2023

EU PHARMACEUTICAL PACKAGE:

A MORE COMPETITIVE AND ATTRACTIVE EU FOR SMALLER COMPANIES

A EUCOPE Position Paper

EUCOPE
European Confederation of Pharmaceutical Entrepreneurs AISBL

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Executive Summary

EUCOPE acknowledges the objectives of the EU Pharmaceutical Package. The revision of the general pharmaceutical legislation, the Orphan Medicinal Products (OMP) and Paediatric Regulations, is fundamental to fostering innovation, access and ensuring a future-proof, crisis-resistant EU regulatory ecosystem. Such a revision should build on the success over the last 20 years and enhance the biopharmaceutical competitiveness and attractiveness of the European Union (EU).

EUCOPE welcomes several of the proposals, such as the streamlining, digitalisation and acceleration of regulatory processes, strengthening (early) scientific advice for orphan medicinal products (OMPs), and openness to Real-World Evidence (RWE). However, these aspects do not outweigh other provisions, especially the proposed reduction of baseline incentives in the EU, with the linkage of conditionalities which will be unnecessarily difficult to achieve. Such provisions introduce more risks and unpredictability into the ecosystem, and will likely hamper innovation, reduce investments, and make EU life sciences less competitive and attractive, particularly for small and mid-sized companies. This would have long-term implications for the availability of innovative therapies in the EU and jeopardise access to medical innovations for EU citizens living with all kinds of diseases, from acute to chronic, as well as rare diseases, 95% of which have no treatment options yet.

(High) Unmet Medical Need (HUMN)
EUCOPE acknowledges the need to steer investments toward underserved areas, but this should not be done on the basis of the strict and unpredictable concept of (high) unmet medical need ((H)UMN). Vague concepts such as ‘exceptional therapeutic advancement’ and ‘meaningful reduction in morbidity or mortality’ introduce more unpredictability and unclarity. The Commission’s approach introduces uncertainty in the ecosystem and does not address the underlying barriers to research and development (R&D), especially in rare diseases. Labelling a product as not addressing (H)UMN will have significant P&R implications, inform investment decision whether to pursue R&D activities in certain disease areas and the commercial viability of a therapy, and it will ultimately jeopardise broader patient access. First-to-market therapies do not necessarily address the needs of the entire patient population living with a given disease. Modulation based on HUMN risks hampering innovation and overlooking the needs of diverse patient populations living with a rare disease.

Incentives
Regulatory Data Protection (RDP) is recognised as a key incentive for developing innovative treatments. Similarly, a predictable Orphan Market Exclusivity (OME) framework provides incentives to develop orphan medicines for rare diseases. The proposed reduction of baseline incentives, such as RDP and OME, and modulation based on conditionalities will hinder innovation and make the EU less competitive on the global stage, undermining what used to be a competitive advantage for the EU. Any reduction in RDP will disproportionately affect biopharma companies, especially small and mid-sized ones. Conditionalities will increase unpredictability and risk reducing investments in the EU, with knock-on effects on innovation for

patients. Many small and mid-sized companies have a limited portfolio of therapies, which means that a strong and predictable incentive framework is fundamental to their sustainability within the EU, and for investment and research into complex areas.

Launch conditionality

EUCOPE's members are committed to making their therapies available to patients as widely as possible. However, launching in all 27 Member States is virtually impossible, particularly for Advanced Therapy Medicinal Produc (ATMP) and OMP developers or smaller companies. A launch conditionality ('released and continuously supplied'), where developers only receive their full exclusivity period for launching in all Member States within a limited timeframe is punitive and will not address the underlying access challenges. The proposal does not appropriately consider the infrastructure requirements, implications of small patient populations, or resource limitations of smaller developers. It poses unfeasible challenges for smaller companies in terms of navigating complex reimbursement processes, pricing negotiations, supply logistics, and market access requirement. These processes are not only time-consuming and resource intensive, but the outcome is uncertain, as it does not depend solely on the developer or marketing authorisation holders (e.g., P&R decisions or national priorities).

Recommendations

EUCOPE has developed the following recommendations to ensure the revision of the pharmaceutical legislation builds a future-proofed ecosystem that balances innovation and access, and keeps the EU attractive and competitive for pharmaceutical investments, especially for small and mid-sized companies.

- **Recommendation 1**: Remove the HUMN concept from the Regulation, which will be replaced with an alternative approach to modulation (see Recommendation 3)
- **Recommendation 2**: De-link the use of a concept such as UMN as the main criteria for modulation of the incentive framework, while maintaining a broad understanding of unmet needs for regulatory purposes, namely continued use of existing regulatory instruments (e.g., conditional marketing authorisation, PRIME) to anticipate stepwise, breakthrough or incremental innovation.
- **Recommendation 3**: Adopt a modulated approach to OME that reflects the framework and principles outlined by the OD Expert Group, introducing three distinct architypes, while maintaining the 5 years for well-established use therapies. Such an approach will support development for the 95% of rare diseases that have no authorised therapies, while continuing to allow for innovation in disease areas where patients can benefit from it.
- **Recommendation 4**: The legislation must not remove incentives to develop new indications for a given medicinal product with an orphan drug designation. Update the proposed GOMA principle (Global Orphan Marketing Authorisation – whereby an API receives only one period of Market Exclusivity) to ensure that it remains attractive (instead of riskier) for developers to invest in continued research for established therapies which might address existing unmet needs by extending the period of duration of exclusivity and number of times an extension can be offered.
- **Recommendation 5**: The reference to 'substantial part' should be removed from the legally binding definition of Significant Benefit, or be replaced with 'relevant part', ensuring that sufficient flexibility is built into the system allowing for a nuanced assessment that avoid therapies that merit Orphan Drug Designation from being unnecessarily disqualified to the detriment of patients and developers.

