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

A1: *The Netherlands considers that the orphan legislation has been established to address unmet medical needs of rare diseases by tackling the challenge of their small populations and subsequent small markets and providing an incentive, amongst others, through market exclusivity to overcome such hurdles and stimulate the development of innovative treatments for orphan diseases. The paediatric legislation aims to address that the lack of appropriate dosage, dosage forms and formulations for children and to stimulate the development of medicines to alleviate or treat diseases affecting mainly children. While both legislative pieces have improved the state of affairs, the Netherlands still detects barriers in the development of treatments for rare diseases and for children. Specifically in what concerns the paediatric legislation, inefficient and burdensome procedures can deter development, as identified in the recent EU pharmaceutical strategy. Given that the paediatric regulation is based on the principle that a medicine is developed both for adult and paediatric populations, it does not stimulate the development of medicines for diseases that occur only in children. As to the orphan designation, the impact of introducing a time-based expiration for an orphan designation needs to be carefully assessed. If the company provides a good justification on why a given designation has not lead to the development of a specific medicinal product, then the designation should remain valid. The data and rationale underlying the delays or lack of development of a medicinal product could furthermore be of great value. A tracking system to register such information could be used to identify the causes/determinants of unmet medical needs and to redirect or stimulate further research & development. For example: if several companies hold an orphan designation for a given indication, and the (credible) claims for such delay are due to lacking scientific knowledge, then pathways to stimulate further research & development for that condition might be necessary/further addressed. A last option to improve development is by considering to vary the lengths of market exclusivity that different products can receive. Especially for repurposed products, we consider that a shorter term of market exclusivity than the current standard of ten years, could make it more commercially viable for new market participants to enter the market and improve on existing treatments. Longer terms of market exclusivity then could be available for the developers of fully new and innovative products.*

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

A2: *The Netherlands sees three valuable lessons to be drawn from the COVID-19 crisis that could be explored when addressing the needs of orphan diseases and paediatric medicines. Generally, one*

must note that the COVID-19 crisis has had its own, particular challenges and the measures applied throughout cannot be directly implemented to the legislation for orphan or paediatric medicines. There is a need to assess their feasibility and suitability to this specific context. First, the rapid development and production of Covid-19 vaccines and treatments has shown that (near-) guaranteed purchase of products can act as a strong incentive to boost late-stage development and production – thus establishing advanced purchase agreements in addition to granting market exclusivity could pose an interesting option for the legislative framework to advance research and to boost the availability of orphan treatments. Second, another interesting consideration is that a considerable public investment can be effectively combined with concrete pricing and profit conditions. Finally, during the COVID-19 pandemic, certain marketing authorization procedures were altered or accelerated. Inevitably, many changes are not applicable other than in acute emergency situations, but it could be beneficial to explore and assess whether any of the applied registration measures might be implemented more broadly.

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

Approaches	**Very / Moderately / 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.	*Very*
Some diseases occur frequently, but last for a relatively short period of time (e.g., 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.	*Very*
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.	*Very*
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.	*- (niet beantwoorden)*

Other (please suggest any other criteria/approaches you think might be relevant).
2000 character(s) maximum
A3: *The proposal in the first option, to assess the impact of modifying the current threshold of total number of cases at a specific time (prevalence) to that of identifying specific rare cases (incidence) is welcomed. Additionally, to ensure that the regulation specifically targets the rarest diseases, requirements should be set so that market exclusivity cannot be applied to subsets of more frequent indications , e.g. by accumulating market exclusivity across indications which contemplate smaller groups of people affected, one is, de facto, targeting a bigger collective group with the same medicine within the same therapeutic area. To take this a step further – the Netherland proposes to explore the option to also take into account the size of the patient population across all conditions*

which are being treated by one and the same medicine - and not only for rare diseases – at the time of approval and when making decisions about subsequent indications.

We also support the second option. We agree that there is a high need for appropriate treatments for this type of diseases, but admit that there is a significant difference between the stimuli needed to address this category when compared to the stimuli to tackle orphan diseases.

The Netherlands considers that fourth option to be interlinked with the third– as the third option mentions a 'clear benefit to patients'. Both options address unmet need, but in different magnitudes. If a new medicine provides a clear benefit when compared to an existing treatment that means a medical need was still unmet, even though a previous treatment was available. Therefore, we read the contrast between the third and fourth options as whether:

- treatments addressing unmet medical needs are to be granted additional rewards and incentives (fourth option)

OR

- only those treatments offering a clear benefit are to be rewarded or incentivized (third option).

