efpia
European Federation of Pharmaceutical Industries and Associations

Attachment to EFPIA's response to the European Commission's open public consultation on the revision of the general pharmaceutical legislation

Introduction

EFPIA shares a vision of a healthier future for Europe. A future based on innovation that can address unmet medical needs (UMN), increase access to new treatments and achieve better outcomes for patients across Europe.

With over 8,000 potential medicines and vaccines in our pipeline, our researchers are driving therapeutic progress and deliver new treatments to provide solutions and better health for patients across Europe. A study commissioned by EFPIA found out that in 2020 alone, around 5,000 clinical trials were launched across disease areas to tackle unmet medical needs. Over the past five years, and despite the disruption caused by COVID-19, the volume of trials has even increased. 40% of these trials are on substances targeting rare diseases, with ground-breaking cell and gene therapies growing in importance.[1]

Our capacity to keep on developing and deploying the results of these efforts, however, requires fresh thinking about Europe's research ecosystem and healthcare infrastructure. Today, only 22% of global new treatments originate in Europe, while almost half of them come from the United States.[2] This represents a complete reversal of the situation just 25 years ago, and latest numbers show a continued acceleration of the US's lead. In contrast, Europe's research and development (R&D) base is gradually eroding. During the past 30 years, R&D investment in Europe has grown 4.9 times, while in the US it has multiplied by more than 9.5 times.[3] If pioneering research continues to leave towards other regions of the world, so will the opportunity to deliver the best care to patients across Europe.

Reversing this trend of life science investment being relocated away from Europe requires that any new policy ecosystem be globally competitive. Only through a future-proof, innovation-minded regulatory framework, able to evolve with advances in science and technology to adapt to tomorrow's innovation, can Europe become a true world-leader in health, life science and innovation. There are significant interdependencies between the R&D policy environment and the manufacturing ecosystem downstream, the location of manufacturing units often following R&D. As the European Union (EU) has embarked in a comprehensive review of the pharmaceutical policy ecosystem, we now have a once-in-a-generation opportunity to implement learnings from COVID-19 and ensure a competitive regulatory framework that fosters innovation, helps ensure Europe remains a world leader in pharmaceutical discovery and responds quickly to patient needs.

To continue to attract investments in Europe as a true research, innovation and advanced manufacturing hub, the intellectual property (IP) and incentives ecosystem must also be world-class, robust and predictable. The stability of the current system has proven to be effective to enable our industry to invest in research and development, and to deliver new medicines to patients, healthcare systems and society in spite of long development processes with a high risk of failure. Reducing or limiting existing IP and R&D incentives would risk accelerating the erosion of Europe's research base.

A wave of new potentially curative treatments being discovered and becoming available to patients is revolutionising the way we think, manage and resource healthcare. But innovation only matters if it reaches patients in a timely manner. While ensuring that patients get faster, more equitable and sustainable access to innovative medicines in Europe is a common ambition that we share with patients, EU institutions, and national governments; availability, access and affordability of medicines depend on several interlinked factors at mostly Member States level that cannot be solved through EU legislation. A dialogue with all relevant stakeholders is required to make sure to address current

[1] https://www.efpia.eu/media/602563/iqvia_efpia_pipeline-review_final.pdf
[2] The Pharmaceutical Industry in Figures, Key data 2021, Pharmaprojects & SCRIP, March 2021
[3] The Pharmaceutical Industry in Figures, Key data 2021, EFPIA member associations & PhRMA, yearly publications 1990-2021

barriers to patients getting access to new treatments. EFPIA is ready to work together with policy makers and stakeholders to co-create new, flexible and collaborative solutions, a number of which are presented in the following pages.

This document highlights EFPIA's position on the main topics described in the open public consultation. We will be happy to continue the discussions in the framework of a targeted stakeholder consultation to achieve the common objectives of ensuring quality and safety of medicines for European patients, while boosting industry's global competitiveness.

Regulatory review

The European regulatory system has helped to attract the 39 billion Euros that the pharmaceutical industry invests in European research and development every year,[4] and allowed for the safe authorisation of over 1,400 new medicines since the creation of the European Medicines Agency in 1995.[5]

Based on a thorough and comprehensive review of the current regulatory system and assessment of future needs and best practices[6], EFPIA is proposing changes to the system to keep pace with advances in science, technology and medicines and be able to face unprecedented challenges, posed by the COVID-19 pandemic, ageing population and an increasing burden of chronic diseases, putting at risk the sustainability of our health systems.

In particular, through analyses and prioritisation, EFPIA has identified four key areas for legislative change that will ensure Europe remains a world leader in pharmaceutical discovery and responds quickly to patient needs, namely:

1) Reinforcing expertise-driven assessment and enable a more agile centralised authorisation framework
2) Enhancing expedited pathways framework supporting innovation
3) Expanding the role of EMA in the assessment of drug-device/diagnostic combination products
4) Replacing the paper patient information leaflets with electronic versions

Reinforced expertise-driven scientific assessment and agile decision-making process

The key objective is to ensure global competitiveness through enhanced expertise-based assessment and an efficient and swift process for the legally binding decisions, e.g. decision-making timeframe of maximum seven days (instead of current maximum 67 days) with limited exceptions.

Scientific Assessment

The key future objective is to ensure delivery of high-quality assessments based on best expertise. This drives a proposal for changes to the committee structure that offers the opportunity to improve efficiency in the system and enhance the ability for Member States to bring forward their expertise. The building blocks for the new model are:

- **Domains** involving the best experts. These will be established for clinical assessment for different therapeutic areas, pre-clinical, assessment, quality and pharmacovigilance. They deliver the scientific assessment of products in the relevant areas and hence are the engine for scientific opinions.
- **A committee delivering collective scientific opinions**. The final scientific opinion will be adopted by a separate committee representing all Member States to create a collective and inclusive decision moment and ensure appropriate checks and balances by all Member States while avoiding any potential conflict of interest with the scientific assessment process.
- **Advisory Expert Groups** (e.g. Paediatrics, Rare Diseases, ATMP, combination products, digital tools, methodology (incl. RWD, Big Data, AI), inspection, HCPs, patients) established with clear

[4] https://www.efpia.eu/media/602709/the-pharmaceutical-industry-in-figures-2021.pdf
[5] https://ec.europa.eu/health/documents/community-register/html/reg_hum_act.htm?sort=n
[6] https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Revision-of-the-EU-general-pharmaceuticals-legislation/F2242371_en
Furthermore, EFPIA has assessed the EU regulatory system and gained direct experimental insights from its member companies (https://efpia.eu/media/636564/evidence-mix_final-9-dec-2021.pdf) and looked at specifically on how to improve time to patient access to innovative oncology therapies in Europe (https://efpia.eu/media/636486/improving-regulatory-timelines-to-optimise-patient-access-to-innovative-oncology-therapies-in-europe.pdf).

governance to support the Agency and the domains on all parts of the system, including above product considerations and guidelines.

- **EMA**, with its own expert staff, with a much stronger scientific role, in particular managing and deciding on paediatric plans and orphan designations, advanced therapy medicinal products (ATMP) classifications, expedited pathways management, and post-authorisation safety study (PASS) protocol adoption. Moreover, EMA, with support of its evolving IT infrastructure, will enable a strong interface between the different activities for consistency of managing benefit-risk assessments. Beyond that, the EMA of the future must utilise and maximise the potential of advanced analytics, cloud technology and Artificial Intelligence (AI)/Machine Learning (ML) to derive deeper insights from data and to use those to create efficiencies and expedite work processes and assessment procedures. To capitalise on these opportunities, it is imperative that the EMA ensures the upskilling of staff expertise.

Finally, EMA will have a strong role in fostering capability building of experts in the EU for their participation in the domains, committees and expert groups.

Legally binding decision-making phase

The current decision-making process, involving a Standing Committee with representation of all Member States, was established 30 years ago to create a system of checks and balances for marketing authorisations following delegation of authority from Member States to the European Commission (EC). EFPIA's analysis calculated the potential impact of delays through the decision-making process. For eleven oncology products, these could mount up to 18,600 years of potential life loss. There are efficiency-gaining opportunities in the current system that could potentially deliver a much-needed faster decision-making process at scale in the future.

Potential solutions have been identified, noting that these could be used in combination:

- Conduct the decision-making phase in parallel to the linguistic phase, thereby allowing marketing authorisation to be potentially granted 12 days earlier.
- Increase the use of digital tools during the linguistic phase, which could shorten this phase by ten days.
- Provide an opportunity to shorten the written procedure in cases where Member States foresee no objections, thereby shortening the decision-making phase by 15 days.

Combining these solutions has the potential to save thousands of years of potential life across the European Union. Improving the transparency and predictability of the process between the final Committee for Medicinal Products for Human Use (CHMP) opinion and the EC decision would allow for better planning. In the last ten years, EC decisions have always aligned with CHMP opinions.

EFPIA has already started to engage in a conversation with the Commission on the efficiency of the current decision-making process with a particular emphasis on past experiences (e.g. how frequently the Standing Committee brought up additional scientific questions or came to different conclusions than the CHMP). This includes:

- The current and future role of the Standing Committee for checks and balances considering the role of the scientific committees and the evolution of separate national systems (e.g. health technology assessment, HTA) to address national access considerations.
- The potential for streamlining and accelerating the decision-making process beyond products subject to accelerated assessment.
- The potential for the legally binding decision for orphan designations be taken at EMA, similar as for paediatric investigation plans.
- A more radical solution to adapt the regulatory system for the future would be to transfer the process for issuing the market authorisation decision from the Commission to the EMA. This

would fulfil a key aim to reduce complexity by removing unnecessary interfaces between EC, EMA and Committees.

For any future structural changes to be successful in delivering an efficient and high-quality marketing authorisation system, an agile and flexible mindset will be critical.

Enhancing expedited regulatory pathways framework supporting innovation

There are several EU regulatory tools that can be described as expedited regulatory pathways (ERP) such as PRIME, conditional marketing authorisation (CMA) and accelerated assessment (AA). To date, their use has been limited (particularly when compared to use of comparable pathways in other regions), but effective ERPs are needed in a future-proofed regulatory framework to deliver the wide range of innovative treatments in the pipeline today and tomorrow. In addition, digitalisation of health data will modernise evidence generation as well as regulatory processes and procedures by taking advantage of e.g. Machine Learning, Cloud System, IT technology platforms and Artificial Intelligence. It is therefore of utmost importance to update how the ERP framework functions to ensure it is fit for the future, supporting the delivery of those innovative treatments to patients. As always in treatment development, ensuring patient safety is of paramount importance and the robust existing legal framework for pharmacovigilance will play a key role in implementation of the ERP framework.

