Commentaries

Orphan Medicines for Pediatric Use: A Focus on the European Union

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ABSTRACT

Purpose: European policy makers have provided a number of incentives for the development of medicines for orphan diseases as early as 1999 through the Orphan Regulation and created obligations for medicines developers to investigate their products in children through the Paediatric Regulation adopted in 2006. This article describes the challenges that developers of orphan medicines are facing with pediatric indications, discusses the interplay between the Orphan Regulation and the Paediatric Regulation, and provides some recommendations on how to optimize drug development under the current European Union regulatory framework.

Methods: This article discusses the European Union's Orphan Regulation, Paediatric Regulation, and the implications of the intersection of the regulations on the development of orphan medicines for pediatric use.

Findings: Although these regulations have been successful in meeting their objectives separately, different regulatory frameworks entail separate governance, multiple assessments, varying approaches and priorities to unmet medical needs, and joined-up regulatory process coordination. Better integration of regulatory pathways would therefore be helpful in stimulating more global drug development of pediatric orphan medicines, including optimizing the interaction between both regulations, using innovative drug development approaches while considering alternatives to randomized clinical trials, better identification and prioritization of unmet medical needs in pediatrics, and ensuring the alignment of regulatory processes.

Implications: Rare diseases are categorized as "orphan diseases" because their occurrence in a small number of patients means that, regardless of the apparent high unmet medical need, there is limited public and market interest to justify the high development risk and significant investment to develop new treatments. However, unexplored potential within the area, as well as a conducive regulatory environment, can further support the development of medicines to treat rare diseases, including for children. (*Clin Ther.* 2019;41:2630–2642)

Key words: Europe, orphan, pediatric, rare diseases, regulatory.

INTRODUCTION

More than 5000 rare diseases exist, affecting between 6% and 8% of the global population in total and >30 million people in the European Union.

Accepted for publication October 11, 2019
https://doi.org/10.1016/j.clinthera.2019.10.006
0149-2918/$ - see front matter

Approximately 80% of rare diseases have identified genetic origins, whereas the rest are linked to viral, bacterial, environmental, degenerative, or proliferated causes. Symptoms often appear at birth or during childhood, frequently with progressive and life-threatening consequences.[1] In fact, 75% of rare diseases are known to affect children, and ~3 of 10 of these children die before reaching 5 years of age.[2]

To date, medical and scientific knowledge of rare diseases remains limited. It is reported that only ~1000 distinct rare diseases benefit from any scientific knowledge.[2] Affected individuals face a number of challenges, including delays and errors in diagnosis, a lack of clinical expertise, and limited information and support, all of which considerably affects their lives and their families or caregivers.[3] Furthermore, only 5% of rare diseases have a treatment option,[4] which leaves 95% of rare diseases without any approved therapeutic option. In the absence of approved treatment options, physicians will turn to off-label use of medicines: drugs that have been approved for adults only, or for a different indication altogether. Even if off-label use is not undocumented or unsafe by definition,[5] there are measurable benefits from bringing such use under the regulatory regime, as discussed in this article.

In the European Union, a disease is defined as rare (also called an "orphan" disease) if it is a life-threatening or chronically debilitating disorder that affects <5 in 10,000 people in the European Union. However, the prevalence can be much lower, leading to the concept of the "ultra-orphan disease" (as introduced by the UK National Institute for Health and Care Excellence) for diseases with an estimated prevalence of <1 in 50,000 people.[6] Such low prevalence, together with the limited available scientific knowledge, explains the challenges sponsors face when developing orphan medicines (eg, lack of relevant endpoints, limited sample size, costly process).

The present article describes some of the challenges faced by sponsors of orphan medicines when developing pediatric indications and the interplay between the orphan and the pediatric regulations. We also provide some suggestions on how to further optimize drug development under the current European Union regulatory framework.

EUROPEAN UNION ORPHAN AND PEDIATRIC MEDICINES REGULATIONS

In the European Union, the Orphan Regulation (EC No. 141/2000) was adopted in 1999 (and came into force in 2000) with the aim of stimulating the development of medicinal products for the treatment of rare conditions. The regulation established the Committee for Orphan Medicinal Products (COMP) and sets the framework for orphan medicines designation and available incentives. It is supported by additional implementing regulations and guidelines that elaborate on critical definitions and considerations related to the criteria for orphan designation, as well as its orphan status maintenance at the time of marketing authorization.[7]

Separately, the Paediatric Regulation (EC No. 1901/2006), which came into force in 2007, established the Paediatric Committee (PDCO) and is aimed at increasing high-quality, ethical research and information on medicines for children and improving the availability of authorized medicines without conducting unnecessary studies on the young or delaying authorization for adults. In addition, it sets out the procedures, incentives and rewards, and requirements for authorization, including the requirements for a pediatric investigation plan (PIP) (Table I).

