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ORPHAN MEDICINAL PRODUCTS LEGISLATION

THE WAY FORWARD

A Position Paper developed by the EUCOPE Incentives Steering Group

EUCOPE
European Confederation of Pharmaceutical Entrepreneurs AISBL

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THE ORPHAN MEDICINES REGULATION - THE WAY FORWARD

The European Commission launched an evaluation of the legislation on medicines for children and rare diseases. EUCOPE seizes the opportunity to outline ways to **strengthen the whole EU environment for the development of rare disease treatments**, of which the Regulation (EC) No 141/2000 on orphan medicinal products (OMP Regulation) is a key pillar.

Executive summary

The European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) Position Paper on the review of the OMP Regulation is composed of the three following sections:

1. **APPROACH AND COMMITMENT**
2. **RECOMMENDATIONS**
3. **CONCLUSIONS**

The first section outlines the approach we adopted to develop recommendations targeted to the review of the OMP Regulation, a key pillar of the EU environment for the development of OMPs. We believe that the review of the OMP Regulation should build on the success of the current EU legislation and recognise that addressing unmet needs in rare diseases is a multifaceted issue that cannot be solved by the revision of the Regulation alone. Hence, EUCOPE takes the approach of looking at solutions along the **whole lifecycle of rare disease therapies**. This approach is underpinned by our **commitment to multi-stakeholder collaboration**, involving Member States, medical and research community, biopharmaceutical industry and patients.

The second section presents four key recommendations aimed at the revision of the OMP Regulation and at strengthening the EU environment for the development of OMPs**.**

A. **An environment that fosters rare disease innovation in Europe**: the EU needs to strengthen its OMP R&D ecosystem by focusing on supporting the pre-clinical and clinical research into OMPs for European citizens. Support for research and development should be accompanied by appropriate healthcare infrastructure to fully exploit the potential of OMP development. Together, these elements would ensure support for rare disease innovation in Europe from R&D to delivery of care. This approach should take stock of and include existing initiatives such as the European Joint Programme on Rare Diseases, the European Reference Networks (ERNs) and the emerging European Health Data Space.

B. **A broad unmet need framework that attracts developers to underserved areas**: we need a holistic framework that attracts developers to underserved areas to ensure the unmet needs of rare disease patients are addressed. Improved incentives in the OMP Regulation, together with recommendations included in this paper, aim to provide the tools to address the unmet needs in the area of rare diseases. Rather than defining unmet need in the OMP Regulation, we call for a broad, criteria-based approach to orphan medicine designation and incentives that, as is the case now, goes beyond the absence of any approved therapeutic options. Disease severity, burden of illness and impact on the quality of life of patients (and specific subgroups among them) as well as the significant indirect costs for families and caregivers are also essential

elements when defining unmet needs. Predictable criteria to identify the rare disease patient population and award Orphan Drug Designation (ODD) are key components of addressing unmet needs and ensuring a stable framework for developers of OMPs. To ensure predictability and stability of the system, EUCOPE calls for the current prevalence threshold to be maintained as the main ODD criterion.

C. **Increased certainty around the concept of significant benefit**: a stable and predictable system to award and maintain ODD is a vital precondition to ensure continued investment in OMP R&D. The concept of Significant Benefit plays a pivotal role in this respect. On the one hand, there needs to be more alignment in the evidentiary standards required for the Significant Benefit assessment and for Marketing Authorisation (MA), for example by establishing a "conditional" Significant Benefit status, where evidence for proving Significant Benefit would continue to be provided post-MA. Such a concept needs further reflection and analysis with the cooperation of all relevant stakeholders. On the other hand, an ODD designation is not only a corner stone of the OMP Regulation, but should also serve as a building block for P&R processes at Member States level.

D. **A thoughtfully calibrated incentive design**: developing a thoughtfully calibrated incentive framework requires a thorough assessment as outlined by the Commission. We believe that modulating market exclusivity alone will not suffice, and especially if it only consists of a reduction in the current exclusivity period. From the perspective of small to mid-sized companies, we also urge caution against making the extension of market exclusivity conditional on launching a product in most or all Member States. This would be particularly challenging for smaller companies that do not have a presence and sufficient resources to launch in all 27 EU Member States and in the three European Economic Area countries. While market exclusivity should remain the main tool of the OMP Regulation, additional incentives need to be carefully designed to incentivise OMP developers to go into areas where standard innovation models alone might not be effective.

