WRITTEN BY

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Pediatric Clinical Trials: The Need for Regulation (Part 1)

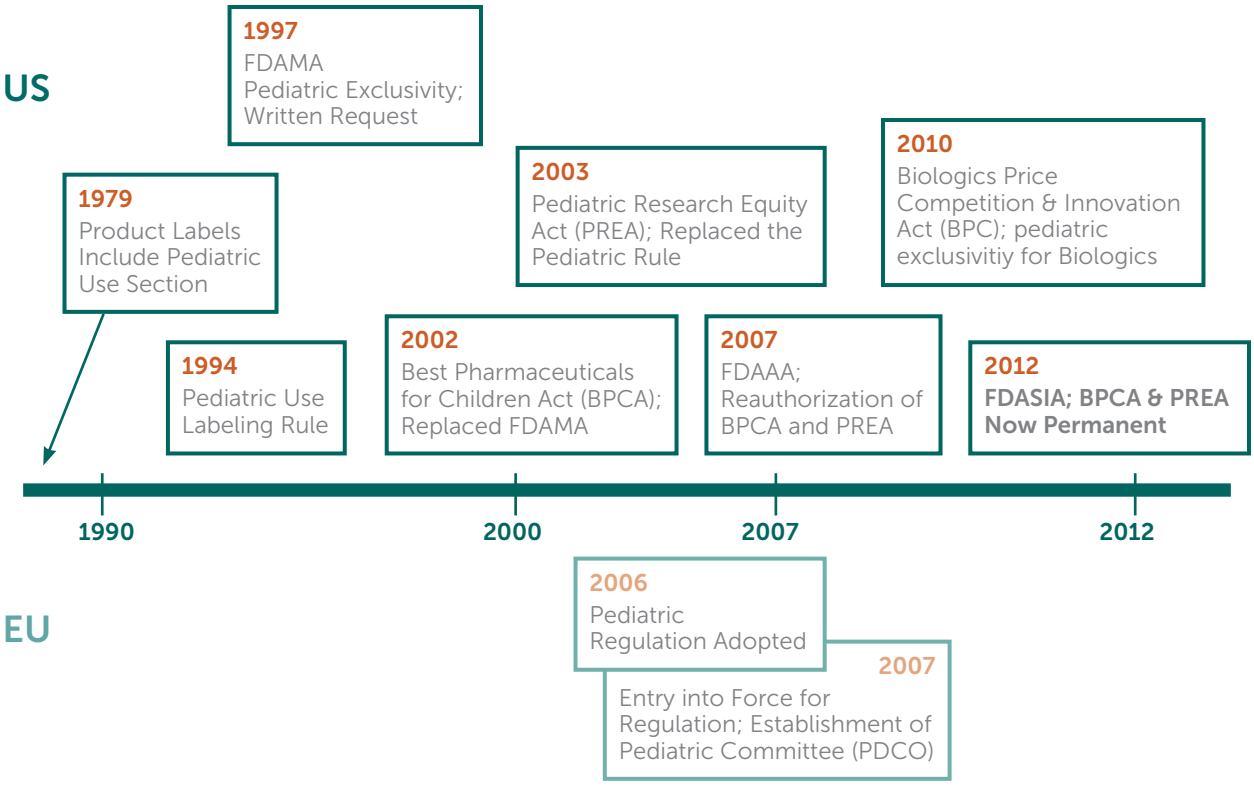
Despite the fact that some labeling for children did exist since 1979, more than 80 percent of listed medications' labels lacked prescribing information for children because most of them were being used off label. Why? Because 50-90 percent of medicines being used for children were not tested and evaluated in children. Even in hospitals, at least one third of hospitalized children and 90 percent of neonates in ICU were receiving off-label prescriptions. Needless to say, this was not a good situation due to the risks posed for ineffective under-dosing, or worse, adverse effects from overdosing. It was exceptionally hard to determine formulations for pediatric populations and this resulted in delayed access to innovative medicines for children.

But how could this problem be solved? There had been a limited number of clinical trials for children and a limited number of participants even in those trials. There was no suitable trial methodology and no real infrastructure for pediatric trials, in part due to a lack of funding for this research. All of the regulatory bodies knew this situation had to change.