Since its implementation, the Paediatric Regulation has contributed to the improvement of child health in the European Union by stimulating the development and access of drugs suitable for children and building significant pediatric expertise and knowledge.[8] The landscape of pediatric clinical research is evolving, with growing infrastructure and more clinical trials to support regulatory submissions. The regulation has been successful in stimulating the delivery of new medicines/indications for treating children, with >260 new medicines/indications developed since 2007. New formulations suitable for children have also been developed to enable them to take their medicines easily. It is recognized that more can be done to increase the number of medicines for children and that important unmet needs remain for the treatment of childhood conditions. Furthermore, given the long development cycle of new medicines, including pediatric medicines, the full impact of the regulation is still yet to be realized.[9]

Table I. Description of a pediatric investigation plan (PIP).

A PIP serves as a basis for the development and authorization of medicinal products for pediatric use. A sponsor is required to provide a proposed PIP before the marketing authorization process to the European Medicine Agency's Paediatric Committee, which then evaluates and validates the plan.

PIPs include information on:

- The measures to be conducted in children using the medicine
- Ways to adapt the formulation for pediatric use; for example, in liquid form vs (large) tablets
- Needs of all age groups of children
- Timing of measures in children vs adults

A PIP must also set the full quality, preclinical and clinical development, including long-term follow up studies

From the European Medicines Agency. Paediatric investigation plans. https://www.ema.europa.ey/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans. Accessed May 21, 2019.

The orphan and pediatric regulations meet when the developer of an orphan-designated medicinal product completes a PIP. The PIP has to be agreed with the PDCO and must reflect the results of the completed PIP in the product information, in compliance with the Paediatric Regulation. In this situation, the 10-year period of orphan market exclusivity may be extended by 2 additional years. Another reward offered under the Paediatric Regulation is the 6-month extension of the supplementary protection certificate (SPC); that is, extending a product's patent-based exclusivity, which is, however, only available to non-orphan and patented products.

Orphan Medicines

Orphan medicines are "medicinal products intended for the diagnosis, prevention, and treatment of rare diseases."[10] In the European Union, incentives are offered to companies to encourage the research and development of medicines for rare diseases, such as fee exemption or reduction for scientific advice (known as protocol assistance for orphan medicines) and grants. Companies can apply for orphan designation if the medicine meets the following criteria[1]: (1) Its use is intended for the treatment, prevention, and diagnosis of life-threatening or chronically debilitating disease; (2) the disease must not affect more than 5 in 10,000 people in the European Union, or there is an unlikely chance for the medicine to generate sufficient returns to justify the necessary investment for its development; and (3) there is no existing satisfactory method of diagnosis, prevention, or treatment of the condition that has been authorized in the European Union, or, if such method exists, the medicine must be of significant benefit to those affected by the condition.

Orphan designations are granted by the EU Commission based on a positive opinion adopted by the European Medicine Agency's (EMA) COMP. It is important to note that a designation is not equivalent to a marketing authorization. Marketing authorization applications for orphan-designated medicines must subsequently be evaluated by the EMA's Committee for Medicinal Products for Human Use (CHMP) and must adhere to the same strict quality, safety, and efficacy standards applied to all medicines before they can be marketed in the European Union.[11] However, because an orphan designation can be received at any point in drug development, and often at an early stage, it is important to remember that the number of medicines that receive a marketing authorization will depend on the generation of sufficient and acceptable data to support their authorization. This process can take as long as for a non-orphan product; orphan-designated medicines are also subject to similar attrition rates as non-orphan medicines during development.[12]

When an orphan-designated medicine is eventually submitted for a marketing authorization, it must show that it continues to meet the criteria for orphan designation, such as its significant clinical benefit compared with other available treatment options at that time. Orphan status maintenance is indeed a prerequisite to the market exclusivity incentive. It is not uncommon for medicines that were initially orphan designated to "lose" their orphan status at this point, despite completing the lengthy research, development, and authorization processes and procedures. Recent court cases highlight this issue

and the strict approach of the EMA and European Union Commission in this regard.[13]

The Orphan Regulation has contributed to accelerating innovation and improving patients' health. Its introduction has helped increase research and development in rare diseases and assisted in addressing this area of high unmet medical need, in which individual member states cannot achieve results by themselves. Indeed, there is still more to be done to help develop new treatments for the >95% of rare diseases without a treatment option. This goal can be achieved by ensuring that the right regulatory, scientific, and economic environment for orphan medicine development is maintained.

Development of Pediatric Orphan Medicines

The Orphan Regulation can be seen as a success for the development and authorization of orphan medicines based on the numbers of designations and marketing authorizations. Since implementation of the regulation in 2000, a total of 2121 medicines were granted orphan designation (Figure 1).[14] Some 40% of these designations were also for conditions with a prevalence <1 in 10,000 people in the European Union.[15] Of the total orphan drug designations, 57% were for both adult and pediatric use and 12% for pediatric use only (Figure 2). This shows that the majority of orphan designations relate to potential treatments for children, either specifically or together with adults.