Our preference is that addressing an unmet medical need should be considered a baseline to determine whether a reward or incentive is to be granted.

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
A4: *In general, a significant increase in efficacy, safety and quality of life counts as a benefit, and the reason for this increase can vary: curing vs. treating, alleviating symptoms, easier to use, enabling treatment at home rather than in hospital setting. Patient benefits are the key factor at every deliberation. However, should all factors be equal, one medicine can also benefit the healthcare system by 1) being more convenient to use, 2) being less labor-intensive in a hospital setting or 3) by contributing to the security of the supply of medicines. However, rating the magnitude of the benefit is to be linked to rating the magnitude of the incentive. This will prevent a small benefit from receiving a one-size-fits-all reward or incentive.*

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

Options	**Yes/No**
Authorized medicines for a particular rare disease or a disease affecting children are not available, and no other medical treatments are available (e.g. surgery).	*Yes*
Treatments are already available, but their efficacy and/or safety is not optimal. For example, it addresses only symptoms.	*Yes*
Treatments are available, but impose an elevated burden for patients. For example, frequent visits to the hospital to have the medicine administered.	*No*

Treatments are available, but not adapted to all subpopulations. For example, no adapted doses and/or formulations, like syrups or drops exist for children.	*No*

Other (please specify).
2000 character(s) maximum
A5: *All options above include situations whereby, a medical need is somehow unmet, yet the extent of the unmet medical need varies. This difference should be reflected in the incentives to be granted – a medicinal product or treatment that meets a greater or more severe medical need should be proportionally matched. The third and fourth option seem to be examples of treatment optimization, which requires incentive types other than the development of entirely new quality, safe and efficacious treatment options. The exact divide between what is to tackle an unmet medical need and what is treatment optimization should be further discussed with organizations within the life sciences and health sector and agreed upon between Member States and the Commission. In the context of the evaluation of the paediatric and orphan regulation, the Netherlands reiterates the need for a clear definition and common criteria at the EU level to establish what constitutes an unmet medical need, yet one that should also be applicable outside the context of rare and paediatric diseases. In addition, it is important to identify the root causes of unmet medical needs and determine whether there are lacunae in scientific knowledge, or whether the market is unattractive. Different root causes will require different solutions.*

A relevant note on the first option is that while we generally prefer authorized medicines to magistral preparations, the medical need is significantly less 'unmet' when a magistral preparation is available to patients. For some ultra-orphans, registration might not be a feasible path and a magistral preparation can be an acceptable endpoint. In these situations, it could be preferable to explore pathways to increase greater treatment availability, while bearing in mind the available evidence base and potential safety of use.

As to the third and fourth options, we acknowledge that when it concerns children, less burdensome treatments and adapted dosages could meet the threshold and be considered as responding to an unmet medical need.

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)

Measures	**1-10**
Assistance with Research & Development (R&D), where medicines under the development can benefit from national and/or EU funding	*8*
Additional scientific support for the development of medicines from the European Medicines Agency	*8*
Assistance with authorization procedures, such as priority review of the application from the European Medicines Agency and/or expedited approval from the European Commission	*3*
Additional post-authorization incentives that complement or replace the current incentives and rewards	*7*

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

medicinal products?
2000 character(s) maximum
A6a: *It could prove useful to gain more institutional insight into the reasons why certain developments are lagging – more research into the limiting factors for specific types of disease (i.e. is there a lack of scientific understanding and knowledge about disease etiology, or rather production issues, or even regulatory hurdles, etc.). These could eventually be tackled through targeted incentives – which do not necessarily have to encompass market exclusivity, but rather be designed to address the determinant factors as identified above.*

Do you see any drawbacks with the approaches above? Please describe.
2000 character(s) maximum
A6b: *Not necessarily drawbacks but rather points to bear in mind – if R&D stimulus and support are to be channeled through funding, they should be combined, proportionally, with requirements on access, such as licensing, pricing, availability etc. While a priority review might help improve accessibility and availability, we are hesitant to forecast that expediting approval, per se, will have a significant effect on development of new medicines. We consider that accelerated approvals could be beneficial to timely market introduction, but might not boost R&D investment for new treatments.*

As an additional note: it is inevitably difficult to assess whether additional post-authorization rewards or incentives would be effective when it is not clear what these would entail. Novel incentives must stimulate research and development of medicines for the greatest unmet medical needs, without a significant impact on accessibility and affordability. A balance needs to be struck.

