Modeling for Success: A Case Example for Oseltamivir Phosphate

2021 CRCG PBPK workshop:

Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches

Session 3: Challenges and Successful Cases for Oral PBPK

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Disclaimer

This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies

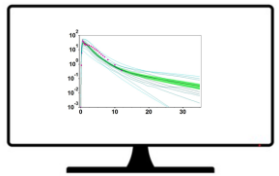
Objectives

I. Describe the challenges in developing PBPK model in pediatrics

II. Describe a PBPK model for oseltamivir phosphate and its metabolite in both adults and pediatric to establish dissolution safe space using virtual bioequivalence (BE) simulations

Challenges with Developing Pediatric PBPK Models

- Some degree of model validation with pharmacokinetic data is required to support regulatory decisions
- Limited application of PBPK modeling, especially in a regulatory filing for pediatric indications



Model application

Model development

- Depends on the confidence of assumed processes
- No general guidance to choose appropriate variability in model parameters
- Simulations carry intrinsic error from reality

Age-dependent changes

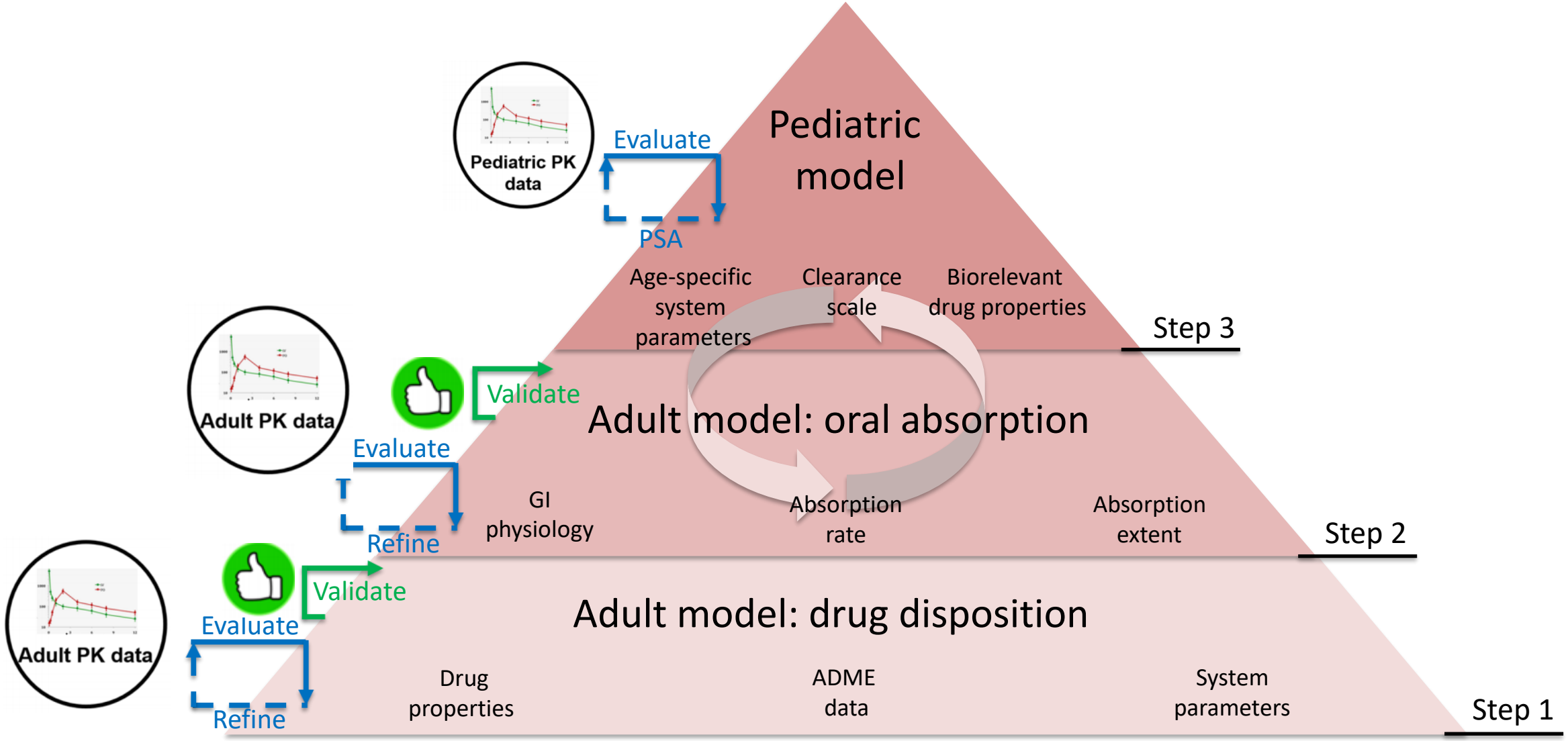
Scaling

- Changes in gastrointestinal (GI) pH, transit times, fluid composition and volume, surface area and length, and enzyme/transporter localization and abundance
  - Impact on solubility and in vivo dissolution

- Allometric scaling accounts for changes in body size
- Scaling from in vitro and preclinical in vivo data to human in vivo behavior