The future expedited regulatory pathway system should:

- Embed PRIME in legislation (as proposed by the Commission's Pharmaceutical Strategy for Europe) ensuring there are resources from the EU regulatory network with permanent EMA staff to support PRIME.
- Expand the scope of PRIME/ERP eligibility and allow earlier PRIME access with procedural improvements:
  - PRIME's value is to go beyond scientific dialogue to facilitate fast-paced evidence generation.
  - PRIME should promote a smooth integration with other EU expedited pathways, such as interactive/iterative processes, accelerated assessment and conditional approval.
- Expand ERP to new indications and line extensions (NILEX):
  - Medicines are developed through a global continuum of evidence generation that requires expansion of existing global ERP tools to new indications and other post-approval variations, where applicable. The benefits of ERP may be needed in subsequent indications and this is recognised in other regions that have expanded use of ERP to NILEX.
- Enhance ERP with broad use of early multistakeholder discussions, iterative/agile scientific advice and thoughtful implementation of iterative data submission and assessment. A key aspect will be to support the joint advice with HTAs to ensure their readiness to accept the iterative data generation.
- Include reviewed eligibility criteria and resourcing to ensure ERP toolbox can be combined as needed for optimal product support.
  - There is a need to improve consistency and predictability on the outcome of PRIME eligibility, while improving the EU network's knowledge sharing.
- More global alignment is desirable to achieve a harmonised global drug development across regions without delaying the final outcome.
- Increased procedural flexibility to retain a broader subset of AA products on the pathway could be achieved through leveraging iterative scientific dialogue and staged submission of data.
- Be supported and future-proofed with a sandbox environment offering a customised regulatory approach for cutting edge solutions that could not easily be regulated under the

current framework and connected to an approval mechanism, this may require an experimentation clause in the legislation.

Giving EMA accountability in assessment of drug-device combination products, increased role in coordination of assessment of companion diagnostics, and creating legal certainty

The intersection between devices and medicines is becoming ever more important for an optimised use of innovative medicines. The EU must be prepared for this as it is crucial to ensure that European patients can benefit from these innovative medicines in a timely manner. We must simplify, streamline and accelerate clearer decision-making for combination products (>25% of products in the current industry pipeline) and enable full potential of precision medicine and integrated healthcare solutions (e.g. AI-based tools). Efficient and multistakeholder co-development and approval pathways for medicinal products and companion diagnostics (CDx) are also key enablers for precision medicine. Clarifying broader EMA accountability for the assessment of drug-device combination products and the coordination of the assessment of companion diagnostics are needed to give the predictability and certainty in the EU that are currently missing.

The future streamlined assessment framework for combination products and CDx should:

- Create a new legal category for those combinations of medicines and medical devices that are regulated as medicinal products in the EU. This will put the EU on par with other regions (US, Canada, Japan, China) and recognise that such combinations generate unique regulatory and legal issues. The change can be anchored in legislation (upcoming revision of Directive 2001/83/EC), while maintaining flexibility to evolve with science. This solution would provide more leeway to adapt the definition to accommodate future technological advancements.
- Codify already existing EMA device tasks (defined in medical devices and *in vitro* diagnostics regulations, MDR and IVDR) in the pharmaceutical legislation, would add more clarity and an additional level of detail as relevant.

The new legal category will be a driver for an extended EMA remit to coordinate and arbitrate for combination products. These would remain regulated as medicinal products and this will not change the distinct regulatory pathways for medicines and medical devices in Europe. The new category should reflect the scope of the recent EMA quality guideline (June 2021) that has been vetted with Member States.

There is an opportunity to leverage the Commission proposal for the EMA to provide a coordinating role during future health crises. The proposal covers both medicinal products and medical devices.

In order to provide an integrated scientific advice pathway for combination products and CDx, the technical expertise of Notified Bodies (NB) may in some situations be required. NB's opaque timelines need to be reinforced and aligned with the ones from medicine regulators. While ensuring that the EMA Scientific Advice Working Party (SAWP) has access to device expertise (national competent authorities/expert panel), the legislation should also clarify that NB participation in EMA scientific advice and qualification procedures is permissible and does not constitute consulting.

Phasing out the paper patient information leaflets with electronic versions

Electronic product information (ePI) ensures that healthcare professionals (HCPs), pharmacists, patients and their carers always have access to the latest EU product information for medicinal products and comes with benefits that will not only increase patient safety but also facilitate mitigation of shortages.

To support electronic patient information, the future framework should:

- Continue the technical development of ePI and recognise these formats as the norm in legislation.
- Support the phasing-out of paper leaflets in a stepwise approach, including ensuring the legislative possibility for all EU products/procedure types.
- Consider further improvements to health literacy, beyond non-legislative measures, especially since the package leaflet is derived from the summary of product characteristics (SmPC) there are some artefacts that are difficult to be changed because of legislation.
- Remove any barriers in the legislation to transitioning off paper package leaflets.

Future benefits include:

- ePI would empower patients by granting them access to the most recent regulatory-approved product information, rather than relying on potentially out-of-date paper package leaflets. This is even more important during health emergencies when frequent updates of the product information are needed.
- In the coming decades, the number of people who cannot access information electronically is expected to decrease, and the number of digital advancements to increase, which will make paper by itself increasingly obsolete, as observed in other sectors. For this reason, it will be important to future-proof legislation by providing flexibility as stakeholders agree on a stepwise approach.
- ePI would facilitate the mitigation of product shortages and increase availability in small markets by enabling easier supply without the need for re-labelling, in particular for medicines with very small batch sizes, e.g. orphan medicines.
- Furthermore, for hospital products and vaccines, it can be assumed that availability of electronic format alone could be an appropriate solution. Pilots with that regard are already ongoing in some Member States. This is especially important in times of increased risk of medicinal product shortages as observed with the COVID-19 pandemic.
- In addition, this will support the Green Deal and the Commission agenda to minimise environmental impact of paper waste. However, these benefits would not be realised if ePI was to be complimentary to paper information package leaflets.

Definitions

Certain definitions and the scope of the legislation may need to be updated to reflect scientific and technological developments in the sector. At the same time, Europe must put in place a framework to accommodate tomorrow's innovation, with the regulatory flexibility to adapt as and when the technology does. Hard law measures, and specific definitions settled in law, are not always the most effective and meaningful due to their rigidity, increased bureaucracy and lack of adaptability. EFPIA's considerations on some of the definitions suggested in the consultation survey can be found in Annex 1.

Lessons learnt from the COVID-19 pandemic for the future regulatory system

EFPIA's and Vaccines Europe's research has confirmed that regulatory flexibilities provided during the pandemic have been of critical value to provide accelerated rapid innovation and a number of these flexibilities will be of importance to maintain in the post-pandemic era. These flexibilities should not be read as lowering the standards, but more to streamlining the procedures and removing red tape to make the system more agile to operate in. They can serve two of the objectives outlined for the review of the current legislation: (1) removing unnecessary often historically grown administrative challenges in the system to free resources for innovation, and (2) improving EU's competitiveness in access to innovation by facilitating development, approval and supply.

Actions undertaken during COVID-19 that were particularly valued include flexible and frequent Scientific Advice meetings, rapid agreement of PIP (and joint procedural advice between the EU and US), highly rated rolling reviews, facilitated arrangement of quality variations, opportunities to use alternative trial and laboratory sites, opportunity for remote inspections, derogation from various individual national genetically modified organisms (GMO) requirements as well as flexibilities for labelling and packaging, importation testing and extended good manufacturing practice (GMP) certification assuring efficient supply.

Tackling the GMO requirements was highlighted in the EU's Pharmaceutical Strategy. A permanent science-based scheme for derogation from GMO requirements is urgently needed[7] if we are to attract investments in the field of ATMPs and vaccines to Europe and improve patient access to these key breakthroughs via clinical trials.[8] The pandemic has also demonstrated that developing new medicinal products requires significant investment by all involved while not all products will finally be successfully entering the market. The learning includes the observation that further improving competitiveness of the EU regulatory system will require also investment into regulatory agencies resources both on EMA and national level.

Use of medicinal products outside of the EU regulatory framework

The EU regulatory system for innovative medicinal products has taken decades to develop. The framework is recognised as a global benchmark for ensuring European public health and patient safety while at the same time encouraging world class innovation. The European regulatory framework therefore dictates that no medicinal products are allowed on the European market without prior marketing authorisation. Some exceptions to the aforementioned rule were created for use under certain conditions. For example, when a healthcare professional decides that his/her patient for medical reasons cannot be treated with an authorised medicinal product, a pharmacist is allowed to prepare an unauthorised pharmacy preparation (complementary pharmacy preparation) based on a prescription. Other examples are the off-label use of medicinal products, where an HCP assesses whether the benefits exceed the risks of off-label use of medicinal products for a specific patient before he/she prescribes an unauthorised medical product; and the hospital exemption for ATMP.

Instances of these exceptions being used for economic rather than medical reasons are increasingly being observed. Such use is clearly inconsistent with the objectives of the EU regulatory framework: to protect public health by assessing medicines to rigorous scientific standards, to ensure efficacy and safety of medicines across Europe, and to promote research and innovation in medicines development. Given the budget pressures on European healthcare systems, there is a risk that the use of these exceptions – off-label use of medicinal products, pharmacy preparations and the ATMP hospital exemption – for economic reasons could grow over the coming years. If this was to occur, it would become common for medicines to be used without regulatory approval, thereby circumventing the regulatory system that has served patients over the last five decades. This could compromise patient safety, given that patients might be treated with ineffective medicines with greater risk of side effects, and negatively impact public health.

As the use of medicinal products outside of the EU regulatory framework can have implications on quality, safety and efficacy, patients could lose confidence in the regulatory system. The greater use of exceptions by European healthcare systems could lead to new requirements by procurers to ensure products' quality and efficacy, leading to duplicative national, regional or local processes, as we had prior to the development of the European regulatory system. This process of relaxation in the application of EU regulatory requirements could have consequences beyond the EU, thereby reversing the positive spill-over that the European regulatory system has delivered so far. We therefore

[7] https://www.liebertpub.com/doi/pdf/10.1089/hum.2021.058
[8] Trends-in-Clinical-Trials-2019-Final_Digital.pdf (alliancerm.org)

recommend clarifying that exemptions to the regulatory framework are subject to the fulfilment of the "special needs" requirement in line with Court of Justice of the European Union case law (C-185-10, Commission vs Poland) and conditions for exemption defined under article 5 (1) of the Directive.

