Preclinical In Vivo, Clinical PK, PK/PD Tools to Assess Food and Vehicle Effects

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CHALLENGES AND STRATEGIES TO FACILITATE FORMULATION DEVELOPMENT OF PEDIATRIC DRUG PRODUCTS

June 9, 2016

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I am an employee and share-holder of Merck & Co.

The comments presented are my own and not meant to represent those of Merck & Co.

Agenda

- ***Introduction***
- Preclinical in vivo tools
- Clinical tools
- Modeling and simulation tools
- Regulatory issues
- Summary and conclusions

Introduction: de-risking food, vehicle effects

- Approaches differ for formulations that are not mixed with a food vehicle versus formulations that require mixing with a food vehicle
- Formulations that can be taken as is or with water
  - Solutions, suspensions, orally dispersible tablets, chewable tablets or gums
- Multiparticulate formulations that must be taken with a food vehicle
  - Granules, “minitabs”
- Approaches differ for BCS Class I/III drugs versus BCS Class II/IV drugs

Products that are not mixed with a food vehicle prior to administration

- *BCS Class I*
  - May be possible to waive in vivo clinical oral bioavailability (BA) as well as food-effect (FE) studies
  - May need to consider an in vivo BA study for Class I drugs if adult and pediatric formulations have dissimilar (f2<50) dissolution profiles
- *BCS Class II/III/IV*
  - May be necessary to conduct an in vivo study in adult subjects comparing oral BA of adult versus pediatric formulation
  - Should characterize FE; usually in adult subjects

Is a separate FE study needed for a pediatric formulation?

Depends on whether FE observed with adult formulation

No clinically significant FE with adult formulation	Clinically significant FE with adult formulation
• Should not be necessary to conduct a FE study on pediatric formulation	• Consider conducting a FE study with pediatric formulation • May also consider evaluating meals with differing calorie content

Products that require mixing with a food vehicle

- Vehicles include applesauce, yogurt, pudding
- Pharmacokinetic (PK) studies in adults can evaluate drug BA when the pediatric formulation is mixed in the vehicle
  - The minimum amount of food vehicle should be used (e.g., 1 tsp or 5 mL of applesauce)
  - It may be advisable to determine drug BA in the pediatric formulation under fasting conditions
- Mixing with the food vehicle in adult PK studies should mimic the pediatric administration process
  - This will facilitate the ability of PK/PD modeling to predict dosing for pediatric PK and Phase III studies

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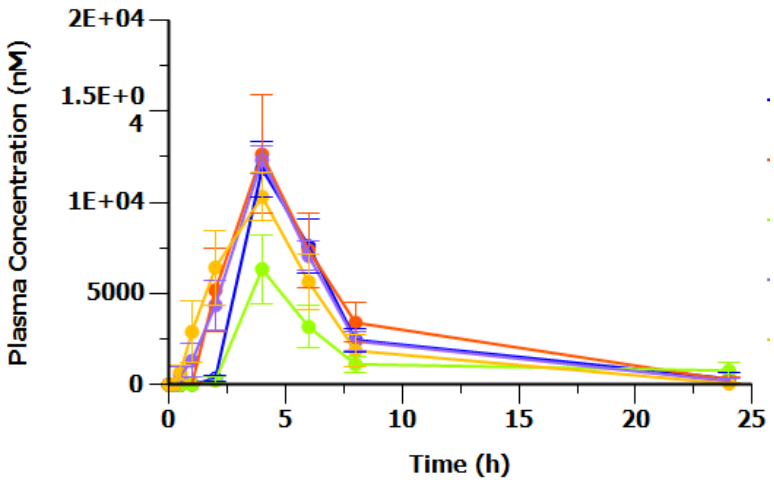
Use of preclinical in vivo studies for evaluating pediatric formulations

- The dog model is useful for several reasons
- Can quickly and efficiently screen a variety of conditions in a small number of dogs
  - Optimize amount of coating for taste masking
  - Optimize other formulation processes
  - Compare BA when formulation is given in the fasting state versus mixed in a food vehicle
  - Screen a number of different food vehicles
- Multiparticulate formulations can be administered with minimal stress
- Dosing can be completed within 10-20 seconds per dog