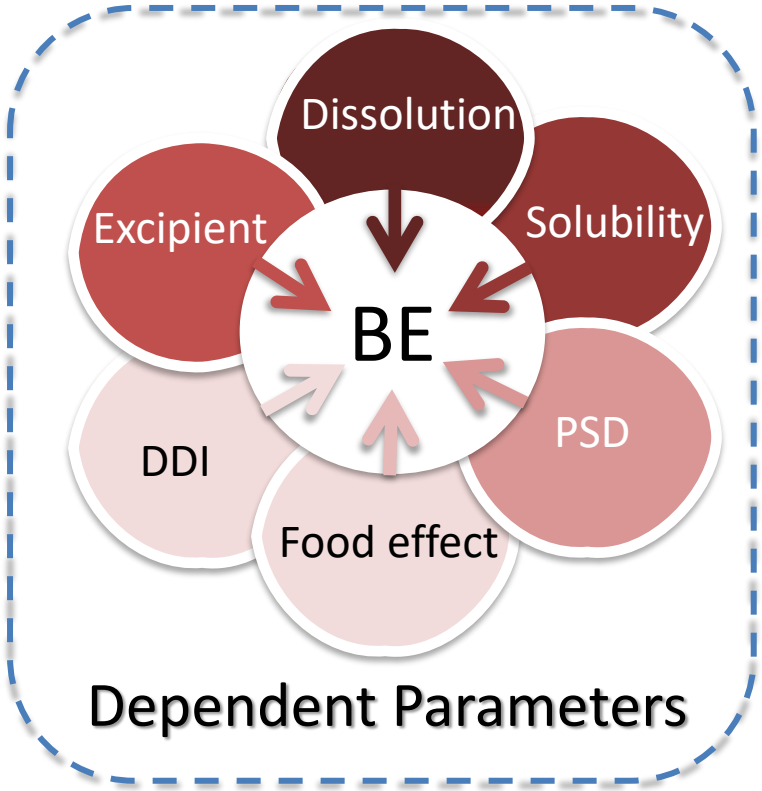
- Journal of Pharmacy and Pharmacology, 71 (2019), pp. 603–642
- Sanghavi M, Physiology Based Pharmacokinetic Modeling in Generic Drug Development and Regulatory Decisions- Opportunities & Challenges, Simulation-Plus, Apr 30, 2019

General Approach for Developing PBPK Model

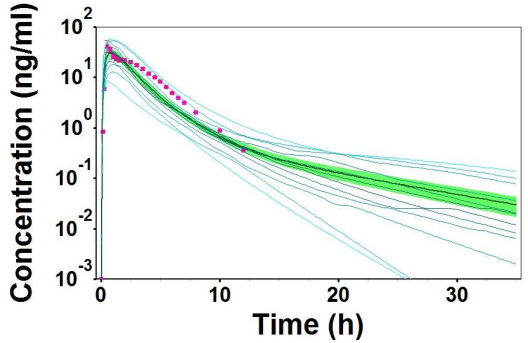


- Journal of Pharmacy and Pharmacology, 71 (2019), pp. 603–642
- The AAPS Journal (2020) 22: 146

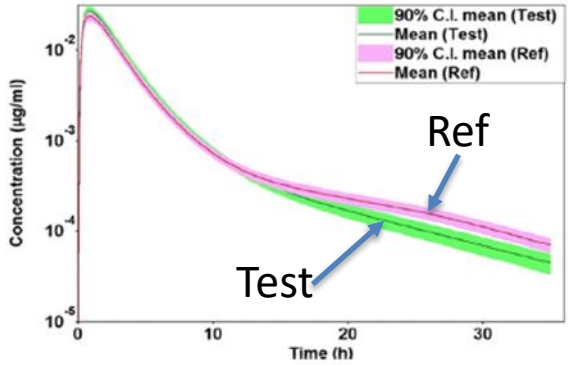
Application of PBPK Modeling in Regulatory Submissions for Generic Drugs



PBPK absorption model



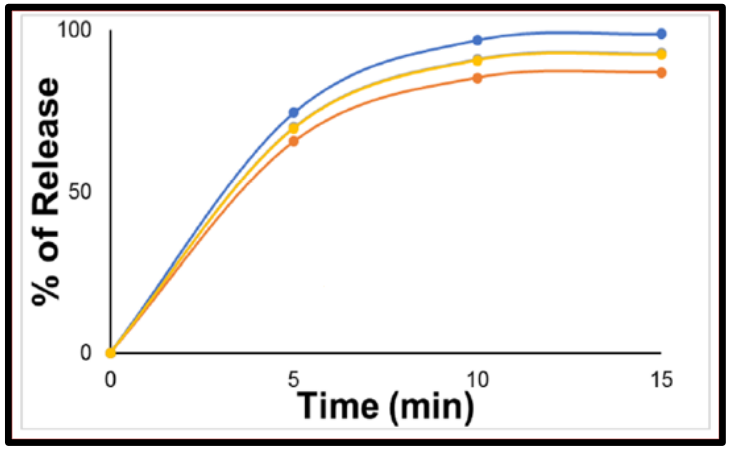
Fitting the model to reference PK data

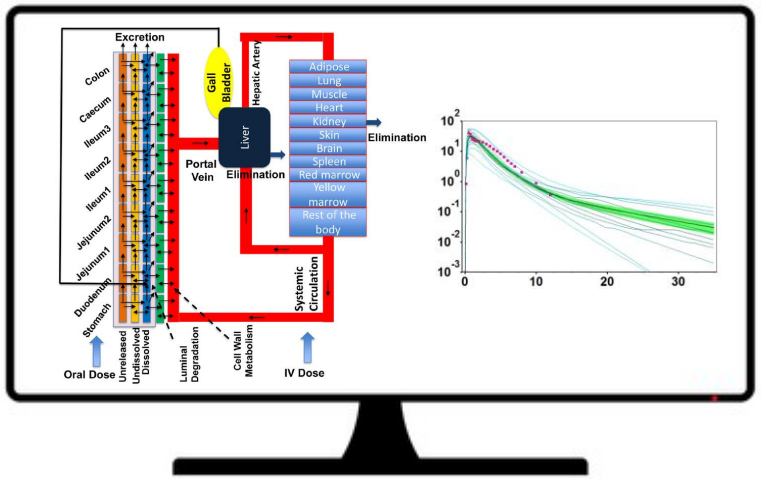


Virtual BE between test and reference with cross-over population and incorporated variability

BE: bioequivalence; **DDI**: drug-drug interaction; **PSD**: particle size distribution