In its conclusions, EUCOPE reiterates its commitment to **engage with all relevant stakeholders** throughout the OMP Regulation review process to discuss actionable solution to address rare diseases unmet needs. EUCOPE would also underline that the development of orphan medicines is a global endeavour – developers concentrate their efforts in those environments which stimulate the most innovation. EUCOPE's membership consists of European and global companies – we are all committed to Europe and to ensure that **Europe remains an attractive place to undertake research and launch products for rare disease patients.**

1. APPROACH AND COMMITMENT

EUCOPE shares the European Commission objective of addressing unmet needs via an incentive system that is "fit to embrace technological and scientific advances"[1] and deliver the treatments people with rare

[1] Revision of the EU legislation on medicines for children and rare diseases Inception Impact Assessment https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/1248-Evaluation-of-the-legislation-on-medicines-for-children-and-rare-diseases-medicines-for-special-populations-_en

diseases need. Nevertheless, we want to emphasise that the review of the Regulation alone will not be sufficient to address the unmet needs and will not directly provide solutions to improve access and affordability of OMPs. A holistic approach along the whole lifecycle of rare disease therapies is needed to strengthen the EU environment for the development of OMPs and foster a virtuous cycle that **allows for re-investment in R&D of therapies for rare diseases patients.**

Over 20 years, the OMP Regulation brought substantial achievements in fostering research to the benefit of rare disease patients, their families and caregivers. However, there are more than 6-7,000 known rare diseases globally and 95% of these do not have an authorised treatment option. For those 5% of rare disease patients that do have an approved treatment, the patient journey is not simple, as the treatment they receive is often far from transformative or curative.[2] Overall, **for a large share of the 95% of rare diseases without an authorised treatment,** development incentives may be so weak that the **standard innovation model alone is not effective to incentivise OMP developers to go into these areas**. In these cases, addressing unmet needs require all stakeholders to imagine **different ways of partnering and collaborating to bring about sufficient levels of R&D.**

Finally, the Regulation review should **adopt a global perspective** and consider the interplay between the European framework and the incentive environment for the development of rare disease therapies in other geographies. Global regulatory alignment and a competitive incentive system that attracts investment in rare disease innovation in Europe should be core elements of the review process**.**

OUR COMMITMENT

EUCOPE co-leads and takes part in multi-stakeholder partnerships with the goal of tackling rare disease patients' unmet needs by means of consistent collaboration along the whole lifecycle of treatments. Examples of these partnerships include the European Expert Group on Orphan Drugs Incentives and RWE4Decisions.

[2] A recent EURORDIS Rare Barometer revealed that, from a pool of 7,500 responders, 69% of rare disease patients had received treatments for their rare disease but only 5% had received a transformative one.

2. OUR RECOMMENDATIONS

Considering the review of the OMP Regulation, **EUCOPE calls upon the European Commission, Parliament, Council of the EU and Member States to consider the following recommendations**:

- **A.** Supporting an environment that fosters rare disease innovation in Europe;
- **B.** Creating a broad unmet need framework that attracts developers to underserved areas;
- **C.** Ensuring certainty around the concept of Significant Benefit and flexibility of the regulatory pathway;
- **D.** Developing a thoughtfully calibrated OMP incentive framework.

A. PROMOTING AN ENVIRONMENT THAT FOSTERS RARE DISEASE INNOVATION IN EUROPE

Europe is home to a rich innovation ecosystem with start-ups, world-class research institutions, some of the world's top universities for life sciences and many small to mid-sized pharmaceutical and biotech companies. However, we often see challenges in scaling up pre-clinical and clinical research into OMPs for European citizens. Hence, **a policy framework that holistically supports research, development and appropriate healthcare infrastructure for rare disease patients is essential to fully exploit the potential of OMP development.**

This approach should take stock of and build on existing initiatives[3] that can be leveraged to fill the aforementioned gaps. Building on the existing framework of the European Reference Networks (ERNs), we believe it would be paramount to establish a multi-stakeholder governance for the ERNs as well as an information management system that further integrates the mechanisms that are available today. The current ERN structure needs to be enhanced with appropriate resources and responsibilities to ensure faster and smoother collaboration among clinicians, researchers, EU and national institutions and patients as well as a sounder structure for cooperation with industry. We should also build on the experience and results of the European Joint Programme on Rare Diseases to support timely scientific cooperation among clinicians, industry, academics and public sector.

An integrated ERN management system would also leverage the provisions of the European Health Data Space (EHDS), and other initiatives that support the uptake of real-world evidence, to tackle issues of evidential uncertainty in rare diseases from research to care. The EHDS could also provide the infrastructure for harmonised EU clinical diagnosis guidelines, **full implementation of the ORPHA CODES[4] and interoperability of disease registries (from national to European)**. As with the exchange of knowledge among stakeholders, more data interoperability would also be extremely beneficial at the pre-commercial stage to allow basic research to be better aligned with clinical development and rare disease patient needs early on.

