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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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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

First, it should be noted that the U.S.—through a willingness to support an IP-enabled innovation ecosystem, including by providing for fair value for investment in innovation—drives most global drug development, including orphans. If Europe was to lead the world again in this respect it would result in substantially more drug discovery worldwide. The Commission should seize the opportunity of its Pharmaceutical Strategy to drive competitiveness and attract investment.

There are an estimated seven thousand rare diseases, and significant heterogeneity within this group. Rare diseases are often biologically complex and much remains to be known about their underlying causes. Developing medicines therefore presents significant scientific and operational challenges. Moreover, almost 85% of rare diseases affect single patients or single families and have a prevalence rate of below one in a million. This distribution is a major barrier to creating a Regulation that would effectively support investment to develop medicines for such rare diseases.

Also, due to the inherently small population of rare disease patients, enrolling enough in clinical trials is challenging. Pediatric trials especially, as parents may be hesitant to expose children to experimental treatments. Nevertheless, even given the limits of existing regulations, industry is focused on new medicines – today, a third of those in drug development are for rare diseases.

On access, we respectfully disagree with the Commission's assessment that the OMP Regulation is a principal cause of "unequal availability, delayed access and often unaffordable treatments". In fact, the Commission's study is clear that "the observed [availability and access] problem can only be addressed by EU Regulation to a very limited extent, as a substantial part of the observed unevenness stems from national policies and decision-making processes". (Technopolis, p. 148)

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 bio-pharmaceutical industry has played a central role to combat the pandemic, including through government partnerships to rapidly move through the drug development process and voluntary collaboration and technology transfer among manufacturers to expedite delivery. In a general sense, future policy reforms should reflect this role and the industry's contribution to healthcare systems resilience.

More specifically, the pandemic has provided evidence for the following items that are universally applicable in drug discovery and development:

- It is imperative to understand the biology of the disease and of potential technologies where there are no sufficient treatment options: public-private partnerships on basic science are essential;
- Decentralized trials allow for faster product development, showing it is essential the EU does not diverge too far from other regions in the world;
- Expedited regulatory approvals and rolling reviews allow for earlier access to innovation;
- Without strong and clear Intellectual Property rules, there would be neither effective partnerships, nor the possibility to transform basic science into a concrete medicine, or for increased manufacturing and distribution, to engage additional trusted partners into the process;
- Digital technologies and the collection of real-world evidence have proven crucial to crisis management and rapid authorization of vaccines and therapies – this should inform future reforms.

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

Any changes to the Regulation should provide greater certainty regarding industry's eligibility for adequate intellectual property rights, in order to facilitate increased investment. The development process for new orphan medicines is lengthy and risky, making adequate intellectual property rights even more important. In the U.S., orphan drugs are designated based on clear criteria related to disease prevalence. Prevalence of the disease is assessed at the time of the designation request and is not reassessed at the time of approval. Orphan designation can be revoked only for narrow reasons, such as an untrue statement or material omission in the designation request. Having a single assessment provides certainty for sponsors when making investment decisions.

Further, as discussed further in the following section, incentives should encourage the development of multiple treatments for a rare disease.

Lastly, the Chamber believes that any new limitation on orphan eligibility criteria would represent a step backward. As described in previous Chamber responses, orphan drug development has accelerated in recent years, and narrowing eligibility criteria would undermine this progress. In particular we would strongly caution against adopting an incidence criterion, which would discriminate against the deadliest diseases.

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 compared with the U.S. particularly, there are already very strict criteria in place to evaluate whether one medicine for a rare disease brings more benefits compared with other available treatments. There is a strict significant benefit test at the time of marketing authorization at EU level, while at national level, a health technology assessment will very often compare the product in question with the available standard of care.

The Chamber supports structuring incentives to promote the introduction of more than one orphan drug per disease where possible. In the United States, orphan drugs are subject to the same safety and effectiveness standard governing all drugs. There is no requirement to demonstrate additional "clear benefit," nor to demonstrate superiority over another treatment, unless the sponsor wishes to secure orphan exclusivity for a product that is structurally the "same drug" as a previously-approved orphan product and treats the same condition.

This approach encourages development of multiple treatments for rare diseases, thereby promoting marketplace competition and expanding options for patients. As noted below, orphan incentives in the United States have been very successful in promoting approval of new drugs for rare diseases and conditions.

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

All of the situations described above are unmet therapeutic needs. Indeed, the above criteria are consistent with how the U.S. FDA defines unmet medical need for purposes of eligibility for expedited programs, which entitle industry to extra guidance from FDA, expedited review and/or accelerated approval.

