# Pediatric Clinical Research: Legislation Has Brought Progress, But More is Needed

## Highlights:

- Progress has been made in the labeling and development of pediatric medication since implementation of pediatric legislation in the U.S. and EU.
- However, today, over 50% of medicines administered to children still have never been tested in this population.
- Discover historical governance of children's medicines in the U.S. and EU and how these countries are also collaborating.

## Introduction

Progress has been made in pediatric medication development since the implementation of pediatric legislation in the U.S. from 1979 on, and through implementation of the Regulation in the EU, starting in 2006. Today, all applications for marketing authorization for new medicines must include data in children as described in the pediatric plan, unless the medicine is exempt, or benefits from a deferral or waiver.

New trial methodologies such as extrapolation, modeling and simulation techniques are well accepted to optimize and reduce the number of pediatric study subjects to the minimum necessary to obtain adequate results. Both the FDA and EMA have published Pediatric Extrapolation Guidances that permit the extrapolation of adult efficacy data to children and from one age group of children to another. The extrapolation concept is based on three foundational requirements that need to be satisfied before implementing such an approach. If these three conditions can be satisfied, it may be possible to extrapolate the efficacy data generated in adults (and/or older children) without having to conduct powered (Phase III) efficacy studies in pediatric patients:

1. The disease or condition in adults and children is essentially the same.
2. The response to treatment is anticipated to be comparable in children and adults.
3. An exposure-response (PK/PD relationship) can be established that will permit the use of pharmacokinetic extrapolation (i.e. dose adjusted exposure-matching) between adults and children of different ages.

Today, the Pediatric Investigation Plan (PIP) template of the EMA includes (section D) dedicated subsections for Modeling & Simulation studies and for Extrapolation Studies. Similarly, in the initial Pediatric Study Plan (iPSP) in the U.S., these are under section 10 - "Planned Clinical Studies."

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 patient representatives as members, and patients are represented in Scientific Advice Working Party and at the CHMP (Committee for Medicinal Products for Human Use). Also, national competent authorities involve children, families, and/or patients' organizations in activities related to pediatric medicine development.

## Challenges

However, even with these advances, there is still room for progress to be made. We are still, today, at a high level of off-label use of medicines administered to children reaching up to 90% in neonates in the ICU. To address this need, additional guidances and regulations are already being put into place and others will be coming in the near future. But several challenges exist.

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 a burden of only 5% but being covered in 21% of the PIPs and 13% of the PIPs, respectively.

Diseases and cancers unique to children are often neglected. For neonates, there are limited incentives and poor market signals, resulting in this group still being somewhat ignored. 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 U.S. 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 only allow reimbursement of the cheapest product for a given active ingredient and do not take into account whether that product has an approved pediatric labeling.

## Historical Governance for Children's Medicines

In the U.S., several regulations govern pediatric clinical trials. They include:

- **Pediatric Use Subsection** in the **Precautions Section of Product Package Inserts (21 CFR 201.57 (f)(9))** (1979), **Pediatric Use Labeling Rule (21 CFR 201.57(f)(9))** (1994), **Food and Drug Administration Modernization Act (FDAMA) of 1997** – for product labels.

- **Best Pharmaceutical for Children Act (BPCA)** (1997/2002) – with incentives for additional marketing exclusivity if the sponsor conducts requested studies in a Written Request for indication(s) to be studied in pediatrics. The FDA publishes a list of pharmaceutical products needing pediatric studies.
- **Pediatric Research Equity Act (PREA)** (2003) – requires sponsors to determine safety and efficacy of new drugs and biological agents in pediatric patients unless a waiver is granted or the product is exempt. An initial Pediatric Study Plan (iPSP) must be submitted for medicines falling under PREA.
- **Food and Drug Administration Safety and Innovation Act (FDASIA)**, 2012 – makes BPCA and PREA permanent law.
- **FDA Reauthorization Act of 2017 (FDARA)** including **The Research to Accelerate Cures and Equity (RACE) for Children Act** – The RACE for Children Act aims to spur new cancer treatments for children and ends exemption of PREA obligations for cancer drugs with orphan drug designations for molecular targets relevant to children's cancer. On August 18, 2017, The RACE for Children Act was signed as part of the 2017 FDA Reauthorization Act, as an amendment to PREA. The goal of RACE is to further development of new cancer treatments for children. Pediatric trials for medicines can be required if a drug or biological product intended for the treatment of an adult cancer is directed at a molecular target deemed by the FDA to be substantially relevant to growth or progression of children's cancer. RACE ends exemption of PREA obligations for cancer drugs with orphan designations for these molecular targets that are on the list published by FDA.

