Clinical Considerations in Pediatric Drug Product Development from an Industry Perspective

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Agenda

As a background for the Clinical break out sessions:

- Clinical Program (establish safety and efficacy)
- Clinical Pharmacology support
  - Doses and Strengths
  - Formulation

Clinical Program

A. Specific pediatric indication(s) different from adult indication(s)
   - evidence from adequate and well-controlled investigations in pediatrics
   - full (pediatric) development program – e.g. Phase 2 and 3 trials

B. Same indication(s) approved for adults but not directly extrapolatable (Partial Extrapolation)
   - prior disease and exposure-response knowledge from studies in adults and relevant pediatric information to design new pediatric studies
   - Confirmatory evidence from adequate and well-controlled investigations in pediatric populations to support the same indication(s) approved for adults. Typically a single efficacy/safety trial that may or may not be adequately powered.
   - Currently most common pathway

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FDA, Guidance for Industry: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products. 2014. https://www.fda.gov/media/90358/download

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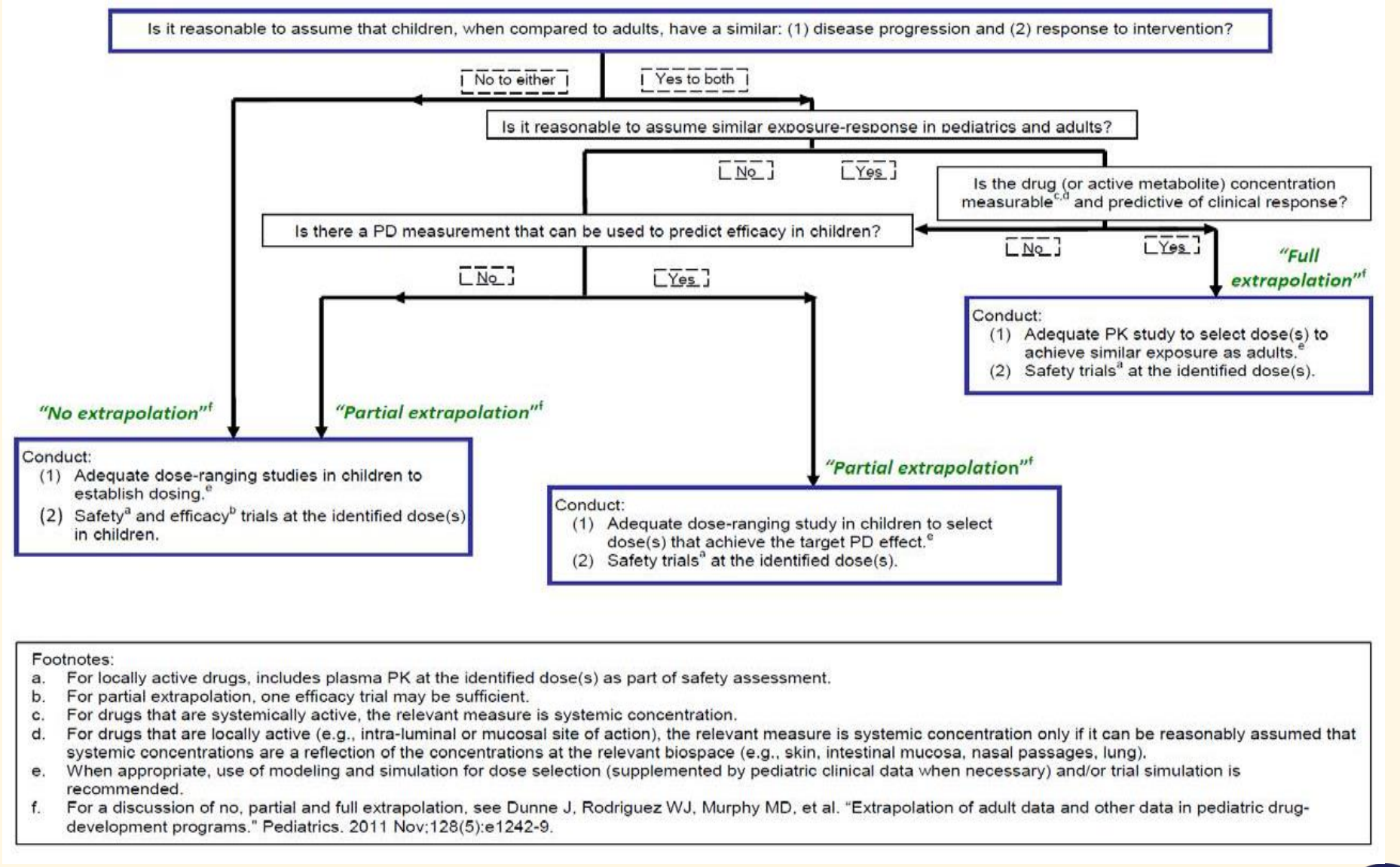
Clinical Program (Cont.)