- **Recommendation 6**: Build on the current strong and predictable regulatory protection framework, ensuring a baseline of 8 years of regulatory data protection (RDP), followed by 2 years of market protection as a minimum threshold.
- **Recommendation 7**: Leverage existing legislation, such as the Transparency Directive, the Cross-border healthcare Directive and the S2 Regulation, to make products available and improve access to innovative therapies across the EU. The launch conditionality should be removed from the proposal as it will not address the desired aims.
- **Recommendation 8**: Implement a more balanced, proportionate and science-based approach that focuses on the primary goal of granting more equitable access to high-quality and innovative medicines and does not overburden small and mid-sized companies with comprehensive additional environmental compliance requirements.
- **Recommendation 9**: Request that the shortage prevention plan (SPP), established in Article 117 of the Regulation, is applied only for medicinal products on the EU list of critical medicines, and automatically exempt products, such as ATMPs and OMPs, from SPP.
- **Recommendation 10**: Reduce the marketing authorisation holder notification requirements, set in Article 116 Regulation, to four (4) months for permanently ceasing or withdrawing marketing of a medicinal products, and to two (2) months for temporary suspension or disruption of supply.
- **Recommendation 11**: Ensure that the scope of the Regulatory Sandbox is flexible enough to anticipate technological advancements including healthcare solutions encompassing medical devices or in-vitro diagnostics.
- **Recommendation 12**: Ensure all OMPs are eligible for the PRIME scheme.
- **Recommendation 13**: Provide the EMA with the necessary capacity, expertise and resources to carry out its tasks, as well as retaining the expertise gained over time from current committees (CAT, COMP and PDCO) in the form of working parties.
- **Recommendation 14**: Perform the switch from paper to electronic package leaflets as quickly as possible, starting with hospital-only products.
- **Recommendation 15**: Create a Master File for Platform Technologies in the Directive in line with the proposal for an Additional Quality Master File.
- **Recommendation 16:** Calls for increased harmonisation regarding the use of Hospital Exemption (HE) and a clear definition of the concept of non-routine use. The use of HE should be limited to circumstances when there is no authorised ATMP, clinical trial or compassionate use programme the patient would be eligible for.
- **Recommendation 17**: Ensure that, in line with scientific realities, appropriate time is given in cases of PIP deferrals and that they are not capped at 5 years.
- **Recommendation 18**: Maintain the requirement of ‘placing on the market’ as currently required by article 33 of the Paediatric Regulation No 1901/2006.
- **Recommendation 19**: Define strict rules under which article 75.1(b) of the Regulation apply (e.g., oncology products only).
- **Recommendation 20**: Implement a framework for safe off-label use and pharmaceutical compounding, to meet patients' individual medical need.

Introduction

EUCOPE acknowledges the overall objectives of the proposed EU Pharmaceutical Package: we are committed to creating an innovative and competitive EU healthcare ecosystem at a global level, investing in R&D, and increasing equal access to and availability of innovative medicines to patients across the EU. We call for a careful and better-balanced approach between sustaining innovation and providing patient access. As part of the ongoing review, it is essential that the new system builds on the successes of the past 20 years and does not disregard them.

We welcome maintaining a separate Directive and Regulation for decentralized and central approval processes. We appreciate measures that aim to accelerate, streamline and adapt regulatory processes to scientific progress, but we are concerned that certain provisions will undermine R&D, innovation, and EU competitiveness, therefore delaying access to innovative therapies. This would be detrimental for healthcare systems, small and mid-sized innovative biopharmaceutical companies, and most importantly, for patients living in the EU. The innovative pharmaceutical industry incurs significant risks in discovering and developing new medicines.

A competitive environment will increase investments in R&D in the EU, therefore bringing more innovative products to patients, which will therefore benefit from more treatment options. The 2016 Council Conclusions recognised the potential need for a revised pharmaceutical framework, but stressed that any revision, including to the incentive framework, should not discourage the development of medicinal products needed for the treatment of rare diseases[1].

Unmet Medical Needs (UMN) and High Unmet Medical Needs (HUMN)

Recognising that important unmet needs remain among patient populations and diseases areas, EUCOPE is concerned about using concepts such as UMN (Art. 83 Directive) and HUMN (Art. 70 Regulation) to narrowly label therapies and modulate incentive frameworks. This will have serious and far-reaching implications for patients because of its potential impact on the development and commercial viability of therapies that could otherwise bring significant improvements to patients' lives.

We are concerned that the proposed concepts of UMN and HUMN in the EU Pharmaceutical Package have restrictive interpretations which can stifle innovation by introducing additional unpredictability into the system. The use of concepts such as 'meaningful reduction of morbidity or mortality' and 'exceptional therapeutic advancement' are also unclear and open to interpretation, reducing predictability thereby increasing investment risks, including in therapy areas which are already at a high risk of failure (e.g., neuroscience). The need to demonstrate (H)UMN at an early stage of development also poses challenges.

[1] Council Conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States. July 2016, available at https://op.europa.eu/en/publication-detail/-/publication/b49097b2-5096-11e6-89bd-01aa75ed71a1/language-en.

In some cases, the full benefit or impact of a therapy may only be demonstrated with real-world data or following long-term post-authorisation studies. Such longitudinal evidence cannot exist at the point of marketing authorisation, representing a significant barrier for developers.

The first-to-market products do not necessarily address the needs of all the patients in a population group. Not all patients are the same, both across disease areas and within the same disease; some might not respond to or benefit from existing therapies, while others may still benefit from further innovation that offers better or more appropriate treatments. In many new scientific areas, research for treatment options usually moves from treating symptoms of a disease, to treating the root cause of a disease or even prevention. Similarly, the discussions around (H)UMN also risk excluding subpopulations within a disease area if the concept is not appropriately framed. By introducing an exclusively binary system for interpreting patient needs – it intrenches only certain unmet needs and discourages innovation in areas where patients could continue to benefit from innovation.

Concepts such as HUMN risk creating a *de facto* ranking of people living with a rare disease and overlooking the needs of diverse patient populations. Linking HUMN to the OMP incentive framework does not recognise the fundamental challenges and shortcomings contributing to the 95% of rare diseases that have no authorised treatment, mostly due to a lack of basic scientific knowledge and small patient populations. Moreover, in many cases where treatments are available, they are symptomatic, and further innovation could bring significant benefits to patients' lives, in addition to contributing to advancing scientific progress, disease diagnosis and the general knowledge (e.g., natural history) of rare diseases.

In the context of OMPs, developers must already demonstrate significant benefit and clinical superiority of a therapy before they receive orphan designation. Thus, the 'test' of HUMN creates additional hurdles for developers, especially as these 'tests' look at similar criteria, through different lenses, requiring additional clinical data to meet a nebulous concept.

The discussion is further complicated by the fact that UMN assessments already take place at the national level with HTA and P&R bodies having their own (different) definitions. Thus, an EU definition could lead to a situation where a therapy needs to be assessed for (H)UMN on several different occasions, creating further bureaucracy that deters investment and innovation.

