Improving Medicines for Children with Advancements in Paediatric Clinical Research

Much progress has been made in paediatric medication development since the implementation of paediatric legislation in the US and EU. Today, marketing authorisation for new medicines, as well as applications for modification of existing registrations under patent (such as addition of a new indication, new dosage form, new dosing regimen, new route of administration), must include paediatric assessments as described in a paediatric study plan, unless it is exempt due to deferral or waiver, or the medicine does not fall under the scope of the paediatric regulations.

How are regulatory authorities working to improve paediatric drug development? And what still needs to be done?

Historical Progress

In the US

Several regulations have governed paediatric clinical trials in the US:

- **Paediatric Use Subsection** in the Precautions Section of Product Package Inserts (21 CFR 201.57 (f)(9)) (1979), Paediatric 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 paediatrics. The FDA publishes a list of pharmaceutical products needing paediatric studies.
- **Paediatric Research Equity Act** (PREA) (2003) – requires sponsors to determine safety and efficacy of new drugs and biological agents in paediatric patients unless a waiver is granted or the product is exempt. An initial Paediatric 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.

In August 2018, the FDA published a list of molecular targets (205) substantially relevant to growth and progression of paediatric cancer as well as a list of those not relevant.

Congress reauthorised through 2020 the Rare Paediatric Disease Priority Review Voucher programme in the 21st Century Cures Act in 2016.

In the EU

Though the EU established paediatric rules later than the US, it has leveraged lessons learned from the country. One difference in the EU is that there is only one Paediatric Regulation (Regulations 1901/2006&1902/2006) covering requirements and incentives. Guidance documents are issued to ensure proper implementation of the Regulation.

Significant milestones included:

- **The Paediatric Regulation of 2006** – to facilitate development of high-quality, appropriate medicines for children without needlessly exposing them to clinical trials or deterring or delaying medicines for adults.
- In July 2007 – **the Paediatric Committee** was established, replacing the Paediatric Working Group to determine studies required for children.
- Progress of the Paediatric Regulation is reported every five years by the EMA and EU Commission. In October 2017, the European Commission report, **"10 Years of the EU Paediatric Regulation"** revealed that the Regulation's system of obligations, rewards, and incentives appeared to have had a positive impact overall.
    - From 2007–2016, over 260 new medicines were authorised for use in children through new marketing authorisations and indications, and, in 2017, there were over 1000 agreed PIPs.
    - While the Regulation has had an encouraging impact, positive results are not evenly spread among therapeutic areas. Orphan rewards do not seem to be driving paediatric development for rare diseases, for instance. The Commission will further examine challenges, with findings expected to be delivered in 2019.
- A revised and revoked class waivers list of medicines not required to submit a PIP was put into effect in the EU on July 28, 2018.

Clinical Trials Regulation No 536/2014 (signed April 2014) is set to replace the EU Clinical Trials Directive (EC) No. 2001/20/EC by earliest end 2020. It will enable drug developers to submit clinical trial applications through one portal for regulatory and ethics committee review, instead of in each country where the trial will be conducted. The Regulation includes 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.).

With neonates having the highest unauthorised or off-label use of medicines across paediatrics, 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.

Global Collaboration

In many cases, authorities are joining forces with stakeholders.

In March 2018, the EMA and EU Commission held a workshop with patients, academia, healthcare professionals, industry, and FDA representatives to discuss how to better apply the Paediatric Regulation to boost development of medicines for children.

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 paediatric medical needs
2) Strengthening cooperation of decision-makers
3) Ensuring timely completion of PIPs
4) Improving handling of PIPs
5) Increasing transparency around paediatric medicines

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

With development of the European Network for Paediatric Research at the European Medicines Agency (Enpr-EMA), a network of research networks, investigators, and centres performing paediatric trials, we have seen greater collaboration between stakeholders, networks, industry, regulators and patient/parent organisations. 48 networks are in place (June 2019), including in the US, Canada, Japan, and in therapeutic areas where none existed 10 years ago.

The Enpr-EMA networks' support ranges from advising on PIP or study protocol development to identifying study sites and supporting patient recruitment. Enpr-EMA suggests companies consider using this support to optimise PIP planning and execution to:

- Meet patients' needs with targeted and evidence-based feasibility
- Enhance product development by helping to create a relevant drug development plan
- Optimise PIP development focusing on key studies and developing a long-term strategy
- Efficiently conduct clinical trials
- Save time and money. See Consultation Diagram (Figure 1)

More information can be found in the Enpr-EMA Working group on public-private partnership Network consultation recommendation. A pilot phase for the network consultation started early 2019.

Collaboration between the US, EU, and globally has increased as well.

The guideline ICH E11 (R1) "Clinical Investigation of Medicinal Products in the Paediatric Population" aims to advance paediatric research with clear, compatible guidance specific to global product development of paediatric medicines. The addendum R1 provides clarification and current regulatory perspectives in paediatric drug development with the following added:

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

The guideline ICH S11 "Safety Testing in Support of Development of Paediatric Medicines" is expected to reach the final stage, Step 4, in June 2019.

