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Bioequivalence Evaluation of Pediatric Products Using Physiologically Based Pharmacokinetic Modeling

October 2021

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Office of Generic Drugs

U.S. Food and Drug Administration

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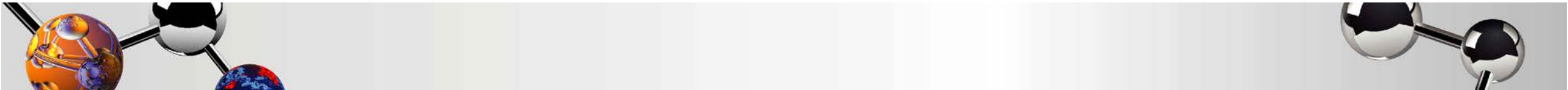

Session Description and Objectives

- This presentation will introduce the regulatory research results on using physiologically based pharmacokinetic (PBPK) modeling to evaluate the bioequivalence for pediatric products.

- This presentation will also introduce how to implement these approaches in assessing the impact of product quality attributes (e.g., dissolution) on the bioequivalence of generic drugs for both adults and pediatrics

Objectives of this session:

- Understand the challenges and opportunities that we are facing when evaluating pediatric products during drug development
- Learn risk factors associated with the bioequivalence and relative bioavailability studies for pediatric products
- Know how to implement in vitro biorelevant dissolution as well as modelling and simulations in assessing the risk for having undesired relative bioavailability or bioequivalence results in pediatrics

Biography and Contact Information

- Current: Senior Pharmacologist and Scientific Lead for PBPK in Division of Quantitative Methods and Modeling (DQMM), Office of Research and Standard (ORS), Office of Generic Drugs (OGD), U.S. Food and Drug Administration (FDA)

- More than 9 years FDA experiences, had been a biopharmaceutics reviewer in Office of Pharmaceutical Quality and a research fellow in Office of Clinical Pharmacology