At the end of 2018, a total of 164 of these orphan-designated medicines had been granted a marketing authorization, and 22 received an extension of indication. Of the 164, a total of 107 are currently active marketing authorizations in the European Union register; the remainder (57) have either had a withdrawal of their orphan status or the expiration of their market exclusivity.[15] In contrast to Figure 2, which details orphan designations, Figure 3 shows that 38% of authorized medicines are for both adults and pediatric use and 6% for pediatric use only. This suggests a lower success rate for orphan products addressing pediatric diseases compared with those addressing adult diseases.

A study conducted in 2018 by European Union regulators reviewed 157 orphan-designated medicines registered between 2000 and 2013 and found that orphan medicines have a lower approval and success rate compared with non-orphan medicines.[12] Determinants for marketing authorization success included compliance with protocol assistance and company size. Indeed, although orphan developers were more common among small companies, these companies were less

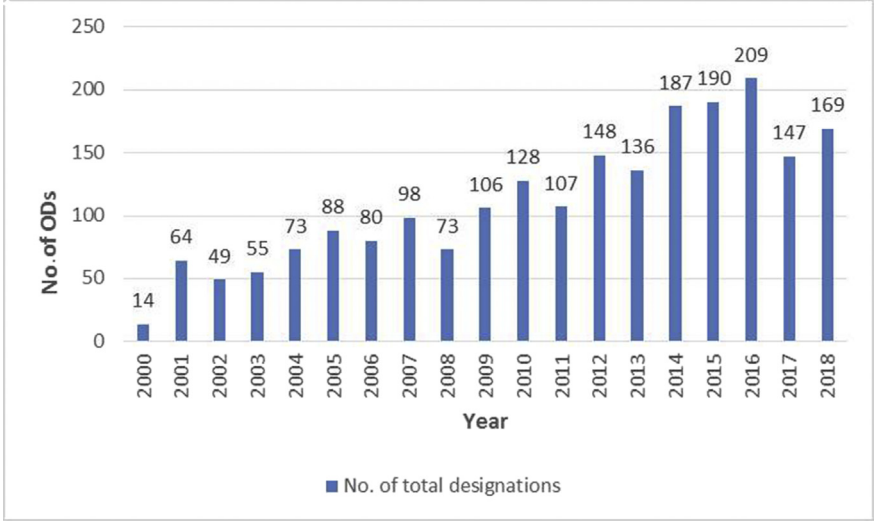

Figure 1. Total number of orphan designations (ODs) (2000–2018). From the European Medicines Agency.[15]