Incentives and rewards for innovation to unlock tomorrow's cures

Pharmaceutical incentives and rewards are the foundation on which innovation is built: they encourage and protect innovation, driving research and development investments into areas of unmet medical need.

The existing framework provides companies researching and developing new medicines the certainty that if a product makes it through the authorisation and pricing and reimbursement process, it will be protected from unfair competition for a certain period of time. This incentivises companies to invest in the long, complex, risky and costly process of delivering new medicines to patients, healthcare systems and society. As such, the incentive framework underpins the sustainability of the pharmaceutical innovation system, funding the next wave of research and development, and turning ideas into assets that address patients' unmet medical needs. Existing incentives therefore should not be reduced, as they have proven to be effective.

The stated goal of the Pharmaceutical Strategy for Europe is to ensure available, accessible and affordable, medicines for all, while supporting the competitiveness, innovation and sustainability of the EU's pharmaceutical industry. The Strategy recognises that investment in research and development for innovative medicines and treatments is essential for making progress in preventing and treating diseases.

Some of the changes to the current incentives system outlined in the public consultation would not help improve access to innovation for unmet health needs; they however risk undermining the innovation ecosystem that patients, healthcare systems and society are relying on. EFPIA is committed to work with all relevant stakeholders and EU institutions to find solutions for concerns raised about the appropriateness of the current incentives framework to attain the societal goal of reducing unmet medical needs, while ensuring value-for-money and long-term sustainability for health systems. Such solutions must be based on a holistic approach putting in place a set of interdependent scientific, regulatory and economic solutions to address the hurdles for innovation to flourish.

An effective incentive ecosystem is required to ensure pharmaceutical innovation and competition

The patent system is fundamental to support research in new medicines, by providing a limited period of exclusivity to inventors to commercialise their inventions and thereby encouraging private entities to invest into risky and lengthy research and development processes. The patent system at the same times makes important discoveries public, so that they can be used by anyone once the patent expires.

Over time, policymakers in the EU and elsewhere have finetuned this incentive regime to better align it with societal needs and the realities of pharmaceutical innovation, by compensating for part of patent life lost in the rigorous development, testing and approval process (supplementary protection certificates, SPCs), by protecting innovators' development data against unfair commercial use (regulatory data protection, RDP), and finally by encouraging research in areas of high unmet medical needs (e.g. medicines for children and rare diseases).

Supplementary Protection Certificates (SPCs)

Unlike in most other industries, around half of the standard 20-year patent term in the pharmaceutical product is spent on rigorous clinical trials to demonstrate the safety and efficacy of the medicine before it can be made available to patients. Recognising this disadvantage, the EU introduced

supplementary protection certificates to offset part of the lost patent term and ensure sufficient protection is available to continue encouraging sustainable and appropriate funding for the next wave of biopharmaceutical research and development.

Between 1996 and 2016, the time to develop new products has increased and the effective protection period has declined from an average of 15 to 13 years[9]. This is due to additional regulatory requirements and companies taking on more complex and risky research and development projects with longer expected development times. The SPC system has therefore never been more relevant.

EFPIA supports the Commission's continued efforts to reduce fragmentation of the EU SPC framework, as outlined in the Pharmaceutical Strategy and the IP Action Plan. Any further changes to this critical IP right, though, should be carefully assessed in terms of their impact on future innovation. In particular, the innovative industry remains doubtful if the SPC manufacturing waiver introduced by the European Commission in 2019 to boost the competitiveness of Europe's generics and biosimilar industry will manage to achieve its intended purpose.

Regulatory Data Protection (RDP)

In order to obtain a marketing authorisation, pharmaceutical companies need to submit extensive data relating to preclinical and clinical trials to demonstrate the quality, efficacy and safety of the medicine to be approved. RDP protects innovative companies' investment in generating this extensive body of data through a limited period of exclusivity on the data, starting from marketing authorisation. Such time limited protection is crucial to incentivise the significant investment necessary to demonstrate the safety and efficacy of new medicines, while nevertheless enabling other companies to eventually register their products on the basis of this data.

In some situations, patent (and SPC) may not provide an adequate protection for a new medicinal product, and RDP remains a vital and sometimes even the only effective incentive for R&D. For example:

- **Medicinal products having long(er) development times**: the development time of medicinal products is increasing over time. When this is significantly longer than the usual 12-15 years, remaining effective patent/SPC protection can become slim by the time a product reaches the EU market. The longer the development time, the higher the R&D costs, making the protection provided by the RDP even more important. In such cases, the RDP can make the difference between stopping or continuing a challenging programme and leading to a new medicinal product for European patients.
- **Insufficiency/inadequacy of patent protection**: as technology and science evolve and enable the development of new treatments, RDP can develop into a primary form of protection for more complex innovations that do not necessarily fit within the traditional patent model.
- **New indications**: there is an increasing interest in investigating new uses for existing medicinal products. However, while the science and the understanding of a disease and its biology may indicate that a given product that was licensed for a certain disease can be used in another, significant additional R&D – entailing further risk, complexity and costs – needs to be undertaken for the purposes of seeking regulatory approval for such new uses. In such cases, RDP may be the only available incentive to support these investments. Under EU law, where such R&D is undertaken by the original marketing authorisation holder (MAH) (or a company connected with it), one extra year of marketing protection may be available (provided it meets the criteria of significant clinical benefit). For an independent developer, a full period of RDP (8+2 years) may be available, albeit only protecting the new indication/form. RDP incentives in this area are limited, but are important in stimulating the repurposing of existing medicinal products.

[9] Copenhagen Economics, 2018

RDP is therefore an essential component of the incentives available to foster new developments and attract investment for pharmaceutical research projects. EFPIA believes that some of the proposed options outlined in the consultation survey relating to RDP and the Bolar exemption would undermine the strength, simplicity and predictability needed for a sustainable innovation ecosystem. The option of providing for different RDP protection periods depending on the "purpose of the medicine" disregards the reality of science, is unpredictable and risks negatively impacting innovation in Europe.

It is equally crucial to challenge the misconceptions regarding RDP and its effects on the launch of generic/biosimilars. Indeed, the RDP system also benefits generic and biosimilar manufacturers. It allows them to reference the innovators' safety and efficacy data in follow-on marketing authorisation applications (through an abbreviated procedure), rather than being required to fund their own costly and lengthy clinical studies. This was not possible prior to the introduction of RDP and abbreviated pathways, as generic manufacturers were required to generate their own regulatory data for the follow-on approval. It is therefore imperative to ensure that the RDP system in Europe remains strong, predictable, comprehensible and of sufficient duration.

The incentives review should not jeopardise Europe's innovation ecosystem

While we welcome the Commission's ambition to clarify a shared understanding of unmet medical needs across all stakeholders (see below the dedicated section), we caution against attempting to limit incentives only for treatments that fit a certain narrow definition of unmet needs. The concept of unmet medical needs has different meanings depending on different stakeholders' perspectives and decision-making level. Moreover, R&D aimed at addressing a certain disease area often leads to positive developments, and even breakthrough innovation, elsewhere; limiting incentives to certain defined categories therefore disregards the reality of science.

Where there is a lack of viable market (for instance, antimicrobials, see the dedicated section), novel incentives such as transferable exclusivity extensions (TEE) should be considered. As we have discussed already in the framework of the evaluation of medicines for rare and paediatric diseases, novel incentives could also be considered for some of these underserved areas. This requires a careful consideration of the underlying reasons of lack of investment in certain areas, or lack of productivity where investments occurred, but no treatments succeeded.

In addition, we disagree with the approach to link incentives for metrics on R&D costs or similar initiatives to link R&D costs at a product level to authorisation, pricing and reimbursement. Focusing on R&D costs is a misguided approach to addressing the underlying aims of the Pharmaceutical Strategy. At the product level such costing exercises are inevitably complex. There is no unified methodology for estimating product-level costs, and different methods will lead to very different answers to similar questions. Moreover, these exercises can potentially have unintended consequences that are counterproductive to their underlying aims.

For every medicine which is approved for use, there are approximately nine others which are tested in humans but found to be either unsafe or ineffective. These terminated projects are sometimes called "failures", but the knowledge spill-overs they create are in fact an essential part of the process of discovery of successful new products. Moreover, in some cases, medicines have "failed" at their original intended purpose but are later found to be valuable for treating other conditions, as exemplified by the repurposing of existing medicines to treat COVID-19. However, the size of the contributions of knowledge spill-overs to specific individual products is impossible to quantify. By the same token, therefore, how the costs of "failures" should be attributed between specific individual products in order to estimate product-specific R&D costs is inherently ambiguous, and any procedure to do it will inevitably be arbitrary.

Addressing unmet medical need for patients across Europe

An unmet medical need should be understood as a condition that is not adequately prevented, treated or diagnosed by authorised interventions. So far, there is no agreed common definition of the concept of unmet medical need.

Perspective matters, inclusivity is crucial

The definition varies in content and has different meanings depending on the context, stakeholders' perspective and level of decision making. A broad, holistic unmet medical need framework should recognise and tackle the many ways in which UMN manifest. A meaningful multistakeholder dialogue, including patient representatives, industry, clinicians, regulators, health technology assessment experts and payers, can allow to continuously refine and update existing assumptions on unmet medical needs.

EFPIA believes that meeting one of the first three criteria mentioned in the consultation should be considered as enough to define unmet medical needs. Requiring all three criteria to be jointly met has the potential to stifle innovation in an area with large consequences for individual patients and the healthcare system as a whole.

Patient perspectives should be considered in the notion of "major therapeutic advantage", defined as a clinically relevant advantage or a major contribution to patient care, for instance through improved efficacy, better safety profile or tolerability, ease of self-administration, and improved adherence. We would like to stress the importance to keep all these criteria while thinking about the concept of major therapeutic advantage over existing treatments.

Finally, we caution against using the fourth criterion – lack of access for patients across the EU to an authorised treatment – in the unmet medical needs' discussion. Access is a national issue typically relying on market dynamics, which are most of the time independent from the will of marketing authorisation holders.

