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Open Public Consultation on the revision of EU rules on medicines for children and rare diseases

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Introduction

The EU rules on medicines for rare diseases and medicines for children were adopted in 2000 and 2006, respectively. The rules were designed to improve the treatment options available to 30 million European patients affected by one of over 6000 rare diseases, as well as for 100 million European children affected by paediatric diseases. At the time, there were limited or no medicinal products available for treatment of both groups.

A recent evaluation of the rules showed that they have stimulated research and development of medicines to treat rare diseases and other conditions affecting children. However, the evaluation also revealed shortcomings in the current system. The rules have not been effective for stimulating the development of medicines in areas of unmet needs (e.g. 95% of rare diseases still have no treatment option), and they have not ensured that the medicines are accessible to all European patients across all Member States.

The rules provide incentives and rewards, and their design can influence business decisions on research and development for new medicines, as well as whether such investment can be focused in areas of the greatest need for patients. In addition, the system of incentives can impact market competition and indirectly influence the availability of and access to those medicines by EU patients.

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European Expert Group on Orphan Drug Incentives

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Questionnaire on the revision of EU rules for medicines for rare diseases and children

Q1: The main problems identified in the evaluation of the legislation for medicines for rare diseases and for children were the following:

- **Insufficient development in areas of the greatest needs for patients.**
- **Unequal availability, delayed access, and often unaffordable treatments for patients in the EU Member States.**
- **Inadequate measures to adopt scientific and technological developments in the areas of paediatric and rare diseases.**

In your opinion, are there any other barriers to the development of treatments for rare diseases and children?

2000 character(s) maximum

There is a lack of basic and early translational research. Today, for many rare diseases, the scientific base from which drug development can depart from is either non-existent or insufficient. In addition, it is difficult to find and secure funding not only for the basic research itself, but also for translating it into development-ready research.

Despite some improvement due to ERNs, rare disease research is still scattered across different institutions, held in few centres and geographically uneven. There are insufficient information and studies on what causes delays or absence of access to treatments and medicines.

There is, therefore, a need to think beyond the current incentive models to tackle rare disease challenges as 95% of them are still without an authorised treatment and the available treatments for the 5% are not necessarily transformative or curative. It is crucial to promote incentives before development and incentivise collaboration before competition.

An additional area of concern for OMPs is the high rate of attrition along the development path. Only around 17% of OMPs reach market approval and even fewer succeed in pricing and reimbursement negotiations. To overcome the current situation, the flexibility and predictability of OMP regulatory pathway should be improved. Flexibility is essential to adapt to the specific challenges of the rare diseases, especially for innovative treatments and treatments for extremely rare diseases where drug development is even more complex.

The regulatory pathway also needs to be flexible and predictable to maximize the full potential of incentives. Currently, certain aspects are not sufficiently predictable, which adds unnecessary risk to OMP development. For instance, there is a lack of alignment between OMP development and payers, prescribers and patients' needs due to heterogeneous regulatory, national HTA and P&R procedures and requirements.

Q2: In your opinion, and based on your experience, what has been the additional impact of COVID-19 on the main problems identified through the evaluation? Is there a 'lesson to be learned' from the pandemic that the EU could apply in relation to medicines for rare diseases and children?

2000 character(s) maximum

• COVID-19 placed patients in a similar situation as rare disease and paediatric patients and has brought many learning and awareness to the general public. However, it is not a carbon copy as the situation is not comparable. According to a EURORDIS survey on rare disease perspectives on the COVID-19 pandemic, 83% of rare disease patients' care was disrupted. In fact, 8 out of 10 people had rehabilitation therapies postponed or cancelled and 6 out of 10 people 6 were unable to receive medical therapies such as infusions and chemotherapies. The pandemic has, therefore, accentuated rare diseases' challenges, i.e. scarcity of data, uncertainty and vulnerability of the patient population, access inequalities, and shown even further the importance of pulling together resources, expertise and efforts at EU level to fight common challenges.

• In this context, cross border cooperation has become even more important, for diagnosis, care and treatment of patients. It is, therefore, essential to carry out the OMP legislation review from a holistic approach and build on the lesson learnt from the COVID-19 pandemic on regulatory, political and scientific cooperation.