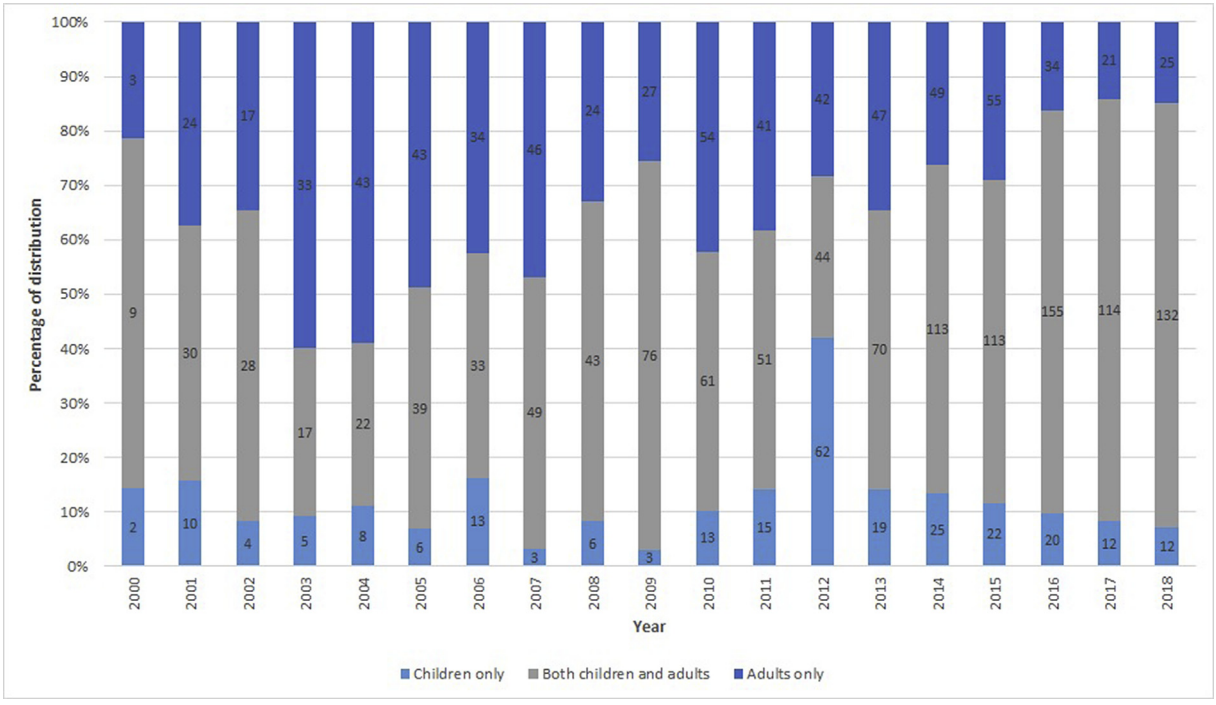

Figure 2. Percent distribution of orphan designations for adult and pediatric use (2000–2018). From the European Medicines Agency.[15]

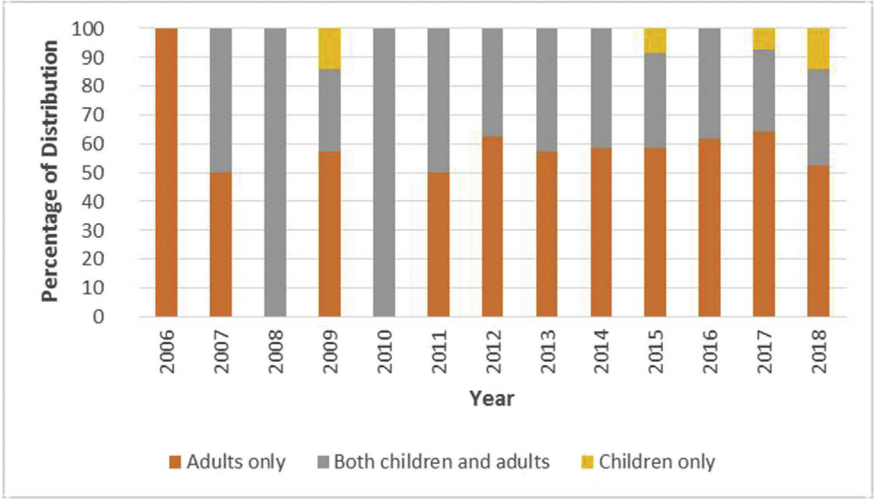

Figure 3. Distribution of authorized orphan-designated medicinal products for adult and pediatric use (2000–2018). Authors' elaboration based on data from Orphanet. Lists of medicinal products for rare diseases in Europe. Orphanet Report Series. https://www.orpha.net/orphacom/cahiers/docs/GB/list_of_orphan_drugs_in_europe.pdf. Published April 2019. Accessed July 12, 2019.

likely to obtain a positive marketing authorization compared with medium-sized and larger companies, as their proposals were considered insufficient to meet the needed regulatory standards and because they have limited human resources and investment capital to change the development plan in compliance with the scientific advice provided. Finally, the study showed that, at the time of marketing authorization, loss of orphan designation was primarily due to the lack of demonstration of significant benefit.

The 10-year report on the Paediatric Regulation conducted by the European Union Commission underscored the significant progress achieved since its introduction in stimulating the development of medicines for children and building a holistic and significant approach to pediatric research.[8] The number of new medicines and indications that were centrally authorized for use in children has more than doubled since the inception of the regulation in 2007: from 31 new authorizations and indications before 2007 (2004–2006) to 68 (between 2012 and 2014)[7] (Figure 4).

The number of changes in the information regarding the use of medicines in children (more specifically, safety information and warnings, undesirable effects, and pharmacodynamic properties) increased from 68 to 180 during the same 2 periods.[8] The report also highlights that unmet medical needs remain to be addressed for childhood diseases, particularly on the development and availability of orphan medicines[14] (eg, in the field of pediatric oncology and neonatology).[8] The report found that between 2007 and 2015, the number of PIPs has progressively increased for orphan-designated medicines (Figure 5).

A study conducted in 2014 regarding the influence of the Paediatric Regulation on marketing authorization of orphan medicines for children found that this regulation had a limited impact on the development and availability of orphan medicinal products for children, notably with regard to research quantity and quality in children through the PIPs.[16] Unfortunately, it is not possible to identify the number of PIPs that relate to medicines to treat rare diseases but which are not orphan designated, as these data are not available.