[3] Further recommendations that substantiate our call for a strong Rare diseases R&D environment can be found in the resources issued by the IRDiRC Taskforces, the Rare 2030 initiative and the European Expert Group on Orphan Drug Incentives

4 The Orphanet nomenclature (ORPHA codes) provides a unique, time-stable and non-reusable numerical identifier to rare diseases. The Orpha codes system is designed based on Orphanet data https://www.rd-code.eu/introduction/

B. CREATING A BROAD OMP UNMET NEED FRAMEWORK THAT ATTRACTS DEVELOPERS INTO UNDERSERVED AREAS

In its Inception Impact Assessment, with regards to all the options for review of the OMP Regulation, the European Commission writes: "Criteria to determine unmet needs for patients suffering from rare diseases would be set up in the legislation and a system to identify products developed to address such needs."[1]

B.1 Rare disease unmet needs

The interpretation of what constitutes 'unmet needs' varies in content and has different meanings depending on different stakeholders' perspectives (e.g. patients, developers, clinicians, regulators, HTA, payers) as well as to whose need one refers (e.g. individual or societal). While crucial, the absence of any treatment is not the only unmet need to consider. Disease severity, burden of illness and impact on the quality of life of patients, as well as the significant indirect costs for families and caregivers, are also essential elements to consider. For example, an international study found that the annual cost of supporting a patient with Duchenne muscular dystrophy exceeded $120,000[5], less than half were direct medical costs. In addition, in many cases specific subgroups of patients may present specific unmet medical needs.

Furthermore, it is worth noting that rare disease patients' unmet needs differ from the unmet needs in other crucial public health areas identified by the Pharmaceutical Strategy, such as paediatrics, antimicrobial resistance and neurodegenerative diseases. The review of the Regulation should take fully into account the specificity of the OMP area.

B.2 A broad criteria-based approach that attracts developers into underserved areas

We agree with the position shared by the umbrella organisation of rare disease patient organisations, EURORDIS, in response to the Inception Impact Assessment:[6] a **legally binding definition of unmet needs for rare diseases could raise more problems than it would solve**, leading potentially to long discussions to the detriment of patients.

In the current version of the OMP Regulation, Article 3 refers to the life-threatening or chronically debilitating nature of the condition as a requirement for orphan designation of a medicine. Unmet needs are implicit in the 'Significant Benefit' criteria for designation. This approach should be maintained in the review of the OMP Regulation. An additional definition of unmet needs in the Regulation would not add clarity, instead, it would potentially create confusion and further barriers to the detriment of patients. Instead, the entire OMP Regulation, with its concrete checks and balances, and for instance, the specific provisions on ODD and the significant benefit criteria, provide the tools to address unmet medical need in the area of rare diseases.

A holistic framework that attracts developers to underserved areas is what we need to ensure unmet needs

[5] Berdud, M., Garau, M., O'Neill, P., Rozanova, O., Bell, E. (2020). Economic and Financial Challenges of Developing Orphan Medicinal Products. Does the European Regulation Tackle them? OHE Consulting Report, London: Office of Health Economics, p 21 https://www.eucope.org/wp-content/uploads/2020/04/ohe-omp-regulation-28-feb-2020-fv.pdf
[6] http://download2.eurordis.org/documents/pdf/EURORDIS_Response_IIA_OMP_2021.pdf

of rare disease patients are addressed. Multi-stakeholder dialogue should take place at a very early stage, including patients' representatives, developers, clinicians from the ERNs, regulators, HTA experts and payers, to continuously refine and update existing assumptions on unmet needs.

B.3 The current prevalence threshold to remain the main ODD criterion

An important aspect related to the definition of unmet needs concerns the proposed changes to the criteria to award ODD. Once again, we echo the voice of patient groups across Europe who highlighted in their Inception Impact Assessment responses the importance of maintaining **the current prevalence threshold as the main criterion for awarding ODD.**[7]

In its Inception Impact Assessment, the Commission proposes additional criteria e.g. incidence with the aim to better address the uneven distribution of patients across the continuum of unmet needs. **We need to urge caution about this change** as there are challenges and possibly unintended consequences in using the incidence criterion. These **might defy the very purpose the provision aims to address.**

It will prove impractical to set the threshold of awarding ODD on the basis of incidence, as the number of patients will have to be monitored every year. This is a moving target in rare diseases, where tracking all patients at all times is extremely difficult and costly. Evolving diagnostic techniques and practices also have an impact on reported incidence. The incidence criterion might also be providing an inaccurate picture of unmet needs[8], inter alia, for diseases with a high mortality rate which might fall "out'' of the designation criterion, as also noted by some patient groups.[9] This uncertainty would make it challenging for industry to invest in these areas without a clearer understanding of the incentives and rewards that might be available.

