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

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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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 – 1992 characters

There are indications in which not enough research has been conducted to date. However, insufficient development in areas of unmet medical need, unequal access, and inadequate measures to capture technological as well as scientific advances are the consequences of existing barriers but are not barriers in themselves. Existing barriers need to be mapped and well understood, before any policy actions are being taken. So far, the EC has missed out to do so.

The current range of therapies for the treatment of patients with rare diseases (RD) and of children is encouraging and has been boosted by different EU initiatives, especially the introduction of the OMP regulation in 2000 as well as the introduction of the Paediatric Regulation in 2007. Both have worked well, have been successful in attaining their goals and should remain.

The rare disease space is highly complex, covering more than 7000 varied diseases – it is no surprise that many of them could not be addressed yet. The vast majority of RD affect only very few patients (89,1% of RD affect a total of 11,4% of patients) which makes research both highly challenging in a scientific way (e.g. lack of scientific knowledge and harmonized/accepted endpoints/methodologies), in terms of practical realization (e.g. patients are not (yet) diagnosed, few patients are scattered around the globe) and it poses economic challenges.

The Paediatric Regulation, by design, did not incentivize paediatric-focused development (i.e. without an adult reference population). Barriers to paediatric-focused development are of scientific nature (e.g. lack of translational research, difficulties to conduct trials in paediatric populations) as well as practically and economically demanding due to the small size of the population that is further segmented into 5 different age categories. Increased administrative burden and longer time to market when modifying a paediatric investigation plan (PIP) can be discouraging for using this reward.

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 – 1997 characters

The pandemic revealed how crucial a vital innovation ecosystem is to overcome global health threats. But COVID-19 has diverted global attention from other diseases, not least rare and children's diseases. The full effects are yet to be seen.

vfa members are proud to have contributed to therapeutic solutions against COVID-19 in a short time. The technology (platforms) and science that led to vaccines and therapeutics were already well understood and built on prior decades of research, thanks to the already existing IP framework.

During the pandemic, regulatory agencies have proven their agility, considering more rapid development, use and acceptance of preliminary data packages in rolling reviews and complementary/alternative evidence (e.g. RWE) and the use of conditional MA, which could be valuable for OMPs and Paediatric medicines. Labelling flexibilities applied to COVID-19 products

could also be considered in the OMP/Paediatric product space which, by definition, will be for limited number of patients. Sufficient resources on all levels must be ensured to allow this agility further.

All COVID-19 vaccines - and many other products - have ongoing global paediatric development programs based on EU and US paediatric investigation plans. Both agencies have increased collaboration during the pandemic, aiming to agree as much as possible on a common strategy. This could be expanded.

However, it is obvious that COVID-19 is anything but rare – the response by industry, governments, authorities et al. to a global pandemic cannot directly be replicated or extrapolated to diseases that may not be global in nature and affect relatively few patients. But the pandemic should be used as an opportunity to streamline procedures, increase the use of digital solutions, foster global convergence and specifically strengthen innovative industries and technologies. Above all, this includes enhancing the networking and cooperation of all stakeholders of the healthcare system in future.

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

at most 1 answered row(s)

	Very	Moderately	Not at all
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 – 1893 characters

The current range of treatment options for patients with rare diseases and for children is encouraging and has been promoted by a wide variety of initiatives in the past. At the same time, it is evident that developing such treatments still is a challenge. It is necessary to continue research and development in order to find first-time, as well as additional, treatment options that address unmet medical needs for patients with rare diseases and for children.

The present orphan designation criteria provide predictability, which is essential to encourage the development of products for RD. 98.6% of RD patients are affected by 10.9% of the more prevalent rare diseases: lowering the prevalence criterion is a risk, as is a cumulative prevalence criterion for products with more than one orphan designation. It will not redirect investment to rarer diseases but could reduce investment in other rare diseases as they would no longer be eligible for OD and incentives, but still hold the challenges of science & methodology in diseases with very low patient numbers.
The orphan designation criteria already include that only products bringing a clear benefit to patients should be incentivized. This framework should be maintained and should remain different and separate from HTA standards.

In addressing the concern around the relevance of orphan conditions, a novel approach to the definition of condition should be developed based on scientific reality that conditions can be defined both by classic disease type/histology and by genetic disorders or deviations that cause disease without doing "salami slicing".

As all rare and paediatric diseases constitute unmet need and the existence of a treatment does not make a 'need met' per se, additional incentives, such as additional transferable vouchers for priority approvals or regulatory incentives can promote innovation in these areas.

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 – 1415 characters

All factors considered in Commission notice 2016/C 424/03, clarifying the concept of significant benefit Article 3(2) of Regulation (EC) No 847/2000 as 'a clinically relevant advantage or a major contribution to patient care' are important, incl.:

- improved efficacy for all or parts of the population
- better safety profile or tolerability for all or parts of the population
- ease of self-administration
- improved adherence to treatment

The question whether all these factors are relevant to determine the willingness to pay of healthcare systems is a national matter and should not shape a European incentive framework to foster R&D.

Currently, identification of the comparator can be very late, which presents a challenge for collecting meaningful data for the comparison. This can be improved, by setting a cut-off point for comparator identification earlier in development like at the time of scientific advice when the pivotal study for submission is fixed to allow better evidence development decision-making.

The procedure to confirm orphan designation criteria at time of marketing authorisation should be streamlined, i.e. the COMP should start its review earlier in order to ensure that the confirmation of orphan designation is available and shared with CHMP ahead of the B/R evaluation. However, the CHMP B/R evaluation should remain clearly separate from the OD evaluation, including the SB assessment.

