

Consultation in relation to the Paediatric Report

Ref. PCPM/16 – Paediatric Report

1. PART I - GENERAL INFORMATION ABOUT RESPONDENTS

Your name or name of the organisation/company: EURORDIS-Rare Diseases Europe

Transparency Register ID number (for organisations): 93272076510-87

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Received contributions may be published on the Commission's website, with the identity of the contributor. Please state your preference:

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Please indicate whether you are replying as:

- A citizen
- A business

A non-governmental organisation (NGO)

- An industry association

A patient group

- A healthcare professional organisation
- Academia or a research or educational institute
- A public authority
- Other (please specify)

If you are a business, please indicate the size of your business

- Self-employed
- Micro-enterprise (under 10 employees)
- Small enterprise (under 50 employees)
- Medium-sized enterprise (under 250 employees)
- Large company (250 employees or more)

Please indicate the level at which your organisation is active:

- Local
- National
- Across several countries

EU

- Global

2. PART II – CONSULTATION ITEMS

(You may choose not to reply to every consultation items)

2.1. More medicines for children

Consultation item No 1: Do you agree that specific legislation supporting the development of paediatric medicines is necessary to guarantee evidence-based paediatric medicines?

The Paediatric Regulation has made a substantial impact on the development of paediatric medicines with a significant number of new medicines authorised for their use in children. In particular, 89 new medicines out of a total of 352 (26%) were centrally authorised for paediatric use from the moment the regulation came into force and up to 31 Dec 2015. About 50% of people affected by rare diseases are less than 19 years old and therefore EURORDIS has intensely advocated for a specific regulation to ensure that the specific therapeutic needs of the paediatric population are met and to avoid off-label use of medicines and the associated risks in terms of safety and efficacy. In 2005, EURORDIS published its [position paper](#) on the **proposal for a regulation of medicinal products for paediatric use: “Medicines for children: better, more and faster”**. In 2006, EURORDIS published a [fact sheet](#) on paediatric medicines and rare diseases that was updated in 2007, when the regulation came into force. EURORDIS welcomed the new rules as the concrete opportunity to address paediatric unmet needs. It is worth considering that children living with a rare disease are particularly vulnerable to the impact of the lack of knowledge in the absence of paediatric studies. Since 2007, two patient representatives nominated by EURORDIS have sat on the Paediatric Committee (PDCO) at the European Medicines Agency (EMA). Furthermore, the 8th and the 24th editions of the [EURORDIS Round Table of Companies](#) (ERTC) workshops aimed at improving the implementation of the Paediatric Regulation and its impact on the development of orphan medicinal products. In 2008, the [8th ERTC workshop](#) focused on the interplay between the Paediatric Regulation and the Orphan Regulation, while the [24th edition](#) was held in 2016 in the context of the 10th anniversary of the Paediatric Regulation. This workshop was the opportunity to look back at the experienced gained during the past 10 years and it also examined how the needs of young rare disease patients are currently addressed and what needs to be improved, taking on board patient centricity and the emerging innovative approaches for clinical trials and extrapolation methodologies. EURORDIS has continuously supported the complementary nature of both the Paediatric and the Orphan Regulations with an especial emphasis on the 2-year extension of the market exclusivity for paediatric orphan medicines. The mandatory nature of the development of paediatric investigation plans (PIPs), together with the incentives and rewards covered in the Paediatric legislation, ensure that new medicines are adapted to children needs and that the paediatric population is not neglected despite the forces of the market.

2.2. Mirroring paediatric needs

Consultation item No 2: Do you have any comments on the above? To what extent and in which therapeutic areas has the Regulation contributed to the availability of important new treatment options?

It is without doubt that the Paediatric Regulation has had a positive impact on both the number of new paediatric medicines authorised and the number of new paediatric indications for already authorised products, as well as on the information on the use of medicines in children, which has

highly improved since the Regulation came into force. Nevertheless, the progress in paediatrics is linked to the development in adults and dependent on the companies' adult pipeline, therefore only some therapeutic areas have been favoured while others remain neglected. Not only more research is needed in some therapeutic areas, but also particularly vulnerable groups like neonates are not being systematically included in PIPs, thus perpetuating the lack of knowledge about drug effects and off-label use in this subgroup¹.