Tackling the global challenge of antimicrobial resistance

According to the European Centre for Disease Prevention and Control (ECDC), the health burden of infections due to antimicrobial resistance (AMR) is comparable to that of influenza, tuberculosis and HIV/AIDS combined, and is estimated to cause 33,000 deaths in the EU yearly. Antimicrobial resistance also increases the cost of healthcare, being associated with 1.5 billion Euros lost in healthcare costs and productivity losses.[10]

Tackling antimicrobial resistance is a key priority in the Pharmaceutical Strategy for Europe, and the Horizon Europe research calls for 2021-2022 include a request to develop work that prepares for a European pull incentive for new antimicrobials. The newly-established Health Emergency Preparedness and Response Authority (HERA) was also designed to complement current EU efforts in addressing AMR. Although these initiatives represent important steps, further action is needed to address the market failure for antimicrobials, so as to drive sustained private research and development investments in this critical field. To achieve this objective, we call for the development of a new incentive at the EU level, in the form of a transferable exclusivity extension.

Transferable exclusivity extension to revitalise antimicrobial R&D

To revitalise antimicrobial R&D, it is essential to reward successful innovation at a level that is sufficient to attract the investment required, and incentivise companies to take on the substantial risks of antimicrobial R&D.

[10] https://www.efpia.eu/media/554822/strengthening-health-systems-through-smart-spending.pdf

The concept of TEE has been discussed in the expert literature for several years and proposed as a potential solution to address the current economic challenges constraining R&D in this field.[11] A research-based company successful in bringing an eligible priority antimicrobial to the market, would be entitled to receive a transferable right to extend the exclusivity period of another product. This TEE could be applied either by the same company that developed the new antimicrobial within its own portfolio or sold to another company.

There is also increasing expert literature estimating the size of the incentive required to boost the development of new antimicrobials. A global reward of 2.2-4.8 billion US Dollars would be needed to incentivise a developer to engage antimicrobial R&D despite the significant risks and costs and the very limited commercial returns for any potential new antimicrobial.[12]

Advantages of Transferable Exclusivity Extensions (TEE)

As a new incentive, a TEE in the EU would have several significant advantages.

- It is pro-stewardship and respects prudent use, leading to improved medical outcomes for patients by delinking financial reward from the volume of prescriptions, which underpins the standard R&D model.
- It can be implemented via EU-level legislation.
- It does not require upfront government funding and is not dependent on a Member State's economic or political situation.
- It would address the failure of the current incentive framework by offering a potential incentive at the scale required to drive greater R&D in new antimicrobials and that recognises their broader societal value.
- It would support pharmaceutical companies of all sizes, including small and medium sized companies (SMEs) as they would be rewarded as early as regulatory approval for a new antimicrobial. It would also increase the attractiveness of the antimicrobial field for private financing mechanisms, such as venture capital.
- It would be complementary with other EU and national initiatives, such as HERA and country-level health technology assessment and reimbursement reforms.
- Since so much of modern medicine is dependent upon the safety net of antimicrobials, the TEE appropriately pays for antimicrobial innovation through longer exclusivity periods on other medicines.
- It provides an opportunity for the EU to lead in the development of a new form of incentive that could be replicated in other regions.

Compatibility of TEE with other measures

It is important to set out how TEE would work with other EU policy initiatives, such as joint procurement and stockpiling via the newly-created HERA and other EU pandemic preparedness initiatives. As announced in September 2021, HERA will have widespread responsibilities (monitoring, R&D, manufacturing, stockpiling, joint procurement), but given the budget allocated (directly 6 billion Euros for all HERA activities during 2022-2027) and the extensive range of competencies, it is unlikely that it will be able to incentivise antimicrobial R&D at the scale required. Hence, HERA-related initiatives do not replace the need for a new pull incentive such as a TEE but could complement it, depending on its structure. Indeed, EU joint procurement could be used as a mechanism to contract with antimicrobial providers and thereby increase the sustainability of the provision of antimicrobials.

Finally, while the TEE would incentivise and reward a successful R&D process for novel antimicrobials, in order to ensure sustainable access after regulatory approval, additional measures are needed in

[11] Rome and Kesselheim, 2020
[12] Outterson, 2021

particular at country level. This would require HTA and reimbursement reforms to appropriately assess antimicrobials' value to ensure sustainable antimicrobial provision.

Competitive, efficient and sustainable off-patent markets

EFPIA firmly believes in supporting and encouraging competitive, efficient and sustainable off-patent markets for generics and biosimilars, as these medicines play an important role in the long-term sustainability of health systems and the promotion of a healthy innovation lifecycle.

Despite the robustness of EU-level rules, market and patient access remains a national competence and we see a high divergence in P&R approaches at Member State level, leading to a heterogeneous market access environment with wide variations in terms of access to medicines for patients. More can be done to strengthen and improve national rules and procedures to increase access to medicines.

Sustainable market for off-patent biologics

Strong and clear incentives must be in place for continuous and sustained investment in innovative biologics as well as in off-patent biologics and biosimilars, both from a R&D perspective as well as with regards to manufacturing. It is important to keep in mind that biosimilars are developed following new and existing biological medicines, therefore increased availability and patient choice is contingent on supporting the development of novel biologics.

Health care sustainability should be viewed from a holistic perspective recognising the long-term societal benefits and cost savings that sustainable competition and access to medicines provides to European health systems. As such, pricing and reimbursement policies for all biologic products, including biosimilars, should be tailored to and reflect the unique characteristics of these medicines, including the substantial resources, risk and technical capacity required for developing and manufacturing a large molecule biologic medicine.

At the same time, procurement practices play an important role in ensure broad access and sustainable and competitive market, but they should:

- Be performed solely at a molecule level.
- Include the possibility of a wide variety of products from multiple suppliers (as opposed to a "winner takes all" tender).
- Ensure an effective supply term that ranges between a minimum of 12 months and a maximum of 24 months.
- Include an option for physicians to opt-out individual patients based on their medical needs at the physician's discretion.

In addition, the COVID-19 pandemic has generated renewed interest in cross-border joint procurement in the healthcare sector. Complex cross-border procedures come with increased challenges that can pose significant risks in terms of duplication and exacerbate some of the negative effects of poorly designed national procurement practices. As such, EFPIA believes that joint procurement should be limited to emergency situations that pose serious threats to health and that, beyond remaining a voluntary tool, it should be structured so as to avoid duplication and stockpiling at national level.

EFPIA considers that one of the core tenets of a competitive market for off-patent biologics is physician autonomy and patient choice. Physicians should have autonomy to prescribe what they consider to be the most appropriate medicine for their patients. As such, the substitution of a biologic medicine with another biologic medicine should not happen automatically; it may only take place in

cases where it is recommended by the physician; and consented to by the patient. As a general rule, patients undergoing treatment should only be switched between biologic medicines if the physician and the patient have both consented to the switch and the patient is closely monitored following the switch.

In light of the above, EFPIA considers that Member States should refrain from adopting policies with a potential to undermine sustainability of the market, such as:

- Treating off-patent biologics as "bio-generics" with measures aimed at generating savings or inducing uptake that may be in place for generic medicines not requiring an extensive R&D phase and being significantly less complex to produce compared to biosimilars.
- Adopting extreme discriminatory measures and/or preferential treatment (including within the pricing and reimbursement, procurement and clinical practice aspects) that impede competition and may limit physician autonomy and patient choice.
- Placing physicians and patients under unwarranted restrictions or limitations with regards to their freedom to choose the most suitable treatment for their needs.
- Using policies such as International Non-proprietary Name (INN) prescribing and/or pharmacy-level substitution that greatly complicate product traceability in cases of adverse drug reactions.

An EU-wide scientific recommendation on interchangeability for specific biosimilars

EFPIA believes that, should an EU-wide scientific recommendation on interchangeability for specific biosimilars be made, then the competent authority (we infer, in this case, that it would be the EMA) needs to base its decision following robust and appropriate scientific criteria based on evidence submitted by the manufacturer, to ensure safety and build confidence in biosimilar products for patients and prescribers.

Beyond this, several measures need to be strengthened at national level, such as appropriate pharmacovigilance systems, enhanced traceability systems for biologics (prescription practices by brand name vs INN are required), appropriate record keeping at pharmacy level (if pharmacy level substitution is enabled at national level) so as to ensure a high degree of trust and patient protection.

A broad Bolar exemption should not undermine the effectiveness of the IPR enforcement system

Any harmonisation to the Bolar exemption should not lead to a scope extension from a genuine research exemption to anything allowing for launch preparation, stockpiling or other disguised commercial activities. Specifically, EFPIA supports that the Bolar exemption covers:

- Activities directed to generating data with a view to obtain a marketing authorisation for any medicinal product – generic, biosimilar **or innovative medicines**. There is no legitimate reason to differentiate between generic/biosimilar and innovative medicines in the application of the Bolar exemption. This could be clarified and harmonised should the general pharmaceutical legislation be revised.
- **Manufacturing and supplying by third parties of (patented) active pharmaceutical ingredients (API)** for the exclusive purpose of seeking a marketing authorisation for any medicinal product. EFPIA believes it falls within the scope of "consequential practical requirements", already exempted in the current Directive. This interpretation should however be clarified via Commission guidelines or in the Directive, should the general pharmaceutical legislation be revised.

While we are supportive of the above interpretations, we are concerned with some proposals to extend the Bolar exemption to (national) "administrative actions", such as pricing and reimbursement listing, tenders, etc. Such a broad exemption could undermine the effectiveness of the IPR enforcement system.

Working together to address access, availability and affordability of medicines

As illustrated by the most recent data in the Patient W.A.I.T. Indicator Survey in 2020, the average time to reimbursement for innovative treatments across EU and European Economic Area (EEA) countries continues to be as long as 504 days, ranging from 120 days in Germany to over 883 days in Romania.[13] The industry shares concerns about this, and recognises that delays and the unavailability of medicines harm patients.

Over the past two years, EFPIA has documented the drivers behind unavailability of and delays to innovative medicines across EU markets. As shown in the CRA analysis, these reasons are multifactorial. These are rooted in the medicines access systems and processes in the Member States and the corresponding impact on commercial decision-making. These include a slow regulatory process, late initiation of market access assessment, duplicative evidence requirements, reimbursement delays, and local formulary decisions.[14] As these root causes are multifactorial, they can only be solved by different stakeholders working together. To consider different policy solutions and how these could work in practice and to jointly create proposals, EFPIA calls for a High-Level Multistakeholder Forum on Access to Innovation.

EFPIA intends to work together with the EU institutions, Member States and stakeholders to speed up access and create a system where pharmaceutical companies can file Pricing and Reimbursement applications in all EU Member States within 2 years of EU market authorisation. A number of proposals and initiatives would create the right environment for this to be successful, and are highlighted below.