C. Same indication(s) approved for adults and directly extrapolatable (Full Extrapolation)
   - Assumption: course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to permit extrapolation of the adult efficacy data to pediatric patients (Dunne, Rodriguez et al. 2011).
   - Typically a single pediatric study to determine a dose in the pediatric population that provides a drug exposure similar to the exposure that is effective in adults.
   - If there is a concern that exposure-response relationships might be different in pediatric patients, studies relating blood levels of drug to pertinent pharmacodynamic effects other than the desired clinical outcome (exposure-response data for both desired and undesired 100 effects) for the drug in the pediatric population might also be important.

Dunne J, Rodriguez WJ, Murphy MD, Beasley BN, Burckart GJ, Filie JD, Lewis LL, Sachs HC, Sheridan PH, Starke P, Yao LP. Extrapolation of adult data and other data in pediatric drug-development programs. Pediatrics. 2011 Nov;128(5):e1242-9. doi: 10.1542/peds.2010-3487.

FDA, Guidance for Industry: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products. 2014. https://www.fda.gov/media/90358/download

Pediatric study decision tree.



Footnotes:

a. For locally active drugs, includes plasma PK at the identified dose(s) as part of safety assessment.
b. For partial extrapolation, one efficacy trial may be sufficient.
c. For drugs that are systemically active, the relevant measure is systemic concentration.
d. For drugs that are locally active (e.g., intra-luminal or mucosal site of action), the relevant measure is systemic concentration only if it can be reasonably assumed that systemic concentrations are a reflection of the concentrations at the relevant biospace (e.g., skin, intestinal mucosa, nasal passages, lung).
e. When appropriate, use of modeling and simulation for dose selection (supplemented by pediatric clinical data when necessary) and/or trial simulation is recommended.
f. For a discussion of no, partial and full extrapolation, see Dunne J, Rodriguez WJ, Murphy MD, et al. "Extrapolation of adult data and other data in pediatric drug-development programs." Pediatrics. 2011 Nov;128(5):e1242-9.

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Clinical Pharmacology Facilitation of Formulation Development

- Typically 2 objectives:
  - First: Estimate doses for pediatric subjects (helps choose formulation strengths)
  - Then possibly: Do necessary characterization
    - If enabling formulation used in clinical trials, establish BE of commercial formulation.
    - Estimate relative BA versus adult formulation
    - Estimate effect of food (or show what foods don't have a clinically important effect on PK).

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Clinical Pharmacology – Doses & Strengths