A study published in 2014² analysed the EMA's inventory for paediatric needs, the off-patent priority lists and the PIPs submitted to the EMA and identified that some therapeutic areas for which a paediatric need was identified, i.e. psychiatry, pain, nephrology and anaesthesiology, were under-represented in the PIPs. Although around 50% of current PIPs are for rare diseases, it appears that the impact of the Regulation on the development of paediatric orphan products has been limited with little differences between the number of orphan paediatric medicines approved before and after the Regulation³. In addition, the therapeutic needs in paediatric oncology remain to be fully addressed as pointed out during the past [Better Medicines for Children Annual Conference](#) held at the EMA in October 2016. Only 4 medicines to treat paediatric cancers have been approved since 2008, compared to 70 new oncology products in adult indications authorised from 2011 to 2015. In addition, almost all oncology products have been granted a deferral, thus slowing its development in children. Favouring the development of paediatric-only developments through voluntary PIPs would help to improve this situation. As it is further discussed in consultation item number 10, EURORDIS highly supports the possibility of submitting a voluntary PIP and encourages the Agency to disseminate this option, and its associated incentives, among medicines developers.

2.3. Availability of paediatric medicines in the EU

Consultation item No 3: In your experience, has the number of new paediatric medicines available in Member States substantially increased? Have existing treatments been replaced by new licensed treatments?

¹ [Turner MA, Catapano M, Hirschfeld S, Giaquinto C. Paediatric drug development: The impact of evolving regulations. Adv Drug Deliv Rev. 2014;73:2-13.](#)

² [Wimmer S, Rascher W, McCarthy S, Neubert A. The EU paediatric regulation: still a large discrepancy between therapeutic needs and approved paediatric regulation plans. Paediatr Drugs. 2014;16\(5\):397-406](#)

³ [Kreeftmeijer-Vegter AR, De Boer A, Van der Vlugt-Meijer RH, De Vries PJ. The influence of the European paediatric regulation on marketing authorisation of orphan drugs for children. Orphanet J Rare Dis. 2014;9:120](#)

2.4. Reasonable costs

Consultation item No 4: Do you have any comments on the costs for pharmaceutical companies to comply with an agreed paediatric investigation plan?

EURORDIS does not have the knowledge of the precise costs incurred by pharmaceutical companies to comply with an agreed paediatric investigation plan.

One of the incentives provided in the Regulation is the 6-month extension of patent protection once the marketing authorisation has been granted. Although the impact of this measure on the return on the investment has not been tested, there is evidence of benefit with analogue provision in the US legislation. In its Paediatric Exclusivity Provision, the FDA can also grant 6 additional months of drug marketing rights and studies have shown positive returns on investment under the protected period^{4,5}. A good level of alignment between EU and US regulations ensures that the EU remains attractive to long-term investments in the field of innovative paediatric medicines and competitive in the global marketplace.

Moreover, extrapolating adult efficacy data when developing paediatric medicines is expected to shorten development times and accelerate patient access. Extrapolation reduces the requirements of data from children, hence reducing study sample size and improving trial feasibility, thereby reducing the time to study completion and its associated costs. The use of extrapolation is supported, and recommendations for its use have been made in both the addendum to [ICH E11 guideline on clinical investigation of medicinal products in the paediatric population](#) and in the [EMA's reflection paper of efficacy and safety in paediatric medicine development](#).

2.5. Functioning reward system

Consultation item No 5: Do you agree that the reward system generally functions well and that early, strategic planning will usually ensure that a company receives a reward?

Answer to 2.5 and 2.6: Both the Orphan and the Paediatric legislations include rewards and incentives to increase the development of therapies for children living with rare diseases. During the [24th EURORDIS Round Table of Companies Workshop “Bringing solutions to rare young disease patients”](#) held in Barcelona, Spain, on 27 Sep 2016, it was expressed that the **understanding of both Orphan and Paediatric legislations should be improved, as the incentives and rewards created to encourage development exist in areas that are generally overlooked and therefore are underutilised by companies**. Particularly, companies' uptake of the 2-year extension of the period of market exclusivity is clearly limited as only 7 products have benefited from this reward so far. In addition, protocol assistance concerning advanced therapies holding an orphan designation appears not to be considered by companies, although the overall number of protocol assistance requests has increased over the years.

Considering that more than half of rare diseases affect children, deep understanding of both regulations will tremendously help medicine developers to optimise their paediatric investigation plans and make the most of the incentives and rewards.

