SIOPE Draft Response

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 affectedby 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 medicinesto 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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The European Society for Paediatric Oncology (SIOP Europe, SIOPE)

* Organisation size

- Micro (1 to 9 employees)
- Small (10 to 49 employees)
- Medium (50 to 249 employees)
- Large (250 or more)

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Questionnaire on the revision of EU rules for medicines for rare diseases and children

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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?

1537 characters out of 2000 character(s) maximum

Overall, the Paediatric Regulation was drug centric instead of being patient centric. The Orphan Regulation was extremely beneficial for the development of anticancer drugs in adults but not at all for children and adolescents with cancer.

- We support having paediatric drug development driven by mechanism of action (MoA), disease biology and patient needs (this includes suppression of article 11b of the paediatric regulation).

- Delays in starting the development of paediatric medicines must be reduced and better tailored incentives need to ensure early start of paediatric drug development.

- Better global alignment between authorising bodies is crucial to accelerate the drug development.

- Incentives and rewards work in certain areas, and sometimes overcompensate the costs of development. Revising rewards for better 'fit for purpose' incentives concerning neglected areas such as paediatric cancers is urgently required.

- Another solution is simplification of the PIP process and implementation of life cycle management of PIPs.

- Lack of support and unrealised potential of drug repurposing is a major obstacle. The key is facilitating repositioning of drugs failing in adults for the treatment of paediatric diseases, when there is a scientific and preclinical rationale. This concerns off label medicines, but also experimental medicines that are shelved by companies.

- Sustainable funding to boost collaboration between academia and the private sector in generating more knowledge and speeding drug development is pivotal.

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?

1801 out of 2000 character(s) maximum

Innovative therapies in early clinical trials can provide a second chance at life for children with cancer in treatment failure or relapse. Access to such trials is already sub-optimal as they are not covered by cross-border reimbursement while being only available in few centres in Europe. Barriers to access have been exacerbated because of Covid-19.

The Innovative Therapies for Children with Cancer network (ITCC) reports: "in most countries, the initiation of new trials during the pandemic is restricted to trials aimed at testing treatments or diagnostics for COVID 19. For the paediatric oncology community, it is frustrating not to be able to progress new trials during this period": https://www.itcc-consortium.org/scripts/files/5ea1492bcae7d9.71206892/itcc-trials-and-the-covid19-pandemic--1.pdf

For example, the ITCC clinical trial units in Spain report personnel shortages and difficulties in enrolling patients, ensuring treatment continuity, and conducting trial assessments. Monitoring was postponed for 73% trials, and 49% interrupted recruitment. Only 2 patients were enrolled during the pandemic (75% reduction relative to expected number): https://doi.org/10.1007/s12094-020-02399-3

Another critical dimension is the funding of childhood cancer research, much of which depends on charitable giving and philanthropy which has been negatively impacted by the pandemic. Despite the

pandemic, there is still urgency for continued and expanded specific EU investment to address the unmet needs in childhood cancer research.

Lessons learnt: The pandemic demonstrated the capacity to speed dramatically the authorisation and implementation of clinical trials. Based on this experience, simplification of the administrative processes should be implemented rapidly to save time and resources.

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 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 elementof the EU rules on medicines for patients suffering from rare diseases.	X	X	X
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, becausemany patients acquire such diseases during a specified, limited period of time, those diseases should not be considered as rare inthe EU anymore.	X	X	X
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	X	X	X

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.	X	X	X

Other (please suggest any other criteria/approaches you think might be relevant).

1925 characters out of 2000 character(s) maximum

The topic of Rare Cancers being defined (or not) as Rare Diseases need be carefully addressed to avoid strong negative impact on innovation for children and adolescents with cancer.

Indeed, adult cancers represent 70% of Orphan Drug Designations (ODD) Indications (including melanoma, ovarian, pancreatic cancer, and multiple myeloma). Anticancer medicines represent 50% of global market sales and some medicines are blockbusters in their rare cancer indication. This situation needs to be addressed in the revision of orphan drug regulation, to avoid overcompensation and over-rewarding of medicines with a large Return On Investment (ROI).

However, this situation does not concern Paediatric Cancers at all. Each childhood malignancy is rare, they represent only 2% of ODD cancer indications and very few rare anticancer medicines are approved for the treatment of childhood cancer. (http://dx.doi.org/10.1016/j.ejca.2017.07.021)

The Orphan Regulation should be reinforced in terms of rewards to better incentivise therapeutic innovation for childhood cancers and other rare specialties, such as neonatology.

When revising the Orphan Regulation, differences between adult and paediatric cancers must be taken into account.

As proposed by the European Commission, we fully support using incidence and not prevalence for the definition of a rare cancer and strongly support keeping rare cancers as rare diseases, in a new context that would carefully address the current situation (as described above).