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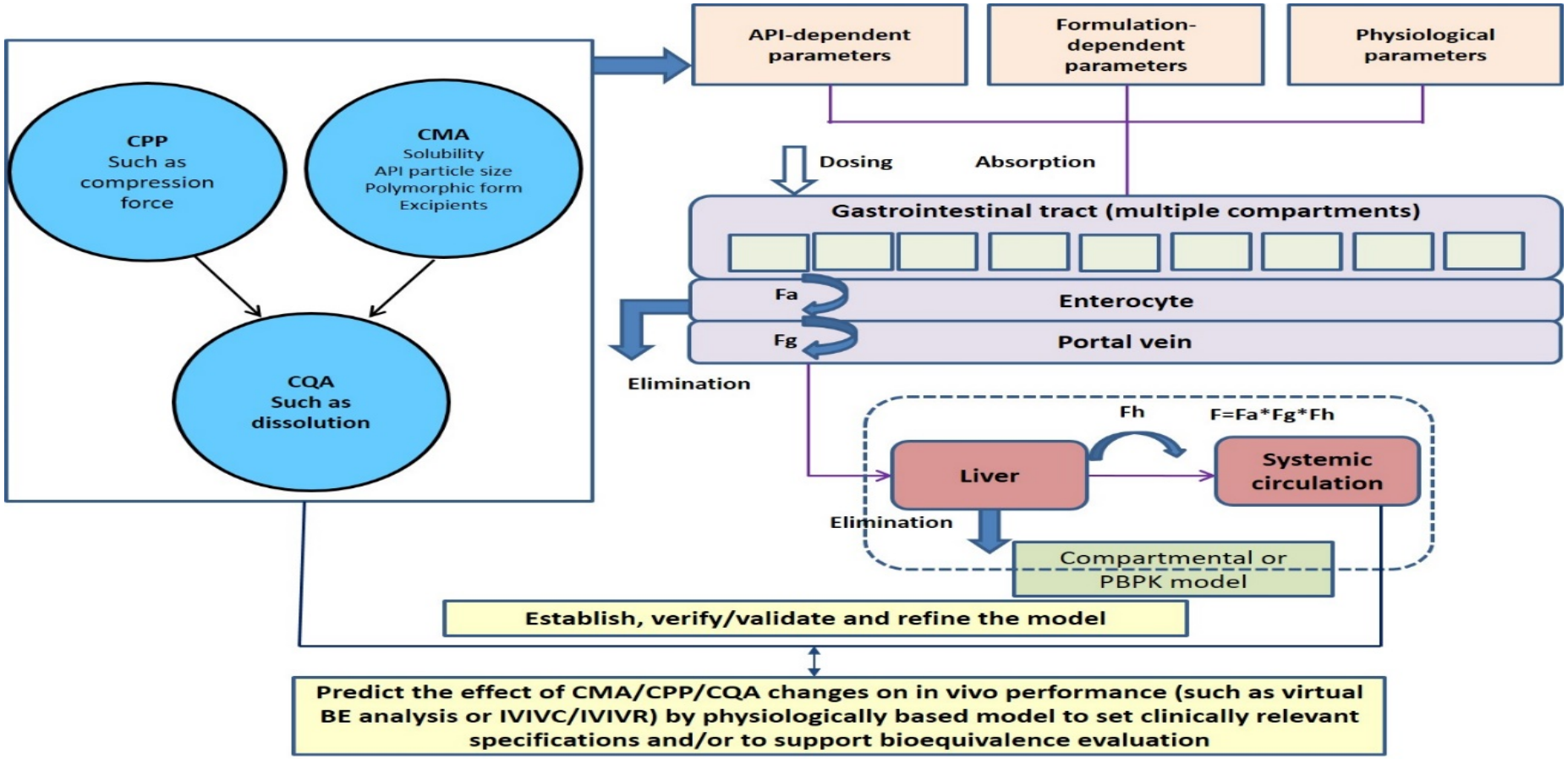
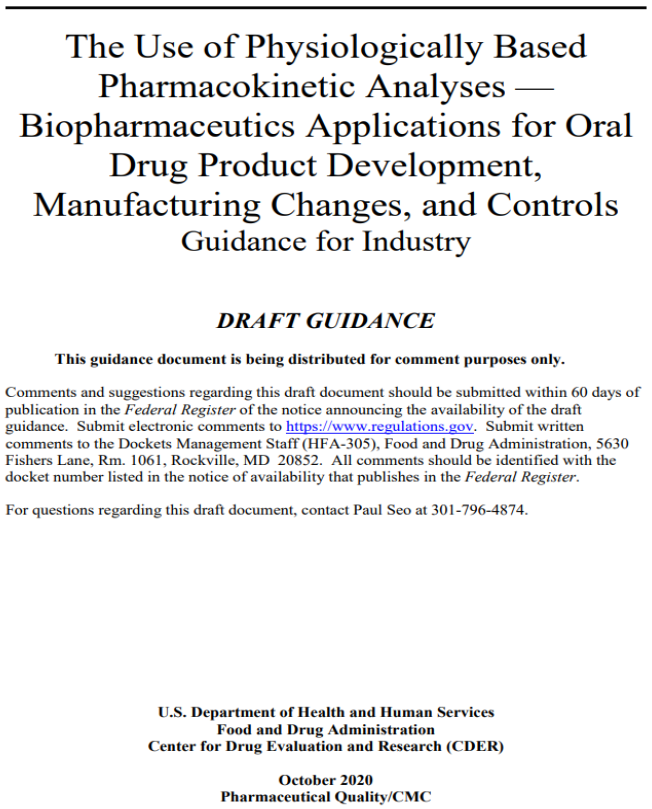
PBPK Absorption Model



CPP: Critical Process Parameters; CMA: Critical Material Attributes; CQA: Critical Quality Attributes; API: Active Pharmaceutical Ingredient; IVIVC/R: In Vitro In Vivo Correlation/Relationship

Reference: Wu F, Shah H, Li M, Duan P, Zhao P, Suarez S, Raines K, Zhao Y, Wang M, Lin HP, Duan J, Yu L, Seo P. Biopharmaceutics Applications of Physiologically Based Pharmacokinetic Absorption Modeling and Simulation in Regulatory Submissions to the U.S. Food and Drug Administration for New Drugs. AAPS J. 2021 Feb 22;23(2):31.