Most importantly, the current infrastructure at EU level is not fully equipped for an accurate reporting of incidence. To define "incidence'' we need to carefully assess the right threshold, and to do so, we need a comprehensive way to appropriately and timely identify rare disease patients in Europe. To achieve this, **important pre-requisites include harnessing the full potential of the EU Health Data Space to foster data interoperability and exchange**, as outlined in the recommendations of the previous paragraph on data interoperability, national and European Registries.

7 ''A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish: that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons'' Regulation 141/2000 on orphan medicinal products https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32000R0141

8 The European Haemophilia Consortium (EHC) stated to be against replacing the prevalence criterion with incidence, especially for rare bleeding disorders. They gave the example of Von Willebrand Disease. Although encouraging earlier diagnosis can be seen in younger patients, which is increasing the incidence slowly, this does not mean patients have adequate treatment options. https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12767-Medicinali-per-uso-pediatrico-e-malattie-rare-norme-aggiornate/F1408653_it

9 The Asociación de pacientes ASMD España (feedback) and the Asociacion Española de Enfermos y Familiares de la Enfermedad de Gaucher (AEEFEG) (feedback) showed their concerns about the proposal to change the orphan designation form prevalence to incidence, as this may penalise the development of new treatments for rare diseases with high mortality, which will no longer be considered rare. https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12767-Medicinali-per-uso-pediatrico-e-malattie-rare-norme-aggiornate/F1385451_it; https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12767-Medicinali-per-uso-pediatrico-e-malattie-rare-norme-aggiornate/F1368491_it

C. INCREASING CERTAINTY AROUND THE CONCEPT OF SIGNIFICANT BENEFIT AND FLEXIBILITY OF THE REGULATORY PATHWAY

The predictability of the regulatory and market access pathways are key components that, if improved, could tackle some crucial hurdles that OMP developers encounter. The concept of Significant Benefit plays a pivotal role in this respect.

C1. ODD confirmation before MA

Proving Significant Benefit over existing therapies is a difficult exercise, as is illustrated by the number of designations that have been lost at the maintenance review just before the MA is granted or just before a broader indication is approved. In addition to the initial orphan designation step, to be maintained, EUCOPE proposes to move the designation review to an earlier stage. The confirmation of ODD would thus occur before the MA application is submitted but once the key data for the MA application are already available. The test would assess whether at the time of the confirmation review, sufficient data are available that demonstrate, or at least provide a presumption, that the designation criteria are met at the time of the application for confirmation.

The criterion of presumption is especially necessary for the significant benefit criterion, as defined in the OMP Regulation. It may be very difficult in the area of rare diseases to gather absolute proof of significant benefit over certain other products, particularly at the late stages of MA application. Proving Significant Benefit is even harder in the case of a conditional marketing authorisation, which is especially designed to bring new and potentially transformative therapies to the patients sooner.

Once the ODD is confirmed under the new procedure, as outlined above, **we propose that there is no further reassessment at the time of the marketing authorisation** or when the therapeutic indication (in the label) within the same designation (the orphan indication) is broadened.

There would, however, remain a general review possibility as currently envisaged under Article 8(2) of the Regulation.

The general rule would remain that the review could be started after five years, with a possibility to reduce the market exclusivity to six or eight years (as is the case now).

C.2. Alignment of evidentiary standards through a "conditional" Significant Benefit status

According to Article 3(1) of the Regulation, an ODD is only granted if there is "no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of Significant Benefit to those affected by that condition." Significant Benefit is defined in Article 3(2) of Regulation (EC) No 847/2000 as "a clinically relevant advantage or a major contribution to patient care". Therefore, **an ODD is only granted by the European Commission if there is no alternative therapy or if the OMP in question provides a benefit over existing therapeutic alternatives**. This assessment should be taken into account throughout the whole lifecycle of an OMP, from the ODD to the pricing and reimbursement process at national level.

The current regulatory framework is inconsistent as it provides for the possibility of a conditional Marketing Authorisation (MA) in advance of providing full evidence, but still requires full proof of Significant Benefit at

the time of the initial approval. In situations where an OMP developer is unable to provide comprehensive safety and efficacy data at the time of MA, and is therefore granted a conditional MA, the level of evidence is sometimes not enough for the Significant Benefit assessment. This means that an OMP may be granted conditional marketing authorisation but may lose ODD due to a lack of proof of Significant Benefit, thereby causing high degree of uncertainty on the future of the product.

Therefore, **there needs to be more alignment in the evidentiary standards required for the Significant Benefit assessment and for MA, ideally by a "conditional" Significant Benefit status,** where evidence for proving Significant Benefit would continue to be provided post-MA. Such a concept needs further reflection and analysis with the cooperation of all relevant stakeholders including, the European Commission, the European Medicines Agency, regulators, companies, patients, researchers, healthcare professionals and payers.