Recommendation 1: Remove the HUMN concept from the Regulation, which will be replaced with an alternative approach to modulation (see Recommendation 3)

Recommendation 2: De-link the use of a concept such as UMN as the main criteria for modulation of the incentive framework, while maintaining a broad understanding of unmet needs for regulatory purposes, namely continued use of existing regulatory instruments (e.g., conditional marketing authorisation, PRIME) to anticipate stepwise, breakthrough or incremental innovation.

Orphan Incentive Framework

Orphan Market Exclusivity (OME) is a key incentive to develop OMPs due to the inherently small patient populations.

EUCOPE acknowledges the need for and ambition behind a modulated OME framework. Such an approach should incentivise the development of therapies in areas with no meaningful treatment options, without discouraging innovation for conditions where patients can continue to benefit from it. Therefore, rather than the Commission's proposed approach to modulating OME (Art. 71 Regulation) based on HUMN and a requirement to 'release and continuous supply' a therapy in all 27 Member States, EUCOPE calls for the introduction of the modulated framework developed within the OD Expert Group which allows for upward and downward modulation. The approach to modulation developed by the OD Expert Group, a multi-stakeholder group of rare disease experts, introduces three archetypes on which OME would be based:

1. 12 years for the first authorised product for the treatment, diagnosis or prevention of a given rare condition;
2. 10 years for products based on new technology/mechanism of action for a given rare condition, or addressing a population subset/clinical manifestation of a rare condition not sufficiently served by existing authorised products;
3. 8 years for all other products.

This approach is based on 5 key principles:

1. The orphan incentive framework should be modulated to incentivise the development of different OMPs, differing in terms of their investment case;
2. Modulation should be based on a combination of criteria, not solely a restrictive unmet need definition;
3. Legal certainty and predictability are key;
4. Incentives need to include and go beyond modulation of ME;
5. Maintain broad orphan drug designation and modulate within.

EUCOPE is concerned by the approach taken by the Commission **in implementing the concept of a "Global Orphan Marketing Authorisation" (GOMA)**, namely a single dossier for new indications under the same marketing authorisation (MA), providing a single period of orphan market exclusivity for each 'molecule' rather than the disease area (Art. 71.3 Regulation). In its current form, it risks discouraging stepwise innovation, which is essential to people living with a rare disease, as well as investments in additional indications more broadly, due to the increased risk. The proposal presented by the Commission discourages developers from continuing to leverage the knowledge related to a compound or mechanism of action into a new indication. A reasoned approach should be taken to encourage developers to continue building on the scientific knowledge about disease status and therapy modes of action to address unmet needs, especially if this opens the door for treatments for those patients with no other options.

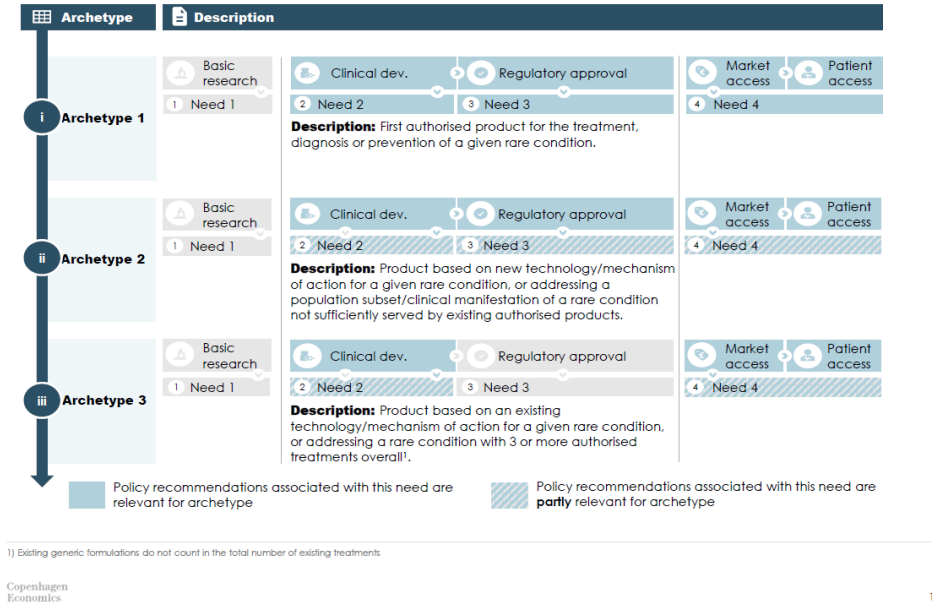
Significant Benefit (Art. 2.7 Regulation) is the 'entry door' for all orphan incentives, at both EU and national level. The concept of Significant Benefit in its current form has worked well and should be maintained. Making it more difficult to be designated as an OMP, or to receive an orphan MA, will not solve the problem

of the 95% of rare diseases not having an authorised treatment. The concept of 'substantial part' in the proposed definition, is hard to define and adds further unpredictability into the system, making it even harder for companies to invest in OMPs, an already risky investment. As a step forward, the Commission should also move away from the current system where Significant Benefit must be reassessed at several points in the development lifecycle. The current model of reassessment introduces further uncertainty into the already highly risky orphan development process. Other world regions, such as the United States of America, forgo the reassessment of orphan status after it has been granted.

Finally, the change in competence, whereby the European Medicines Agency has the authority to award Orphan Drug status is welcomed, as it will reduce timelines and administrative procedures when compared to the current system, and hopefully free up resources for the Agency and Commission.

Recommendation 3: Adopt a modulated approach to OME that reflects the framework and principles outlined by the OD Expert Group, introducing three distinct architypes, while maintaining the 5 years for well-established use therapies. Such an approach will support development for the 95% of rare diseases that have no authorised therapies, while continuing to allow for innovation in disease areas where patients can benefit from it.

