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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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Standing Committee of European Doctors (CPME)

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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

The existing legislative framework does not provide adequate safeguards to protect against its abuse. Therefore, financial support intended for making rare disease medicines “sufficiently profitable” in many instances is diverted to fund the development of blockbuster products.

The presumed lack of profitability of medicines for rare diseases was an essential reason for the adoption of the Orphan Regulation. In practice, however, the actual economic conditions have as yet never been examined when orphan drug incentives are granted to the industry or at any later stage.

The lack of any corrective mechanisms, i.e., a withdrawal procedure which could prevent overpricing and excessive profits, is a major reason for the limited effectiveness of the orphan drug legislation.

Another problem are market exclusivities widely granted to all orphan medicines and subject to no patentability-like tests. Companies benefit from them regardless of their added therapeutic benefit, whether they address an unmet medical need, whether they are innovative* and whether they have already received orphan drug designation for different indication(s).

For these reasons, the regulation turned orphan medicines from an uninteresting category into a new particularly profitable sector for the pharmaceutical industry. In addition, the regulation’s aim and potential to increase the medicines' development has not been achieved for the vast majority of rare diseases.

Regarding paediatric regulation, the major problem is the lack of innovation focused on paediatric needs. Rather than being developed for specific paediatric disease, medicines are often tested for paediatric use only after they are approved for adults.

There is also no sufficient cooperation among academia, patients, industry and regulators to identify the most needed paediatric medicines that should be prioritized for development.

*For the definition of “innovative" see OECD report on Pharmaceutical Innovation.

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

The lack of sufficient preparedness to the pandemic has illustrated the public sector's key responsibility to ensure that the pharmaceutical sector is able to deliver products that meet public health needs.

This includes taking an active role in defining directions of health innovation, guaranteeing fair return on public investments (including obliging companies to pay back incentives if they have been misused) and ensuring transparency in public spending and interaction with private companies.

These essential facts should be taken into consideration when reshaping the market for medicines for rare diseases and children. Misplaced incentives under the current system have resulted in public support being often diverted to fund the development of blockbuster medicines. The EU's decision not to include an effective mechanism to prevent overpricing and overcompensation has also contributed to this unintended outcome.
The Commission and Member States need to ensure transparent and efficient public funding that directs the development of orphan and paediatric medicines towards areas of unmet medical need.

Regarding the impact of COVID-19 on paediatrics, clinical trials involving children were mainly affected by reduced access to outpatient study clinics. Mobile visits by the study team could be helpful in this regard. Also outside of health emergencies, the possibility for the research team to examine patients on site and collect data for clinical trials, would increase participation.

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

Regarding the first proposed approach, there is compelling evidence that the presumption that a medicine developed for no more than about 250,000 people is not profitable is unjustified (see https://www.bmj.com /content/370/bmj.m2983). Rising orphan medicine prices and extended periods of exclusivity through combining indications make orphan medicines among the most profitable in companies' portfolios. Based on these findings, the current prevalence threshold should be re-examined.

In terms of introducing a new system of incentives, the Commission should limit the granting of market exclusivity and provide tailored and proportionate rewards for relevant innovations.

The value of the granted incentives should aim at achieving the Regulation's objective i.e., to allow for orphan medicines to be sufficiently profitable, while avoiding overcompensation. Obligatory disclosure of R&D costs (including public contribution) and transparency on the marketing authorization holders' revenue from orphan products are therefore indispensable. In consequence, if orphan designation is granted for a medicine that has been already used to treat a given rare disease "off label", the commercial reward should reflect limited development risk and costs (for more information on the orphan medicines' profitability see the above mentioned BMJ article).

The concept of significant benefit should be revised and the evidence required to support it should be more stringent. This will ensure that orphan medicines provide for patients with rare diseases real added therapeutic benefit over the already existing treatments.

The approval of orphan medicines by EMA is often based on limited evidence as to their efficacy and safety. Therefore, postmarketing studies as a main source of convincing evidence for clinical decision making are of paramount importance. If marketing authorisation holders are required to conduct them, they should be held accountable for doing so.

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?

2000 character(s) maximum

When assessing whether a medicine for a rare disease offers additional benefits, the following factors should be taken into account, among others: improved survival time, improved quality of life, prevention of hospital stays due to outpatient treatment options, fewer follow-up visits, better spectrum of side effects (lower toxicity), improved forms of application and thus adherence, shorter treatment time or less invasive follow-up visits.

Medicines for rare diseases should be tested in clinical trials not (only) against placebo but also against the best available therapy.

Comparable data are critical for informed marketing authorisations, granting of regulatory incentives and assessing the potential benefits and harms of new medicines against existing ones. They are also indispensable for making pricing and reimbursement decisions and for allowing doctors and patients to make the best choice of treatment.

Once orphan medicines are approved, their added therapeutic value should be independently assessed by the health technology assessment bodies.

