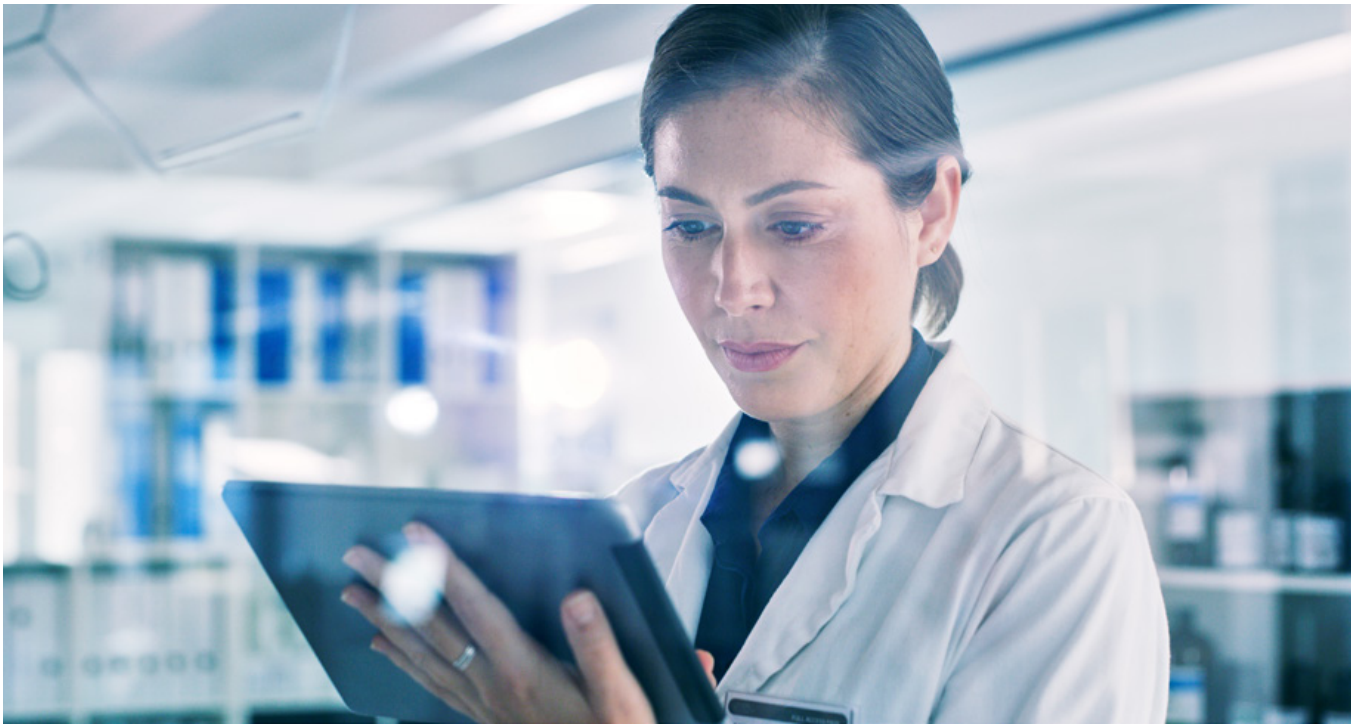
European Federation of Pharmaceutical Industries and Associations

Assessment of main provisions and key EFPIA recommendations on the revision of the pharmaceutical package

October 2023



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EXECUTIVE SUMMARY

- On 26 April 2023 the European Commission published the Pharmaceutical Package revising the existing legislation on pharmaceuticals, with the stated intention of enhancing the accessibility and affordability of medicines, including vaccines, while boosting scientific research and innovation in Europe for the benefit of patients.

- However, contrary to Commission's intentions, the likely net impact of the proposals in the Package would be to reduce access for European patients to cutting-edge science and innovative treatments. It will hamper research and development (R&D) of innovations important for patients, and heavily undermine the competitiveness of an industry that contributes more to the EU's trade balance than any other sector. In particular, the approach to improving access across Europe, through legislation meant to incentivise R&D and ensure safety and efficacy of medicines, will undermine the predictability of the EU intellectual property rights framework without tackling the actual barriers to access in EU Member States. These problems are set to be compounded by negative synergies with parts of the proposed Patent Package, significantly weakening the EU's incentive regime. Unless significant changes are made, the new legislation is very likely to further accelerate the loss of Europe's industrial base, R&D, investment, jobs and growth, to other regions of the world, undermining Europe's position in a strategic industrial sector that is essential for human health.

- While commending the European Commission's efforts to future-proof the regulatory framework and strengthen antimicrobial R&D and access in the proposals, EFPIA raises strong and serious concerns regarding some other proposed measures in the Package. Notably, the reduction of the current regulatory data protection (RDP) and Orphan Market Exclusivity (OME) baselines, the inclusion of unfeasible conditionalities linked to the recovery of any reduced incentives, the introduction of several disproportionate proposals concerning shortages management and environmental requirements will, taken together, undermine any regulatory improvements proposed.

- Over the coming months, we are committed to working with the European Commission, Members of the European Parliament (MEPs), Member States and other stakeholders to take the opportunity of the revision of this legal framework to close, rather than widen, the gap between the EU and other regions of the world as an attractive place for pharmaceutical research and innovation. The COVID-19 crisis clearly showed the importance of where R&D takes place, of whether drugs are discovered in Europe or elsewhere, and of whether we are a client or driving innovator. These issues matter for our jobs and growth, for our strategic resilience and, ultimately, for the health of our citizens. We must ensure that the revised pharmaceutical legislation meets the needs of patients, carers, healthcare and public health systems, Member States and Europe's life science sector for the next 10 to 20 years, while minimising impact on the environment.

This means:

- In line with the European Council Conclusions (March 2023), Europe needs to strengthen, rather than cut, the region's RDP baseline and OME.
- Providing meaningful and predictable incentives, attainable fairly, that would encourage additional R&D investment compared to today.
- Jointly addressing barriers and delays to access based on a shared understanding of the evidence generated by the European Access Hurdles Portal[1].
- Limiting Bolar exemption for activities related to seeking regulatory approval.
- Developing a patient-centred, more inclusive definition of unmet medical need. By acknowledging the value of innovation and encouraging advancements in prevention, treatments and care, Europe can ensure that no patient is left behind.
- A robust framework for mechanism of action Paediatric Investigation Plans (PIPs) is essential to ensure that this new obligation is effective to achieve its purpose and is manageable for developers.
- Further optimising the regulatory framework and ensuring maximum use of expedited pathways in support of patient needs.
- Ensuring that supply chain and environmental requirements are proportionate and fit-for-purpose while not prohibiting or delaying patient access to medicinal products.

[1] https://www.efpia.eu/media/677291/european-access-hurdles-portal-efpia-cra-report-200423-final.pdf

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DELIVER FASTER, MORE EQUITABLE ACCESS TO MEDICINES FOR PATIENTS ACROSS EUROPE

EFPIA supports the objectives of enhancing the availability and accessibility of medicines, while fostering an environment conducive to R&D in Europe. According to the most recent data in the Patient W.A.I.T. Indicator Survey in 2022, the average time to reimbursement for innovative treatments across EU and European Economic Area (EEA) countries has reached 517 days, ranging from 128 days in Germany to 1,351 days in Malta. The tenfold variation in speed of access across the EU is unacceptable and must be addressed via appropriate actions. The Pharmaceutical Package is, however, not an effective or appropriate channel to do so.

To that end, in April 2022, EFPIA and its members made a series of commitments independent of the legislative review, including to file pricing and reimbursement applications for new medicines in all EU countries no later than two years after EU marketing authorisation, provided that local systems allow it. The European Access Hurdles Portal (the Portal) was also launched in April 2022 to increase visibility regarding the root causes of unavailability of innovative medicines in Europe – a key issue affecting our overriding objective to speed up patient access.[2]

Modelling by IQVIA predicts that the commitment to file, if possible to implement, would increase the availability of medicines from 18% to 64% in several countries. This remains dependent on payer's resources for assessing the increased number of applications. Critically, the modelling also estimates that the commitment would reduce the time patients wait for new medicines by 4 to 5 months in several countries such as Bulgaria (-179 days), Poland (-129 days) and Romania (-155 days).

However, the time between getting marketing authorisation and companies filing for pricing and reimbursement in a country is just one part of the story.

Let's get medicines to patients

FASTER

Industry's commitment to file would increase the availability of medicines from 18% to 64% in several countries and reduce the time patients wait for new medicines by 4 to 5 months.

As the Commission has highlighted in the Pharmaceutical Strategy for Europe *"inequal access to innovative medicines can be due to various factors, such as national pricing and reimbursement policies, size of the population, the organisation of health systems and national administrative procedures resulting in smaller and less wealthy markets"*[3].

This is confirmed in the recent analysis conducted by Charles River Associates; there are 10 interrelated factors that cause barriers and delays in patients getting access to new medicines. These causes are rooted in Member States' access systems and processes and

[2] https://www.efpia.eu/media/677291/european-access-hurdles-portal-efpia-cra-report-200423-final.pdf

their corresponding impact on commercial decision-making. This is why the commitment to file is supported by the launch of an online portal where marketing authorisation holders (MAHs) can provide timely information regarding the timing and processing of pricing and reimbursement applications in the EU-27 countries. Bringing greater visibility to the barriers and delays to access will facilitate finding solutions in partnership.

EFPIA is also opening discussions on a more equitable system for EU Members States where the price of innovative medicines can vary between countries depending on their economic level and ability to pay, anchored in the principle of solidarity enshrined in the EU treaties. To deliver an equity-based, fairer system requires the Commission and Member States to amend external reference pricing systems and undertake mechanisms to prevent the unintended consequences of internal trade in medicines.

Let's make access to medicineS

FAIRER

Each country's ability to pay for innovative medicines is different.

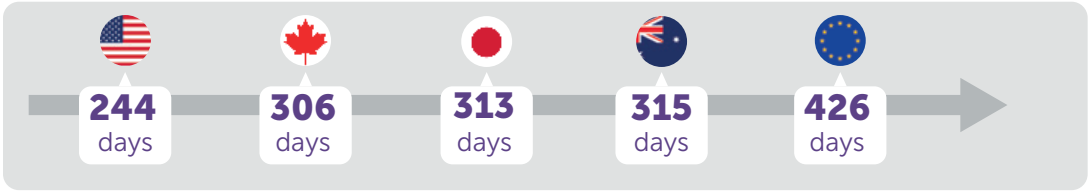
Industry has proposed exploring a model where less wealthy EU countries would pay less than wealthier countries for innovative medicines.

DEEP DIVE ON MAIN PROVISIONS AND KEY RECOMMENDATIONS

1. REGULATORY PROVISIONS

Pharmaceutical legislation is an important modulator of the pharmaceutical innovation system, and the EU pharmaceutical legislation has evolved in the past 20 years into a complex framework. EFPIA welcomes the efforts to enhance the efficiency and competitiveness of the EU regulatory framework. It is essential to accompany the proposed legislative provisions with increased resources and competencies for EU regulators across the regulatory network. Therefore, we acknowledge several provisions in the proposed legislation that will complement the implementation of EMA Fees Regulation (EC 297/95) currently under revision and will enable a more sufficiently resourced EU regulatory system. EFPIA is strongly supportive of this direction and considers that it will be essential that the EU regulatory system expands its capacities and capabilities by recruiting technical expertise in cutting edge fields and retaining experienced talent.

Europe is the slowest region to approve new medicines in comparison to the US, Japan, Canada and Australia.



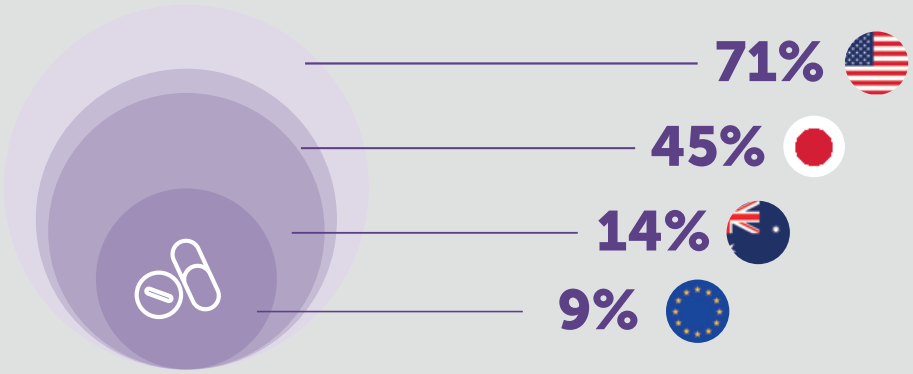
1.1 Elements that support innovation

STREAMLINING DECISION MAKING AND EXPERTISE-DRIVEN ASSESSMENTS

EFPIA welcomes the proposal to streamline the EMA governance and committee structure, focusing on the Committee for Human Medicinal Products (CHMP) and Pharmacovigilance Risk Assessment Committee (PRAC) as the key scientific committees supported by expert scientific advisory groups and increasing the involvement of patients, civil society and healthcare representatives. The reduction of the overall approval times for normal marketing authorisation application (MAA) from 210 to 180 days is strongly welcomed. It is also helpful that the time between the opinion of the CHMP and the final decision on the application for a marketing authorisation is stated in the recitals to be, in principle, no longer than 46 days. However, whereas the timelines for the steps in the decision-making process for the EMA and Commission are confirmed in the articles, the timeline for the Standing Committee step is not. Considering the need to make medicinal products swiftly available to patients following predictable timelines, we believe it should be clarified that the communication of the Standing Committee opinion will not exceed 10 calendar days [Reg Article 13 & Dir Article 42].

New therapies approved via expedited reviews in 2021

When compared to other regions of the world, in 2021 the EMA had an extremely low percentage of new active substances approved via expedited reviews.



ENHANCING PATIENT ACCESS THROUGH EXPEDITED REGULATORY PATHWAYS

Several EU regulatory tools can be described as Expedited Regulatory Pathways (ERP). These include PRIME, Conditional Marketing Authorisation (CMA) and Accelerated Assessment (AA). To date, their use has been limited to a small number of products, in contrast to numbers seen in other regions. Globally competitive, effective, and interlinked ERPs are needed to accelerate development and access to medicines needed by patients and to close the gap between Europe and other regions.