Another study claimed that the regulation has resulted in the unintended delay in the initiation of early-phase clinical trials by companies because, to apply for a PIP, a detailed development plan is required at a time before relevant clinical data are

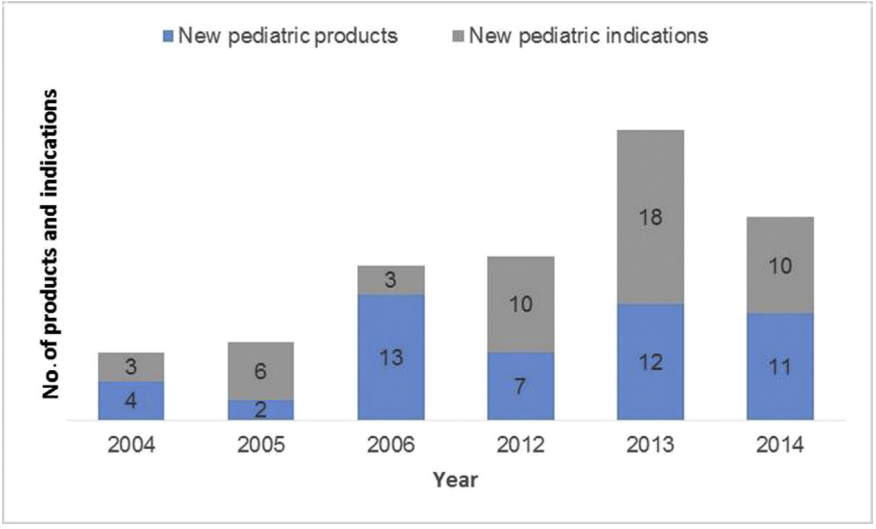

Figure 4. Number of new pediatric product and indications (2004–2006 and 2012–2014). From the European Medicines Agency.[8]

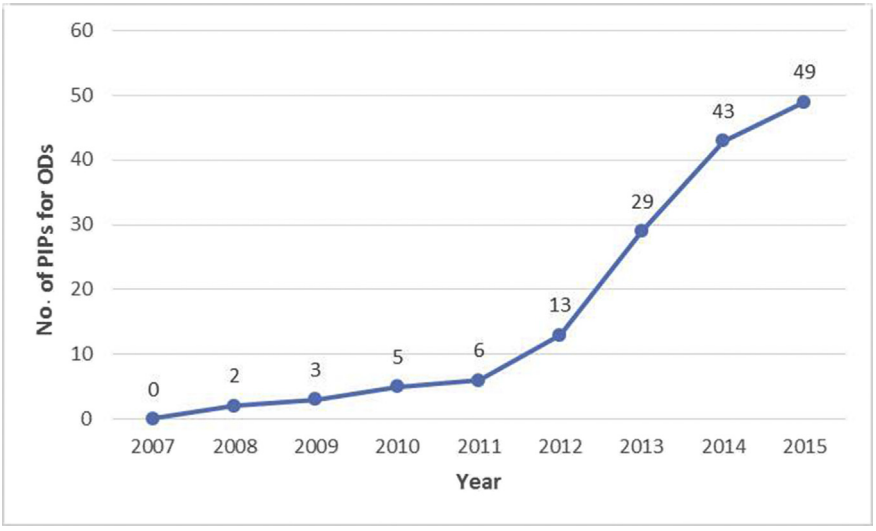

Figure 5. Number of pediatric investigation plans (PIPs) for orphan designations (ODs) (2007–2015). Medicines for which OD were withdrawn, or whose market exclusivity expired, were excluded from the analysis, as well as those medicines whose development was discontinued. From the European Medicines Agency.[8]

available, including challenges relating to several PIPs being delayed for approval for the same rare condition.[17] In this regard, the EMA annual report presents concrete actions to help address these issues, such as: (1) reviewing the processes and expectations of handling applications for PIPs; (2) increasing dialogue across stakeholders on opportunities for pediatric needs; and (3) conducting a joint evaluation of the pediatric and orphan regulations to effectively drive development in subpopulations of particular need.[14]

PRACTICAL CHALLENGES TO THE DEVELOPMENT OF PEDIATRIC ORPHAN MEDICINAL PRODUCTS

Overall, and separately, both regulations—pediatric (which is essentially a mandatory regime) and orphan (which is voluntary)—are considered successful in meeting their objectives. However, practical challenges remain for any product being developed for children with rare diseases, as they fall within the scope of two separate regulatory frameworks, as explained in the following sections.

Separate Governance

The evaluation of applications for orphan designation is under the responsibility of the COMP, whereas the PDCO is responsible for supporting the development of pediatric medicines by providing scientific expertise and defining pediatric needs. Although both committees consider products in their early phases of development, they have different remits. The COMP assesses orphan designation applications while the PDCO scrutinizes the detailed development plans for the study of the product in children through PIPs. Developers need to carefully schedule their interactions with both these committees during the medicine development process. Conversely, both committees should ensure that decision-making processes are aligned. This is often resource intensive for both the medicine developers and the 2 committees. Furthermore, both the COMP and the PDCO need to coordinate later with EMA's main scientific committee, the CHMP, which has the sole responsibility of assessing the data for marketing authorization of all products, regardless of patient age group or whether the product is orphan designated.

