaccines and ultra cold-chain (-70ºC) supply (Reference 21: Increase in vaccine manufacturing capacity and supply for COVID-19 vaccines from AstraZeneca, BioNTech/Pfizer and Moderna), and unprecedented levels of collaboration with contract manufacturing organizations and other manufacturers (Reference 21: Increase in vaccine manufacturing capacity and supply for COVID-19 vaccines from AstraZeneca, BioNTech/Pfizer and Moderna), where existing products often have to be moved to different facilities to enable manufacture of the third party vaccines. This has led to enhanced focus on the capacity of those facilities and their adaptability in response to emergencies. Within an innovation perspective, the ecosystem for companies to make significant long-term investment in European facilities and skills demonstrates the absolute necessity for the right incentives as those investment decisions are being made now, and potentially elsewhere in the world.

Innovations in Manufacturing and Supply Technologies for the Green and Digital Transitions

These are discussed in more detail in sections 2.3 and 2.4. below.

2.1.2 Regulatory

Standards/Requirements

- Harmonisation and reliance

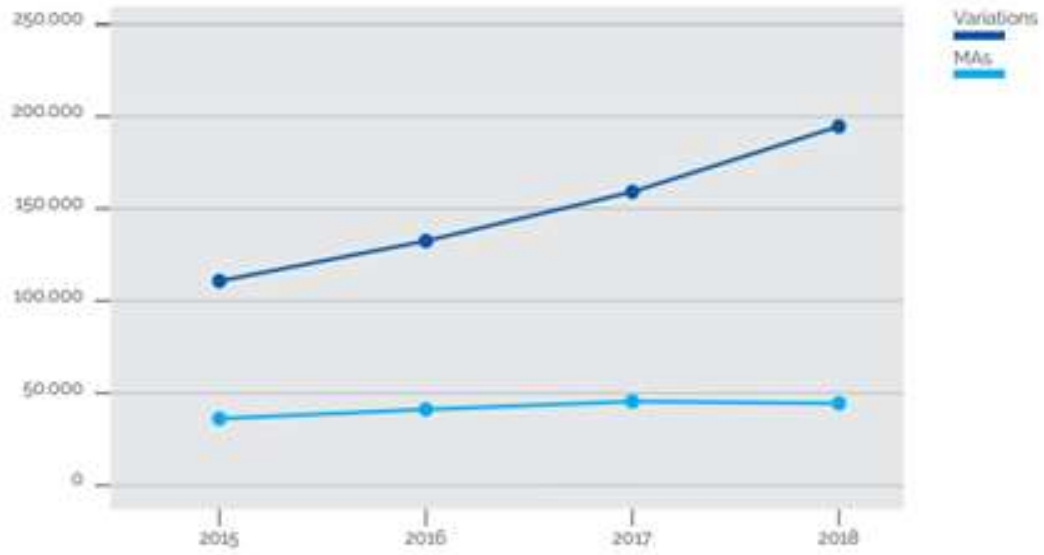
  The Covid-19 experience showed that innovative regulatory approaches could enable the industry to massively scale up output to meet demand (surges for chronic medicines, ICU medicines, vaccines) without affecting quality. International regulators and industry associations are now collaborating to explore approaches for enabling manufacturing capacity in the COVID-19 Pandemic. (Reference 22. ICMRA-IFPMA Workshop (2021)) Flexibilities introduced with these innovative regulatory approaches should become permanent features of the regulatory system (for example simplified labelling, digital leaflets) because they reduce supply vulnerabilities associated with complexity. (Reference 18: Inter-Association paper on ePI).
  Mutual Recognition Agreements are effective mechanisms for aligning regulatory requirements between EU and other countries and can be developed to support public health without needing full Trade Agreements. However, MRAs may not include all pharmaceuticals, for example, vaccines may be excluded. One example of regulatory innovation would be to introduce the concept of reliance, offering similar benefits to MRAs under controlled, defined circumstances, for example by referring to countries that are members of PIC/s. (Reference 23: EFPIA Annual Regulatory GMP/GDP Inspection Survey 2020 Data)

- Post-approval Changes

  The Commission's Pharmaceutical Strategy includes the flagship initiative to revise the Variations framework (Reference 24: Pharmaceutical strategy for Europe). Revision is needed to fully implement ICH Q12 'Product Lifecycle Management' in Europe (Reference 25: EMA ICH Q12) and incorporate regulatory tools that can facilitate implementation of post-approval changes, which can necessitate the generation of extensive scientific data for review and regulatory approval, and take many years to implement globally (Reference 26:

PDA PAC iAM 2017 Survey on Post Approval Change: Is the Regulatory Environment Hindering Much-Needed Innovation in the Pharma Industry?; Reference 27: IFPMA The complex journey of a vaccine Part II). This is a welcome and important opportunity to enable the adoption of innovative technologies in existing products and other changes associated with the modernisation of manufacturing and supply, including changes that could enhance the resilience of supply chains, decrease the environmental impact and/or increase sustainability of supply chain operations. EFPIA and Vaccines Europe have developed proposals for revisions to the Variations framework (See Appendix 8). Experience from the COVID-19 pandemic also shows how important this could be for facilitating expanded supply in pandemics and for supply from accelerated development programmes in general. The Medicines for Europe Regulatory Efficiency Report, from 2015 (Reference 28: MfE Regulatory Efficiency Report) showed that there are increasingly more variations filed by MAH which concern solely API information. Up to 60% of variations (related to quality) submitted by Marketing Authorisation Holders (MAHs) are related to changes to the API. The report shows that Marketing Authorisation Holders are dedicating a large amount of their resources to the API life-cycle management (submission of API related variations). For outsourced APIs, nearly 2 out of 3 quality variations relate to the API. In addition, given the high level of API outsourcing in the generic medicines industry, most of these changes will be filed multiple times through each and every 'user' of the concerned API. Based on data gathered from 2010-2018, the number of variations per MA and per year appears to have increased about 75% since 2010.

Trend in numbers of Variations and Marketing Authorisations (MAs) (2015-2018)



There has been a considerable increase in the overall number of variations submitted and processed by the EU Regulatory Authorities network since 2008 (Reference 29: MfE/AESGP Why is now the right time to modernise the EU variations system?). This puts a big pressure on efficiency of regulatory operations and adherence to timelines in view of limited resources on both authorities and industry side.

- Environmental standards

Global environmental standards may need to be adapted for application to pharmaceutical manufacturing and medicines, for example to meet Quality requirements. Rules on single use plastics and reuse of solvents might require specific systems or requirements for pharmaceuticals. A WS4 team member did not fully agree with these statements, arguing that exemptions are not a solution: The EC has set the zero pollution ambition that means

"chemicals, materials and products have to be as safe and sustainable as possible by design and during their life cycle". (Reference 30: COM (2021) 400 final, p. 11). They argued that the Pharma industry cannot be exempted totally from the transition, which is the necessity. Instead of categorial exemptions, it is desirable to raise awareness through the whole supply chain, create dialogue between different sectors, and provide systematic support for transformation of processes in cases where essential need for preserving the status quo cannot be justified. Harmonisation of environmental standards globally will help to create a 'level playing field' of common regulatory requirements adopted by countries around the world, avoiding a 'race to the bottom' (Reference 31: Implementing the Circular Economy for Sustainable Development). The level playing field serves in several ways to support resilience, including greater likelihood of multiple suppliers. There are also opportunities for harmonisation within the EU, for example, GMO legislation is currently defined by Member States.

It was noted that regulatory oversight of pharmaceutical GMP and environmental standards should not be combined because they require different subject matter experts. A WS4 team member disagreed with this statement, arguing that the inclusion of environmental aspects in the GMP is desired and it does not mean combining GMPs and environmental standards. They suggested "In the formulation of international standards, for example including environmental aspects in the GMPs, the expertise of environmental regulators and legal scholars should be utilised more."

Processes

- Digitalisation

Streamlining of regulatory processes could be facilitated by further application of digital technologies to regulatory processes and the maintenance of information in Marketing Authorisations, and for inspection management. This could reduce the administrative burden and optimise the use of resources in both industry and regulatory agencies in managing post-approval changes. Digitisation of the regulatory system could also contribute to visibility of supply chain risks. The Accumulus Synergy initiative is a global data sharing / information exchange platform to transform how drug innovators and health regulators interact to bring safe and effective medicines to patients faster and more efficiently.

- Scientific dialogue and advice

Improved processes for scientific dialogue and advice between industry and regulators are needed for manufacturing and supply topics. Better dialogue can ensure that regulatory guidance and oversight is appropriate for the introduction of new technologies (whether at first approval or via post-approval changes) and other changes to existing products. Regulatory agencies need to have the resources to enable this dialogue, which frequently needs to be outside of the scope of scientific advice because more general, non-product-specific information is required.

- Increased flexibility and modernisation of regulatory processes

Increasing the overall flexibility and agility of the EU Medicines Regulatory Network is needed to support the implementation of innovative technologies and approaches discussed in this report. An example of additional agility that could be introduced to address an issue with innovation for alternative supply chains was noted by patient group EURORDIS (see Appendix 1). Regulatory agencies will therefore need appropriate funding and resources to deliver, for example, faster procedures for review and approval and mechanisms supporting increased interactions for dialogue and advice with industry and other stakeholders, including regulatory experts in Third countries.

Modernizing the EU regulatory system would also include enhancing coordination among Member States' Competent Authorities, and between Member States and the Commission. This should include improved coordination between the different legislative areas

(medicines, food, chemical, environment, trade, tax etc) to ensure there is a complete view of impact on the different actors within the complex value chain (e.g. end-to-end considerations from starting materials, intermediates, active ingredients, excipients, packaging components, finished medicines, and distributors to the patient/health care professional, for both generic and innovative medicines).

Regulatory bodies strategies will need to support the transformations discussed in this report through process innovation and increased agility to meet the needs of society, for example building on the learnings from the response to the COVID-19 pandemic.

- Green transition

This is listed as part of processes here, in addition to a dedicated section later, as this is a process integral to medicines supply. Pollution prevention should be actively supported in all relevant EU policies. (Reference 30: COM (2021) 400 final, p.3) Innovation-friendly regulatory environment that enables and supports transformation to more sustainable processes and products, should be created.

This is in line with the Chemicals Strategy's statement: "A more coherent, predictable and stronger regulatory framework, combined with non-regulatory incentives, will drive the necessary innovation, deliver increased protection, while enhancing the competitiveness of the European chemical industry and its value chains. To ensure a level playing field between EU and non-EU players, the EU must ensure full enforcement of its rules on chemicals both internally and at its borders, and promote them as a gold standard worldwide, in line with our international commitments." (Reference 9: COM (2020) 667 final, p.3)

2.1.3 Industrial Ecosystem

Intellectual Property

The intellectual property framework is designed to reward and encourage innovation and risk taking, including innovation in manufacturing and supply. Waiving intellectual property protection as a mechanism to increase the supply of new innovative medicine and vaccines will act as a dis-incentive for innovation and will not have the desired effect because the constraints are elsewhere. For example, the supply of highly specialised raw materials could be disrupted by manufacturers competing to secure these materials; highly skilled scientific and engineering human resources are needed for successful technology transfer to partner contract manufacturing organisations that have suitable infrastructure; and ensuring that the quality, safety and efficacy is maintained during scale-up through appropriate oversight by industry quality assurance organisations and regulatory agencies is of paramount importance.

Procurement/Pricing/Tax/Incentives

Innovation in manufacturing would be supported by removing tax and administrative barriers for investments in manufacturing, providing continued incentives for private and public investments in the R&D ecosystem (research sector including Universities and small and medium enterprises). This should include public-private partnerships and venture capital funding mechanisms.

New pricing models could be established for off-patent medicines to allow prices to be adjusted for higher COGs or regulatory costs.

Innovation is needed in procurement practices to address problems related to off-shoring to low-cost countries. Tender procedures should reward quality and promote innovation by ensuring that tenders are awarded based on a price-quality assessment, including an appropriate mix and weighting of qualitative selection and award criteria (such as the quality of the products, the services infrastructure associated with the product, lead times, predictability of volume, volume purchase commitments, robust supply chains, sustainability etc.). Procurement processes should

guarantee supply volumes and fair competition between all potential suppliers by using effective multi-awardee framework contracts to safeguard the long-term presence of multiple suppliers on the market, and to mitigate the risks and consequences of shortages. A WS4 team member noted that initiatives by Member States (e.g. Sweden) to include environmental criteria in calls for tender, should be supported.

It is important to address shortcomings in national and cross-border joint procurement processes that negatively impact the sustainable supply of medicinal products to national markets, to avoid administration burdens for both industry and purchasers. This could be addressed by the European Commission adopting (on the basis of Article 168 of the Treaty on the Functioning of the European Union) best practice guidance in dialogue with Member States in order to improve the working of procurement processes to best meet societal expectations and patient needs. In addition, EU Member States (including national/regional competent authorities) should establish annual structured discussions with key stakeholders to progressively evolve national procurement processes to take into account best practices described above.

Education sector

Education is a clear point of strength for Europe and this should be mobilised to address the subjects linked to resilience of medicines. This reaches back in the university graduate programmes and is an opportunity to look at global factors that impact supply chains for Europe. Whilst there are some clearly identified examples linked to the supply of medicines, the education pathways are diverse that lead into the sector and the challenge will be to ensure that supply chain considerations can become part of such courses. Increased awareness of supply chains within key supporting disciplines (engineering, chemistry, biochemistry, chemo-informatics, green and sustainable chemistry, environmental chemistry etc.) will help to develop post-graduate awareness and studies linked to sector resilience.

Knowledge of industrial ecosystems such as industrial process, digitalisation and regulatory frameworks should integrated into all education courses clearly linked to medicines development to provide preliminary awareness in career development.

Public-Private partnerships

In the last decade, Europe has developed public private partnerships across medicines (IMI, following on to IHI), bioindustry (Bio-Based Industries Joint Undertaking) and manufacturing (Factories of the Future). They have demonstrated significant industry appetite for pre-competitive collaboration on key topics of common interest. Europe has the opportunity to integrate key aspects of medicines and advanced manufacturing resilience into all such programmes and connect them where they are integrated into different initiatives.

2.2. Are there barriers/challenges to manufacturing in the EU being globally competitive? What are they? Are specific industrial policy measures needed to cope with the issues identified?

2.2.1 Lack of Incentives/Investment

As discussed below, economic factors drive the decisions companies make on the areas for investment to sustain and grow the business. Unless there is a business case for a suitable return on the investment in manufacturing and supply initiatives, companies will not be able to make the investments in areas such as manufacturing capacity and supply chain vulnerability.

- Investment not rewarded: As discussed below, lack of incentives for investments to support the green transition or address supply chain vulnerabilities will act as a barrier because a return on investment in these areas cannot be obtained through other procurement/pricing

mechanisms. Most medicines procurement in the (off-patent) competitive sector is based on a form of molecule pricing. There are limited possibilities to reward companies for investment in resilient supply chains or for environmental efforts in procurement policies that are based on the lowest molecule price – which is the case for almost all procurement in Europe (see Appendix 4).