Case Example: application of PBPK modeling to determine bioequivalent dissolution “Safe Space” for Oseltamivir Phosphate





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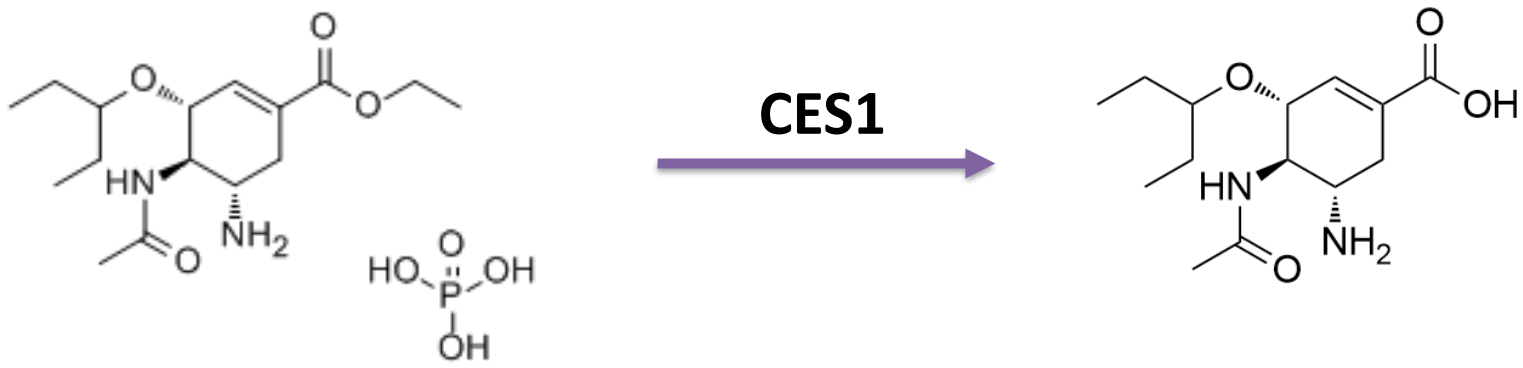
Background

Oseltamivir Phosphate (OP)

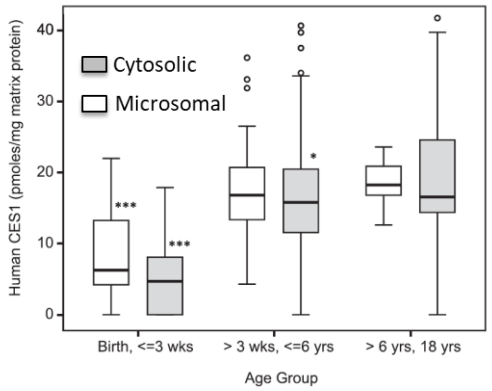
- Antiviral medication, for influenza A and B
- A pro-drug of the active metabolite Oseltamivir Carboxylate (OC)