Objectives for pediatric research established

Both the EU and the US had the same goals: to improve the health of children through high quality, ethical research that would increase the availability of authorized medicines for children and increase information on these medicines, without unnecessary studies being conducted on children and without delaying authorization for adults. Over time, several different rules and regulations have been in effect, with the Pediatric Regulation of 2006 and the FDASIA of 2012, which made BPCA and PREA permanent, having the greatest significance.

History of Pediatric Regulations in the US and EU



Collaboration becomes the key to improvement

Since 2007 when the EMA and FDA agreed upon collaboration and common principles of interaction, a great deal of progress has been made. A monthly teleconference to discuss product specific pediatric drug development and general scientific, regulatory and safety issues has been held. Japan PMDA and Health Canada joined, initially as observers in 2009 and 2010, respectively, and both are now active participants. Documents are exchanged through a secure link, Eudralink.

This communication does not mean that pediatric development programs will have exactly the same protocols or ask the same question or even arrive at the same regulatory decisions. However, the objectives of the exchanges are valid — to avoid exposing children to unnecessary trials and to enhance the science while decreasing the risk to children.

Where are we now – 10 years later?

Pediatric development has now become part of drug development. The proportion of clinical trials including children under 18 has increased to approximately 19 percent with about 350-400 trials per year in the EU. In the US, in 1999, 20 percent of new medicines relevant to pediatrics had pediatric information. By 2008, it was 41 percent. In the EU, by the end of 2011, 70 percent of all new medicines were included in PIPs (pediatric investigation plans).
The European Commission's first progress report on medicines for children covering the first 5 years

of its Pediatric Regulation was published in June 2013. It identified that the EMA had approved more than 600 PIPs, of which 33 had been completed. 34 percent of new medicines authorized had a pediatric indication; 72 new pediatric indications were approved for already authorized products; and 26 new pharmaceutical forms were authorized for use in children. Pediatric indications are included in 70 percent of all new medicinal products. Marketing Authorization Applications (MAAs) showed that the Pediatric Regulation, with its legal requirement to promote the development of children's medicines, had closed the gap to include new medicines with potential pediatric usage. More information is available than ever before with changes in the summary of product characteristics and package leaflets.

Transparency is enhanced. For the first time ever, results of pediatric studies are publicly available – more than 3200 reports are included in a searchable and specific database published by the EMA, with approximately 3,000 more being added over time. In addition, general information on pediatric trials being conducted is available on the European CT Register, which presents protocol-related information on all pediatric trials with investigators in the EU or anywhere in the world when the trial was part of PIP. In recent years, even neonates and infants have been included in trials. Currently 30 percent of PIPs include studies with newborns. Perhaps most important, there have been no delays in authorizations of medicines for adults due to the implementation of the Pediatric Regulation.
A new guideline on the application of PIPs was published by the Commission in September 2014 helping to create improvements and to streamline paper work. Only one PIP is now required for drugs that have applicability in more than one condition. New trial methodologies are also available, with modeling and simulation allowed. Extrapolation of data is available in a reflection paper.

While progress has definitely been made, there is still work to do. Come to the SynteractHCR **blog** for Part 2 next month!

About the Author:

Dr. Dehlinger-Kremer has more than 28 years of experience in the research industry, including more than 24 years of regulatory affairs leadership. For 19 years, she served as a vice president of International and Global Regulatory Affairs and Global Medical Affairs at various CROs headquartered in the U.S. She has also served as the chair of the Pediatric Working Group of EUCROF, and as lead member of the Pediatric Franchise at a large CRO.

About SynteractHCR:

SynteractHCR has conducted over 50 pediatric trials in 30+ countries across multiple therapeutic areas in the last 5 years alone. Over 35 percent of these trials have been in rare or orphan indications. Our pediatric specific operational and regulatory expertise gives us a clear understanding of the unique factors to consider when conducting trials with vulnerable pediatric patient populations. For more information on how we can support your pediatric drug development needs, contact Kim Martinez, Executive Director Business Development at **kim.martinez@synteractHCR.com**.

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