



## Pediatric Drug Development Conference – Budapest 27-28 April 2016



What are the regulatory hurdles for the development of new drugs for children? Are new design approaches needed for paediatric clinical trials? Do we have the right infrastructure for running paediatric trials on a global scale? Are the current regulatory incentives working for children and adolescents? What is the expected role of academia and patients' organisations in paediatric drug development?

These and many others were the challenging questions raised during the recent paediatric drug development conference that was held in Budapest on April 27-28. Delegates from industry, academia and contract research organisations travelled from the US and other EU countries to gather in Budapest for the second conference organized by the Medicines for Children Research Network (MCRN) Hungary. Over the course of two days the delegates were challenged by interesting presentations and a roundtable discussion, which defined the main issues currently affecting the development of specific medicines for younger patients.



The Paediatric Medicine Regulation (PMR) and its equivalent pieces of legislation in the US have undoubtedly stimulated new research efforts in paediatrics. As a matter of fact, before the PMR introduction in Europe, only one third of the approved drugs had a paediatric indication described in their marketing authorizations. Ten years on that percentage has risen to 70% for all newly approved medicines, as detailed by Martine Dehlinger-Kremer in her presentation about the current regulatory outlook. Martine is Chair of the EUCROF Paediatric Working Group, and Global Vice President Medical and Regulatory Affairs at SynteractHCR. In addition to having more approved drugs with paediatric label, the huge body of paediatric studies is now captured in public databases and made available. For example, it has

been estimated that more than 3,000 reports on the results of paediatric studies are included in searchable and specific databases published by EMA. This includes all paediatric trials with



investigators in the EU or anywhere in the world when the trial was part of a PIP. This is undoubtedly very valuable information for paediatricians and clinicians across the world.

However, not everything is positive about the PMR as there are still areas where the legislation did not have a significant impact. Let us review a few examples.

Neonates are still largely neglected in terms of new drug development. There are still too few studies for this very vulnerable segment. Moreover, paediatric development is still largely dictated by adult development. Take for example the case of oncology. Industry generally develops drug for the more widely occurring adult cancers. Cancers in children tend to be different diseases. As these adult cancers do not occur in children, companies can easily obtain a waiver (i.e. exemption from the obligation of conducting paediatric studies). This situation may lead to wasted opportunities for children with cancer as some of these adult drugs may be potentially effective against certain childhood cancers, because of their mechanism of action. The current legislation does not create obligations for companies and does not create sufficient incentives for the development of new treatment for rare paediatric diseases in general.



Another cause of disappointment comes from the documented failure of the Paediatric Use Marketing Authorization (PUMA) to stimulate new drug repurposing projects in paediatrics. PUMA confers 10 years data and market exclusivity for any off-label compounds that has been re-purposed to treat any paediatric disease. The results have been disappointing with only 2 PUMAs

awarded over the past ten years. Helen Shaw, Medical Director at Proveca provided a nice overview of the process, as she was responsible for the very first PUMA programme approved by the EMA (oral Midazolam). Beside the natural disincentives for companies to engage in programmes with more modest financial returns, such as drug re-purposing projects, there seem to be some intrinsic problems with the PUMA programme itself, as it tends to be unreasonably very resource-intensive. Helen also quoted problems regarding the rigidity of some PUMA requirements as off-patent products are not new chemical entities so there should be more regulatory flexibility to take this fundamental difference into account. It would appear that this is not always the case when interacting with the regulators.

Once the paediatric plans are approved the challenges come from actually executing these study plans. Patient recruitment for paediatric trials often demand 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. The Medicines for Children Research Network (MCRN) Hungary is one such example. MCRN Hungary is a national networks of investigators across the main paediatric 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. William Treem (Janssen) presented an ambitious project to connect the various national initiatives and create a public-private partnership for a global paediatric network. This is an Innovative Medicines Initiative (IMI)-sponsored project that is scheduled to launch later in 2016. The goal is to create a



comprehensive network capable of running Phase I-IV trials for all age groups, from neonate to adolescents. The funding would come from a public-private partnership with multiple stakeholders (academia, hospitals, industry, SMEs and patients organisations). 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.

The need for efficient and patient-friendly clinical networks is also felt at a more local level. Beate Wulff (University Hospital of Essen) presented the challenges faced by hospitals in Germany for the creation of a regional paediatric oncology network. Young patients that go into relapse are eligible to be enrolled in the clinical trials of new investigational drugs. This, however, poses some practical challenges to these patients and their families. Children with late-stages diseases would have to travel across the country. Parents and families often hesitate before enrolling children in clinical trial, precisely for this reason. Better infrastructures and new recruitment strategies are needed to improve patient recruitment in early phase paediatric oncology trials in Germany.