Guidances Supported by PBPK Regulatory Applications and Research Issued in 2020



The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

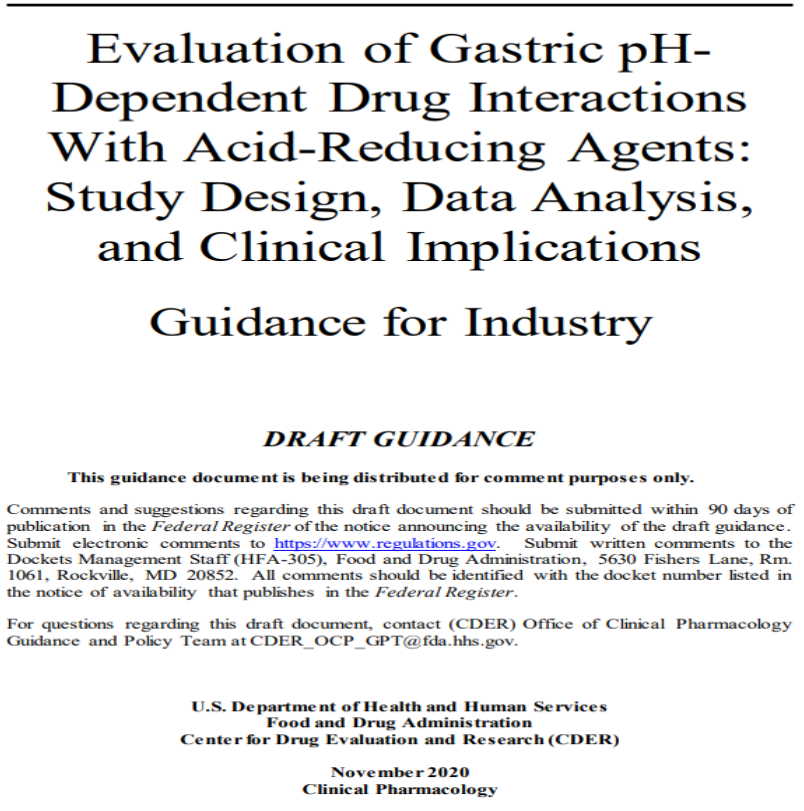
Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Paul Seo at 301-796-4874.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2020
Pharmaceutical Quality/CMC

Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-physiologically-based-pharmacokinetic-analyses-biopharmaceutics-applications-oral-drug-product.



Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications

Guidance for Industry

DRAFT GUIDANCE

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Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

