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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.

About you

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Business association

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*Organisation name

255 character(s) maximum

Vereniging Innovatieve Geneesmiddelen

*Organisation size

Small (10 to 49 employees)

Transparency register number

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Netherlands

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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?

2,000 character(s) maximum

The Vereniging Innovatieve Geneesmiddelen (VIG) perceives the orphan legislation as a means to develop therapies for patients with unmet medical needs. Its introduction in 2000 has established incentives which have led to novel treatments for rare diseases (RD). This has resulted in the introduction of 164 therapies introduced between 2000 and 2018, while only 8 therapies were introduced before 2000. This is a demonstration of the effectiveness of these incentives. Therefore, the incentives should remain in place. At the same time has 95 percent of the rare diseases no existing treatment. Also, most of these rare diseases are in fact ultra rare (89,1% of the rare diseases affect 11,4% of the patients), which makes research both highly challenging scientifically and practically as well as, very often, unsustainable economically.

Subsequently, the introduction of the Paediatric Regulation in 2007 has led to the obligation for all medicines for the adult population, to also be developed for children. The result was that the development of therapies for specific paediatric diseases, without an adult population, was not incentivised.

Various barriers exist for the development of treatments for paediatric diseases such as scientific (e.g. lack of translational research), operational (difficulties to conduct trials in paediatric populations, preclinical data, recruitment and retention, trial design, informed consent). Furthermore, there are practical and economic barriers due to the size and heterogeneity of the population, which is subsequently segmented in five different age categories.

Before deciding on any new policy measures for any Regulation, the existing incentives and barriers to development must be identified and properly understood. Tailor-made policies are essential here.

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?

2,000 character(s) maximum

Since the start of the COVID-19 pandemic, the focus of all stakeholders has been to address this crisis. This effort has been at the expense of many other diseases, not in the least rare diseases and paediatric diseases. The consequences of this will become clear in the coming years. The innovative pharmaceutical industry has delivered, in a short timeframe, a major contribution to address the COVID-19 crisis, both preventive and therapeutic. These results were built on years of research stimulated through the existing intellectual property framework.

At the same time regulatory authorities have shown the ability to respond flexible to innovations, evaluate preliminary data as it became available with rolling reviews and making use of real-world data. The use of conditional market authorisation is a lesson which could be used for therapies for rare diseases and paediatric medicines. It is important to sufficiently strengthen the European Medicines Agency to continue their flexibility following the pandemic. Also, collaboration between FDA and EMA should continue and develop a common strategy to facilitate the development of therapies for orphan and paediatric medicines.

Furthermore, member states have demonstrated their willingness to ensure fast access to vaccines and therapies against COVID-19. It would be good to evaluate at member state level which lessons can be drawn from the pandemic to improve patient access to orphan and paediatric medicines.

Finally, we have to remember that COVID-19 cannot be compared with rare diseases. Therefore, the lessons which can be learned are limited.

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

	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).

2,000 character(s) maximum

The existing criteria for orphan designations are clear and have demonstrated to be effective in the stimulation of the development for medicines for rare diseases. Despite these successes, there are still many rare diseases without treatment. Current incentives may not be sufficient to stimulate the development of therapies in these areas. Lowering the criterium for prevalence or introducing a criterium for cumulative prevalence will make the development for therapies even less attractive and will not redirect investment to rare diseases. Furthermore, differentiating between rare cancers and other rare diseases is concerning. Patients suffering from rare oncological disorders should be just as entitled to treatments as patients with other rare diseases. This proposal discriminates against patients suffering from deadly diseases. In order to include advancing scientific knowledge in the definition of a disorder, it is important to take into account both classical histology and genetic abnormalities or defects that cause disease.

The existing orphan designation already incentives products which have a clear benefit for patients when compared to other available treatments. This framework should be maintained.

The fact that a treatment for a rare or paediatric disease exists does not mean that no unmet medical need remains. Additional incentives should also be possible for therapies in disease areas with existing therapies.

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?

2,000 character(s) maximum

In the past the European Commission published a notice aimed at providing more information on the concept of Significant Benefit. The factors which are considered by the Commission as 'a clinically relevant advantage or a major contribution to patient care' are important and include: improved efficacy; better safety profile or tolerability; ease of self-administration; improved adherence to treatment. Removing any or all of these elements would have a significant impact on the development of orphan therapies.

The framework for Significant Benefit would be improved by allowing an earlier cut-off point in the development for the identification of a comparing therapy. This would support better decision making and the improved development of evidence.

Furthermore, it should be stressed that products with market authorisations are to be preferred in comparison to products used off-label use, compounded, and hospital exemptions. Both as treatments as well as comparator for Significant Benefit. The replacement of registered orphan drugs with unregistered pharmacy preparations is a development that undermines the regulatory system. Patients with a rare disease have just as much right to medicines that have been studied in accordance with the guidelines for good clinical practice and have received an EMA approval. In addition, registered orphan medicines can be marketed in all Member States and pharmacy preparations are only available locally, which limits the number of patients who have access to this therapy.