EFPIA welcomes many aspects of the proposed legislation including the inclusion of phased reviews [Reg Article 6(2)], codification of PRIME in law [Reg Article 60], Exceptional Circumstance marketing authorisations (MA) for new indications [Reg Article 18], CMA for new indications [Reg Article 19] and the new Temporary Emergency Marketing Authorisation (TEMA) [Reg Section 3].

To make the system truly future proof and ensure robust scientific assessment of safety, efficacy and quality, the following shortcomings should be addressed:

- **Phased reviews [Reg Article 6(2)]:** The text in the Regulation is considered over-prescriptive in parts, and amendments are needed to simplify it. This will ensure this important option for acceleration is not inadvertently limited in the future by detailed legislative text.
- **Accelerated Assessment (AA) [Reg Article 6(7)]:** To ensure the framework is competitive and future proof, the timeline should be explicitly defined as a 'maximum' of 120 days (instead of current 150 days) to encourage even shorter assessment timelines and to ensure the AA pathway remains valuable given that general timelines have also been shortened to 180 days (instead of current 210 days). AA should also be available for marketing authorisation extensions (such as introduction of a new formulation) that are grouped with a new indication.
- **PRIME [Reg Article 60]:** PRIME eligibility is overly complex, limiting its value as an innovation tool. The amendments introduced should clarify and broaden PRIME eligibility e.g. requiring fulfilment of one, rather than all, conditions listed in the article. It is unclear whether it is open to new indications and automatic eligibility to other tools such as AA is missing.

ENHANCING TEMPORARY EMERGENCY MARKETING AUTHORISATION

Furthermore, EFPIA welcomes the introduction of a Temporary Emergency Marketing Authorisation (TEMA) [Reg Article 30-37] as an additional option to provide rapid approvals in emergency situations.

EFPIA believes the following changes would improve clarity in the proposed legislation in line with the experience gained from the COVID-19 pandemic:

- Allow the use of TEMA also for approving new indications for products already marketed.
- Retain the intent of an "agile, fast and simplified process" as described in the Explanatory Memorandum of the Regulation and make it clear that TEMA might not follow the requirements of Annex II (e.g. eCTD structure).
- Introduce communication mechanisms between EMA and developers/MAH before drawing up the opinion.
- Set up a smooth administrative transition procedure from TEMA to CMA or full MA.
- Set up of a transition period at the EU level by EMA in cases where an application to transition to a conditional or a full marketing authorisation has been submitted following the TEMA, to allow uninterrupted supply across the EU.
- In this transition period, keep the option of also treating new patients to retain flexibility for each Member State to manage its specific epidemiological situation.

ENABLING PARALLEL INDICATIONS

Recital 51 in the Directive supports the focus on indications by stating

"the inclusion of new indications to an authorised medicinal product contributes to the access of patients to additional therapies and therefore should be incentivised".

In addition to regulatory support, incentives should be considered. Modern methods of medicines development can lead to efficient generation of evidence to support the use of a new medicine in multiple indications; however, neither the current nor the proposed legislation allows submission of data to support a new indication while the initial application is under review. This results in a bureaucratic delay in access for EU patients. The reform of the general pharmaceutical legislation is a unique opportunity and therefore EFPIA proposes to amend the proposed legislation [Dir Article 6] to enable submissions of new indications in parallel with the assessment of the initial MAA for the same product. Based on case examples shared by EFPIA members, this would potentially enable up to 10-12 months earlier authorisation and thus access for patients to these indications.

ENABLING PARALLEL SUBSTANTIAL MODIFICATIONS OF THE CLINICAL TRIAL APPLICATION BY DEROGATION OF THE CLINICAL TRIALS REGULATION 536/2014

Article 177 of the proposed Regulation allows necessary amendments to be introduced to Annexes of the Clinical Trials Regulation 536/2014 (CTR) without having to reopen the CTR itself for a full revision. The current prohibition of simultaneous or parallel

submission of multiple substantial modifications to the Clinical Trial Application makes it slower and more complex to conduct clinical trials in the EU. CTR Annex 2 should be amended to allow an application for authorisation of a substantial modification of a clinical trial when another substantial modification is already under review by the Member States concerned. Substantial modifications include submissions of protocol amendments as well as annual safety updates (Investigator Brochure - IB) and quality updates (IMPD) which are critical to the running of the trial and to ensuring safety of patients.

EXPANDING THE SCOPE OF REGULATORY SANDBOX

EFPIA welcomes the provisions for a regulatory sandbox [Reg Articles 113-115]. Equipping the pharmaceutical legislation with a regulatory sandbox mechanism will contribute to future proofing the system in anticipating and facilitating the uptake of innovation through experimentation. A regulatory sandbox will provide a transparent and tailored path for innovative solutions to emerge even in situations where unforeseeable gaps in the legislation exist today. A sandbox may allow such solutions to reach patients, which otherwise would not have been possible in its absence. The regulatory sandbox should work according to the following principles:

- Foster partnership & collaboration
- Apply a risk-based approach toward safeguards and customisation of regulatory frameworks
- Offer an end-to-end approach; from development (by facilitating agile development and evidence generation) to approval (by offering a tailored path to market)
- Provide transparency between the different stakeholders, for example on what, how and when the regulatory sandbox can be used
- Focus on achieving milestones or outcomes rather than procedures
- Take measures to capture knowledge acquired to inform legislation, regulations & guidance
- Create an adapted, agile and predictable regulatory framework for novel medicines and healthcare technologies as they arise

In the era of global competition, such an adaptive tool supports access for European patients to unprecedented medical innovation and contributes to attracting and retaining highly innovative businesses. In the absence of such a tool, innovative medicine developers may consider regulatory hurdles to be a hindrance to development of, or investment in, their complex product.

While the provision of a sandbox is welcome, limiting its use solely to pharmaceuticals is a missed opportunity. With the acceleration of scientific and technological advances, pharmaceutical products are increasingly integrated with other fields such as nanotechnology, biotechnology, medical device, in vitro diagnostics, data and artificial intelligence applications, which are transforming the way we innovate. It is therefore crucial to expand the scope of the regulatory sandbox beyond pharmaceuticals as its use may be required specifically at the interplay with different sectoral legislations (e.g. MDR EC 2017/745, IVDR EC 2017/746 and CTR 536/2014). This would ensure that these integrated solutions are adequately addressed and regulated. EFPIA supports amending the current provisions to allow this.

SUPPORTING MEDICAL DEVICES AND IN VITRO DIAGNOSTICS (IVDS) THAT COME IN CONJUNCTION WITH MEDICINES WITH OPTIMISED SCIENTIFIC ADVICE AND ASSESSMENT PATHWAY

The specific use of medical devices and in vitro diagnostics (IVD) in conjunction with medicinal products is expected to grow further and faster over the coming years as a means of enhancing patient treatment. EFPIA very much welcomes the aspects of the proposed legislation that address many of the current legal obstacles that delay European patients' access to these new therapies. The legal definitions introduced specifically define medicinal products used in combination with medical devices and, importantly, differentiate between integral combinations [where medicinal product and medical device form an integral product] and medicinal products in exclusive use with a medical device [presented in the market package or to be used with, specifically referenced in Summary of Product Characteristics].

The proposed legislation provides much needed clarity on EMA's remit in scientific advice on, and regulatory assessment of, such product types. However, there are some aspects that would benefit from further refinement and clarification.

Specifically, EFPIA believes the following changes are necessary to ensure that the scope of scientific advice extends to medicinal products that are used in conjunction with an IVD (including companion diagnostics) and to clarify the evidence requirements to support a Marketing Authorisation Application:

- **Scientific Advice [Reg Article 58] and Parallel Scientific Advice [Reg Article 59]:** The inclusion of device expertise in Expert Panels is welcome recognition of this specific expertise. However, articles still need to be fully inclusive of medicinal products used with IVDs/companion diagnostics. They also need to ensure that Notified Bodies can be included in scientific advice procedures as they are important stakeholders.
- **Integral combinations of medicinal products with medical devices [Dir Article 18]:** Changes are suggested to make clearer the evidence available from a Notified Body for integral products and to differentiate it from CE conformity assessments for medical devices.
- **Medicinal products in exclusive use with medical devices [Dir Article 19]:** Changes are suggested to make clearer the evidence available for CE conformity assessments for medical devices, and better differentiating it from integral products (see Article 18 above).

EXPANDING THE SCOPE OF MASTER FILES CONCEPT

The Commission's stated ambition is to maintain and enhance Europe's manufacturing capacity, and enable innovation, including digitalisation and greening of production processes. While some enhancements put forward in the proposed legislation are welcome (e.g. expanding use of master files and measures on decentralised manufacturing), these will not be sufficient to dramatically increase Europe's competitiveness as far as modern/advanced manufacturing is concerned. Currently, master files are only applicable in the EU for active chemical substances. Under Directive Article 26, this concept is extended to a more general Quality Master File, which could apply to any component of the finished product, including excipients, biological drug substances, adjuvants etc. While this extension of master files is a welcome enhancement, it still leaves out the key priority of a Platform Technology Master File (PTMF). Such master files (typically considered for manufacturing technologies) would be a significant enabler of innovative manufacture in Europe. Examples include manufacturing platforms for mRNA vaccines, oligonucleotide therapeutics, ATMP viral vectors or continuous tableting platforms.

KEY RECOMMENDATIONS

- Expedited Regulatory Pathway provisions on Priority Medicines Review (PRIME) and Accelerated Assessment (AA) require further clarifications. AA needs to be expanded to be available for marketing authorisation extensions that are grouped with a new indication.
- Temporary Emergency Use Application (TEMA) provisions need to be amended with experience gained during COVID-19 pandemic.
- There is a need to introduce a legal provision to enable submissions of new indications in parallel with the assessment of the initial MAA for the same product.
- An opportunity to introduce necessary changes to Clinical Trials Regulation 536/2014 should be utilised, to allow submission of parallel substantial modifications to the same Clinical Trials Application.
- The scope of the regulatory sandbox concept should be broad enough to address the needs of future (unknown) innovations beyond just a medicinal product.
- The new provision offering an integrated scientific advice support and assessment pathway for medical devices used in conjunction with medicinal products need to be expanded to also consider combinations of in vitro diagnostics used in conjunction with medicines.
- A further expansion of the master file concept to include platform technology master files would enable a world-leading regulatory framework for new pharmaceutical manufacturing technologies in Europe.

1.2 Better information to patients through electronic Product Information (ePI)

Electronic Product Information (ePI) provides significant advantages for patients, healthcare professionals, industry, regulators and the environment by offering accessible and up-to-date information on medicines. ePI strengthens supply chain agility and is a unique opportunity to mitigate and prevent shortages while contributing to environmental sustainability. The proposed legislative revision [Dir Article 63] acknowledges the importance of ePI, makes the future transition from paper product information to ePI possible, and increases the flexibility to make patient information more impactful. However, the proposed gradual implementation of ePI, driven by Member States' readiness, could be challenging to operationalise, particularly if the Member State by Member State implementation period extends over a lengthy period.

As such, EFPIA would suggest to:

- Start the transition from paper to electronic product information with products administered by healthcare professional (HCPs), including vaccines, with a short implementation window (immediately after the entry into force of the directive) in light of multiple positive pilot experiences already in place. This would, in the first instance, not include products intended to be delivered to the patient for self-administration. This measure would also cover an information gap that patients experience today as highlighted in the hospital pharmacist survey[4].
- Keep the "Member State by Member State" implementation phase as short as possible and consider pragmatic implementation needs such as in the case of multi-country packs.
- Find a digital-inclusive solution in each Member State to make paper package leaflets available to those who need them, as no patient should be left behind.

[3] https://www.eahp.eu/practice-and-policy/ehealth-and-mhealth/ePIsurvey

KEY RECOMMENDATIONS

* Implementation of ePI must take into account the practical, operational and patient aspects, e.g., allowing HCP administered products, including vaccines, to be transitioned first with a short implementation window due to multiple positive pilot experiences already in place. Pragmatic implementation needs should be considered, such as in the case of multi-country packs, and the development of a system in each Member State where a paper package leaflet is available for those who need them.

1.3 Optimising decision relevant data, avoiding double standards for evidence evaluation and ensuring a collaborative mechanism for involvement of medicine developers on label changes

USING FIT-FOR-PURPOSE REAL WORLD EVIDENCE IN REGULATORY DECISION MAKING

In Article 166 of the Regulation on personal health data, it is stated that the Agency may consider and decide upon additional evidence available, *independently from the data submitted by the marketing authorisation applicant or marketing authorisation holder.* On that basis, the *Summary of Product Characteristics (SmPC) shall be updated if the additional evidence has an impact on the benefit-risk balance* of a medicinal product by regulators and MAHs.

As part of the lifecycle management of a medicine, innovative companies update the SmPC and the patient information leaflet when new efficacy or safety evidence is generated or collected and are already obliged to keep their product labels up to date with the current scientific knowledge, in accordance with the current Directive 2001/83/EC. This includes evidence generated using real world data sources, and EFPIA supports the use of fit-for-purpose real world evidence in regulatory decision making.

However, data-driven evaluation of medicines is underpinned by the principle that assessments should be informed by the totality of evidence. All evidence streams, irrespective of origin, should be subject to the same consistent level of scrutiny with appropriate procedural safeguards that include participation of medicines developers, considering the MAH is and remains fully responsible for their product in use for all its authorised indications, regardless of the origin of the data supporting them. To ensure transparency of any such procedure, developers should be provided with all the additional evidence, including any relevant study documentation, upon which the regulatory decision is based. The revised legislative framework needs to continue to ensure that MAH retains responsibility and control for product labelling.

