WRITTEN BY

Dr. Martine Dehlinger-Kremer
Vice President, Global Medical and Regulatory Affairs, SynteractHCR

CONTACT INFORMATION

SynteractHCR
5909 Sea Otter Place, Carlsbad, CA 92010
SynteractHCR.com | +1 760 268 8200

Pediatric Clinical Research: Successful Regulation, But Still Some Progress Desired (Part 2)

While progress has definitely been made in pediatric medication, i.e., more medicines for children, better product information, more pediatric trials and pediatric research, since the implementation of pediatric legislation in the US (1997) and EU (2006), there is still work to do. Additional regulations are already being put into place and others will be coming in the near future.

In September 2014, a new guideline on the application of PIPs was published by the European Commission helping to create improvements and to streamline processes. Only one PIP is now required for drugs that have applicability in more than one condition.

New trial methodologies such as extrapolation, modeling and simulation techniques are well accepted to reduce the number of study subjects as much as possible. The FDA has, over the last decade, modified its approaches towards extrapolation. The EMA is exploring approaches toward extrapolation beyond efficacy to include extrapolation of safety. The EMA has established an extrapolation expert group and released a reflection paper on 09 October 2017 with the aim to propose a framework that supports an explicit and systematic approach to extrapolation as basis for regulatory decision-making in pediatric developments.

There is a recognized need to involve patients (children) and their families in the planning of clinical research and the development of medicines they need. The Pediatric Committee of the EMA (PDCO) has three patients' representatives as members, and patients are represented in scientific advice and at the CHMP. Also, national competent authorities involve children, families or patients' organizations in activities related to pediatric medicine development.

Challenges

Since the implementation of the pediatric legislations, there has indeed been great progress in respect to new medicines for children. However, the pediatric needs are not yet completely met.

The PIPs do not always match the disease burden of disability-adjusted-life-years – a time-based measure that combines years of life lost due to premature mortality and/or years of life lost due to time lived in a state of less than full health – as established by the World Health Organization. For example, mental/behavioral disorders have the highest burden (20%), whereas the indication is covered in only 3% of the PIPs. On the other hand, we have infectious diseases and malignant neoplasms representing only a burden of 5% but being covered in 21% of the PIPs and 13% of the PIPs respectively.

Diseases and cancers unique to children are still neglected. For neonates, there are limited incentives and poor market signals, resulting in this group still being somewhat neglected. More therapeutic areas must address children's needs; currently, the majority of studies being performed reflect adult needs.

In the quest to allow greater access to innovative medicines and new formulations, legislation is needed that outlines the move from off-label use to approved drug use. Both the EU and the US have made significant investments in research on off-patent medicines; despite the stimulation in research, it has not yet made much difference in licensing.

Further support is needed once a drug enters the market. Addressing the unmet medical need should be taken into account by Health Technology Authorities and payers for approved drugs that are being used off label for children. Currently a large number of reimbursement policies allow the reimbursement of the cheapest product for a given indication and do not take into account whether that product has an approved pediatric labeling.

Pediatric networks support research into medicines for children

With the development of the European Network for Paediatric Research at the European Medicines Agency (Enpr-EMA), we have seen better coordination of research among members, patient associations, academia and the pharmaceutical industry. Twenty-four qualified networks were in place as of October 2017, including networks from the US and Canada; a further 22 are under process of qualification, including a network from Japan. The networks' support ranges from advising on the pediatric drug development strategy, the study protocol development through to identification of suitable study sites and support of patient recruitment. The creation of a pan-European pediatric clinical trials network for the conduct of interventional drug trials will further improve the research in pediatrics. Present plans also include the development of a global pediatric network.

ICH E-11 Addendum (R1) sought to increase harmonization globally

In August 2014, the International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) released a Working Group (EWG) addendum that included input from the US, EU, Japanese and Canadian health organizations. Everyone recognizes that it is critical to provide drug developers clear and compatible guidance specific to global product development of pediatric medicines. The addendum R1 reflects the latest thinking in both technical

and scientific knowledge as well as regulatory approaches, recognizing that there are still key topics where consensus has not yet been achieved.