⁴ Baker-Smith CM, Benjamin DK, Grabowski HG, Reid ED, Mangum B, Goldsmith JV et al. The economic returns of pediatric clinical trials of anti-hypertensive drugs. *Am Heart J.* 2008;156(4):682-688

⁵ Li JS, Eisenstein EL, Grabowski HG, Reid ED, Mangum B, Schulman KA et al. Economic return of clinical trials performed under the pediatric exclusivity program. *JAMA.* 2007;297(5):480-488

Of all medicinal products that were granted an orphan designation since 2000, about 65% are products intended for a paediatric indication (15% of these are for paediatric use only). Companies are making use of the incentives as shown by the 139 protocol assistance requests (scientific advice requests related to orphan products) reviewed during 2015 by the Scientific Advice Working Party (SAWP). However, when it comes to advanced therapy medicinal products (ATMPs) holding orphan designations, very few companies are asking for protocol assistance or apply for early interaction with the EMA's Committee for Advanced Therapies (CAT) for ATMP classification. In addition, very few orphan ATMPs have an agreed PIP. Moreover, there is little consideration regarding the timings of procedures and the benefits of engaging early with regulators. The areas of overlap of the two legislations should be considered by applicants: 1) how the Committee for Orphan Medicinal Products (COMP) and the Paediatric Committee (PDCO) are identifying conditions (the Paediatric legislation targets a wider population than the Orphan legislation); 2) use PIP, waiver or deferrals for one or several orphan conditions/designations for a given product; 3) how to use protocol assistance efficiently to benefit from fee reductions associated with paediatric development (rewards, such as the 6-month SPC extension, the PUMA data protection for off-patent products); 4) timing of implementation of a PIP (it takes about one year); and 5) loss of the 2-year additional market exclusivity if a PIP is completed outside a granted 10-year market exclusivity. Interestingly, the uptake of these benefits and rewards by the industry is limited as shown by the following data from the EMA 10-year report on the experience with the paediatric legislation: only 3 orphan medicinal products have obtained a 2-year extension of the marketing exclusivity versus 39 six-month patent extensions for paediatric medicines and only 2 Paediatric-use marketing authorisations (PUMAs).

EURORDIS is supportive of strategies to disseminate and clarify to the pharmaceutical industry the advantages of the synergistic use of the provisions of both legislations as a way to favour the development of more and better therapies for children. We also encourage the early dialogue between regulators and sponsors to streamline regulatory processes, speed up development programmes and ultimately improve timely access of medicines to patients.

2.6. The orphan reward

Consultation item No 6: How do you judge the importance of the orphan reward compared to the SPC reward?

Answered in the previous consultation item.

2.7. Improved implementation

Consultation item No 7: Do you agree that the Regulation's implementation has improved over time and that some early problems have been solved?

EURORDIS has continuously advocated for an optimal implementation of the Paediatric Regulation as stated previously (see consultation item 1). Significant improvements for an optimal implementation of the legislation have been made, such as the simplification of PIP opinions and the reduction of modifications when non-significant changes to the PIP are made, as covered by the 2014 EC guideline on the format and content of applications for agreement or modification of a PIP. EURORDIS highly supports Early Paediatric Interaction Meetings between the Agency and

medicine developers to encourage discussions on the paediatric needs and to optimise the development strategy of a paediatric product when the submission of a PIP. The impact of these early meetings remains to be evaluated due to its recent implementation and feedback from the industry is currently being sought⁶.

In addition to early EMA-industry interaction, increased interoperability across EMA's scientific committees and working parties is crucial to optimise clinical trial designs and paediatric medicine development in general. In this regard, inter-committee meetings are excellent fora where trustworthy relationships are built, thus favouring smoother interaction and knowledge sharing among members of different committees. Particularly, aligning the requirements from PDCO and the Scientific Advice Working Party (SAWP) would result in smoother and faster completion of PIPs with less deferrals and modifications. The participation of disease-specific patient experts to PDCO, as it is already done in scientific advice and protocol assistance discussions at SAWP, would also help to identify and incorporate patients' needs and perspectives more consistently into the development plans. In addition, patient-centred designs, including the assessment of clinically meaningful outcomes or broader inclusion criteria, are more likely to be accepted by participating patients, thus mitigating withdrawal rates and leading to smoother PIP completion. Examples of committee interoperability can be found in newly launched schemes (i.e. PRIME) in which a rapporteur from either CHMP or CAT is assigned to a specific product candidate along the regulatory process to marketing authorisation.