PROPOSING MAJOR REVISIONS TO REPURPOSING FRAMEWORK

Article 48 of the proposed Regulation lays out the proposed regulatory framework to support repurposing of already authorised medicines. According to this, the concerned MAHs would not have a role in the decision on the inclusion of a new indication in the summary of SmPC and patient information leaflet of their product, based on data generated by a third party.
In EFPIA's view, MAHs need to remain in a position to decide about the inclusion of a new indication in this circumstance. In doing so, MAHs will have to consider a multitude of factors, including their expertise in the therapeutic area, critical liability issues and pharmacovigilance responsibilities, as well as manufacturing and supply chain constraints for such label development. EFPIA is furthermore concerned that the imposition of labelling changes which have not been thoroughly reviewed and discussed with the MAH, will not serve the interests of patients. The expertise and capacity of the MAH as the developer, and having the deepest knowledge of the medicinal product, is essential to inform and support the development of the label and the prescribing and practical use of the product for HCPs and

patients. For these reasons, EFPIA strongly believes that any measures to stimulate repurposing need to closely involve relevant MAHs in the process. This can be achieved through a non-binding system for scientific assessment of evidence for repurposing and should be based on the lessons learned on the ongoing multi-stakeholder repurposing pilot project led by EMA with support of National Competent Authorities and other stakeholders (including patients and industry). In addition, safeguards should be built in to assure patients that the same level of evidentiary standards for decision making will be applied, independent of the nature of the application.

PRINCIPLES FOR FOLLOW-ON BIOLOGICALS

As for all types of medicinal products, EFPIA believes that all follow-ons to biologic medicines should be regulated based on sound scientific principles and established regulatory standards of safety, efficacy and quality. The European Commission has proposed a new category of "bio-hybrids" [Dir Article 12], which are biosimilars but with change in strength, pharmaceutical form, route of administration or therapeutic indication. If implemented, EFPIA considers that this additional category, beyond the well-established and understood definition of "biosimilar", would introduce unnecessary confusion for all stakeholders, and importantly, for patients and healthcare providers. EFPIA proposes that all follow-ons to biological medicines should be appropriately assessed following an enhanced Article 11 of the proposed Directive ('applications concerning biosimilar medicinal products'). Furthermore, to ensure robust scientific assessment, all of these products should be included in the Centralised Procedure by updating Annex 1 of the Regulation accordingly.

KEY RECOMMENDATIONS

- All evidence streams, irrespective of origin, should be subject to a consistent level of rigorous review with appropriate procedural safeguards for medicines developers to be involved in the decisions on their own label.
- Measures to stimulate repurposing need to closely involve relevant MAHs in the process and build on a non-binding system for scientific assessment of evidence for repurposing.
- We should ensure that sound scientific principles already in place to assess follow-ons to biologic medicines continue to be used and no unnecessary, complex new categories are created such as "bio-hybrids".

1.4 Enhancing innovative manufacturing in Europe and securing quality of medicines

To incentivise and facilitate the processes of technology update and to reduce unnecessary burden which does not add to quality of medicines or security of supply, it will be important to address the following shortcomings.

REQUIREMENTS FOR MARKETING AUTHORISATION APPLICATION (MAA) – ANNEX II

The structure and the level of detail of Annex II (current Directive Annex I) equates in practice to a "technology lock". The structure and requirements are unsuited to alignment with modern ICH guidance as the overarching aspect for the future of digital improvements, are omitted and are poorly designed to incorporate innovative manufacturing technologies. Furthermore, the current rigid structure limits the implementation of key guidelines developed to enable innovation such as ICH Q12 (Technical and regulatory considerations for pharmaceutical product lifecycle management) and will severely hinder the implementation of the revised ICH M4Q (Common technical document for the registration of pharmaceuticals for human use – quality) and any future redesign of the quality dossier to enable digital submissions or manufacturing controls. As such, EFPIA recommends that the Quality part of Annex II is comprehensively simplified and revised. The Commission has indicated that this will follow as a delegated act and ensuring appropriate content, flexibility and level of detail will be key.

PROVISION FOR ALIGNMENT OF PHYSICAL WITH FINANCIAL FLOW

Historically, many pharmaceutical companies have separated the physical and ownership (title) flow of their products for various business reasons aligning with respective financial regulations. A typical example of such a situation occurs when a medicine is manufactured within the EU but is owned by another affiliate of the same corporate group based outside the EU (e.g., in Switzerland, the UK, or the U.S.). The local distribution in each Member State is handled by a local affiliate of the company, which is duly authorised as wholesaler. Customers (independent distributors, hospitals or pharmacies) place orders for supplies with that local wholesale entity, which then arranges for the products to be physically brought to the customer from EU territory and invoices the products after having obtained ownership from the non-EU entity of the same corporate group.

New provisions under Article 166 of the Directive aim at addressing the concern that, when ownership of a medicinal product is held by an entity outside the EEA, it can be difficult to ensure the integrity of the supply chain and to identify who is responsible for the medicinal product in case of deficiency. We believe that this concern is unfounded. There is no loophole in supply chain liability, regardless of who holds the legal title of the products. EU and Member State laws applicable to wholesale distribution, together with respective Good Distribution Practice (GDP) requirements introduced with the Falsified Medicines Directive, provide for a closed EU supply chain with multiple, overlapping controls, which are pre-approved before a marketing authorisation for the product is granted. These apply at every stage of the supply chain up to and including the delivery of the product to the patient. When legal title to a product stored within the EU is temporarily held outside the EEA, all EU/EEA supply chain rules are applied in full including GDPs, in accordance with their purpose: (i) authorities pre-approve specific requirements for manufacturing and distribution of medicinal products; (ii) all batches are certified before release; (iii) stocks are shipped only between authorised actors within the EEA territory; (iv)

due diligence on suppliers is required and must cover their reputation and reliability, as well as any offers likely to be falsified, unusually large offers, or out-of-range prices; (v) specific verification to prevent entry of falsified products are put in place; (vi) all transactions are recorded, available for inspection and products can be fully traced; and (vii) finally, all parties in the EEA supply chain are under a legal obligation to cooperate with any recalls.

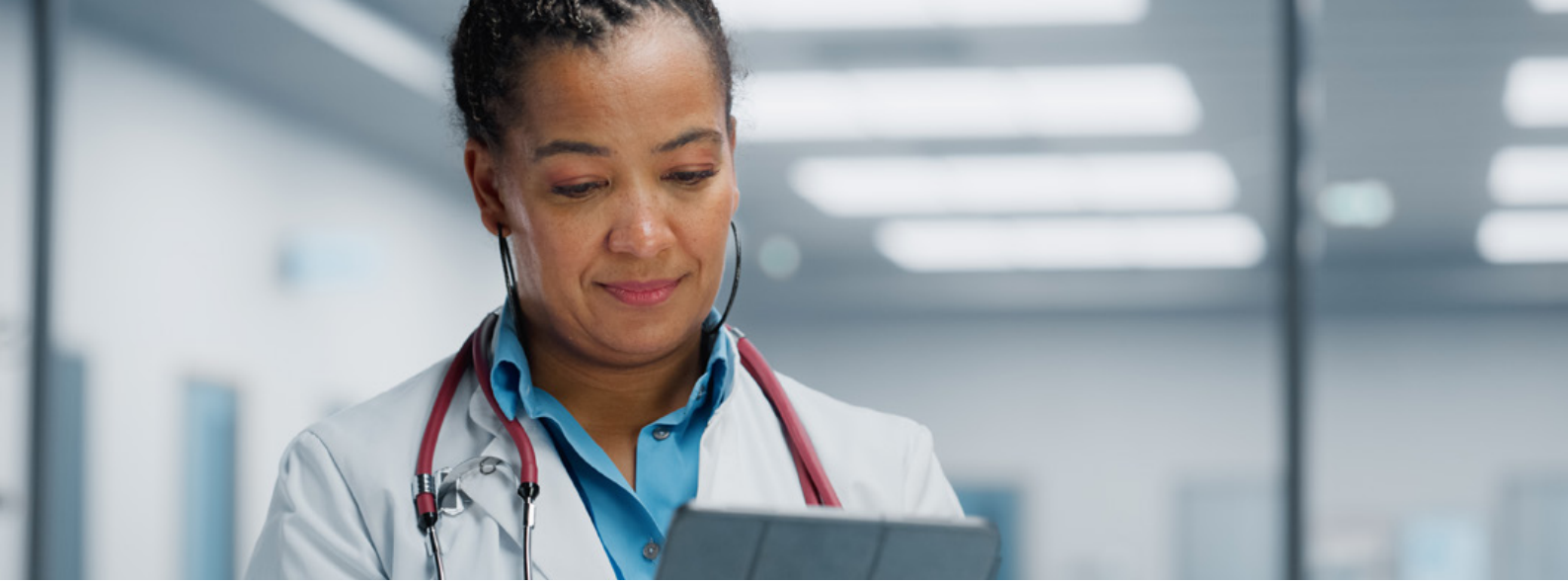
These measures ensure the quality and integrity of the products and the supply chain and enable the competent authorities to verify at all times where the products are. They are, therefore, able to enforce all the rules affecting the safety of the products and the integrity of the supply chain. None of the obligations to ensure the integrity of the products, the integrity of the EU/EEA supply chain and the safety of consumers are in any way related to the ownership of, or legal title to, the medicinal products. In addition, no actor in the EU supply chain would be able to deny responsibility or liability for compliance with EU supply chain rules by stating that ownership of the product is temporarily held by another legal entity within a corporate group. The same applies to patient claims under product liability nor GMP/GDP rules. Such claims are not dependent on the legal title either.

APPLYING CONCEPTS OF UNILATERAL RELIANCE WITH TRUSTED NON-EU AUTHORITIES FOR WAIVING OF IMPORT TESTING

The release testing of medicinal products imported from third countries remains mandated by the proposed legislation [Dir Article 153.1b]. This duplicates the release testing at manufacture, is not environmentally friendly, reduces shelf-life and essentially destroys valuable medicines which cannot reach patients. Such mandatory testing can already be waived where appropriate arrangements are made, such as through Mutual Recognition Agreements [MRA /AACA; Dir 153.2]. Waiving of duplicative release testing should be further expanded by applying the new concept of unilateral reliance for inspections by trusted non-EU authorities to waiving of release testing [Dir Articles 188.4a and 190.1d]. As such, waivers for release testing could be applied to supply from those 'countries on a list' according to the procedure in Dir Article 158.3.

KEY RECOMMENDATIONS

- Prevent a "technology lock" by introducing a proportionate structure and level of detail in Annex II (current Directive Annex I) that is compatible with relevant ICH Q12 and M4Q guidelines.
- Waive the provision for alignment of physical flow with financial flow for transactions within the same corporate group.
- Apply concepts of unilateral reliance with trusted non-EU authorities to enable possibilities for waiving duplicative release testing.



1.5 Supporting increased transparency, coordination and harmonisation of hospital exemptions

EFPIA welcomes the new rules in the proposed legislation [Dir Article 2] for introducing increased transparency, coordination, oversight, and harmonisation across Member States for advanced therapy medicinal products (ATMPs) prepared under hospital exemption. These rules and the proposed implementing acts to follow should ensure the use of hospital exemption stays true to its intended purpose: to allow the clinical use of ATMP without a marketing authorisation in exceptional circumstances for an individual patient with an urgent unmet medical need under certain conditions. To this end, EFPIA calls for clarification [Dir Art 2.1] on the interpretation of *'non-routine basis'* to ensure a hospital exemption approval is only granted when no authorised therapeutic alternative or clinical trial could satisfy the specific needs of the patient. Where possible, clinical trials should always be preferred to hospital exemption since the clinical trial review process offers a higher safety standard for patients, and where clinical trial findings can benefit other patients. Information collected about the uses of hospital exemption should be made publicly available and the data collection and reporting requirements [Dir Art 2.4-6] should ensure data related to product quality issues are collected and reported even if they do not result in any immediately obvious impact on safety and efficacy. Learnings from quality data on the manufacture of ATMPs under the hospital exemption setting would be useful for both regulators and developers and can only be analysed and understood if reported.

KEY RECOMMENDATIONS

* Clarify the interpretation of 'non-routine basis' to ensure a hospital exemption approval is only granted in cases when no authorised therapeutic alternative or clinical trial could satisfy the specific needs of the patient.

1.6 Welcoming a centralised procedure for assessment of investigational medicinal products (IMPs) that consist of genetically modified organisms (GMOs)

EFPIA welcomes the introduction of a streamlined and centralised procedure for environmental risk assessment and authorisation to use a medicinal product containing a GMO in a clinical trial [Reg Article 177 amending Clinical Trials Regulation (EU) No 536/2014]. The Commission's proposal represents an improvement to the current fragmented requirements across Member States' GMO competent authorities and is a positive step toward ensuring a more efficient and well-functioning clinical trials environment for these types of innovative products in the EU. An Environmental Risk Assessment (ERA) of the medicinal product (along with any other documents, such as Common Application Forms) will be submitted via the EU Clinical Trials Information System, and it is understood that no additional national requirements or submissions related to GMOs will be required. We call for this to be made explicitly clear in the delegated act [ref to Reg Article 177.1]. This delegated act should also ensure the ERA is sufficiently tailored to medicinal products despite the reference to Annex II of Directive 2001/18/EC; address how commercially confidential information will be protected; and incorporate a risk proportionate approach toward the content and procedure for harmonised assessment of the ERA for more well-characterised investigational medicinal products containing a GMO that do not survive in the environment, e.g., rAAV, CAR-cell products, and those products that have already been assessed as part of a previous clinical trial.

KEY RECOMMENDATIONS

* Use the delegated act to explicitly confirm that no additional national requirements or submissions related to GMO will be required and incorporate a risk proportionate approach toward the content and procedure for harmonised assessment of the environmental risk assessment.

1.7 Clarifying the interplay between the medicines legislative framework and Regulation for Substances of Human Origin (SoHO)

The interplay between the proposed Regulation [Article 201] and Directive for medicines and the proposed Regulation on Substances of Human Origin (SoHO) [Article 14] is an important aspect for ATMPs as it relates to classification of 'borderline products', import and export of SoHOs intended for manufacture of a medicinal product and applicability of SoHO requirements for investigational medicinal products. The increased coordination of decisions on regulatory status is a positive step to avoid potentially conflicting decisions across Member States. However, the process should ensure efficient communications between the SoHO Coordination Board and EMA and ensure confidentiality risks are mitigated.