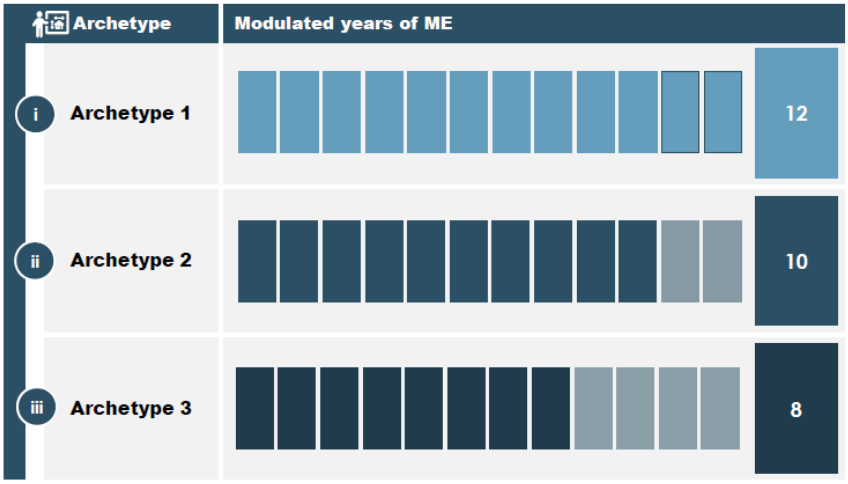
The operational model for modulation consists of 3 archetypes of OMP development projects



1) Existing generic formulations do not count in the total number of existing treatments

Copenhagen Economics

OD Expert group proposal for modulation of ME



Recommendation 4: The legislation must not remove incentives to develop new indications for a given medicinal product with an orphan drug designation. Update the proposed GOMA principle to ensure that it remains attractive (instead of riskier) for developers to invest in continued research for established therapies which might address existing unmet needs by extending the period of duration of exclusivity and number of times an extension can be offered.

Recommendation 5: The reference to 'substantial part' should be removed from the legally binding definition of Significant Benefit, or be replaced with 'relevant part', ensuring that sufficient flexibility is built into the system allowing for a nuanced assessment that avoid therapies that merit Orphan Drug Designation from being unnecessarily disqualified to the detriment of patients and developers.

Regulatory Data Protection (RDP)

Regulatory Data Protection (RDP) is a key incentive to translate research into development of innovative therapies, and to ensure those therapies enter the EU market and are available to patients in a timely manner. RDP rewards companies for the investment and risks associated with developing a therapy and undertaking the needed clinical trials. It makes the EU more attractive and competitive at the global level, incentivising companies to invest in the development of innovative therapies. It also supports commercialising such therapies in the EU, as it protects clinical trial data, while giving time to companies to go through lengthy HTA and P&R procedures, across the different 27 EU Member States.

The EU is a leader in early research but faces barriers in overcoming the innovation gap – translating research into development. RDP helps to address this specific challenge, by allowing developers to build on innovative thinking and make it available to patients. This process requires predictability in the incentives, which would be missed by reducing RDP baseline and extending it by attaching conditionalities, such as

the definition of UMN and 'launch' ('released and continuously supplied') in all EU Member States. These conditions are very hard to meet and unlikely to compensate for the loss of the predictable RDP period.

The proposed modulation of RDP (Art. 80-81 Directive) will hinder innovation and accessibility of this innovation to patients in the EU, and make the EU less competitive at global level, taking away what was an advantage for the EU in attracting investments, and turning it into a regulatory burden for industry. The uncertainty around the incentive period could lead to changes in investment decisions, including research and launch priorities. Any reduction in RDP will disproportionately affect small and mid-sized companies who often depend on external investments. Increased unpredictability will affect companies' R&D investments in the EU, reducing development of innovative therapies and limiting patients' access to innovative medicines against life-threatening diseases. Many small and mid-sized companies have a limited portfolio of therapies, which means that RDP is imperative to corporate sustainability within the EU. When considering the increased uncertainty regarding regulatory stability and revenue brought on by the modulated RDP system, biotech companies that are not profitable and do not have operations in Europe will not be able to afford the required investment to set up operation in the EU. This translates to fewer investments in this region and a reduction in access to medicines to patients.

The new provision (Art. 84 Directive), rewarding repurposed products with 4-year RDP, is welcomed. However, restricting incentives for drug repurposing to very old off-patent medicines (over 25 years), and only offering data protection periods once for any given medicinal product, may limit the impact of such provision. We urge removing these restrictions on repurposed products, to ensure innovation is continuously carried out in this field.

Recommendation 6: Build on the current strong and predictable regulatory protection framework, ensuring a baseline of 8 years of regulatory data protection (RDP), followed by 2 years of market protection as a minimum threshold.

Launch conditionality ('Released and continuously supplied')

EUCOPE welcomes the Commission's aim to provide broader and more equal access for patients in all EU Member States. EUCOPE's members are committed to making their therapies available as widely and quickly as possible, through any existing paths, be it filing and undergoing P&R procedures, cross-border healthcare, compassionate use, early access programmes, named patient programmes, patient supply or individual reimbursement. Crucially, the review of the pharmaceutical legislation also represents an opportunity to reflect on how existing pathways which are beyond the scope of this legislation can be updated and optimised to truly address the fundamental access barriers.

However, the proposed launch conditionality ("*released and continuously supplied into the supply chain in a sufficient quantity and in the presentations necessary to cover the needs of the patients*", Art. 81 Directive and Art. 72 Regulation) does not address the underlying challenges to patient access and may instead have a negative impact on access. Launching in all Member States within two or three years from marketing authorisation is virtually impossible, especially for small and mid-sized pharmaceutical companies who

would struggle or be unable due to their limited resources (for instance, no commercial presence in a Member State makes is difficult to go through the HTA and P&R process or limited manufacturing capacity). It is equally challenging for specific therapies, such as OMPs and ATMPs, where patient populations, adequate infrastructure and/or expertise may not be present in all Member States.

First, it is essential to recognise that the biopharmaceutical industry is not the sole decision-maker involved in launch and access decisions within the EU. Various factors and different determinants shape access decisions, not only price, many of which are outside the control of industry. National health priorities and budgets, healthcare infrastructure, how HTA bodies determine value and commercial viability are some of the factors that inform access decisions. Moreover, several EU Member States cannot complete a pricing discussion before a developer has completed P&R processes in a number of other countries (the so-called "external reference pricing" system). Examples of this practice include Bulgaria, which requires five (5) markets to be funding a therapy before they will engage in P&R discussions, as well as Romania which requires twelve (12)[2], [3] markets to have reached a pricing agreement with public prices before P&R negotiation begins. A consequence of this policy is that it can lead to delays or longer timelines for therapies to be launched in specific Member States.

Moreover, as currently proposed, most of the burden falls on the developer. Member States would have full negotiation power and there is little to no incentive for them to offer a waiver and no means (such as a "dispute resolution mechanism") to appropriately address the scenario whereby, even if both parties negotiate in good faith, an agreement cannot be reached in the pre-defined timeframe, in which case, only the developer will be penalised with a reduction in their protection period. To this extent, the "Transparency Directive" contains important provisions, such as timelines for P&R decisions, which should be properly implemented.