Speed up the regulatory process, delivering safe and high-quality diagnostics, vaccines and treatments to patients as fast as possible

There is shared aspiration to reduce regulatory approval times in Europe and bring these in line with international best practice.[15] There are several areas for action within the existing legislative framework to address this: encourage the use of new types of clinical trials; admit greater use of data from real-world use; allow ongoing dialogue between the developer and the regulator about a treatment throughout development continuum (dynamic regulatory assessment); and simplify how medicines and other healthcare products are regulated, e.g. by closing the gap for genetically modified organisms and combination products compared to medicinal products and streamlining the biomarker validation process. The evaluation and the revision of the basic pharmaceutical legislation will provide further opportunities and should reinforce expertise-driven assessment and enable a more agile centralised authorisation framework by removal of unnecessary interfaces between the European Commission, the European Medicines Agency and Committees (Member States representatives); enhance the expedited pathways framework; expand the role of EMA in the assessment of drug-device/diagnostic combination products and replace the paper package information leaflets with electronic versions (see above the dedicated section for more granularity on EFPIA proposals).

Increased transparency of information regarding placing on the market of centrally approved products

EFPIA already contributes to transparency on unavailability and delay with its yearly published W.A.I.T. report, highlighting the delays to patient access across the EU, as well as the CRA report on the ten most common root causes of unavailability and access delays. There are a number of ways transparency could be increased. Horizon-scanning improves transparency regarding future products,

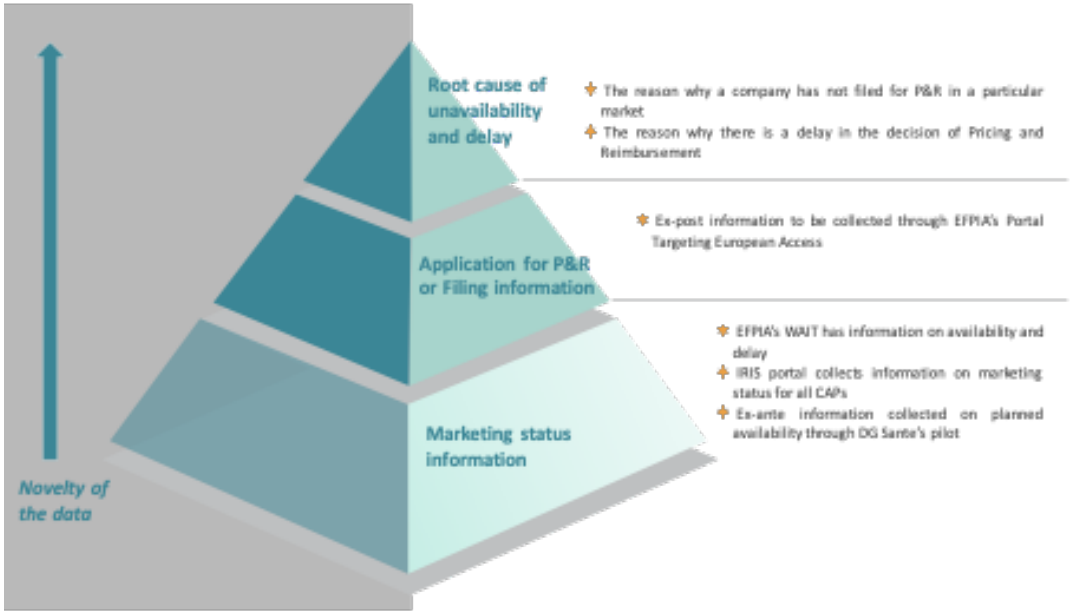
[13] https://www.efpia.eu/media/602652/efpia-patient-wait-indicator-final-250521.pdf
[14] https://www.efpia.eu/media/554527/root-causes-unavailability-delay-cra-final-300620.pdf
[15] Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions, Pharmaceutical Strategy for Europe, 2020

facilitating early dialogue and consideration of health system consequences. This already occurs in some Member States, but there is an opportunity for joint horizon scanning.

In order to further improve information regarding root causes of unavailability and delay, the industry is currently developing modalities to further monitor European access hurdles. This would include timely collection of the considerations underlying unavailability and the degree to which this reflects barriers within the environment, and commercial decisions arising in light of the Member States' pricing and reimbursement processes. **With the support of a third-party administrator, EFPIA is setting up a system for collecting information from marketing authorisation holders regarding the timing and processing of pricing and reimbursement applications of their centrally approved medicines on a voluntary basis**. This would include ex-post information regarding products with a marketing authorisation during a fixed window of time. The proposed mechanism would be designed to ensure minimal burden for companies (it would be based on published regulatory data, data submitted to EMA IRIS Portal and the existing W.A.I.T. database) and to be in compliance with EU competition law.

Aggregate data collected on timing of filing/no filing and root causes of individual products could be disclosed through a regular report that tracks progress in lowering the hurdles causing unavailability and delay. The proposal is currently being tested and discussed with interested stakeholders. The increased transparency of the barrier and delays to access will allow stakeholders to identify and address these in partnership.

Figure 1: Potential for more granular data on unavailability and delay



Facilitate a process that allows prices to align with value and long-term affordability

This includes encouraging the flexibility for **novel payment and pricing models**. The industry believes that when used appropriately and tailored to the situation, these schemes can accelerate patient access, allowing payers to manage clinical uncertainty, budget impact and sustainability of the healthcare system, whilst providing sufficient incentives for innovation.[16] Although there are examples

[16] https://efpia.eu/media/554543/novel-pricing-and-payment-models-new-solutions-to-improve-patient-access-300630.pdf
https://www.efpia.eu/media/602581/principles-on-the-transparency-of-evidencefrom-novel-pricing-and-payment-models.pdf

of novel pricing and payment models being used today, legal barriers, a lack of appropriate data infrastructure, and an unwillingness to adapt current systems often prevent their use.

Improve the efficiency and quality of value assessment

HTA bodies currently reach different conclusions on the medical impact (relative efficacy and/or relative effectiveness assessment) of new pharmaceuticals, even though the data studied is predominantly the same for all markets – such as safety and efficacy data from registration trials. This is because they adopt different approaches to rating and interpreting the data, often further segmenting the market to smaller more specialised patient groups. This might apply to trial design, relevant endpoints, appropriateness of defined patient subgroups and treatment comparators. A critical step towards harmonizing and streamlining evidence requirements and decision making at national level has been achieved with the political agreement reached on the EU HTA Regulation. While the Regulation establishes the framework, the implementing modalities will be instrumental towards ensuring that the future system improves and facilitates access and does not constitute an additional hurdle. For this purpose, national level adaptations will be required to ensure that the EU level outputs (submission dossier and joint clinical assessment report) can be integrated seamlessly in the full HTA process. EFPIA member companies remain committed to contributing to putting in place an efficient system of European assessments of relative efficacy at time of launch to achieve the objectives set out by the EU HTA Regulation.

Ensure access and solidarity across EU Member States through Equity-Based Tiered Pricing

New approaches that improve access need to be considered. Conceptually **Equity-Based Tiered Pricing**[17] could improve access, but it needs to be anchored in in the concept of solidarity –– including a recognition that wealthier EU Member States should not benefit from the lower prices that ought to be available, in the interests of patient access, to less resourceful countries. This cannot be solved on a country-by-country basis, but would likely require an intergovernmental framework articulating solidarity/affordability for different EU Member States and addressing specific issues related to the EU internal market and external reference pricing. Any discussion needs to consider the broader global context and spill-over effects to other regions. EFPIA is ready to engage in concrete discussions on how to implement such an approach.

The need for a dialogue on how to improve availability and reduce delays is clear. Although it is inevitable that availability will vary to some extent across European markets, patients in one part of Europe should not have to wait seven times longer for a new medicine than those in another part. Patients living with one condition in a country should not have to wait longer than patients living with the same condition in a different country. We need to work together to ensure that access to medicines is based on the patient's clinical need, not on their postcode.

Continuous supply of medicines to patients who need them

Ensuring continuous supply of medicines to patients who need them remains a top priority for EFPIA and its members. EFPIA members have established resilient supply structures and prevention programmes to deliver on that objective in the most efficient way. These systems have a long track-record of success and withstood a serious stress test during the first wave of the COVID19 crisis, demonstrating their ability to meet the soaring demand under particularly challenging conditions. Shortages are nevertheless still a concerning reality and should be prevented. They stem from numerous and intertwined root-causes, which are not always well documented. EFPIA notes that in a vast number of cases, shortages result from an unpredictable increase of demand. EFPIA welcomes

[17] Equity-based tiered pricing is the pricing of medicines based on a country's ability to pay with the objectives of improving patient access (defined broadly in terms of speed and availability) across Europe. Equity-based tiered pricing recommends using factors such as the gross national income in purchasing power parity or the human development index as the basis for determining relative prices for countries.

the use of the revision of the pharmaceutical legislation to address the current gaps, based on a thorough evidence-based analysis and guided by the principles of efficiency (resources to be commensurate of risk), sustainability and forward-looking. Finally, EFPIA recommends that if measures address both supply and demand sides, a particular attention should be paid on improving the visibility of demand for the revision to be effective.

The action put in place to prevent and mitigate shortages must be differentiated

As shortages result from a variety of root-causes, and apply in a variety of conditions for a variety of medicines, one-size-fits-all measures are unlikely to succeed.

The EC's structured dialogue process clearly demonstrated that shortage mitigation and management measures need to be adapted to the specifics of each particular situation, e.g. therapeutic area, category of product and presence of alternatives on the market, etc. EFPIA therefore calls for the future legislation to allow the flexibility that will ensure the different actors can take the necessary steps in order to ensure the availability of the respective medicines. In this regard, some measures put forward by a few stakeholders in the context of EU Structured Dialogue on Supply of Medicines such as mandatory dual sourcing of Active Pharmaceutical Ingredients (APIs) could fail to deliver on their objective, and at worse be counterproductive, for example for innovative and/or low volume products. Priority should be given to critical products, with high potential medical impact and with a potential risk of shortage.

Action should be coordinated at European level

Action will be most efficient and relevant if organised and coordinated at above-country level. Companies run global supply chains, and are more likely to ensure continuous supply to all EU countries if the action is coordinated at international level. The EU offers the right political and legal platform to build a European integrated system, based on Member States solidarity and coordination. This should be based on a continuous dialogue between competent EU and national competent authorities and manufacturers with a view to addressing any imbalances between demand and supply. Concrete actions taken by the European Commission and the European Medicines Agency in the early phase of the COVID-19 crisis led to clear improvement after the early weeks of the crisis, and demonstrated the relevance of a European coordinated action. Action taken on a national level can have a detrimental effect on the supply of medicines in other countries, e.g. mandatory national stockpiling requirement of finished products would be duplicative and suboptimal, preventing the reallocation of stocks where most needed by patients. This structural inefficiency can result in waste and shortages.