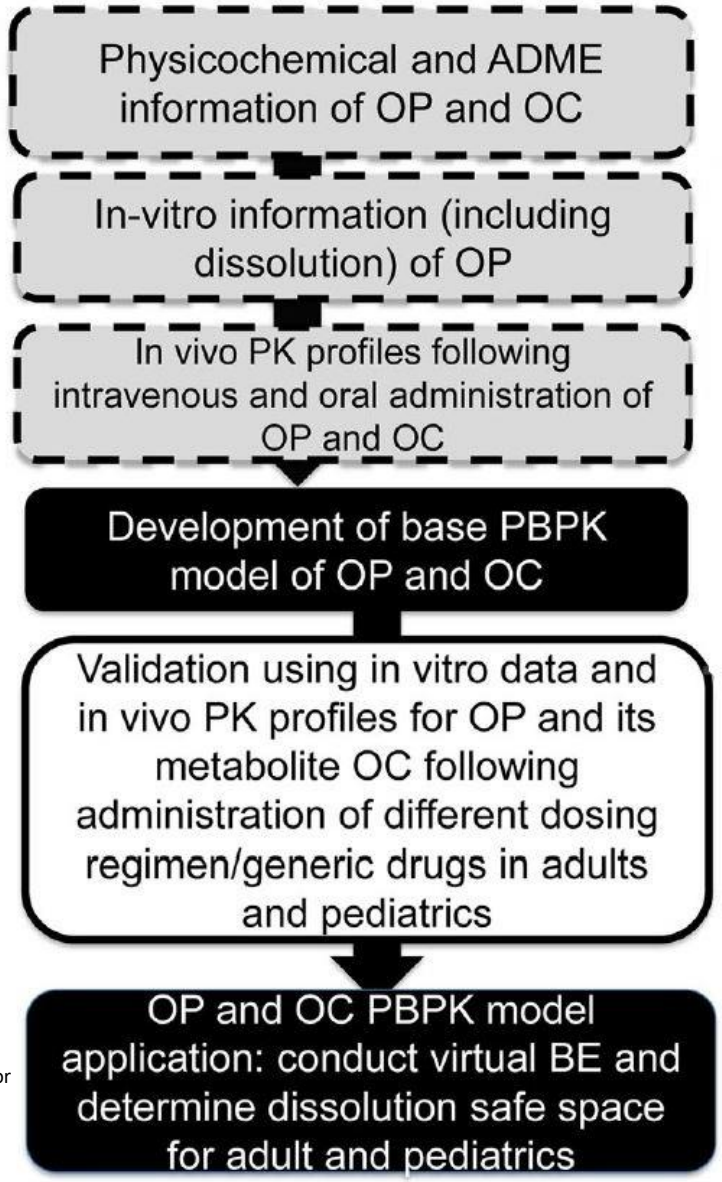


OP **OC**

PBPK Model Development

Properties	Value
LogP (OP/OC)	0.36/− 2.1
Molecular weight (OP/OC)	312/284
pKa (OP/OC)	7.70/8.2
Distribution	
Human blood to plasma ratio (OP/OC)	1/0.6
Fraction unbound in plasma (OP/OC)	58%/97%
Elimination	
CL_{renal} (L/h) (OP/OC)	4.2/18.8 (adults, for i.v. and oral)
V_{max} (mg/s/mg-CES1)*	0.52 (adults, for i.v. and oral) 0.53 (9–18 years, 1–5 years, 3–9 months, 0–2 months)
K_m (mg/L)*	599 (adults, for i.v. and oral) 431.4 (3–9 months, 1–5 years, and 9–18 years) 331.1 (0–2 months)
CES1 (mg/g tissue)	0.12 (adult) 0.04 (0–2 months) 0.06 (3–6 months) 0.09 (1–18 years)
Aqueous solubility (mg/mL)	250/15.79
Dissolution	Direct input of dissolution profiles for oral solid dosage forms
Absorption	
Effective permeability (P_{eff}) (cm/s)	$1.01*10^{-4}$



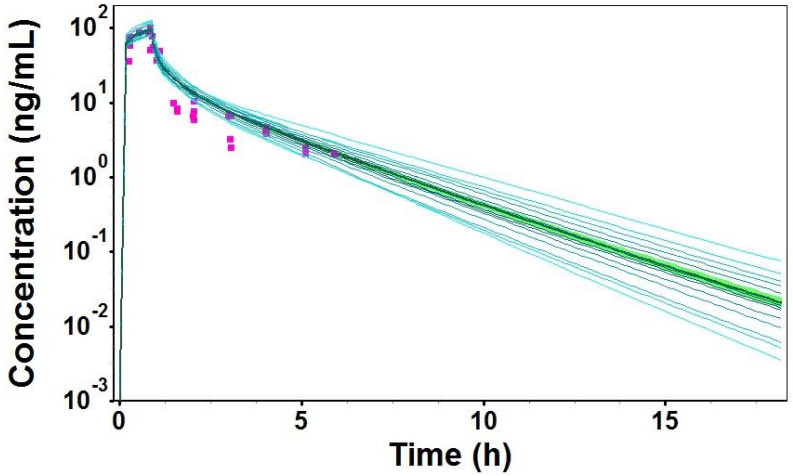


- Miao L, Mousa YM, Zhao L, Raines K, Seo P, Wu F. Using a Physiologically Based Pharmacokinetic Absorption Model to Establish Dissolution Bioequivalence Safe Space for Oseltamivir in Adult and Pediatric Populations. AAPS J. 2020 Aug 10;22(5):107.
- Drug Metab Dispos 44:959–966, July 2016

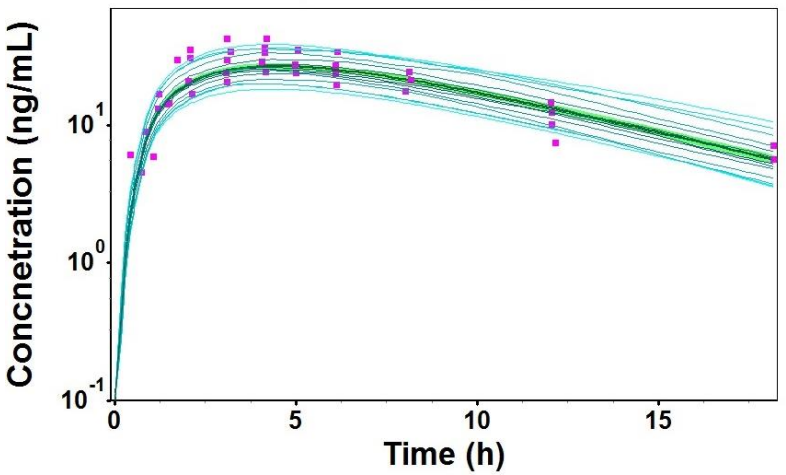
PBPK Model for Intravenous OP

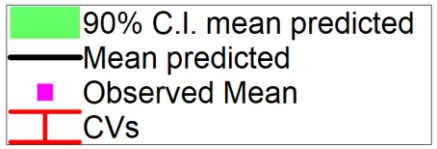
- GastroPlus™ with PBPKPlus™ module was used for modeling and simulation
- **15 mg intravenous OP**

