



Editorial

Pediatric Drug Development: Challenges and Opportunities



Introduction

What are the regulatory challenges for the development of new drugs for children? Are new clinical designs needed for pediatric clinical trials? Do we have the right infrastructure for running pediatric trials on a global scale? Are the current legislative incentives working for children and adolescents? What is the expected role of academia and patients' organizations in pediatric drug development?

These and many others were the challenging questions raised during the pediatric drug development conference that was held in Budapest, Hungary, in November 2017. Delegates from industry, academia, and contract research organizations traveled to Budapest for the event organized by the Medicines for Children Research Network (MCRN) Hungary, an association focused on supporting the clinical development of better medicines for children. This editorial intends to provide an overview of the main topics presented by the speakers, as well as introduce the specific commentaries and reviews contained in this issue.

It is generally agreed that that the Pediatric Medicine Regulation (PMR) in Europe and its equivalent legislation in the United States have stimulated new research efforts in pediatrics. As a matter of fact, before the PMR introduction in Europe, only one-third of approved drugs had a pediatric indication described in their marketing authorizations. Ten years on, that has risen to 70% for all newly approved medicines, as detailed by Christina Bucci-Rechtweg and Martine Dehlinger-Kremer in their presentations describing at length the current regulatory outlook.

Christina Bucci-Rechtweg, head of pediatrics and maternal health policy at Novartis, provided a comprehensive overview of the regulatory landscape for pediatric drug development and clearly summarized many of the concepts and ideas presented by the other speakers. The first legislative steps aimed at regulating and promoting pediatric drug development saw their light in the United States with the Best Pharmaceuticals for Children Act and Pharmaceutical Research Equity Act, which were enacted between 2002 and 2003 and made permanent in 2016. These pieces of legislation created a set of obligations and incentives for the development of pediatric medicines. The spirit of these acts was later essentially adopted in Europe with the introduction of the PMR in 2007. According to Bucci-Rechtweg, this regulatory framework was instrumental in the creation of a better environment for the development of medicines for children.

However, two major shortcomings were highlighted by Bucci-Rechtweg. First of all, we have the problem of segmentation into

different patient populations, with different needs and priorities. For example, neonates are still largely neglected in terms of new drug development. There are still too few studies for this very vulnerable segment. It also highly debatable whether adolescents should not be included in adult trials when from a physiological and medical point of view there is no compelling reason for running separate trials.

Another problem is the limited development of drugs targeting rare pediatric diseases. Generally speaking, pediatric drug development is driven by adult drug development, which is not a problem when a disease (eg, asthma) occurs in both groups. It may be a problem when a disease occurs only in pediatric populations. Take for instance, the case of oncology. There are compounds in the pipeline for cancers such as leukemia that occur in both adults and children, but there are hardly any compounds in development for diffuse intrinsic pontine glioma, which is a pediatric brain cancer. Cancers in children tend to be different diseases. Because adult cancers do not occur in children, companies can easily obtain a waiver (i.e. exemption from the obligation of conducting pediatric studies). This may lead to wasted opportunities for children with cancer because some of these drugs may be effective against certain childhood cancers due to their mechanism of action. The current legislation does not create obligations for companies and does not create sufficient incentives for the development of new treatments for rare pediatric cancers and other diseases in general.

Regulators in the United States have been trying to address the problem by creating more powerful incentives. The 2012 Creating Hope Act extended the scope of the Food and Drug Administration (FDA) priority review voucher by extending this voucher opportunity to any company developing a drug for a rare pediatric disease and, furthermore, making this voucher fully transferable. Since its inception, the scheme has seen the award of 7 priority review vouchers that were later sold by the holders for sums ranging from \$65 million to \$350 million. Only time will tell if this incentive will be sufficient to stimulate new drug development addressing rare pediatric diseases.

Another very interesting perspective is provided by Martine Dehlinger-Kremer, chair of the EUCROF (the European Contract Research Organizations Federation) Pediatric Working Group and global vice president medical and regulatory affairs at Synteract-HCR. Her presentation focused on the new Clinical Trial Regulation in Europe, which is bound have an important influence on pediatric trials, particularly regarding ethical considerations. The new directive was approved in 2014 and should go into full force in

2019, when it will be adopted automatically by all European Union members, although it does leave room for national requirements (e.g. informed consent and data protection).

This new legislation is expected to overcome the previous regulatory fragmentation that led to increased costs and longer timelines because it often involved multiple submission requirements and safety reports. The end result was a decrease in the number of trials in the European Union. Now, submission through a common European Union portal will become the common practice.