We support the proposal to reward only medicines bringing a clear benefit to patients. However, “who decides” will be a key question and should not be limited to HTAs (as currently operating).

In addition, this is proposed from the Orphan Regulation perspective. If it would be applied to the Paediatric Regulation (e.g. reward only if medicines provide benefit to children) this would profoundly affect how the regulation works.

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?

880 characters out of 2000 character(s) maximum

There is pronounced lack of newly approved medicines in paediatric oncology and an urgent need to expand the amount of compounds in development to maximise the number reaching approval stage.

One mechanism to prioritise and decide which compound should be pursued in the development stage is through multi-stakeholder forums (ACCELERATE Platform) to address prioritisation of drugs (based on biology and MoA) within pipelines across companies, especially where companies are developing drugs against the same target and define how best to implement multi-compound / multi-company trials.

To specifically address the question, decisions on rare medicines in relation to other available treatments must be evidence based, considering the limitations brought by concerned rare population. Randomised clinical trials are very often not feasible, while this is a standard for evaluation by EMA and even more for HTAs. Innovative designs including single arm trials, use of real-world data, post-marketing follow up should be more systematically considered. HTA representatives should be engaged early in the development plan evaluation. In addition, the specificities of the population must be considered during HTA evaluation of new medicines and proposing of reimbursement schemes.

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

Multiple choice answer

1. 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).

2. Treatments are already available, but their efficacy and/or safety is not optimal. For example, it addresses only symptoms.

3. Treatments are available, but impose an elevated burden for patients. For example, frequent visits to the hospital to have the medicine administered.

4. 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).

1998 characters out of 2000 character(s) maximum

Four proposals are types of unmet needs in children suffering of cancers & rare diseases. Indeed, if there is no treatment to address these paediatric needs, they are unmet. Seems the question aims at indirectly ranking needs, and we strongly believe this should not come through the set of criteria & the score that would be applied in all paediatric diseases

Examples in paediatric oncology mirroring these four types of unmet needs:

1. This does not exist since we have at least palliative care for all paediatric cancers, incl. 30% off label anticancer medicines. It exists in Progeria etc

2. This is not limited to symptomatic treatments. But concerns treatment of most paediatric cancers with lack of efficacy and or safety

3. This is not limited to hospital visits. Burden of anticancer treatments cause long term toxicity affecting 2/3 of childhood cancer survivors

4. 1/3 of oral chemotherapy medicines daily used have no age-appropriate formulation. This generates stress for parents (who need to open capsules containing dangerous substances) & risk of low efficacy (prescribed dose is not well absorbed)

How to prioritise drug development and investments?

The unmet medical needs (UMN) should be defined for each disease/group of diseases with all stakeholders and discussion on how to address needs considering current knowledge and available therapeutic options should be held at same time. This will facilitate prioritisation

- We fully support targeting investments & prioritisation of developing most promising compounds towards UMN

- Fixed set of criteria would be counterproductive & would not consider necessary diversity of UMN and change of needs over time

- The definition of UMN should be dynamic & established in multi-stakeholder setting. In paediatric oncology we demonstrated value of multistakeholder approach in ACCELERATE Platform

- The regulations should provide a structure & framework to continually identify & evaluate needs and prioritise drugs via multistakeholder process

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	x	x	x	x	x	x	x	x	x
Additional scientific support for the development of medicines from the European Medicines Agency	x	x	x	x	x	x	x	x	x	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	x	x	x	x	x	x	x	x	x
Additional post-authorisation incentives that complement or replace the current incentives and rewards	x	x	x	x	x	x	x	x	x	x

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

1890 characters out of 2000 character(s) maximum

Next to previous recommendations, following action areas with regards to paediatric cancers for further EU action should also include:

- Allocating and integrating sustainable new public investment into specific areas of orphan and paediatric medicines, linking with Cancer Mission and other Horizon Europe funding streams. Progress requires solid support for dedicated international academic research platforms, crosslinked to and informed by adult cancer and industry-driven research.

- Pursuing multi-stakeholder dialogue and cooperation to improve the implementation of the legislations for children and set up a mechanism to prioritise the best potential medicine candidates. Furthermore, there is high need for rapid access to expertise (ITCC) and facilitated participation and engagement of patients, parent and survivor representatives (Childhood Cancer International – Europe).

- The global alignment is extremely important and continuous dialogue between FDA, EMA and regulatory networks.

- We propose to incentivise starting paediatric development early by introducing changes to the timing and nature of rewards. For products addressing UMN we support a novel reward that would complement or replace the SPC prolongation. To this extent transferable vouchers are particularly attractive to incentivise First-in-Child development and medicinal products specific in paediatrics. In addition, new incentives such as 'tax credit for development' addressing unmet paediatric needs should be considered

- Enabling academic collaborations to collate and use Big Data and develop novel applications in Artificial Intelligence to foster discoveries across the research and care continuum. Overcoming the current limitations related to data silos will allow full exploration of integrated datasets with great potential to gain new insights in paediatric cancer genesis, development and cure.