C.3. Recognise the Significant Benefit decision in national pricing and reimbursement

There is no doubt that only the EU Member States have the competence to regulate the price of medicines. However, Member States and their authorities must comply with EU law when exercising their power to regulate the price of pharmaceuticals. National public health authorities are bound by the principles of EU law if they perform a public service. Article 288 (4) Treaty on the Functioning of the EU explicitly states that a "**decision shall be binding in its entirety**".[10]

The EU courts have clearly underlined that a broad interpretation of the concept of OMP market exclusivity is needed to ensure the effectiveness of this provision and that an off-label use prescribing "should not be facilitated". [11] The General Court of the EU recently also highlighted that in **decisions about the maintenance of an ODD, an off-label use comparator should not be considered**.[12]

The Inception Impact Assessment on the OMP Regulation states that ''account should be taken of the jurisprudence of the EU courts with regard to the designation criteria for orphan medicinal products''. **The aforementioned rulings are important milestones in providing stability and confirming the value of ODD and further confirm that** Member States and their authorities have to comply with EU law when exercising their power to regulate the price of pharmaceuticals**.**

C.4. OMP and non-OMP designation in the same MA

Finally, another aspect to take into account when considering how to increase predictability of investment decisions for OMP developers, is the possibility of **mixing orphan and non-orphan indications within one MA**. This is not possible under the current regulatory framework. In the current system a sponsor can

[10]For example, the decision making of GBA in Germany is clearly subject to scrutiny by EU law: CJEU, judgement of 26 October 2006, "Pohl-Boskamp", C-317/05, paragraph 22. Furthermore, CJEU, judgement of 29 March 2012, "Commission / Poland", C-185/10, paragraph 47: *"It must be noted in that respect, first, that although EU law does not detract from the power of the Member States to organise their social security systems and to adopt, in particular, provisions intended to govern the consumption of pharmaceutical products in order to promote the financial stability of their healthcare insurance schemes,* ***the Member States must, however, comply with EU law in exercising that power****…"*(emphasis added).

[11]GC, judgement of 11.06.2015, "Laboratoires CTRS / Commission", T-452/14, paragraph 78 and 79: "***the off-label prescribing of a medicinal product for therapeutic indications covered by the market exclusivity*** *attaching to another medicinal product by virtue of that provision* ***should not be facilitated****."*

[12]GC, judgement of 23.09.2020, "Medac / Commission", T-549/19.

decide to file for a separate MA and apply for a non-orphan indication under another brand name for the same product. However, **we invite the Commission to consider the system from the standpoint of small to mid-sized companies**. Filing for a separate MA might be a viable option for larger companies who can undertake the additional bureaucratic costs. However, it might very well discourage smaller companies from pursuing a non-orphan indication that might be of support and benefit to an additional patient population not targeted by the first indication.

D. DEVELOPING A THOUGHTFULLY CALIBRATED INCENTIVE FRAMEWORK

The current EU OMP Regulation grants approved OMPs market exclusivity that protects such medicinal products from competition from similar ones targeting the same rare disease for 10 years. Along with the fee reduction for small to mid-sized companies, the market exclusivity is currently the main incentive provided by the OMP Regulation.

Among its options, the Commission's OMP Inception Impact Assessment proposes to continue using market exclusivity as main incentive or replacing it with novel incentives. Possible novel rewards could involve the extensions of regulatory rewards (data and marketing protection) or various types of transferable "vouchers" (e.g., priority review or regulatory rewards vouchers).

MARKET EXCLUSIVITY

In order to build on the success of the current regulatory system and ensure a sufficient level of predictability for investment decisions of OMP developers, we believe **that market exclusivity should remain the main incentive** provided by the OMP Regulation.

Both for the market exclusivity and this new category of "novel incentives'', the Commission proposes the use of a **modulated approach** whereby the level of incentives provided (e.g., the length of market exclusivity or additional incentives) will depend on a number of predefined criteria.

While EUCOPE recognise that the attractiveness of business cases can differ between OMP development projects, we call upon the Commission to consider a wider spectrum of possibilities when thinking of the length of market exclusivity.

Our proposal is based on the observation of the current OMP environment, where EUCOPE sees two main areas where modulation, i.e. the adjustment of incentives to fit the business case for different drug development projects, can improve the current incentive environment. These areas constitute two extremes of the OMP spectrum:

On the one side, some areas are affected by a lack of or insufficient R&D activity because they are considerably less attractive for developers to go into due an extremely small patient population or a complete lack of initial research. Within this area, we even find diseases that are so rare or so complex that they may never constitute a sufficiently strong business case for developers. In these cases, **modulating 'upward'** (e.g. beyond the current 10 years) by substantially improving incentives for development is key to address such unmet need. Moreover, a mere (upward) adjustment of market exclusivity is unlikely to be sufficient to meet unmet needs and instead, substantial **additional incentives,** building on the examples

proposed by the Commission, or even radically different funding models such as **Public Private Partnerships, may be required**.