As ATMPs are within the scope of the centralised procedure under EMA, a meaningful connection in the form of a cross-reference between the relevant parts of the Regulation [Article 61] and the Directive [Article 201] would ensure that Member States communicate with EMA on questions related to the regulatory status of these products. This is important because of the need to avoid the potential for disharmonised decision-making on products involving tissues and cells that could fall under the definition of an ATMP. It will be important to clarify the efficient operation of the proposed pharmaceutical legislation in relation to the SoHO Regulation [Article 42] for the import and export of SoHOs intended for manufacture of medicinal products to ensure additional redundant regulatory burden is avoided. There is currently a lack of clarity on the application of the proposed SoHO Regulation to investigational medicinal products as no reference is made in the proposed SoHO Regulation [Articles 2.3 and Recital 11] to medicinal products or ATMPs produced within scope of the Clinical Trials Regulation 536/2014. The proposed Medicines Regulation [Article 177] seeks to amend the Clinical Trials Regulation and could be used to clarify that the proposed SoHO Regulation only applies to activities not already covered by the Clinical Trials Regulation in respect to investigational medicinal products.

KEY RECOMMENDATIONS

* Ensure the proposed legislation of medicines is aligned seamlessly with the Clinical Trials Regulation and the Regulation for Substances of Human Origin.

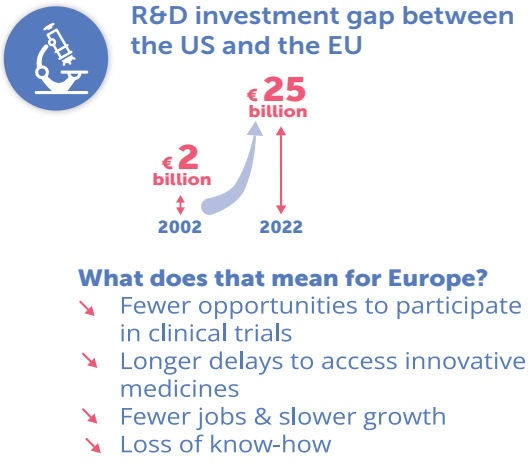
2. REGULATORY DATA PROTECTION PROVISIONS

2.1 Regulatory data protection baseline reduction and modulation

- EFPIA calls for a robust, reliable intellectual property (IP) framework to support the innovative biopharmaceutical industry in Europe. Companies submit a significant body of data related to pharmaceutical tests, pre-clinical tests, and clinical trials as part of the marketing authorisation process. Currently, this data is protected during a set period during which it cannot be relied upon by a follow-on applicant to obtain a marketing authorisation.

- The current EU legal framework aims to create a healthy and competitive market for medicines as the period of exclusivity allows the inventor to cover their investments, but also enables off-patent producers to enter the market quickly following the loss of market protection. Altering this equilibrium should be carefully evaluated. We note that the Regulatory Scrutiny Board has stated that the reduction of the regulatory protection periods could impact *"the sector capacity to finance future innovation and international competitiveness"* and there could be *"unintended consequences for the long-term capacity on innovation, pricing, access, and competitiveness".*

- Europe has for several decades been falling behind other regions both in terms of competitiveness of the system and R&D investments, as well as access to medicines. If the EU seeks to be at the forefront of biopharmaceutical innovation, attracting investments into the development of novel medicines and cutting-edge clinical trial participation for its patients, it must take this opportunity to strengthen – rather than undermine – this critical underlying framework via robust, achievable and predictable incentives that reward R&D investment and encourage



the pharmaceutical sector's growth. In parallel to the pharmaceutical legislation, the proposed reduction in RDP protection is compounded by proposed changes to the intellectual property framework for medicines in the Patent Package (including EU-wide compulsory licensing). Together, these measures offer negative synergies that represent a significant weakening of the EU's incentive regime.

THE COMMISSION PROPOSAL

In Art. 80-82 of the draft Directive the Commission proposes to reduce the current baseline for data exclusivity from eight to six years with various extension possibilities, depending on MAHs fulfilling certain conditions. These articles also provide for two additional years for releasing and continuously supplying the products in all 27 Member States within two years of marketing authorisation (three years for SMEs), half a year for meeting the definition of unmet medical need, and half a year for performing comparative clinical trials. Finally, there is a possibility for one additional year for one new therapeutic indication only. The current condition of authorisation of a new indication bringing significant clinical benefit and the two years of market protection following RDP, during which a product cannot be placed on the market, would remain the same.

EFPIA PERSPECTIVE

EFPIA has strong concerns regarding the Commission proposal, which undermines the predictability of the existing IP framework in the EU. This will not only fail to improve access to medicines for European patients, but rather harm the innovation pipeline which is not aligned with the intent of making Europe an attractive Innovation hub.

RDP baseline reduction

Europe has lost ground as a location for R&D investment to the US and China in the last 20 years. This trend has to be reversed and aligned with the European Council Conclusions of March 2023 according to which Europe should look to strengthen, not to weaken incentives for medical innovation. A reduction of the data exclusivity baseline from eight to six years would be a step in exactly the wrong direction, reducing the attractiveness of the EU as a locus for R&D investment.

RDP is a key, ex-ante consideration for all R&D investment, and the last-to-expire protection and key exclusivity driver for approximately 1/3 of innovative medicines – and is particularly important for advanced, complex therapeutics and therapeutic areas with a long or difficult development time. Where patent/SPC protection may not be reliable or last long enough due to extended development time, RDP is a guaranteed period of exclusivity on which businesses can reliably plan investment and mitigate associated risks.

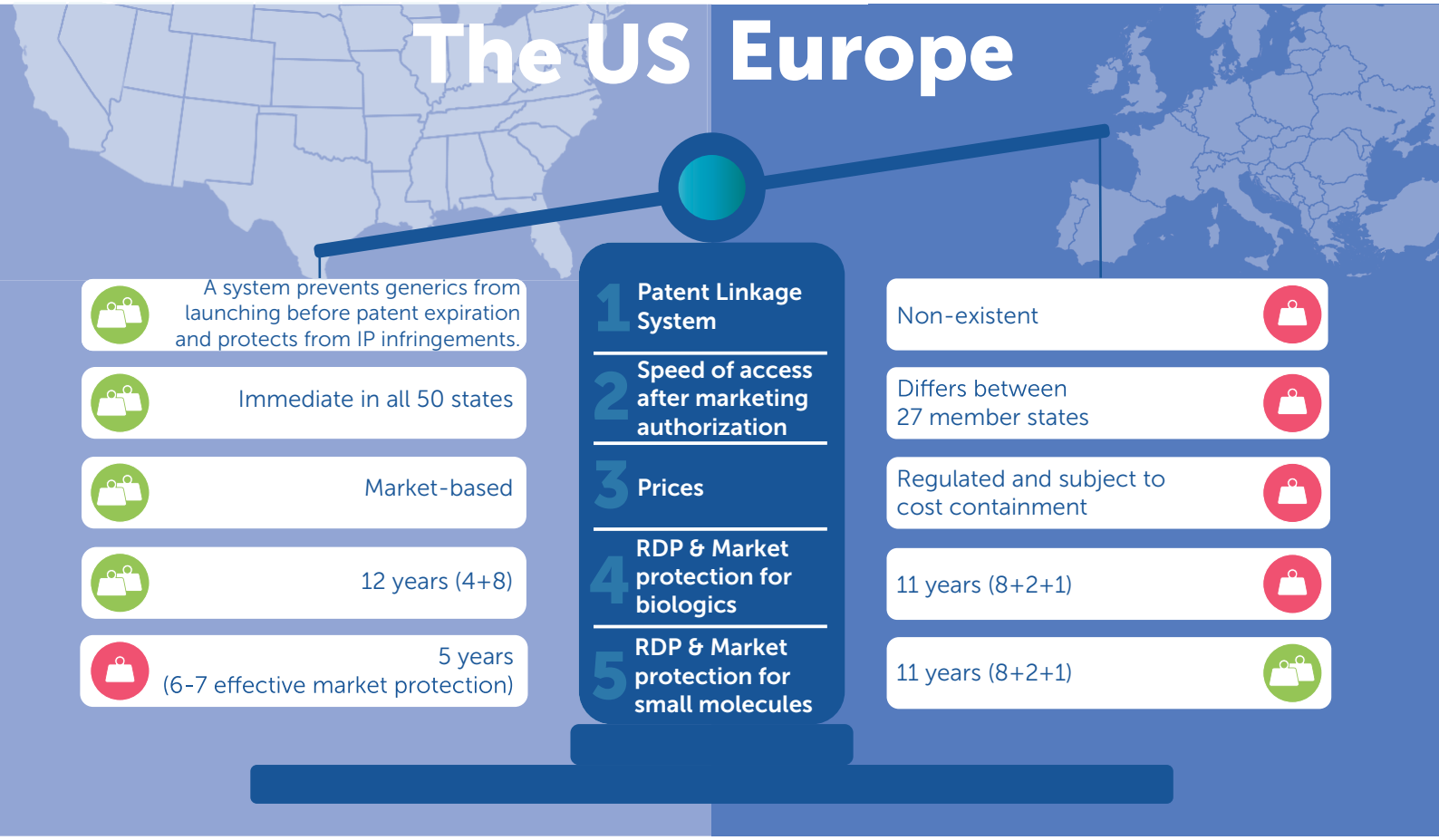
Concretely, the current RDP proposal could lead to a decrease in investments for products that are more susceptible to replication, irrespective of the benefits they offer patients and even more so in complex products that require lengthier clinical trials. A blanket reduction of the baseline by a full two years – and making its recovery unpredictable and in practice not feasible to achieve, further dependent on factors outside of a company's control, i.e., the release and continuous supply of a given medicine in all 27 Member States within two years of marketing authorisation – will only erode confidence needed to support reliability of investing precious R&D resources in the EU.

The remaining newly proposed modulations relating to unmet medical needs and comparative trials, are under-powered in terms of the incentive they offer in relation to the costs and time incurred to reach the objectives, and/or have narrow, impossible to predict success criteria. Taken all together, the proposal is therefore in effect a reduction of incentives for R&D.

All this will exacerbate the growing gap of Europe's R&D attractiveness and competitiveness on the global stage, especially vis-à-vis the United States, which has grown by EUR 23 billion over the last two decades. In comparing the two jurisdictions and ecosystems, the US provides patent linkage for dependable IP enforcement, faster access to the market in all 50 states via FDA approval, simplified market-based pricing, and more generous protection for biologics. The sole positive point of comparison for the EU is its more generous RDP regime for small molecules: the precise incentive the Commission proposal seeks to erode. The adoption of this proposal will have a chilling effect on the EU's pharmaceutical ecosystem, accelerating Europe's 20-year decline as a location for R&D and manufacturing investments.

In parallel to the pharmaceutical legislation, the proposed reduction in RDP protection is compounded by proposed changes to the intellectual property framework for

Why is the US more attractive for R&D?



medicines in the Patent Package (including EU-wide compulsory licensing). Together, these measures offer negative synergies that represent a significant weakening of the EU's incentive regime.

RDP and linkage to access and continuous supply

EFPIA strongly opposes the proposed approach to link data protection periods meant to incentivise R&D to access conditions in Member States. The linkage to "release and continuous supply" in 27 Member States means that incentives for R&D become dependent on conditions that are at least partially outside of the control of medicine developers, and therefore become impossible to predict. Multiple factors outside the EU's jurisdiction and outside the control of medicines developers, such as Member State's healthcare budget, healthcare priorities and infrastructure, pricing and reimbursement frameworks, and administrative capabilities, play a significant role in access disparities and delays. Even in the best of circumstances, concluding pricing and reimbursement negotiations with 27 Member States within two years would be an almost impossible condition to fulfill for most companies, and particularly unrealistic for SMEs (even if the time-limit for SMEs is put at two years).

Fundamentally, RDP conditionality does not address the underlying reasons explaining unequal access across the EU, and therefore will have no meaningful impact on access and affordability in practice. National governments already have and use tools to facilitate access to new medicines, while ensuring budget sustainability. Pharmaceutical expenditure has been stable as a share of total healthcare expenditure in all European countries for the last 20 years, converging at around 15% of total healthcare expenditure.

EFPIA member companies have already taken concrete actions to contribute to a more equitable system for patients in Member States. According to our data, industry's published commitment to file for pricing and reimbursement of medicines in all 27 Members States no later than two years after marketing authorisation would increase access by 18%-64%, versus the 8%-15% estimated by the European Commission for its proposed measures.

RDP and linkage to unmet medical need (UMN)

The development of medicines takes many years and is always done with the ambition to address an UMN, which can be described as any medical condition that is not adequately prevented, treated or diagnosed by authorised interventions. It is, however, impossible to know in advance whether a particular investment into a given project will eventually address a specific UMN. Given the long and risky development timelines, it is possible that the remaining UMN can change during this period. If so, and the definition of UMN is defined very narrowly, this leads to a lack of predictability of the incentive, weakening its impact and therefore reducing or removing the stimulus for companies to invest in R&D. 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. Therefore, it is crucial to develop a patient-centred, more inclusive definition of UMN. By acknowledging the value of innovation and encouraging advances in prevention, treatments and care, Europe can ensure that no patient is left behind.

RDP and linkage to comparative trials

Finally, it is inappropriate to suggest comparative trials shall be incentivised for the sole reason of supporting downstream decision-making on pricing and reimbursement. This assumption fails to adequately consider both the scientific and ethical considerations for development programmes. Those should be explicitly prioritised where patient populations are limited (children, rare diseases) and the expanded use of real-world health data or current clinical practice is crucial. However, acknowledging and truly rewarding the substantial efforts in conducting a comparative trial, where justified, is important. This incentive should be expanded to allow post-approval submission of comparative clinical trial data. This is needed, as often it is not possible to deliver comparative data at time of initial marketing authorisation application submission e.g., confirmatory data for conditional MAAs are provided post-approval, comparative data as part of a new indication or any other post-approval variation.

Closing the gap

A genuine desire to be a world leader in pharmaceutical R&D and to increase the attractiveness of the EU as a location for R&D investment will require a stronger and more predictable incentive system. EFPIA recommends the provision of meaningful and predictable incentives, attainable fairly, that would encourage additional R&D investment relative to today. Concretely, this would mean strengthening the baseline of RDP and OME compared to the existing legislation as well as *de facto* incentivising medicinal products that meet a patient centric definition of UMN and the conduct of comparative clinical trials. It is important to ensure any incentives for innovation are linked to innovation and not access provisions that are often outside the marketing authorisations holders' control – and are not possible to implement for products such as vaccines, given the current procurement system in Europe. Such measures would bolster EU competitiveness versus other regions, and thereby revitalise the innovative medicines pipeline and help bring the latest in technology to European patients.