Developers may seek scientific advice, usually via protocol assistance. To qualify for protocol assistance, it is recommended to apply for this regulatory interaction at the early stage of drug development. An analysis of the approach of PDCO and COMP regarding the defining conditions for PIP or orphan designation performed by European Union regulators shows that the substantial majority of cases reveal no divergence between the conclusions of COMP and PDCO with regard to the condition for which a medicine is to be developed. The authors concluded that a collaborative approach allows for both regulations to work synergistically, fostering pharmaceutical development for childhood rare diseases.[18]

We note that the Paediatric Regulation allows the European Commission to impose financial penalties in case of any infringement in the provisions of the regulation or the implementing measures adopted (pursuant to Article 49.3).[19] This was confirmed in early 2019 in European Union Regulation 2019/5. To our knowledge, no financial penalties have been imposed in relation to the Paediatric Regulation.

Clinical Trials

Developing a new compound for pediatric use has its own challenges, whether scientific, operational, regulatory, or ethical. First, the pediatric population is heterogeneous, with 5 defined age groups,[20] from newborn to adolescence stage; each age group requires their own studies to understand drug disposition across the pediatric age continuum for the design and implementation of an optimal drug regimen to treat the disease. Second, challenges arise when conducting a pediatric clinical trial, particularly regarding globally dispersed patient recruitment and retention, which are even more important if the indication is targeting a rare disease in a small patient population.[21] Third, the ethical component is important because a large number of orphan indications are genetic and fatal within the first few years of life. If the treatment is not studied in this population, it will never be authorized because the patients will not be available to test its safety and efficacy.

Multiple Assessments

As a new medicinal product or indication progresses toward a marketing authorization application, the complexity in dealing with separate committees becomes increasingly apparent.

Before any marketing authorization application is submitted and as soon as the clinical studies in adults have been completed, and unless a pediatric waiver was granted, the PDCO must perform a first PIP compliance check; this check is a prerequisite to the marketing authorization application validation and evaluation by the CHMP. Similarly, at PIP completion, a second PIP compliance check is performed by the PDCO in advance of the submission of pediatric data to allow its evaluation by the CHMP, for new marketing authorizations, as an extension of the indication to pediatric patients, or as an update of the existing product information. In parallel to the CHMP evaluation, the COMP is required to assess the maintenance of the orphan designation status, which must be confirmed at the time of marketing authorization grant.

These multiple assessments are required not only for the first marketing authorization of the product but also for subsequent extension applications, including those for new indications. Managing these overlapping processes can be challenging, especially where the outcomes do not align. Closer coordination and alignment between the various EMA committees involved would improve the efficiency and predictability of the regulatory processes.

Market Exclusivity

Orphan-designated medicines are entitled to benefit from 10 years of market exclusivity once they receive a marketing authorization in the European Union, provided their orphan status has been confirmed at the time of the granting of the marketing authorization. Market exclusivity is an essential incentive intended to encourage the development of medicines for rare diseases that provides protection from competition from similar medicines for the same indication, during a limited period. For orphan-designated medicines meeting all the requirements of the Paediatric Regulation, following completion of the agreed PIP, the market exclusivity period is extended by 2 additional years to reward the pediatric development investment. In some cases, however, a product's patent and SPC provide a more effective form of exclusivity compared with the orphan market exclusivity.

Although both incentives exist, they cannot both be obtained for the same medicine and pediatric development investment. In such a case, to obtain a 6-month SPC extension, the developer must request the removal of the medicine from the Register of Orphan Medicinal Products (voluntarily revoking its orphan status).

FOSTERING A MORE INTEGRATED APPROACH TO PEDIATRIC ORPHAN MEDICINAL PRODUCT DEVELOPMENT

It is clear that the system of obligations and incentives for pediatric and orphan drug development has resulted in a positive shift on drug development and people mind-set. Nonetheless, further integration to optimize development of pediatric orphan medicines could be useful and may be pursued through the following considerations.

Interaction Between PIPs and Orphan Designations

As early as 2012, pediatric oncology had been identified as a neglected therapeutic area with little progress to deliver new and better treatments for childhood cancers. This was attributed in part to the difference in clinical conditions between adults and children.[22] Five years later, EMA cited 6 new anticancer medicines that had been authorized in children since the Paediatric Regulation came into force. During the same period, 10% of all PIP decisions (89 of 935) were for 73 anticancer medicines with >35 different mechanisms of action (eg, acute lymphoblastic leukemia, Ewing sarcoma, medulloblastoma, neuroblastoma, rhabdomyosarcoma). Of the 58 anticancer medicines authorized via the centralized procedure after the Paediatric Regulation came into force, 35 (60%) were authorized for a condition for which pediatric studies had been waived (product-specific waiver or class waiver). The remaining 23 (40%) of the 58 medicines had an agreed PIP.[14]

In 2015, the PDCO revised the list of class waivers,[23] changing many waivers for adult oncology conditions to limit the application of the waivers to older products with a known mode of action. This revocation came into play in 2018 and leads to more consideration now being given to the oncology products' mechanism of action, which could lead to new approaches in addressing unmet medical needs in children beyond the adults' indication. Similar or novel approaches focused on extending adult indications to children may be considered for other therapeutic areas.