Second, a blanket approach to driving launch does not take into account the unique characteristics of innovative technologies, such as ATMPs, or specific disease areas, such as rare diseases. EUCOPE members are committed to making their therapies available as widely as possible. However, major practical barriers exist. Small or non-existent patient populations in the case of rare diseases or infrastructure requirements for ATMPs mean launching in all Member States would not be technically feasible. This approach could lead to a delayed launch in the EU, giving advantage to other markets, ultimately achieving the reverse of the EU's objectives.

The discussion is further complicated by the fact that what constitutes "released and continuously supplied into the supply chain" is not clear in the legislation – introducing further uncertainty into the system. Different Member States can apply different criteria for what launching would entail in their jurisdictions, and have

[2] Radu, C.P et al, 2018. Drug Policy in Romania. Value in Health Regional Issues (16). Available at https://www.sciencedirect.com/science/article/pii/S2212109918300529#:~:text=Romania%20uses%20an%20external%20reference,drug%20and%20the%20therapeutic%20area.

[3] Kanavos, P et al, 2019. Does external reference pricing deliver what it promises? Evidence on its impact at national level. The European Journal of Health Economics (21). Available at https://link.springer.com/article/10.1007/s10198-019-01116-4

different rules apply to different therapies. Such a system would be opaque, unpredictable, and burdensome especially for small and mid-sized companies, undermining the attractiveness of the EU market without addressing the fundamental access barriers.

EUCOPE welcomes the Commission's recognition that small and mid-sized developers do face unique circumstances, but it still does not consider the challenges for such companies to launch in all EU Member States, maintaining a highly punitive approach. Fundamentally, due to the high barrier set by such a requirement, small and mid-sized developers may delay launching in the EU, so that they can establish the necessary resources and capacity to meet such conditions. This will lead to a scenario where access to innovative therapies is delayed.

Recommendation 7: The Union should leverage existing legislation, such as the Transparency Directive, the Cross-border healthcare Directive and the S2 Regulation, to make products available and improve access to innovative therapies across the EU. The launch conditionality should be removed from the proposal as it will not address the desired aims.

Environmental Risk Assessment (ERA)

EUCOPE supports the principle that medicinal products should have a minimal impact on the environment but questions the proportionality of the tightened environmental risk assessment (ERA) requirements the Commission is proposing. The more comprehensive ERA requirements are likely to increase the burden of compliance and costs, particularly for small and mid-sized companies. The challenge of pharmaceuticals in the environment requires a balanced approach, addressing the roles and responsibilities of all parties involved, from public services and industry to doctors, pharmacists, and patients. Refusing, suspending or withdrawing a marketing authorisation may jeopardise patient access to innovative and very often, life-saving therapies and undermine the Commission's objective to provide more equitable and affordable access to patients across the EU. Any measure, particularly *ultima ratio* measures such as the refusal or withdrawal of a marketing authorisation, must be proportionate, not jeopardise access to established as well as innovative medicines and guarantee a process to establish environmental compliance in a reasonable timeframe. The compliance should be based on qualitative evidence of the environmental risk, taking severity and impact on the environment into careful consideration.

More particularly, linking the decision on the prescription status to the presence of a persistent, bioaccumulative and toxic etc. substance in the medicinal product (as foreseen in Article 51(1) lit. f of the Directive) without taking the actual concentration of the substances and handling of the medicinal product into consideration, is not appropriate. To secure an adequate consideration of these environmental aspects of a medicinal product regarding the prescription status, the criterion foreseen in Article 51(1) lit. f of the Directive should be linked to the actual concentration of the (persistent etc.) active substance in the medicinal product and the actual risks.

Updating the environmental assessment for already approved products and the envisaged programme to update the ERA for products approved before 30 October 2005 will involve significant financial and human resources and will burden particularly small and mid-sized companies. There may also be the risk that companies reconsider commercialisation of their portfolio of approved drugs, potentially making established drugs unavailable to patients in the long term. The ERA for already approved products should be the rare exception and only apply in cases where there is an evidence-based, material environmental risk.

Recommendation 8: Implement a more balanced, proportionate and science-based approach that focuses on the primary goal of granting more equitable access to high-quality and innovative medicines and does not overburden small and mid-sized companies with comprehensive additional environmental compliance requirements.

Medicine Shortages

EUCOPE supports the goal of addressing medicine shortages in the Regulation and securing supply chains. However, a shortages mitigation and prevention framework must be reasonable, shortage-risk adequate and only apply to a list of critical medicines in the EU where unavailability or shortages may result in a serious threat to public health (including cross-border). The EU list of critical medicines must be drawn up in collaboration with marketing authorization holders (MAHs) and allow for consultation and objection (based on justifiable reasons) by MAHs. EUCOPE further calls on the Commission to eliminate the duplication of requirements at national levels, which encumber small and mid-sized companies. Usually, research-based companies do not face shortage issues and rely on API and supply chains based in the EU (or the US, to a lesser degree).

The level of detail required in a shortage prevention plan (SPP) triggers additional bureaucracy and is burdensome for small and mid-sized companies, particularly due to their limited resources. Moreover, it should be considered to limit this requirement solely to critical medicines and exclude products, such as ATMPs and OMPs, which are unlikely to face shortage issues, but rather require unique and tailored go-to-market models and distribution requirements (e.g., direct-to-hospital supplies).

The proposed notification requirements for upcoming cessations, suspensions or withdrawal of the marketing of medicinal products, especially in case of disruptions, are not realistic, as company decision-making process depend on various factors and cannot always be anticipated in the timeframe set out in the proposal (six or even twelve months in advance). We see the risk that the proposed notification periods could lead to a higher risk of shortages or jeopardise security of supply. More realistic notification requirements should be considered, for instance, a two-month notification period for temporary disruptions and a four-month period for withdrawal decisions. Moreover, it is fundamental to apply the Quality Risk Management principles to commensurate the level of documentation with the level of risk, as it would be the case of different notification requirements at EU and Member States levels. A better coordination of such processes should be ensured by the Regulation.

We also call on the Commission to keep the requirements for contingency stocks or other relevant measures with the companies, because such measures could contribute to shortages and disruptions.

Recommendation 9: Request that the shortage prevention plan (SPP), established in Article 117 of the Regulation, is applied only for medicinal products on the EU list of critical medicines, and automatically exempt products, such as ATMPs and OMPs, from SPP.

Recommendation 10: Reduce the marketing authorisation holder notification requirements, set in Article 116 Regulation, to four (4) months for permanently ceasing or withdrawing marketing of a medicinal products, and to two (2) months for temporary suspension or disruption of supply.