On the other side, today, some areas in the **orphan space are more mature** where a lot of knowledge exists and where the presence of several authorised treatments has created a functioning market. While having markets is a success in itself (leading to a choice between different innovative treatment options and price competition), certain projects might still bring valid business cases, even with a lower level of incentives than they would receive under the current system. It is, however, clear that high unmet needs can still exist in areas where several therapeutic options have been authorised (e.g. not all sub-populations of a disease respond to a treatment). Policy changes that *only* consists of downward modulation (e.g. reducing the length of market exclusivity for certain projects) will not address unmet needs and would therefore fall short of the Commission's goals.

MODULATION

The exact design for how to **modulate incentives requires a thorough and separate assessment**, as pointed out in the Inception Impact Assessment itself.

Against this background, EUCOPE raises three key points:

D.1) Modulation of market exclusivity needs to be thoughtfully considered;
D.2) Designing a modulation mechanism requires a thorough assessment;
D.3) Devising additional incentives is crucial to address unmet needs.

D.1) The modulation of market exclusivity needs to be thoughtfully considered

The Commission is considering modulating market exclusivity to match different levels of incentives needed for different drug development projects. The Commission is also considering the use of market exclusivity to incentivise or reward desired behaviours by OMP developers, such as ensuring broad access to OMPs. In both cases, **great care is warranted to make sure that policies are fit for purpose** and do not lead to unintended negative consequences (e.g. diminishing investments in rare disease research in Europe).

As noted by a study from the Office of Health Economics (OHE)[13], **curtailing incentives could represent significant risks for the OMP development environment.** The analysis finds that reducing market exclusivity could drive innovation away from rare diseases and in certain cases threaten the very existence of rare disease specialised companies. This is of particular importance to EUCOPE's members. EUCOPE represents 130 small to mid-sized companies playing a key role in the European pharmaceutical environment, many focused on rare diseases. Some of them have unique profiles due to their highly specialised product portfolio, no or limited revenues to date and/or highly risky R&D investments. For these companies, incentives are crucial to sustain (re)investments and planning cycles required to foster research

[13] Berdud, M., Garau, M., O'Neill, P., Rozanova, O., Bell, E. (2020). Economic and Financial Challenges of Developing Orphan Medicinal Products. Does the European Regulation Tackle them? OHE Consulting Report, London: Office of Health Economics. https://www.eucope.org/study-economic-financial-challenges-of-developing-omps/

in rare diseases. Building on the finding of this study, we **call for a careful consideration of downward modulation of the market exclusivity period.**

Instead of focusing solely on reducing market exclusivity, we call for a broader approach that also takes into account **upward (i.e. above 10 years) modulation of the market exclusivity period**. Modulation can be a tool to attract research into areas with no treatment, while keeping incentives for developing OMPs in other areas where further improvement of therapeutic options is vital to continue to address patients' unmet needs. A longer exclusivity period offers an opportunity to generate revenues for a longer period, which can be particularly useful for **very rare diseases**.

As mentioned above**, the Commission is also considering using market exclusivity as a reward for the launch of OMPs** in most or all EU Member States. While EUCOPE agrees that equal access for rare disease patients to medicines should be improved, market exclusivity is not the right tool to tackle this issue.

Delays in or heterogenous market access cannot be viewed purely as the consequence of companies' business decisions. **Instead, market launches are typically determined by the length and heterogeneity of pricing and reimbursement processes in Member States.** Different systems are used to inform national reimbursement decisions, this poses a greater challenge to companies and impacts their ability to launch EU wide. Heterogeneity across Member States informs the length of the processes and resources needed for the pricing and reimbursement procedure, the data requirements and the different price comparators. For instance, despite a marketing authorisation holder submitting a dossier around the same time it can take one month to process in one country and 30 or more months in another country. One country can accept a certain data package while another country might reject the very same data package. As a result, heterogenous market access and interpretation of data practices by payers cannot be solved by merely incentivising companies. Incentives will only be effective once the regulatory and policy barriers to equal access are tackled.