- Intellectual Property erosion: The industry sector does not believe that waiving intellectual property protection is a solution that would increase the speed with which manufacturing capacity can be increased for new life-saving medicines such as the COVID-19 vaccines, as has been suggested in some countries (Reference 15: Pfizer open letter). On the contrary, such an approach would be disruptive and sub-optimal by creating unco-ordinated competition for scarce resources such as specialised excipients and manufacturing materials, and increasing the workload of regulatory agencies who would need to confirm the quality, safety and efficacy of medicines/vaccines that have not gone through a technology transfer process. Many innovations in manufacturing are led through the development of innovative medicines and therefore global competitiveness of the EU as a location for high-value manufacturing needs to be fostered through an appropriate intellectual property framework that balances access and affordability for both innovative and generic medicines.
- Recovery funds: The Commission has proposed targeted technology support for recovering API production in the Recovery and Resilience Fund and many Member States (e.g. Italy, Spain, Portugal, Poland, Hungary, Greece, and others) are applying for funding to rebuild API production. However, these Member State applications are struggling due to the complexity of EU state aid rules (See Appendix 4)

2.2.2 Procurement/Pricing

The loss of capacity in certain sectors of EU manufacturing (e.g. fine chemicals) has been driven by cost - manufacturing has moved to low-cost countries because of pressure on pricing/reimbursement. The rare diseases patient group EURORDIS also pointed to the challenges for funding new therapies in relation to increased expenditure on medicines in other areas (see Appendix 1).

- Tender processes

  Tenders typically are won by the bidder with the lowest cost and may not take into account other desirable factors such as the relative environmental impact of different supply chains or the robustness of a supply chain. Furthermore, if the tender process results in a single winner, this may create a vulnerability in supply if the winner subsequently encounters problems.

- Reimbursement

  In the EU, and in other countries globally, the price of off-patent medicines is often fixed through reimbursement practices based on reference pricing – a process to set the molecule price according the lowest price in the market (or compared to foreign markets for external reference pricing). The profitability of a medicine is therefore maximised by driving the costs as low as possible, because there is little or no opportunity to differentiate generic medicines from different manufacturers through branding, for example by creating brand value linked to supply reliability, manufacturing location or low environmental impact.

2.2.3 **Regulatory**

- Lack of harmonisation

  Having a single set of regulatory requirements can facilitate supply by reducing the diversity of requirements for different markets, so harmonisation is needed globally to

create consistent quality and environmental regulatory requirements. It should be noted that EU requirements frequently inform the development of regulatory requirements in other countries and regions, and also there are strong ties to the WHO, so the EU can build on this by playing a leading, but collaborative, role in the global development of regulatory science and thinking.

Harmonisation of Quality requirements globally is important to facilitate supply chain resilience. As a founding member, the EU has a strong voice in ICH, which is the leading forum for harmonisation of Quality requirements. However, there is no equivalent forum for harmonisation of environmental regulatory requirements (which are typically not developed for specific industry sectors such as pharmaceuticals, but rather to be applicable to all industries) and therefore there are limited opportunities to create environmental requirements that are globally adopted and enforced(Reference 31: Implementing the Circular Economy for Sustainable Development)

Although the pharmaceutical manufacturing requirements are largely harmonised across the EU/EEA, there are further opportunities for harmonisation within the EU, particularly in those areas related to the supply chain where there are differences in interpretation and/or differences in requirements at Member State level (e.g. in relation to the Qualified Person – see Appendix 3).

- Conservatism, Additional Requirements and other Legislative barriers

  In the main pharmaceutical legislation (Directive 2001/83/EC and Regulation 726/2004) some potential barriers have been identified that could inhibit the adoption of new manufacturing technologies including modular, mobile manufacturing which can increase manufacturing agility and supply chain resilience (see Appendix 3). Embodying key principles in legislation is appropriate, but the inclusion of detailed requirements can inadvertently create barriers as science and technology advances. While there may be relatively few barriers in the main legislation, regulatory guidance may create barriers, as described below. Paradoxically, a lack of regulatory guidance may also create barriers due to uncertainty about the regulatory acceptability of new technologies and approaches, which results in companies persisting with old approaches and failing to implement new technologies. This is particularly true for the new digital technologies, as discussed in section 2.3.

  EU regional interpretation of harmonised requirements from ICH can be more conservative than other regions, impairing the global competitiveness of the EU and delaying access to medicines. Examples include the implementation of the Q8-Q11 series of ICH guidelines, which are intended to support the ICH vision for modern manufacturing (see Appendix 5). Conservatism in the interpretation of regulatory requirements can also inhibit the implementation of new technologies. An example is the Addendum to the CHMP NIR guideline, which inhibits the implementation of continuous manufacturing (see Appendix 6).

  Regulatory guidance should therefore incorporate flexibility in the way to meet requirements and embody science- and risk-based approaches that focus on what is critical for the patient. Opportunities for agencies to refer to voluntary consensus standards (ISO, ASTM International etc.), rather than developing detailed guidance, could enable optimisation of regulatory resources. Voluntary consensus standards are developed by stakeholder experts, including experts from regulatory agencies. More frequent and rapid revisions of these standards to take into account the latest developments in science and technology could also be possible.

- Slow/inadequate processes

  Experience from the COVID-19 pandemic may have created the impression that the EU is falling behind when the speed of EU regulatory processes is compared with other leading regulators (Reference 32: Reuters article).

  Innovation in regulatory requirements to qualify second sources could help to address supply chain vulnerabilities, while finding approaches to expand the use of dynamic regulatory assessments for post-approval changes could accelerate change processes.

  There is a challenge in Europe to improve on well-established molecules – for example to use modern manufacturing and chemistry (including complex production like nanotechnology) to improve the formulation of medicines for better safety or efficacy. According to IQVIA (Reference 33: IQVIA Report A digital future for value added medicines), the US accounts for 70% of the global market for these improved medicines thanks to its dedicated regulatory pathway (502(b)2). This encourages the development and manufacture of these complex products in the US (even if they are developed in Europe) rather than in Europe. By encouraging this form of innovation, the EU would stimulate investments into more complex manufacturing on a large scale (as these are volume products) and contribute to a more modern manufacturing ecosystem in Europe.

  Opportunities for engagement between the industry, either as individual companies or trade associations, and EU regulators to discuss manufacturing and supply topics are limited and inadequate. (See Appendix 6 and Appendix 7)

- Intersection of different Regulations

  The manufacture and supply of medicines is highly regulated to contribute to the protection of public health. As noted above, the regulatory requirements mean that implementation of changes can be both resource intensive for all stakeholders, and a protracted exercise, and because of this it is important that the impact on the medicines sector is fully considered when, for example, changes are proposed in food or chemicals legislation, and especially when restrictions may be placed on the use of materials in the development and manufacture of medicines. The application of food standards to medicines (e.g. per DIRECTIVE 2009/35/EC) is a current example of this in relation to the use of Titanium Dioxide E171 in oral medicines. The potential limitation of use of E171 in medicines, despite a long history of safe use, could have significant impact on future availability of many medicines for European patients, The imposition of export restrictions (e.g. Commission Implementing Regulation (EU) 2021/111, and subsequent amendments including 2021/1071, on the authorisation requirement for exports of Covid-19 vaccines and their active substances including master and working cell banks) is another example of regulations that can impair the smooth functioning of supply chains. These examples can create new vulnerabilities in supply chains and therefore improvements in the interactions between the Directorates within the Commission could avoid this. A WS4 team member noted that coordinated approaches, such as "One substance, one assessment approach", included in the Chemicals Strategy, are desired. (Reference 9: COM (2020) 667 final, p. 14–15)

2.2.4 Skills/Knowledge gaps

WS4 agreed there is a need to consolidate and enhance key skills needed for the modernisation of manufacturing. Representatives from the University sector in WS4 reported limited availability of graduate/post-graduate courses on pharmaceutical/biopharmaceutical manufacturing and supply. A strategy is needed to prepare for the current and future needs, including for the green and digital transitions (as discussed below) that can build on some existing initiatives and strengthen partnerships between industry and academia. For example, the EU STARS project (Reference 34: EU Strengthening Regulatory Science in Academia) notes that 'translating research findings into

medicinal products for clinical practice requires knowledge, skills and facilities that typically reside in pharmaceutical companies and not in public research institutes. Such companies have the resources to, for example, develop a product that complies with quality and manufacturing standards, compile a dossier that meets all requirements for regulatory acceptance, and upscale the manufacturing process'. The need was stressed for systematic inclusion of a lifecycle approach in the education of pharmaceutical and medical sciences (Reference 35: Siven et al (2020); Reference 36: Professorship in sustainable development). The educational programmes should be interdisciplinary to draw a comprehensive picture of all relevant aspects of pharmaceutical lifecycle. A systematic education model will ensure a new generation of skilled workforce.

Broader awareness and skills development is also supported through use of programmes such as the EC PACT for Skills initiative (Reference 44), which aims to engage communities including companies, workers, national, regional and local authorities, social partners, cross-industry and sectoral organisations, education and training providers, chambers of commerce and employment services.

Finally, EU programmes such as EIC have a role to play within skills development as it targets technologies with high potential and at a stage where market access is close and has a knowledge development aspect within activities.

2.3. What are the challenges the EU pharmaceutical manufacturing value chain will be faced to keep up with digital transition? How would the digital transition contribute to the increased resilience of the supply chains?

2.3.1 Digital opportunities in Manufacturing and Supply

The fourth industrial revolution applied to the pharmaceutical industry is being driven by digital technologies including artificial intelligence (AI), machine learning (ML), robotics, blockchain, virtual and augmented reality (VR, AR), faster mobile communication (5G), the Internet of Things (IoT). Machines and devices are communicating, continuously and in real-time, generating large amounts of data that must be validated, stored and available for use by advanced data analytical tools for predicting, modelling, controlling, and trending manufacturing and supply operations.

The digital transition would enhance Europe's competitiveness by reducing production costs and cycle times, improving customer service and access to medicines. Potentially, this could close the gap in terms of costs compared with low-cost countries, reduce dependencies and support sustainability for European manufacturing.

Not only it is essential that Europe does not fall behind in the digital transition, but an ambitious set of policy initiatives needs to be implemented so that Europe is able to secure the benefits of this transition to help address the vulnerabilities identified in supply chains and gain efficiencies in operations that can help to support the additional cost for the green transition discussed in section 2.4 below.

2.3.2 Capacity/Maturity of the Regulatory Framework

- Regulation and Guidance

  Regulatory bodies face the challenge to interpret the regulatory quality/GMP requirements and how they should be applied to digital technologies, without creating obstacles to innovation. The principles for GMP are well-established and remain applicable in a digital world; the pace of change for digital technologies means that incorporating detailed requirements in regulation could result in the regulation quickly becoming out-of-date. Regulatory guidance must enable modern, state-of-the-art manufacturing while continuing to assure that products for patients are safe, efficacious and of suitable quality (Reference 37: EFPIA MQEG Discussion Paper: Digitalization in Pharmaceutical Manufacturing)

One challenge is the interpretation of GMP requirements from the perspective of paper-based systems, and failing to take into account the opportunities to fully realise the benefits of digital technologies. For example, 'double signature verification' is not required where the digital system has this verification inbuilt. The absence of guidance can lead to uncertainties on the acceptability of approaches and hence act as an inhibition to the adoption of these technologies, but conversely very prescriptive, inflexible guidance may also act as a barrier, especially as there is the same risk of the guidance quickly becoming out-of-date. Achieving the necessary agility in the European regulatory framework for oversight of the implementation of digital technologies requires more frequent and intensive dialogue among stakeholder experts, for example, through the creation of processes and forums that can quickly resolve issues and accelerate the adoption of these technologies (See Appendix 7).

- Administrative Burden

  The current EU Variations framework is not well-adapted to modern manufacturing approaches in which, for example, processing conditions may be adapted in real-time based on information from online sensors feeding process models. The revision of the framework, as a flagship initiative in the Commission's Pharmaceutical Strategy, is therefore a timely opportunity to update and future-proof the Variations framework to facilitate digital and other innovations in manufacturing and supply by reducing the administrative post-approval burden for both industry and regulatory agencies (See Appendix 8).

  As noted above, adaptations to the regulatory framework (e.g. update to guidelines and addendums) need to keep pace with the development of digital technologies. Other trading blocs have created forums for dialogue between industry and regulators to enable adaptation of regulatory practice, reduce uncertainties and accelerate adoption and Europe needs to make improvements in this area. Regulatory agencies need to be resourced to develop greater expertise and capability to support the digital transition.

2.3.3 Workforce

Realising the benefits of the application of these new digital technologies to pharmaceutical manufacturing and supply operations necessitates a skilled and knowledgeable workforce in both the industry and regulatory agencies. The collaboration between academic sector, industry and regulators needs to be strengthened and supported with additional resources to develop a common understanding of these digital technologies and support their further development and implementation.

2.2.4 Digitising the Supply Chain

Using digital technologies to increase the visibility of inventory along the supply chain could play a major role in helping to prevent or mitigate shortages. Connecting data from the users of the medicine - patients/Healthcare Professionals - to the supply chain could enhance the accuracy of demand forecasts, and optimise deliveries. (See Appendix 1). There is also a need to connect actors along the supply chain to enable data to be transmitted between suppliers and manufacturers and initial steps are being taken to establish standards (for example see Reference 38: ASTM International E3077)

There is a need to agree electronic data interchange technologies between supply chain actors. European Medicines Verification System (EMVS) has been established to counter the threat of falsified medicines entering the legal supply chain, but there is not yet agreement on expanding its role in fully digitising the value chain. Discussion in WS4 acknowledged various challenges that would need to be overcome to achieve this goal, for example, in providing a legal environment to

enable secondary use of data; respecting GDPR and personal privacy rights (see Appendix 1); governance that enables appropriate access to all stakeholders; and technology standards and solutions for interoperability, enabling connections across data networks of suppliers, manufacturers, wholesalers/distributors and regulatory agencies.

2.3.5 Costs

Support for investments in new digital technologies from EU structural funds and Member State national investments will help to accelerate the digital transition and countries to adopt best in class systems. Since the digitalisation of the supply chain involves multiple stakeholders within the industry sector and regulatory agencies across the Member States, a strong, centrally co-ordinated and funded, initiative will be needed to make this happen.

2.4. What are the challenges the EU pharmaceutical manufacturing value chain will be faced to keep up with green transition? How would the green transition contribute to the increased resilience of the supply chains?

2.4.1 Introduction

With significant changes anticipated across all sectors in response to the green transition, the resilience of the medicines supply chain will be impacted, particularly as the full life cycle must be considered. This will have differing significance for the supply chain for currently vulnerable points; however, innovation must be viewed in the context of a long-term green transition. Europe must not be limited to considerations of sustainability within its own territory – it must push for worldwide sustainability and recognise that significant manufacture will continue to take place beyond Europe, even if re-shoring or expanded production within Europe is achieved.

The supply of medicines must be part of the green transition, it is not exempt from such ambition, and there are multiple aspects that compose the ecosystem in which medicines are developed and used, including:

- Production pathway of medicines, including packaging: This takes place within a complex global supply network. The European Union must consider sustainability development within Europe and also strive to enable non-EU locations to achieve green transition.
- Processes associated with medicines supply and use by patients: This is more directly within the control of the European Union, as it addresses people within the European Union at the point of supply and management of medicines and associated services.