The following topics are addressed:

- Ethical considerations in pediatric studies
- Age classification and pediatric subgroups including neonates
- Pediatric formulations
- Commonality of scientific approach for pediatric development programs to address issues to aid scientific discussions at various stages of pediatric development in different regions
- Pediatric extrapolation and introduction of modeling and simulation
- Practicalities in the design and execution of pediatric trials including discussions on feasibility, outcome assessments and long-term clinical aspects

Where are we today?

On 26 October 2017 the European Commission presented its report on "10 Years of the EU Pediatric Regulation" to the European Parliament and the Council. The report reveals that the Regulation's system of obligations, rewards and incentives appears to have had a positive impact on the development of pediatric medicines in the EU. From 2007 through 2016, more than 260 new medicines were authorized for use by children through new marketing authorizations and indications, and, in 2017, there were over 1000 agreed PIPs. According to the report, the number of PIPs completed grew considerably, with over 60% finalized in the last three years.

"One of the Regulation's undisputed achievements is bringing more attention and financial investment to pediatric development," the report says. "Pharmaceutical companies now consider pediatric development as an integral part of the overall development of medicinal products," it later continues.

Additional conclusions from the report include that:

- While the Pediatric Regulation has had an encouraging impact on the development of medicines for children in Europe, these positive results are not evenly spread among therapeutic areas. The Regulation appears to be most effective when adult and pediatric needs overlap. Fewer advances have been made in diseases that are rare or unique to children.
- While some instances of over- or under-compensating drug developers with financial rewards exist, the overall benefits seem to outweigh the costs and the Regulation appears to be positive in improving availability of pediatric medicines.

Resulting from these mostly positive findings, the European Commission has stated that it does not recommend re-opening the legislation at this stage. It will, however, evaluate both pediatric and orphan Regulations to better understand their combined effects and why the orphan reward does not seem to be driving pediatric development for rare diseases. Findings of this combined analysis are expected to be delivered in 2019, to permit the next Commission to make informed decisions about possible policy options. This will also allow the results of the SPC evaluation to be taken into account.

In the meantime, the European Commission and EMA are expected to begin working on pragmatic measures to streamline application and implementation of the Regulation. This might include changes to deferrals, revisiting the PIP process and, if needed, adapting the corresponding Commission guideline, multi-stakeholder discussion of pediatric needs, measures to encourage international cooperation and harmonization.

We also anticipate seeing a revision of the US FDA's Safety and Innovation Act (FDASIA), which was signed into law in 2012. When available, the report will appear on the FDA site.

Overall, the progress that has been made to date is encouraging, and future progress will certainly help to bring more approved drugs to market that will help to control diseases in children or cure them.

Bio for Dr. Martine Dehlinger-Kremer

Vice President, Global Medical and Regulatory Affairs at SynteractHCR

Dr. Martine Dehlinger-Kremer has 30 years of experience in the clinical research industry, including more than 27 years of progressively higher levels of Regulatory and Medical Affairs leadership responsibility. She has contributed to the global development of numerous products, including orphan drugs and biosimilars. She has participated in more than 100 New Drug Applications (NDAs) and Marketing Authorization Applications (MAAs) globally and in numerous clinical studies across all phases.

Dr. Dehlinger-Kremer has served as Chair of the Pediatric Working Group of EUCROF since 2008 and has influenced the standards, protocols and number of trials conducted for drugs being administered to children. Dr. Dehlinger-Kremer is chair of the EFGCP Children Medicines Working Party and is also a member of Working Parties of Enpr-EMA, the European Network of Pediatric Research at the European Medicines Agency.

Dr. Dehlinger-Kremer is also the President of EUCROF, the European CRO Federation, which represents approximately 400 CROs. In addition, she is a Board member of EFGCP, the European Forum for GCP. In August 2015, she was named one of PharmaVOICE 100's Most Inspiring People in Life Sciences as an industry leader recognized for impact, experience and advocacy in clinical research.

Dr. Dehlinger-Kremer holds a Doctorate in Sciences from the University of J.W. Goethe in Frankfurt, a general academic studies degree in neurophysiology from the Louis Pasteur University in Strasbourg, France, and a Master of Science from the University Moulin de la House in, France.

5909 Sea Otter Place, Carlsbad, CA 92010
SynteractHCR.com