Results of a dog PK study of a pediatric oral formulation

15% coating + vehicle
15% coating, fasted
20% coating, fasted
Uncoated, fasted



	AUClast Ratio	AUC0-8hr Ratio	Cmax Ratio
15% coating / uncoated			
Drug A	1.14	1.05	1.02
Drug B	1.11	1.05	1.03
20% coating / 15% coated			
Drug A	0.45	0.40	0.52
Drug B	0.91	0.79	0.89
15% coating, given with vehicle / 15% coating fasted			
Drug A	0.81	0.82	0.94
Drug B	0.88	0.79	0.84

- The uncoated formulation and 15% coating provided comparable exposure in dogs when dosed in fasted state, while the exposure of 15% coated formulation was more variable
- The exposure in 20% coated formulation for Drug A was about half of that in 15% coated formulation. The exposure of Drug B was also lower in 20% coated formulation but to a much less extent.
- The exposure of Drug A and Drug B in 15% coated formulation when co-dosed with a small volume of food vehicle is considered comparable to that dosed in fasted state.

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Clinical tools for evaluating *BA* of pediatric formulations: general considerations

- PK studies characterizing drug BA from a pediatric formulation are generally conducted in adults
- Studies generally designed as single dose, randomized, crossover
  - Compare BA from adult formulation versus pediatric formulation
  - Provide data for PK/PD modeling to predict doses in pediatric PK and Phase III studies
- What if the BA from the pediatric formulation differs significantly from that of adult formulation?
  - May be necessary to dose-adjust for pediatric studies
  - May be necessary to reformulate

Clinical tools for evaluating *food* effects: general considerations

- FE on drug PK is initially characterized in healthy adult subjects
  - Single-dose, randomized, crossover studies comparing drug given in fasted state versus drug given with food
- May be necessary to investigate FE on pediatric formulation
  - To answer questions about whether FE on drug BA differs with the pediatric v adult formulation
  - To provide data for pharmacokinetic / pharmacodynamic (PK/PD) modeling to predict doses in pediatric PK and Phase III studies

Clinical tools for evaluating *vehicle* effects: general considerations

- BA studies can be conducted in healthy adult subjects
  - Single-dose, randomized, crossover design
- Can compare drug BA from adult formulation versus BA from pediatric formulation given in the dosing vehicle
  - Should design to dose pediatric formulation in the same manner as will be used in PK and Phase III studies in pediatric patients
  - Will provide data for PK/PD modeling to predict doses in pediatric PK and Phase III studies

Case 1: design of a BA study for a pediatric formulation

Formulation

- Must be given in a dosing vehicle
- No clinically significant FE on drug substance

Study objectives

- To characterize BA in adults of pediatric formulation in dosing vehicle
- To assess palatability

Assessing palatability

- One approach is to compare coated versus uncoated pediatric formulation
- Administer questionnaire to subjects

Case 1 (continued)

Study design

Randomized, single-dose, open-label, crossover, three-period, three-treatment study in healthy adult subjects

Treatments

Treatment 1	Adult formulation
Treatment 2	Pediatric formulation, uncoated, in dosing vehicle
Treatment 3	Pediatric formulation, coated, in dosing vehicle

Case 2: clinical BA study program for a pediatric formulation

Initial study compared BA of pediatric formulation in dosing vehicle versus adult formulation

Results showed that BA from pediatric formulation differed significantly from that of adult formulation

Were these differences due to dosing vehicle or to formulation?