Resilience of supply is impacted by many aspects of production that are linked to climate change itself and the transition to sustainable practice:

- More extreme weather patterns that will disrupt production and transport, particularly linked to single producers or producing regions. This is especially relevant in regions of the world that are experiencing extreme weather regularly and lack the wider infrastructure to prevent or mitigate impact on production. This points to the priority for Europe to have more production within its own territory and also to support robust global supply chains through diversity of producers. Input from a patient group noted the need for patients to be informed about storage requirements to assure the stability of medicines in extreme temperature conditions such as 40oC where air conditioning may not be available to maintain storage at normal room temperatures of less than 25ºC (see Appendix 1). Industry generates stability data for short-term temperature excursions (e.g. at 50ºC), but this is not typically included in information for patients.
- Ingredients and intermediates becoming unavailable as part of transition to more sustainable production and environmental impact. Impacts include lack of availability, unreliable availability, compromised quality and higher cost

- Revised waste management that makes existing processes non-viable for either technical or cost perspectives. The first territory in which this is likely to happen is Europe, which makes it a priority that existing processes are reviewed for their risk of change in response to legislative changes. Medicines supply should be proactive in this scope rather than reactive once legislative change is enforced.
- Technology-readiness of alternative ingredients and processes: In a heavily regulated sector, there is the need for a harmonised approach to changes. There is a significant need for cross-sectoral industry liaison and agreement on aligned progression. A 'patchwork' landscape of potential advances in manufacture does not support rapid and widespread industry uptake. An element of agreement is required for production as a whole to progress.
- Regulatory frameworks lack preparedness, capability, speed and capacity to address replacements to existing materials and introduction of advanced future products and processes. This is critical in relation to most of the points above and European regulatory frameworks need to be proactive now to address these issues of highest vulnerability with regard to green transition changes that will come from multiple sources

The green transition is important for existing medicines, including those within generics production and also next generation medicines.

The green transition is not isolated from the other European priorities and present an innovation opportunity for Europe, rather than a challenge when addressing resilience of the medicines supply chain:

- Need for a robust supply chain, both within Europe and part of secure global networks
- Need for the delivery of the green transition, with tangible CO2 targets within 10 years
- Need for economic recovery and growth (not just 'build back' but also 'build forward')

The green transition is also interlinked with digital transition aims. They do not stand apart. Optimising all aspects of manufacture and medicines use through the diverse options of digitalisation, creates an efficient supply chain, with reduced energy input and use of resources (including waste) throughout the healthcare lifecycle.

Short term vs long term green transition within the context of medicines supply resilience

In the short term, the focus is on immediate actions to address existing failures within supply chain, which does not necessarily have green transition considerations or actions. These are considered to be reactions to urgent or critical supply chain vulnerabilities and involve only existing production pathways. These may be considered temporary compared to longer term needs. Beyond the immediate short term, it is important that actions that alter product development, acquisition and use should be considered in all aspects for delivering a green transition, as an integral part of supply chain resilience and sustainability. There are various initiatives that aim to help address the broader aspects of sustainability (see, for example, Reference 39: Chemicals strategy; Reference 40: IMI PREMIER)

2.4.2 Challenges for the EU pharmaceutical manufacturing value chain within the green transition

a. Substances in products and process: Costs

The challenge

Work with WS 4 focussed very quickly on cost as part of the Green Transition. It has already been highlighted throughout this report that the focus on cost of medicines is a significant factor in the current supply chain fragility that was exposed through COVID-19. Tender and procurement processes with a narrow focus on cost have reduced supply options and removed the economic incentive to invest in next generation production technologies.

From a European perspective, this is a double bottleneck – not only are more sustainable technologies not economically viable to develop (within the EU) but they are also ensuring that the offshore nature of supply using older processes will remain the status quo. This position currently exists globally. Healthcare systems worldwide have contributed to a lack of innovation in sustainable production pathways in any meaningful way. As identified in the introduction to this section, current costs cannot be sustained to achieve a resilient medicines supply and Europe must address the certainty of rising costs due to changing supply chain requirements, viewing this through a longer term vision of future costs rather than current. This creates opportunities that should be taken proactively to build a European position, rather than reactively when new suppliers emerge outside Europe.

Procurement and tender innovation: Europe has the opportunity to address the primary bottleneck to investment in next generation sustainable technologies and a) incentivise production within Europe and b) enable improved sustainable production world-wide. If the procurement of medicines broadens its focus to recognise innovation and sustainability value, producers are rapidly incentivised to invest in next generation technologies and for more actors to enter into production.

- Technical innovation in manufacturing process/technologies existing and novel medicines: Europe has the opportunity to take an intellectual and market lead in novel sustainable production pathways for existing medicines with a focus on minimisation of costs through design and scale up and creation of alternative options to high risk existing inputs. Safer by design will enable reduced risk of hazardous materials but does not address the drive to remove substances of hazard more generally from use, which will impact availability where use may be dominant for another non-medical application for which it is withdrawn. This impacts innovation and economic growth within Europe and leads a global drive towards more sustainable medicines production. It already has the tools and framework through public private partnerships and Horizon programmes to enable technical responses to create intellectual property within Europe and an open pipeline for uptake into industry.

Impacts on supply chain resilience

- Expansion of stakeholders active within the supply chain in response to sustainability and innovation recognition within the procurement process
- Greater concentration of production within Europe as next generation manufacture becomes commercially competitive
- Novel therapeutics are accessible within Europe at an earlier stage through more commercially accessible landscape

b. Regulatory Readiness and agility

The challenge

Beyond the initial cost drivers of medicines development, regulatory frameworks were identified as another bottleneck to achieving the green transition. The currently complexity of regulatory requirements in delivering safe medicines in Europe has implications for making more sustainable pathways and products. One such example is changing the process or source of (identical) packaging, both of which require regulatory permission. The current regulatory framework does not allow this to be done quickly and demands additional data before a change can be made. This adds an additional layer of resistance (beyond the cost barrier) to the development of more sustainable production pathways, even for identical final products.

With regard to novel medicines, their development and production will have an increasing focus on sustainability as an integral design element, particularly in manufacturing pathways. As Europe seeks to become more attractive for the manufacture of novel medicines, particularly advanced technologies, novel sustainable manufacturing aspects will become part of the regulatory pathway. Europe needs to become more agile from a regulatory aspect when novel technologies are presented. For regulatory preparedness and decision making, it has been proposed that integrated

systems should be created to enable timely communication between different actors from the start of the innovation chain to manage the challenges associated with integration of emerging technologies (Reference 41: Linkov, I. et al (2018), Reference 42: Miettinen, M (2020)).

COVID-19 demonstrated that regulatory agility was possible without compromising product or patient safety.

The innovation pathway and opportunity

- Green transition of manufacturing processes of current medicines: Regulators and industry work jointly to address pre-competitive aspects of transition into more sustainable aspects of production
- Green transition of novel medicines (next generation platforms): Regulators and industry work jointly from early stages to identify sustainability aspects of technologies to establish targets for green transition performance within these classes of technology. This stakeholder collaboration should also define realistic transition timelines to enable regulatory compliance without compromising supply continuity.

Impacts on supply chain resilience

- Encouraging for expert supply chain steps to be based within Europe with an engaging regulatory framework in commercially competitive replacement/adaptation of existing supply chains
- Incentivises producers of novel and advanced medicines to become more active in Europe early in product development through active engagement of regulators around sustainability issues

c) Skills Progression

A strong theme throughout the WS4 is the need for significant focus, networking and alignment on skills development. This was highlighted as an essential part of the digital transition, and it is equally important in addressing an effective green transition.

The challenge

There is significant fragmentation in skills focus and development between academic, Research and Technology Organisations (RTO), industry, public bodies, regulators and policy makers at national and EU level. The risk is that each community continues to develop independently with regard to sustainability priorities, language and actions. There is a need to ensure that these communities develop common understanding of priorities, plus agreed language and taxonomy used to address sustainability in medicines development and supply. A shared communication platform for joint development is critical.

There is insufficient critical mass of skills to support industry's green transition. Higher focus on education and skills development for sustainable commercial production at scale is a priority, with significant market demand already evident. An example of the need for knowledge development and communication to promote sustainability along the pharmaceutical supply chain is given in paper by Villena (Reference 43: Villena V.H. (2019)).

The innovation pathway and opportunity

- Identify good practise in skills development linked to sustainability of pharmaceuticals production through universities (all relevant topics, including economics, engineering and digitalisation) and target the scale up of courses across Europe, interlinked to connect cross-discipline strengths between countries
- Increase formal industry–research-regulatory frameworks. This is an opportunity to focus on pre-competitive next generation target prioritisation, making use of Europe's diverse research and industry landscape.

- Create significant research targets linked sustainability pathways across programmes such as IHI and Horizon Europe (including ERC and EIC) to ensure a significant innovation pipeline in Europe linked to the key stakeholders for its implementation
- Skills base sufficient to enable next generation sustainability intellectual property and implementation in Europe
- Aligned skills base across key stakeholders within the medicines supply chain

Impacts on supply chain resilience

- Smooth communication in aligned topics across stakeholders accelerates action and avoids dead ends, bottlenecks or knowledge within silos that will impact other parts of the manufacture supply chain
- Accelerated development of next generation products and processes to market, enabling Europe to pre-empt supply chain issues from changed availability of ingredients and obsolete production processes

Innovation priorities to achieve medicines supply chain resilience
The focus of these recommendations is to enable supply chain resilience actions required within the larger context of the green transition. There is a requirement for joint action, as this cannot be addressed on an individual company or country basis.

- Long term formal programme to proactively identify greatest supply risks from a green transition perspective, with all actors involved (policy, research, procurement, industry, cross-sector regulators, health services, national, EU and global)
- Agreed prioritisation of target substances for green transition where supply is vulnerable
- Priority skills development - identifying key skills gaps and aligned development across the medicines development and supply ecosystem
- Where vulnerabilities exist, consider exemptions to short term bans on substances until replacement can be implemented - but within awareness of changes in supply and cost as the substances decline in production
- Map European capabilities for green transition in target substances/processes (including assessment of feasibility) and focus on accelerated joint research and regulatory pathways
- Implement green/sustainable certification/criteria to be used in imports and procurement in order to ensure a level playing field and incentive investment within Europe and elsewhere. (Note that before a certification can be performed, standards and norms need to be developed, established and potentially inspected. Thus there is the potential for an overregulated environment that could create supply vulnerabilities and delays and also impact EU competitiveness, if this is not carefully considered and involves all stakeholders to avoid unintended consequences)
- Make best use of upcoming legislation (e.g. potential revision of the pharmaceutical legislation (Directive 2001/83/EC, Regulations 726/2004; Reference 24: A Pharmaceutical Strategy for Europe),) and ensure that this does not act to isolate and dis-incentivise investment in EU manufacture within the global framework.
- Address financial issues that reduce incentives to invest in advanced technologies e.g. de-link R&D from sales revenues and reduce the costs of clinical research and trials
- Address the green transition and medicines supply chain within a global context, to enable green transition of robust supply chains worldwide

2.4.3 Contribution of the green transition to increased resilience for Europe

The green transition contributes indirectly to increased resilience, through playing to the strengths of Europe in developing next generation (sustainable) products and process. It is critical that the innovation in research and early commercialisation is anchored into Europe through an ecosystem in which encourages large scale industrial investment. Key points on regulatory pathways and medicines procurement are core to this, as this report has highlighted. Wider European support in skills development and research prioritisation underpin the viability of the green transition in Europe. Europe's competitiveness and supply resilience may be placed at risk if Europe does not enable such changes as i) next generation products and processes will be developed outside of Europe and ii) pre-existing processes remain outside of Europe with the same restricted geographical diversity of the production base as now.

3. Key deliverables

3.1 Enablers for EU Competitiveness

The attractiveness of the EU as a location for the manufacture and supply of medicines is evident from the large, positive balance of trade in medicines made in the EU (approx. 92 billion euros Reference 6 ECIPE reports 2020 and 2021)). Ensuring that the EU continues to be a leader in the supply of medicines globally is dependent on the following enablers:

- A supportive business environment that has competitive tax rates, procurement and reimbursement policies, and open trading without export restrictions.
- An intellectual property framework that rewards innovation and encourages risk-taking is critical for encouraging investment and the creation of start-ups/entrepreneurs.
- A skilled workforce that is nurtured and developed through collaborations between industry, academia and government, building on Europe's strength in this area
- An agile pharmaceutical regulatory framework that has world-leading, fast and efficient processes for the review and approval of new products, and especially for changes to existing products and the regulatory oversight of commercial supply. The regulatory burden can be reduced for regulators and industry by harmonising requirements, both within the EU and globally, and optimising the use of resources by enabling reliance and work-sharing mechanisms (that can build on the EU expertise in this area). Regulatory barriers to the implementation of new manufacturing and supply technologies need to be removed from legislation and guidance, and improved forums and processes for engagement/dialogue between stakeholders created. Regulatory agencies need to be properly funded and resourced to achieve this agility while discharging their prime responsibility for protection of public health.
- A fully integrated regulatory framework, where initiatives in the food, chemical, environmental, tax, trade etc. areas are fully assessed and understood for their impact on pharmaceutical supply chains to inform benefit/risk-based decision-making.
- An integrated strategy that incorporates the above enablers through the ICH Q10 product lifecycle of Pharmaceutical Development, Technology Transfer, Commercial Manufacturing, and Product Discontinuation, both for innovator and generic medicines

3.2 Enablers for Innovations that increase Manufacturing Capacity and Supply Chain Resilience

The implementation of technological innovations that can help to address drug shortages and enable the EU to secure sufficient manufacturing capacity for critical medicines will largely be supported by the same enablers, described above, that will ensure the EU is an attractive location for the manufacture of medicines. Specific innovation areas discussed by WS4 included:

- Procurement/Reimbursement. The regulator for a major trading partner has concluded that 'Economic forces are the root causes of drug shortages' (Ref. FDA Drug Shortages report 2019, updated in 2020). WS4 discussed innovation in tendering processes that could enable multi-winner tenders, widening the supply base, or include supply chain robustness, in addition to cost, as a factor to be considered in awarding contracts.
- Manufacturing technologies enabling capacity. These include continuous manufacturing, for both active ingredients (including flow chemistry for synthetic small molecules, and also continuous manufacturing of biologics) and medicinal products, and autonomous and portable, pre-fabricated modular manufacturing facilities are emerging manufacturing approaches applicable to both active ingredients and finished medicinal products, that offer the possibility of faster scaleability or capacity expansion. Single-use-systems are increasingly used to enable fast and flexible manufacturing, especially for biological

medicines and vaccines. Digital technologies will be integral to these manufacturing approaches and the regulatory framework.

- Digitising the value chain. Connecting the suppliers along the chain and gathering data from the end user (patient and/or healthcare professional) to forecast demand more accurately for products and optimise manufacturing and logistics will provide information for industry and regulatory agencies to prevent or mitigate shortages. Discussions in WS4 are aligned with WS1 on this aspect.

3.3 **Enabling the Digital Transition**

The digital transition is necessary to support the innovations needed for both EU competitiveness and supply chain resilience, and can also support the green transition. The development and application of digital technologies is rapidly evolving and the following aspects need to be addressed:

- Education to develop and maintain the workforce (industry and regulators) with the skills and knowledge for a common understanding to realise the benefits of digital technologies. Collaboration with the university sector is critical to build a common body of knowledge.
- Regulatory capability and agility to provide suitable guidance that provides predictability and reduces uncertainty about expectations, and that does not introduce real or perceived barriers for the adoption of these technologies. The tools used to provide guidance need to be flexible enough to cope with the evolving technologies, and could include, for example, the use of voluntary consensus standards.

