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CERSI Workshop Report: Innovative Approaches to Pediatric Drug Development and Pediatric Medical Counter Measures: A Role for Physiologically-Based PK?

Program Committee: Thomas Dowling, Jian Wang, Gil Burckart

The workshop addressed three major objectives: (1) to review current practices and application of pediatric PBPK modeling from industry, academia, and FDA; (2) to define demonstrated and potential limitations and advantages of PBPK in pediatric drug development with special attention to MCM; and (3) to assess the utility of the current PBPK methodologies and specialized software for PBPK modeling in pediatric drug development. The workshop provided an opportunity for industry, academia, and regulatory agencies to share their experience and discuss the best practices related to PBPK in pediatric drug development and pediatric MCM.

Attendance at the workshop was great. We had as many as 100 people in the room, and the online Adobe Connect audience peaked at 300 people additionally. The online audience was boosted by emails to all of the clinical pharmacy and pharmacology organizations.

Dr. Burckart gave the introduction for the workshop and reviewed the recommendations of the 2012 Clinical Pharmacology Advisory Committee related to this workshop. The primary points made by the workshop speakers were:

Vikram Sinha

- The missing piece is the link between drug concentrations and clinical outcomes
- Huge increase in PBPK review by OCP in 2013, but pediatrics is a consistent 20% of those submissions

- Reviewed the applications of PBPK that were used in pediatric submissions

- How to submit PBPK information to the FDA

- Model has to be verified in adults before it should be applied to pediatric subjects

Ine Rusten

- The advantage being the mechanistic basis which, when scientifically well founded, allows greater confidence in extrapolation outside the studied population

- Impact of the M&S exercise should determine regulatory scrutiny

    o Examples HIGH- waiver of in vivo study of CYP enzymes; MEDIUM to HIGH – predicting optimal doses; LOW – predicting plausibility for disposition parameters

- PBPK only used in 3.7% of dose investigations of PIP's as of 2014 publication

- Examples for PBPK: oftent to replace or reduce the pediatric PK study

- Confirmation that pediatric PBPK data does predict pediatric PK is needed

Jeff Barrett

- DDI is the primary use of PBPK in industry

- PBPK for pediatrics is driven by regulatory inquiry

- Industry research is exploring ROI for PBPK and pediatrics

- Incorporate maturation effect into PK model, use PBPK-PD model when possible to account for pediatric PD effects, use an adaptive approach to refine the model with pediatric data.

- Request for regulatory input as to what "purposes align best with each approach based on the availability of certain data types"

- Both PBPK and PopPK are complimentary and can be used to refine each other, depending on the purpose.

Lippert

- Rivaroxaban example in pediatrics was presented

- "Agencies could develop an across-industry knowledge base of priors for future data interpretation and predictions!"

Parrott

- Oseltamivir example of the use of PBPK for inter-species scaling

Watt

- Inability to conduct studies in "normal" pediatric patients leads to wide variability in observed plasma concentrations.

- This variability is amplified in premature infants

Panel 1

- The panel discussion was started by short presentations by Dr.'s Dionna Green and Jiang Liu of the Office of Clinical Pharmacology.

- An excellent panel discussion was conducted with Dr. Dionna Green as the moderator. Although 4 panel questions were formulated, the discussion never made it beyond question #1.

- Rostami: None of the data generated for the PBPK model is useless; it is all important information.

Panel 2

- D. Jian Wang led off the panel session with a short presentation on the experience with drug development in neonates.

- An excellent discussion was moderated by Dr.'s Thomas Dowling and Sander Vinks.

- Barrett: we should consider premies/neonates a continuum rather than a "special population".

NEXT STEPS

A discussion following the workshop with the leadership in the FDA's Office of Clinical pharmacology was held, and the next steps for the workshop issues were considered to be:

- Publish what are the appropriate constituents of a study that supports PBPK predicts pediatric PK in the age group under 2 years of age

- Complete analysis of what was used in successful and failed trials to determine dose in neonates/infants

- Is there an opportunity for us to build a knowledge base of prior information (including inter-species scaling) so that every PBPK model is not just a "one off" exercise that has no usefulness for the future?

- Validation of pediatric models? Is this the same as the first note?

- PANEL 1: Ontogeny is still a question (Bruno-Davis). Should we summarize data available and the need for more in vivo ontogeny information?

- With Pediatric Study Plans, we can identify all drugs which will have studies in <2 yo. Should we track those drugs so that we can have input into dose selection and optimization?