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?

Options	**Yes/No**
Greater availability of alternative treatment options. For instance, by allowing a generic or biosimilar product to enter the market faster.	*Yes*
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.	*Yes*
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 authorization.	*Yes*

Other (please suggest any other solution you think might be relevant).
2000 character(s) maximum
A7: *Variable durations of market exclusivity could open up the field sooner to competitors to supply markets not yet being served by the exclusivity holder. Especially for repurposed products, there is a higher chance that new market participants will enter the market after a shorter term of market exclusivity than when it concerns a fully new product. Nevertheless, this solution only works when the market is sufficiently big to attract other players. For some ultra-orphans, the market is too saturated to allow a second player. Exploring solutions to support healthy competition in such cases could help improve availability and accessibility.*

As to the last option, while timely introduction could prove a pathway to improve availability and

accessibility, attention is to be paid to subsequent stages of market access to ensure that no perverse incentives eventually arise during its implementation. For example, abiding to such a rule should not enable companies to exert pressure during price negotiations.

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

Er is geen ruimte voor toelichting bij deze vraag dus voegen we apart een bestand in met de volgende toelichting:

The justification for our choice for the second option on Question 8 is that the reward or incentive should not be enhanced, but rather that the basic incentive of 10 years market exclusivity should be adjusted. A newly adjusted stepping-stone of 5 years of market exclusivity, with the potential 'enhancement' for new (i.e.: not repurposed) medicines, so that it would not add up to a longer period of protection that is currently the standard, i.e. 10 years.

The length of market exclusivity for repurposed orphan medicinal products (i.e. a known active substance already in the market, but used off-label for an orphan indication, which then obtains a marketing authorization for the orphan indication) should be shorter than for innovative products, as in general R&D activities were limited. If a company applies for extension of the period of market exclusivity, insufficient return on investment could be considered as a standard criterion for extension of, provided that the burden of proof is on the company-side to provide the information and full transparency is required. For this particular option, there needs to be a previous discussion and agreement about the data to be submitted and how these will be assessed.

Amending the length of market exclusivity for repurposed orphan medicinal products will pose the question of how the distinction will be made between medicines that are indeed innovative and those that are not 'new and innovative' enough. We acknowledge that it will be difficult to find objectively quantifiable criteria that do justice to the complex process of medicine development. Still, we have seen instances whereby marketing authorization holders make minimal adjustments to existing medicines, or register active substances that had been used off-label for a long time – and yet being granted the full ten years of market exclusivity. At this point, that practice, while not in the spirit of the legislation, abides completely within to the regulation. We would recommend taking steps to amend the regulation in a way that it becomes more closely aligned with its spirit and expectations – rewarding efforts made to research *and* develop, register *and* produce medicine for rare diseases. The fact that establishing a clear legal distinction might pose difficulties should not deter the process of starting a discussion on this point. Notwithstanding, the importance of introducing a clear, legal definition is key when selecting criteria.

Q9: Despite the presence of a dedicated procedure (the Paediatric Use MarketingAuthorisation, 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 is. 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
A9a: *It is reasonable to assume that the economy of scale can be impacted negatively if a medicine is produced only for a smaller group of people - particularly when such increase is reasonable and proportional to the amount of effort/investment.*

How would you suggest stimulating further development of appropriate dosage or formulation suitable for children of such older medicines?
2000 character(s) maximum
A9b: *At this point, a compulsory character could be considered. After marketing authorization, data is often compiled which could be sufficient and relevant to registering an appropriate dosage or formulation. For companies that do not have access to all the necessary data, subsidies could be available, or exemptions could be applied when the data collation would prove to be an undue burden. At this point, one can carefully conclude that offering incentives has not led to the desired result; therefore, we advocate introducing a more compulsory attribute, even if only for a limited list of medicines for which a marketing authorization for an appropriate dosage or formulation are deemed essential.*

How can it be ensured that such developed products are reasonably profitable for companies and also reach patients?
2000 character(s) maximum
A9c: *A stimulating measure in the form of an obligation, reward or incentive could be considered, if availability and access are not unduly hindered. In order to do so, the impact assessment is a very important tool to be able to evaluate the consequences of possible measures and their likely effects.*