2.2 Bolar exemption

THE COMMISSION PROPOSAL

In Art. 85 of the Directive, the Commission has proposed to broadly expand the scope of the Bolar exemption. Previously, the scope of the Bolar exemption only included actions by generic manufacturers taken in view of obtaining a marketing authorisation (MA). Now, the broadened exemption is worded in a way that would further include in its purview studies and trials to generate data for Health Technology Assessments (HTAs) and the Pricing & Reimbursement (P&R) process, and activities necessary for these purposes, including by third parties.

EFPIA PERSPECTIVE

EFPIA is very concerned about the expansion of the Bolar exemption beyond marketing approval, which could undermine the effective enforcement of fully valid IP rights for pharmaceuticals in the EU and reduce confidence in the reliability of the IP regime as a whole and, thereby, threaten European competitiveness.

As a preliminary issue, the need to expand the Bolar exemption is not well articulated. According to the latest IQVIA figures, the generic industry is already launching at or near the day IP protection expires ("Day 1") in the four largest EU markets overall, and, on average, they are launching even earlier in Central and Eastern Europe. Generic/biosimilar applicants also have no need to conduct studies or trials to generate data in support of applications for HTA or P&R. They are not in scope of the former and do not need to generate any data for the latter. We also note that the impact assessment did not consider such an extension of the Bolar exemption.

A further weakening of IP rights is not necessary to encourage generic launch: IP is not an impediment to their business model within the EU pharmaceutical environment given that it is proven that they can and do launch where there are commercial opportunities to pursue. On the contrary, the language of the proposal could cause undue harm to the innovation ecosystem. Indeed, without a patent linkage

system in the EU such as that which exists in the US, holders of IP rights must rely on actions such as applications for P&R as a trigger point to prevent launches at risk. Indeed, these are largely viewed by courts as a threat of imminent infringement. The language in the proposal reads in such a way as to make P&R activities exempted from infringement and/or no longer serving as a trigger for preliminary injunction proceedings. Without clarity as to this key trigger, the proposed language would not only undermine the enforceability of patent/SPC rights in the EU but also encourage launch at risk by exempting additional, otherwise infringing pre-commercial activities.

Overall, it would damage the fine balance drawn between timely launch of generic competitors and the ability of innovators to enforce valid patents and prevent launches at risk, given the lack of patent linkage in the EU. This threatens to undermine the integrity of the IP system that innovators rely on in the EU to continue to invest significantly in researching and developing novel therapies for European patients.

EFPIA supports a Bolar exemption for activities related to seeking regulatory approval, that can facilitate efficient approval while preserving the integrity and function of the patent and regulatory review system. We support reversing the expansion of the Bolar exemption, limiting it to activities undertaken exclusively for Marketing Authorisation purposes, including by innovator or third parties.

KEY RECOMMENDATIONS

- To close the gap of R&D expenditure between the EU and other jurisdictions, a stronger and more predictable incentive system is required.
- EFPIA also recommends the provision of meaningful and predictable incentives, attainable fairly, that would encourage additional R&D investment relative to the present day.
- EFPIA supports a Bolar exemption for activities related to seeking regulatory approval, that can facilitate efficient approval while preserving the integrity and function of the patent and regulatory review system. We support reversing the expansion of the Bolar exemption, limiting it to activities undertaken exclusively for Marketing Authorisation purposes, including by innovator or third parties.

3. UNMET MEDICAL NEEDS

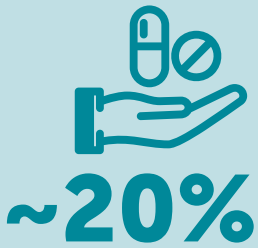
Addressing UMN is a cornerstone of pharmaceutical innovation as industry aims at developing medicinal products that will improve and extend patients' lives. UMN is a relevant concept throughout the whole value chain from drug discovery to P&R. Given the diversity of stakeholders and incentives involved, aligning on a common definition to assess those needs is an important and, at the same time, challenging exercise. It requires a holistic understanding as UMN can manifest in very different ways and evolve over time.

COMMISSION PROPOSAL

Directive Art. 83 and Regulation Art. 70 propose to extend the duration of incentives or to give access to various regulatory facilities (e.g., PRIME), if a product meets the following UMN-defining criteria: disease level (life-threating or seriously debilitating) and product level (whether there is another medicinal product already authorised and, if so, whether there is a remaining high mortality or morbidity of the disease). As orphan medicinal products (OMPs) would be considered by default as addressing an unmet medical need, the Commission further considers criteria for high unmet medical need (HUMN), which would trigger longer orphan market exclusivity. These shall be met if there is either no medicinal product available or if the medicinal product under development will bring an exceptional therapeutic advancement (in addition to the significant benefit already required for orphan products). In both cases the new product must meaningfully reduce remaining mortality or morbidity. In addition, Regulation Art. 162 lays out that the Agency may extend the consultation process on UMN guidelines beyond HTA bodies and national P&R bodies to patients, medicine developers, HCPs, industries and other stakeholders.

EFPIA PERSPECTIVE

A centralised and narrowly applicable definition of UMN does not align with a patient-centric approach as it ignores the variety of patient relevant outcomes as well as the potential for broader societal benefit from a medicinal product. In addition, it can stifle valuable incremental innovation, as often observed in the field of oncology and chronic diseases such as diabetes and cardiovascular disease. This has raised significant concerns among various stakeholders, including patients, researchers, and industry. EFPIA analysed whether the 169 new active substances which received an



Of the 111 non-orphan medicines authorised between 2019 and 2022, only around 20% would potentially meet the UMN criteria included in the Commission's proposals. Medicines that could improve the lives of people living with migraine, cardiovascular disease, diabetes and many other conditions would not satisfy the criteria. This would disincentivise R&D investment in these areas and hinder the development of important therapies for patients.

Source: EXON EFPIA report: The Commission's criteria to define unmet medical need and high unmet medical need: Implications of a proposed incentive framework, October 2023

EMA marketing authorisation between 2019 and 2022 might meet the UMN criteria as now laid out in the Commission's proposal. Under the Commission's proposed definition, only around 20% of non-orphan products were deemed likely to fulfil the proposed UMN criteria while around 50% of OMP would fulfil the HUMN criteria.

With its proposed approach, the Commission is moving away from the current incentive system where regulatory incentives for medicine development are technology neutral, i.e., given independently of the type of product, technology or disease area, and where the relative therapeutic value of the medicinal product is subsequently assessed and rewarded at HTA/P&R stage in line with patient needs. Two implicit assumptions seem to underpin the Commission's proposed approach: firstly, that "breakthrough" innovation is separate from, and inherently more valuable than, incremental innovation. Secondly, that incentivising "breakthroughs" will lead developers to focus their activities more on "breakthrough" innovation compared to a situation today where they would "inefficiently" focus too much on incremental innovation. This ignores the reality that incremental innovation brings value to patients, contributes to advancing knowledge about a disease and generates important spillovers that reinforce and facilitate "breakthrough" innovations. Furthermore, although this is outside of the scope of the general pharmaceutical legislation, this approach also ignores the benefits for payers of competition within a therapeutic class.

The development of medicines takes many years and is always done with the ambition to address an UMN, which can be described as any medical condition that is not adequately prevented, treated or diagnosed by authorised interventions. It is, however, impossible to know in advance whether a particular investment in a given project will eventually address a specific UMN. Given the long and risky development timelines, it is possible that the remaining UMN can change during this period – for instance, a company may be disincentivised to pursue a candidate in an area where there is already a product at an advanced development stage, e.g., phase II. However, this project might fail and yet, a narrow definition of UMN could have stifled any competition and hopeful prospects. Moreover, having distinct standards for high UMN in orphan medicines compared to UMN is challenging for many reasons, not least because it raises ethical concerns: defining a UMN as "high" implies that other UMN are of less importance, either to patients or society, which would be inappropriate.

Current debates over UMN are part of a broader set of challenges related to the availability, accessibility, and affordability of innovative medicines and the long-term sustainability of health systems. The definitions proposed in the texts miss the patient perspective and the acknowledgement of how new potentially curative treatments and vaccines are being discovered and developed with the potential to transform the lives of patients, and the way we think, manage and resource healthcare. A truly patient-centred definition of UMN in the legislation can support investment to meet the needs of tomorrow. It should not be misused to address affordability concerns as those require collaborative efforts to find access solutions.

To discuss UMN properly requires a holistic approach – the following principles should be considered:

1. Perspective matters and decision context is key

What is considered a UMN depends on the perspective that is taken. Patients suffering from a disease may identify different individual needs than would be perceived by wider society. For example, individual patients value the impact of new medicinal products on any immediate threat to life (e.g. from life-threatening diseases) but may also value the impact of a new formulation (e.g. a single dose pill) or fewer side effects on quality of life. However, society as a whole may place a higher value on incremental improvements of diseases with a high societal burden, or those that help to protect the most vulnerable populations (e.g. preventing communicable diseases among persons who are at increased risk of infection, serious consequences or

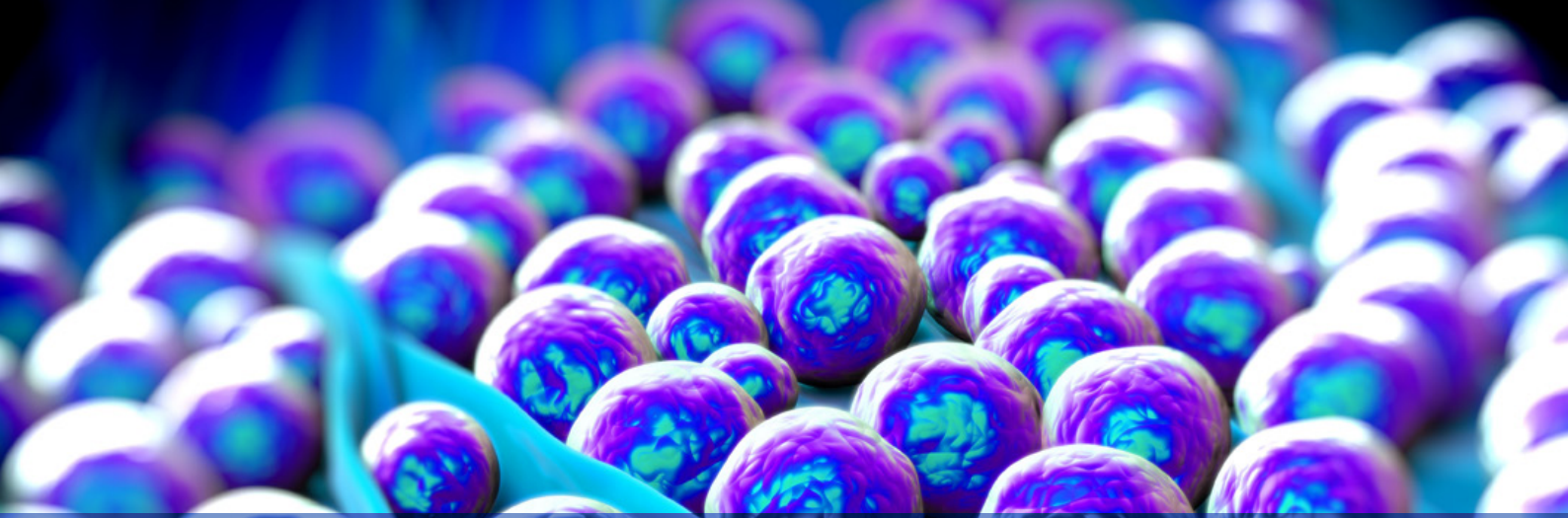
death) or on advances that help prepare for future pandemics. Health care systems may decide to allocate resources to various needs, or make the overall system more efficient. Perspectives on whether something is a UMN can also evolve as scientific opportunities emerge. While different stakeholders may perceive UMN differently, it is crucial to recognise that, from an ethical standpoint, the patient or target population perspective should be the primary driving force behind medical innovation. The focus should be on delivering solutions to patients, improving outcomes, minimising side effects, preventing the spread of infectious diseases and alleviating the burdens on caregivers.

2. Inclusivity is crucial

It is of utmost importance that the relevant stakeholders are actively engaged in identifying UMN from different perspectives. Collaborative efforts are necessary to establish a shared understanding of UMN and to determine appropriate incentivisation strategies for specific UMNs, considering context-dependent criteria throughout the entire value chain. These multi-stakeholder collaborations should involve representatives from diverse patient groups, alongside broader societal and healthcare system stakeholders, including industry. For this purpose, clear rules of engagement should be developed.

KEY RECOMMENDATIONS

- Developing a patient-centred, more inclusive definition UMN. By acknowledging the value of innovation and encouraging advances in prevention, treatments and care, Europe can ensure that no patient is left behind.
- Taking the evolution of science and patient needs as a starting point, we understand a UMN as a condition that is not adequately prevented, treated or diagnosed by authorised interventions.
- Any assessment of UMN should incorporate all patient relevant outcomes, and the potential for broader societal benefits, not only morbidity and mortality.
- Actively engage all relevant stakeholders to identify UMN from different perspectives. These multi-stakeholder collaborations should involve representatives from diverse patient groups, as well as broader societal and health care system stakeholders. For this purpose, clear rules of engagement should be developed.



4. INCENTIVES FOR R&D OF NEW ANTIMICROBIALS

THE COMMISSION PROPOSAL

Innovators that discover new "priority antimicrobials" will be eligible for a transferable exclusivity voucher (TEV), which will allow its holder one additional year of data protection. A maximum of 10 vouchers can be granted over a 15-year period, after which all TEV provisions will cease to apply. The TEV proposals come with several caveats, including the threat of invalidation if the antimicrobial is withdrawn from the market, or if certain access requirements are not met. The value of the TEV that is sold must also be disclosed to the EMA and made public.

EFPIA PERSPECTIVE

To effectively combat AMR and provide new antimicrobials for patients with UMNs, a comprehensive package of policies is required. We welcome the Pharmaceutical Package's objective to incentivise the development of, and improve access to, novel antimicrobials. The TEV mechanism to promote antimicrobial R&D, outlined in articles 40-43 of the proposed Regulation, is a positive development, despite the limitations of its current design.

The additional incentives outlined in the *Council Recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach* of 13 June 2023 have the potential to serve as valuable complementary tools to the TEV, in ensuring sustainable supply and facilitating access to new antimicrobial treatments. However, the effectiveness of voluntary, non-legislative measures heavily relies on the political will of Member States, and it is unlikely that such measures can generate sufficient resources and offer predictable outcomes for all stakeholders involved. As such, they should not be relied upon as a tool to incentivise innovation in lieu of a centralised, EU-wide measure (namely, the TEV).