Regulatory provisions

EUCOPE appreciates the Commission's goal to promote innovation and novel technologies in the EU by **simplifying and streamlining the regulatory framework** to reduce the regulatory burden. In particular, EUCOPE is pleased to see the strengthened scientific advice and regulatory support of EMA for developers of products addressing unmet needs, as well as the proposal's efforts to enhance digitalisation (for instance, through mandatory electronic submissions and new provisions on ePI). EUCOPE also sees opportunities deriving from adapted clinical trials, use of real-world evidence (RWE), and the introduction of a regulatory sandbox concept. We regret the limited scope and lack of flexibility regarding the eligibility for **PRIME** (PRIority MEdicines) scheme, being limited only to OMPs that address a HUMN. We welcome the integration of a **phased review** of data but recommend a more flexible approach which is not solely limited to those products which may offer an 'exceptional therapeutic advancement' in the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious chronic condition in the Union. The current wording (Art. 6.2 Regulation) also suggests that only complete data packages can be subject to a phased review (next to the other mentioned requirements), which would undermine the use of a phased review in situations where needed.

The planned introduction of the **electronic package leaflet (ePi)** is highly appreciated. ePI is user friendly and easily available, and it delivers important drug information to the right recipients at a fast pace, thus strengthening patient safety. Since ePI will be available in different languages it will facilitate drug supply across Member States and, therefore, help to ameliorate or prevent potential drug shortages. ePI is a part of the European digitalization strategy. We recommend that the switch to electronic package leaflets is performed as quickly as possible and that the necessary transition phase during which two versions (paper and electronic) are supplied is kept as brief as possible, in order to support mitigation of supply challenges and increased access to information for patients. For example, the switch to "ePI only" could occur very quickly for hospital only products. Establishing the legal equality of the paper version with the electronic version would also be useful. The neat integration of ePI structures under development at EMA (authoring tool/ repository) with national authority platforms is as mandatory as the obligation to use the ePI common standard across the EU for all national ePI solutions.

We welcome the **streamlining of the EMA's committee structure** in consideration of the overall broadening of competencies of the EMA in other areas (e.g., Joint Audit Programme, ERA requirements, availability and security of supply of medicinal products already introduced with the Extended Mandate Regulation in April 2022) and the reduction to two permanent committees (CHMP and PRAC), as a provision that could accelerate decision-making within the Agency and reduce silos, while still ensuring quality, safety and efficacy of new medicinal products and maintaining qualitative expertise. We also welcome the broader representation and increase of expertise from healthcare professionals and patients. It is of ultimate importance to provide EMA with the necessary capabilities, capacity, expertise and resources to carry out its tasks, as well as retaining the expertise gained over time from current committees (such as COMP, CAT and PDCO). Such expertise should inform the scientific working parties or scientific committees that EMA will create in return for abolishing certain permanent committees. Due to the unique nature of these therapies, the dedicated expertise is particularly important. As an example, the EMA should retain the expertise to assess cases of borderline when discussing ATMPs. It is also crucial that the level of transparency of EMA remains at the highest standard, both at the level of the permanent committees and working parties, in order to ensure adequate reporting and information on the Agency's processes and decisions.

We also appreciate that the **regulatory decision-making timelines** are reduced from 210 to 180 days to issue the CHMP opinion, and from 67 to 46 days to grant the MA by the European Commission; this would allow streamlining regulatory decisions and make patient's access to innovative therapies faster, yet subject to national pricing and reimbursement decisions.

However, the Directive and the Regulation do not establish clear time limits for the validation of MA applications (and variations) although several time limits are connected to the validation and processing of a MA application or variation (e.g., Article 29 (4), Article 30 of the Directive). If the competent regulatory authority does not validate the application, the time limit of 180 days (Article 30 of the Directive) and other time limits cannot start. Thus, delays in the procedure are currently not being sufficiently prevented. In addition, the rules on deficiencies of MA applications should be slightly adjusted for the benefit of legal certainty. Article 29 (3 and 4) of the Directive as well as articles 5 (6) and 10 (2) of the Regulation currently stipulate that in case of failure of the applicant to provide missing information or address deficiencies within the given time limit, the MA application "*shall be considered as withdrawn*". This may cause considerable legal uncertainty for the applicant as well as for the competent regulatory authority, as it may not always be clear if the requirements that trigger the consideration of withdrawal are met.

EUCOPE welcomes the introduction of the **"Regulatory Sandbox"** concept into the pharmaceutical sector and to transfer the learnings from other highly regulated sectors, such as the financial services/technology sector. EUCOPE believes that such a framework must be broad enough in scope to allow for technological developments which are already a reality today or are yet to emerge. A future-proof regulatory ecosystem that is fit for purpose for the next 25 to 30 years requires a framework that allows regulatory experimentation for products and healthcare solutions that cannot yet be described. Such a system serves as a basis for the approval of new, innovative and often revolutionary technologies (including products and services using artificial intelligence (AI), evolving drug-device combination products, personalised medicine, platform

technologies, etc.) while ensuring compliance with laws and regulations, particularly with respect to efficacy, safety and the risk-benefit profile of a product or service without undermining the established regulatory system. A Regulatory Sandbox must naturally come with appropriate regulatory guardrails.

There could be a need to further experiment with the interface between therapies (including ATMPs) and medical devices. We therefore call for a predictable system with sufficient flexibility for regulatory science to evolve together with the advances in science and technology in line with the Commission's intention for a system that takes proactive regulatory learnings.

Recommendation 11: Ensure all OMPs are eligible for the PRIME scheme.

Recommendation 12: Perform the switch from paper to electronic package leaflets as quickly as possible, starting with hospital-only products.

Recommendation 13: Provide EMA with the necessary capacity, expertise and resources to carry out its tasks, as well as retaining the expertise gained over time from current committees (CAT, COMP and PDCO) in the form of working parties.

Recommendation 14: Ensure that the scope of the Regulatory Sandbox is flexible enough to anticipate technological advancements including healthcare solutions (e.g., combination products) encompassing medical devices or in-vitro diagnostics.

Platform technologies

Platform technologies, including mRNA technologies, the use of AAV, and some gene therapies, are an area of innovation for both current and future therapies. The potential of these technologies, including in the development of faster vaccines and therapies for patients, is recognised by the U.S. Congress Consolidated Appropriations Act, 2023, (P.L. 117-328) and the Commission in art. 15 of the proposed Directive. To maximise the impact of such therapies, a separate regulatory 'Master File' should be established for Platform Technologies, building on the Additional Quality Master File proposed by the European Commission in art. 26 of the proposed Directive.