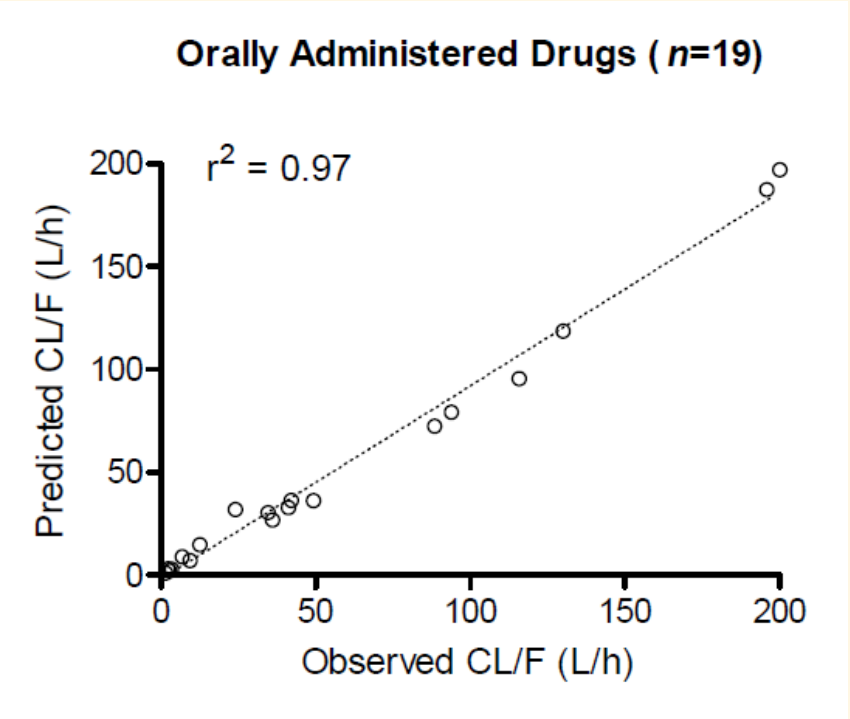
- Typical Groups to Consider

  ≥1 month to <6 months
  6 months to <24 months
  2 years to <6 years
  6 years to <12 years
  12 years to <17 years

- Not every program considers every group
  - Many disease do not manifest or can't be diagnosed until a certain age.
    - Waivers of studying certain groups can be granted.

- All paradigms (full development or extrapolation) typically start with an assumption that need to matching adult efficacious exposures in pediatrics.

Clinical Pharmacology – Dose Estimation



Lily Mulugeta, Pharm.D, Adolescent PK Studies Under PREA and BPCA. FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology Meeting March 14, 2012, National Harbor, MD

Good News

- Adult exposure typically predictive of efficacy
- Predict adolescent doses well, other groups typically adequately
- Predicted CL= Adult CL * (adolescent wt/70kg) $^{0.75}$
- Approved adult and adolescent drug dosing is equivalent for
- 94.5%of products with an adolescent indication studied since the FDA Amendments Act of 2007.

Challenges for Dose Strengths

- Dose range over typical weights from 0 to 18 yrs is about 10 fold (given a single dose level for adults)

Momper JD, Mulugeta Y, Green DJ, Karesh A, Krudys KM, Sachs HC, Yao LP, Burckart GJ. Adolescent dosing and labeling since the Food and Drug Administration Amendments Act of 2007. JAMA Pediatr. 2013 Oct;167(10):926-32. doi: 10.1001/jamapediatrics.2013.465

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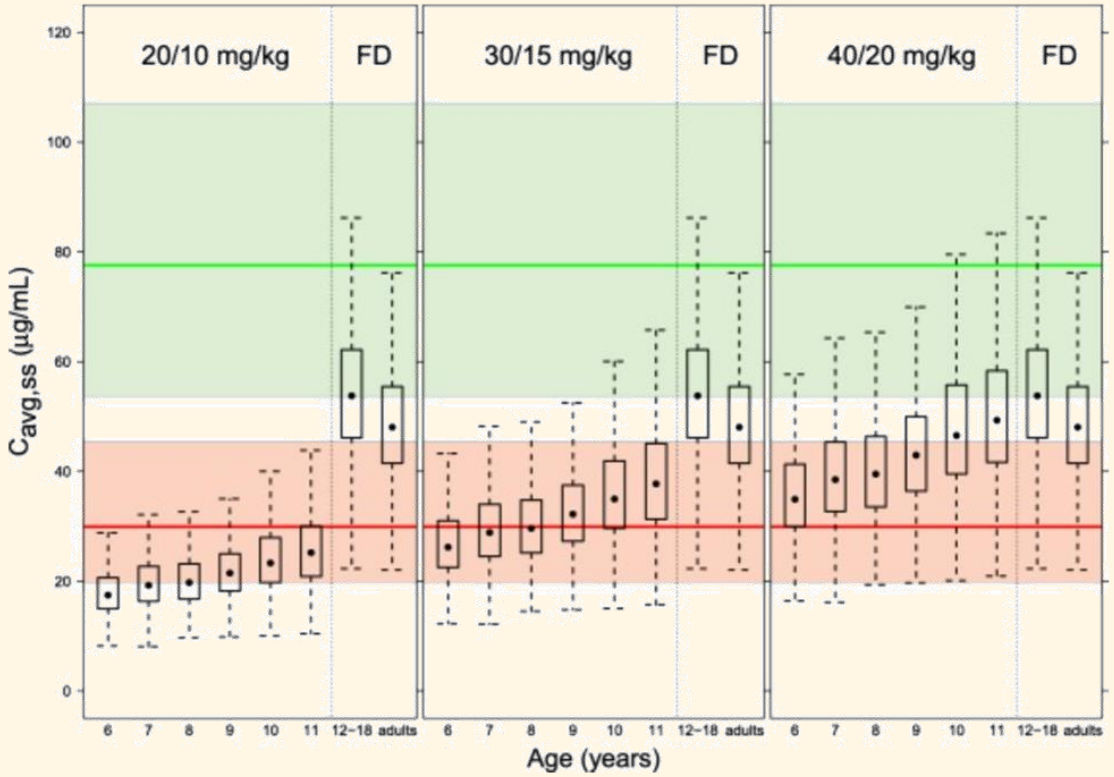
Clinical Pharmacology – Dose Estimation (Can select strengths through simulation)