Over the years, there has been an increase in the number of orphan-designated medicines indicated for both adults and children, demonstrating this positive shift (Figure 2). However, only a limited proportion of these orphan-designated medicines are authorized for both adults and children or children only (Figure 3).

Since the entry into force of the Paediatric Regulation, >150 PIPs have been agreed for medicinal products that also received an orphan designation. This indicates that there is a progressive increase in the number of PIPs for rare pediatric diseases.[14]

Continued Shift Toward the Use of Innovative Approaches

There has been a shift toward the use of more innovative approaches in pediatric medicine development, which has been facilitated through different initiatives. After an EMA/European Federation of Pharmaceutical Industries and Associations workshop in 2011 on modeling and simulation (M&S), the EMA Modelling and Simulation Working Group was established in 2013 to provide specialist scientific support on M&S to the EMA committees. As a result, experience and use of M&S in pediatric drug development has increased, and 52 PIPs have been agreed that include explicit extrapolation measures.[18] More are expected with the implementation of the 2018 EMA Reflection Paper of Paediatric Extrapolation[20] and the release of the future International Council for Harmonisation E11A guideline on the same topic. The EMA committees (PDCO, COMP, and CHMP) have a unique opportunity to embrace new approaches and to work more closely together to ensure that these innovative methods are used where appropriate.

Alternatives to Randomized Controlled Studies in Rare Pediatric Populations

Because randomized controlled studies are often not feasible in small populations, alternative study design options as recommended by the International Council for Harmonisation E11 (R1) pediatric guideline[24] (pediatric extrapolation, as well as other approaches)

could be considered; these other approaches include single-arm studies, use of registries for indirect comparisons, withdrawal designs, and quantitative or Bayesian approaches. These would help avoid undue exposure of children to new medicines and also generate the evidence that will support a marketing authorization. Interestingly, in 2013, an algorithm[25] was even proposed as a useful tool for selecting an appropriate study design in the development of orphan medicines for a given disease treatment–outcome situation; such an algorithm would certainly warrant more attention.

In addition, to efficiently overcome the difficulties of clinical research in small populations, the European Commission has funded 3 international multidisciplinary research consortia under the FP7 Health projects framework to identify promising approaches: ASTERIX[26] (Advances in Small Trials Design for Regulatory Innovation and Excellence), IDEAL[27] (Integrated Design and Analysis of Small Population Group Trials), and InSPiRe[28] (Innovative Methodology for Small Population Research). Other ongoing initiatives, such as the European Network of Paediatric Research at the EMA (Enpr-EMA[29]) or the Innovative Medicines Initiative Conect4children (C4C[30]) project, will certainly help in delivering more pediatric studies.

The Small Population Clinical Trials (SPCT) Task Force[31] set up by the International Rare Diseases Research Consortium issued recommendations for studying treatments for a rare disease to contribute toward successful therapy development and clinical use. Although randomized clinical trials are still considered the gold standard, the SPCT recommended the following: (1) systematically take into consideration alternative trial design options; (2) combine different sources of safety data to give a fuller picture of a therapy's safety profile; (3) consider multiarm trials as an opportunity for development of rare diseases therapy; (4) perform such trials via international networks; (5) involve patients in trial design and therapy development; (6) seek input from multiple regulatory agencies early and throughout the clinical development; and (7) consider parallel advice for multiregional development programs.

All these recommendations are relevant when developing orphan pediatric medicines and could be considered in the development phase. Furthermore, additional measures should be considered to optimize patients' access to clinical trials and to new medicines, where appropriate: (1) use of disease registries or electronic health records; (2) use of digital technologies to generate real-world data; or (3) use of remote decentralized clinical trials to facilitate patients' recruitments in clinical trials (eg, Innovative Medicines Initiative Trials@Home project).

These considerations align well with the EMA's "Regulatory Science to 2025" strategy[32] for advancing EMA's engagement with regulatory science over the next 5–10 years. This strategy was likewise welcomed by the European Federation of Pharmaceutical Industry and Associations, which recently underscored industry priorities, namely: (1) fostering innovation in clinical trials; (2) diversifying and integrating regulatory advice along the development continuum; and (3) promoting the use of high-quality real-world evidence in decision-making.[33]

Better Identification of Unmet Pediatric Needs

Because a majority of orphan diseases start in childhood, optimizing pediatric development is expected to benefit orphan diseases as well. An important area is better identification of unmet medical needs for children that will provide a common basis for strategic decision-making. Multiple stakeholders (eg, industry, regulators, epidemiologists, academia, patients' representatives, pediatric networks) should come together to assess and build an inventory of disease-based unmet pediatric needs. The inventory should indicate clearly for each need if there is research ongoing and what type of research, ensuring transparency for all stakeholders of areas in which research is most needed to avoid subjecting the pediatric population to unnecessary or unfeasible trials. This approach will allow better integrated scientific and regulatory dialogue when developing pediatric medicines, improve the efficiency of PIPs already underway, and speed up the development process and, ultimately, the availability of medicines to children.