3.4 Enabling the Green Transition

The green transition is necessary to ensure the long-term sustainability of manufacturing and supply of medicines. This requires the development of a long term, integrated programme of initiatives that involve all stakeholders including those responsible for policy, research and education, procurement, industry, cross-sector regulators, health services, national, EU, and global governments. As noted above this could be realised through an innovative programme that includes elements similar to a Public-Private Partnership, operating at a global level. Elements of such a programme to enable this transition could include:

- Prioritisation of target substances for green transition which may be vulnerable to sustainable supply; mapping EU capabilities for these priority substances; identification of measures that can mitigate these vulnerabilities during the transition; benefit/risk assessment of patient needs and environmental impact
- Structures/platforms (for regulatory preparedness) that enable systematic, timely communication between different actors from the very beginning of the innovation chain should be created, so that all relevant information would be available for decision-makers
- Skills and capability development, including early stage research, that make use of EU strengths and support the transition with expertise in industry and regulatory agencies. [1]
- Regulatory agility and capability for change management for replacement and adapted products and processes (e.g. faster processes for greener products/processes); internationally agreed certification/criteria for green/sustainable materials to be used in imports and procurement; avoiding the creation of additional vulnerabilities in medicines supply as a consequence of use restrictions in other sectors; global alignment of environmental standards and requirements to avoid dis-incentivising investment in EU manufacture or driving sourcing from countries with lower standards; facilitating qualification of second sourcing, and thereby increasing supply chain resilience
- Financial measures (incentives/support or revisions to the procurement and/or reimbursement models) are needed to reward companies along the value chain that invest in greener products and processes. For example, environmental considerations should be

included in procurement and tender processes to avoid cost being the sole criterion. Another example is from the wholesalers/distributors sector where incentives might be needed to support the move to a 'green fleet' of vehicles.

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4. Conclusions

The EU is a leading manufacturing location for innovative, patented active ingredients and medicines, generic medicines and biosimilars, and synthetic chemical active ingredients. The EU should ensure its continued competitiveness as a location for manufacturing and supply operations through an integrated strategy considering the ICH Q10 product lifecycle of Pharmaceutical Development, Technology Transfer, Commercial Manufacturing, and Product Discontinuation , both for innovator and generic medicines, that comprises: a supportive business environment that has competitive tax rates, procurement and reimbursement policies, and open trading without export restrictions; an intellectual property framework that rewards innovation and encourages risk-taking; a skilled workforce that is nurtured and developed through collaborations between industry, academia and government; an agile pharmaceutical regulatory framework, and a regulatory framework where initiatives in the food, chemical, environmental, etc. legislation are fully assessed and understood for their impact on pharmaceutical supply chains to inform benefit/risk-based decision-making.

Innovation in manufacturing and supply operations is a critical requirement for Europe to maintain its competitiveness and leading position as a supplier of medicines to the world. Innovation in these areas can also provide solutions that will help address the vulnerabilities and challenges in the supply chain identified by WS1 and WS3, and thereby secure the supply of medicines for European patients. Certain technologies might be important to help enhance resilience in the supply chains for critical medicines identified using the methodology proposed by WS2.

Given the urgency to address vulnerabilities identified by WS3 and WS1 and reduce drug shortages then implementation of innovative technologies that can help to address these issues and increase the agility and capacity of manufacturing and supply operations, should be prioritised. The EU fine chemicals industry is particularly concerned about its capacity and capability to manufacture mainly off-patent small molecule active ingredients, where this capacity has been lost to low-cost countries, and there is a corresponding concern that cost frameworks for generics medicines inhibit investment in measures that could address supply vulnerabilities or support the green transition. Investing in innovation to further strengthen the resilience of EU supply chains may require structural interventions to prevent or mitigate shortages, but it is also clear that Europe cannot re-shore the entire API production needed for its internal market demand. Considering EU competitiveness with other the trading blocs, particularly USA, India and China, it would be of crucial importance to develop, in parallel, new cooperation strategies to ensure the continuity of sourcing of selected critical raw materials, precursors and APIs as well as of some critical commodity materials needed for pharmaceutical production.

Examples of manufacturing technologies, for both active ingredients and medicinal products, that could help to address supply vulnerabilities are discussed in section 2.1, and include innovations such as portable, modular manufacturing facilities, and single-use-systems that enable faster development and expansion of supply. The overwhelming majority of the technologies discussed in section 2.1 will include digital components to enable the technology, and some of these innovations are specifically focused on implementation of digital systems to leverage the information from the value chain.

Implementation of these technologies will be slow unless enhancements to the regulatory framework to remove barriers, improve processes and engagement/dialogue between stakeholders are also implemented as a matter of priority. Regulatory agencies need to be adequately funded and resourced to make these enhancements to avoid becoming rate-limiting for the modernisation of EU manufacturing capability and capacity.

The improvements described above will also enhance Europe’s competitiveness globally as a location for manufacturing operations, and continue the very strong positive contribution to the balance of trade from export of medicines made in Europe (approx. 92 billion euros). The EU can

reinforce these efforts by leading the establishment of globally-harmonised quality-GMP pharmaceutical and environmental standards.

It is also important to recognise that Europe is a leading manufacturing location for innovative, patented medicines, both as the active ingredient and the finished dosage form. European patients must also have access to new therapeutic modalities, and the innovator industry believes that Europe needs to ensure that this competitive position is maintained and enhanced through measures including creating a more agile regulatory framework, investment in the academic sector and collaborative partnerships, and avoiding erosion of intellectual property protection that will dis-incentivise innovation and risk-taking

The application of digital technologies to manufacturing and supply operations is a key enabler for increasing the visibility of inventory, helping to prevent or mitigate shortages, and to enhance the quality and reliability of manufacturing processes. Efficiencies can also be gained in industry and regulatory agencies through the digitisation of processes, and environmental benefits may also be realised through the reduction of waste. Although the industry sees considerable benefits from the provision of patient information electronically rather than via paper leaflets, there are concerns raised by groups representing patients and health care professionals about the equity of this proposal for all patients, and certain practical issues that will need to be tackled. Collaboration between the stakeholders, especially utilising the expertise and capacity in the academic sector, is important to develop the skilled and knowledgeable workforce in industry and regulatory agencies to implement and sustain the digital transition. EU and Member States should be involved in co-ordinating and supporting education programmes to achieve this. The pace of change of digital technologies means that there is an urgent need for increased resources and the implementation of measures in the academic sector that can support the digital transition.

Apart from the reduction in waste-paper associated with the replacement of paper leaflets by the introduction of electronic Product Information (ePI), WS4 did not identify opportunities from the green transition that will, in the short term, increase the resilience of supply chains. Regarding the role and impact of the Green transition, the conclusion reflects the introduction that this is a process in which all future medicines supply chain activities must be framed. Changes are underway now to deliver the green transition and these will impact many decisions made regarding the global supply chain. Europe is in a strong position to create competitive advantage for its healthcare industries within the context of the green transition and this will directly contribute to a resilient domestic supply chain. The cost barrier is central to this and the report proposes innovation across technologies, regulation and procurement to ensure that Europe is able to anchor innovation within a green transition context locally for investment and resilient delivery to patients. A global level playing field for maximum momentum within the green transition will also enable Europe to establish a more robust medicines supply and the ecosystem (regulatory, purchasing etc) as referenced in the report is a necessity to deliver this. As stated in the Chemicals Strategy “A more coherent, predictable and stronger regulatory framework, combined with non-regulatory incentives, will drive the necessary innovation, deliver increased protection, while enhancing the competitiveness of the European chemical industry and its value chains. To ensure a level playing field between EU and non-EU players, the EU must ensure full enforcement of its rules on chemicals both internally and at its borders, and promote them as a gold standard worldwide, in line with our international commitments.” (Reference 9: COM(2020) 667 final, p.3)

Next steps in the structured dialogue around innovation in manufacturing and supply could include securing further input from groups representing patients and health-care professionals who were unable to fully participate in the WS4 discussions. Similarly, to more fully understand innovation the supply chain it would be valuable to obtain the perspective from manufacturers and suppliers of excipients, packaging materials/components, ancillary materials (e.g. disposable/consumable components such as filters etc.), testing materials/reagents, and manufacturing and testing equipment, together with engineering companies involved in constructing manufacturing, laboratory and storage facilities, since these organisations all provide important contributions to the manufacture and supply of medicines.

WS4 has provided some reflections on the manufacturing technologies associated with the medicines suggested for evaluation using the methodology to identify critical medicines proposed by WS2. However, WS4 was not able to take into account the output from the pilot on critical medicines proposed byWS2, so further exploration of the linkage between the identified critical medicines and innovations that could help secure the supply of these medicines would be an important next step.

5. List of relevant documents, reports, statistics

1. IQVIA Report for EFCG: EU Fine Chemical Commercial KPI (2020)

2. GDUFA Facility Payments List

3. Progenerika: Where do our Active Pharmaceutical Ingredients come from? - A world map of API production

4. Commission Staff Working Document Strategic dependencies and capacities (2021)

5. EFPIA contribution to DG Trade Consultation on "A renewed trade policy for a stronger Europe" (2020)

6. ECIPE: Key Trade Data Points on the EU27 Pharmaceutical Supply Chain, (2020) and International EU27 pharmaceutical production, trade dependencies and vulnerabilities: a factual analysis (2021)

7. Chemical Aspects of Human and Environmental Overload with Fluorine (2021) Han, J. et al. Chem. Rev. 2021, 121, 8, 4678–4742

8. Antibiotic expansion examples Sandoz antibiotic manufacturing expansion; Fresenius Kabi antibiotic manufacturing expansion

9. Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions. Chemicals Strategy for Sustainability Towards a Toxic-Free Environment COM/2020/667 final

10. FDA Drug Shortages report (2019, updated 2020): Drug shortages: Root Causes and Potential Solutions .

11. ICH Q13: Continuous Manufacturing of Drug Substances and Drug Products. Final Concept paper dated 14 November 2018.

12. ASTM International Standard E2968 (2014) Standard Guide for Application of Continuous Processing in the Pharmaceutical Industry

13. FDA Advanced Manufacturing

14. EFPIA paper on Autonomous & Portable Manufacturing (2021)

15. FDA approves first ever 3D printed drug product: Spritam (2015)

16. Top 10 Pharma Industry Trends and Innovations in 2021

17. An open letter from Pfizer Chairman and CEO to colleagues

18. Inter-Association paper (2021) Electronic Product Information: from principles to actions

19. GIRP Annual Report 2020-2021

20. EFPIA and PhRMA Joint Submission to the Call for Proposals for EU-US Regulatory Cooperation Activities (2019)

21. Increase in vaccine manufacturing capacity and supply for COVID-19 vaccines from AstraZeneca, BioNTech/Pfizer and Moderna

22. Reference ICMRA-IFPMA Workshop (2021) Enabling Manufacturing Capacity in the COVID-19 Pandemic

23. EFPIA Annual Regulatory GMP/GDP Inspection Survey 2020 Data

24 Pharmaceutical strategy for Europe

25. EMA ICH Q12

26. PDA PAC iAM 2017 Survey on Post Approval Change: Is the Regulatory Environment Hindering Much-Needed Innovation in the Pharma Industry?

27. IFPMA The complex journey of a vaccine – Part II (2016)

28. Medicines for Europe Regulatory Efficiency Report (2015)

29. MfE/AESGP: Why is now the right time to modernise the EU variations system?

30. Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions. Pathway to a Healthy Planet for All EU Action Plan: 'Towards Zero Pollution for Air, Water and Soil' COM/2021/400 final

31. Wiesmeth, H. Implementing the Circular Economy for Sustainable Development, Chapter 15. 2021

32. Reuters article: Pressure mounts on EU drug regulator to approve Pfizer COVID-19 vaccine

33. IQVIA report (2019) A Digital Future for Value Added Medicines

34. EU Strengthening Regulatory Science in Academia

35: Siven et al (2020) Generation Green - A holistic approach to implementation of green principles and practices in educational programmes in pharmaceutical and medical sciences at the University of Helsinki

36. The world's first professorship in sustainable development in pharmacy planned in Helsinki

37. EFPIA MQEG Discussion Paper: Digitalization in Pharmaceutical Manufacturing

38. ASTM International Standard E3077 (2017) Standard Guide for Raw Material eData Transfer from Material Suppliers to Pharmaceutical & Biopharmaceutical Manufacturers

39. Chemicals strategy High Level Roundtable on the implementation of the Chemicals Strategy for Sustainability (E03757)

40. IMI PREMIER Prioritisation and risk evaluation of medicines in the environment

41. Linkov, I et al (2018) Comparative, collaborative, and integrative risk governance for emerging technologies

42. Miettinen, M. (2020) "By Design" and Risk Regulation: Insights from Nanotechnologies

43. Villena, V.H. (2019) The Missing Link? The Strategic Role of Procurement in Building Sustainable Supply Networks

44. European Commission 'Pact for Skills' Initiative.

Appendix 1a: Questions on Innovation for Patient and Health Care Professional groups developed by the WS4 Rapporteurs

Appendix 1b: EURORDIS Response to Patient/HCP Questions from WS4

Appendix 2: WS4 reflections on medicines from WS2 criticality evaluation pilot phase

Appendix 3: EFPIA MQEG Assessment of Potential Barriers in EU Pharmaceutical Legislation – Directive 2001/83/EC and Regulation 726/2004

Appendix 4: Medicines for Europe Case Studies on Incentives for Manufacturing Process Innovations

Appendix 5: EU Industry Response to EU Commission Questions on use of Design Space and PACMPs (2019)

Appendix 6: Examples of Regulatory Barriers in Pharmaceutical Guidance

Appendix 7: EFPIA and Vaccines Europe Cross-Trade Key Proposals – Variation Framework

6. ANNEX

Participants list

First name	Family Name	Organisation	Country	Title
Camille	Andries	Medicines for Europe	Belgium	Junior Manufacturing Advisor
Guillaume	Atoui	Sanofi	France	Chief of Staff, Sanofi Global Industrial Affairs
Gianmario	Baccalini	EFCG	EU	Vice President
Giorgio	Bertolini	Olon SPA	Italy	Director of R&D
Kaja	Blumritt	European Commission	EU	DG for Internal Market, Industry, Entrepreneurship and SMEs Directorate F: Chemicals, Food, Retail
Vittoria	Carraro	Eucope	EU	Public affairs
Andreas	Charalambouts	Cyprus University of Technology	Cyprus	
Magda	Chlebus	EFPIA	Belgium	Exec Director Science & Regulatory
Graham	Cook	Pfizer	UK	Senior Director Global Quality Operations
Christophe	Eychenne-Baron	EFCG	France	R&D Director Seqens
Cristina	Fernandes	Fresenius Kabi	Portugal	Plant Manager
Martin	Fitzgerald	GIRP	EU	Deputy Director General
Marc	Gasper	Agency for medicinal products	Slovenia	
Alejandro	Granados	Janssen	Switzerland	Vice President of Manufacturing EMEA
Bernard	Grimm	EuropaBio	EU	Director Health Biotech
Behnam	Heidari	Sanofi	Ireland	Head of supply chain
Zdravka	Knezevic	JGL pharma	Croatia	Scientific Operations Director
Koen	Laenen	Medicines for Europe	Belgium	Quality and Regulatory Affairs Senior Manager
Thierry	Lhuilier	UPSA	France	Director of Operations
Justas	Macinskas	Ministry of Health	Lithuania	Advisor of Pharmaceutical Activity Division
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Søren Thuesen	Pedersen	Novo Nordisk	Denmark	Senior Director, Quality Intelligence and Inspection
Giuliano	Perfetti	Holding FIS & EFCG	Italy	Chief Commercial Officer (EFCG Board)
Anna	Rafferty	Janssen	Ireland	Director of Strategy
Luis	Rhodes Baiao	AESGP	EU	Public affairs
Giovanna	Rizzetto	EFPIA	Belgium	Senior Manager regulatory, manufacturing
Juergen	Ross	Siegfried (CDMO)	Switzerland	
Maggie	Saykali	EFGC / CEFIC	Belgium	Director Specialty Chemicals
Marc	Schmit	Ministry of Health	Luxembourg	Inspector
Claire	Skentelbery	EuropaBio	Belgium	Director General
Dennis	Stern	German Association of Medicines Manufacturers (BAH)	Germany	Referent Homöopathische und Anthroposophische Arzneimittel
Adrian	van den Hoven	Medicines for Europe	Belgium	Director General
Dirkjan	Van Zoelen	Aspen Pharma	Netherlands	Manager Development and Technical Support
Massimo	Verzini	Flamma SPA	Italy	Director Generics & Global R&D

Reflection on the process

Please see the introduction for discussion about connections needed across Workstreams to ensure all stakeholder views are reflected in the discussions, because not all stakeholder groups (e.g. patient groups, HCPs) were represented in Workstream 4. It is important to note the limitations of the process: the extent to which Team members were able to contribute varied and there were disagreements about the scope of the Structured Dialogue and/or content of the report that resulted in some participants dis-engaging from the process.

