INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

Extrapolation: A New Tool Making Pediatric Drug Development More Feasible

The IQ Consortium is a not-for-profit organization of pharmaceutical and biotechnology companies with the mission of advancing science and technology to augment the capability of member companies to develop transformational solutions that benefit patients, regulators and the broader R&D community.

iqconsortium.org

The Clinical Pharmacology Pediatric Working Group endeavors to become "the voice of industry" for pediatric and clinical pharmacology by (i) coordinating scientific expertise and exchange; (ii) generating and providing meaningful contributions to knowledge in pediatric clinical pharmacology; and (iii) influencing the regulatory process for development of new therapies for pediatric populations.

CONTRIBUTED BY:
Sebastian Härtter (Boehringer Ingelheim)

COLLABORATORS:
Ashley Strougo (Sanofi)
S.Y. Amy Cheung (Certara Strategic Consulting)
Angela James (Astellas Pharma)

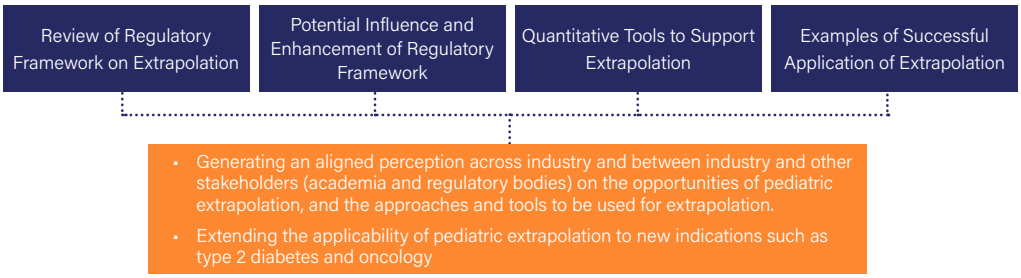
WORKING GROUP:
Jeffrey Barrett (Gates Medical Research Institute)
Dionna Green (U.S. Food and Drug Administration)
Albert J. Allen (Eli Lilly and Company)
Carlo Bello (Pfizer, Inc.)
Raafat Bishai (AstraZeneca)
Francois Bouzom (UCB Biopharma)
Christina Bucci-Rechtweg (Novartis)
Yuan Chen (Genentech, Inc.)
Nancy Chen (Takeda)
Nianhang Chen (Bristol-Myers Squibb)
Yu-Yuan Chiu (Sunovion Pharmaceuticals Inc.)
Solange Corriol Rohou (AstraZeneca)
Richard Czerniak (Takeda)
Loeckie De Zwart (Janssen)
Amit Desai (Astellas Pharma Inc.)
Günter Heimann (Novartis)
Tycho Heimbach (Novartis)
Michael Henley (Takeda)
Reza Khosravan (Pfizer, Inc.)
Masakatsu Kotsuma (Daiichi Sankyo, Inc.)
Steven Kovacs (Novartis)
Mengyao Li (Sanofi)
Jing Liu (Pfizer, Inc.)
Shailly Mehrotra (Otsuka)
Murad Melhem (Vertex)
Denise Morris (Gilead Sciences)
Kevin Krudys (U.S. Food and Drug Administration)
Andres Olivares (F. Hoffmann-La Roche Ltd.)
Apurvasena Parikh (AbbVie)
Neil Parrott (F. Hoffmann-La Roche Ltd.)
Italo Poggesi (Janssen)
Donald Sarubbi (Boehringer Ingelheim)
Birgit Schöberl (Novartis)
Edgar Schuck (Eisai, Inc.)
Bernard Sebastien (Sanofi)
Satyendra Suryawanshi (Bristol-Myers Squibb)
Kunal Taskar (GlaxoSmithKline)
Alice Tsai (Vertex)
Letizia Ubiglia (Novartis)
Linh Van (Novartis)
Konstantina Vanevski (Bayer U.S. LLC)
Jan Wahlstrom (Amgen, Inc.)
Xiaofeng Wang (Otsuka)
Larissa Wenning (Merck)
Stefan Willmann (Bayer U.S. LLC)
Guangqing Xiao (Sunovion Pharmaceuticals Inc.)
James Yates (AstraZeneca)
Ka Lai (Kelly) Yee (Merck)
Yeruk (Lily) Mulugeta (U.S. Food and Drug Administration)
Lian Zhou (Eli Lilly and Company)
Mike Zientek (Takeda)
Suzie (Xinyuan) Zhang (U.S. Food and Drug Administration)
Flora Musuamba Tshinanu (EMA MSWG (Belgium))
Yaning Wang (U.S. Food and Drug Administration)