The Chamber recommends avoiding a restrictive approach defining unmet medical needs as those conditions with no treatment approved. Instead, we recommend following the approach taken by the FDA.

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 U.S. framework for encouraging private investment in development of treatments for rare diseases provides a model for potential improvements. As covered above, exclusivity for orphan drugs is available in the U.S. based on orphan designation and approval, without the need to show benefit over structurally unrelated drugs. An orphan designation is also subject to reconsideration only in narrow circumstances, providing certainty about the availability of adequate intellectual property rights. Further, a six-month extension of applicable exclusivities can be awarded if the manufacturer conducts a pediatric study or studies that fairly respond to a written request from the FDA. These incentives have been highly successful in driving investment in rare disease treatments and medicines for children.

In addition to providing exclusivity periods, FDA also issues priority review vouchers for qualifying applications for drugs that treat a rare pediatric disease. Rare pediatric disease is defined as a disease that is “a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals from birth to 18 years” and meets the Orphan Drug Act’s definition of a “rare disease or condition.” The promise of receiving such a voucher for obtaining approval of a drug for a rare pediatric disease can drive investment in drugs for rare pediatric diseases.

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

2000 character(s) maximum

In some instances, the current intellectual property rights are inadequate to attract investment as the economic outlook of a successful product would not be positive - for instance when the patient number is extremely low. A ‘transferable exclusivity extension’, along the lines of that described above, could help overcome this. By transferring the exclusivity, it allows investment in a product that has no commercial viability on its own.

Another issue is a lack of ‘pull incentives’ and lack of willingness to pay by countries: as mentioned previously, and in contrast to anecdotal high-priced products, most orphan medicines will have a very low turnover i.e. close to 50% with less than €10m p.a. (Technopolis study, p.150). Market access incentives such as the ones in place in Germany or Italy are key to stimulate innovation. They should also include greater predictability for industry, through flexibility of methodologies/evidence requirements from HTA bodies. The pandemic has also demonstrated that there is a general need for investment in European health systems and related infrastructure, to help provide stable and sustainable access to medicines.

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?

- [ ] 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

Access to medicines is a responsibility shared by companies and public authorities. Access discussions are based on procedures set by governments, which often differ: regulatory requirements, differences in medical practices, speed of pricing and reimbursement negotiations, the ability to achieve a price acceptable for both payers and industry, health expenditure levels, layers of decision making, and strength and scope of health systems/infrastructure. None of the measures above are based on root cause analysis of differences in access, nor do they provide a viable way to address them.

Root cause analysis would show that EU MS have enacted price controls that have unintended consequences. Next to reducing the amount of innovation generated, measures such as international reference pricing discourage companies from prioritizing countries with lower GDPs. There is wide variation in the amount of resources devoted to healthcare by EU MS. A minimum level of investment would go a long way in reducing access disparities.

There is no easy fix to improve access, but it is key to disentangle root causes and avoid unintended consequences. For instance, IP rights related to rare disease and pediatric illnesses fulfil the same basic function as other rights e.g. patents or regulatory data protection, in support of investment in innovation. Nevertheless, because the opportunity to earn a return on investment here is more limited, rights may need to expire later, and be more readily enforceable, to adequately attract investment. Global IP frameworks, including WTO TRIPS, do not allow conditioning the grant or enjoyment of such rights in certain markets based on launch (or lack thereof) and certainly not based on launch in different markets. There is a risk that by pursuing some of the options under consideration the EU will not only not solve access issues; moving away from global IP and trade norms would also reduce competitiveness and investment in future treatments.

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

Where a pediatric formulation has been developed to meet children's needs, it will be preferable to children to receive this formulation rather than one intended for adults. A tailored approach is required in order to meet safety and efficacy standards. Oftentimes this requires sustained investment and full clinical development (i.e. clinical trial data must be regenerated for submission and approval, necessitating the conduct of a new trial).

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

2000 character(s) maximum

n/a

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

2000 character(s) maximum

We would argue that this innovation should not be foregone on account of its potential budget impact – pricing and reimbursement is established further along in the process, at national or sub-national levels, based on a range of factors including value and ability to pay. Access hurdles are complex and numerous. Streamlining procedures, aligning evidence requirements and removing barriers to differential pricing would all facilitate access to such developed products.

The Chamber also believes that the U.S. model for rare disease incentives, described further in the answer to Question 6, would benefit patients by making more treatments available and would protect the original investment, thereby encouraging additional investment in rare disease treatments.

Contact

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