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

- ☑ 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).
- ☑ Treatments are already available, but their efficacy and/or safety is not optimal. For example, it addresses only symptoms.
- ☑ Treatments are available, but impose an elevated burden for patients. For example, frequent visits to the hospital to have the medicine administered.
- ☑ 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).

2,000 character(s) maximum

All four options described above form an unmet need, which is defined as a condition which is not adequately prevented, treated or diagnosed by approved interventions. Limiting incentives to exclude one or more of the propositions can be detrimental in the development of therapies in that area. We have seen in the past that following the approval of a first in class treatment for a condition has led to the development of other therapies, with improved clinical outcomes. These have broadened the arsenal of healthcare professionals. Would incentives have been restricted, treatment options would have remained limited and medical progress would be blocked.

A similar development has been seen at the time of the introduction of the Paediatric Regulation. Incentives were not applicable to existing therapies. As a results the current incentives have not lead to the development of paediatric formulations for older products because of unwillingness of payers to reimburse these due to financial reasons. We propose the introduction of supplementary incentives, even at national level, to improve patient access to therapies and areas underserved due to market failure.

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)

	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?

2,000 character(s) maximum

The development of new orphan medicines is an uncertain, costly and lengthy process, in which patients, public and private partners intensively cooperate. For example academic or research centres focus on the development of initial concepts and ideas, but are unable to bring their discoveries to patients because of the required capacity and capabilities for the development of therapies. These concepts and ideas are acquired by innovative pharmaceutical companies, based on market-established agreements, which further develop these into therapies and make them available to patients.

The decision of companies to invest in a disease area or a potential therapy are driven by various factors, such as: scientific; economic; and policies for a regulatory framework, IP, and pricing and reimbursement. Each barriers requires a different approach and different incentives to stimulate the development. A thorough analysis of the root causes behind the lack of treatment or requirements to fulfil the desire of society to invest in specific areas needs to be conducted.

Furthermore, it is equally important to be critical of barriers at member state level which limit (time to) patient access and how pricing and reimbursement decisions can have a detrimental effect on decisions to invest in specific disease areas.

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

2,000 character(s) maximum

To support the additional measures it is imperative to provide additional resources to the regulatory authorities. This can ensure the development of a world class regulatory framework adapted to the requirements of scientific innovations. The past year, during the COVID-19 crisis, existing resources were redirected in support of efforts to tackle the pandemic. However, this cannot be maintained indefinite.

It is unclear what the European Commission means with post-authorisation incentives. We think that additional and novel incentives can be valuable to stimulate development and improve patient access. However, it would be necessary to conduct a deep dive analysis to identify specific barriers and to propose measures to address these. Any proposal should not negatively impact the development of treatments or stimulate market failure. Naturally, any new incentives should be complementary to existing incentives and not replace current, effective incentives.

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).

2,000 character(s) maximum

All options proposed could prove counterproductive, because they take insufficiently into account the broad spectrum of drivers which have an impact on patient access. The limited development of generic alternatives for therapies for paediatric and rare diseases is due to the fact that these markets are commercially insufficiently attractive.

We fear that any requirements for incentives being linked to the launch of products will not improve patient access. Furthermore, decisions about the reimbursement of medicines are the prerogative of the member states. Therefore, the European Commission should not interfere in this process through any policy measures. Also, we fear that these proposals will have a negatively impact on the attractiveness of Europe for conducting research and development.

Barriers in patient access to innovative therapies cannot be solved with a revision of the OMP and Paediatrics Regulation. To address the existing issues it is necessary to conduct an analysis of root causes of delays and the lack of availability of specific products. To address this it is required to bring all relevant stakeholders, in particular the European Commission, the Member States and the pharmaceutical industry, round the table to jointly develop proposals to improve access to innovative medicines.

Furthermore, companies engage in collaboration, licensing deals, and purchasing of products by other companies. We have seen several demonstrations of this over the last year, during COVID-19 pandemic. It is unnecessary to take additional measures to make this happen.

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.

2,000 character(s) maximum

To ensure adequate therapies for children, both in terms of efficacy and safety, it is important to study medicines in children. It is a misconception to consider children as small adults, rather than individuals with specific physiological processes, which need to be taken into account. A company will only undertake the necessary steps to acquire market authorisation when sufficient drivers and incentives exist for the required investments.

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

2,000 character(s) maximum

Pharmaceutical companies develop innovative products to translate cutting-edge science into new treatment options for patients, including paediatric formulations for any new compound if appropriate. In accordance with the obligations of the Paediatric Regulation, many paediatric formulation developments have been performed for older products that are still patented.

Novel incentives and public or philanthropic funding to support SMEs, academia, or contract manufacturers can provide the necessary stimulus for the development of paediatric formulations for off-patent products. However, the challenges of producing products with a small volume, such as paediatric formulations, have to be taken into account.

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

2,000 character(s) maximum

Medicines can only deliver a return on investment for researchers, academia and companies when they are prescribed. Furthermore, their value must be reflected in their reimbursement. When Member States are unwilling to pay for innovation and new therapies, there is a significant risk that any incentive developed by the European Commission will not have the desired effect and not lead to novel treatments and patient access.

Contact

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