Recommendation 15: Create a Master File for Platform Technologies in the Directive in line with the proposal for an Additional Quality Master File.

ATMPs

EUCOPE welcomes the Commission's endeavours to facilitate multi-country clinical trials in the EU by exempting ATMP developers from parts of the **GMO Directive** (Directive 2001/18/EC). The changes foreseen in Article 177 of the proposed Regulation that would ensure developers only need to submit a single assessment for therapies containing or consisting of a GMO in the context of the ERA, rather than receiving approval in each Member State a clinical trial will be conducted. This is an important step in the

right direction and would significantly reduce administrative burdens. This will facilitate the conduct of multi-site/national clinical trials and address challenges regarding the EU's global competitiveness and patient access to potential new therapies. EUCOPE would urge the EU to go further and provide a full derogation for therapeutic ATMPs from the GMO Directive, as was done in the case of the COVID-19 vaccines and is provided for in the current proposal in the case of Compassionate Use.

EUCOPE strongly welcomes the Commission's efforts to strengthen the collection of data regarding the use, safety, and efficacy of **hospital exemption** (HE) in the Directive (Art. 2 Directive) which will provide an essential overview of HE, safeguarding patient safety and providing a basis for evidence-based and informed future policy-making. We also welcome the continued use of HE as an exemption and an important tool to address the unmet needs of individual patients, when there are no authorised ATMPs for a given indication clinical trial or compassionate use programme. The Directive puts forward important proposals that will improve the harmonisation of the HE across the Union which is welcomed by EUCOPE.

Recommendation 16: Calls for increased harmonisation and a clear definition of the concept of non-routine use. The use of HE should be limited to circumstances when there is no authorised ATMP, clinical trial or compassionate use programme the patient would be eligible for.

Paediatric

EUCOPE welcomes the Commission's commitment to maintain the six-month supplementary protection certificate (SPC) as the primary incentive to foster innovation in the paediatric R&D environment. To further stimulate paediatric R&D, we urge to expand this incentive to all products, including those granted via DCP/MRP and not authorised in all Member States (Art. 86.3 Directive). Moreover, to continue encouraging R&D, we call to ensure adequate reward for such products (e.g., prolonged SPC extension).

The introduction of 'evolutionary and simplified' Paediatric Investigation Plan (PIP) can also be a tool to support faster developments in the paediatric field. However, EUCOPE is concerned about the introduction of the five-year deferral cap for PIP completion (Art. 81.3 Regulation). Developers of paediatric medicines face great scientific, regulatory, and operational challenges. Extensive experience shows that there are difficulties in recruiting paediatric patients, especially when the study is placebo-controlled. Doses in paediatric studies need to be determined for each age-group by modelling and simulation, and each group may require a separate study to understand the safety and efficacy of therapies (starting with adolescents, then moving separately to younger children). Furthermore, innovative modalities, such as gene therapies or gene editing, require specific caution in transitioning from adult studies to paediatric ones if the targeted condition affects both groups. Paediatric diseases often exhibit significant heterogeneity. Developing a gene therapy for paediatric conditions, such as paediatric neurological disorders, requires identifying and targeting specific genetic mutations, which can vary among affected children. Ensuring the long-term safety and efficacy of gene therapies in paediatric populations is crucial. Monitoring patients over extended periods and understanding the potential risks associated with genetic modifications requires intensive efforts. Different issues arise with gene editing treatments for paediatric conditions. For instance, delivering gene editing tools to specific target cells in paediatric patients can be challenging since some delivery methods

pose safety concerns or are more invasive and may not be suitable for young children. Importantly, paediatric development is likely to be an iterative rather than a predictable linear process with long follow-ups for safety. Therefore, a blanket five-year expectation for completing a PIP is unrealistic and arbitrary, considering many advanced therapies are not scientifically compatible with paediatric development realities. On top of that, requiring companies to request a prolongation of deferrals at the latest 6 months before the deferral expires (Art. 82 Regulation) will place further regulatory burden on developers, as in certain cases, the need to prolong a deferral may also arise at a later stage.

In addition, Article 59 of the Directive requires, within two years from the date on which the paediatric indication is authorised, the compulsory placement on the market of medicinal products authorised for a paediatric indication in all Member States where other indications have been authorised. This is a more stringent obligation compared to the current legal framework, which requires placement in at least one Member State for centrally authorised products. Such requirement is not always feasible, especially for small and mid-sized pharmaceutical companies that struggle due to their limited resources. This provision does not consider the limited role that MAH have in the access processes and could lead to penalties for reasons that are out of the MAH's control. Finally, it does not consider that certain demand thresholds from patients must be reached before supply to a specific Member States becomes viable. This will further weaken the environment for investing in paediatric medicines in Europe.

In the proposed Pharmaceutical Package, a MAH is required to inform the competent authorities of its intention to discontinue the placing of the medicinal product on the market no less than 12 months before the discontinuation (Art. 60 Directive). The proposed timeframe of 12 months is not realistic, as MAH cannot foresee at such an earlier stage its intention to discontinue a product. Such notification period risks creating hiccups in availability of paediatric products. The current six-month period in the Paediatric Regulation (No 1901/2006) is therefore a more realistic timeframe.

The proposed Regulation introduces new requirements for PIPs in the development of medicinal products. Under these requirements, an applicant can still request a waiver if they provide evidence that the disease or condition targeted by the medicinal product only occurs in adult populations. However, based on existing scientific data, if the product targets a molecular target that is known to be responsible for a different disease or condition in children within the same therapeutic area, the paediatric requirements will apply (Art. 75.1(b) Regulation). This means that the developer is obliged to develop the product not only for the intended disease or condition in adults but also for the different diseases or conditions in children that the product effectively targets. This makes R&D for innovative medicines particularly unpredictable and burdensome for small and mid-sized companies, due to limited resources and budgets. Should this provision remain in place, strict rules and requirements under which conditions such developments might be performed must be defined (for instance, applying to oncology products only), to avoid undue burden on MAH alone.

Recommendation 17: Ensure that, in line with scientific realities, appropriate time is given in cases of PIP deferrals and that they are not capped at 5 years.

Recommendation 18: Maintain the requirement of "Placing on the market" as currently required by Article 33 of the Paediatric Regulation No 1901/2006.

Recommendation 19: Define strict rules under which Article 75.1(b) of the Regulation apply (e.g., oncology products only).