Alongside operational challenges there may be medically-related difficulties in running paediatric trials. Psychiatry, for example, is an area normally very challenging for paediatric studies. Both Agota Barabassy (Gedeon Richter) and Philippe Aubry (Lundbeck) provided two very interesting presentations about the pitfalls and potential for paediatric development for psychotic disorders. Diseases like

Schizophrenia are difficult to diagnose and treat in children and adolescents. In paediatric and adolescent psychiatry there is often the problem of inappropriate formulations, lack of appropriate PK studies and big placebo responses to account for. Moreover, pharmacokinetic studies often do not confer tangible benefits to participants. That is why it is often advisable to extend the treatment of compassionate grounds.

Whenever a PIP is planned, it is essential the early guidance is received from the Paediatric Committee (PDCO) on how to conduct the studies and to what extent data could be extrapolated. This point was also stressed by Marja Agema (Astellas) in her presentation. This early guidance is essential for PIP preparation and execution, as it provides clarification on age stratification and can forecast difficulties that are likely to be encountered with ethical committees. For example, placebo-controlled paediatric studies are generally non feasible in Europe and this is a recurrent challenge for many trials.

One way in which sponsor can tackle challenging paediatric clinical studies is to introduce changes in the trial design in order to make these studies more feasible. In some cases studies can be planned with a so-called adaptive design, which involves modifications along the trial on the basis of an interim analysis. Massimo Iacobelli (Techitra Srl Managing Director) gave a very interesting perspective on this approach, largely drawing from his own experience as Chief Medical Offices of a small biotech company developing defibrotide for veno-occlusive disease (VOD) in children. Adaptive



design has the potential to aid drug development in those situations that have difficult experimental situations, without lowering scientific and regulatory standards.

This approach may indeed be the best options when developing new drugs for rare, paediatric diseases. In these cases a single Phase II/III trial is often justified. Adaptive design can lead to a smaller sample size and reduced time for completing clinical development, if handled correctly. Any protocol change, though, should be based on pre-specified rules in order not to introduce any bias and avoid the chance of damaging the integrity of the whole trial. To this end it is advisable that the interim analysis should be provided by an independent statistician to an independent decision making committee, and that the sponsor should be blinded. This approach was shown to work well with defibrotide so, according to Massimo, there are solid grounds to consider adaptive design for other paediatric rare diseases.



One point was made clear by all these presentations, though.

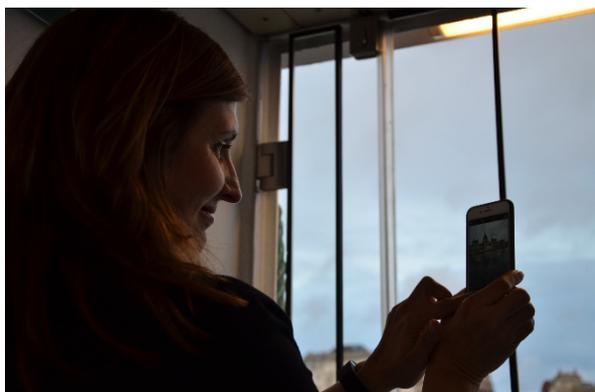
Paediatric development requires a complex set of skills in order to recognize the specific challenges that start at the preclinical level with the necessity to invest in deeper toxicological studies. Children are not just simple sized-down adults. Age and developmental maturation of the patients is expected to have an impact on both pharmacokinetic and pharmacodynamics data. The development of an appropriate formulation is also a crucial element of any successful paediatric plan. All these concepts were brilliantly summarized by Martin Graham's presentation. Martin is the CEO of Kinderpharm, a CRO, like Auxiliis, specialized in paediatric drug development. One important comment, made by Martin is that it is extremely important to seek proper advice from regulators on either side of the Atlantic as early as possible in the development process and take advantage of the available regulatory support. EMA, for example, offers free consultation to companies planning paediatric studies in any therapeutic area.

In the end, what is the future of paediatric research and drug development? Do we need new operational models?

According to Martin Austin (TransformX Ltd), we should expect more paediatric trials in the years to come. There is an ever growing interest in developing treatments for orphan indications and take advantage of regulatory incentives, bearing in mind that more than 60% of all rare diseases are conditions affecting children and adolescents. Martin very clearly illustrated the financial implications noting that it is true that approved drug for rare paediatric conditions may be able to claim premium prices. This model, however, is not sustainable in the long run with the ever growing disease segmentation and the emergence of precision medicines. New drug development models and partnerships are needed. Cesare Spadoni illustrated some examples of how patients' organization could de-risk paediatric drug development for pharma and biotech companies. Cesare



is Director of business development at Auxilliis but he's also the chairman and co-founder of, aPODD, a London-based charity focused on drug development of childhood cancers. Collaboration among different charities with common drug development goals and the willingness to partner with industry holds the key to accelerate the development of better medicines for children with cancer, an area traditional neglected by the pharmaceutical industry.



Overall, the event was very informative and allowed a very open and productive exchange of ideas and experiences. We are looking forward to meeting new attendees and welcoming back returning ones at our next 2017 conference in Budapest.

Above all we welcome the feedback of anybody involved in drug development for children and adolescents. We would be very much interested in hearing your views on what the biggest challenges are and what we can do to improve the whole process.

**Please do not hesitate to get in touch and contribute to the discussion!**



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