To effectively encourage the development of a sustainable and robust R&D pipeline for novel antimicrobials, while ensuring access to these treatments, it is essential that any pull incentive meets certain criteria:

- Incentivises innovation and appropriate use: an incentive large enough to incentivise sustainable innovation, aligned to the EU contribution or fair share of the needed global incentive. Delinked from revenue and therefore aligned to stewardship;
- Value for money: represents a proportionate cost to society and an efficient approach;
- Predictability: provides clarity for all stakeholders, including innovators, the generic industry and payers;

To be effective, pull incentives should meet a set of key criteria

- Feasibility: is implementable given the current context, framework and policy debate; and
- Supports timely access: can be implemented relatively quickly in the EU, given the urgency to address the AMR threat, and contributes to patient access through the increased supply and availability of new antimicrobials.

Based on our analysis and the principles at hand, it is evident that the stringent conditions associated with the TEV proposed in the draft Regulation significantly undermine the effectiveness of the incentive. Therefore, it is key to review and reassess these conditions to uphold the TEV as a powerful tool for encouraging the advancement of antimicrobial R&D. This is particularly critical considering the small pool of products potentially benefiting from the extended exclusivity under the TEV, due to the fact that it solely extends RDP, not SPC or patent protection. This condition alone already considerably weakens the effectiveness of the incentive and reduces its size below what is needed as the fair European share of the required global reward size.

KEY RECOMMENDATIONS

- To effectively incentivise R&D in new priority antimicrobials, it is crucial to focus on their clinical benefit and effectiveness in combating resistance. To establish a rigorous and evidence-based assessment, it is highly recommended that the EMA establishes a dedicated expert group and initiates early dialogues with developers. This approach ensures a thorough evaluation process that prioritises the clinical usefulness of the antimicrobials in question, rather than relying on predetermined criteria for TEV eligibility.
- TEVs should be allowed to benefit any product that has at least two years of regulatory data protection remaining. The proposed change expands the range of recipient products, while ensuring sufficient predictability for generic manufacturers. A broader range of recipient products increases the chances that TEV can be effectively used and therefore enhances the potential impact and appeal of the incentive programme.

- The original proposal would allow the Commission to revoke the voucher prior to its transfer if a request for supply, procurement or purchase of the priority antimicrobial in the Union has not been fulfilled. However, during crisis situations, such as pandemics or unforeseen emergencies, the ability of the industry to supply products may be significantly hindered due to various factors beyond its control. These factors could include global disruptions, trade restrictions, uncoordinated national stockpiling initiatives, or overwhelming demand that exceeds the manufacturing capacity. In such cases, it is unreasonable to hold the MAH accountable for the inability to fulfil requests for the priority antimicrobial.

- The incentive programme should be reviewed after 15 years, considering predefined outcomes and future medical needs. This is crucial because a fixed 15-year sunset clause does not align with the timeline of research and development and overlooks the possibility of alternative incentives not being successfully implemented during that period. Conducting regular reviews ensures the ongoing effectiveness, adaptability, and responsiveness of the programme to address evolving challenges in AMR.

- The starting time of the new rules should be unambiguous. Considering the urgent need to address the pipeline failure and accelerate the entry of late-stage products into the market, it is critical that the new rules become applicable as early as possible, specifically from the entry into force of the Regulation, rather than its application date.

- Furthermore, the original proposal appears to mandate the TEV request to be made to the Commission concurrently with the submission of the marketing authorisation application to the EMA. This requirement is excessively restrictive. It should be sufficient for the TEV request to be made at any point while the marketing authorisation application is under consideration. This change would provide developers with greater flexibility and eliminate unnecessary bureaucratic hurdles, enabling them to benefit from the TEV when it is most relevant to their specific circumstances.

5. ORPHAN MEDICINAL PRODUCTS

The Orphan Regulation has been a true European success story, progressing care in many overlooked conditions and ensuring predictability in investment decisions. Within the last 20 years, the innovative pharmaceutical industry has been investigating areas of UMN to develop treatment options for patients living with rare diseases. As a result, over 200[5] new treatments for orphan diseases have been approved, delivering care for up to 6.3 million patients. This success should not be jeopardized. More is needed to address the needs of patients, building on what has already been achieved.

EFPIA recognises that many patients still do not have a satisfactory treatment option and shares a vision of a healthier future for Europe, where people with rare diseases are not left behind. The lack of adequate therapeutic options in some areas is a consequence of cumulative scientific, regulatory and economic barriers to development, further compounded by uncertainties relating to P&R. As science, economics, and policy come together to inform investment decisions, no single solution or stakeholder stands to meaningfully stimulate and successfully carry on the development of new therapies in the underserved areas. Instead, a set of interdependent solutions must be implemented and funded by the private and/or public sector in a collaborative fashion for innovation to flourish in rare diseases. This will require joint action from all stakeholders.

[5] European Commission: https://health.ec.europa.eu/medicinal-products/orphan-medicinal-products_en

5.1 Encouraging innovation: Orphan market exclusivity

THE COMMISSION PROPOSAL

Articles 71 and 72 of the Regulation suggest a move from the current orphan market exclusivity (OME) approach, which provides a separate period of OME for each new indication for a different orphan designated condition, towards a "Global Orphan Marketing Authorisation (GOMA)" system. Under the proposal, a company would only be granted a single OME period per active substance, with a limited set of possible extensions of that duration, applicable to the full product scope.

EFPIA PERSPECTIVE

Robust and reliable incentives remain essential, as the economic case for investment in rare diseases is only marginal. Therefore, if the EU seeks to be an attractive location for R&D investment, attracting the development of novel medicines and cutting-edge clinical trial participation for its patients, it must take this opportunity to strengthen the current baseline. In addition, there may be further potential to boost the orphan incentive system to encourage further investment in certain underserved areas where R&D is especially challenging.

Therefore, EFPIA supports a simple and predictable system of orphan incentives with a strengthened market exclusivity baseline, and modulation that takes into account the specific challenges related to development of treatment options for certain conditions. EFPIA supports additional market exclusivity for first-in-condition products or products addressing diseases with a very low prevalence (<0.5/10000). In these underserved areas, a basic scientific understanding of the condition is often missing and the challenges of conducting clinical trials in small populations are exacerbated. This is also the reason why EFPIA, jointly with other partners[6], call for a Moonshot for basic and translational research for adult and paediatric rare diseases. By contrast, the duration of market exclusivity could be reduced for well-established use products, as there will already be existing knowledge and data about these products.

In addition, the development and approval of additional therapeutic indications in different orphan conditions should be encouraged, not penalised. These can provide important treatment opportunities to additional patients living with a rare condition. As a result, while EFPIA can support the GOMA system, EFPIA

As currently drafted, the Pharmaceutical Legislation proposals would discourage the development of 45 rare disease treatments in the EU by 2035 impacting

1.5 million
RARE DISEASE PATIENTS

[6] Moonshot partners: BBMRI-ERIC, Critical Path Institute, EATRIS, ECRIN, EFPIA, Eucope, Europabio, Eurorids.

believes that no limitation should be placed on the number of OME extensions to additional orphan conditions for a given product. Similarly, recognising the significant effort and investments required to bring a new indication to patients, especially in a new condition, EFPIA believes these deserve a more meaningful extension.

A maximum period of exclusivity could however be considered, to provide certainty to other stakeholders. Finally, all orphan medicines should continue to be eligible for either additional OME or the current six-month SPC extension for completion of their obligations under the Paediatric section of the Regulation.

5.2 Embracing inclusivity: Orphan drug designation (ODD)

THE COMMISSION PROPOSAL

Art. 63 of the Regulation introduces the possibility to derogate from the current prevalence criterion and to set specific, additional or different, criteria for certain conditions, "due to the specific characteristics" of these.

EFPIA PERSPECTIVE

Currently, 88.6% of rare disease patients are affected by 10.9% of the more prevalent rare diseases (Wakap, et al., 2019). Those patients still have many UMNs as well as those who currently have no treatment options. Changing the prevalence criterion would be a detriment to the majority of rare disease patients and will not automatically redirect investments to rarer diseases. On the contrary, introducing the possibility of setting specific ad-hoc criteria for certain conditions creates significant uncertainty about whether a product may obtain and retain ODD. Without predictability, companies and investors may be discouraged from investing in R&D. Current EMA[7] figures show that R&D activities take place across the prevalence spectrum, underlining that UMN persists, even if there is a treatment option. For that reason, keeping the current prevalence threshold at five in 10,000 is critical to maximise the effectiveness of the orphan framework.

THE COMMISSION PROPOSAL

Art. 66 of the Regulation introduces a validity cap for ODD, according to which these shall be valid for seven years.

EFPIA PERSPECTIVE

Introducing a limited validity to the ODD will only add undue regulatory burden and further uncertainty to the development process of OMPs, which is already particularly difficult. In addition, the rationale for such a measure is unclear. Conducting clinical trials in rare diseases is challenging due to the small, heterogenous patient populations affected by a given rare disease which are often also geographically dispersed. This presents multiple infrastructure challenges, as well as challenges in collecting the relevant data required by regulators. Considering these issues, delays cannot be avoided at times, although manufacturers always strive to conduct clinical programmes as efficiently as possible. There are examples for OMPs where the marketing authorisation was obtained more than 20 years after the first clinical trial was

[7] https://www.ema.europa.eu/en/documents/other/orphan-medicines-figures-2000-2022_en.pdf
Prevalence superior 3-5 in 10,000 patients: 53 Orphan Drug Designation
Prevalence superior 2-3 in 10,000 patients: 37 Orphan Drug Designation
Prevalence superior 1-2 in 10,000 patients: 70 Orphan Drug Designation
Prevalence < 1 in 10,000 patients: 132 Orphan Drug Designation

initiated[8]. Measures which would introduce time caps on the validity of an ODD risk hampering development, instead of accelerating it, potentially contributing to fewer treatment options being developed. The current absence of a time limit allows flexibility, reflecting the reality of rare disease medicines development.

5.3 Equalising inequalities: Addressing unmet medical need in rare diseases

THE COMMISSION PROPOSAL

OMPs would be considered as addressing UMN as per Article 83(2) of the Directive. In addition, the Commission suggests criteria for *high* unmet medical need (HUMN) in Art. 70 in the Regulation. If the HUMN criteria are satisfied, the product would be eligible for longer OME. These shall be met if there is either no treatment available or, if so, the treatment under development will bring (additionally to the significant benefit) exceptional therapeutic advancement and result in a meaningful reduction in mortality or morbidity.

EFPIA PERSPECTIVE

Current debates over UMN or HUMN are part of a broader set of challenges related to the availability, accessibility, and affordability of innovative medicines and the long-term sustainability of health systems. As discussed above, this conversation misses the patient perspective. In addition, as unmet medical needs can evolve over time, limiting incentives to treatments that fit a very narrow definition of UMN or HUMN today, risks excluding the development of important therapies for patients tomorrow. It will reduce the overall predictability for companies and disincentivize them from investing in R&D in the EU that may have addressed patients' unmet medical needs.

[8] https://copenhageneconomics.com/publication/development-of-novel-therapies

When evaluating UMN, perspective matters, context is key, and inclusivity is crucial. For example, patients suffering from a disease may identify different individual needs than society in a broader sense. The term of high UMN is in this regard challenging for many reasons, not least because it raises ethical concerns: defining a UMN as "high" implies that other UMN are of less importance, either to patients or society, which would be inappropriate. EFPIA, therefore, does not support any gradation of unmet medical need. A definition of UMN requires a holistic understanding as it can manifest in very different ways.

The OMP framework was introduced on the assumption that all rare diseases presented specific challenges and UMN. Despite the progress of the past decades, there are still many challenges remaining (even in diseases already served with a therapeutic option) and the ongoing revision should help address these rather than undermine scientific opportunities.

KEY RECOMMENDATIONS

- Encouraging innovation – OME: Robust and reliable incentives remain essential. To address the needs of patients suffering from rare diseases, and in line with the EU Council conclusions of March 2023, these should be strengthened as the economic case for investment in rare diseases is only marginal. There may be additional potential to boost the orphan incentive system to encourage further investment in certain underserved areas where R&D is especially challenging. Therefore, EFPIA supports a simple and predictable system of orphan incentives with a strengthened market exclusivity baseline, and modulation that takes into account the specific challenges related to a given type of development.

- Embracing inclusivity – ODD: Keep the current prevalence threshold of less than five in 10,000. Patients still have unmet medical needs, even if there is a treatment option.

- Equalising inequalities – Addressing UMN: All authorised OMP address a UMN in rare diseases. Modulation based on gradation of UMN is not appropriate and should instead take into account the specific challenges related to certain conditions.

6. PROPOSALS FOR PAEDIATRIC MEDICINES

The current Paediatric Regulation has delivered 290 new treatments for sick children in Europe. While this represents tremendous medical progress, the legislation can be improved to better address children's UMN. This goal cannot be achieved by the Regulation alone. Creating a thriving R&D ecosystem through involving all healthcare stakeholders will be crucial to deliver on this objective.

It will be of utmost importance that the strengthened regulatory obligations are underpinned by science and can lead to clinically meaningful and feasible developments that benefit paediatric patients, without undue burden on biopharmaceutical innovation. Implementing guidelines must be developed in consultation will all interested parties to leverage their expertise in paediatric medicines development and involve them in driving the ecosystem forward.

6.1 Speeding up paediatric research

In the spirit of speeding up the regulatory process for paediatric investigation plans (PIPs) and thereby paediatric R&D in the EU, EFPIA welcomes the Commission's proposals to streamline and simplify the EMA's committee structure, while retaining the right expertise for paediatric medicines development. This should reduce the administrative burden on regulators and industry and increase the effectiveness and efficiency of the scientific assessment and associated regulatory procedures.

EFPIA also supports the implementation of a more pragmatic approach on the level of detail to be included in an initial PIP application, including commitments to submit a more fully developed PIP as and when data become available, incorporating the current pilot project of the 'stepwise PIP' in the proposed legislation (Article 74 of the Regulation). However, EFPIA does not see the need for a specific procedure with different timelines (as proposed in Article 77 of the Regulation) from the standard PIP that might undermine the speed and agility of this positive development.