Open, flexible approaches in terms of methodologies and new real world data collection strategies are needed to facilitate PIP conduct and completion. Particularly important for rare diseases it is to explore innovative methodologies to design and carry out clinical trials in small populations, hence overcoming feasibility and recruitment problems, which invariably delay PIP completion and hamper access to innovative medicines. EURORDIS also supports initiatives on exploring small population clinical trial designs, being part of the patient think-tank in the [ASTERIX](#) project. In addition, EURORDIS is supportive of the [recommendations](#) issued in June 2016 by the International Rare Diseases Research Consortium ([IRDiRC](#)) Task Force on Small Populations Clinical Trials (SPCTs) after the workshop held at the EMA in March 2016. Adaptive designs (e.g. cross-over clinical trials), innovative statistical methods and extrapolation are some of the approaches recommended by IRDiRC when a randomised controlled design is not feasible. With the release of the [Guideline on clinical trials in small populations](#) in 2006 the EMA accepts the use of these methods to increase the efficiency of clinical trials in small populations.

Extrapolation methods should be consistently considered during the development of a PIP and could be the subject of early interaction meetings. Specifically, the Modelling and Simulation Working Group provides support to scientific committees and working parties, including the Committee for Medicinal Products for Human Use (CHMP), the PDCO and the SAWP.

Global development programmes favoured by the creation of the paediatric cluster to facilitate the inter-agency collaboration between EMA and FDA intended to exchange information on paediatric drug developments and to reach faster agreement on PIPs. Initiatives like the [collaborative approach on Gaucher disease](#) are highly welcomed to support the simultaneous development of treatments for a particular rare disease.

⁶ [Highlights of the 2nd EMA-Industry Stakeholders Platform meeting on Paediatric medicines. EMA/272465/2016. 9 June 2016](#)

2.8. Waivers and the ‘mechanism of action’ principle

Consultation item No 8: Do you have any comments on the above? Can you quantify and qualify missed opportunities in specific therapeutic areas in the last ten years?

The regulation must ensure that children should only participate in clinical studies where there is a well-founded assumption that the product is likely to provide a significant therapeutic benefit. Waivers were created with such an aim, and also to avoid testing unsafe drugs or those targeted for exclusively adult diseases. Even before the adoption of the Regulation, EURORDIS in its [2005 position paper](#) (see section 2.1), while in principle supporting waivers, warned that they should not be over-used. We have seen, however, that the use of waivers has been criticised as appearing excessive⁷. In 2015 a major revision of the class waiver list was undertaken by the PDCO to reflect newly available paediatric evidence and hence preventing that an obligation is waved based on old scientific data. Current advances in genomics show that mutations in a single gene can translate into different clinical phenotypes making a distinct classification between adult and paediatric diseases much blurrier than before. In this regard, EURORDIS welcomes the organisation of a [multi-stakeholder paediatric oncology strategy workshop on cancers with anaplastic lymphoma kinase \(ALK\) aberrations](#) at the EMA to review the unmet needs of children affected by this type of mutations that can result in a variety of paediatric rare cancers. EURORDIS highly supports multi-stakeholder meetings as an ideal platform to reach consensus about the therapeutic needs of a given disease, among researchers, clinicians, regulators, patients and the industry, to drive the development of meaningful, innovative therapies for populations with unmet medical needs.

Furthermore, medicine developers should be encouraged to undergo voluntary PIPs when they identify that the mechanism of action once attributed to an adult condition causes also disease in children. (Regarding voluntary PIPs see also consultation item No 9).

2.9. Deferrals

Consultation item No 9: Do you agree with the above assessment of deferrals?

Although deferrals are justified as a measure to protect children from potentially toxic products, until enough safety data has been gathered in adults, they may have undesired effects. If the adult product comes onto the market before the paediatric indication is approved, clinical trial recruitment is jeopardised as parents may prefer that their child receives the adult product off-label. This poses a greater problem as off-label medicine use is empirical and even could be regarded as a one-person clinical trial. The US experience on deferrals showed that between 2004 and 2007, a deferral was granted in 55% of new and supplemental applications⁸. This article also shows that deferrals can be subsequently extended leading to significant delays (up to 10 years) in paediatric study completion.