• The COVID-19 crisis has also further confirmed the potential of digitalisation (including RWE) and regulatory flexibility. Digital tools have significantly contributed to speed up development and improve care across the EU. Many regulators and healthcare authorities have shown more flexibility in using digital solutions for clinical trials, regulatory submissions, and home care (e.g. in clinical trials, monitoring, treatment and care of patients). These tools are also essential to monitor, collect and analyse pharmacovigilance data and post launch RWE. Although the value of digitalisation is undeniable and clearly the right way forward, we should avoid that digital literacy and tools, which are not yet uniformly present across and within all EU Member States, create additional access barriers.

Q3: In your opinion, how adequate are the approaches listed below for better addressing the needs of rare disease patients?

at most 4 answered row(s)

	Very adequate	Moderately adequate	Not at all adequate
When considering whether a particular medicine is eligible for support, the rarity of the disease – the total number of cases of a disease at a specific time, currently less than 5 in 10 000 people – forms the main element of the EU rules on medicines for patients suffering from rare diseases.	◉	○	○

Some diseases occur frequently, but last for a relatively short period of time (for example, some rare cancers). These are covered by the EU rules on medicines for rare diseases and the principle of rarity. However, because many patients acquire such diseases during a specified, limited period of time, those diseases should not be considered as rare in the EU anymore.	○	○	◉
Amongst all medicines for rare diseases which become available to the EU patients, only those bringing a clear benefit to patients should be rewarded. Clear rules should apply to decide if one medicine brings a clear benefit to patients when compared to any other available treatment in the EU for a specific rare disease.	○	○	◉
Additional incentives and rewards should exist for medicines that have the potential to address the unmet needs of patients with rare diseases, for example in areas where no treatments exist.	◉	○	○

Other (please suggest any other criteria/approaches you think might be relevant).

2000 character(s) maximum

- Despite some progress achieved through the European Reference Networks, scientific knowledge on rare diseases is still scattered across different European institutions and initiatives. In a fragmented ecosystem, the full potential of European research efforts is not exploited. Hence, we believe a crucial step to better address the needs of rare disease patients is to establish a collaborative EU rare disease hub, which builds upon the ERN infrastructure, as a one stop-shop for collaboration between all actors in the sharing of knowledge, generation of new evidence, and in diagnosis.

- Rare disease basic research in Europe is often not developed enough to enter the development stage (preclinical or clinical). Research needs to enable this sponsor to translate the research into treatments for patients without incurring a prohibitive level of uncertainty or delay. This requires common guidelines, which could come from the work of the International Rare Diseases Research Consortium (IRDiRC), and a framework with appropriate incentives for producing development-ready research.

- In order to generate sufficient research to address unmet needs, the EU should increase the scale and continuity of funding for basic research and early preclinical development above and beyond the EJP RD. For instance, a private-public partnership (PPP) with funding conditionality, where the financial responsibility of serving more rare disease patients with effective treatments is mutually shared by public and private financing sources.

- Lastly, it is important that policy solutions build on the many existing structures and initiatives that already make up the EU rare disease R&D infrastructure – and include better funding, better and modulating incentives for development-ready research and the necessary collaborative infrastructures for all stakeholders in R&D.

Q4: What factors are important to take into consideration when deciding if one medicine for a rare disease brings more benefits compared with other available treatments?

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We should build on the current Significant Benefit (SB) criteria:

• We should build on elements already defined in the Regulation 141/2000 (definitions of the concepts 'similar medicinal product' and 'clinical superiority' and 'significant benefit') and in the Commission notice on the application of Articles 3, 5 and 7 of Regulation.

• In addition, engagement with organizations of patients (and patients' families) should be key as they are the ultimate recipients of innovative treatments and play an essential role in the OMP environment through patient advocacy, raising funding for research and participating in clinical trials and other studies.

• We also believe there needs to be more clarity on what is meant by 'greater efficacy' and more alignment in the evidentiary standards required for the Significant Benefit assessment and for marketing authorisation (MA) – ideally by a 'conditional' Significant Benefit status, where evidence for anticipated significant benefit would continue to be provided post-MA. The concept of Significant Benefit should be given clearer and more transparent guidance and closer cooperation on a case-by-case basis between the OMP developer and the COMP, as well as Member States authorities, in defining the data requirements early on.