Europe needs state-of-the-art tools to ensure visibility on the supply chain

As the COVID-19 crisis vividly evidenced, the opacity of the supply chain downstream prevents manufacturers to allocate demand where patient needs are. This constitutes a major weakness of the system, which EU should address by building an integrated system allowing for the supply of medicines at the right place and in the right moment, connecting upstream supply with patient demand. This should be made possible through:

- **A harmonised definition of a shortage, to serve as a basis for a European reporting system based on a standardised format.** The information should be uploaded onto a common portal to ensure a streamlined and effective alert system as well as an alignment across the data provided from different sources and based on a consistent and workable definition of medicine shortages. A shortage of a medicinal product for human use occurs at country level when supply does not meet patient need at a national level for a period of time depending on the criticality of the medicine . Wholesalers' orders reflect the economic demand for medicines, which is based on a number of factors beyond local patient needs, such as precautionary orders (hoarding), demand for re-exportations (intra-community trade), or

simply fluctuations in the safety and working stock of an economic operator. Wholesalers' orders do not constitute a satisfying and workable proxy for the management of shortages of medicinal products, since some circumstances will disconnect them from the reality of medical and patient needs and introduce economic considerations that should be left to a normal customer-supplier relationship. Such a proxy will induce a bias that might lead to an overreporting of shortages, and thereby weaken the shortage management and mitigation system entirely.

- **Transparency and understanding of patient demand, through timely (current and forward looking) epidemiological data**. The European Centre for Disease Control (ECDC) should release modelling data, as well as patient need data and hospital capacity data in the Member States. Industry needs real data on patients in need and in addition, a collaboration mechanism for better coordination of allocation of medicines across Member States. Information is crucial for manufacturers to adequately forecast demand and make the necessary planning in terms of manufacturing capacity and detailed distribution arrangements to supply those medicines to the right regions at the right time.
- **More transparency of the supply chain.** Competent authorities could use the EMVS (European Medicines Verification System) data repositories set up in the context of the EU Falsified Medicines Directive to monitor, at aggregate level[18]. They could follow when and how various medicinal products/INNs are placed on which markets as well as the rate of their consumption at national level. The confidential use and analysis of these data would also allow them a better understanding of the root-causes of shortages, to develop adequate responses, as required by the specific situation observed, and to proactively mitigate risks of shortage in the future.

Measures implemented should favour the availability of medicines and the development of future treatments

As always when dealing with a complex environment with multiple factors interplaying one with another, policy measures can have undesirable side-effects. EFPIA is concerned, that some of the measures meant to prevent shortages are likely to have an impact on the availability of current and future medicines, and could eventually affect patients.

Measures requiring a disproportionate use of resources will typically have a deterrent economic effect on the marketing of products. This calls for policy measures that have demonstrated their ability to deliver on their objective (evidence-based), and applied meaningfully (risk-based approach).

The framework designed to prevent shortages should safeguard an environment where the research-based pharmaceutical industry can develop solutions to today's unmet needs, and ensure that Europe continues to be an attractive location for R&D investment and industrial development to respond to tomorrow's patients' needs. Implementing inefficient and suboptimal measures to prevent medicines shortages might inevitably divert resources away from other important expenses and investment. Even though some measures will be on the supply chain actors' responsibility, their cost will eventually be borne by the community (via social security schemes) and the individual patient (co-pay or delayed access), tapping into finite resources. It is therefore essential to design highly efficient measures to prevent shortages, i.e. they should optimise the level of resources required with the expected outcome (availability of medicines).

More detailed considerations on the options put forward in Question 11 of the consultation survey can be found in Annex 2.

[18] https://www.frontiersin.org/articles/10.3389/fmed.2021.579822/full

Quality and manufacturing

The EU is a leading manufacturing location for innovative, patented active ingredients and medicines. 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 can also provide solutions that will help to secure the supply of medicines for European patients and address vulnerabilities and challenges in the supply chain noted in the previous section. Manufacturing and supply should not be considered in isolation, but in relation to all aspects of the medicine's lifecycle, from discovery and design, drug development, commercial production processes to end-of-lifecycle management. Long-term resilience of supply chains will be strengthened through innovation throughout the product lifecycle from all business operators involved with the supply chain, and measures to enable them to share appropriate information on quality, safety and efficacy must respect obligations to maintain commercial confidentiality and avoid anti-competitive practices.

The principles and guidelines of GMP and other requirements in the EU pharmaceutical legislation are sufficient to ensure that a manufacturer must have production processes that ensure that medicines are of consistent high quality and suitable for their intended use, meeting the requirements of the marketing authorisation or clinical trial authorisation. EU requirements frequently inform the development of regulatory requirements in other countries and regions, and there are strong ties to the World Health Organisation (WHO) guidance. Harmonisation of quality requirements globally is important to facilitate supply chain resilience and can also support EU manufacturers to export medicines around the world. As a founding member, the EU has a strong voice in ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use), which is the leading forum for global harmonisation of quality requirements for medicines. It is very important that the EU continues to play a leading role in ICH and other similar fora to agree globally-aligned quality requirements and facilitate harmonised implementation. Increasing the reliance on oversight of supply chains by regulatory authorities in third countries with comparable GMP and Good Distribution Practices (GDP) standards, such as participating authorities of the Pharmaceutical Inspection Co-operation Scheme (PIC/S), will be a more efficient and effective way to leverage the resources and expertise of the inspectors from the European Medicines Regulatory Network and enable Member State surveillance of the supply chain to be focused in the areas of greatest risk to public health.

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 and GDPs where there are differences in interpretation and/or differences in legal requirements at Member State level. For example, further harmonisation of the requirements and expectations for qualified persons at EU level could be helpful to the smooth operation of supply chains across Member States. In addition, quality requirements for clinical studies can still differ significantly between EU Member States, impacting the development of new medicines, the attractiveness of the EU as a site for clinical studies, and early access to patients.

As noted above, the current regulatory framework assures the provision of high-quality medicines to European patients and patients in export markets. Nevertheless, there are opportunities to improve the framework to take advantage of scientific developments and experience with the application of the current legislation, and incorporate reliance approaches when similar requirements are enforced in third countries.

During the COVID-19 pandemic various flexibilities were introduced to facilitate ongoing operations and continued supply of medicines. It is important that the learnings from the pandemic (including but not limited to the flexibilities implemented by EU regulators) are implemented to enhance the agility, responsiveness and resilience of manufacturing and supply operations moving forward. EFPIA recommends that the innovations described in the EFPIA paper on COVID-19 chemistry, manufacturing and control (CMC) development, manufacture and supply form the basis of plans to address quality requirements for the future development of new medicinal products for unmet medical need.[19]

It is also important to take this opportunity to remove some potential barriers that could inhibit the adoption of new manufacturing technologies and harm Europe's competitiveness. Among the barriers that should be addressed are the following:

- Enabling the **provision of patient information electronically** (see above).
- A **manufacturing site authorisation applies only to the local premises** specified. This is a potential barrier to the use of mobile/modular manufacturing units that could increase the flexibility of manufacturing operations, enabling faster scale-up/scale-out (e.g. needed in pandemics), promote supply chain resilience, and reduce the environmental footprint of manufacturing operations. It could also be a barrier to the introduction of "point of care" manufacturing, increasingly relevant to new therapeutic modalities, such as advanced therapy medicinal products.
- **Full import testing** for medicines imported into the EU from third countries 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 only possibility to waive import testing is if a mutual recognition agreement (MRA) is in place. Reliance on regulatory oversight by regulatory authorities in third countries adhering to comparable GMP standards (e.g. PIC/S member authorities) can provide similar benefits to MRAs, and import testing should not be required when science- and risk-based approaches that leverage robust quality systems can mitigate risks and provide assurance on the quality of medicines imported from third countries.
- **OMCL (Official Medicines Control Laboratory) testing for vaccines and biologics** is similar to import testing in that it adds complexity to supply chains and may in some circumstances delay the availability. The current legislation includes flexibility for Member States to consider if it is necessary, but the reality is that OMCL testing is imposed for every single batch, apparently without consideration of the risks to patients or requirements described in other legislation such as Directive 201/63/EU.
- The Commission's Pharmaceutical Strategy includes the flagship initiative to revise the **Variations Regulation**. Revision is needed to fully implement ICH Q12 "Product Lifecycle Management" in Europe 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. This is an 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.
- Implementation of regulatory tools to facilitate **new platform technologies** such as platform technology master files across modalities.

While regulatory guidance may inadvertently create obstacles, a lack of regulatory guidance may also result in barriers due to uncertainty about the regulatory acceptability of new technologies and approaches, which may result in companies continuing with old approaches and failing to implement

[19] https://www.efpia.eu/media/554681/cmc-development-manufacture-and-supply-of-covid-19-therapies-and-vaccines.pdf

new technologies – especially digital technologies that are key enablers for modern manufacturing and quality approaches – that could deliver improvements in quality assurance and enhance the competitiveness of European manufacturing operations. 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 new product development and modern manufacturing. 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 (e.g. ISO, ASTM International, and other recognised international standards), 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 consider the latest developments in science and technology could also be possible.

Finally, measures to ensure manufacturing and distribution of high-quality products should also include improvements to the processes within the EU regulatory framework. Regulatory “sandboxes” should be created to enable enhanced dialogue between industry and regulators, facilitating learning and skills development to enable regulatory guidance to be easily adapted to take account of scientific and technological developments. Because the manufacture and supply of medicines is highly regulated, and introducing changes can be a protracted effort, it is also 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 (e.g. banning Titanium Dioxide E171 as an approved food colour).

Environmental impact

Since 2006, it has been a requirement to include an environmental risk assessment (ERA) in the regulatory dossier for the medicine. This is focused on the impact of the use of the medicinal product and does not explicitly include considerations of the environmental impact of the manufacturing process, but the scope is broader than environmental impact related to antimicrobial resistance. Nevertheless, the environmental impact (e.g. waste disposal, discharges) of manufacturing operations must comply with requirements defined in the environmental legislation of EU/EEA or third countries and EFPIA supports the enforcement of these requirements. Harmonised guidance is published as OECD Sustainable GMPs (SGMP). EFPIA member companies are supportive of a circular approach to their operations and products and aligned with the European Commission's Circular Economy Action Plan. The most effective ways to assure that our medicines are manufactured to high environmental standards are:

- Enhancing international cooperation and harmonisation efforts for environmental standards across global manufacturing and distribution chains, e.g. by implementing OECD SGMPs.
- Strengthening regulatory oversight of local manufacturing by third countries.
- Considering environmental topics holistically with manufacturing needs and patient requirements.
- EFPIA companies see environmental sustainability as a key element in the drive to accelerate delivery, improve efficiency and sustain the transformation of health innovation. Our industry encourages appropriate use of a risk-based approach to environmental challenges and undertakes initiatives to promote greater environmental responsibility worldwide.