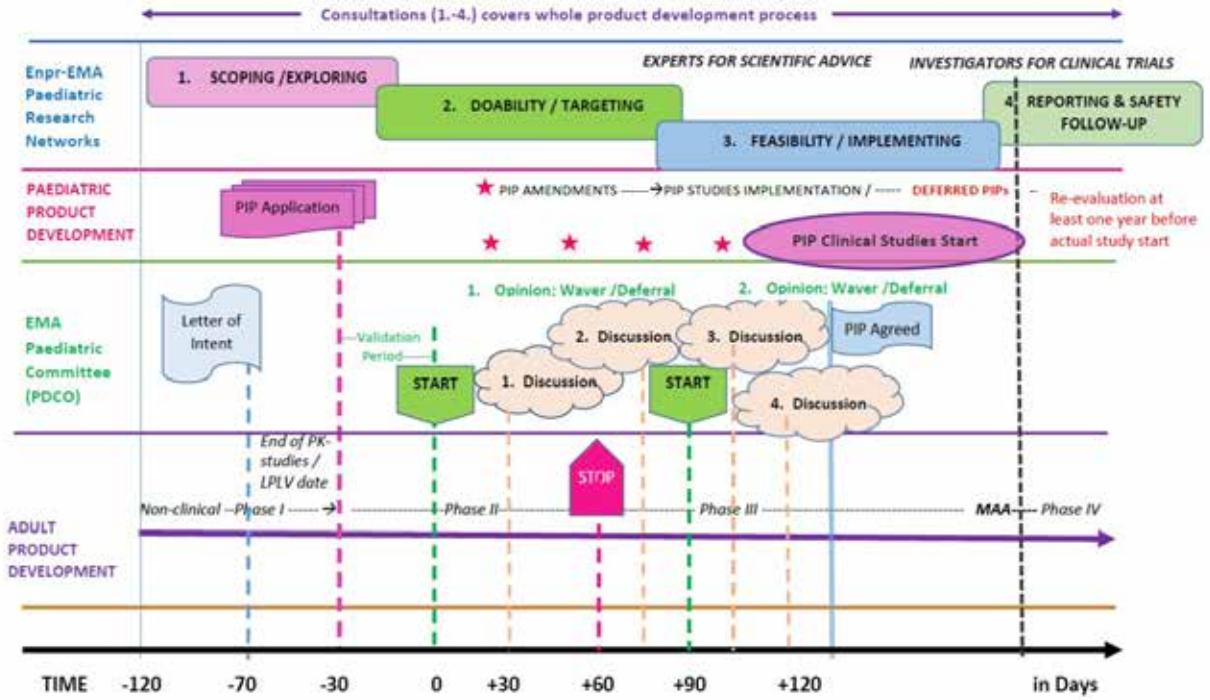

Figure 1: Consultation Diagram

Source: European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA); Enpr-EMA Working Group.

Hoping to harmonise paediatric clinical trials globally, the ICH has issued new draft guidance urging drug sponsors to consider whether they need to conduct non-clinical safety experiments on drugs before moving to paediatric trials. The guideline, ICH S11, recommends taking an integrated, weight-of-evidence approach to non-clinical 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 "Paediatric Extrapolation Guideline" is expected to be available for public comment by November 2020 (Step 2a/2b). A concept Paper was finalised in October 2017. With the expert working group identified, next steps include aligning terminology and evaluating strategies for paediatric extrapolation, study designs, statistical methodologies, and modelling and simulation.

Further initiatives include the creation of paediatric networks and advisory groups, such as:

- **Institute for Advanced Clinical Trials for Children** (I-ACT), established by Critical Path Institute in the US in March 2017 to optimise and accelerate biomedical innovation via child-centred clinical trial networks and collaboration with like-minded institutions, trial sponsors, and others.

- **The conect4children** (c4c) launched in May 2018 in the EU as a collaborative paediatric network facilitating development of drugs and therapies for paediatrics. It is a six-year IMI2 project.

- **International Children's Advisory Network** (iCAN), 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 Europe.

Other signs of EU and US collaboration include the following.

While the RACE for Children Act is US law (Title V of the FDA Reauthorization Act to amend the Paediatric Research Equity Act (PREA) (21 US Code 355c) (applicable in August 2020), the FDA and EMA collaborate on the establishment of the list of molecular targets for products to treat cancer that will no longer be exempt from PREA when having orphan drug designation. Representatives from both agencies attended a meeting in April 2018. Under Title V of the FDA Reauthorization Act, sponsors developing a new molecular therapy to treat a rare adult cancer are now required to evaluate new molecular targeted drugs or biologics in paediatrics if the molecular target is substantially relevant to the growth or progression of a paediatric cancer. The FDA has published a list of relevant targets.

Similarly, in one of the 21 actions following their March 2018 meeting, the European Commission and EMA identified a goal to establish a framework for collaboration with EMA/PDCO and the FDA's Oncology Center of Excellence to assess relevant molecular targets in paediatric cancers by December 2019.