• Furthermore, the heterogeneous national HTA and P&R procedures contribute to a lack of alignment between OMP development and payers, prescribers and patients' needs. This creates uncertainties on the willingness to pay for OMPs, the size of patient population, access conditions and price level. Better alignment between requirements of Regulatory, HTA and Payers is also needed – e.g. sources assessment of OMPs by European Regulators and subsequent relative effectiveness assessment (EMA / EUnetHTA).

Q5: What do you consider to be an unmet therapeutic need of rare disease patients and children?

- [x] Authorised medicines for a particular rare disease or a disease affecting children are not available, and no other medical treatments are available (e.g. surgery).
- [x] Treatments are already available, but their efficacy and/or safety is not optimal. For example, it addresses only symptoms.
- [x] Treatments are available, but impose an elevated burden for patients. For example, frequent visits to the hospital to have the medicine administered.
- [x] Treatments are available, but not adapted to all subpopulations. For example, no adapted doses and/or formulations, like syrups or drops exist for children.

Other (please specify).

2000 character(s) maximum

Currently, there is no agreed common definition for the concept of unmet medical need. In this sense, it is important to acknowledge unmet needs do not only exist where there is no authorised treatment for rare diseases, but depending on disease severity, burden of the illness and impact on patient quality of life, the absence of transformative and curative treatments also qualifies as an unmet need. In addition, the indirect burdens for families and caregivers are essential elements of unmet need.

Hence, we believe that, based on current understanding, a legally binding and restrictive definition of unmet need that guides the modulation of incentives, i.e. by limiting (additional) incentives to a strictly defined area of unmet need, is not an appropriate policy tool and would create more problems than it would solve. Instead, a broad and holistic unmet need framework would recognize the many ways in which 'unmet need' manifests itself, while attracting development into underserved rare disease areas. Multi-stakeholder dialogue along the OMP development path, including patient representatives, developers, clinicians, regulators, HTA experts and payers, can then allow to continuously refine and update existing assumptions on unmet needs. In that context, a broad holistic definition of unmet medical need would be helpful, but will need consultation and inclusiveness.

Q6: Which of the following measures, in your view, would be most effective for boosting the development of medicines addressing unmet therapeutic need of patients suffering from a rare disease and/or for children? (1 being the least effective, 10 being the most effective)

at most 4 answered row(s)

	1	2	3	4	5	6	7	8	9	10
Assistance with Research & Development (R&D), where medicines under the development can benefit from national and/or EU funding	○	○	○	○	○	○	○	◉	○	○
Additional scientific support for the development of medicines from the European Medicines Agency	○	○	○	○	○	○	○	◉	○	○
Assistance with authorisation procedures, such as priority review of the application from the European Medicines Agency and/or expedited approval from the European Commission	○	○	○	○	○	○	◉	○	○	○

Additional post-authorisation incentives that complement or replace the current incentives and rewards	○	○	○	○	○	○	◉	○	○	○

Do you have other suggestions that would allow the EU to boost the development of specific medicinal products?

2000 character(s) maximum

• The current policies provide one-size fits all incentives across OMPs and insufficiently incentivises certain types of projects for which investment incentives are particularly weak. A modulated approach to OMP incentives can provide a level of incentives that is just enough to make different OMP development projects (with different investment cases) sufficiently profitable.

• We suggest introducing novel financial incentives, such as a transferable voucher or tax credits for drug development, and thinking of supporting development along the pharmaceutical value chain. A transferable voucher could be used as a targeted market-driven incentive for directing investments into priority diseases and would benefit from a higher participation of smaller rare disease-focused companies, foundations and academic institutions since they can sell their priority vouchers to fund additional research in the rare disease field.

• The voucher could reward OMP development in any of the following ways: accelerated regulatory review (similar to US Rare Paediatric Voucher); extension of market exclusivity; automatic access to the PRIME scheme. However, we caution against replacing the current incentive system completely with novel incentives as it might bring too much uncertainty.

• The EU should also consider the creation of partnership models including a collaborative European rare disease hub to share expertise and knowledge between stakeholders, establish guiding principle for translational research (building on IRDiRC) and PPP with funding conditionality to early translational research where the financial responsibility of serving more rare disease patients with effective treatments is mutually shared by public and private financing sources.

Do you see any drawbacks with the approaches above? Please describe.

2000 character(s) maximum

• We would first like to highlight it is not clear what is it exactly meant by R&D assistance (where medicines under the development can benefit from national and/or EU funding) in the previously mentioned options for boosting the development of medicines addressing unmet therapeutic need.