In addition, small and mid-sized companies are more affected by the obstacles created by heterogenous pricing and reimbursement procedures. This is because they face greater operational and financial constraints. In fact, in many cases small and mid-sized companies first test and establish their business in a limited number of countries. **Small and mid-sized companies would be less able to benefit from or would be disproportionally penalised by a system where the length of market exclusivity is linked to products availability in all or most Member States.**

Finally, beyond the consideration made by the Commission, we highlight another possible use of **market exclusivity, to incentivise behaviours that benefit the EU rare disease R&D ecosystem**. As outlined previously, a thriving R&D ecosystem is the very precondition to bring more R&D and innovation to rare diseases. For instance, **the generation and sharing[14] of (commercially valuable) data, such as Real-World Evidence (RWE)**, could be rewarded through an extended exclusivity period. This would ensure that there is an incentive to share important data across the rare disease R&D community, thereby facilitating knowledge sharing and the development of effective therapies.

[14]Such proposals should comply with competition law in terms of sharing RWE from a company to another.

D.2) Designing a modulation mechanism requires a thorough assessment

Modulating incentives presents the challenge of defining 'categories' for modulation, i.e., identifying drug development projects that require additional incentives and those that may still be developed even if the current level of incentives is reduced. While an *ideal* modulation mechanism would differentiate OMPs and set incentives according to their unique business cases, a *practical, predictable and actionable* policy may have to work with categories of OMPs. In this case, **any choice of categories should be based on a careful, objective assessments of the business cases across different drug development projects and not build on pre-conceptions of the risks, costs and value attached to different OMP development projects**.

The categories currently proposed under option 1 of the Commission's Inception Impact Assessment for the modulation of market exclusivity (innovative products, repurposed products, second/multiple indications) would therefore require further study and refinement. Furthermore, we need a detailed and careful definition of what each category for modulation of market exclusivity encompass. For instance, the term **"repurposed products"** in the OMPs space has historically been used for cases where there is a well-established off label use of an old medicine and the registration for a new indication solely consists of a literature submission. This is not the case for a totally innovative use for an already approved molecule, possibly also involving a new method of administration, for which the development process and cost more closely mirrors the development of a completely new product (including e.g., a clinical trial programme). The new modulation system will have to face the challenge of avoiding one-size-fits-all solutions while still provide the necessary predictability and stability to plan R&D investment cycles in rare disease therapies.

D.3) Devising additional incentives is crucial to address unmet needs

Additional financial incentives are a crucial way of steering development into areas of unmet needs if they are carefully designed to achieve favourable outcomes for society at large. For incentives to be relevant for OMP developers, they need to improve the business case either by **decreasing costs** during the R&D and development phases, shortening the time to market or **increasing rewards** at the time of market access.

When assessing which incentives would be most suitable, the Commission should take **a holistic look at the barriers that currently exist along the OMP development path**, in particular in those areas where there is high unmet need. At the same time, the development of policy solutions that truly help address unmet need may also mean an increase in complexity and an increased risk of adverse effects. Therefore, EUCOPE calls for a **multi-stakeholder dialogue to accompany the design of additional incentives**. The types of incentives proposed below for the Commission's consideration should be seen as an initial **proposal for such a dialogue**.

ADDITIONAL INCENTIVES

EUCOPE suggests that the European Commission consider the following two policy solutions to develop incentives that should be additional or **complementary to market exclusivity**, in order to address challenges that a standard business model alone cannot overcome:

D.3.1) A transferable voucher system;
D.3.2) Tailored solutions for extremely rare diseases.

D.3.1) A transferable voucher system

First, the European Commission should further consider the idea of a **transferable voucher**. A transferable voucher means awarding companies that develop OMPs for specific disease areas (e.g. where development incentives are particularly weak), with some (well-defined) additional rewards that they can use for a future medicine in their portfolio.

One benefit linked to transferability, i.e. the possibility to trade such vouchers in a secondary market, is that the voucher can become an **important source of inter-company funding within the industry**: smaller, innovative companies that bring innovative OMPs to the market can sell the voucher on the secondary market to larger companies that intend to use it to obtain additional rewards for a higher revenue medicine. The high value that the larger companies attach to reward means a high transfer-value and therefore equally high funding for the smaller OMP company. The United States of America's experience with transferable vouchers can be useful in identifying the possible risks and best design choices for the European environment.

Importantly, the beneficial nature of the voucher hinges on its design, in particular:

- **The choice of reward provided by the voucher.** The design choice is mainly between regulatory vouchers and market exclusivity vouchers. A regulatory voucher could provide several benefits linked to the regulatory pathway such as an accelerated regulatory review which would award the developer with a faster regulatory process and therefore quicker market access for a future drug. A market exclusivity voucher could grant additional years of market exclusivity to the voucher holder for any future drug.
- **The type of medicines the vouchers can be used for.** This design choice concerns the restrictions (if any) imposed on the type of medicine that the voucher can be used for, which will impact the value of the voucher for its holder.