In August 2018, the FDA published this list of molecular targets substantially relevant to growth and progression of pediatric cancer as well as a list of those that are not relevant. The list of molecular targets is designed to provide guidance, in accordance with the amended provisions of the PREA, on planning initial Pediatric Study Plan (PSP) submissions for new drugs or biologics for cancer. The FDA and National Cancer Institute (NCI), including the Pediatric Early Phase Clinical Trials Network and Pediatric Preclinical Testing Consortium, are expected to continue to collaborate on keeping the list current.

Congress reauthorized through 2020 the Rare Pediatric Disease Priority Review Voucher program in the 21st Century Cures legislation.

In the EU, the Pediatric Regulation of 2006, established on January 26, 2007, mandates pediatric drug development. This Pediatric Regulation comprised of Regulation (EC) No 1901/2006 and Regulation (EC) No 1902/2006, aims to facilitate development of high quality, appropriate research and medicines for children without needlessly exposing them to clinical trials or deterring medicines for adults. It also established the Pediatric Committee (PDCO), replacing the Pediatric Working Group. The PDCO determines the studies that companies must carry out on children as part of pediatric investigation plans (PIPs).

On October 26, 2017, the European Commission released its report to the European Parliament and the Council on "10 Years of the EU Pediatric Regulation." 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 in 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 and children's' age groups.
- 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 improving availability of pediatric medicines.

Resulting from these primarily positive findings, the European Commission has stated 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. These findings are expected to be delivered in 2019, to permit the next Commission to make informed decisions about possible policy options.

In that respect, the European Commission's DG SANTE organized a conference on Medicines for rare diseases and children in Brussels on June 17, 2019. About 150 experts were present from across the EU, representing national governments and health authorities, academia, patient and health professionals' organizations and pharmaceutical industry.

The conference took place as part of the joint evaluation of both EU Regulations on Orphan Medicinal Products and Paediatric Medicines. It allowed stakeholders to make their voices heard and come forward with their views, suggestions, and ideas with respect to the two Regulations. Discussions focused, among others, on the following topics:

- The importance of a common understanding and of quantifying unmet medical needs.
- The need to increase basic research and the collection and sharing of data in order to speed up the process from research and development to patient.
- The need for incentives that support real innovation in the orphan therapeutic landscape.
- Better guarantees that a reward is proportionate, including a better coordination and identification of priorities.
- The need for a dedicated R&D strategy for pediatric-only medicines development.
- The benefits of multi stakeholder engagement to overcome changing evidence standards, taking into account new scientific developments

A detailed report of the conference will be available on the DG SANTE website later in the summer of 2019.

In the meantime, the European Commission and EMA are expected to begin working on measures to streamline application and implementation of the Regulation to encourage international cooperation and harmonization.

On March 20, 2018, the EMA and EU Commission held a workshop with patients, academia, healthcare professionals, and industry regarding PIPs in MAAs. Taking into account the feedback of the stakeholders, the EU Commission and EMA published in October 2018 a plan, with 21 actions in five topic areas:

1. Identifying medical needs of children
2. Strengthening cooperation between decision-makers
3. Ensuring timely completion of PIPs
4. Improving handling of PIPs
5. Increasing transparency around children's medicines

Completion of this plan was initially aimed within two years. Due to implications of Brexit (EMA relocation and business continuity plan) some deadlines have been extended beyond 2020.

A revised and revoked class waivers list, of medicines not required to submit a PIP (Pediatric Investigation Plan) as part of an MAA (Marketing Authorization Application)—either because they are considered unsafe or ineffective in children, lack benefit for them, or are for conditions that affect only adults—was put into effect in the EU on July 28, 2018. All regulatory submissions are subject to this revised waiver list, and regulators will expect companies to have considered product mechanism of action and pediatric needs prior to decision.

With neonates having the highest unauthorized or off-label use of medicines across pediatrics, the EMA released a "Concept Paper on the Need for Revision of the Guideline on the Investigation of Medicinal Products in the Term and Preterm Neonate" in September 2018. The paper recommends a review of the Guideline which came into effect in 2010 (EMEA/536810/2008), and assessing PIPs covering neonates, research trends, and standards, suggesting existing guidance is not adequately addressing development and investigation of products in term and preterm neonates. It recommends the new draft guidance be available before Q4 2020.

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. 48 networks are in place (June 2019), including in the US, Canada, Japan, and in therapeutic areas where none existed 10 years ago.

The networks' support ranges from advising on the pediatric drug development strategy and study protocol development to identification of suitable study sites and support of patient recruitment.