THE CHALLENGE

Pediatric extrapolation utilizes and integrates available knowledge in adult populations ("priors"), and identifies critical gaps and uncertainties in that knowledge, to define a targeted set of required clinical data to fill the knowledge gaps for application to pediatric patients. Although the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA) and National Medical Products Administration (NMPA) have adopted the International Council for Harmonization (ICH) Guideline: E11 (R1) Addendum thereby encouraging extrapolation, good use cases were lacking and the full potential and application opportunities were not fully realized. In particular, questions of general applicability of pediatric extrapolation to a certain disease, disease similarity, and whether or not these are pertinent to the use of a new molecular entity in pediatric patients were sometimes the reason for controversial perceptions of industry, academia and even between regulatory bodies.

OBJECTIVES & APPROACH

For more than two years, the CPLG Pediatric Working Group (WG) investigated the topic of pediatric extrapolation to foster collaboration and knowledge generation and sharing between pharmaceutical industry, regulatory agencies (i.e., EMA and FDA) and academia. After initial interaction and publication on the topic, the WG decided to focus on the applicability of pediatric extrapolation to two therapeutic areas: type 2 diabetes mellitus (T2D) and oncology. The final goal was to align among key stakeholders on specific challenges and opportunities to generate a common understanding about the extrapolation concept and how to use it in a specific pediatric development strategy.



The four pillars of the extrapolation project (blue boxes) of the IQ CPLG Pediatric WG, which were pursued over the last two years aiming at the final goals (in orange box).

RESULTS

The CPLG Pediatric WG published a review on how pediatric extrapolation can be used to address challenges in pediatric drug development including examples of diseases/indications where extrapolation has been used.[1] This work was also presented at the PAGE meeting in 2018. Thereafter, the group organized a pre-conference focusing on the use of pediatric extrapolation at the ASCPT meeting in Orlando, FL in March 2018. At the meeting, a new presentation concept was used with the dialogue of a "mock" development team for a virtual T2D product, consisting of all core expert functions, including medicine, statistics and clinical pharmacology. Following the pre-conference, an ASCPT/IQ webinar on "Strategies to Address Opportunities in Oncology Pediatric Drug Development" was conducted. The CPLG Pediatric WG also presented at the IQ Symposium in March 2019, illustrating some examples of the application of extrapolation considering the pediatric dose definition.

Most recently, a manuscript summarizing the outcome of the T2DM mock team from the ASCPT pre-conference in 2018 has been published online.[2]

IMPACT

This project primarily helped to disseminate the general concept of extrapolation and clarify potential gaps in the regulatory framework via the initial publication. This publication was also timely to influence the ICH E11 Addendum dealing with extrapolation. Secondly, the project helped to define a more practical approach on how to apply the concept particularly in the two disease cluster where extrapolation initially seemed not applicable (i.e. T2D and Oncology) by a conference, a webinar and a summarizing publication integrating and aligning the view of regulatory agencies.

Employment of a "mock" development team mimicking a subject matter expert team within a pharmaceutical company was a novel approach to exemplify the obstacles in the application of extrapolation and the difficulties in harmonizing different approaches and understanding of the various team members depending on their scientific background (medical, statistics, pharmacometrics, regulatory).

The concept of extrapolation has multiple benefits. Pediatric patients might be able to avoid unnecessary tests and the availability of relevant medications may be accelerated for this fragile population. Pediatricians may be able to enlarge their pharmacological treatment options and save resources otherwise spent in unnecessary clinical trials in support of pediatric drug approval. Extrapolation can also facilitate an increase in the feasibility of pediatric development programs at pharmaceutical companies as it allows the use of prior information and relies on modeling and simulation in lieu of observed clinical data. Finally, regulators may benefit from extrapolation because this concept depends on objective and quantifiable information which may help in the assessment of an early pediatric development program as presented in a pediatric investigational plan.

[1] Barrett, J.S. et al. (2018). Challenges and opportunities in the development of medical therapies for pediatric populations and the role of extrapolation. *Clinical Pharmacology & Therapeutics, 103(3), 419-433.*

[2] Barrett, J.S. et al. (2020). Pediatric extrapolation in Type 2 Diabetes: Future implications of a workshop. *Clinical Pharmacology & Therapeutics.*