6.2 PIP submissions and deferrals

The early existence of a PIP does not determine the speed of a development programme. However, there seems to be a misperception that the timing of PIP submissions (Article 76 of the proposed Regulation), and the granting of scientifically justified deferrals of paediatric studies (Article 81 of the Regulation) are the main causes of delays in paediatric medicine development. This is not the case: the speed of development is mainly driven by the ability to conduct paediatric studies to generate the necessary data for regulatory assessment. Developing a new medicine for pediatric use has very specific challenges which may be scientific, operational, regulatory, or ethical. For example, there may be a lack of early research (animal models), or insufficient infrastructure to carry out paediatric clinical trials and small populations of relevant patients which may be very globally dispersed. From a scientific point of view, each PIP and its timing of completion needs to be considered independently on its own merits. The Commission proposal to set an arbitrary five-year time limit for deferred PIP measures (Article 81 of the proposed Regulation) is not scientifically sound, does not take into account feasibility and recruitment challenges, and is inconsistent with internationally agreed standards for conducting clinical trials. At worst it may even lead to the unintended effect of reducing R&D in new innovative treatments for children in Europe, rather than increasing it.

6.3 Need for a robust framework for Mechanism of Action PIP

COMMISSION'S PROPOSAL

To better address paediatric-only diseases, the Commission has proposed (Article 75 of the Regulation) to restrict the granting of waivers where the intended condition for adults does not occur in children. In such cases, the developer would be required to conduct a PIP based on the molecular target of a product which could have an impact on a different disease in children, if and when there is scientific evidence to support this. However, the draft legislation lacks any detail on how this will be implemented.

EFPIA PERSPECTIVE

The Commissions' proposal is similar to EFPIA's vision for a mechanism of action (MoA) PIP, based on how a product does what it is meant to do, e.g., to act on an enzyme to stimulate insulin production. EFPIA understands and supports that this change is intended to increase paediatric research and address UMN in children. However, we urge the Commission to implement a robust framework underpinned by science to ensure that this new obligation will lead to scientifically and clinically meaningful, doable R&D that benefits paediatric patients, and does not place undue burden on innovators and developers. An implementing guideline should be developed in consultation with all interested parties to leverage their expertise in paediatric medicines development.

Furthermore, such studies can be expected to be more complex and scientifically challenging than standard PIP studies and developers undertaking MoA PIPs should be rewarded fairly for their additional efforts to meet this new obligation. A 12-month extension of SPC protection for products for which a MoA PIP is completed would be appropriate.

6.4 Paediatric medicines development – a collaborative effort

EFPIA concurs that moving with science is important. Open and collaborative scientific dialogue is a basic driver of industry's R&D endeavours. Consequently, medicines developers should be consulted and closely involved in the procedure when modifications to their PIPs are requested by the EMA (as proposed in Article 84 of the Regulation) based on external scientific data not generated by the PIP holder. Such discussions and sharing of information with the developer will ensure that a holistic view of the product development is integrated and translated into the right medicines for children.

Furthermore, the PIP applicant/holder's ability to request a re-examination of the EMA's decisions on PIP applications and modifications, which has been removed in the proposed legislation, should be reinstated (in Article 87 of the Regulation) since it provides an essential right to be heard for the stakeholder most directly affected by such decisions.

6.5 Proportionate obligations to ensure availability of paediatric medicines

The Paediatric Regulation (EC) No 1901/2006 contains a requirement that the MAH, following completion of an agreed PIP for a product which was previously on the market for other (adult) indications, must place that product on the market "taking into account the paediatric indication" within two years of authorisation of the paediatric indication.

The proposed revision (Article 59 of the Directive) would expand the current obligation to require the product to be placed on the market, taking into account the paediatric indication, in all Member States where the product is already on the market, within two years of paediatric indication authorisation. EFPIA understands that this expansion of the obligation is aimed at addressing access and availability gaps for paediatric medicines across EU Member States. However, companies face severe practical, stock and supply difficulties in launching certain paediatric products on the markets, in the conventional sense, when there may be very limited demand for them and/or significant pricing and reimbursement challenges.

EFPIA therefore believes that this expanded obligation should be framed in such a way as to achieve, in a more flexible and proportionate way, the same aim as the Commission, of making paediatric medicines available where actual patient need and demand exist across the EU.

KEY RECOMMENDATIONS

- A robust framework for MoA PIPs is essential to ensure that this new obligation is effective to achieve its purpose and manageable for developers. With this increased obligation should come an increased reward and EFPIA is calling for a twelve-month SPC extension for MoA PIPs.
- Where the EMA requests PIP modifications based on external scientific evidence (not generated by the PIP holder) there must be a consultative and collaborative process with open scientific discussions and sharing of information with the PIP holder. The applicant's right to request a re-examination of the EMA's decisions on PIP applications and modifications should be reinstated.
- The expanded obligation to place paediatric products on the market of all Member States should be framed in a more flexible and proportionate way, to meet actual patient needs and demands across the EU.

7. MEDICINES SHORTAGES

7.1 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 risk-based 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 COVID-19 crisis, demonstrating their ability to meet the soaring demand under particularly challenging conditions. The medicine shortages study released by the European Commission in December 2021 shows that most shortages involve older, off patent and generic medicines, and that originator product shortages are often quickly resolved.

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. In the majority of cases, shortages result from an unpredictable increase of demand. EFPIA welcomes 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 with risk), sustainability and forward-looking. EFPIA recommends that if measures address both supply and demand sides, particular attention should be paid to improving the visibility of demand for the revision to be effective. We also note that this is a multifaceted issue involving many stakeholders, not just the MAH, and this should be a joint effort where all parties contribute to the solution and enhance cooperation through regular dialogue.

7.2 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 Commission'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 find the best solution for each specific situation to ensure the availability of the respective medicines. Priority should be given to critical products, with high potential medical impact and where there is a potential risk of shortage.

7.3 Action should be coordinated at European level

Action will be most efficient and relevant if organised and coordinated at above-country level, avoiding the multiplication of uncoordinated measures adding complexity to the system. Companies run global supply chains and a coordinated process across EU countries will allow EU and national competent authorities to leverage the current systems and facilitate new efforts to ensure continuous supply. The EU offers the right political and legal platform to build a European integrated system, based on Member State solidarity and coordination. This should be based on a continuous dialogue between EU and national competent authorities and manufacturers with a view to anticipating and 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 coordinated European action. Unilateral and uncoordinated action taken on a national level, including divergent definitions of critical medicines, could have a detrimental effect on the supply of medicines in other countries, e.g., mandatory national stockpiling requirements of finished products would be duplicative and suboptimal, preventing the reallocation of stocks where they are most needed by patients. This structural inefficiency can result in both waste and shortages, and is particularly worrying at moments of supply constraints, where priority should be given to ensuring products reach patients rather than being stocked in warehouses.

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

The revision of the EU pharmaceutical legislation provides a unique opportunity to simplify, harmonise and modernise the current system. New digital technologies can help to better understand and forecast demand as well as strengthen supply chain resilience, all of which will help to anticipate and address shortages. Policy solutions to tackle shortages should be designed and implemented proportionally to the risk, giving due consideration to unintended effects, and need to be supported by strong evidence:

- The six-month prior notification of a temporary disruption of supply (shortage), as proposed in the Commission's document, is only possible in very limited number of cases, considering that most of the current shortages cannot even be reported in the current two-month mandatory timeline. Extending the timeline for mandatory notification to six months will have no effect on the prevention and mitigation of shortages. On the contrary, it is likely to have a detrimental effect on the effective mitigation of shortages, due to the increased administrative burden it is

likely to generate, including resources spent on "false alarm" cases that in the end do not lead to actual shortages.

- Thoroughly crafted, up-to-date shortages prevention plans (SPPs) are essential. Imposing such a requirement on medicines that are not critical is, however, too resource-intensive for both manufacturers and competent authorities and will likely be disproportionate, especially in the absence of a harmonised EU definition of critical medicines. This might drive efforts and resources away from critical issues, wasting time and resources on non-priority issues – potentially hampering the prevention and mitigation of shortages for critical medicines.
- Improved transparency across the supply chain has the potential to increase resilience and prevent shortages. Leveraging data available from other systems such as the National Medicines Verification Systems (NMVS),[9] IRIS, SPOR and other data sources e.g., ECDC epidemiological data, into the European monitoring system will dramatically expand authorities' visibility and understanding of a complex environment. This will enhance the capacity of competent authorities to take appropriate mitigation action.
- The diversity in data required in different formats from different Member States negatively impacts supply chain robustness without increasing knowledge. By contrast, standardisation of reporting and a harmonised EU prevention and mitigation system will support resilient supply chains.

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

KEY RECOMMENDATIONS

* The creation of a harmonised EU prevention and mitigation system, based on a standard definition of medicine shortages, and an interoperable IT European monitoring/ notification system: information should be uploaded onto a common IT portal to ensure a streamlined and effective alert system as well as alignment of data from different sources, based on a consistent and workable definition. EFPIA recommends keeping the mandatory notification timeline at two months and opening the system for voluntary earlier notifications. This would ensure that the very limited cases of shortages that can be anticipated several months in advance are reported as soon as information is available.

- Increased transparency and understanding of the demand, through timely (current and forward looking) epidemiological data: the European Centre for Disease Prevention & Control (ECDC) should aim for the timely release of modelling data covering the needs of patients, National immunisation Programmes and hospital capacity in the Member States. This should also combine any such forecasting data with real data on usage (medicines consumption and vaccines administration), and other relevant data that can provide information on supply.

- Use of the European Medicines Verification System (EMVS) for medicine shortage prevention and monitoring of MAHs' supplies to wholesalers and pharmacies: the data stored in the EMVS could provide timely intelligence regarding the number of packs for all prescription products supplied by manufacturers on EU markets, the number of packs dispensed in national pharmacies, the number of packs exported (and/or imported), as well as the level of stocks present in the supply chain at country level. The real time information in the EMVS data repositories can be analysed according to very granular timeframes (per day, per week, per month etc.) as well as per region (postal codes). Wholesalers and traders as well as national competent authorities have access to the data stored in National Medicines Verification Systems. A shared analysis of the EMVS data could be part of a regular dialogue between EU and national competent authorities, MAHs and other supply chain stakeholders. This would allow collaboration to anticipate and effectively address supply chain related issues.

- A risk-based approach focussing on critical products/critical shortages, leading to the implementation of targeted shortage prevention plans (SPP) for critical products through a collaborative process: EFPIA fully supports the development of a fit-for-purpose SPP in a common format for a risk-based selection of critical medicines, i.e., history of supply issues and patient impact. SPPs should be kept by the MAH and made available upon request by authorities during inspections. They should be kept confidential given the sensitive information they include. A clear harmonised definition and list of critical products is needed to ensure a consistent approach at EU level.

8. MANAGING THE ENVIRONMENTAL IMPACT OF THE MEDICINE'S LIFECYCLE

The pharmaceutical industry recognises and understands concerns raised by stakeholders regarding the presence of pharmaceuticals in the environment (PiE). The industry is committed to playing a leading role in addressing these concerns and is actively engaged in managing and controlling the impact of PiE. To this end, the Eco-Pharmaco-Stewardship[10] framework (that applies the widely accepted principles of product stewardship) was developed and is being implemented. Furthermore, companies are implementing appropriate controls and wastewater management[11] throughout the manufacturing process to address concerns.

Pharmaceuticals transform the lives of patients across multiple disease areas. However, as an inevitable consequence of patients receiving their treatments, traces of pharmaceuticals can find their way into the environment. It is therefore essential to assess the potential impact that pharmaceuticals can have on the environment. This is why, since 2006, producers must include an environmental risk assessment (ERA) when seeking approval for a human medicine.

The ERA is indispensable in assessing the potential environmental risk of pharmaceuticals, and the pharmaceutical industry recognises the potential impact of human medicines and their manufacture on the environment. We therefore propose an extended ERA to proactively address and manage the environmental risks associated with the patient use of human medicinal products[12]. We do, however, have some concerns over provisions in the Proposal for a Directive on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC.

[10] https://www.efpia.eu/media/636524/efpia-eps-brochure_care-for-people-our-environment.pdf

[11] https://www.efpia.eu/media/677262/technical-guidance.pdf

[12] https://www.efpia.eu/media/677261/interassociation-paper-on-extended-environmental-risk-assessment.pdf

COMMISSION PROPOSAL TO STRENGTHEN THE ENVIRONMENTAL RISK ASSESSMENT OF MEDICINES

Currently, in the EU, a prospective ERA is required since 2006 (CPMP/SWP/4447/00, 20061), when an MAA is submitted for a new human medicinal product or where there is potential for a significant increase in environmental concentrations as a result of modifications to existing marketing authorisations (e.g., addition of new indications). Human medicinal products approved prior to this date had no requirement for an ERA.

Among the proposed measures to strengthen the ERA, we would like to comment on the following:

8.1 Refusal of a Marketing Authorisation

THE COMMISSION PROPOSAL

In the proposal for a Directive, the European Commission introduces the possibility to refuse, suspend, revoke, prohibit supply or withdraw a marketing authorisation based on environmental grounds or if the ERA is incomplete or insufficiently substantiated or if the risks identified in the ERA have not been sufficiently addressed (Articles 47, 195, 196).

EFPIA PERSPECTIVE

The proposal to strengthen the ERA by introducing options for refusal and other measures on marketing authorisation (post approval) is a new and potentially far-reaching enhancement of the use of the ERA. There is concern on the strong wording "shall be refused" in Art. 47 and in Art. 47(d) which specifies that ERAs considered "incomplete or insufficiently substantiated [...] or if the risks identified [...] have not been sufficiently addressed" would be sufficient to restrict a marketing authorisation.

The proposal is contradictory to the European Parliament resolution of 2020: *'the environmental impacts of pharmaceuticals should be included in the benefit-risk assessment of human medicines, as is already the case for veterinary medicines, provided that marketing authorisations are not delayed nor refused solely on the grounds of adverse environmental impacts'*[13] . In light of this EP resolution, and the broader goals of the EU of improving patient access to medicines, it is concerning that the Commission proposes that a marketing authorisation shall be refused automatically due to environmental concerns without holistically considering the benefit-risk assessment, nor providing a clear definition or threshold for such concerns to justify a refusal.