Generally speaking, there will be more transparency for clinical data. For example, all data must now be published within a year of study completion and the requirement is actually 6 months for pediatric studies. The huge body of pediatric studies will be captured in public databases and made available. This is undoubtedly very valuable information for pediatricians and clinicians across the world.

Another important aspect stressed by Dehlinger-Kremer is that ethical requirements are now spelled out more clearly. Clinical trials in children remain tightly regulated and high importance is given to the information to be provided to the child and the parents/legal guardians. The new regulation underlines the importance of taking into account the wishes of children with regard to trial participation and their full engagement, aiming to treat children as developing autonomous beings whose maturity gradually evolves with age and experience.

Dehlinger-Kremer also pointed to some important differences between the legislative requirements in European Union and United States. One example is the fact that in Europe studies must be registered first, before recruiting patients, unlike in United States where the FDA mandates registration within 21 days after recruitment start and no obligation for Phase I. These and other more subtle differences may add to the complexity and challenges of running pediatric studies on a global scale.

The differences between European Medicines Agency (EMA) and FDA regulatory pathways were brilliantly presented by Mette Due Theilade Thomsen, managing director at PIP Adviser, who also presents a review article on the topic. Thomsen emphasized the need to coordinate the regulatory work between the two main agencies. In fact, tools to align FDA and EMA processes and include the same information in the respective pediatric documents are already in place. There is an active dialogue between FDA and EMA to harmonize their activities, and there is the opportunity for members of EMA Paediatric Committee and the FDA Pediatric Medicines Office to call into the weekly Pediatric Review Committee meeting and vice versa for Pediatric Review Committee members to remotely participate in EMA Paediatric Committee discussions. This collaboration between the agencies has already led to the creation of a pediatric cluster with joint EMA/FDA early pediatric interactions issuing a common commentary. The first jointly organized EMA/FDA workshop was held in June 2017 at EMA's premises on the topic of pediatric pulmonary arterial hypertension. It is not unreasonable to expect that this may further evolve with the creation of 3-party meetings that also involve sponsors and, possibly, input from regulators in Canada, Japan, and Australia.

The challenges of geography and jurisdictions were highlighted by Benoit Hebert, vice president of business development at Pediapharm, a pediatric specialty pharma company operating in Canada. Unlike in the United States and the European Union, in Canada there is neither pediatric exclusivity nor a separate pediatric approval process. This creates challenges in getting pediatric products approved in that country. The uncertainties regarding approval and reimbursement have often discouraged pediatric drug development in Canada. However, there are signs of innovation, with the creation of a new federal center working on pediatric formulations, as well as the creation of dedicated companies like Pediapharm itself. In the end, when there is a clear unmet need and

the regulatory framework is simplified, it is a natural process to see more initiatives emerging.

Indeed, the current regulatory landscape provides several potential pathways for pediatric drug development. Evgenia Mengou, owner and managing director of EV Consulting, provided a nice overview of the possible pathways and regulatory incentives in Europe.

There are certainly several possible accelerated pathways in Europe, which may take into account the orphan status of a drug in development, as well as the unmet medical need requiring early access to patients. One pathway in particular generated high expectations when it was introduced with the PMR in 2007. It was believed the incentives provided by the Paediatric Use Marketing Authorization (PUMA) would stimulate the repurposing of generic drugs to specific pediatric diseases, with PUMA conferring 10 years of data and market exclusivity for any off-patent compound that was repurposed to treat a pediatric disease. The results have been disappointing: Only 4 PUMAs have been awarded since its inception. Besides the natural disincentives for companies to engage in programs with more modest financial returns, such as drug repurposing projects, there seem to be intrinsic problems with the PUMA program itself because it is still rather resource-intensive. Many believe that because generics are not new chemical entities there should be more regulatory flexibility to take this fundamental difference into account. It appears that this is not always the case when interacting with regulators.

Early interactions with regulators are indeed the key to success for pediatric development. This concept reverberated through the event. Mengou stressed that, for instance, pediatric advice is provided free of charge by EMA in Europe and companies should explore as early as possible the various accelerated pathways that may be available for their products. However, companies should bear in mind that accelerated approval pathways do not necessarily mean that these should be considered shortcuts. In the end, companies need to provide the necessary resources for pediatric drug development, particularly if this is not their focus and this is done only as complement to adult medicine development.

Despite the apparent consensus that pediatric regulations in the European Union and United States, with their balance of incentives and obligations, have provided a positive stimulus to the development of better drugs for children, a powerful dissenting voice was heard at the event.