OP



OC





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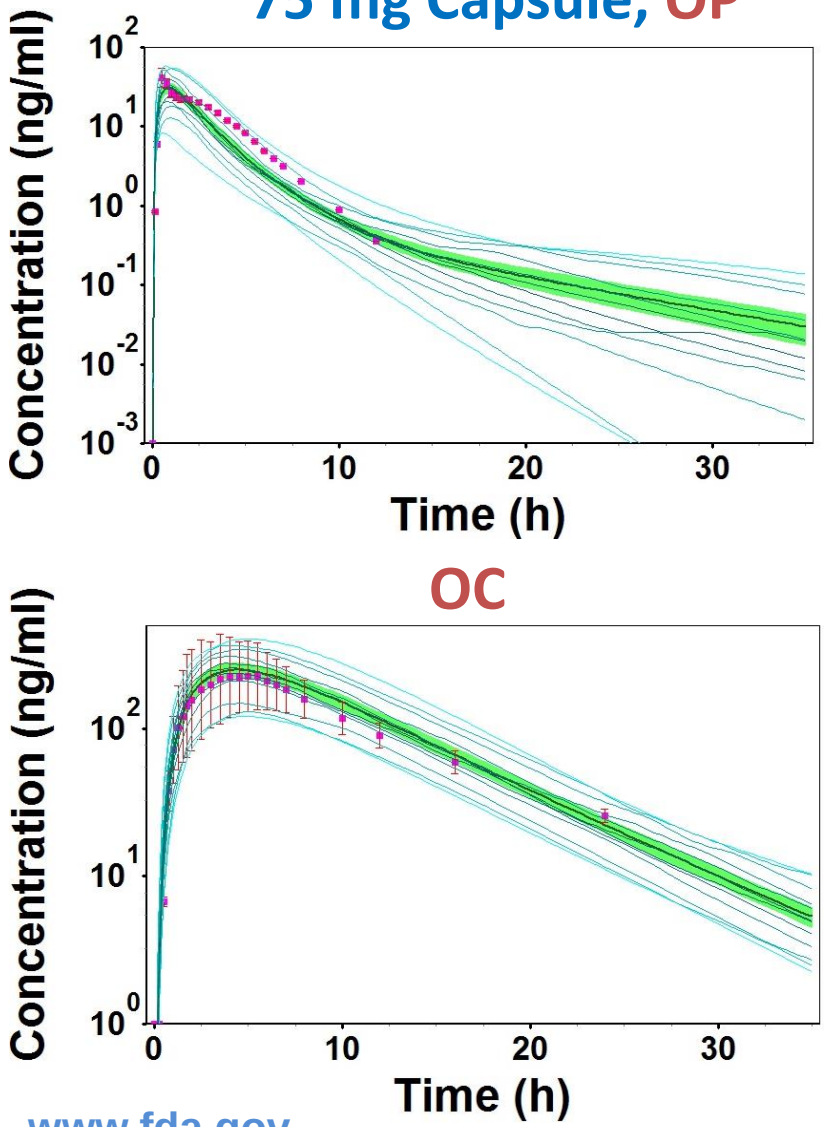
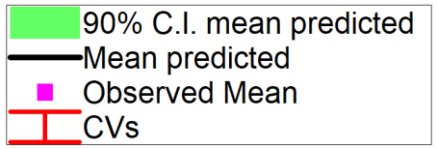
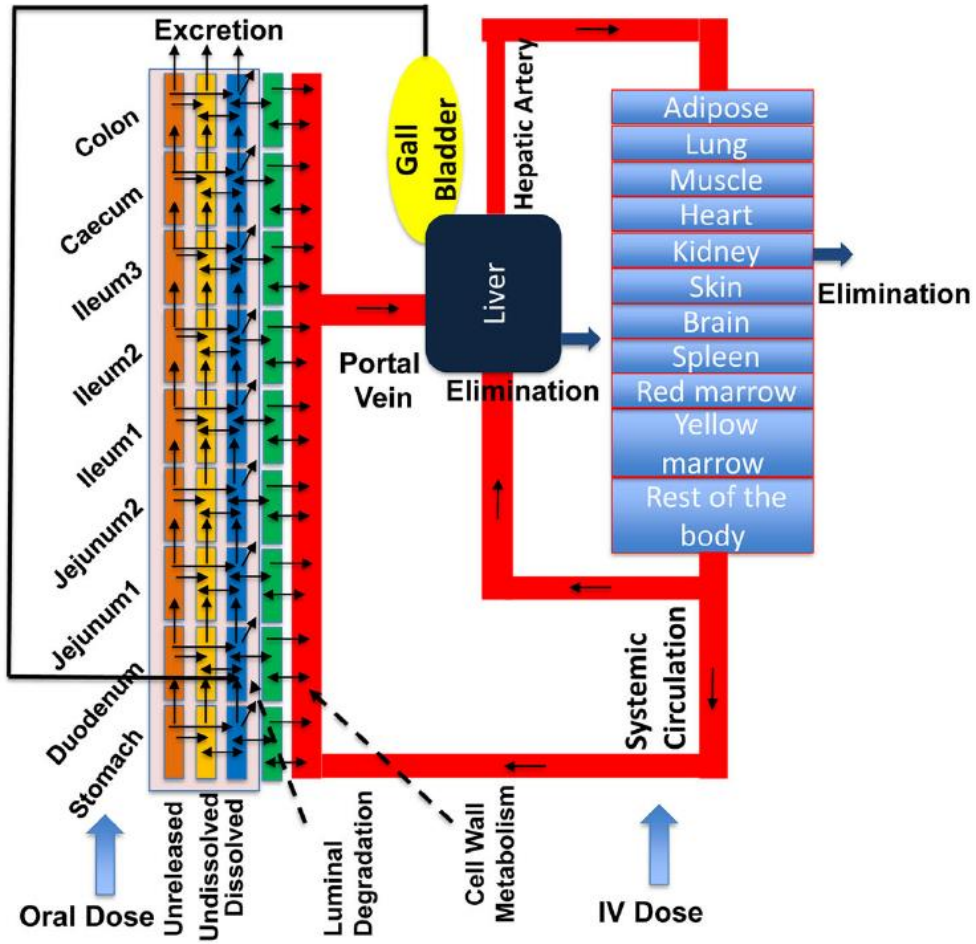
PBPK Model for Oral OP







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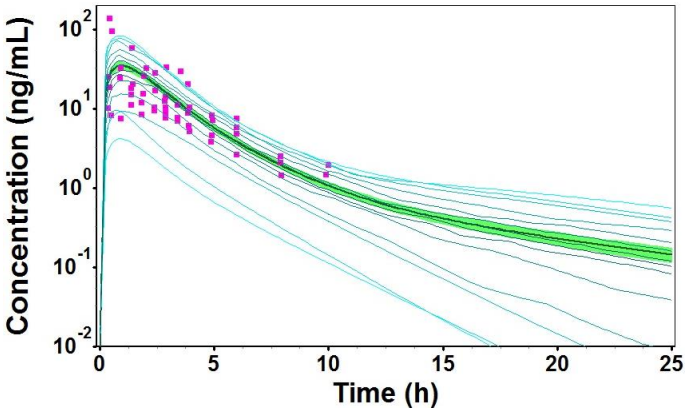
Validation of PBPK Model for Oral OP

