Session 6 (Biopharmaceutics and Clinical Pharmacology Considerations) breakout discussion topics

Topic A. Approaches to assure ongoing quality/equivalence of pediatric products and Implications for extemporaneous formulations

Moderator: Shirley Seo, Lucy Fang, and Jack Cook

What comments do you have on the suitability of the following methods to assure ongoing quality/equivalence of pediatric products (e.g. for pediatric products undergoing a SUPAC change):

In vivo bioequivalence in adults

Biowaiver based on adult BCS

In vivo bioequivalence in pediatric population

Biowaiver based on pediatric BCS

What are the advantages/disadvantages in employing extemporaneous formulation in pediatric clinical research?

A manufacturer indicates that a pediatric formulation cannot be manufactured, such that the manufacturer proposes extemporaneous compounding of a clinical trial formulation. What evidence should the manufacturer provide to indicate that a product cannot be manufactured?

Apple sauce is not readily available in all parts of the world. For formulation in food, what specific alternatives are there to apple sauce (e.g. other mashed food alternatives)?

Topic B. Utility of PBPK modeling to facilitate pediatric drug development

Moderator: Tycho Heimbach

When should PBPK modeling be conducted for pediatric populations?

Should a PBPK model be qualified in adults before attempting to predict pediatric populations? How (i.e. methodology and criteria) would a model be qualified?

What drug input parameters and physiological systems parameters are required?

What non-drug-specific system physiology parameters are unknown?

Under what circumstances does PBPK modeling offer advantages in pediatric drug development compared to conventional approaches? In such situations, in what way are these tools adequate or need further refinement?

When are empirical models best used?

What parameter sensitivity analyses should be conducted to inform clinical trials and health authority requests?

Can PBPK be used to evaluate ethnic differences/sensitivities and PK or PD?

It sometimes is critical to achieve dosing accuracy in the clinic, especially for neonates and infants; what best practices do you recommend for dosing accuracy?

Topic C. Pediatric BCS

Moderator: James Polli

Regarding pediatric BCS, for which pediatric ages, if any, is the adult BCS adequate for biowaiver of pediatric products? With an eye towards a pediatric BCS to allow for biowaiver of pediatric products, suggest attributes and test methods for a pediatric BCS. What research is necessary for the development of a pediatric BCS?

Assume a pediatric BCS is developed and differs from the adult BCS and that it is more restrictive (i.e. adult BCS allows more biowaivers than pediatric BCS across same drugs). For a compound/product that meets the adult BCS biowaiver criteria, but does not meet it for the pediatric BCS biowaiver criteria, how should bioequivalence be established?

- In the case of a drug that fails to meet pediatric BCS criteria but meets adult BCS criteria, doing an in vivo BEstudy in adults would not add assurance for equivalence in pediatric population. By meeting adult biowaiver criteria, BE in adults is demonstrated. However, requiring an in vivo BE study in adults would unnecessarily be subjects at risk with no gain in knowledge.

- If a BE trial must be done in a pediatric population, consider that it would likely be done in patients who would receive benefit. This design would likely mean a significant duration of treatment in a pediatric BE trial (or some kind of extension trial).

Literature references

Topic A. Approaches to assure ongoing quality/equivalence of pediatric products and Implications for extemporaneous formulations

Batchelor HK, Fotaki N, Klein S. Paediatric oral biopharmaceutics: key considerations and current challenges. Adv Drug Deliv Rev. 2014. 73:102-26. doi: 10.1016/j.addr.2013.10.006.

Topic B. Utility of PBPK modeling to facilitate pediatric drug development

C Wagner PZ, Y Pan, V Hsu, J Grillo, SM Huang, Sinha, V. 2015. Application of Physiologically Based Pharmacokinetic (PBPK) Modeling to Support Dose Selection: Report of an FDA Public Workshop on PBPK. CPT Pharmacometrics Syst Pharmacol 4:226-230.

H. M Jones, Y. Chen, C. Gibson, T. Heimbach, N. J Parrott, S. Peters, J. Snoeys, V. V Upreti, M.Zheng and Stephen Hall, PBPQ IQ Consortium Expert White Paper, PBPK modelling in drug discovery and development: A cross pharmaceutical industry position, Clin Pharmacol Ther. 2015 Mar; 97(3):247-62. http://www.ncbi.nlm.nih.gov/pubmed/25670209

Topic C: Pediatric BCS

Gandhi, S., Rodriguez, W., Khan, M., and Polli, J.E. (2014): Considerations for a Pediatric Biopharmaceutics Classification System (BCS): Application to Five Drugs. DOI: 10.1208/s12249-014-0084-0. AAPS PharmSciTech. 15:601-611.

The following two reports are available from https://bpca.nichd.nih.gov/collaborativeefforts/initiatives/Pages/index.aspx

Intra-Agency Agreement Between the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the U.S. Food and Drug Administration (FDA) Oral Formulations Platform—Report 1

Inter-Agency Agreement Between the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the U.S. Food and Drug Administration (FDA) Final Report