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THE EU PAEDIATRIC REGULATION

INNOVATION FOR OUR FUTURE

A EUCOPE Position Paper

EUCOPE
European Confederation of Pharmaceutical Entrepreneurs AISBL

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THE EU PAEDIATRIC REGULATION – INNOVATION FOR OUR FUTURE

The European Commission has launched an evaluation of the Orphan Medicinal Product (OMP) and Paediatric Regulations. EUCOPE seizes the opportunity to outline ways to **strengthen the EU environment for the development of rare and paediatric disease treatments,** of which the Regulation (EC) No 1901/2006 on medicinal products for paediatric use (Paediatric Regulation) is a key pillar.

OUR APPROACH

Propose actionable solutions to **strengthen the cycle of biopharmaceutical innovation for rare disease patients and children.**

The review of the Regulation will not directly provide solutions to improve access and affordability of rare disease and paediatric treatments. A holistic approach is needed to foster a **virtuous circle that allows for re-investment in R&D of therapies for children and rare disease patients.**

EUCOPE supports a broad understanding of incentives. Provisions across **the whole lifecycle of the product, along with a strong and predictable incentive framework** are key to overcome the considerable challenges across the rare disease and paediatric patient pathway.

As part of this approach, multi-stakeholder collaboration is key. To make significant strides in the battle against
unmet need, we need to think of solutions that involve the whole EU innovation environment, building on the **collaboration of all relevant stakeholders** including EU institutions, patients, Member States, industry, clinicians and researchers.

OUR RECOMMENDATIONS

In light of the review of the Paediatric Regulation, EUCOPE calls upon the European Commission, Parliament and Member States to consider the following proposals:

1. **AN EU ENVIRONMENT THAT ACTIVELY SUPPORTS AND STIMULATES R&D;**
2. **A BROAD UNDERSTANDING OF UNMET NEED THAT ATTRACTS INNOVATION TO UNDERSERVED AREAS;**
3. **A PREDICTABLE AND ATTRACTIVE INCENTIVE SYSTEM AIMED AT FOSTERING PAEDIATRIC MEDICINES DEVELOPMENT.**

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1. AN EU ENVIRONMENT THAT ACTIVELY SUPPORTS AND STIMULATES R&D

15 years ago, we were at a very different place in the conversation about availability of licensed paediatric medicines in Europe. The Paediatric Regulation has contributed and will continue to contribute to scientific breakthroughs which translated into new treatments for children.

Considering the length of clinical development programmes, the full effects of the Regulation are yet to be unveiled. Completion of paediatric investigation plans (PIPs) can take several years, innovation in complex diseases is still forthcoming.

EUCOPE supports the full implementation of the Paediatric Action Plan, of which many initiatives are still in progress. Furthermore, the Action Plan addresses many of the shortcomings later identified in the European Commission's Inception Impact Assessment on the Paediatric Regulation. Therefore, the Action Plan should be the foundations on which the review of the Paediatric Regulation should build.

Furthermore, the Regulation's provisions can be rendered more effective by creating **an environment that actively supports and stimulates R&D activities in the field of paediatric medicines.** Such an environment should involve patients, academia, clinicians, industry and regulators.

Building on existing platforms and pulling together the scattered and scarce resources in the paediatric field will considerably help to further R&D for medicines for children in Europe. This approach should take stock of and leverage existing initiatives and EU policies, for instance, **EU funded paediatric R&D projects**.

Examples of these projects are:

- **the European Paediatric Translational Research Infrastructure** (EPTRI), a Horizon 2020 Project proposing developmental models for a future research infrastructure focused on paediatric medicines, integrating technology-driven aspects with clinical trials;
- **ACCELERATE,** an international platform aimed at boosting innovation in drug development for children and adolescents with cancer; and
- **c4c (conect4children)**, a large collaborative European network that aims to facilitate the development of new drugs and other therapies for the entire paediatric population.

Building on the 2018 Paediatric Action Plan implementation, we call upon the Commission to consider different ways to improve PIPs in the current legal framework. Based on the average duration of the EU ordinary legislative procedure, it can take ~ 5 years from a Commission proposal to publication, and an additional ~ 3 years until entry into force of a legislation.[1] In the meantime, there is still room for regulatory improvement in the context of the current Paediatric Regulation for those paediatric plans that are currently

[1] Recent pharmaceutical legislation revisions can give us a sense of the length of the legislative process, the examples don't include new legislative proposals that can often been stalled between Council and Parliament at first reading (e.g. EU HTA)

- Medical devices, **proposal in 2012, expected adoption 2021**: Directives 93/42/EEC and 90/385/EEC will be replaced by Regulation (EU) 2017/745
- In-vitro diagnostic medical devices **proposal in 2012, expected adoption 2022** Directive 98/79/EC and Comission Decision 2010/227/EU will be replaced by Regulation (EU) 2017/746
- Medicinal Products for veterinary use, **proposal in 2012, expected adoption 2022:** Directive 2001/82/EC will be replaced by Regulation (EU) 2019/6

underway or that will start in the next few years. Furthermore, enacting these changes in the immediate future will reduce the need to adapt certain aspects of the regulatory system once the revised Paediatric Regulation comes into force.