To proactively engage in environmental considerations, the innovative, self-care and generics industries (EFPIA, AESGP, Medicines for Europe) have collaborated to develop and implement the Eco-Pharmaco Stewardship Initiative (EPS).[20] This initiative strives to ensure patient access to medicines, while addressing environmental aspects by strengthening the environmental risk assessment process and considering the entire medicines' life-cycle. Multiple actions under the EPS have led over the last couple of years to improving scientific understanding, finding new ways to detect the trace amounts of pharmaceuticals in the environment, comprehending their impact, prioritising active pharmaceutical ingredients posing a potential risk to the environment and also further reducing discharges from manufacturing plants.

Innovative risk-based frameworks such as our extended Environmental Risk Assessment (eERA) model and research initiatives like the Innovative Medicines Initiative (IMI) iPiE[21] and IMI PREMIER[22] recognise the importance of bringing different stakeholders together to address the ongoing concerns around PiE.

The environmental risk of human PiE is currently managed though the implementation of a prospective ERA which is produced prior to approval as part of the marketing application. The environmental risk of human pharmaceuticals is the result of multiple factors such as the intrinsic properties of the molecule, its environmental exposure, and emerging scientific information on environmental exposure and effects. It is therefore important to not only consider environmental risks at the point of application but throughout the life-cycle of an active pharmaceutical ingredient. Industry has been committed for many years to supporting the progress of the ERA guidance for pharmaceuticals to ensure a science- and evidence-based process which identifies and prioritises those molecules which pose the greatest risk.

[20] https://www.efpia.eu/media/636524/efpia-eps-brochure_care-for-people-our-environment.pdf
[21] https://i-pie.org/
[22] https://imi-premier.eu/

The outcomes of the IMI iPiE (Intelligence-led Assessment of Pharmaceuticals in the Environment) project (2015-2019) enabled consortia members, in collaboration with the European Commission, to develop a prioritisation framework to help identify those medicines that are most likely to present a risk for the environment. This multi-stakeholder project created a publicly accessible database on environmental information including more than 2,000 studies for hundreds of existing APIs and other science-based tools to identify the risks that medicines pose across Europe. ERAs were conducted for over 120 previously untested APIs, with full environmental datasets according to 2006 EMA guideline requirements using country specific consumption data under worst case exposure scenarios, that indicated potential risks were limited to less than 5% of medicines and a small number of mechanisms of action.

To further improve environmental data and also our capacity to prioritise, predict and assess potential environmental risk of yet untested medicines, we continue our research under the current IMI PREMIER project (Prioritisation and Risk Evaluation of Medicines In the Environment), which started in 2020. The aim is to improve models that can predict the environmental exposure and effects of APIs. The outputs may also be applied to screen new APIs to advance drug candidates for development that are less likely to be problematic from use and disposal, and in development to target environmental testing needs. PREMIER will also increase the transparency and accessibility of environmental data to all stakeholders through an intelligent digital assessment system. We believe this IMI project will provide scientific evidence to support several actions proposed by the EU Strategic Approach to PiE, such as facilitate the identification of potential environmental risks associated with APIs earlier in development or explore the feasibility of greener drug design.

While the aspiration of addressing environmental challenges (e.g. AMR) is important, self-regulatory approaches and continuous scientific dialogue with regulators allow for faster and more agile integration of technologies into practice, and are therefore preferable to legislative solutions.

The next cross-sectorial Innovative Health Initiative (IHI) also offers the opportunity to consider future projects to improve environmental impacts. EFPIA's additional considerations on the proposals in the consultation survey can be found in Annex 3.

Annex 1 – Definitions

Need for legal definition

Medicinal products used with a medical device, or a device part, so called drug-device combinations

As explained in one of the priority legislative proposals above, EFPIA would welcome an anchor reference to "medicinal products used with a medical device, or a device part" in the primary pharmaceutical legislation with a specification that the exact scope of, and device requirements for, this category of products will be defined in secondary EU legislation. Considerations include:

- According to its latest position, the EMA refers to combination products as "medicinal products used with a medical device", which it divides in three categories (integral, co-packaged, referenced), defined in its recent Quality Documentation guidance.
- Given the fragmented landscape described above, it is recommended to insert a definition of combination products in the Medicines Directive in order to define the related EMA role – regardless of whether this remains the same or is modified – in accordance with such definition and improve consistency and legal certainty for medicines developers.
- Which term is most adequate to define a new legal category of "combination products" will depend on the types of products such category will eventually cover. The term "combination product" seems indeed too broad to define a core legal category.
- To date, it appears that the term proposed by the EMA in its Quality Documentation guidance – "medicinal products used with a medical device" – might be appropriate because: (i) it emphasises the medicinal product aspect of the combination; and (ii) "used with" is sufficiently broad not to limit the use to drug-delivery devices, thereby leaving more room for other combinations including digital health technologies. In addition, the term is already used by the EMA.
- A new legal category for combination products, including definitions of the different types of products (to the extent necessary), would need to be inserted in the Medicines Directive as it would apply across the different regulatory pathways and procedures. However, the creation of such category (regardless of its exact scope) may not lead to the desired legal certainty unless it is combined with a clearly defined – corresponding – EMA role in the medicines legislation (most likely the Medicines Directive and the Medicines Regulation) as well.

NOTE: We do not believe that the insertion of a definition or category of combination products, such as "medicinal products used with a medical device", would require a modification of the MDR and/or IVDR as long as the definition of the overarching category and the relevant definition(s) of the different product types included therein are consistent with the terms of the MDR.

Condition

The term "condition" is foundational to four of the main procedures in current EU pharmaceutical law: marketing authorisations, orphan designation (ODD), PIPs and PIP waivers, and "repeat/multiple PIPs". Currently, there is no proper definition of "condition" in EU law (only in non-binding Commission guidelines) – and the concept of a "condition" has been interpreted in different directions particularly in OMP and paediatric discussions. The current vagueness has led to "unguarded" decision-making on PIPs and ODDs that does not meet the standard of scientific excellence. Furthermore, a proper, science-based discussion on obligations and rewards is not possible without a science-based definition of the concept of a "condition" (i.e., what the patient has).

EFPIA proposes a definition of condition that goes beyond the traditional approach that is largely based on classifying characteristic sets of signs and symptoms in certain organs, tissues and parts of the body (we call this the "**vertical element**" of the condition). The proposed definition of condition is based on science and recent CHMP practice, and would require the EU institutions (and medicine

developers) to **acknowledge**, in the definition of condition the "**horizontal element**" (i.e., the disorder or deviation that is the ***pivotal cause*** of the signs and symptoms). All elements and links must be **established by *scientific excellence***. The wording below is currently considered as the most concise expression of this.

> ***"Any deviation from the normal structure or function of the body, as manifested by [VERTICAL ELEMENT] a characteristic set of signs and symptoms (typically a recognised distinct disease or a syndrome), including [HORIZONTAL ELEMENT] the pivotal cause of such deviation, with each element and causal link having been established in accordance with the principle of scientific excellence."***

No need for legal definition

Advanced Therapy Medicinal Products (ATMPs) vs "Innovative Behind-the Counter"

The existing ATMP regulatory framework is fit for purpose to address evolving science and provides stability and flexibility, which are essential to facilitate innovation. ATMPs represent a wide variety of product modalities with complex mechanisms of action and have the potential to provide life-changing benefits to patients. Ensuring that substantially manipulated cell-based products and cell-based products intended for non-homologous use remain part of the established ATMP framework is key to make sure consistently high-quality products are administered to the patients. Any blurring of boundaries between ATMPs and "Innovative Behind-the-Counter" will result in increased risks for patient safety and public health and dampen future investment in Europe's cell therapy and ATMP sector.

Artificial Intelligence – need for definition BUT not in Medicines Directive/Regulation

The current AI legislative proposal is horizontal and covers all aspects, from facial recognition to application in clinical trials. Any definitions applicable to the healthcare sector should be embedded in the European Health Data Space legislation.

Annex 2 – Comments on the options for question 11

Q.11.1 Maintain the current rules

While the strengths of the current legislation should be preserved, rules need to evolve and take into account the developments that occurred over the past 20 years. EFPIA supports a change of the legislation based on evidence, i.e. introducing modern tools that have demonstrated their efficacy, have the potential to embrace new manufacturing methods and allow the industry to stay globally competitive, e.g. risk-based management, e-leaflet.

Q.11.2 Earlier reporting of shortages and market withdrawals to national authorities in a common format

Earlier reporting is not desirable as it is not likely to improve the prevention of shortages; a common format is. Industry supports the notification of shortages to ensure authorities can take mitigation measures and prevent impact on patient. In order to identify the few shortages that can be anticipated very early on, the legislation could prescribe to notify confirmed anticipated shortages (not to be confused with risk of shortages) as early as possible, and competent authorities could encourage early dialogue between themselves and the manufacturer, as this is common practice in Germany. Supply shortages can result from many root-causes, often intertwined, that may not always be prevented in advance. EFPIA observes that a vast number of shortages occur at a very late stage of the supply chain, and cannot be reported within the two months obligation provided by the current legislation. Most supply disruption risks identified early on can be mitigated by the manufacturer, and will not result in an actual shortage of the finished product. Imposing an earlier notification would therefore not efficiently help preventing shortages.

EFPIA fully supports the use of a common format for reporting shortages in one platform of interconnected systems (to avoid duplication and errors). The core information should be available to all competent authorities (EMA, Member States' authorities), in order for them to take adequate measures. While Member States requirements on data may vary, it is important to ensure a core set of common features is identified in order to ensure interoperability of the system. The system must be easy to be updated on a continuous basis and as new information is made available, and compatible/interoperable with other existing databases (IRIS, EMVS, etc.).