The distribution of average concentrations within a dosing interval at steady-state ($C_{avg,ss}$) with different dosing regimens across the age ranges to be studied in the phase III study. Each panel shows a dosing regimen in children compared to the fixed dosing (FD) regimen in adults of 1,680/840 mg. Left: 20/10-mg/kg; middle: 30/15-mg/kg; and right: 40/20-mg/kg. Distributions of $C_{avg,ss}$ after the low dose (pink) and high dose (green), as observed in the phase II study,6 are shown in the background, with the line indicating the median and the shaded area indicating the 95% prediction interval.

Tammara BK, Harnisch LO. Dose Selection Based on Modeling and Simulation for Rivipansel in Pediatric Patients Aged 6 to 11 Years With Sickle Cell Disease. CPT Pharmacometrics Syst Pharmacol. 2017 Dec;6(12):845-854. doi: 10.1002/psp4.12263.

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Clinical Pharmacology – Dose Verification

- Dose selection is typically confirmed via dosing in efficacy/safety trial
- Often done in a sequential manner – oldest group first then going to younger groups when dose is confirmed
- Often done in a subgroups (initial 6 or more patients in each age group) when larger efficacy trials are needed.
- This is typically done in the study noted in the terminal box presented earlier in the pediatric study decision tree.

Clinical Pharmacology

Ethical Considerations

- For IRB approval of a clinical investigation under 21 CFR 50.52, an **enrolled child must have a prospect of direct clinical benefit** from administration of the investigational product. Thus, only patients with a therapeutic need for the investigational drug product can be enrolled in such trials. **Consequently, healthy pediatric subjects (i.e., without a disorder or condition which is the focus of the research) cannot be enrolled in clinical pharmacology studies** absent a determination by the Commissioner, after consultation with a panel of experts in pertinent disciplines and opportunity for public review and comment, that the conditions in 21 CFR 50.54 (which allows clinical investigations to proceed that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children) are met.
- So even in the full extrapolation model (efficacy proven by adult data) … one does the PK in a small efficacy trial so pediatric patient receives benefit

The BIG question: What formulation to use in efficacy trials?

Market Image or Commercial Formulation

- Pros
  - No Biopharmaceutic risk
  - No bridging BA/BE studies needed
- Cons
  - Requires large lead time and significant advance planning
  - Upfront cost for product development

Enabling Formulation

- Pros
  - Minimal upfront development cost
  - Commercial age appropriate formulation development can be staged
  - Shorter lead time
- Cons
  - More biopharmaceutic risk
  - Will need eventual BA/BE study for the commercial formulation.

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Purohit, V.S., Biopharmaceutic Planning in Pediatric Drug Development, AAPS Journal, 14 (3), 2012.