100 mg Capsule, OP



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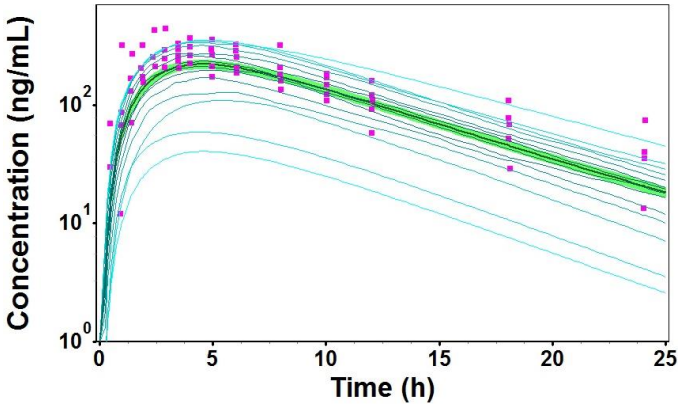
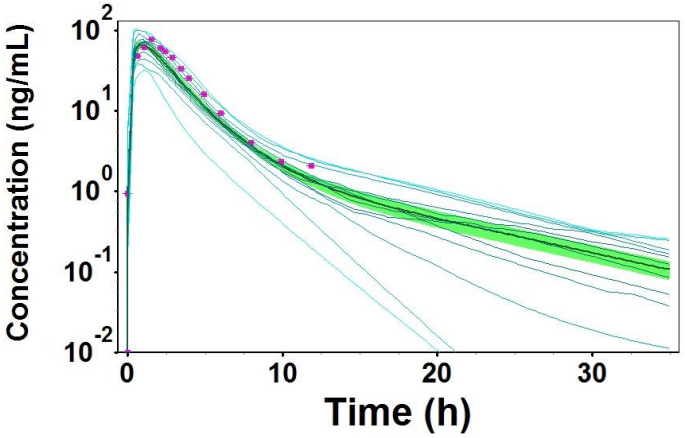


150 mg Capsule, OP



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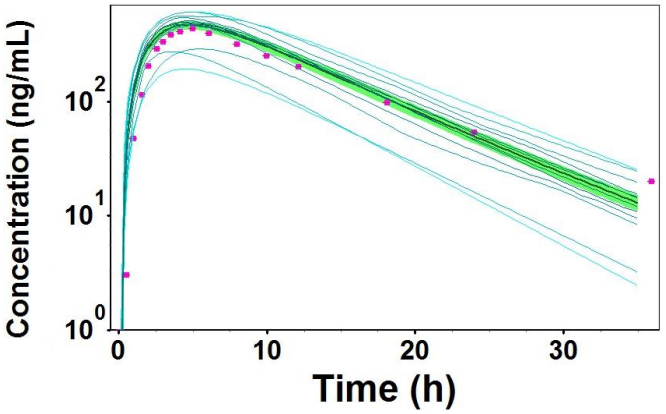

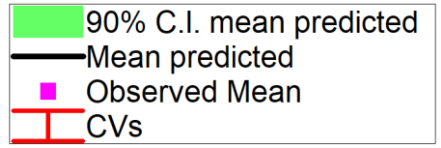

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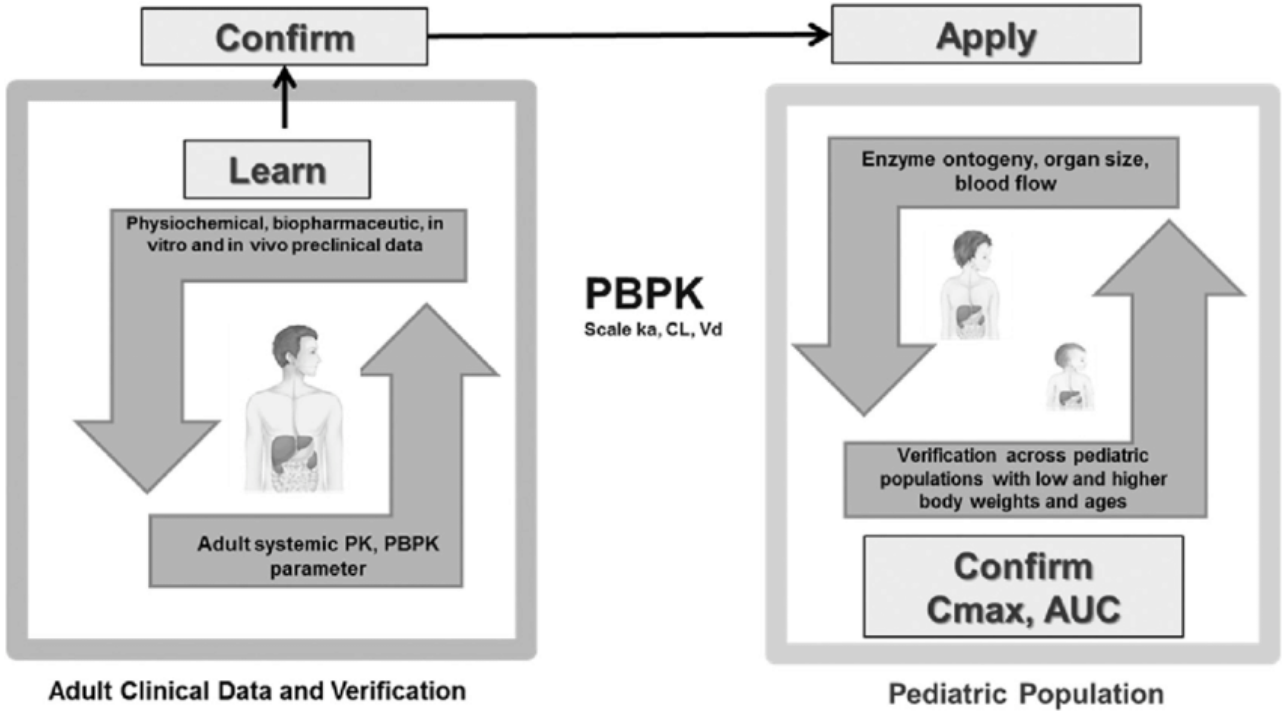
Pediatric PBPK Model Extrapolation