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.

- [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 – 634 characters

The term unmet medical need is perceived in different ways. All of the above constitute an unmet medical need but are not sufficient on their own. Therefore, a common understanding amongst all stakeholders, including the industry, is necessary. What is decisive here is that the concept of an unmet medical need may not be equated with the lack of a pharmaceutical product. In other words, it is necessary to make continuous investments in research and development in order to develop both new and further treatment options for a disease. In consequence, incentives for developments should not be restricted to subtypes of unmet 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)

at most 1 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									x	
Additional scientific support for the development of medicines from the European Medicines Agency							x			
Assistance with authorisation procedures, such as priority review of the application from the European Medicines Agency and/or expedited approval from the European Commission								x		
Additional post-authorisation incentives that complement or replace the current incentives and reward									x	

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

2000 character(s) maximum – 1354 characters

The innovative pharmaceutical industry is operating in a complex ecosystem to bring an idea to patients. In addition to research activities being carried out in the research departments of pharma companies, research projects driven by academic centres or spin-off research centres affiliated to universities focus on initial ideas. However, the latter will neither have the capacity nor capability to take on the high development risk and bring it to market. Thus, pharmaceutical companies can buy out the initial project, against a market-based price (upfront, royalities or a mix) agreed between both parties. The biopharmaceutical ecosystem consistently highlights the complementary and interwoven nature of the public sector and the private sector in supporting biopharmaceutical R&D.
Each part of this complex research and development chain relies on a multitude of support elements to ensure they can be productive at targeting complex diseases. Therefore, all of the options above are useful elements to support activity in areas of unmet need, especially in conjunction with lowering barriers (for instance by fostering a better collaborative knowledge gathering and R&D network environment, having a better convergence with other major markets, encouraging an appropriately value recognition of these medicines and calling for strong IP rights).

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

2000 character(s) maximum – 735 characters

Balance is key in any policy measure providing incentives to include right safeguards and to ensure that there is no over-incentivisation or negative impact on other actors of the development chain. However, this does not exclude the consideration that incentives could also be thought of in a complementary way.

Regulatory support has been and continues to be a very useful mechanism. Protocol assistance for development of OMPs is highly valued. If additional responsibilities are put on the regulatory framework and EMA, appropriate resources also need to be provided. Therefore, more resources and better integration of all development support activities should be considered for a scientifically strong regulatory system in Europe.

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?

None of the below options should be ticked

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 – 1956 characters

Reducing incentives and rewards or even linking them with obligations to launch in a specific number of markets will not solve the access issue but will, in consequence, reduce R&D activities in the relevant fields of paediatric and RD. Instead, EC should consider all options including non-legislative ones.

In contrast to the situation in Germany, where patient access to medicines from day 1 of approval enjoys high priority and gives proof to the national dimension of this issue, vfa recognises the unequal access to and lack of availability of medicines in other EU Member States as a problem that requires solutions. It is therefore understandable that the EC is considering measures to improve access to and affordability of medicines. The measures now proposed would, however, fail to achieve this goal and will not contribute to the solution. On the contrary, they could produce negative effects on future supply in Germany and Europe and especially regarding the development of new treatment options.

Ideas about a mandatory market launch of pharmaceuticals for the pharmaceutical manufacturer in all EU Member States impair competitive solutions. In addition, they appear to be contrary to the intention of Europe to create solid basis and framework conditions for a forward-looking innovation agenda.

Also because of the dependence of generic and biosimilar competition on economic reasons and the resulting limitation for OMPs vfa supports a thorough analysis of root causes of unequal patient access to innovative and care-relevant treatments as a necessary basis for the discussion of suitable measures. There are multi-factorial reasons for access issues, and these cannot be attributed to the sole decision by individual manufacturers. In order to identify and implement effective approaches to solutions, a trusting, partnership-based cooperation among the EU institutions, the EU Member States and the pharmaceutical industry is required.

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 – 617 characters

To ensure the safety of children, it is particularly crucial to safeguard that the medicinal products they are prescribed follow the appropriate dosage and formulation suitable for use in younger patients. Children are not only 'smaller' adults but present specific biological and physiological differences which need to be properly accounted for in a separate development plan. If a sponsor develops a paediatric formulation of an older existing product, it will need to meet the same quality, safety and efficacy requirements but will only do so if relevant incentives for this development investment are in place.

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

2000 character(s) maximum – 448 characters

So, incentives for off-patent products specifically developed and authorised for children and an improved broader pan-European infrastructure for paediatric-focused development in the Member States are needed. The different reimbursement schemes in the Member States pose a problem here. It must be avoided that a Member State disincentivizes such a product on local level due to its reimbursement scheme, and in consequence devaluates the product.

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

2000 character(s) maximum – 1089 characters

In Germany patient access to medicines from day 1 of approval enjoys high priority. Therefore, the national reimbursement process provides the opportunity to make the product available to patients while simultaneously running through an early benefit assessment as well as a subsequent price negotiation without representing an additional hurdle for patient access.

Since 2007, the Paediatric Regulation has resulted in over 400 new treatment options for children (new marketing authorisations and new indications); thereof 159 were authorised since 2017 alone – a number which is not reflected in the EC evaluation (cut-off date 2016). This shows that the Paediatric Regulation is achieving its objectives. Such positive effects require to be made available and to be stimulated for paediatric-focused development of off-patent products, as well. However, we have seen examples in Germany that a paediatric-focused development of an off-patent product was not deemed to show a relevant additional benefit. Such developments diminish possible positive approaches/incentives on an EU-level.