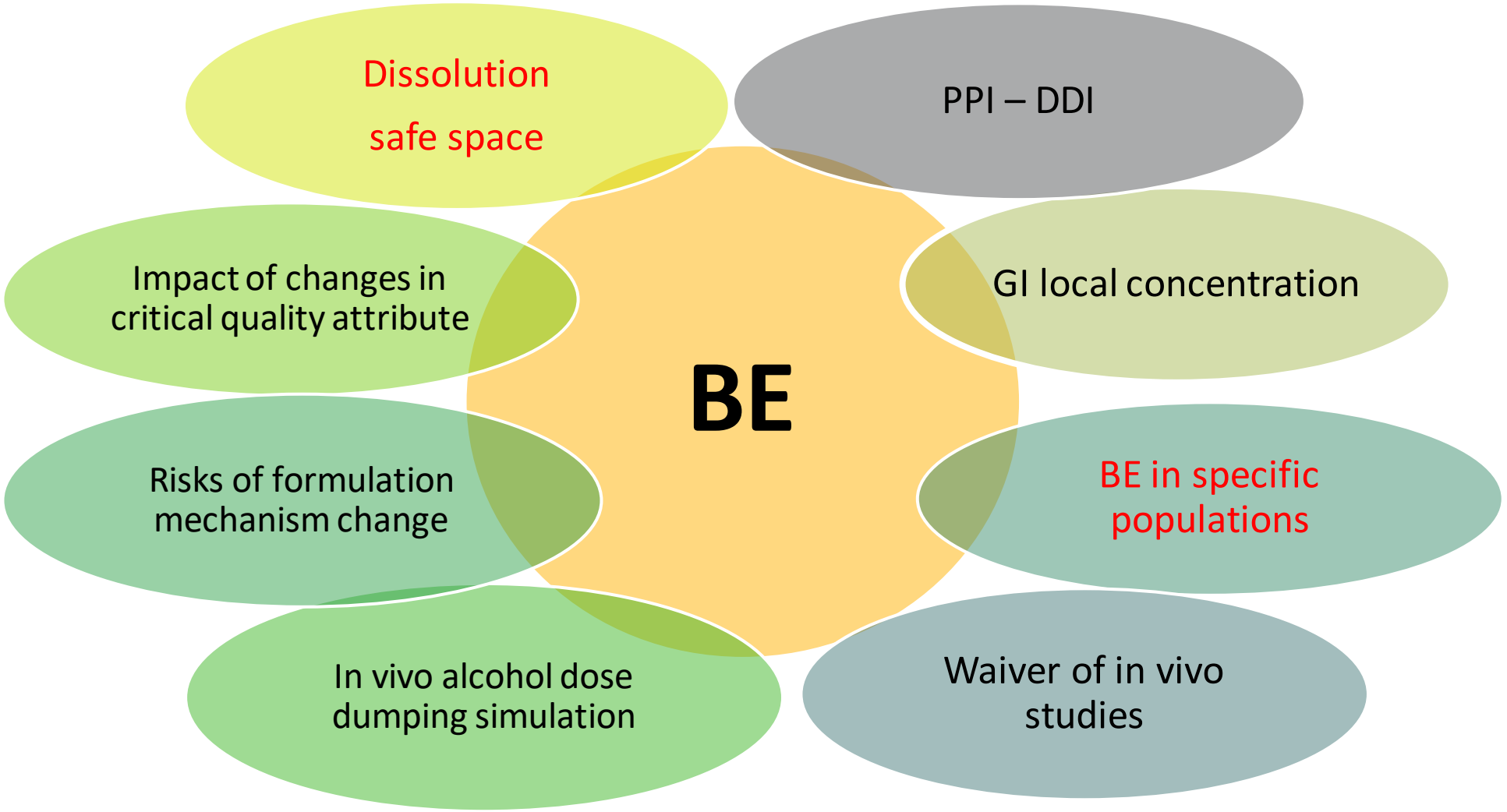
For questions regarding this draft document, contact (CDER) Office of Clinical Pharmacology Guidance and Policy Team at CDER_OCP_GPT@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

November 2020
Clinical Pharmacology

Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluation-gastric-ph-dependent-drug-interactions-acid-reducing-agents-study-design-data-analysis

Regulatory Questions that PBPK Absorption Model can Answer



BE: bioequivalence; PPI: proton pump inhibitor; GI: gastrointestinal; DDI: drug-drug interaction

Reference: Wu F. Application of PBPK Modeling in Regulatory Submission: FDA Experience on Generic Drugs. Podium Presentation, AAPS 360 Annual Conference, 2019

Putative Risk Factors Associated with Significant Differences in PK Parameters in Pediatrics between Reference and Test products

	Putative risk factors	Number of studies identified
Physiological factors (ADME effect)	Age-related absorption effects (e.g., GI motility, GI fluid volume or composition, and GI transit time)	28
	Age-related distribution effects (e.g., protein binding)	2
	Age-related metabolism or clearance effects	15
Drug substance or formulation effects	Drug substance effect (e.g., alternative salt or polymorphic form of drug substance)	5
	Drug product/formulation effects	12
Disease	Age-related disease progression and other disease-related effects	4
Population characteristics	High inter- and/or intra-individual variabilities	18
Study design	Non-equivalent dose effects	2
	Accuracy of administered dose	2
	Poor study design including small sample size	11

- *Note that multiple risk factors may have been extracted from one study*
- Risks were found being associated with products with API belonging to NTI drug category, The drug solubility is low (BCS class II or IV)

Research results from FDA contract: ORS-EXT-2018-09, Risk mitigation in the evaluation of relative bioavailability of pediatric generic products, with University of Birmingham