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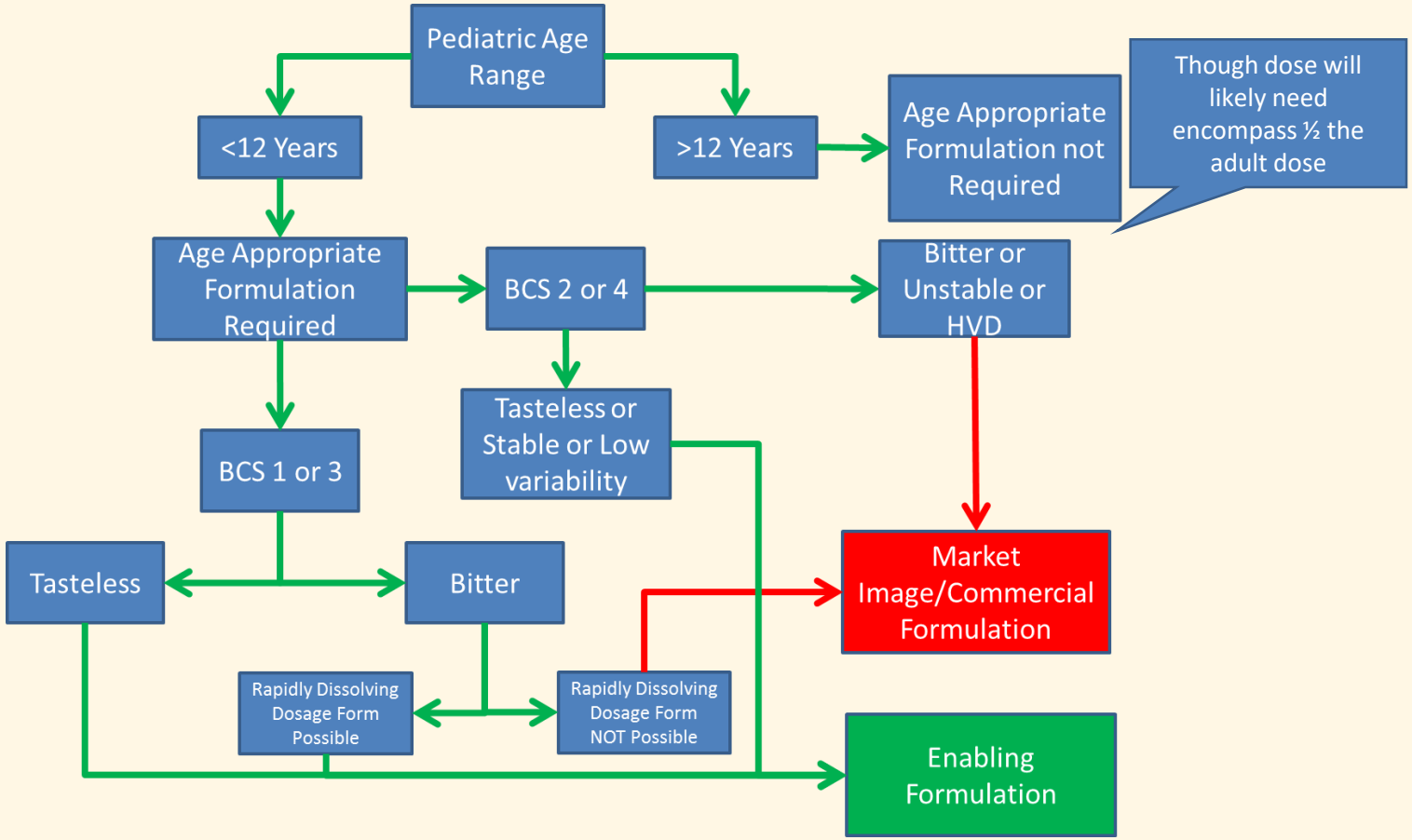
A Decision Tree for Pediatric Formulation Choice Strategy

Consider drug's properties to help make the decision:



Cook, J and Purohit, V. Biopharmaceutical Considerations in Pediatric Formulation Development. Challenges and Strategies to Facilitate Formulation Development of Pediatric Drug Products. M-CERSI, University of Maryland workshop, Hyattsville, MD, June 9th, 2016.

Clinical Pharmacology - Characterization

- BE, relative BA and food effect studies are done in adults
  - Assumption is that the relative performance stays constant across age groups.
- (Personal Note with respect to food trials): Consider that applesauce and chocolate pudding are not routinely available in a significant number of countries world wide.
  - We need a better approach to declare what foods can be given with products

Summary

- The clinical development plan is typically limited (extrapolated pathways) for pediatrics – Less time for formulation development
- Modeling and simulation are effective for predicting pediatric dose range and can aid in selection of formulation strengths
- Compound characteristics can be used to decide on the type of formulation (commercial vs enabling) used in efficacy trials.
- Relative BA, BE, etc studies are done in healthy adults. Any trial involving children must have a prospect of direct clinical benefit