Klaus Rose is an independent pediatric development consultant with more than 30 years of industry experience in pediatrics. Rose's presentation was extremely critical of the current pediatric drug development legislation, particularly the European version. At some point, Rose defined the pediatric medicines regulation as "potentially [the] largest worldwide abuse of patients in medical research in history."

Rose argued that it is not fair to say that children do not benefit from modern medicine, and listed examples of pediatric medicines developed even before the enactment of the pediatric legislation. Moreover, he questioned the assumption that individuals younger than age 18 years should automatically be grouped separately from adults. In fact, there is strong scientific and medical evidence that younger patients, with the exclusion of neonates and preterm babies, could be safely included in adult studies because there is no significant difference in physiological parameters between children and adults. Many teenagers are not distinguishable from adults and the 18 years age limit is primarily a legal boundary rather than a medical boundary.

The other problem highlighted by Rose is the confusion around the term *off label*. This does not necessarily imply danger or lack of safety for patients; we have substantial evidence throughout the history of medicines of careful adoption and recurrent use of medicines lacking a regulatory seal of approval.

Rose argued vehemently that the European Union pediatric regulation creates a cumbersome and largely unnecessary clinical development framework that forces companies to undertake large-scale pediatric efficacy studies when the most appropriate measure would be smaller dose-finding studies. The alleged abuse of patients is demonstrated, according to Rose, by the several large-scale pediatric studies that were requested by regulatory authorities although these studies were not feasible. This forced younger patients to participate in separate, long trials that were not adjusted for the results coming from adult studies. Rose's opinions are described in more detail in 2 articles within this issue, where he makes specific examples of pediatric studies for melanoma, dermatology, and oncology indications that lacked a strong medical rationale and were either unfeasible or did not produce particularly useful data. Whether we subscribe to Rose's view or we do not, the issue of a more flexible age of entry into adult trials is certainly gaining ground and is increasingly supported by key stakeholders.

Regardless of their medical rationale, once the pediatric plans are approved more challenges come from executing these studies. Patient recruitment for pediatric trials often demands access to networks of expert investigators and sites, usually at the international level. In many cases, national networks have been set up in various EU countries. MCRN Hungary is 1 such example. MCRN Hungary is a national network of investigators across the main pediatric disciplines. Access to such networks is essential for quick and effective patient recruitment and it is particularly important in the case of rare diseases where specialist resources are needed. Neonatologist Mark Turner (University of Liverpool) presented an ambitious project to connect the various national initiatives and create a public-private partnership for a global pediatric network. This is an Innovative Medicines Initiative-sponsored project that was launched in 2017 under the Conect4Children banner. The goal is to create a comprehensive network capable of running Phase I through IV trials for all age groups, from neonates to adolescents. The funding would come from a public-private partnership with multiple stakeholders (eg, academia, hospitals, industry, and patient organizations). It is expected that such a network would deliver a sustainable business model based on efficient delivery of trials, breadth of experience, and participation and collaboration of multiple sponsors. The major selling point for sponsors is that this network would offer a single point of contact for study sponsors as well as standardized procedures. Along these lines was the presentation by Jaroslav Sterba (University Hospital of Brno), who presented the pediatric oncology network in use in 8 countries across central Eastern Europe that provides a ready-to-use clinical infrastructure for pediatric oncology clinical trials.

Alongside the traditional challenge of pediatric patient recruitment, we often have to introduce more effective trial designs. This was the main topic of the presentation delivered by Wouter Wijker, a seasoned biostatistician and managing director of Auxiliis BV, a pediatric-focused Contract Research Organization (CRO).

A so-called N-of-1 trial can be thought of as a type of crossover with only 1 patient. Sequences of treatments are repeated in time in a random order. For example, we could have repetitive AB or BA schedules where A could be an active treatment and B a placebo or another active treatment and washout time should be considered to avoid carryover. The number and length of the treatment periods would be dictated by the effect size, and the number of observations or data collection points. A greater number of periods can help reduce the potentially confounding effects of other lifestyle changes.

N-of-1 trials appear to be suited for studies involving very small patient populations, allowing patients with rare diseases to get access to innovative medicines when a larger, more traditional clinical study would be too challenging. Wijker provided a few case studies on this approach in the orphan drug space. A clear advantage

of this design is the truly personalized nature of the treatment, which is generally well received by patients and physicians. On the more negative side, it might be challenging to generalize the findings of such trials and better statistical tools should be adopted. It also requires additional work from physicians, although innovative wireless health monitoring may soon help overcome this burden. Moreover, regulatory acceptance is still uncertain and the design cannot be easily used in conditions that rapidly change, such as in infections studies.