Subsequent studies compared BA under fasting conditions and in two different vehicles

Results suggested that BA differences were due to formulation

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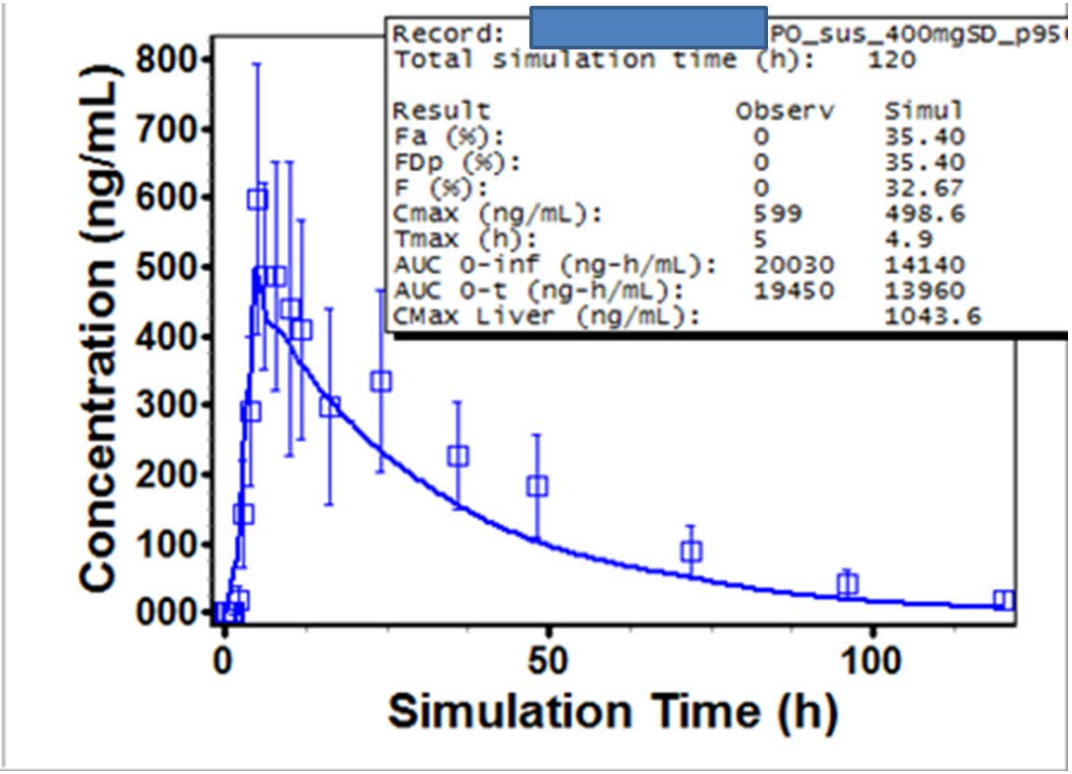
Applications of modeling and simulation in pediatric drug development

To characterize the impact of in vitro dissolution data on human PK	To use PK/PD modeling to guide pediatric PK and Phase III studies	As an alternative to running a PK study in some situations
• Can use to project plasma drug concentrations to more effectively design BA studies in adults	• Based on results of a PK study in adults to compare BA from adult and pediatric formulations	• Both PK/PD and physiologically-based PK (PBPK) modeling approaches are useful, depending on the situation

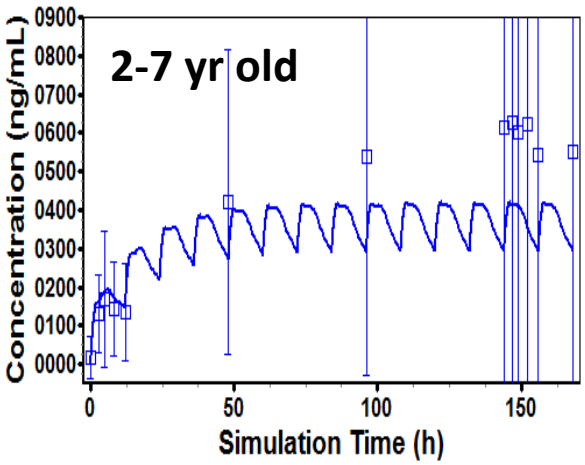
Can PBPK modeling be used to describe a formulation intended to be dosed with food in pediatrics?