The consistent understanding and use of terminology is important. In the Introduction the differences in meaning of the term 'product life cycle' in pharmaceutical guidance and environmental standards are discussed.

The virtual nature of the meetings may also have played a role in limiting the extent to which there could be meaningful dialogue on differences of perspectives that were raised during the process.

The linkages/dependencies between the different Workstreams were acknowledged early in the process, but the timelines were such that Workstream 4 had to complete this report without being able to fully discuss the output from Workstream 2 on critical medicines and identify technical or other innovations that could be relevant to critical medicines. Further consideration of this is recommended.

Finally, the ability to work collaboratively on documents and share information was limited by the lack of a common, suitable technology platform across WS4 team members. Some attempts were made to use the Commission's tool but information was mostly shared with the WS4 team by email and the rapporteurs used Google Drive for collaboration on the development of this report

7. Appendices

Appendix 1a: Questions on Innovation for Patient and Health Care Professional groups developed by the WS4 Rapporteurs

Open question

Where do patients/HCPs see opportunities for innovation that could enhance supply chain resilience and reduce shortages? What unique aspects do they experience linked to disruption, or challenges linked to access, that could be solved by applying digital technologies or green innovations?

Which of the points below are relevant for patient engagement discussion?

1. Development of digital elements for resilience of supply – where it might involve patient data to assess demand and supply and other aspects of transparency into the supply chain to pre-empt changes in orders and production.
2. Support to bring patients to specialist medicines if they cannot be produced directly in their own country – thinking of specialised centres in Europe where the intervention cannot be accessed in all countries due to cost, rarity of disease etc. This is not with a view to fragility is supply due to disruption, but fragmented supply tied to low patient numbers or a highly geographical aspect of supply such as specialist centres.
3. Communications around changes planned to medicines production as part of response to crises. Lack of information around potential changes to oncology supply after production was switched to vaccines in plants across the world. How should this be communicated and who should do it? Is it the role for a body such as Hera?
4. Balance between price and security of supply, if more sources of medicines have to be developed in drugs of particular fragility of supply, the enablers of this are going to be consideration of price to encourage more producers into business.
5. In the transition towards more environmentally sustainable healthcare products and processes – can patient groups help identify where efficiencies can be made?

Other aspects of resilience in the medicines supply chain are relevant for patient inclusion that are not addressed above?

Appendix 1b: EURORDIS Response to Patient/HCP Questions from WS4

Open question

Where do patients/HCPs see opportunities for innovation that could enhance supply chain resilience and reduce shortages? What unique aspects do they experience linked to disruption, or challenges linked to access, that could be solved by applying digital technologies or green innovations?

1. Innovating in alternative supply chains

   There are cases where the Marketing authorisation holder informed authorities on time before withdrawing a product from the market, but the legal timeframe did not permit to find an alternative producer (e.g. mexiletine).

   Instead, hospital pharmacists started compounding the product in parallel to clinical studies to obtain a new marketing authorisation for the new use.

   This includes organisations such as Apotheekzorg or Mosadex Group in the Netherlands, (www.apotheekzorg.nl/ and https://www.mosadexgroep.nl/).

2. Chips for tracking remaining supply

   The unique identifier (Regulation on counterfeit medicines) could be used to track batches and packages in the EU, to have real time information on where supply is stored, in which quantities, in case supply could be shipped from a region where the demand is lower to regions where the demand is higher and exported to other Member States.

   This could require a chip on each package, at a very low cost (0.05 to 0.1€ per package).

3. A “share your extra medicines” digital service

   Some patients are dispensed with 3 months of supply of a medicine or take it on demand and might not need all the supply they have. In case of a shortage, many are willing to share this “surplus” with patients in need. This was observed during the Fabrazyme shortage, where patients will moderately severe Fabry disease proposed to interrupt their treatments (under medical supervision) so that more product would remain available for those in greatest need (severe Fabry disease). In case of distribution chain difficulties of HIV products in France, some patients offered their “extra supply” to others, via a spontaneous solidarity pill exchange (as supply tensions were due to resume shortly after 2-3 weeks)

4. A Google type of app to find out which pharmacy could dispense the product

   This app doesn’t exist anymore as a Google service, but it continues for different uses by different developers

GoogleGoggle was an image recognition mobile app used for searches based on pictures taken by handheld devices. For example, taking a picture of a famous landmark searches for information about it, or taking a picture of a product's barcode would search for information on the product.

The system could identify various labels or landmarks, allowing users to learn about such items without needing a text-based search. The system could identify products barcodes or labels that allow users to search for similar products and prices and save codes for future reference.

The system also recognized printed text and uses optical character recognition (OCR) to produce a text snippet, and in some cases even translate the snippet into another language. The app was officially discontinued on August 20, 2018 with its last update directing users to download Google Lens or Google Photos upon launching the app.

If a database of barcode and product packages would exist (using the unique identifier described above for example), then the pharmacist or the patient could search for the nearest pharmacy which would have the product in stock.

Which of the points below are relevant for patient engagement discussion?

1. Development of digital elements for resilience of supply – where it might involve patient data to assess demand and supply and other aspects of transparency into the supply chain to pre-empt changes in orders and production.
    - Unsure if patient data could really help predict increasing demand. The demand is not driven by the prevalence, but by the number of diagnosed patients, and by coverage / treatment guidelines (that define which patients are eligible for a new treatment), and finally by access barriers.
        - Electronic health records can help complete the information on how many patients stand for a given product and when this is estimated, it usually does not vary with time, except for infectious diseases / emerging diseases
        - But would add information to sales volumes variation?
        - Sometimes the off-label use is more difficult to quantify. For example in the case of supply tensions for Myozyme in 2008, this was caused by adults asking for the treatment (late onset - less severe form) when the enzyme had been developed for children (early onset – severe form). The

exact adult population for Pompe disease late onset form had not been estimated precisely.

- Relevant, but no real concerns if data fully anonymised as per GDPR. Aggregated data can be collected at national level, and then shared at EU level to avoid trans-border data sharing.
- Should not be used to detect and "police" off-label use practices e.g. product used at a different does than the labelled one, or for a different authorisation

2. Support to bring patients to specialist medicines if they cannot be produced directly in their own country – thinking of specialised centres in Europe where the intervention cannot be accessed in all countries due to cost, rarity of disease etc. This is not with a view to fragility is supply due to disruption, but fragmented supply tied to low patient numbers or a highly geographical aspect of supply such as specialist centres.
    - Patients' rights to cross-border care exist, but access to these rights is complex, and in practice, an obstacle.
    - One idea could be to distribute the medicine via pharmacists operating in European Reference Networks: either the product would be shipped to the centre of expertise where the patient lives, or the patient could travel to the centre that will administer the product.
    - In both cases, the product should be procured at the EU level, and be made available to the European Reference Network.
    - For example: gene therapy Strimvelis® currently administered in one centre in the EU, San Raffaele hospital in Milan. But few patients used it, as prior authorisation difficult to obtain. Not that the product is not cost-effective, but payers / insurers are reluctant to pay 500 k€ to a centre in Italy as they would prefer to pay the same amount to a centre in the country where the patient lives

3. Communications around changes planned to medicines production as part of response to crises. Lack of information around potential changes to oncology supply after production was switched to vaccines in plants across the world. How should this be communicated and who should do it? Is it the role for a body such as Hera?
    - And also the new EMA mandate: when difficult measures need to be adopted, to get advice from an ethics committee, and there is no EU ethics committee.
    - First, the decision maker and the decision-making should be clarified, in case the production of some products should be interrupted to scale up the production of others. Such decisions should typically involve representatives of the healthcare professionals and patients. How would this be regulated? Would the industrial sector ask for authorisation to do so to public health authorities? Or would it be lore a "fait accompli"?
    - There is a need to distinguish between the decision-making body and the executive body. Hera, seen more as an executive body, should maybe not be the one to decide and not the one to communicate. The decision-maker should be responsible for communication.

4. Balance between price and security of supply, if more sources of medicines have to be developed in drugs of particular fragility of supply, the enablers of this are going to be consideration of price to encourage more producers into business.

- To multiply the sources of supply, and/or to relocate part of the production in the EU would have a cost for the producer, which, unless compensated, might become an obstacle. There is a general concern in the patient community that the cost consequences of efforts to regain independence in the pharmaceutical sector will be to the detriment of acquisition / purchase / coverage of innovative medicines.
- Incentives, tax credits will not suffice, unless they can cover the totality of the extra cost for the producers, or the pharmaceutical sector is fully reorganised with important efficiency and productivity gains.
- This is because for some 20 years now, payers have been explaining that the pharmaceutical and the healthcare expenditures can not grow more the annual growth, and health budget costs are frequent. The same "cake" needs to be divided into smaller pieces, as new health needs need to be covered.
- Therefore, if health budgets remain the same, with increasing costs of multiplying sources and/or relocating, this would inevitable be to the detriment of healthcare offer.
- Another proposal to reduce the risk of shortages is the creation of stocks. They come with a high cost also (reason why many stocks that existed in the past were reduced), and in some cases, they only differ the shortage, they do not necessarily eliminate them.

5. In the transition towards more environmentally sustainable healthcare products and processes – can patient groups help identify where efficiencies can be made?

   Not sure I can respond to this question. Are there proposals already that we could comment on?

   There are discussions to produce "lower cost gene therapies" for example, where one viral vector is used with several genes to treat several genetic diseases. The same vector would be produced, stored and used for different patients with different conditions. A kind of a multivalent gene therapy. Of course, only one gene would be useful for a given patient, but production costs would be minimised.

   For short-lived products (expiration), and small volumes, some measures could be taken to facilitate the re-export of supply approaching the expiration date, so that it can be dispensed and not destroyed. This would require easy re-packaging. That could apply to some orphan medicines.

   Also:

   - *Stability of medicines now need to be studied for higher temperatures than in the past. Typically, "room temperature" can reach temperatures above 40°C for several days or weeks. To store below 25°, or below 30° can cause problems. Wholesalers and pharmacies have air conditioning, but not the patients. When patients realise their medicines deteriorated due to this, they're likely to rush to the pharmacy at the same time to renew their supply – demand might peak.*
     - Suggestion: mobile apps such as the MedSafety app where patients sign-in the medicines they're own could send alert messages when medicines in question need to be stored in the fridge, depending on weather forecast, and based on the electronic package leaflet data that can make this function fully automated

Other aspects of resilience in the medicines supply chain are relevant for patient inclusion that are not addressed above?

Appendix 2: WS4 reflections on medicines from WS2 criticality evaluation pilot phase

The following medicines were selected by WS2 (draft report 9 July 2021) for the pilot phase for the methodology for identification of critical medicines.:

Medicine	Typical Indications	Pharmaceutical form	Manufacturing considerations	Comments
Propofol	Induction/maintenance of anaesthesia; Sedation	Emulsion for injection; Emulsion for infusion	Synthetic small molecule; Sterile parenteral	1970s
Heparin (excluding LMWH)	Anticoagulant; To maintain patency of catheters, cannulas, other indwelling intravenous infusion devices; Thromboprophylaxis; Treatment of Venous thromboembolism	Solution for injection; infusion	Naturally occurring glycosaminoglycan, typically extracted from porcine tissue (intestinal mucosa); Sterile parenteral	1930s
5-Fluorouracil	Treatment of some solid tumours; Superficial malignant and pre-malignant skin lesions	Solution for injection; Solution for infusion; Cream	Synthetic small molecule; Sterile parenteral	1950s
Avelumab	Metastatic Merkel cell carcinoma; Advanced renal cell carcinoma	Solution for infusion	Monoclonal antibody; Sterile parenteral	Patented medicine (Bavencio™) , first approval 2017
Diazepam	Anxiety; Muscle spasm; premedication; Sedation; Status epilecticus; Febrile convulsions	Tablet; Oral suspension; Oral solution; Solution for injection; Emulsion for injection; Enema	Synthetic small molecule; Oral solids and liquids; Sterile parenteral	1960s

Colistin (colistimethate sodium;colistin sulfomethate sodium)	Serious infections due to selected aerobic Gram-negative bacteria; Management of chronic pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis;	Powder for solution for injection; Inhalation powder; Powder for nebuliser solution	Polymyxin antibiotic; fermentation or biosynthesis; Sterile parenteral; Sterile powder for inhalation	1960s

Medicines in bold text are on the WHO list of Essential medicines

- A range of technologies are used to manufacture the drug substances above, including: synthetic chemistry; extraction from natural tissues; fermentation/biosynthesis and cell culture and purification
- Manufacture of sterile dosage forms is the main finished dosage form manufacturing technology in all the above medicines. (Note that it would be important to differentiate the dosage form when considering criticality e.g. Diazepam oral solution is not inter-changeable with Diazepam Injection)
- Hospital use is the primary care setting in most of the above medicines
- **WS4 recommends consideration of the manufacturing and supply aspects of critical medicines to identify innovations in manufacturing technologies that could help to increase the resilience of supply chains for these medicines**

Appendix 3: EFPIA MQEG Assessment of Potential Barriers in EU Pharmaceutical Legislation – Directive 2001/83/EC and Regulation 726/2004

Legislation	Potential Regulatory Barrier
Directive 2001/83/EC	
Article 42.3: *The authorization shall apply only to the premises specified in the application and to the medicinal products and pharmaceutical forms specified in that same application.*	Article 42.3 refers to Article 41 on manufacturing authorizations. "The authorization shall apply only to the premises specified"- a potential barrier to the use of mobile/modular manufacturing units. Is there a need to provide some flexibility here to enable modular manufacturing to be implemented? We also note that Module 1 of the CTD requires that 'The name and address of the applicant shall be given, together with the name and address of the manufacturers and the sites involved in the different stages of the manufacture (including the manufacturer of the finished product and the manufacturer(s) of the active substance(s)), and where relevant the name and address of the importer.'