If orphan medicines are authorized with limited information on their safety and efficacy, the European Medicines Agency should always require the marketing authorization holder (MAH) to conduct further clinical studies e.g., to prove real clinical benefit instead of achieving surrogate endpoints.

As stated above, if MAHs are required to conduct such studies, they should be held accountable for doing so.

If MAH does not succeed in sufficiently covering the deficit of knowledge about its orphan medicine existing at the time of their approval within the allocated time, the regulatory decision should be revised.

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

Unmet medical need exists when no disease-specific therapy is available and only supportive care is possible, or when an established treatment does not significantly improve quality of life or provide significant or substantial additional benefit.

Besides the above considerations, when defining an unmet medical need different disease-related aspects e. g., mortality and severity of the disease or its prevalence, among others, should also be taken into account.

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

An EU-wide infrastructure for conducting easier and less costly clinical trials (taking into account their design, definition of relevant endpoints and publication of data) should be created. It could take advantage of

the initiatives like the European Health Data Space and the DARWIN project. Importantly, involving academia in the process could bring added value.

When developing medicines for small groups of patients, platform trials with adaptive design should be used allowing a set of drugs to be tested together.

European reference networks (ERNs) bring great added value to the treatment of patients with rare diseases. Their unique potential for integrating expertise should be further exploited to advance the development of new therapies and the design of clinical trials. For this purpose, close interactions among ERNs should be encouraged.

Enhanced collaboration between patients, healthcare professionals, academia, regulators and industry is particularly needed to establish strategies for prioritising the development of the most relevant medicines for children.

Further work is needed to optimise the conduct of clinical trials involving children. This can be done by setting up appropriate structures, such as study centres and registers. These structures can also contribute to intensifying post-marketing surveillance.

The deferral of clinical trials in children leads to medicines being used in paediatrics off-label. In consequence, children with rare diseases who have already received medicines off-label are no longer available for studies. Therefore, studies involving children should be launched and conducted before medicines for adults are approved.

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

2000 character(s) maximum

Public funding for R&D is crucial in areas covered by both Regulations. However, all too often public support is granted without sufficient (or any) conditions. It results in an uneven sharing of risks and benefits between the public and private sectors. The Commission and Member States need to put in place concrete conditions for any kind of public support. Such conditions should ensure that products developed with public contribution are priced fairly and available in all Member States.

As stated in the answer to Q3, the granted incentives should allow orphan medicines to be sufficient profitable, but avoid overcompensation. The new system must move away from the broad granting of market exclusivities and introduce incentives that are tailored and subject to strict conditions. The Commission should prioritise incentives that do not discourage data sharing.

Q7: Which of the following options, in your view, could help all 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?

- [x] Greater availability of alternative treatment options. For instance, by allowing a generic or biosimilar product to enter the market faster.
- [x] 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.
- [x]

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

In addition to the last proposed option, pharmaceutical companies should not be allowed to subsequently withdraw products that benefited from support or incentives from particular markets for commercial reasons.

A major reason for unequal access to medicines are their exorbitant prices which limit their affordability. To address this issue, the Regulation allow for withdrawal of market exclusivity or other incentives if a company charges prices that the public cannot afford, or if its revenues from the orphan product excessively exceed the value of its investment in it. This should be allowed irrespective of the criterion that was used to obtain orphan designation.

For this purpose, a high degree of transparency regarding the companies' R&D costs and revenues is necessary in order to assess whether orphan medicines still qualify for the granted incentives.

The revision of the Regulations should also address commercial strategies that aim to prevent other medicines from entering the market or to extend the period of benefiting from incentives. The Commission should prevent improperly sub-dividing a disease (e.g., in cancer by using biomarkers) into a series of smaller sub-diseases that could qualify as rare. The Commission should also review Article 8 (3)(a) to stop "evergreening" practices that currently allow the holder of a marketing authorisation for an orphan medicine to introduce similar medicines for the same therapeutic indication and as result to delay the market entry of generics.

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

If an increase in the cost of a medicine is reasonable and can be justified, the public may bear it.

Paediatric medicines need to be marketed with a packaging suitable for paediatric use, offered in a safe and suitable form and with adapted package leaflets, with particular attention to dosage accuracy to avoid medication errors.

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

2000 character(s) maximum

The promotion of paediatric studies to determine dosages and formulations appropriate for specific children populations would be very helpful.

The possibility of developing special child-suitable dosages of older medicines is one way of improving medicine therapies for children. However, it is important to ensure that these new dosage forms are actually used and prescribed for children in the long term. Currently, some national laws oblige doctors to use the most cost-effective dosage form rather than the most appropriate one.

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

2000 character(s) maximum

As with the Orphan Regulation, the Paediatric Regulation should aim to increase the development of paediatric medicines by making them sufficiently profitable through the system of tailored incentives. However, it also needs to introduce mechanisms that will prevent overcompensation. All paediatric incentives should be subject to fair pricing conditions and be withdrawn if a company charges prices that the public cannot afford, or if its revenues from the product excessively exceed the value of its investment in it.

Contact

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