One point was made clear by all these presentations: Pediatric drug development requires a complex set of skills, starting at the preclinical level with the necessity to invest in deeper toxicology studies. Children are not just sized-down adults. Age and developmental maturation of patients is expected to have an influence on both pharmacokinetic and pharmacodynamic data.

Furthermore, the development of an appropriate formulation is also a crucial element of any successful pediatric drug development plan. This aspect was nicely explained by Sarah Barthold, project manager at Glatt Pharmaceutical Sciences, a technology company with strong expertise in pediatric formulation development. It is widely held that oral administration is preferred, but this poses challenges in small children because they may have difficulties in swallowing. There is always a need for any taste-masking properties. One possible approach is pellets- and micropellets-based formulations that may address the taste-masking problem and avoid the need to crush tablets, resulting in better patient compliance.

It is true that drug development and commercialization are carried out by for-profit entities such as pharmaceutical and biotech companies, but it would be unwise to downplay the role of academic and nonprofit patient organizations in this process.

Phil Walson, a board-certified pediatrician and visiting professor at the University of Goettingen, Germany, provided a comprehensive overview of academia's role and more details are contained in his contribution to this issue of the journal. Undoubtedly, academia can play a pivotal role in the development of effective but otherwise commercially nonviable products, particularly in the rare diseases space. Most of the incentives described apply to industry. However, academia may collaborate with industry to de-risk programs. We have examples of academic drug development initiatives such as those at Lurie Hospital (Chicago, Illinois) and St Jude (St Louis, Missouri), which at various stages involved collaborations with industry partners. Indeed, 2 of the most successful examples of pediatric-specific product approval, dinutuximab for neuroblastoma (2015) by United Therapeutics (Silver Spring, Maryland) and chimeric antigen receptor T cell therapy for pediatric acute myeloid leukemia (2017) by Novartis (East Hanover, New Jersey), were the end result of strong academic drug development programs that were subsequently taken up by industry.

In my presentation at the conference, I described how nonprofit organizations can collaborate with technology providers and industry to discover and further develop new treatments for rare pediatric diseases. In 2012, I cofounded accelerating Pediatric Oncology Drug Development (aPODD), a London-based charity specifically focused on speeding up the development of better treatments for children with cancer. The basic idea behind the decision to set up this charity was that new business models are needed to support the development of new drugs for childhood cancer. Until now, most charitable funding has gone to academic programs that may generate new knowledge and intellectual property but lack commercialization potential and therefore the new knowledge is not systematically taken up by biotech and pharma companies for further clinical development. Childhood cancer charities need to adopt a bolder model and start taking responsibility for specific drug development efforts. The venture philanthropy model was brilliantly applied by the

Cystic Fibrosis Foundation, leading through its collaboration with Vertex Pharmaceuticals, to the first approval in decades of a drug primarily influencing the cause of the disease. A similar operational model should be applied to pediatric oncology drug development.

Drug repurposing is an area where aPODD is particularly active and this was the specific topic of my presentation. We have launched drug-repurposing projects for medulloblastoma and neuroblastoma in collaboration with Healx, a technology company based in Cambridge, United Kingdom, with strong expertise in drug repurposing. Healx uses bioinformatics and machine learning tools in combination with manual curation to identify novel uses for existing drugs. They have successfully applied this approach to identify drug-repurposing candidates for a number of rare pediatric diseases and they are now applying this approach to pediatric oncology in collaboration with aPODD, which is funding the work. The proposed compounds are being tested in patient-derived cell lines and appropriate animal models. Because we are evaluating compounds that have been in clinics for many years, their safety profiles are very well established. Promising candidates may thus represent drug-repurposing clinical candidates. Therefore, aPODD's

efforts are a clear example of how patient organizations may deliver benefits to patients by exploring different business models.

Overall, the conference was a success and stimulated interesting debates. The clear take-home message is that pediatric drug development is complex and interconnects different stakeholders (eg, industry, academia, hospitals, and patients and their families). Advancement in this area was achieved through close collaboration among all parties and even greater improvements in the future will require much more of the same.

Cesare Spadoni, PhD, MBA*
*aPODD Foundation, London, UK and the Medicines for Children
Research Network (MCRN) Hungary, Budapest, Hungary*

*Address correspondence to: Cesare Spadoni, PhD, MBA
E-mail address: cesare.spadoni@pharma-biomed.com

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