Article 49.2: *A qualified person shall be in possession of a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course of study, or a course recognized as equivalent by the Member State concerned, extending over a period of at least four years of theoretical and practical study in one of the following scientific disciplines: pharmacy, medicine, veterinary medicine, chemistry, pharmaceutical chemistry and technology, biology.* *However, the minimum duration of the university course may be three and a half years where the course is followed by a period of theoretical and practical training of a minimum duration of one year and including a training period of at least six months in a pharmacy open to the public, corroborated by an examination at university level.* *Where two university courses or two courses recognized by the State as equivalent co-exist in a Member State and where one of these extends over four years and the other over three years, the three-year course leading to a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course or its recognized equivalent shall be considered to fulfil the condition of duration referred to in the second subparagraph in so far as the diplomas, certificates or other evidence of formal qualifications awarded on completion of both courses are recognized as equivalent by the State in question.* *The course shall include theoretical and practical study bearing upon at least the following basic subjects:* *— Experimental physics* *— General and inorganic chemistry* *— Organic chemistry* *— Analytical chemistry* *— Pharmaceutical chemistry, including analysis of medicinal products* *— General and applied biochemistry (medical)* *— Physiology* *— Microbiology*	Article 48.1 requires that 'Member States shall take all appropriate measures to ensure that the holder of the manufacturing authorization has permanently and continuously at his disposal the services of at least one qualified person, in accordance with the conditions laid down in Article 49, responsible in particular for carrying out the duties specified in Article 51.' The Legislation is too detailed, nevertheless there are still differences in implementation by Member States that lead to challenges for industry. (Implementation across Member States is not harmonised) Additional detail on disciplines etc. is too detailed for regulation, and scientific disciplines are changing and evolving.

— Pharmacology *— Pharmaceutical technology* *— Toxicology* *— Pharmacognosy (study of the composition and effects of the natural active substances of plant and animal origin).* *Studies in these subjects should be so balanced as to enable the person concerned to fulfil the obligations specified in Article 51.* *In so far as certain diplomas, certificates or other evidence of formal qualifications mentioned in the first subparagraph do not fulfil the criteria laid down in this paragraph, the competent authority of the Member State shall ensure that the person concerned provides evidence of adequate knowledge of the subjects involved.*	
Article 49.3: *The qualified person shall have acquired practical experience over at least two years, in one or more undertakings which are authorized to manufacture medicinal products, in the activities of qualitative analysis of medicinal products, of quantitative analysis of active substances and of the testing and checking necessary to ensure the quality of medicinal products.* *The duration of practical experience may be reduced by one year where a university course lasts for at least five years and by a year and a half where the course lasts for at least six years.*	See comment on Article 49.2 above. Note: we understand that, for example, in German Drug law there is a requirement for QPs to justify and only be qualified to take responsibility in a specific area of medicines manufacturing (e.g. ATMPs)

Article 51.1: *Member States shall take all appropriate measures to ensure that the qualified person referred to in Article 48, without prejudice to his relationship with the holder of the manufacturing authorization, is responsible, in the context of the procedures referred to in Article 52, for securing:* *(b) in the case of medicinal products coming from third countries, irrespective of whether the product has been manufactured in the Community, that each production batch has undergone in a Member State a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the quality of medicinal products in accordance with the requirements of the marketing authorisation.* *The qualified person referred to in Article 48 shall in the case of medicinal products intended to be placed on the market in the Union, ensure that the safety features referred to in point (o) of Article 54 have been affixed on the packaging.* *The batches of medicinal products which have undergone such controls in a Member State shall be exempt from the controls if they are marketed in another Member State, accompanied by the control reports signed by the qualified person.*	Full Import testing is an outdated and burdensome requirement that adds little to the protection of public health, while delaying access to medicines and reducing the efficiency in supply chains. Currently the possibility to waive import testing is only if an MRA is in place, as described in Article 51.2. There is an opportunity for a more science- and risk-based approach that takes into account the MAH oversight of supply chains and enables a better allocation of resources to protect public health. For example, in the case when the manufacturing site in the exporting country (e.g. a Third country PIC/S member) belongs to the same company as the one which is importing in the Community.
Article 58: *The inclusion in the packaging of all medicinal products of a package leaflet shall be obligatory unless all the information required by Articles 59 and 62 is directly conveyed on the outer packaging or on the immediate packaging.*	Article 1.26 Defines a Package leaflet as 'A leaflet containing information for the user which accompanies the medicinal product' The inclusion of paper leaflets in packages for medicinal products adds complexity to manufacturing operations and limits the flexibility needed to adapt supply of medicinal products to meet the demand in different EU/EEA Member States. The option to replace the paper leaflet by the provision of the information to patients via electronic means (an 'electronic patient

	information leaflet' or ePIL) is in line with the requirements for ease of use in Article 59.3 and enable the provision of the latest information in the patients' language. It would align with the digital transition, and the green transition by reducing environmental waste paper. We note that this approach was implemented for COVID vaccines. EFPIA's position on ePI is captured in this paper: https://www.efpia.eu/media/589590/electronic-product-information-from-principles-to-actions.pdf
Article 114. 1. *Where it considers it necessary in the interests of public health, a Member State may require the holder of an authorization for marketing:* *- live vaccines* *- immunological medicinal products used in the primary immunization of infants or of other groups at risk,* *- immunological medicinal products used in public health immunization programmes,* *- new immunological medicinal products or immunological medicinal products manufactured using new or altered kinds of technology or new for a particular manufacturer, during a transitional period normally specified in the marketing authorization,* *to submit samples from each batch of the bulk and/or the medicinal product for examination by an Official Medicines Control Laboratory or a laboratory that a Member State has designated for that purpose before release on to the market unless, in the case of a batch manufactured in another Member State, the competent authority of that Member State has previously examined the batch in question and declared it to be in*	OMCL testing adds complexity and delays to supply of vaccines and biologics and can repeat (duplication/triplication i.e. Batch release + Import testing + OMCL testing) testing for vaccines from Third Countries. Technical transfer of methods can be difficult in some cases. The current legislation leaves appropriate flexibility: " when is considers it necessary ... a MS may require ...", and this is limited to certain products, as listed. However, the reality is that MSs impose retesting by an OMCL, for every single batch, whatever the vaccine is (and regardless other texts such as the Directive on 3R). So, it is in fact not the legislation per se which is an issue but its application.

conformity with the approved specifications. Member States shall ensure that any such examination is completed within 60 days of the receipt of the samples.	
Annex 1 - Module 3: CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL INFORMATION FOR MEDICINAL PRODUCTS CONTAINING CHEMICAL AND/OR BIOLOGICAL ACTIVE SUBSTANCES	EFPIA notes that ICH M4Q will be revised, necessitating revision of this Annex.
Regulation 726/2004	
Article 16a.1: *Variations shall be classified in different categories depending on the level of risk to public health and the potential impact on the quality, safety and efficacy of the medicinal product concerned. Those categories shall range from changes to the terms of the marketing authorisation that have the highest potential impact on the quality, safety or efficacy of the medicinal product, to changes that have no or minimal impact thereon.*	'*…to changes that have no or minimal impact thereon.'* – This adds regulatory burden to the Variations framework for both industry and regulators. Revision of the framework to address this issue, including implementation of ICH Q12, is recommended because the global burden of Variations (can take more than 5 years for changes) is a major inhibition to the adoption of beneficial changes supporting innovation, reduction in environmental impact etc
Article 18.1: *In the case of medicinal products manufactured within the Union, the supervisory authorities for manufacturing shall be the competent authorities of the Member State or Member States which granted the manufacturing authorisation provided for in Article 40(1) of Directive 2001/83/EC in respect of the medicinal product concerned.*	Is this a potential barrier to mobile/modular manufacturing? Could this necessitate flexibility for supervision through co-operation between Competent Authorities?

Article 18.2: *In the case of medicinal products imported from third countries, the supervisory authorities for imports shall be the competent authorities of the Member State or Member States that granted the authorisation provided for in Article 40(3) of Directive 2001/83/EC to the importer, unless appropriate agreements have been made between the Union and the exporting country to ensure that those controls are carried out in the exporting country and that the manufacturer applies standards of good manufacturing practice at least equivalent to those laid down by the Union.* *A Member State may request assistance from another Member State or from the Agency.*	When importing medicinal products from Third Countries we believe the focus of regulatory oversight for quality matters should be the physical product and its location in a member state, not the financial flows.

Appendix 4: Medicines for Europe Case Studies on Incentives for Manufacturing Process Innovations

Case study 1: The absence of economic incentives for investing in greener production processes for pharmaceuticals

The pharmaceutical sector is actively engaged in multiple facets of environmental policy – notably through joint cooperation between EFPIA, Medicines for Europe and AESGP. The EU has adopted numerous regulations to reduce pharmaceutical environmental risks through the water framework directive, the Pharmaceuticals in the Environment (PiE) policy and environmental risk assessments (ERA). However, the industry has also engaged in additional efforts to improve the environment such a strategy to encourage patients to appropriately dispose of unused medicines (http://medsdisposal.eu/), developing joint industry positions to voluntarily reduce the environmental impact of production (AMR Common Manufacturing Framework https://www.amrindustryalliance.org/wp-content/uploads/2018/02/AMR_Industry_Alliance_Manufacturing_Framework.pdf) and to address the risks of legacy products (https://pharmaenvironment.org/project/eco-pharmaco-stewardship-eps/). Individual companies are also making efforts to improve energy efficiency or to rely more on renewable energy for production.

One challenge that arises in Europe, however, is the lack of economic incentive to reward companies that make investments to improve the environment – especially in the off-patent competitive market. Most off-patent markets are driven by price competition either in the reimbursement or the procurement setting. In the reimbursement setting, countries apply a 'reference price' to determine the reimbursement price of a medicine. For more genericised markets, countries will typically set the 'reference price' at or close to the lowest price in the market. In some cases, countries apply the reference in comparison with other EU member states known as external reference pricing. To date, there are no member states that offer a higher reference price for products produced by companies that have invested in environmental improvements. In Finland, there has been an experiment to provide a "green label" to certain OTC products to encourage patients to purchase this product (as these are OTC products, prices are not set by the government).

In the overwhelming majority of procurement markets, there are no rewards or bonuses for companies that invest in environmental improvements. Almost all tenders are determined by the lowest price. There have been small experiments however in some countries. In Sweden, regional hospital procurers have awarded bonuses for companies that can demonstrate social and environmental commitments. Norway has also launched procedures for green procurement (https://sykehusinnkjop.no/nyheter/new-environmental-criteria-for-the-procurement-of-pharmaceuticals). There is also a discussion between Nordic countries to apply green criteria more systematically across the region (https://sudden.fi/wp-content/uploads/2020/09/NordicSeminaronPPofpharmaceuticals_invitationANDprogram_2020_09_30.pdf). The German health insurer AOK has also experimented with a green bonus for an antibiotic tender in 2020 (https://www.eversana.com/2020/07/22/germany-aok/). However, the tender was successfully challenged and temporarily suspended before the German procurement court for other reasons. (Note: the tender also included a bonus for manufacturing in Europe which was successfully challenged as disproportionate). The challenge is that these initiatives, if successful, are still small scale. It would make sense to apply green criteria more generally to reward companies for investing in environmental improvements.

The EU could play a role in encouraging more economic incentives for the environment as it holds legislative power for both reimbursement (the Transparency Directive) and procurement (The EU Public Procurement Directive) under EU Internal Market law. This would logically complement the EU policy for PiE by encouraging industry to act sustainably in many areas (including areas not directly regulated by the EU).

Case Study 2: Process innovation – competition law limitations/lack of regulatory/economic pathway

a. *Competition law limitations to production scale up in a crisis*: EU pharmaceutical manufacturing is an ecosystem of developers and manufacturers with a lot of contract manufacturing across the sector. In a crisis with big demand surges, there are competition law limitations to cooperation between competitors. During Covid-19 there were several examples of this. First, in the early stages of the crisis, there was a massive surge in demand for intensive care unit (ICU) medicines due to the increase in number of patients on mechanical ventilation. Due to the massive increase in demand (requests for +2000% increase in annual supply in March-April 2020 from French hospitals), the industry needed to cooperate to scale up productive output as quickly as possible. However, in practice this is not possible due to competition law. On 6 April 2020, the Commission subsequently granted an antitrust comfort letter to Medicines for Europe to, according to Vice President Vestager: "*to make sure that there is sufficient supply of the critical hospital medicines used to treat coronavirus patients. To avoid the risk of shortages of essential and scarce products and services because of the unprecedented surge in demand due to the pandemic, we need businesses to cooperate and do it in line with European Competition rules."(* https://ec.europa.eu/commission/presscorner/detail/en/ip_20_618*).* The project to which EFPIA was fully associated, followed careful competition law guidance and worked to ensure appropriate regulatory flexibility so that companies could produce as quickly as possible. In the end, there was no need for direct cooperation between competitors as industry output increased, demand calculations by the industry per country enabled the EU and member states to rationalise demand requests (and to target patient delivery instead of hoarding). However, the guidance was critical to initiate the project as most companies would not have engaged in any meaningful way without the comfort letter. Second, in the later stages of the crisis, several vaccines were developed in Europe and approved for Covid-19. There was also a massive demand for these vaccines to inoculate the entire adult EU population (as well as the global population). There was an EU-vaccines industry dialogue (to be filled in by EFPIA) and a vaccines production task force to encourage match-making between developers and contract manufacturers and overall to accelerate the scaling up of production (https://ec.europa.eu/commission/commissioners/2019-2024/breton/announcements/beating-covid-19-scale-vaccine-production-europe_en). Again, competition law guidance was necessary as this is not the common path for drug development and manufacturing in Europe. Following the pandemic, there have been calls to encourage more reshoring of production in Europe – and notably for medicine manufacturers to procure more supply chain inputs from Europe. While this does have some appeal and we note a resurgence of demand for EU API, it is also clear that the industry cannot jointly coordinate private procurement for pharmaceutical inputs – even for a cause like creating jobs and security in Europe – as this would be a clear breach of antitrust rules. One option would be to consider declaring the pharmaceutical sector, under certain conditions, an Important Project of Common European Interest (IPCEI https://ec.europa.eu/competition-policy/state-aid/legislation/modernisation/ipcei_en) which would facilitate the grant of EU Resilience and Recovery Funds for investment into critical pharmaceutical and API production in-line with national plans. Many pharmaceutical industry associations at national level have highlighted that state aid rules are a major barrier to these investments and are blocking the progress on national plans. (According to Farmindustria Director General in Italy: **Brussels barriers:** At the European level, Giorgetti applauded efforts to strengthen strategic autonomy. However, he also pointed to EU state aid rules as posing an obstacle to strengthening the European pharmaceutical industry. "*If we ban state aid even in sectors like this one, how can we be competitive with China, where everything is state aid, and even with the U.S., where they have a very clear idea of strategy and where when necessary they were happy to provide state aid, even in large amounts?*" asked Giorgetti. Cited in Politico Pro Healthcare on 9/7/2021 Medicines for Europe confirms the view of the Italian association for many other countries.)

b. *Lack of economic incentives for process innovation*: The EU lacks a framework for process innovation in the off-patent sector. Many well-established molecules were developed and approved years ago using older chemistry and production technologies. There are many opportunities to upgrade those molecules with more modern process technology – including nanotechnology. There would be security benefits to enabling this innovation as modern process chemistry (or biotechnology) would be applied on a much bigger scale than it is today (mainly to small volume specialty molecules) which would generate investments by pharmaceutical and contract manufacturers into this technology and capability. Consequently, the EU would have a strong manufacturing ecosystem to respond to possible sudden increases in demand for certain medicines or vaccines in a possible future crisis situation. There is a challenge in Europe to improve on well-established molecules – for example to use modern manufacturing and chemistry (including complex production like nanotechnology) to improve the formulation of medicines for better safety or efficacy. According to IQVIA, the US accounts for 70% of the global market for these improved medicines thanks to its dedicated regulatory pathway (502(b)2).[1][1] This encourages the development and manufacture of these complex products in the US (even if they are developed in Europe) rather than in Europe. By encouraging this form of innovation, the EU would stimulate investments into more complex manufacturing on a large scale (as these are volume products) and contribute to a more modern manufacturing ecosystem in Europe. To stimulate this investment, the EU could adopt a regulatory framework similar to the US system but adapted to the EU context as proposed by the Value Added Medicines sector group of Medicines for Europe.(https://www.medicinesforeurope.com/docs/white-paper-VAM22-02-2021.pdf)