Because the Orphan Regulation is not therapeutic-area specific, it is flexible enough to provide research incentives to all therapeutic areas, including oncology products. Given that it is voluntary, the areas being researched in the regulation will depend on the science and research direction of the company/

sponsor. The importance of stimulating more research to better understand disease etiology and underlying mechanistic pathways is necessary to unlock these areas for medicines development.

Identifying research priorities as a way to optimize the implementation of the Paediatric Regulation is included in the concrete actions detailed by the European Commission in their 10 year-report and in the EMA/European Commission joint action plan on pediatrics.[34] In addition, the European Reference Networks (ERNs), which were launched by the European Commission and Member States since 2017 as part of the legal framework of the European Union Directive on Patients' Rights in Cross-Border Healthcare Directive adopted in 2011, will help support these activities.[35] The ERNs provide a resource to discuss complex or rare diseases and are a great device to stimulate research in these areas.[36]

Joined-up Regulatory Support for the Development of Medicines for Rare Pediatric Diseases

The mandatory pediatric regime renders a larger quantity of pediatric research and development but may not furnish the pediatric treatments sought.[8] Conversely, the voluntary, incentives-based orphan regime leads to a smaller quantity of research and development but produces notable breakthroughs in addressing specific, rare pediatric medical needs. Better integration of regulatory systems, such as scientific tools and methods to generate evidence, and the use of regulatory processes and incentives, must be optimized to allow for better outcomes. For example, these include activities that focus on regulatory tools and processes such as parallel consultations of health authorities and health technology assessment bodies, access to the EMA Priority Medicines scheme, and expanded access or compassionate use programs.

In addition, further alignment across other regulatory jurisdictions to reinforce mutual reliance on regulatory assessments of pediatric development-planning documents (eg, pediatric investigation plans in the European Union and pediatric study plans in the United States) could also be advanced to help better frame the discussions within a global context.

CONCLUSIONS

We argue that more can be done to address the demand for therapeutic options and cures to treat rare childhood conditions. Industry is responding to this challenge and believes that the implementation of both the Paediatric Regulation and the Orphan Regulation can be further improved in the near term, through pragmatic changes and collaborative research programs, in support of the EMA/European Commission action plan.[34]

The present article outlines opportunities to help optimize orphan pediatric medicines development, improve PIP efficiency, and avoid duplication of studies and unnecessary trials in children. First, there is a need for increased interaction between PIP development and orphan designations. This can be driven by potential exploration of the pediatric use of existing medicines, where the adult indication is under development (eg, in pediatric oncology). Second, innovative approaches should be used, such as modelling and simulation or extrapolation. A third opportunity is to consider alternatives to randomized controlled studies in small populations (eg, alternative design options, disease registries, digital technology to generate real-world data/real-world evidence, or remote decentralized clinical trials. Fourth, better identification and prioritization of unmet pediatric needs will provide a common basis for strategic decision. This can be achieved through an inventory of disease-based unmet pediatric medical needs that highlight current or ongoing research, as a way to improve efficiency of PIPs and avoid duplication of studies and unnecessary trials in children. Finally, better integration is needed of regulatory systems, such as scientific tools and methods to generate evidence, and the use of regulatory processes and incentives (parallel consultations, EMA Priority Medicines, expanded access, or compassionate use programs), as well as optimized international alignment.

Collaborations within the Innovative Medicines Initiative are already addressing pediatric research needs (eg, to create a pan-EU Paediatric Clinical Trials Network via the C4C project to allow a more efficient system for conducting pediatric studies). Multi-stakeholder discussions for better identification of unmet pediatric needs, better integrated scientific and regulatory dialogue, and improving the efficiency of PIPs are already underway. This will speed up the drug development process and ultimately availability of medicines for children, to support the aim: "…the best way to bolster outcomes and protect children is through research, not from research."[37]

DISCLOSURES

All of the authors hold positions within the pharmaceutical industry but they have not received any grant, honoraria, or other compensation to author this paper.

ACKNOWLEDGMENTS

All authors designed the commentary, analyzed the data, and wrote the manuscript.

The views expressed in this commentary are the independent views of the authors and should not be understood or quoted as being made on behalf of or reflecting of the position the respective companies or any other affiliation.

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