Each of these design choices has benefits and costs for the different stakeholders involved. For instance, on the one hand, a regulatory voucher would reduce the time to market for the medicine it is used for and on the other hand, it would require additional resources from the EMA to comply with the shorter review timeline. In turn, the market exclusivity voucher, if usable for drugs with a large potential market would provide an effective incentive, but may be costly for health systems through delaying generic entry. Therefore, policy makers need to find a balance between the need for the voucher to be a sufficiently strong incentive to be effective (e.g., based on the type of reward provided or the type of medicine the reward can be used for) with the costs that a voucher may create elsewhere (e.g., the cost for society of delaying generic entry or additional resources required).

D.3.2) Tailored solutions for extremely rare diseases

Second, the European Commission should explore tailored solutions that will expedite R&D in the area of ultra-rare diseases. This is relevant to address the fact that most diseases among the 95% for which no authorised treatments are currently available, have extremely small patient populations (some figures below)[15], directly driving a poor business case and difficulties in conducting research.

[15] https://www.nature.com/articles/s41431-019-0508-0

Unpacking rare disease unmet medical needs

- There are 6-7,000 rare diseases
- 80% of population burden of rare diseases is attributable to 149 diseases
- 98% of people with rare diseases have one of the 390 most prevalent rare diseases
- Around 85% of all rare diseases have a prevalence of less than 1 in 1,000,000

For a large share of these ultra-rare diseases, development incentives may be so weak that the standard innovation model alone is not effective in incentivising OMP developers to go into these areas. In these cases, addressing unmet needs may require all stakeholders to imagine different ways of partnering and collaborating to bring about sufficient levels of R&D.

Such ways could include:

- **New funding models for R&D.** Funding is a direct and straightforward tool to incentivise investments in certain areas. Ultra-rare diseases would particularly benefit from funding in support of clinical research due to the challenges posed by the extremely limited and scattered patient population. Funding to ensure manufacturing capabilities could also be considered in certain cases such as gene therapies.
- **Regulatory support for ultra-rare diseases.** Regulatory support is a tool to reduce the risk associated with regulatory approval of OMPs in these areas. Regulatory support includes scientific advice, speedy regulatory review, a pathway that accounts for the additional challenges of these OMPs, such as the limitations of clinical evidence that can be produced.
- **Financing models at the P&R stage.** New financial models at national level, such as advanced purchasing agreements in the ultra-rare space are a tool to increase certainty and reduce risk related to market access. The small and fragmented patient population, the difficulties in meeting the data requirements for value assessment pose additional challenges on market access. In practice, advanced purchasing agreements can take different forms which involve a commitment from national health authorities to purchase a product at pre-determined conditions.

The experiences in the fields of antimicrobial resistance (AMR) provide useful case studies for the design of specific solutions to incentivise and expedite R&D in specific areas through multi-stakeholder collaboration at all stages.

The policy proposals that build on these suggested ways of partnering and collaborating may go beyond the current scope of the OMP Regulation. Therefore, it is important that EU policy makers work on parallel policy tracks next to the OMP Regulation that would allow the introduction such tools.

Finally, the choice and design of the additional incentives proposed here should be carefully tailored to the European context and needs. They should be based on an impact assessment to ensure that the benefits outweigh the costs and should consider the relative effectiveness of each tool.

3. CONCLUSIONS

The ongoing stakeholder consultations leading to a revision of the OMP Regulation is crucial to convey new ideas and approaches and discuss the way forward for the EU legislation on medicines for rare diseases with all the relevant stakeholders.

As previously stated, the review of the Regulation alone may not suffice in addressing unmet needs and will not directly provide solutions to improve access and affordability of OMPs. A holistic approach is needed to strengthen the whole EU environment for the development of OMPs and foster a virtuous cycle that allows for re-investment in R&D of therapies for rare diseases patients.

As we proceed in the review process of the OMP and Paediatric Regulations, we call upon the Commission to foster **a broad understanding of unmet needs in rare disease; devise a thoughtfully calibrated incentive system,** informed by a **thorough assessment** of the impact of these policy changes on the orphan developers investment decisions; and take into account that these policy changes will ultimately influence **developers ability to reinvest in rare disease R&D** and foster the virtuous cycle of innovation in Europe.

The development of orphan medicines is a global endeavour – developers concentrate their efforts in those environments which stimulate the most innovation. EUCOPE's membership consists of European and global companies – we are all committed to Europe and to ensure that Europe will remain an attractive place to undertake research and launch OMPs.

EUCOPE stands ready to engage with the European Commission and all relevant stakeholders, including patients, healthcare professionals, Member States, industry and researchers, to further discuss actionable solution to address rare diseases unmet medical needs.