[1][1] *The US remains the largest market for value added medicines, not least because of its dedicated 505(b) (2) pathway and pricing flexibility. The decline in growth since 2016 is predominantly driven by continued pricing pressures in the US that have affected top brands for the past few years, such as adrenaline in anaphylaxis treatment, but the US still dominates global sales at 70%. https://www.iqvia.com/-/media/iqvia/pdfs/nemea/white-papers/a-digital-future-for-value-added-medicines.pdf?_=1625840588461*

Appendix 5: EU Industry Response to EU Commission Questions on use of Design Space and PACMPs (2019)

1. Background

At the industry and EU commission meeting in March 2019 the Commission asked the question:

"*Why does industry underuse available regulatory mechanisms which are supposed to already provide more flexibility (e.g. PACMP, design space)?"*

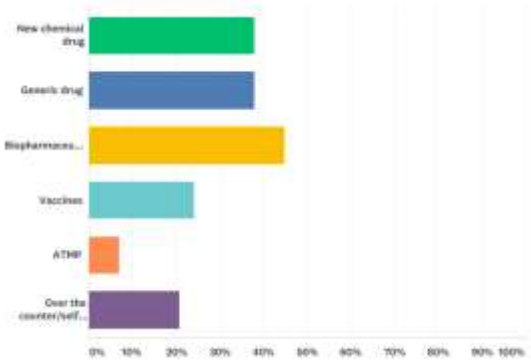
2. Industry Response

In order to address the Commission's questions on Design Space and PACMPs, EFPIA completed a survey of the views of companies who submit MAAs. Two short surveys (see Appendix 1) were organised by EFPIA to establish the experience and viewpoints of EFPIA, Vaccines Europe, Medicines for Europe, and AESGP member companies with Design Space and PACMPs This is a short summary of the outcomes of that survey and includes recommendations from EFPIA and Medicines for Europe for the Commission's consideration.

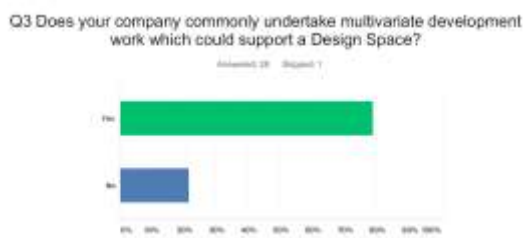
In order to allow for the fact that some companies may have different experience with both design spaces and PACMPs for the different products they supply, companies were able to answer separately for the different product types (e.g. new chemical drugs, vaccines, biopharmaceuticals, ATMPs etc).

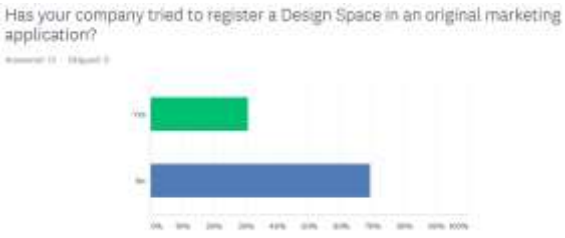
3. Design Space Survey

In total, for the Design Space survey, there were 29 responses to the survey from 20 companies. The responses received covered new chemical drugs, biological drugs, vaccines, ATMPs, generic and over the counter medicines..



In summary, the survey showed that the majority of respondents (79%) commonly undertake multivariate development work which could support a Design Space. However, only 31% of respondents had tried to claim a design space in an MAA and only 10% (one response) claimed a design space in a variation.

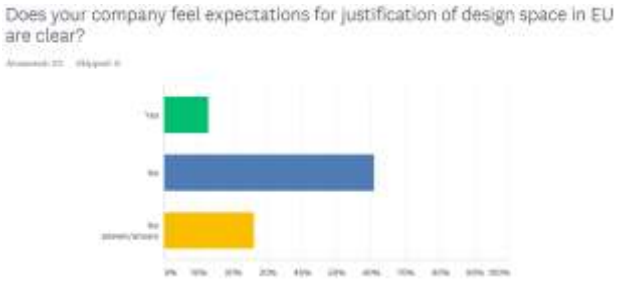


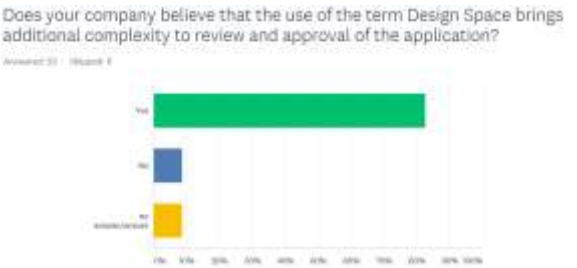


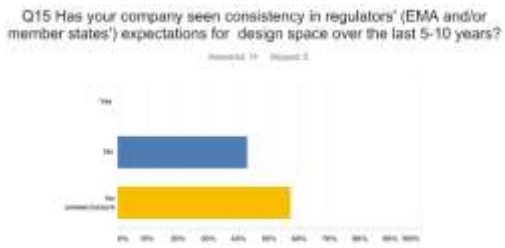
The data indicated that design spaces were most likely to be claimed for new chemical drugs, with 63% of responses indicating that a design space had been claimed in an MAA.

Respondents were also asked to explain why they had not claimed design space and to comment on what might make them more likely to do so. Only 13% (1 response) felt that expectations for design space in EU were clear, with 61% of responses stating that requirements are unclear.

Equally, 83% of responses indicated that companies feel that the use of the term design space brings additional complexity to review of the application, and no responses indicated the view that EU assessors had been consistent with expectations for design space over the last 5-10 years.







Respondents were evenly matched between those who felt that the development of design space was worth the resource required and those who felt that it was not (35% versus 39%).

In a separate question, respondents were asked to select those benefits that registration of the design space by an applicant can bring. The answers were mixed, with companies seeing a mixture of positive benefits and no significant benefit.

In addition, 43% of responses stated that the variations reporting categories for changes to design space discourage companies from using it.

Companies were asked to comment on the survey questions and to explain what was discouraging them from using design space overall. The following recommendations are made by industry based on the information generated by the survey:

- Expectations for justification of design space are unclear in EU, and not aligned with expectations in ICH guidance or in other regions. Respondents were particularly concerned with EU regional expectation, citing the example of *EMA/CHMP/CVMP/QWP/354895/2017 Improving the understanding of NORs, PARs, DS and normal variability of process parameters"* where EU specific considerations for Design Space and PARs (Proven Acceptable Ranges) are not aligned with ICH guidance provided in ICH Q8, Q9, Q10 (e.g. IWG Q8, Q9, Q10 (R4) Q&A 8, or IWG Q8,

Q9, Q10) or the expectations of other regions. Several respondents also highlighted concerns with EU expectations for commercial scale data to verify design spaces.

- The EU variations guidance (sections B.I.e.1. and B.II.g.1.) categorizes all changes to design space as Type II, regardless of the risk to quality. This discourages the use of design space and does not align with the concepts of quality risk management in ICH Q8-11. It is recommended that the Variations legal framework is updated to address this point.
- Industry respondents recognised that updating the Variations legal framework for changes to design space to align more fully with consideration of risk to product quality will also enable implementation of concepts described in the draft ICH Q12 guideline on Pharmaceutical Product Lifecycle Management. In particular, enabling changes to design space to be handled via Type IA or Type IB Variations will support wider usage of design space.

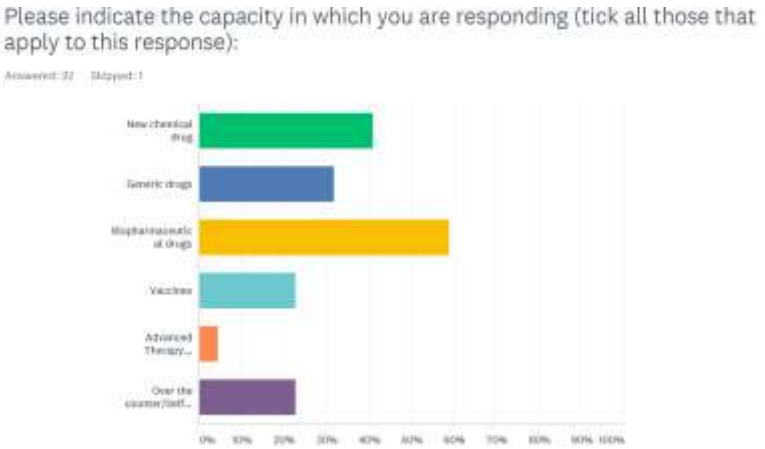
Conclusions and Recommendations on Design Space

In summary, most companies are routinely undertaking enhanced development aligned with ICH Q8-11 and are developing process understanding that could support design spaces. However, companies have become discouraged from attempting to secure a design space by the EU regulatory expectations associated with gaining approval and subsequent maintenance of a design space, and divergent regulatory expectations between regions due to inconsistent implementation of ICH Q8-11.

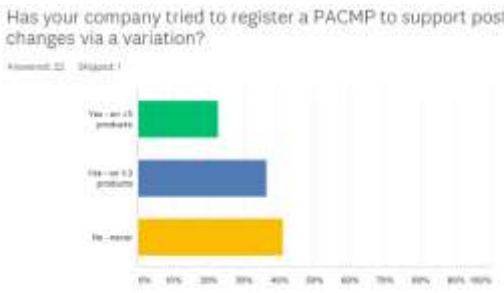
Industry therefore recommends that the EU Commission sponsors a revision of the EU Variations legal framework and associated regulatory guidelines (in particular, the problematic EU-specific guidance provided in *EMA/CHMP/CVMP/QWP/354895/2017)* with respect to the categorisation of Variations for changes to design space, and supports further harmonisation activities within ICH to ensure consistent global regulatory expectations for design space.

4. PACMP Survey

In total for the PACMP survey there were 23 responses to the survey from 16 companies. The responses received covered new chemical drugs, biological drugs, vaccines, ATMPs, generic and over the counter medicines.



Respondents were asked to identify whether they had used PACMPs in an MAA or variation in the last 10 years. The majority of respondents had used PACMPs 1-3 times since 2008. Further analysis of the data showed that respondents were most likely to use PACMPs for biological drugs, with 85% of respondents on biopharmaceutical drugs having submitted a protocol with the MAA and 77% as a variation since 2008.

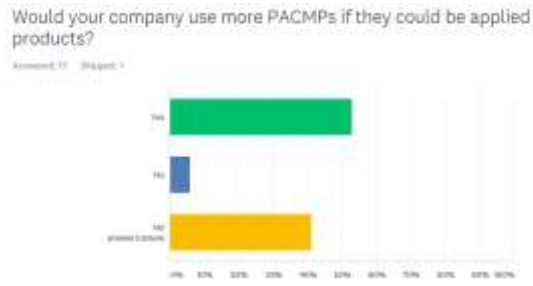


Companies were also asked to indicate what they had used PACMPs for. The most common use was for a change to a manufacturing process or site (76%).

ANSWER CHOICES	RESPONSES	
Managing a change to a single product?	80.95%	17
Managing a change to group of products?	4.76%	1
Changes relating to Manufacturing process/sites?	76.19%	16
Changes relating to Analytical procedures?	14.29%	3
Changes relating to Excipients?	0.00%	0
Changes relating to Specifications?	4.76%	1
Changes relating to Container Closure?y	14.29%	3
Changes relating to Stability?	4.76%	1
No experience of PACMPs	19.05%	4

Respondents were also asked to comment on the uses of PACMPs. Generally, greater predictability of outcomes (68%), reduced reporting categories (64%) and predictable timelines (73%) were considered as positive benefits. 40% of applicants felt that PACMPs support more rapid registration of new medicines by facilitating post approval changes.

ANSWER CHOICES	RESPONSES	
Greater predictability/certainty of outcomes for changes	68.18%	15
Reduced reporting categories for changes to Chemical Drugs	40.91%	9
Reduced reporting categories for changes to Biological Drugs and Vaccines	63.64%	14
Greater predictability/consistency between regions (where PACMPs are accepted)	36.36%	8
Support more rapid registration of new medicines by facilitating post approval changes	40.91%	9
More predictable timelines for implementation of changes	72.73%	16
No experience/no answer	22.73%	5
Total Respondents: 22		



Respondents were also asked to comment on any blockers which discourage the use of PACMPs. 47% cited concerns over requirements or complexity.

In addition to the options in the survey, a number of comments on elements which discourage the use of PACMPs were made by respondents. The following points and recommendations were made in the survey and have been subsequently endorsed by industry:

- There is little flexibility to change a PACMP once it has been agreed, since any change requires prior approval via a Type II variation. There is a need in EU for more flexible mechanisms in the Variations framework to amend or augment approved protocols.
- Because submission of a PACMP for a marketed product is via a Type II variation it can be faster to simply submit the change as a Type II variation. Hence use of PACMPs by companies is likely to be limited to more complex post-approval changes where the greater predictability of outcomes outweighs concerns over requirements or complexity.
- Development of multi-product protocols, to support changes across similar product types, could significantly contribute to consistent use by applicants, and review and approval by assessors, and thereby enhance the effectiveness of PACMPs as a tool to facilitate post-approval changes.
- There is an opportunity to make better use of PACMPs to support common types of change, with similar protocols describing how types of change will be handled, without requiring significant product-specific justification for common types of change (e.g. updating a specification limit once additional manufacturing experience has been acquired).
- There is an opportunity to use PACMPs to support rapid implementation of changes associated with acceleration/access to new medicines.
- Implementation of ICH Q12 should encourage greater use of PACMPs across ICH regions, and perhaps beyond, and industry encourages the EU to continue to lead in this area and share its experience of the use of PACMPs with other regions.

Conclusions and Recommendations on PACMPs

In summary, most companies that responded to the survey have some experience of the use of PACMPs and clearly see the potential benefit. However, companies' experience suggests that there is a need to simplify requirements for PACMPs, introduce more flexible mechanisms to change approved PACMPs, and incorporate multi-product protocols in the Variations framework in order to fully realise the potential benefits in Europe.

Industry therefore recommends that the EU Commission sponsors both the modernisation of the expectations for PACMPs through an update in the EU Variations legal framework and further harmonisation activities with other regions, particularly through the implementation framework of ICH Q12 to ensure consistent global regulatory expectations for PACMPs.

5. Overall Conclusions

Industry welcomes the opportunity to address the EU Commission's questions on the use of design space and PACMPs and to provide data from companies supplying innovative, generic and over-the-counter medicines, vaccines and advanced therapies. Industry would welcome further dialogue on approaches to optimise the use of these regulatory tools with the Commission and with EU regulatory experts.