Refusing marketing authorisation solely on environmental grounds would negatively impact patients' access to medicines.

We propose an extended ERA to proactively address and manage the environmental risks, while balancing it with patient access to medicines.

[13] https://www.europarl.europa.eu/doceo/document/B-9-2020-0242_EN.html

Industry agrees that an ERA is essential. However, we have concerns regarding these bases for refusal or withdrawal of authorisations. We believe that such a measure threatens the long-established authorisation system for medicinal products and would negatively impact patients' access to medicines. Moreover, the general option or requirement to suspend, revoke or vary a marketing authorisation for environmental reasons alone appears disproportionate and unjustified if it is not limited to major shortcomings and does not provide options for post-approval commitments. In our view, any measures should aim to strengthen ERAs while not preventing market access due to formal shortcomings that could adequately be resolved.

The industry agrees that in most situations, a complete ERA should be submitted with the MAA and would be supportive of steps to ensure that this occurs. However, there are certain, critical instances where, despite best intentions, it is not be possible to provide a complete ERA or an ERA without an identified risk. Clarifications are required on what would constitute an incomplete dossier, insufficiently substantiated ERA or acceptable mitigation risks.

Considering the Commission's proposal, it is our understanding that industry could bring to the market an in-licensed product where little or no data are already available – i.e. no post-marketing authorisation commitment would be possible. This would prevent, for example, expedited submissions or orphan drug submissions where the environmental impact is likely to be low (due to rarity of the condition) compared to high patient benefit. Taking into account the definition (Article 4) for an ERA to cover risk prevention, limitation and mitigation measures, this may delay or limit patient access to medicines that could be appropriate for their medical needs. Furthermore, the extended definition of the 'risks related to use of the medicinal product' threatens the core benefit-risk approach of the medicinal product authorisation system for human use, which is driven primarily by protection of human health.

When an ERA-based on worst-case assumptions indicate a potential risk, appropriate binding and time constrained post-authorisation measures should instead be used to give applicants the opportunity to address the potential concerns without delaying patient access to medicines.

8.2 Manufacturing in the environmental risk assessment of antimicrobials

THE COMMISSION PROPOSAL

The proposal for a Directive (Recital 72, Article 22) states that emissions and discharges of antimicrobials into the environment from manufacturing sites may lead to antimicrobial resistance (AMR), which is a global concern regardless of where the emissions and discharges take place. Therefore, the ERA scope has been extended to cover the risk of AMR selection during the entire lifecycle of antimicrobials, including manufacturing.

EFPIA PERSPECTIVE

There are consequences of extending environmental protection requirements to manufacturing for antimicrobials. This expansion would be difficult to implement and would lead to an increase in the resource burden on regulators, reduce flexibility in the supply chain, and have potential impacts on global manufacturing, while negatively impacting patients' access to medicines. The risk to human health from

traces of antimicrobials in the environment (from manufacturing or any other source), resistant microorganisms, and genes that cause resistance traits can currently not be quantified[14]. In a recent publication[15] it states: *"Currently, there is no agreed-upon method for how to develop regulatory values such as EQS [Environmental Quality Standard] and PNECs [Predicted No-Effect Concentrations] protective against AMR"*. Furthermore, the definition for antimicrobials in the proposal for a Directive indicates the term refers to antibiotics, antivirals and antifungals. Without a standardised method for the derivation of resistance based PNECs for all antimicrobials, we believe a robust regulatory evaluation of the risks caused by AMR cannot currently be conducted in a scientifically reliable way.

However, the proposal does offer opportunities to align with existing initiatives. The AMR Industry Alliance has developed an antibiotic manufacturing standard[16] including science-based PNEC targets for risk assessments to effectively control antibiotic releases from operations and supply chain networks. It requires an environmental management system and risk-based approach to assessing and controlling antibiotic manufacturing waste streams, and adherence to the Alliance's published PNEC[17]. We would welcome close collaboration between the AMR Industry Alliance and regulators.

8.3 Prioritisation of ERA for legacy active pharmaceutical ingredients

THE COMMISSION PROPOSAL

In the proposal for a Directive there are provisions for medicinal products without any ERA, authorised prior to October 2005. The EMA is requested to establish a risk-based prioritisation programme for medicinal products for the ERA submission or update by the MAH (Recital 71, 72, Article 23). The programme shall set the scientific criteria for the identification of medicinal products that are potentially harmful to the environment and for the prioritisation of their ERA, using a risk-based approach.

EFPIA PERSPECTIVE

Industry welcomes the proposal for the prioritisation and risk-based approach of legacy human medicinal products, with a focus on pharmaceuticals which are most likely to present a risk to the environment. The prioritisation of testing of legacy APIs and development of intelligent testing methods (to decrease the use of animals) has been, and continues to be, a significant research priority for the pharmaceutical industry and the European Commission through the Innovative Medicines Initiative (IMI). Furthermore, the

[14] Initiatives for Addressing Antimicrobial Resistance in the Environment: Current Situation and Challenges. 2018. https://wellcome.ac.uk/sites/default/files/antimicrobial-resistance-environment-report.pdf

[15] Ågerstrand, M., Josefsson, H., Wernersson, AS. et al. Opportunities to tackle antibiotic resistance development in the aquatic environment through the Water Framework Directive. Ambio 52, 941–951 (2023). https://doi.org/10.1007/s13280-022-01828-7

[16] https://www.amrindustryalliance.org/wp-content/uploads/2022/06/AMRIA_Antibiotic-Manufacturing-Standard_June2022.pdf

[17] https://www.amrindustryalliance.org/wp-content/uploads/2023/02/AMR-Table-1-Update-20230222.pdf

concept of an extended ERA as proposed by industry provides details on how this can be implemented[18].

Industry estimates that there are a large number of legacy APIs (likely to be in region of 1,000 APIs) with incomplete data to adequately conclude on environmental risk. Therefore, the generation of such data needs to be prioritised to avoid unnecessary pressure on limited environmental testing capacity in laboratories as well as an increase in animal (in particular, vertebrate) testing.

The IMI PREMIER[19] project (Prioritisation and Risk Evaluation of Medicines In the Environment) (and the previous iPiE[20] project) developed a prioritisation framework to help identify APIs contained in medicinal products authorised before 2006 that are most likely to present a risk to the environment. We suggest following this approach which is well targeted and best placed for prioritisation of legacy APIs as part of the pharmaceutical proposal.

In addition, industry strongly supports the introduction of a transparent web portal for environmental data and risk assessments. Such data sharing is considered imperative to increase transparency of ERA decisions and the relevant data.

8.4 Increased interlinkage across non-pharma legislations

THE COMMISSION PROPOSAL

The European Commission proposal for a Directive specifically states that applicants should take into account environmental risk assessment procedures of other EU legal frameworks that may apply to chemicals dependent on their use (chemical, biocides, pesticides and veterinary medicines). It further proposes increased consultation between the EMA and other EU agencies, including the European Chemical Agency (ECHA), the European Food Safety Authority (EFSA) and the European Environmental Agency (EEA), when developing scientific guidance or establishing programmes for pre-2006 legacy medicinal products (Recital 69, 71, Article 22, 23).

EFPIA PERSPECTIVE

We are seeing legislation linked to environmental, food, chemical and climate issues increasingly impacting the development, manufacture and supply of medicines. It is important to note that the legislative dossiers mentioned in the draft proposal are all currently under revision and the interlinking impacts are unclear.

Industry supports alignment across agencies and legislative dossiers as long as risk-based approaches are considered, and the EMA maintains overall control of the ERA for human medicines. It is important to avoid unnecessarily increasing the burden on data

[18] https://www.efpia.eu/media/677261/interassociation-paper-on-extended-environmental-risk-assessment.pdf

[19] https://imi-premier.eu/

[20] https://www.imi.europa.eu/projects-results/project-factsheets/ipie#:~:text=The%20goal%20of%20iPiE%20is,the%20

generation or the ERA methodology. We support the principle that other EU legislation offers opportunities to compensate for shortcomings in ERAs. However, the phrasing of the text indicates that a submission will be automatically refused if the ERA does not meet certain, as yet unidentified, criteria.

Furthermore, industry does not oppose the 'one substance – one assessment' (OS-OA) concept, in principle. However, it is our perception that the impact on medicines has not been fully considered. The OS-OA concept must not have a negative impact on ensuring the access of safe, effective human medicines to citizens in Europe. The uncompromised safety, efficacy and quality of a medicine should remain the most important criteria for benefit-risk based product approval. An assessment of the risk to patients will differ strongly depending on the dose, amount, formulation and use of a pharmaceutical ingredient. The impact on simplification of the EU regulatory framework is reasonably expected to result in the removal and replacement of chemicals also used in healthcare products.

8.5 Medicinal products subject to medical prescription

THE COMMISSION PROPOSAL

In Article 51 of the proposed Directive, the Commission is calling for medicinal products to be subject to a medical prescription where it is an antimicrobial or contains an active substance which is persistent, bioaccumulative and toxic, or very persistent and very bioaccumulative (PBT/vPvB), or persistent, mobile and toxic, or very persistent and very mobile (PMT/vPvM). It is also important to note that PBT/vPvB and PMT/vPvM are hazard-based approaches and do not take account of risk. Industry believes measures should be based on risk.

EFPIA PERSPECTIVE

Residues of active pharmaceutical ingredients found in the environment are used in prescription-based and non-prescription products. Therefore, such measures proposed by the Commission may not necessarily reduce emissions significantly. Moreover, shifting to prescription-only could result in product substitutions which increase the use of similar medicinal products that pose a greater environmental risk. Furthermore, while we support the continued requirement for prescriptions for antibiotics, with the expanding of the definition of antimicrobials to include antibiotics, antivirals and antifungals – we foresee avoidable impacts on access and the healthcare system.

For non-prescription human medicines, only essential uses are expected. Non-prescription medicines must be used according to the product information. These products are usually available at a lower dosage than their prescription (Rx) equivalent or for shorter time treatments and, hence, have lower dosages or less units per packaging. They play an important role in reducing the burdens on national healthcare systems and from a public health point of view. Furthermore, requiring a prescription for certain medicines that are currently available ‘over the counter’ would lead to an increased demand for healthcare professionals and increase healthcare costs. Access to certain medicines may become challenging. The balance between patient autonomy, accessibility, and safety considerations should be carefully evaluated in any decision to transition non-prescription medicines to prescription status.

KEY RECOMMENDATIONS

- As part of the extended ERA concept, the ERA should evaluate the impact of active pharmaceutical ingredients (APIs) instead of single medicinal products to capture the latest environmental information and accurately assess potential risks from all medicinal products.
- A marketing authorisation should not be refused, suspended, revoked, prohibited or withdrawn based on environmental grounds alone – instead it should be considered as part of a holistic benefit-risk consideration for the medicinal product. Further clarifications are needed on what constitutes an incomplete dossier, insufficiently substantiated ERA or acceptable mitigation risks.
- Support the prioritisation of ERA requirements for APIs lacking an ERA (registered prior to 2006) using novel prioritisation approaches and exploring opportunities to decrease reliance on animal testing requirements (as proposed through IMI PREMIER).
- Consider established systems for antimicrobials, building on the Antibiotic Manufacturing Standard developed by the AMR Industry Alliance.
- The balance between patient autonomy, accessibility, and safety considerations should be carefully evaluated in any decision to transition non-prescription medicines to prescription status.
- A medicines benefit-risk assessment, including direct consultation with the EMA, should take precedence on decisions on continuity of substances facing restrictions under other legislations that are used within the pharmaceutical supply chain.

EFPIA MEMBER ASSOCIATIONS

Austria
Fachverband der Chemischen Industrie Österreichs (FCIO)

Belgium
Association Générale de l'Industrie du Médicament (pharma.be)

Denmark
Laegemiddelindustriforeningen

The Danish Association of the Pharmaceutical Industry (Lif)

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Greece
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Irish Pharmaceutical Healthcare Association (IPHA)

Italy
Associazione delle Imprese del Farmaco (Farmindustria)

Netherlands
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Norway
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Norwegian Association of Pharmaceutical Manufacturers (LMI)

Poland
Employers Union of Innovative Pharmaceutical Companies (Infarma)

Portugal
Associação Portuguesa da Indústria Farmacêutica (Apifarma)

Russia
Association of International Pharmaceutical Manufacturers (AIPM)

Spain
Asociación Nacional Empresarial de la Industria Farmacéutica (Farmaindustria)

Sweden
Läkemedelsindustriföreningen

The Swedish Association of the Pharmaceutical Industry (LIF)

Switzerland
Verband der forschenden pharmazeutischen Firmen der Schweiz (Interpharma)

Turkey
Arastirmaci Ilac Firmalari Dernegi (AIFD)

United Kingdom
The Association of the British Pharmaceutical Industry (ABPI)

ASSOCIATIONS WITH LIAISON STATUS

Bosnia-Herzegovina: Association of Research-based Medicine Producers (UIPL)
Bulgaria: Association of Research-based Pharmaceutical Manufacturers in Bulgaria (ARPharM)
Croatia: Innovative Pharmaceutical Initiative (iF!)
Cyprus: Cyprus Association of Pharmaceutical Companies (KEFEA)
Czech Republic: Association of Innovative Pharmaceutical Industry (AIFP)
Estonia: Association of Pharmaceutical Manufacturers in Estonia (APME)
Hungary: Association of Innovative Pharmaceutical Manufacturers (AIPM)
Iceland: Icelandic Association of the Pharmaceutical Industry (FRUMTÖK)
Latvia: Association of International Research-based Pharmaceutical Manufacturers (SIFFA)
Lithuania: The Innovative Pharmaceutical Industry Association (IFPA)
Luxembourg: Innovative Medicines for Luxembourg (IML)
North Macedonia: Association of Foreign Innovative Pharmaceutical Manufacturers (HOBA)
Malta: Maltese Pharmaceutical Association (PRIMA)
Romania: Association of International Medicines Manufacturers (ARPIM)
Serbia: Innovative Drug Manufacturers' Association (INOVIA)
Slovakia: Slovak Association of Innovative Pharmaceutical Industry (AIFP)
Slovenia: Forum of International Research and Development Pharmaceutical Industries (EIG)
Ukraine: Association of Pharmaceutical Research and Development (APRaD)

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