To ensure a predictable, yet sufficiently flexible, regulatory framework, the PIP should be a high-level plan, with only **some basic elements agreed upfront**, such as:

- age groups;
- waivers;
- studies to be conducted before and after MAA (only key binding elements);
- and key study design elements**.**

Internal misalignment between the EMA Scientific Advice Working Party (SAWP) and Paediatric Committee (PDCO) can create difficulties for sponsors – a streamlined, joined-up approach is required, with advice previously given by SAWP being adhered to at the time of PIP agreement by PDCO.

Finally, alignment with the United States of America's Food and Drug Administration (FDA) should be sought systematically via existing paediatric clusters. A more global perspective is required in the way regulators look at paediatric developments, as misalignment in requirements between major regulators can result in delay to approval and access to paediatric formulations across the world.

2. A BROAD UNDERSTANDING OF UNMET NEED THAT ATTRACTS INNOVATION INTO UNDERSERVED AREAS

The implementation of the Pharmaceutical Strategy for Europe will have a direct impact on the way we research and develop medicines and how we ensure that they are available and accessible to European patients. Thus, the actions to address unmet need to be treated in a holistic manner. A broad understanding of unmet need that attracts developers to underserved area, should be our guiding principle across the board, including, but not limited to, the areas singled out by the Pharmaceutical Strategy: antimicrobial resistance, cancer, rare and paediatric diseases.

Looking more closely at paediatrics, despite the considerable efforts and advancement, there are still very high areas of unmet needs in this field. We still have a long way to go to unlock the full potential of medicines for children, and more than ever, strengthening **the current incentive ecosystem is crucial to continue attracting R&D in these underserved areas**, rather than restricting incentives.

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). It is also important to consider the specificity of the different areas of unmet needs: paediatric unmet needs differ from rare disease patients' unmet needs and from unmet needs in other crucial public health areas identified by the Pharmaceutical Strategy, namely, antimicrobial resistance. Furthermore, there are additional differences across the spectrum of paediatric needs. **Distinct challenges concern the development of medicines for different paediatric age** ranges e.g., infants, toddlers and adolescents.

One important consideration that concerns both paediatric and rare diseases is that, 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 indirect costs for families and caregivers are also essential elements to consider. Moreover, therapeutic alternatives in paediatric populations are also needed and can create competition in the market which has a positive impact on access and affordability.

In the face of this plethora of challenges and different aspects to consider, we agree with the position shared by EURORDIS, umbrella organisation of rare disease patients' organisations, in response to the Inception Impact Assessment on medicines for children and rare diseases[2]: a **legally binding definition of unmet needs could raise more problems than it would solve**, leading potentially to long discussions to the detriment of patients. We should build on existing criteria **and ensure that we do not resort to a low common denominator approach when identifying unmet needs.**

A flexible and broad framework that attracts developers to underserved areas is what we need to ensure unmet needs of paediatric patients are addressed. Multi-stakeholder dialogue should take place at a very early stage of product development including patients' representatives, developers, clinicians, regulators, HTA experts and payers, and continue regularly to review and update existing assumptions on unmet needs.

3. A PREDICTABLE AND ATTRACTIVE INCENTIVE SYSTEM AIMED AT FOSTERING PAEDIATRIC MEDICINES DEVELOPMENT

While the current incentive system has significantly contributed to fostering the development of paediatric therapies, the revision of the Regulation provides an opportunity to enhance the predictability and attractiveness of the incentive's framework for children's medicines.

EUCOPE calls upon the Commission to focus on the following aspects:

- **3.1** Strengthening and expanding the **resources of the current PRIME scheme** to support further paediatric and rare disease innovation;
- **3.2 Maintaining Supplementary Protection Certificates (SPC)** as primary incentive complemented (and not replaced) by additional incentives;
- **3.3 Taking into account that small to mid-sized companies** would be less able to benefit from or would be disproportionally penalised by a system where incentives are linked to access.

