Challenges and Strategies to Facilitate Formulation Development of Pediatric Drug Products

Biopharmaceutical Considerations in Pediatric Formulation Development

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Questions for Pediatric Drug Development

- How can we use the BCS system to quantify the biopharmaceutic risk during pediatric drug development?
- Can we use data collected during the conduct of pediatric studies to confirm what we know about the biopharmaceutic performance of the drug in adults?
- When should we reconsider the BCS classification of a drug for pediatrics?

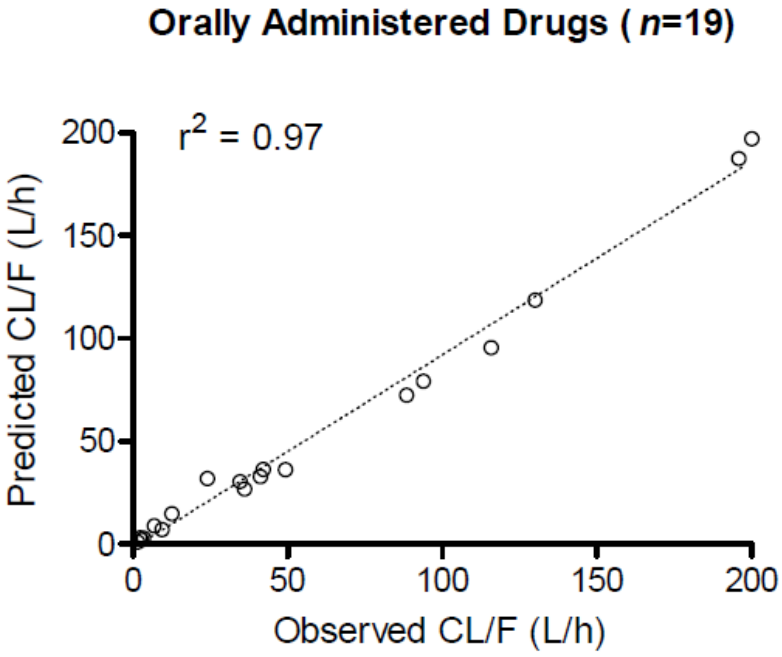
Typically - 2 Objectives

- Initial: Predicting doses in order to develop a pediatric formulation that results in similar exposures in pediatric patients as the adult formulation does in adult patients
  - FDA survey found that Extrapolation of efficacy from adult data occurred for 82.5% of the drug products

    (Dunne,W.J. Rodriguez,M.D.Murphy, B.N. Beasley,G.J. Burckart, J.D. Filie, L.L. Lewis, H.C. Sachs, P.H. Sheridan, P. Starke, L.P. Yao, Extrapolation of adult data and other data in pediatric drug-development programs, Pediatrics 128 (2011) e1242–e1249.)

- Subsequent: Demonstrate bioequivalence of pediatric formulations to a reference

Initial – Predicting Dose



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) $^{0.75}$

Challenges

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

Market Image Vs Enabling Formulations.