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

241 out of 2000 character(s) maximum

The measures proposed above by the questionnaire concern only administrative processes by EMA. Other types of measures are needed to boost development in neglected areas such as childhood cancers and neonatology (as proposed in our comment).

Q7: Which of the following options, in your view, could help all EU patient (irrespective of where they live within the EU) to provide them with better access to medicines and treatments for rare diseases or children?

Multiple choice answer

- 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 characters out of 2000 character(s) maximum

SIOPE support the above-mentioned options fully with further suggestions below.

In addition, according to a survey of the EU Joint Action on Rare Cancers (2016-19), young cancer patients in Europe still experience a lack of access to essential medicines due to shortages, a lack of child-friendly formulations, financial inaccessibility in some countries and for newer medicines, and inconsistent provision of pain control during procedures and course of the disease.

- Appropriate and quick pricing and reimbursement strategies in every country are a must considering the potential life span gained through successful treatment in this age group.

- Harmonisation or centralisation of Health Technology Assessment (HTA) would facilitate equality of access.

- Strengthening collaboration with the HTA bodies and addressing siloed approaches between EMA and HTA evaluation regarding paediatric medicine development is also an important orientation.

- The SIOPE Essential Medicines Project is collecting information on current HTA methodologies for this population and will formulate specific recommendations for paediatric cancers.

- We fully support a pilot project on anticancer drugs for children and adolescents to demonstrate the value of HTA alignment across Europe to assure accessibility of new anticancer medicines in a timely fashion for all children across Europe.

- Reducing shortages of essential medicines in Europe will significantly impact the access to curative standard treatments for all children across Europe. To this extent, SIOPE has established the list of essential medicines to cure children with cancer that should be available 24/7 across all of Europe.

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:

Single choice answer.

1. Both new, innovative medicines and well-known medicines repurposed to treat a rare disease should receive the same reward

2. New, innovative medicines to treat a rare disease should receive an enhanced reward

3. 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 sucholder 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.

656 characters out of 2000 character(s) maximum

The number of anti-cancer medicines available in child-friendly doses and formulations is far below the needs. Indeed, most oral chemotherapeutic medicines are not produced in child-friendly formulations and have to be compounded in pharmacies and pharmaceutical hospital departments. Academic-driven development of child-friendly formulations can play an important role and deserves appropriate funding support.

However, special precautions must be adopted for producing such formulations as dust samples of highly toxic substances may be produced. In addition, medical staff must be protected by individual protection measures and environmental measures.

How would you suggest stimulating further development of appropriate dosage or formulation

suitable for children of such older medicines?

630 characters out of 2000 character(s) maximum

As part of the EU Joint Action on Rare Cancers (2016-19), SIOPE Europe conducted a survey on the accessibility of essential medicines for paediatric malignancies (https://www.annalsofoncology.org/article/S0923-7534(20)43223-5/fulltext). The results confirmed that academia/pharmaceutical departments in some countries are currently preparing ad hoc liquid formulations of several medicines for individual patients. At the European level, the European Society of Oncology Pharmacy (ESOP) Paediatric Working Group in liaison with SIOP Europe are running a project in this field and have good practices and recommendations to share.

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

1888 characters out of 2000 character(s) maximum

As per SIOP Europe, academic-driven research and development of child-friendly doses and formulations of essential anticancer medicines can play a pivotal role, particularly if supported by appropriate public funding. This approach can foster the production of financially accessible medications in a disease area where industry interest may be limited.

It should be noted that lack of child-friendly formulations is just one aspect of the multifaceted medicine access issues in the paediatric cancer sector. The lack of market-driven therapeutic innovation and shortages of essential medicines are contributing to stagnating cure rates and sub-optimal outcomes. As all paediatric cancers are rare and require cross-border cooperation to achieve progress, EU policies and programmes are ideally positioned to make a difference.

We conclude that in paediatric oncology the development of medicines is now driven by the obligation of the Paediatric Regulation (without fair results so far) rather than the attractiveness of incentives in the Orphan Regulation (a voluntary instrument). There are many examples of class-waivered oncology drugs for which the company did not consider a paediatric development. The solution is to implement MoA driven paediatric

development plans within the regulation and to eliminate waivers based only on the grounds that 'the condition does not exist in children'.

Better rewards and incentives than 6-month extension applied at the end of Supplementary Protection Certificate (SPC) to any drug with completed PIP would better attract companies and investors to develop medicines for paediatric life-threatening rare diseases, such as cancer.

Hence, please refer to SIOPE and CCI-E key recommendations for paediatric cancer: https://siope.eu/media/documents/recommendations-for-paediatric-cancer-following-launch-of-the-pharmaceutical-strategy-for-europe.pdf