The Clinical Trial Regulation No 536/2014, signed in April, 2014--and set to go into effect as soon as the Clinical Trials Information System (CTIS) is in place and ready to be used--is to replace the existing EU Clinical Trials Directive (EC) No. 2001/20/EC. It was created to harmonize rules for clinical trials throughout Europe. While it is not specific to just pediatric clinical trials, the Regulation is expected to have a major impact on them. Where today, drug developers are required to submit a clinical trial

application in each country where trials will be conducted, the new CT Regulation will enable them to submit part I of the application dossier through one portal for regulatory and ethics committee review. The electronic portal established with the Clinical Trials Regulation No 536/2014 will provide workspace collaboration, workflow, and document management tools, as well as a place for the public to review information on trials that may benefit them. Clinical Trials Regulation EU No. 536/2014 also seeks to improve standards of safety for children and will require consistent rules for conducting clinical trials throughout the EU.

The CT Regulation includes specific conditions to be met to perform trials in minors (information adapted to the age of child, explicit wish of the child to be respected in view of trial participation, etc.).

## Collaborating to Increase Harmonization Globally

Close collaboration between the U.S. and the EU has helped to improve pediatric clinical research significantly. ICH E11 (R1) "Clinical Investigation of Medicinal Products in the Pediatric Population," which went into effect in February 2018 for Europe and April 2018 for the U.S., aims to advance pediatric research globally with clear, 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, including:

- Ethical considerations
- Age classification and pediatric subgroups including neonates
- Pediatric formulations
- Commonality of scientific approaches for pediatric drug development programs
- Pediatric extrapolation and introduction of modeling and simulation
- Practicalities in design and execution of pediatric trials, including feasibility, outcome assessments, and long-term clinical aspects.

ICH S11 "Safety Testing in Support of Development of Pediatric Medicines" is expected to reach the final stage, Step 4, by the end of 2019.

Hoping to harmonize pediatric clinical trials globally, the ICH has issued new draft guidance urging drug sponsors to consider whether they need to conduct nonclinical safety experiments on drugs before moving to pediatric trials. The guideline, ICH S11 recommends taking an integrated, weight-of-evidence approach to nonclinical trials, considering pharmacology, pharmacokinetic, in vitro, in vivo animal, and clinical safety data to make sure no single factor is considered in isolation.

ICH E11 A "Pediatric Extrapolation Guideline" is expected to reach Step 2a by November 2020. A concept Paper was finalized in October 2017. With the Expert Working Group identified, next steps include aligning terminology and evaluating strategies for pediatric extrapolation, study designs, statistical methodologies, and modeling and simulation.

Additionally, multiple pediatric networks and advisory groups are helping to advance pediatric clinical research:

**Institute for Advanced Clinical Trials for Children (I-ACT)**, established by Critical Path Institute in the U.S. in March 2017 to optimize and accelerate biomedical innovation via child-centered clinical trial networks and collaboration with like-minded institutions, trial sponsors, and other stakeholders.

**The conect4children (c4c)** project launched on May 18, 2018 in Europe, as a collaborative pediatric network that will facilitate development of new drugs and therapies for pediatrics. It aims to enhance the competitiveness of Europe as a critical region for developing medicines for children by using existing expertise, patient access and by developing common processes to be applied to disease natural history studies, registries, and new therapies.

**International Children's Advisory Network (iCAN)**, a worldwide consortium of children's advisory groups, dedicated to giving children and families a voice in health, medicine, research, and innovation by increasing education about the importance of children's involvement. With chapters worldwide (including eYPAGNet in EU), iCAN works with CROs, like Synteract, and partners with local children's hospitals to address the needs of pediatric clinical research and healthcare and advocates for patients globally.

## Conclusion

Overall, the progress made to date in pediatric clinical research is encouraging. Future progress will certainly enable more approved drugs to be brought to market that will help to control diseases in children, as well as offer potential cures.

Collaboration of regulators and stakeholders is on the rise. The intended result is to make more pediatric medicines available to children who need them.

## About Dr. Martine Dehlinger-Kremer

*Vice President, Pediatric Development at Synteract*

Dr. Martine Dehlinger-Kremer has 30+ years of experience in the clinical research industry, including more than 28 years of progressively higher levels of Regulatory, Medical Affairs and Pediatric 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 is an observer member of the Coordinating Group of the European Network of Pediatric Research (Enpr-EMA) at the EMA and a longtime member of Working Parties of Enpr-EMA. She 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.

Dr. Dehlinger-Kremer is also President of EUCROF, the European CRO Federation.. In addition, she is an external advisor to iCAN, the International Children's Advisory Network.

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 Reims, France.

## About Synteract

Synteract is an innovative, full-service CRO supporting biopharma companies across all phases of drug development to help bring new medicines to market. Synteract has conducted 4,000 studies on six continents and in more than 60 countries, working with more than 26,000 investigative sites and 750,000 patients. It has contributed to more than 240 product approvals. Synteract offers a notable depth of expertise in oncology, general medicine, dermatology, and neuroscience indications, as well as rare and orphan, pediatric, and immunotherapy studies.

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