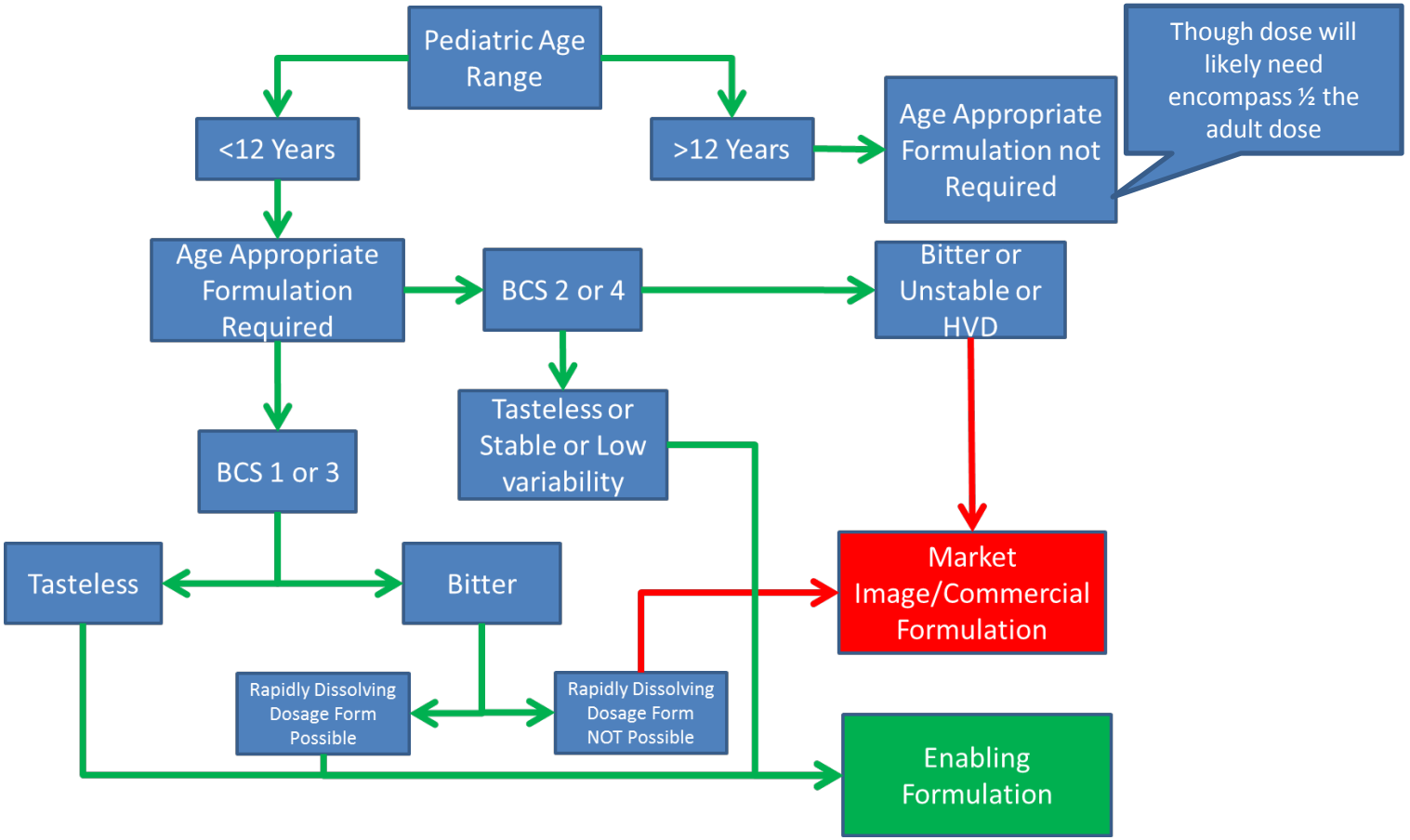
Market Image or Commercial Formulation

- 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.

Decision Tree for Pediatric Formulation Choice Strategy



What next?

- Market image/commercial formulation used during pediatric development – straight forward.
- Enabling formulation used during pediatric development – will require bridging using clinical study or biowaiver argument based on BCS.

Scientific Necessity in Children

- Children should only be enrolled in a clinical trial if necessary to answer an important scientific question:
  - Determine the type and timing of clinical studies required for establishing "safe and effective" pediatric use of drugs, biologics and devices

- Children should only be enrolled if essential (i.e., no other option, whether animal or adult human)

Minimize Risks and Equitable Selection [US 21 CFR 56.111(a)(1) and (b)]
Adapted from Office of Pediatric Therapeutics (Michelle Roth-Cline, MD)

Clinical Bridging Studies for Pediatric Formulations

- Usually done in adult healthy volunteers
- BE in pediatric is implied: if it is BE in adults it will be BE in peds.
- Question often asked: Is demonstration of BE in adults applicable to pediatric populations?
- Concrete data difficult to find.
- BA/BE studies in pediatric populations are not feasible from an ethical perspective.
- Estimation of bioavailability or relative bioavailability possible in pediatrics if PK data on formulations of interest is collected.

AAPS, 2011, Poster # R6349

What About Biowaiver: Is BCS Appropriate for Pediatrics?

- Peds Vs Adults differ in: dose, volume of liquid consumed, gi physiology, transit times, permeability etc.
- Hence, the same BCS assumptions (critical values) may not apply for pediatrics.
- BCS 1 and 3 drugs which are eligible for biowaiver are likely most impacted.

Great area for more research

Summary

- Biopharmaceutical characteristics can help one decide whether to start with the market image or an enabling formulation
- If there are questions regarding the applicability of extrapolating BCS or adult BE to a pediatric population, it may always be better to take the time to develop the market image.