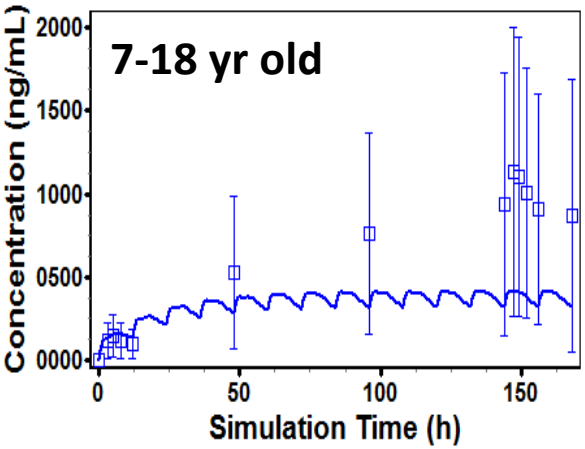


- BCS II compound
- Compound dosed with food in adults
- PBPK model successfully developed to describe fed state administration in adults

Can PBPK modeling be used to describe a formulation intended to be dosed with food in pediatrics?

Fasted simulation underpredicts exposures in both age groups

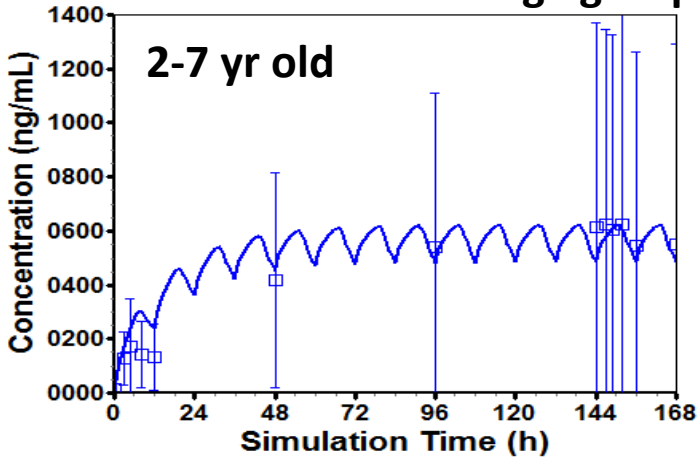


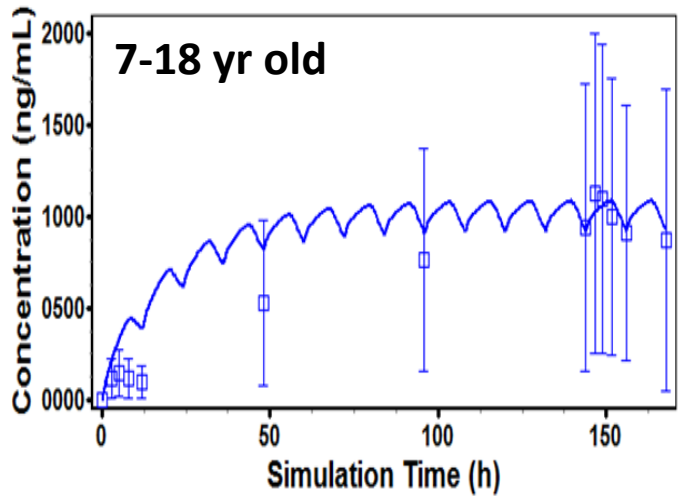


Intermediate-fed model (average of fasted/fed physiology)

High-fat model – similar to adult model

Fed state simulation requires different model for each age group





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Regulatory issues

Teams should seek agency feedback throughout the Pediatric Study Plan (PSP) and Pediatric Implementation Plan (PIP) processes with the FDA and EMA, respectively

It is important to obtain regulatory guidance on how to generate safety / efficacy data during Phases IIB and III with / without food, to support the final product labeling statements

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Summary and conclusions

- Preclinical in vivo studies provide a tool for screening formulations, food effects, and vehicle effects prior for improving clinical trial design
- Clinical in vivo studies characterize effects of formulation, food, and dosing vehicle in healthy adult subjects
- The data from healthy adult subjects forms the basis of modeling and simulation studies to provide recommendations for pediatric PK and Phase III studies
- Important to seek regulatory guidance during PSP and PIP development on how to generate safety/efficacy data to support product labeling

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Thanks

- Marty Behm
- Paul Fackler
- David Harris
- Filippos Kesisoglou
- Amitava Mitra
- David Storey
- Karen Thompson
- Dina Zhang
- Binfeng Xia
- Wei Zhu

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