The EU Commission and EMA also plan to enhance cluster meetings on topics and therapeutic areas requiring greater exchange of information. These monthly meetings were originally set up by the EMA and FDA in August 2007 as a forum to exchange scientific information. They were shortly after joined by Health Canada, Japan's Pharmaceuticals and Medical Devices Agency, and Australia's Therapeutic Goods Administration. Between August 2007 and March 2019, information has been exchanged on 517 products, with 172 discussions on general topics. Frequently discussed product issues include scope of paediatric product development, safety, trial design, endpoints, and study population.

The Paediatric Cluster Common Commentary tool was developed to inform sponsors of products discussed at the Paediatric Cluster, with similarities and/or differences in FDA and EMA approach summarised. An approved 1-2 page common commentary document is sent to the sponsor. Comments sent are not binding on either agency.

The agencies also set an action item to increase transparency on paediatric cluster discussions to better inform sponsors of them and share information regarding outcomes of non-product-related interactions.

Additional collaboration has also included workshops on:

- Gaucher Disease, September 2012
- EMA, FDA & HC Paediatric Pulmonary Arterial Hypertension, June 2017
- Advancing the Development of Paediatric Therapeutics (ADEPT)
  - ADEPT 1: Paediatric Bone Health, June 2014
  - ADEPT 2: Evaluation of Long-term Neurocognitive Development in Paediatrics, April 2015
  - ADEPT 3: Successes and Challenges of Performing Long-term Paediatric Safety Studies, April 2016
  - ADEPT 4: on Big Data, September 2017
- CERSI University of Maryland – Paediatric Heart Failure, October 2017

Other advancements include:

- As new trial methodologies, such as extrapolation, modelling, and simulation become more accepted, the FDA and EMA have established Paediatric Extrapolation Guidances that permit extrapolation of adult efficacy data to children through smaller, focused pharmacokinetic and safety trials.

- Involvement of children and their families in planning clinical research and medicine development is on the rise. The Paediatric Committee of the EMA (PDCO) has three patient representatives as members, and patients are participating in scientific advice procedures at EMA.

Progress Still Welcomed

However, even with these noteworthy advances, there is room for further improvement. On average, over 50% of medicines administered to children still have never been tested in this population.

PIPs do not always match the disease burden of disability-adjusted life years – a measure that combines years of life lost due to premature mortality and/or to time lived in a state of less than full health – from the World Health Organization. Mental/behavioural disorders have the highest burden (20%), but the indication is covered in only 3% of PIPs. Conversely, infectious diseases and malignant neoplasms represent a burden of only 5% but are covered in 21% and 13% of PIPs, respectively.

Diseases and cancers unique to children are often neglected. With the RACE for Children Act in the US, improvement will certainly be seen here. Other drugs with orphan drug designation will, however, continue to be exempt from PREA.

Neonates continue to be overlooked overall, as studies for this group can be challenging given the small market, fragility of patients, and trial operational difficulties such as blood draws, to name a few. Legislation has not yet been as effective at influencing drug development for these younger groups.

Legislation is needed that outlines the move from off-label to approved drug use. Both the EU and the US have made significant investments in research on off-patent medicines; despite stimulation in research, it has not yet made a significant difference in licensing.

Further support is needed once a drug enters the market. Currently, many reimbursement policies allow reimbursement of the cheapest product for a given indication and do not take into account whether that product has an approved paediatric labelling. Collaboration of all stakeholders, including health technology authorities, is needed.

What to Expect in the Future

Because legislation currently does not address all needs, it is likely more regulations will be forthcoming in the US and additional requirements or action plans will be put in place in the EU under the Paediatric Regulation, unless the latter is one day reopened.

With the current political situation in Europe, a big question is: Will Brexit go into effect? If it does come to fruition, it could be a hard Brexit with no deal, giving the UK a status of third country. The impact this could have on clinical research for paediatrics, and adults, is unknown. Will a marketing authorisation from the EU be recognised in the UK? Will drug developers need to abide by separate rules for the UK? While it is not optimal that the UK secede from the EU from a clinical research standpoint, could it shorten timelines to make drug development more attractive?

We still do not know the answers to these and other questions, and there have not been new regulatory decisions since June 2019. Regardless, one thing is certain. Paediatric development is no longer an add-on, but today, is part of drug development.

With collaboration of regulators and stakeholders, global paediatric research is on the rise. The intended result is to make certain more paediatric medicines are developed for children who need them.

Dr Martine Dehlinger-Kremer

Dr Martine Dehlinger-Kremer is VP, Paediatric Development at Synteract. She has 30 years of clinical research experience, including 28 in regulatory and medical affairs. She is observer member, Coordinating Group of Enpr-EMA at EMA; member, External Advisory Board of iCAN; chair, Paediatric Working Group by EUCROF; chair, European Forum for GCP Children Medicines Working Party; board member, EFGCP; president, EUCROF. She has contributed to global development of numerous products, including orphan drugs and biosimilars.