- The pediatric PBPK model was established from the adult PBPK by changing the physiological parameters, predicted using population estimates of age-related physiology (PEAR™) and ACAT™ module

- The pediatric PBPK was developed for four different pediatric age groups: 0–2 months, 3–9 months, 1–5 years, and 9–18 years

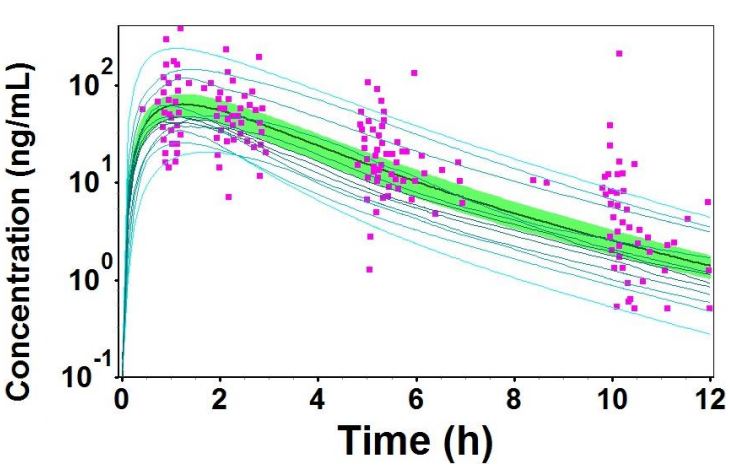


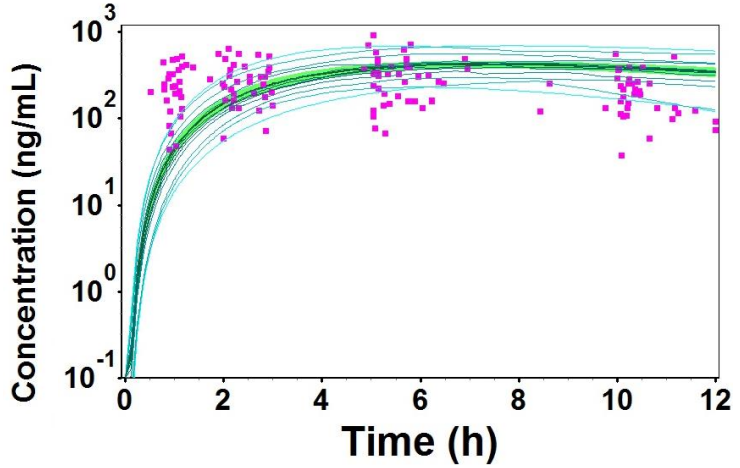
J Pharm Sci. 2016 Oct;105(10):3205-3213.
https://ascpt.onlinelibrary.wiley.com/doi/full/10.1038/clpt.2012.19