EURORDIS strongly supports the use of scientifically-sound methods during the development and approval of paediatric medicines to ensure that children studies are conducted according to the right guidelines, that they receive the appropriate doses and formulations and that the products address age-specific needs. Regarding paediatric rare diseases and other areas of unmet medical needs, natural history studies are essential to understand how the disease progresses and, with that

⁷ Vassal G, Blanc P, Copland C, Pearson A. Will the revised class waiver list make it?. *Lancet Oncol.* 2015;16(9):e425-e426

⁸ Bourgeois FT, Hwang TJ. The Pediatric Research Equity Act moves into adolescence. *JAMA.* 2017;317(3):259-260

information identify study endpoints to ultimately improve the design of clinical trials. Additionally, new strategies to overcome the problems of clinical trial feasibility such as pooling data from previous studies and use them as comparator in new studies are also encouraged. Although conscious of the limitations of this approach, EURORDIS supports also global collaboration between medicine developers in terms of sharing data, so that one placebo arm could serve for different studies and even the set-up of multi-sponsor trials. As mentioned earlier, using already available data from different sources is particularly important when the study population is small, as in paediatric rare diseases. Provided disease similarity is proven, extrapolating data from adults could solve problems of study feasibility and accelerate clinical development.

Proper assessment of these strategies through earlier engagement with regulatory authorities in the form of early interaction meetings is essential to identify potential feasibility issues ahead of time and find suitable alternatives to classical/linear development.

2.10. Voluntary paediatric investigation plans

Consultation item No 10: Do you have any comments on the above?

EURORDIS welcomes the possibility of submitting a voluntary PIP for a paediatric-only development or to complement an adult development with a PIP. Ideally, medicine developers should be aware of this option, including their eligibility for the rewards according to the provisions of the regulation. It is important that this possibility is widely publicised by the EMA to increase awareness with potential developers. Moreover, it would be very interesting to know to which extent this voluntary option has been considered since the Paediatric Regulation came into force (i.e. how many voluntary PIPs have been submitted and accepted) in order to define the information needs and provide guidance to companies.

Despite the Agency's efforts to help medicine developers to identify opportunities through the inventory of paediatric needs, some therapeutic areas are still underrepresented in PIPs. Therefore, there is an urgent need for increasing awareness among companies of the real unmet needs of the paediatric population and drive innovation to these areas. Through a combination of multi-stakeholder meetings to identify the needs of the paediatric population and a call for voluntary PIP proposals, the EMA could 1) enhance awareness of diseases to where research efforts need to be targeted and 2) incentivise the development of new much-needed paediatric medicines.

2.11. Biosimilars

Consultation item No 11: Do you have any comments on the above?

2.12. PUMA — Paediatric-use marketing authorisation

Consultation item No 12: Do you share the view that the PUMA concept is a disappointment? What is the advantage of maintaining it? Could the development of off-patent medicines for paediatric use be further stimulated?

Although clearly underused, PUMA remains a useful concept for the development of off-patent medicines. Its lack of attractiveness for companies lies on the low returns on investment compared to those obtained from on-patent medicines development. However, the consequences of a pure economically-driven paediatric medicines development are that areas of unmet medical needs shall remain neglected and also that off-label use in children will perpetuate. While off-patent compounds may not be on the radar of pharmaceutical industry, including small and medium sized enterprises (SMEs), they are an interesting option for academics that carry out publicly-funded research.

Exploiting the already existing wealth of data generated with the recent advances in basic research, particularly genomics, and information technology (“Big Data”) is an essential step in the search of new therapies for patients living with rare diseases. With this objective in mind, the International Rare Diseases Research Consortium (IRDiRC) has set up a [Data Mining/Repurposing Task Force](#) to encourage the coordination between basic and clinical researchers and to speed up the development of new therapeutic alternatives from products that are already in the market for other indications. To provide funding for such initiatives, the ERA-Net for Research Programmes on Rare Diseases (E-Rare), an EU programme funding transnational collaborative research, has recently launched a call on the clinical research for new therapeutic uses of already existing molecules (repurposing) in rare diseases. Clearly, there is a momentum for the development of off-patent medicines and collaborations between academia and clinical researchers should be encouraged and strengthened in order to achieve the goal of maximising the potential of existing molecules towards new indications. Increasing the awareness of the PUMA concept among researchers may be an incentive to pursue research in the field of drug repurposing for paediatric indications.