3.1 Strengthening and expanding the resources of the current PRIME scheme to support further paediatric and rare disease innovation

We support the Commission's intention of enhancing regulatory support for rare and paediatric disease product developed to address unmet needs. We call for a clear approach from the EMA and the European Commission on what a ''PRIME-like'' scheme, as referred to in the Inception Impact Assessment, would

[2] http://download2.eurordis.org/documents/pdf/EURORDIS_Response_IIA_OMP_2021.pdf

look like. EUCOPE urges the Commission to avoid creating additional frameworks, but rather focuses on **strengthening and expanding the resources of the current PRIME** scheme to support further paediatric and rare disease innovation. The scheme should facilitate non-binding early dialogue to identify and address scientific issues.

To ensure that all applicants continue to see the benefit of using the scheme, **a fast lane approach should be designed for PRIME products** which would include: shorter timeline for PRIME eligibility and kick-off meeting, continuous access to the EMA contact person, rolling opportunity to receive faster scientific advice on product development and the possibility to seek rapporteurs views on certain scientific matters, as well as a 2-pager system similar to that used by the US FDA that allows for a pre-screening of applications, supporting efficiency.

Due to the need for clinical data, one of the current challenges of PRIME, especially for ATMP programmes for rare diseases, is that these are often well into a pivotal stage, with orphan designation in place and PIP submitted by the time of their PRIME kick-off meeting. Earlier PRIME designation would allow support to be in place at time of PIP submission.

Alignment with the US is also important with regard to the conditions for granting exemptions from the obligation to study all new medicines in children. The Commission's Inception Impact Assessment mentions for *all options* the possibility of a revision of the conditions for granting exemptions from the obligation to study all new medicines in children, with possibility for the regulator to request the conduct of paediatric studies based on the mechanism of action of the product rather than the indication sought in adults. To maintain a level playing field and international harmonization we suggest that, like in the US, this exemption only concerns paediatric oncology medicines.

More broadly, EMA and FDA continuous cooperation - in ways that are transparent to and involve drug developers - is essential to avoid duplication and to maintain Europe's competitiveness on a global scale. Furthermore, Brexit has created an additional layer to the need for international cooperation. Thus, we will also need to ensure alignment between EMA and MHRA on paediatric product development and approval.

3.2 Maintaining Supplementary Protection Certificates (SPC) as primary incentive complemented (and not replaced) by additional incentives

As previously mentioned, the current incentive system has significantly contributed to the fostering of paediatric therapies. However, current paediatric incentives do not adequately stimulate the development of OMPs for paediatric use. Furthermore, the hurdles to obtain the approval and, in some cases, to modify a PIP leads to significant uncertainty and administrative burden.

SPC rewards, even if cumbersome to obtain in certain instances, remain the most attractive incentives and should remain the primary one**.** Consideration should be given to whether **SPCs could be further extended beyond 6 months** for paediatric products addressing unmet needs. When looking at the options of the Inception Impact Assessment, we do not support the approach of option 2 that would limit the 6-month extension of the SPC *only* to medicines addressing unmet needs for children. We believe that all research dedicated to children's **medicine conducted in line with a PIP agreed by the PDCO should be appropriately rewarded** to foster incremental as well as breakthrough innovation.

On the other hand, we welcome the approach of maintaining SPC as the primary incentive complemented (and not replaced) by the possibility of additional incentives spelled out in option 3, which requires a thoughtful consideration from the Commission. While the voucher system, as it is in the US, may not be fully suited to the European Union, the possibility to develop additional rewards, tailored to the EU (e.g. the extension of certain regulatory rewards), should be explored with the support and contribution of the whole paediatric community.

3.3 Taking into account that small to mid-size companies would be disproportionally penalised by a system where incentives are linked to access

Another key aspect that the Commission is considering across all the options for regulatory revision, both for OMPs and Paediatric Regulation, is to make incentives conditional on product launch in all or most EU Member States. While EUCOPE agrees that equal access of children's medicine should be improved, regulatory incentives are 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 concerns the length of the processes and resources needed for the procedure, the data requirements, 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. As a result, heterogenous market access cannot be solved by merely (dis)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 to mid-size companies would be disproportionally penalised by a system where incentives are linked to access.**

4. CONCLUSIONS

The ongoing stakeholder consultations leading to new legislative proposals for both the Paediatric and OMP Regulations in 2022 are crucial to convey new ideas and approaches and discuss with all the relevant stakeholders the way forward for the EU legislation on medicines for children and rare diseases.

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

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 paediatric diseases; devise a **thoughtfully calibrated incentive system**, informed by a **thorough assessment** of the impact of these policy changes on the developers' investment decisions; and take into account that these policy changes will ultimately influence developers **ability to reinvest in children medicines R&D** and foster the virtuous cycle of innovation in Europe.

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 and children unmet needs.