Predicting the PK Profiles in Pediatric

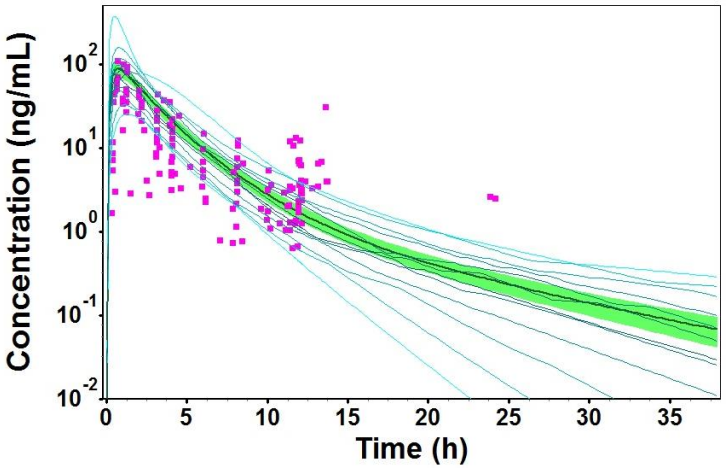
2 mg/Kg, OP | **OC**

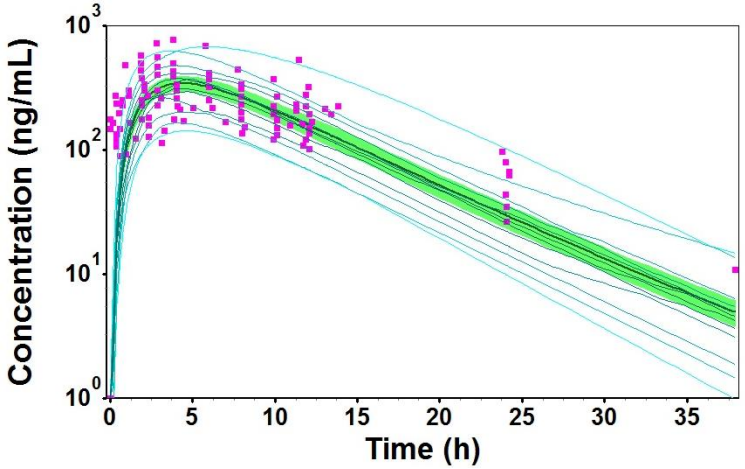
0 – 2 months





9 – 18 years





90% C.I. mean OP Pred.
Mean OP Pred.
OP Obs.
CVs

The pediatric model was also validated in age groups 3- 9 months and 1 – 5 years

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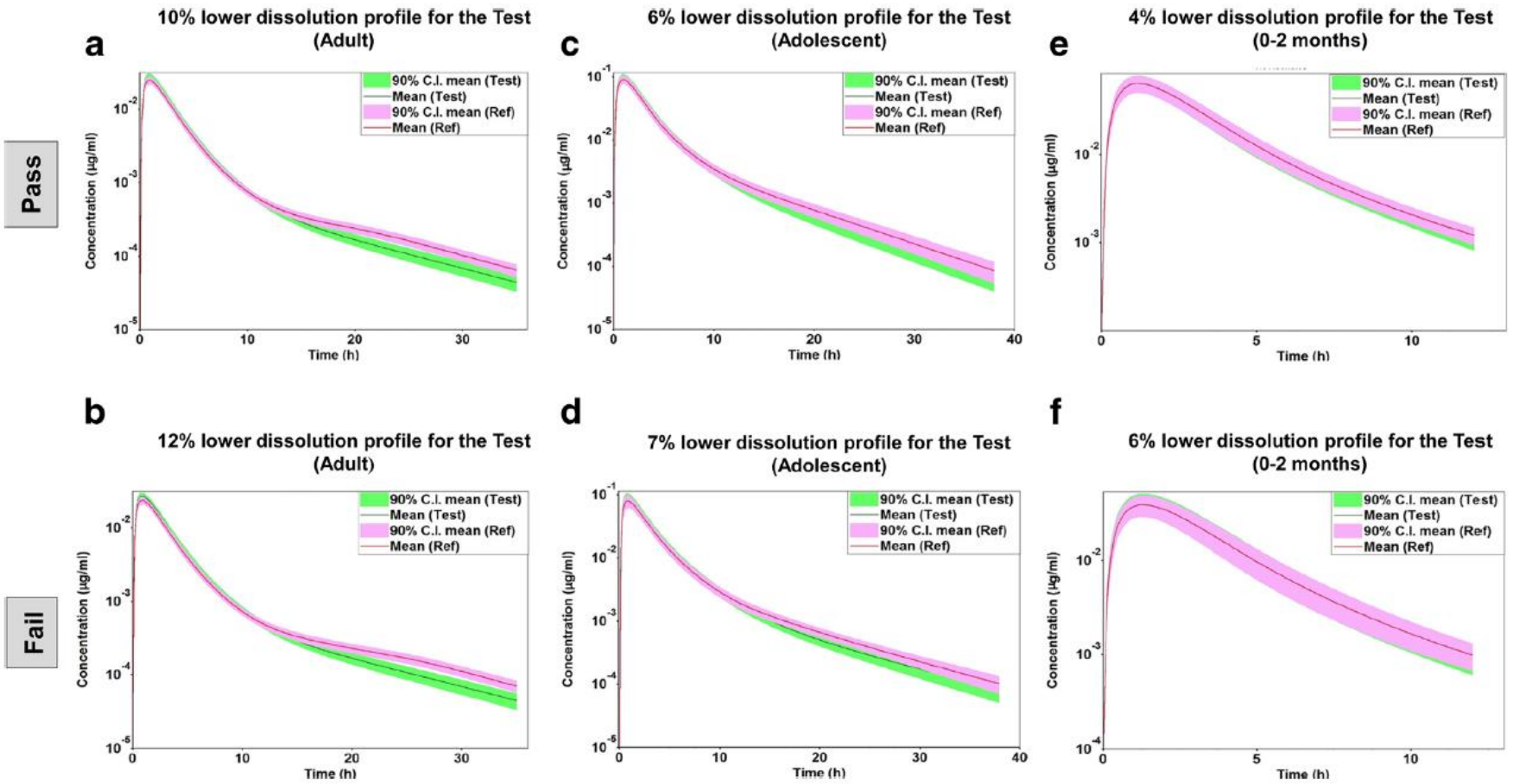
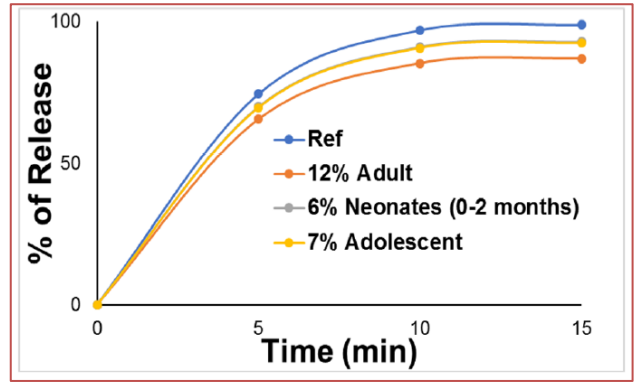
Virtual BE Simulation and Analysis for the Reference and Test OP Products in Adults and Pediatrics to Determine BE Dissolution Safe Space for OP





GMR% (T/R) (90% CI)		
Low dissolution profiles	C_{max}	AUC
Adults		
10%	91.4 (80.7–103.5)	93.8 (83.8–105.1)
12%	88.2 (78.1–99.7)	90.7 (81.1–101.4)
Adolescent		
6%	93.7 (81.9–107.2)	95.8 (83.1–110.4)
7%	92.1 (75.3–112.6)	94.3 (79.2–112.2)
0–2 months		
4%	98.3 (80.2–120.6)	100.1 (82.4–121.5)
6%	94.9 (75.7–118.9)	96.4 (77.3–120.2)

GMR, geometric mean ration; 90% CI, 90% confidence interval

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Generalizing the Approach

- Developing an absorption PBPK model can be utilized to support Critical Quality Attributes (e.g., dissolution) for different orally administered drug products.

- This approach provides more confidence for decision making in accepting dissolution limits and mitigating the risk for non-BE products.

Conclusion

- Establishing the confidence in PBPK model is pivotal for effective application
- Several challenges are associated with developing PBPK model and its extrapolation
- A verified model with high confidence can be used to aid regulatory decision-making and to support generic drug development, for example:
  - Dissolution safe space
  - Product quality
  - pH-DDI
  - Food effect
  - Particle size distribution
  - Virtual simulations

Acknowledgement

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