While academia may be naturally inclined to pursue studies on drug repurposing, the funding to support this type of research might not be as easily found, as low return on investment is perceived as a major drawback by investors. Collaboration between academia and industry is the basis of the US National Institutes of Health’s National Center for Advanced Translational Sciences (NCATS) programme, in which pharmaceutical companies provide academic researchers with the preclinical data (and compound supply) for compounds whose development has been prematurely discontinued. The programme funds academic researchers to continue the development, while the company retains the rights of the compound and the ability to file for a new indication, which would not have been developed otherwise due to low commercial potential⁹. Such programme would certainly represent a win-win for all stakeholders involved, by bringing to surface molecules with potential therapeutic benefit, while optimising data and resources available.

In the EU, we have examples of successful collaboration between private and public partners into carrying out research in off-patent paediatric medicines¹⁰. In the period from 2006 to 2012, 20 Seventh framework programme (FP7)-funded projects studied 24 medicines in 10 therapeutic areas in all paediatric age groups, with 15 approved PIPs referring to 14 projects and 80% of the projects including studies to develop new age-appropriate formulations or dosage forms. The progression of these efforts towards PUMAs remains to be seen.

⁹ [Azvolinsky A. Repurposing existing drugs for new indications. The Scientist. January 2017 issue](#)

¹⁰ [Ruggieri L, Gianuzzi V, Bonifazi P, Davies EH, Giaquinto C, Bonifazi D et al. Successful private-public funding of paediatric medicines research: lessons from the EU programme to fund research into off-patent medicines. Eur J Pediatr. 2015;174\(4\): 481-491](#)

2.13. Scientifically valid and ethically sound — Clinical trials with children

Consultation item No 13: Do you have any comments on developments in clinical trials with children following the adoption of the Regulation and in view of the above discussion?

Collaborative research efforts involving all relevant stakeholders have proven successful in the field of rare diseases, as shows a recent paper of multi-stakeholder collaboration to develop therapies for the treatment of Duchenne muscular dystrophy¹¹. This work showcases a clear example of how constructive dialogue among patients' groups, academia, industry and regulatory agencies allowed to address some of the challenges encountered during the development of new treatments. Development and implementation of standards of care to decrease variability across trial sites was identified as essential to overcome the above mentioned problems associated with multi-centre clinical trials. The direct input of parents and patients with academics was essential to identify new functional outcome measures to assess the clinical benefit of the medicines tested. These new functional outcome measures should be agreed and qualified by regulatory authorities in order to be systematically used (CHMP qualification opinion). This work stemmed from a [multi-stakeholder meeting](#) co-organised by the EMA and TREAT-NMD in 2009 gathering patients' organisations, academics and regulators to discuss the development of antisense oligonucleotide therapies for Duchenne Muscular Dystrophy (DMD). As a follow-up to this meeting, another EMA-TREAT-NMD workshop was also organised in 2015 on developing exon skipping therapies for DMD. In 2016, the [EMA spinal muscular atrophy workshop](#) co-organised by EMA, SMA Europe and TREAT-NMD reviewed critical aspects of each diseases subtype and discussed the challenges encountered when developing treatments for this disease. During this workshop, the use of placebo arm was broadly discussed as parents see it as a barrier to promising, long-awaited therapies. Low patient recruitment could be enhanced by reducing the needs of a new placebo arm for each new study. New methodologies such as pooling together the placebo arms of previous studies (to demonstrate efficacy versus the average placebo effect of a particular disease) and considering the use of a single placebo arm to serve as control for competing trials conducted by different sponsors, should be highly encouraged. EURORDIS considers EMA multi-stakeholder meetings an ideal, safe harbour where to report on the state of the art of a particular disease, explore innovative strategies and agree on common methodologies for an optimal development of paediatric medicines and is hoping to see more of these meetings happening in various medical areas/diseases.

2.14. The question of financial sustainability

Consultation item No 14: Do you have any views on the above and the fact that the paediatric investigation plan process is currently exempt from the fee system?

As mentioned above (see consultation item 5), a functioning reward and incentive system is key to foster innovation in therapeutic areas regarded by industry as less commercially attractive. However, it must be ensured that the assessment of paediatric medicines is done with the same high-quality ethical standards and, therefore devoting comparable resources, to that for adult medicines. Agreements with national agencies should be in place to guarantee the long-term, efficient functioning of the system.