Appendix 6: Examples of Regulatory Barriers in Pharmaceutical Guidance

Example 1: Industry Associations request for revision of CHMP Addendum to the NIR Guideline

On 16 December 2015 EFPIA, on behalf of the industry associations, sent a proposal for a revision of the Addendum to the Guideline on the use of near infrared spectroscopy by the pharmaceutical industry and the data requirements for new submission and variations (EMA/CHMP/CVMP/QWP/17760/209 Rev2), outlining the challenges companies faced applying the provisions of the Addendum. Following the reply received from EMA on 12 January 2017, EFPIA proposed a meeting with the PAT Team in June 2017. On 7 June 2018 the industry associations met with the NIR Drafting Group and discussed the NIR addendum. Through a series of case studies the industry group sought to explain why the current regulatory paradigm does not facilitate the implementation of enhanced approaches to quality assurance such as the use of NIR for PAT, and the consequences for continuous manufacturing systems that would not be usable while Variations were being reviewed. Industry understood that EMA committed to revise the NIR Addendum, incorporating input from the meeting, and indicated that the revised Addendum would be published in due course. As of June 2021 a revised NIR Addendum has not been published.


Letter to EMA_NIR_guidance_fir


EMA%20response_Revision%20of%20NIR%


Revision%20of%20NIR%20Guideline%20Adendum%20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Example 2: API Manufacturer seeking to introduce more efficient enzymatic process to replace chemical synthetic process

The API manufacturer's Asian supplier supplies the Registered Starting Material (RSM). It is made from a plant source by means of fermentation. The API manufacturer converts this RSM enzymatically in one step to the API. The API manufacturer is currently also manufacturing this API by chemical synthesis in several steps using the same RSM. While the RSM (enzymatic route) is the same as the current RSM (chemical route), the new, very efficient, enzymatic route is considered from a regulatory perspective to be too short (See Q5.11 in ICH guideline Q11 on development and manufacture of drug substances (chemical entities and biotechnological / biological entities) – questions and answers). Regulatory agencies are now asking questions about the manufacturing process for the RSM, which the Asian supplier considers to be proprietary, and was not previously questioned.

Appendix 7: EFPIA MQEG survey on 'Innovation in Manufacturing'

The Efpia Manufacturing & Quality Expert Group (MQEG) conducted a survey of member companies during July 2021. Seven member companies were able to provide responses to the questionnaire, which asked the following questions:

1. Has your company engaged direct with Regulators in a scientific dialogue?

2. Have you with regard to the question above experienced any specific barriers in EMA and/or EU Member States (MS)?

3. Do you have good examples from Regulatory agencies which would make them a global leader and champion with regard to introduction of new, innovative technologies in pharmaceutical manufacturing?

4. What kind of support/incentives would motivate your company to expand your manufacturing and supply in EU?

Key points from this survey are:

1. All responding companies have engaged in various activities with regard to new technologies within both small molecules and biologics. A wide range of global regulators were referenced, but primarily FDA, EMA and MHRA. Technology areas discussed with regulatory agencies included

   novel manufacturing approaches (Continuous manufacturing, hot melt extrusion, portable manufacturing); QC Laboratories; microbiologically-controlled areas, digitalization and robotics.

2. In general companies are positive towards the European interactions. However, responsiveness by EU, including face-to-face meetings, was deemed lower than some other agencies (e.g. FDA). There are opportunities to improve the mechanisms for scientific engagement between industry and regulators on manufacturing and supply topics. Multi-national companies typically approach development and manufacturing from a global perspective and European regulators are encouraged to increase their understanding of the global challenges and different regulatory frameworks. There is a concern that the EMA ITF may not be a forum for discussion that is fully inclusive of all sizes of companies

3. Leading regulatory agencies would be characterized as: being interested in innovation, scientifically competent, and adequately resourced for engagement on new initiatives; having mechanisms/processes that enable scientific discussion of non-programme/product-specific (more conceptual) issues; demonstrating a collaborative, solution-oriented approach that helps industry to "think out of the box"

4. Recommendations from respondents include: Formation of a dedicated team of regulatory specialists in EMA/Member State agencies to support and actively promote the adoption of manufacturing innovations (the FDA ETT could provide a benchmark); providing predictability through fixed timelines for feedback and interactions; continuing to promote global regulatory harmonization to facilitate development of new innovative drugs and manufacturing technologies


MQEG%20question naire%2007072021%


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Appendix 8: EFPIA and Vaccines Europe Cross-Trade Key Proposals – Variation Framework

Key%20Proposals_EU%20Variation%20F

Appendix 9: Requests from participants to be removed from the list of contributors to the WS4 Report

This appendix documents the communications associated with the written requests for withdrawal, including amendments to the report.

There were 4 requests for withdrawal from representation in the report:

- 1 withdrawal from Ministry of Health, Welfare and Sport (NL) on the grounds that they had not attended meetings or made any contribution to the report.
- 3 withdrawals requested on 16 July, on the grounds of disagreement with the report, as detailed below. One request to withdraw was addressed following dialogue between the individual and rapporteurs and updates to the WS4 report were made during 17-19 July, enabling the individual to be retained as a contributor.

16 July: Written withdrawal requests

1) Klaus Kümmerer

Professor of Sustainable Chemistry and Resources

Leuphana University Lüneburg

Date: 16 July

The draft report does not contain topics and issues which I addressed and contributed in working sessions including recent comments on it.

For example, the challenges ahead coming along with the APIs themselves and needed basic resources, related environmental burdens and rebounds, sustainability beyond pure technology and manufacturing are not addressed at all. For example, the EU strategy on Pharmaceuticals in the Environment which is important for future APIs is only once mentioned, in the appendix (!). No effort was made to explain what the understanding and facets of „green" and „sustainable" are within this paper. Instead nearly everything is called „sustainable“ whereas most is not, not even "green“. Value chain is the dominating expression instead life cycle (if used then in in a much narrower sense within drug development and manufacturing only).

I asked for a broader view beyond technical/production sustainability many times, which is needed to render European pharmaceutical industry and medical supply truly greener and sustainable in all respects for the future and to take an also advantageous global leading role. I did this because I thought this is also in the interest of a future European pharmaceutical industry and patients (who by the way will also be affected by the presence of pharmaceuticals (APIs, excipients, adjuvants) in ecosystems and drinking water).

My understanding of the work we were asked to do was to collect ideas discuss them with respect how to move European pharmaceutical industries and forward and secure medical supply in the long run by identifying opportunities and becoming a global front runner which would also result in advantages globally, for industry, patients, society, and the environment. Apart from production this is not reflected in the report, let alone conclusions and executive summary. In the introduction it is stated "but only those specifically related to manufacturing and supply were discussed in detail, because this was the scope identified by the Commission (e.g. innovations related to pre-clinical and clinical science were not considered).“

This is at least to my understanding not true. In WS4 it was explicitly asked for a broader understanding and was discussed, however only briefly. There was also ongoing e-mail exchange on these topics. Furthermore, if industry wants to become more completive and truly sustainable a broader view including the whole life cycle of products, adjuvants, auxiliaries etc. is needed-a systems view not only a focus on on piece or station of the life cycle.

Furthermore, academia seems to be seen as the servant of industry. However, for the sake of both there should be a level playing field.

In many parts the draft has more the character of a lobbying paper than a well balanced discussion paper. My self understanding and role is not to be a lobbyist but a scientist.

It was said there is no need to agree, however, how should we demonstrate disagreement (and take advantage on this for all involved by an open discussion) if disagreement is not even visible.

I sent in comments, questions, feed back etc. I often did not receive feed back or answers to my mails including the latest points addressed as for the draft. Instead a much changed file was send yesterday evening. This happened several times. It is not clear how comments (which has to be classified according to disagreement, gaps and edits). At least as for the first two I would have liked to receive a feed back (e.g. why it was not considered in the revision).

Last but not least I do not know whether it is just power play or bad management sending in drafts to be discussed the next morning late in the evening the day before. In any case it is not helpful, not respectful and does not support a process of high quality and high quality outcome.

Summarising: This report in my opinion is more about green washing and sustainability washing then on a sustainable future for all including patients and pharmaceutical industry and does neither reflect my inputs nor my comments. It does neither reflect my understanding of sustainability.

Therefore, please remove may name from the list of participants/contributor/authors.

2) Michael Mueller

Chair of Pharmaceutical and Medicinal Chemistry

University of Freiburg

Please find attached a file on fluorinated pharmaceuticals and another on the use (or rather non-use) of antibiotics. Both, fluorination and antibiotics, are examples of possible misleading sustainability aspects of technology and pharmaceuticals. Securing supply chains with non-sustainable technologies and products therefore guarantees on the long run that Europe will not be the leading science hub and economy in terms of pharmaceuticals.
The draft report has nothing to do with the comments I had made over time (attached), but serves to cement 'business as usual'. The 'green transformations' listed pass for greenwashing at best. Sustainability is usually understood as technologically or economically sustainable, etc....
So, I think it is best to remove my name from the list of people who contributed to the report.

<u>16 July: Workstream 4 Participant discussion</u>

The two written requests above were received during WS4 review of version 2 of the report, enabling their discussion among WS4 participants in the meeting on 16 July that had been arranged to discuss acceptance of the WS4 report. Neither of the individuals above were able to join the call.

Following discussions in the meeting, the Rapporteurs reached out by email and invited each correspondent to share more direct suggestions that would enable them to remain as a contributors to the report. They were also invited to call the Rapporteurs at their convenience to discuss their concerns.

<u>16 July: Rapporteur response (similar email adapted to each correspondent above)</u>

We would like to understand more exactly what changes would be needed to include your perspective in the report, as part of the report editing process in response to the feedback received from participants: as you know the intent is to be inclusive and include divergent opinions.

Our remit in WS4 included responding to the following questions from the Commission Backgrounder document:

What are the challenges the EU pharma manufacturing value chain will be faced to keep up with the green and digital transition?

How would the green and digital transition contribute to the increased resilience of the supply chains?

So while we respect your view that the discussion should have included a 'broader view beyond technical/production sustainability', our remit from the above is 'the EU pharma manufacturing value chain' and 'increased resilience of the supply chains'.

This may help to explain why 'sustainability beyond pure technology and manufacturing are not addressed' because we had to focus our discussion on manufacturing and supply chains. Similarly, the development of non-fluorinated medicines to replace fluorinated medicines (as suggested by Michael) we consider is not a manufacturing and supply issue per se, but a much wider issue for society to debate about the kinds of medicines it wants to be developed and to make available to patients.

As rapporteurs we are happy to include our interpretation of the WS4 remit, together with your suggestion that this should have been wider, in the report.

We are puzzled by your remark that 'academia seems to be seen as the servant of industry' as we have stressed the importance of collaboration between the different stakeholders to address the challenges identified in our discussions. We would like to apologise if that is the impression you gained – it was not our intent – and would welcome suggestions for revisions to the text of the report that would correct this. The report was amended in response to your comments, in order to be clear that wider research contributions should be sought in the next stage. To include a narrow set of specific technology recommendations at this first stage of the process, would be to give a false perception that this was as a result of a wider review and selection. It is entirely appropriate that your research can be referenced as examples within the report, with the clear understanding that the wider research community must be more represented in future stages. You will be aware that we reported we are still working to include in the report the relevant evidence and references provided by WS4 team members.

We would also like to apologise if we did not meet your expectations for responsiveness to emails and would like to assure you that all your comments were considered, and most have been included in revisions to the report. Please find attached the spreadsheet capturing the rapporteurs response to your comments on the previous draft that you sent 12 July at 18.39 (receipt of which was acknowledged with thanks by email from Graham on 12 July 22.55, expressing hope that you would be able to join the meeting on 13 July).

We would also request your understanding that the timelines for this Structured Dialogue resulted in us having to request very fast reviews from all colleagues involved. In the call this morning we explained some of the technical difficulties that we had yesterday, that resulted in a delay sending the report yesterday afternoon, although this was still aligned with the proposal made to the Team in the meeting on the morning of Tuesday 13 July. As we reported during the meeting on Tuesday, we had received a significant number of responses (over 150 comments), and all were reviewed and addressed by the Rapporteurs as far as possible in a very short timeframe, with all responses also planned for inclusion in an annex. We will include your own latest comments within this annex plus the conclusions of the group following the discussion in the meeting today.

If it would be easier, please don't hesitate to call me at your convenience to discuss your concerns and see if we can find an agreeable path forward.

<u>20 July: Additional email correspondence</u>

Professor Klaus Kümmerer:

Thank you for your message and sharing your view and perceptions and the clarifications provided. I'm sorry that I couldn't respond earlier.

As for the changes or topics which I suggested to include my understanding was as follows:

Most of the discussion/work is on sustainable supply of pharmaceuticals in Europe with a focus on technological and economical prerequisites for this which is understandable and fine. However, as for WS4 there was also the broader understanding of sustainability including the whole life cycle-in my perception, not just greener technologies etc. Therefore I addressed this several times why this understanding is important in the long run for industry and patients, „not just“ for environment- a holistic view is needed to cope with the challenges of the future addressed by the topic of the workshop series. Interestingly, No one objected, indicating this is out of scope. Instead there was just a sort of „silence“. Why was the limited scope not clarified than very early (see also my last mail „clarification of the group’s understanding of green and sustainable" and including this into the report?

This perception was obviously not only mine as we had break out sessions on this broader understanding including exchange and discussions on resources and end of life issues such as presence of pharmaceuticals in the environment, how to deal with pharmaceutical waste and out dated medicaments etc. with reference to actual EU strategies, i.e. beyond the value chain. Participants from industry were present too and discussed lively, too, including some with a background on pharmaceuticals in the environment and sustainability, many agreed. There was also follow up e-mail conversations including all participants. Furthermore, I guess I was asked to participate in this working group because of this professional background of mine. I’m not an expert in technology or processing within pharmaceutical industry for example. This may explain why I was very much surprised when reading the draft of the report.

If the task was limited from the very beginning as you’re describing in your mail and that’s the reason why not taking into consideration my (and other participant's) frequent feed backs (including the ones to the draft of the final report) I think this you should clarify the aims and scope of the report with the commission.

As for the point of academia I’m sorry for the strong wording, however, I (and other’s) had the strong feeling that we need to bring this point to attention for the sake of clarification: It has been addressed many times by others and me that academia has to play an important and independent role in such a discussion on the future of sustainable pharmaceutical supply in Europe and that it can and has to make independent contributions. In the draft of the report for example academia was summarised as part of the "industrial ecosystem" and not as an important player and problem solver in its own right. (This point was changed at least a bit in the reworked draft). The point is not some touchiness of academia or even more strange because of not mentioning my own research. That is not the purpose of such an report in my understanding and would be completely misleading. It is because such a mutual understanding necessary to develop together in a true partnership sound solutions for the challenges ahead for the sake of patients, society and industry in Europe and creating opportunities at a global level (see my last mail) needs strong and independent partners. This does not exclude cooperation with industry, in the contrary it will enable a much better one. I’m apologising if my perception was wrong here. Thank you also for clarification from your side.

If you want to to include my (and other participant’s too !) interpretation of the WS4 remit feel free to include the suggestion that this should have been wider, in the report. However, as the report is than, apart from these one or two lines, on topics where I’m not an expert and did therefore not contribute, this does not merit co-authorship in my understanding. Therefore, I'm asking you and the other rapporteurs not to have me listed/named as a co-author or contributor to the workshop as the above mentioned statement is quite obvious too.

I’d be happy to discuss further if needed.

Rapporteurs response:

Thank you for taking the time to provide your additional perspective.

We have respected your request to remove your name from the list of contributors to the report.
You will appreciate that the WS4 report must be submitted today. Nevertheless, the report will include your perspective, together with Professor Müller's, as an Appendix so that the scope and limitations of the report are clear to the Commission.