Well-Established Use Marketing Authorisation

EUCOPE is concerned about the limitation of the application based on bibliographic data (well-established use marketing authorisation, article 13 of the Directive) to cases where no reference medicinal product is or has been authorised in the EU for the active substance of the medicinal product concerned. Due to the broad definition of a "reference medicinal product" in the Directive, the remaining scope of the well-established use marketing authorisation would be substantially limited, as this restriction is not contained in current law. Currently, the use of the relevant active substance in a reference product is – on the contrary – seen as a possible proof of the medicinal use[4]. Linking the well-established use marketing authorisation to the absence of a reference medicinal product could lead to unlimited exclusivity for the reference product or to a market gap, if the MA of the reference product was revoked. With a view to the desired availability and affordability of medicinal products, this limitation of the well-established use marketing authorisation application cannot be understood and should be deleted.

Antimicrobial Resistance (AMR)

EUCOPE welcomes the AMR-related provisions, including the two 'pull' incentive mechanisms, namely the proposed Transferable Exclusivity Vouchers (TEV) as proposed in the Pharmaceutical Package (Art. 40-43 Regulation), and procurement mechanisms outlined in the Council Recommendation on "Stepping up actions to combat AMR in a One Health approach". Any incentive aiming at promoting the development of antimicrobials that are effective against resistant microbes is welcomed, and these EU proposals are a step in the right direction. To fight AMR, it will be important to incentivise the development of the adequate products and provide a financial incentive that is sufficient to encourage increased R&D investment and commercialisation across EU Member States.

Both these proposed provisions could be strengthened, to ensure they are suitable to meet the intended policy objectives, by:

- Avoiding an arbitrary cap on the number of products that can receive a TEV;
- Developing further operational plans for procurement mechanisms, showing coordinated financial commitment across the EU and Member States. This would provide the predictability that will encourage comprehensive commercialisation.

[4] See Notice to Applicants of the Commission (2019, p. 37).

Compulsory licensing

EUCOPE views the proposal for an EU-wide union compulsory license with serious concern since it contributes to undermining the important IP rights, and negatively impacts the life science industry. It will profoundly reduce the willingness to invest and commercialise in the EU. The granting of a compulsory license must in any case be seen as a last resort when all other attempts at voluntary licensing or other measures have failed. The current proposal has too few control mechanisms to ensure that the proposed union compulsory license is the last resort. The criteria for a "crisis mode" or "emergency mode" that would trigger the compulsory licensing option are defined in such a vague manner as it currently stands, that the compulsory license could be applied to scenarios outside of the public health threats (such as COVID-19), that the Commission purports to be contemplating.

We acknowledge that certain aspects of the proposal aim at taking the right holder's rights into account. However, these aspects cannot outweigh the negative signal of framing intellectual property rights as a barrier when in fact other obstacles (e.g., trade barriers, distribution chains and access to raw materials) have presented themselves in the past as preventative to an adequate crisis response. A compulsory license scheme already exists at national and global level (via the WTO TRIPS agreement), and the current proposal for an EU-wide compulsory license would interfere with these systems and it is unclear how this would be handled in practice.

An accelerated process for independent judicial review by the General Court is needed both prior to granting the CL, to make a determination on the Commission decision, and after to allow for independent review and determination of remedies if the CL is found to have been unlawfully granted.

It is also unclear what is meant by "suspension" of data and market protection (Art. 80.4 Directive) and its consequences for products marketed under a union compulsory license. A suspension of RDP might allow the unfair commercial use of the data to obtain marketing authorisation in the EU or other jurisdictions. It is also against Article 39 of the International Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). Moreover, any suspension of RDP must result in an equal extension of the original duration or rights would effectively be removed without compensation. Therefore, EUCOPE recommends that such provision is removed or, should compulsory licensing move forward, much stricter criteria are established for what could trigger a Union compulsory licensing, suspension of IP rights along with the introduction of independent judicial oversight.

Economic off-label use and compounding

While not optimal, off-label prescribing will remain essential to address some unmet needs (e.g., in oncology or paediatrics). However, the way Member States deal with the off-label use of medicines is not harmonised across the EU. Some Member States have passed legislation that promotes the off-label use of medicines for economic purposes. Since off-label products fall outside of the indicated label decided by the EMA, it risks undermining the high standards of regulatory approval concerning safety and efficacy when done at

large-scale and could discourage further innovation, while putting patients' safety at risk. Further, economic off-label use motivated by cost-considerations is not a practice based on individual patient needs, and therefore risks exposing patients to potential safety concerns, often without patients being informed or given a choice. A framework is therefore needed that can ensure good practice for off-label use of medicines, to ensure off-label prescribing can be done in a safe manner, based on patients' individual needs.

Pharmaceutical compounding can similarly play an important role for patients who have unique medical needs. However, recently "economic compounding" has in some cases been encouraged by national authorities to achieve healthcare budget savings to the detriment of patients' health outcomes and safety. There is a need to provide clear standards for compounding pharmaceuticals to ensure a safe and sustainable practice for such products alongside authorised medicines. General principles should be introduced in the legislation to ensure compounding is restricted to use based on medical grounds and not on economic considerations, and compounding should be subject to key regulatory obligations, including good preparation practices, good distribution practices and pharmacovigilance. EUCOPE is concerned by the addition of new text relating to magistral formulations that the Commission has added to the Directive (Art. 1.5 and 1.6). The lack of clarity regarding "in duly justified cases" risks that these provisions may be interpreted as a green light for increased "economic compounding" by pharmacies. Consequently, EUCOPE calls for the removal of, or the inclusion of clear language to define, "duly justified cases".

Recommendation 20: Implement a framework for safe off-label use and pharmaceutical compounding, to meet patients' individual medical need.

Transitional measures & Future Evaluations

There is a lack of clarity regarding the transition to the new Regulation and Directive when it pertains to therapies that were approved under the current (EC 726/2004 or 2001/83/EC) framework, which are extended to new indications after the date of application of the proposals. The uncertainty applies particularly to the regulatory support and incentives offered to those expanded indications, and how they would interact with incentives offered under the current system. All new indications approved after the date of application of the new legislation for a medicinal product approved under the current legislation should continue to fall under the current legislation.

As stated by the Commission (e.g., in SWD(2023)192 final, p. 71 and the Explanatory Memoranda for the Directive and the Regulation, p. 15 respectively), a meaningful evaluation of the results of the revised legislation can only be possible after at least 15 years from its entry into application. In the interest of consistency, the timeframe for the respective assessment reports should be amended accordingly from 10 to 15 years.