Q.11.3 Companies to have shortage prevention plans

EFPIA fully supports the development of a fit-for-purpose shortage prevention plan (SPP) in a common format for a risk-based selection of medicines, i.e. history of supply issue and patient impact. They should be kept by the marketing authorisation holder and made available upon request by authorities during inspections, and kept confidential considering the sensitive information they include. Imposing such a requirement to medicines that are not at risk of shortage might prove too resource-intensive and be irrelevant (the level of effort should be commensurate with the level of risk). It is vital that this planned EU reform harmonises the existing patchwork of SPP requirements proliferating across the EU Member States to facilitate interoperable use of data.

Q.11.4 Companies to have safety stocks

It is important for companies to keep safety stocks, but they should not be prescribed or they would lose their benefit of flexibility. Safety stocks are a valuable shortage prevention tool, if applied flexibly on the basis of risks and needs. They are not to be confused with stockpiling:

- Safety stocks are dynamic, tailored to actual needs based on evidence and risks (patient demand, lead time). They are quickly adjusted as the environment evolves. It is a buffer able to absorb demand variability, and will be eventually used.

- Stockpiling is a fixed quantity not adapted to patient needs and/or changes of the environment. These stocks can generate waste, and require extensive resources to be maintained (storage), they tend to generate inefficiencies in the supply chain.

Companies typically and spontaneously constitute safety stocks, based on their assessment of risks, i.e. on the basis of market demand volatility and supply chain vulnerability. Depending on this assessment and the specific situations, stocks can be constituted at raw materials, intermediate or finished products level. It would be inefficient and, in some cases, disruptive to impose a single stock standard to all medicines or restrict it to the last stage of the supply chain (finished product); bulk products offer more agility.

EFPIA opposes mandatory, across-the-board stockpiling, as it is not an efficient tool to prevent shortages. It constitutes a typical example of obligation that could prove counterproductive as it may result in exacerbating some supply tensions. Stocks are costly, vulnerable to obsolescence, inflexible and not sustainable. Other shortage mitigation measures might be preferable. National/hospital stocks are particularly disruptive, may exacerbate shortages and should be avoided where possible.

The least detrimental way to set up stockpiling would be:

- Limited to a risk-based selection of products, i.e. assessed on the basis of the risk of supply disruption and patient impact.
- Commensurate to other risk prevention/mitigation initiatives and safety stock already available upstream in the supply chain (i.e: API, drug substance).
- At regional (European level) and in a semi-finished form, to allow quick reallocation anywhere where the patient needs are.
- In exceptional circumstances.
- For a limited period of time, agreed for each medicine.

Q.11.5 Monitoring of supply and demand at national level

EFPIA supports increased visibility on supply and demand through the relevant stakeholders. This is the cornerstone of an efficient supply/shortage mitigation system. Increased visibility on supply and distribution bottlenecks could be achieved inter alia through the use of EMVS data which are available and accessible to all National Competent Authorities; demand data should be monitored and analysed on the basis of up-to-date current and forward-looking epidemiological data provided by the ECDC (see above 'Europe needs state-of-the-art tools to ensure visibility on the supply chain').

Q.11.6 Introduce a shortage monitoring system at EU level

EFPIA supports a coordinated monitoring system of shortages at EU level, based on a common and workable definition of shortages and core set of data. All competent authorities should have access to this information.

Q.11.7 Require companies to diversify their supply chains, in particular the number of key suppliers of medicines and components

Diversification is only possible/desirable for some products. Mandating diversification for all products without distinction of their status and environment is likely to affect availability. EFPIA warns against the across-the-board obligation to diversify suppliers of raw materials, as it could play against the availability of certain medicines. Whereas dual sourcing is an option and a reality already today for many medicines with high volumes and with established technologies, it might not be a feasible for some medicines, including, but not limited to, innovative low-volume medicines or vaccines where the technology either does not exist in a second manufacturing facility, pose further quality issues, or may be very costly to maintain, or complex and difficult from a regulatory point of view to build and sustain over time leading to output inconsistencies and hence an increased risk of shortage.

Mandatory diversification of suppliers might constitute a serious obstacle or at best considerably extend the timeline for the launch of innovative products, which production is generally scaled up from a very small basis started during clinical development. Industry calls for EU to remain aligned with global standards in terms of quality and registration requirements, otherwise EU runs the risk of getting access to new products significantly later than other world regions.

Effective Business Continuity Plans on products at risk of supply disruption could be an effective alternative where supplier diversification is not suitable.

Q.11.8 Companies to provide more information to regulators on their supply chain

EFPIA supports greater visibility of supply chains for the competent authorities, with the use of EMVS data. For risk-based selected products, SPP might also be helpful in preventing some supply disruption (see Q.11.3).

Considerations:

- It is key to apply these requirements efficiently, limited to a scope of products defined on a risk-based approach, i.e. define categories of products for which this would actually bring value (resources to be commensurate of the risk).
- Authorities need to guarantee adequate safeguards to ensure the high confidentiality of data, e.g. capacity of production.

Q.11.9. Introduce penalties for non-compliance by companies with proposed new obligations

Sanctions can act as an incentive or a disincentive. If penalties are too high it may discourage MAHs to make their products available in the various markets, take part in tendering processes, etc. On the other hand, targeted sanctions or penalties can help alleviating supply shortages in specific conditions, including when applying for tendering processes.

The legislator should also bear in mind, the side-effects induced by penalties. The current national legislations already allow Member States to impose financial sanctions if supply responsibilities are not met. Where linked to the reporting of shortages, they for instance often lead to overreporting, compromising accuracy and undermining the overall efficiency and success of the regulation in meeting its objective.

Q.11.10 EU coordination to help identify areas where consolidation in the supply chain has reduced the number of suppliers

EFPIA recommends addressing this issue with a broader scope. Such an analysis should be coupled with an assessment of the instances, where such a consolidation has led to an increased risk of supply, and carry out a proper assessment of the root-causes of the phenomenon. Some tendering practices such as the “winner takes all” system may have contributed to the weakening of certain supply chains (EFPIA recommends to use the MEAT (Most Economically Advantageous Tender) criterion to ensure continuous supply). The repetitive, yearly focus on lowest possible price, led to consolidation and search for economic efficiencies overseas (industry relocation in third countries). A variety of medicines should be available for physicians and patients instead of a single medicine. Public procurement should foster this diversity of suppliers by ensuring the final award of contract is not limiting doctors/patients to one choice of treatment.

Annex 3 – Comments on the options for question 13

Q.13.1 Maintain the current rules

We believe it is important to maintain consistency within the assessment, application and rules around environmental risks of human medicines. However, changes to the ERA paradigm are no doubt required in some areas in order for the latest science to be incorporated into regulations. It is important to emphasise the rules related to patient access and environmental risk (i.e. environmental risk not being part of the benefit risk assessment) should remain. It has been demonstrated in several studies[23] that the vast majority of pharmaceuticals present low to insignificant risk to the environment through patient use, and therefore any measurable impact is restricted to a small number of cases. In the rare instances where an environmental risk exists this should be managed appropriately in conjunction with industry, but not in such a way as to restrict patients access to beneficial medicines. Consistency in the current rules allows better comparisons of current and future medicinal products and also allows the focus to be on those pharmaceuticals which have been demonstrated to present the highest risks in the environment.

Q.13.2 Strengthen the environmental risk assessment during authorisation of a medicine, including risk mitigation measures, where appropriate

Most APIs pose low or insignificant risk and any strengthening of the ERA should primarily focus on risk refinements prior to risk mitigation or labelling measures. Importantly, the options for post-approval commitments should remain. We have concerns that access to medicines bringing significant benefits to patients and society as a whole could be delayed, denied or restricted. It is therefore important to ensure that mitigation measures are only implemented where actually necessary to reduce impacts on the environment.

Current risk assessment approaches make a number of worst-case assumptions, such as the use of a maximum daily dose, 1% market penetration, no consideration of patient metabolism, of degradation during wastewater treatment, and of biological degradation in the environment. These conservative assumptions still lead to very few conclusions of risks despite clear overestimation of true environmental risk. Whilst it is possible to refine a number of the assumptions in the risk assessment, in practice these are not required for the majority of medicines and where they are, clearer guidance and more available refinements would help strengthen both the individual risk assessments and the wider environmental database on pharmaceuticals.

Q.13.3 Harmonise environmental risk assessment by national regulators, including risk mitigation measures

We feel it is critically important to put in place harmonised procedures and guidance for not only preparation of ERAs, but also the review and subsequent decision making. This increases the applicants' ability to promptly provide the required data and assessments with confidence and rely less on post-approval commitments. Furthermore, harmonisation is considered crucial to avoid conflicting conclusions and decisions to those products submitted through national procedures both from an industry, national authority and prescriber/patient perspective.

Q.13.4 Increase information to the health care professionals and the general public about the assessment of environmental risks of medicines

Increasing transparency of data to stakeholders sensitive to environmental issues is important and will reassure the wider community that most APIs pose a low or insignificant risk to the environment. It will also help mitigate and manage any ongoing environmental risks or uncertainties. However, we are concerned that increasing the environmental information available to the general public and

[23] Gunnarsson et al., 2019; Roos et al., 2012.

health care professionals without the right context could result in unintended consequences (delayed, denied or restricted use) related to patients access to crucial medicines. Non-experts without ERA training may make inappropriate decisions that have patient and environmental consequences (e.g. increase the exposure and risk of other therapies). ERAs are not all like-for-like. The ERA is an iterative assessment, that is, one only refines the assessment enough to demonstrate insignificant risk (i.e. PEC/PNEC <1). Therefore, ERA may suggest a better environmental profile for a specific product simply because it has more refinements than another, irrespective of their true environmental impact. Furthermore, as discussed previously, conservative ERA assumptions mean that risk quotients are not necessarily reflective of what the true environmental risk might be from patient use.

We welcome the actions in the ad hoc Working Group on PiE of the Pharmaceutical Committee where Member States are working on the development of guidelines for healthcare professionals on prudent use and on stepping-up medical training. This activity is crucial to increase the understanding on ERAs and their interpretation.

Q.13.5 Use existing data about environmental risks for authorisations of a new medicine to avoid duplicating tests

A mechanism to permit and promote the transparency and use of data between companies is very important to increase trust in the regulatory process. Improved accessibility of data will further minimise conflicting ERAs through harmonisation of risk refinement approaches and by reducing duplicate testing. This is in particular needed to avoid unnecessary vertebrate testing, as is already implemented, e.g. under REACH.

Industry proposes the eERA approach[24], to help facilitate this through, prioritising ERAs on legacy APIs, helping to formalise post-approval commitments and ensuring environmental risk is appropriately addressed prior to loss of data exclusivity.

[24] https://www.efpia.eu/media/25278/pillar-3-extended-environmental-risk-assessment-eera.pdf