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No longer an option: Pediatric considerations in drug development

By Melissa Fassbender

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Ignoring pediatric considerations is no longer an option for the development of new medicines – though clinical trials in children are still not widely accepted by society, explains industry executive.

A pediatric development plan is required in the US, the Pediatric Study Plan (iPSP), and Pediatric Investigation Plan (PIP) in the EU, explained Dr. Martine Dehlinger-Kremer, VP of pediatric development at Synteract.

Pediatric regulations in the US, including the Pediatric Research Equity Act (PREA), Best Pharmaceuticals for Children Act (BPCA), and the Food and Drug Administration Safety and Innovation Act (FDASIA) have been a success, she said.

"The industry and regulators are working together to improve the research in pediatrics and ensuring medicines are developed adequately for children," added Dehlinger-Kremer.

However, orphan drugs are currently exempt from PREA requirements in the US, though the FDA Reauthorization Act of 2017 (FDARA) and the RACE for Children Act – both signed into law on August 18, 2017 –will eliminate this exemption for cancer drugs.

"In the EU, the pediatric regulation entered into force much later than in the US and has showed being a great success in respect to number of new drugs approved for children in the EU," said Dehlinger-Kremer, adding that there is *"still some room for improvement as not all PIPs are realized on time."*

The European Commission report on the state of pediatric medicines in the EU published late last year showed the encouraging effects of the pediatric regulation adopted in 2006. Though Dehlinger-Kremer said the regulation *"appears most effective when adult and pediatric needs overlap."*

"Fewer advances have been made in diseases that are unique to children. While some instances of over- or under-compensating drug developers with nancial rewards exist, overall bene ts seem to outweigh costs," she added.

According to Dehlinger-Kremer, the European Commission does not currently recommend reopening the legislation, but will instead evaluate pediatric and orphan regulations to understand better why rewards do not seem to be driving development. The report's ndings are expected to be delivered in 2019.

"Meanwhile, the European Commission and EMA have started to streamline application and implementation of the regulation, including making changes to deferrals, revisiting PIP processes and other aspects," said Dehlinger-Kremer. A revised and revoked class waivers list will be effective this month, July 2018.

The EU Commission and EMA also recently held a workshop with patients, academia, and health care professionals, discussing potential improvements to implementing the regulation. An action plan will be published later this year and commitment to implementation expected within two years.

"For pediatric research, there is close collaboration between the US and the EU," said Dehlinger-Kremer. *"This has improved research in children signi cantly, and can only bene t the populations who need the medicines."*

"Ignoring pediatric considerations is no longer an option for the development of new medicines, new indications, new dosing forms, new dosing regimens," she added.

Designing pediatric clinical trials

Still not widely accepted by society, there is often reluctance to involve children in clinical trials due to fears of harming children by exposing them to uncertain treatment effects.

As Dehlinger-Kremer, parents are often anxious about their child being treated, and whether or not they may be administered the test drug or a placebo. Additionally, she said investigators also are apprehensive of recruiting children because of the trial burdens, including an *"overwhelming amount of information"* that must be provided to the families.

"Assisting investigators to understand families' perceptions of trials and providing support will be a great step forward and improve recruitment of children in pediatric trials," said Dehlinger-Kremer.

> *"Increasingly, the importance of engaging children and families in the recruitment, consent and design of trials is a key factor."*

According to Dehlinger-Kremer, some ways to aid parents in the decision-making process include improving the readability of informed consent documents. "*When plainspoken, clear documents are oriented to children and parents, more graphical in nature for younger age groups, using infographics or pictures, it is helpful to the families and to the children,"* she said.

Additionally, while parent or guardian consent is a legal requirement for pediatric trials, Dehlinger-Kremer noted that a child's autonomy must be respected and investigators must include them in the process as much as possible, depending on age and maturation.

"Children's dissent must be respected, particularly if their dissent is different from their usual response to the same procedure in normal clinical care," added Dehlinger-Kremer. *"If the child is really afraid, the investigator cannot include them; if the parents cannot convince them, ethics guidelines do not allow it – for all groups."*

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