¹¹ Straub V, Balabanov P, Bushby K, Ensini M, Goemans N, De Luca A et al. Stakeholder cooperation to overcome challenges in orphan medicine development: the example of Duchenne muscular dystrophy. 2016;15(8):882-890

2.15. Positive impact on paediatric research in Europe

Consultation item No 15: How do you judge the effects of the Paediatric Regulation on paediatric research?

As mentioned earlier, EURORDIS has long advocated for a specific regulation to protect and to meet the needs of the paediatric population. The overall positive effects of the legislation have been described above. However, there are still knowledge gaps concerning the understanding of the underlying disease. Natural history studies should be encouraged to increase these understanding, as well as to determine the prevalence of the disease, which has a direct impact on the study size and its feasibility. Collection of natural history data will also be useful to define the most adequate, clinically meaningful outcome measures to be used in future clinical trial design. EURORDIS is conscious of the current challenges in this regard and is welcoming the IMI call on the creation of a pan-European paediatric clinical trials network that will facilitate the development and availability of new drugs and other therapies and expanding knowledge about currently used medicines in the paediatric population. This project aims to build the infrastructure and best practices required to support planning and conduct of coordinated research in multiple study sites, hence helping to meet recruitment needs in a competitive environment, mitigating delays and driving studies to completion. Similarly, we also embrace the creation of the Paediatric Clinical Research Infrastructure Network (PedCRIN) that will bring together the expertise and resources of paediatricians and other partners internationally to overcome known challenges in paediatric research and carry out trials with the highest quality and ethical standards.

In addition, the recent adoption of European Reference Networks for rare diseases will have also a positive impact on paediatric research. These networks will allow thousands of doctors and researchers to share their knowledge and resources and collect data in a coordinated manner. ERNs are also intended to gather a critical mass of patients and data to support rare disease registries and clinical research. Rare disease registries set up in context of ERNs will also facilitate long-term follow up of paediatric patients, thus allowing to collect safety data on the long-term effects of medicines in children and to comply with the data requirements set in post-marketing obligations. ERNs will certainly have a positive impact on the Paediatrics field as 50% of people affected by rare diseases are less than 19 years old.

2.16. “Mirror, mirror on the wall” - Emerging trends and the future of paediatric medicines

Consultation item No 16: Are there any emerging trends that may have an impact on the development of paediatric medicines and the relevance of the Paediatric Regulation?

Emerging trends in medicines design, formulation and delivery, as well as concepts such as iterative development or personalised medicine, are already being addressed under the current legislation framework.

Medicinal product development according to the adaptive pathways scheme is based on early engagement in scientific advice and use of conditional marketing authorisation for products addressing high unmet needs, with two possible scenarios: 1) to initially target a reduced population to posteriorly broaden the indication to a larger patient community, or 2) apply for a conditional marketing authorisation based on early data and confirm benefit/risk through collection of post authorisation (real-life) data. The adaptive pathways scheme relies on existing regulatory tools and

encourages discussion of the clinical development through parallel HTA/EMA scientific advice. Similarly, the recently launched PRIME scheme also is supported by existing regulatory tools and by a coordinated action among EMA scientific committees and working parties to accelerate access of promising medicines providing a major therapeutic benefit to most vulnerable patients. The emerging field of precision or personalised medicine is focusing on strategies tailored to patients' needs and both scientific and patient expertise will be fundamental to guide the development of such innovative therapies to marketing authorisation. EURORDIS considers essential to maximise the existing expertise between EMA committees and to favour cross-committee interoperability for the successful implementation of these new approaches. The inclusion of patient representatives as full member in EMA committees ensures that patient-relevant aspects of medicines development are taken into account. In addition, we consider that the involvement of disease-specific patient experts during PIP assessment would tremendously help overcome study feasibility issues, for instance, and obtain higher alignment between PDCO advice and that provided at SAWP level. (See also consultation item number 7).

2.17. Other issues to be considered

Consultation item No 17: Overall, does the Regulation's implementation reflect your initial understanding/expectations of this piece of legislation? If not, please explain. Are there any other issues to be considered?

EURORDIS has always advocated for the adoption of both the Orphan and the Paediatric Regulations, as they are complementary and ensure that pharmaceutical development is incentivised in populations in great need of safe and effective therapies targeting their specific characteristics. Nevertheless, the incentives and rewards are still underutilised by companies developing paediatric medicines thus hampering further development of promising therapies in this field. Similarly, the interplay between the Paediatric and the Orphan legislation and its associated synergies should be emphasised to companies to foster their interest in developing products for children living with rare diseases.