• Above all we believe the system should remain stable and predictable. As stated in the above section, replacing the current incentive system completely with novel incentives might bring too much uncertainty.

• Innovation follows science. Science, data and innovation barriers can only be addressed by scientific progress – we need to be mindful that no amount of incentive will completely address the issue.

• In addition, it is not possible to achieve progress without adequate resources to EMA and strengthening of COMP and coordination with CHMP. COMP plays an essential role as it is the body within the EMA that knows best the hurdles of OMP development. Therefore, COMP should be endowed with sufficient resources and experts to ensure that the regulatory pathway is best suited to guide OMP developers. The role of the COMP should also be strengthened within the EMA, so that it can follow OMPs throughout all the stages of the regulatory pathway.

Q7: Which of the following options, in your view, could help <u>all</u> EU patients (irrespective of where they live within the EU) to provide them with better access to medicines and treatments for rare diseases or children?

- ☐ Greater availability of alternative treatment options. For instance, by allowing a generic or biosimilar product to enter the market faster.
- ☐ Allowing companies that lose commercial interest in a rare disease or children medicine product to transfer its product to another company, encouraging further development and market continuity.
- ☐ For companies to benefit from full support and incentives, products need to be placed timely on the market within all Member States in need as soon as they received a marketing authorisation.

Other (please suggest any other solution you think might be relevant).

2000 character(s) maximum

The options outlined above do not take into account the root causes of why e.g. product transfer and faster entry of generics cannot fully address availability issues. Being access primarily a Member State competence, we call for a multi-stakeholder approach, including national level policy-makers. This approach consists of four proposals that require political will and action beyond the OMP Regulation review:

1. Establishing an iterative early dialogue for EMA-HTA bodies and OMP developers: early alignment on the evidence requirements for the value assessment of a specific OMP would reduce on evidentiary requirement for developers. We propose the establishment of a framework where delegates from HTA bodies accompany OMP developers throughout the regulatory process, together with the EMA, building on the existing joint EMA-EUnetHTA Scientific Advice framework.

2. Building a common EU value assessment for OMPs: A common value assessment framework, building on the EU HTA Regulation, would explicitly define how clinical value is determined, what evidence is required and how evidence is used in the value assessment. It will also have to build upon proposal 1 and be a crucial precondition to a common access pathways for specific cases.

3. Pilot a common EU access pathway: Any joint price negotiations by Member States or led by the European Commission must build on a joint assessment of the value of the product, which is binding to all participating Member States (proposal 2). A common EU access pathway could be a useful forum to develop ways to overcome the challenges that market access poses to very specific groups of OMPs such as ultra-rare.

4. Facilitating homogeneous access to OMPs across Member States, for instance by creating an incentive-based Special Access Program for OMPs. OMP developers would have the opportunity to sign up to the program which would require them to market their OMP in a selected number of countries in return for defined rewards.

Q8: Most of the medicines for rare diseases are innovative medicines. However, in some cases, an older, well-known medicine for a common disease can be repurposed (i.e., using existing licensed medicines for new medical uses) to treat a rare disease. In your view, what would be the appropriate way to award innovative medicines in cases where other treatments are available:

- ○ Both new, innovative medicines and well-known medicines repurposed to treat a rare disease should receive the same reward
- ○ New, innovative medicines to treat a rare disease should receive an enhanced reward
- ◉ Do not know/cannot answer

Q9: Despite the presence of a dedicated procedure (the Paediatric Use Marketing Authorisation, PUMA) in the Paediatric Regulation, many older medicines that are currently used to treat children have only been studied for use within adult populations, and therefore lack the appropriate dosage or formulation suitable for use in younger patients. However, the development of medicines that have been adapted for use in children could also result in a product being more expensive than its adult-focused counterpart. In your view:

Should the development of appropriate dosage or formulation suitable for children of such older medicines be stimulated even if their price will be higher than that of the available alternatives?

- Yes
- No
- Do not know/cannot answer

Please explain your answer.

2000 character(s) maximum

How would you suggest stimulating further development of appropriate dosage or formulation suitable for children of such older medicines?

2000 character(s) maximum

How can it be ensured that such developed products are reasonably profitable for companies and also reach patients?

2000 character(s) maximum

Contact

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