Reference: *Pawar G, Wu F, Zhao L, Fang L, Burckart GJ, Feng K, Mousa YM, Naumann F, Batchelor HK. AAPS J. 2021 Apr 21;23(3):57. doi: 10.1208/s12248-021-00592-y*

PBPK Modeling to Evaluate High Risk Scenarios

- For high-risk scenarios, e.g., narrow therapeutic index (NTI) drugs or drugs with low solubility, using PBPK modeling and simulations as supportive evidence, e.g., by conducting virtual BE assessment in pediatrics

- Case Example: Application of PBPK modeling to determine bioequivalent dissolution "Safe Space" for Oseltamivir Phosphate (OP)

(Note that this example is for demonstrating a PBPK tool and OP is a putative BCS Class I/III drug)

- Research for other model drugs (NTI and BCS class II drugs) is ongoing with contract ORS-EXT-2018-09

Reference: Miao L, Mousa Y, 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 Journal, 2020. DOI : 10.1208/s12248-020-00493-6

Purpose of Case Example for Oseltamivir

Purpose:

- Develop a PBPK model for a putative BCS Class 1/3 drug, oseltamivir phosphate (OP) and its metabolite oseltamivir carboxylate (OC) in both adults and pediatrics
- Conduct virtual BE simulations to establish BE dissolution safe space for OP in both adults and pediatrics

Reference: Miao L, Mousa Y, 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 Journal, 2020. DOI : 10.1208/s12248-020-00493-6

Background

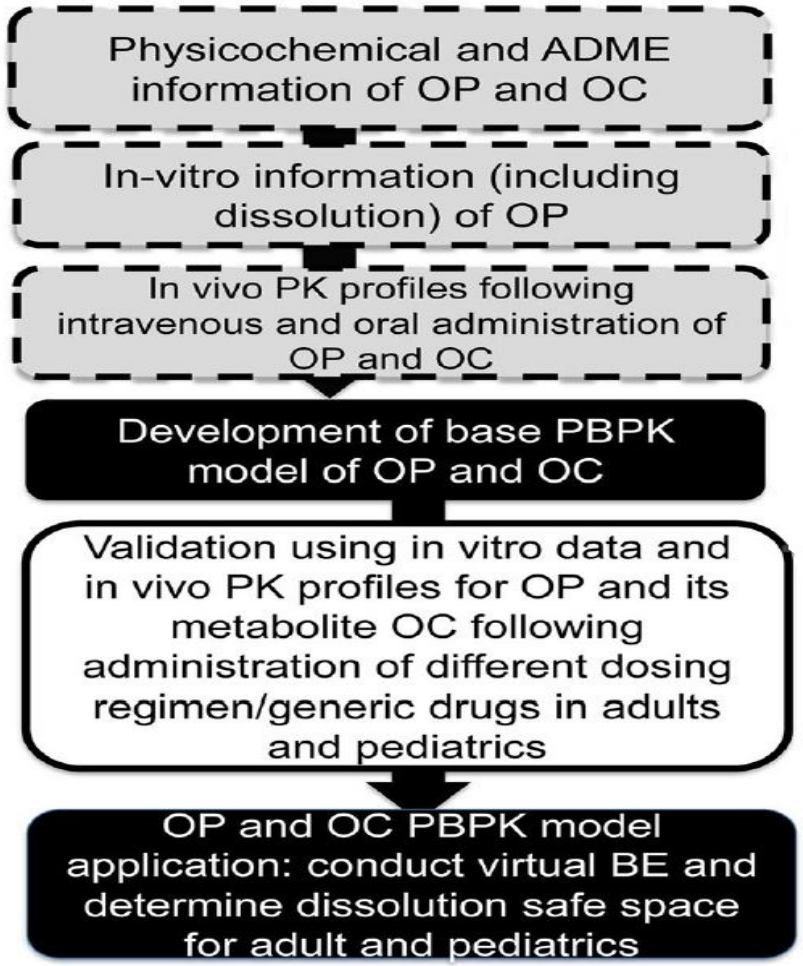
Oseltamivir Phosphate (OP)

- 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)	$1.01*10^{-4}$

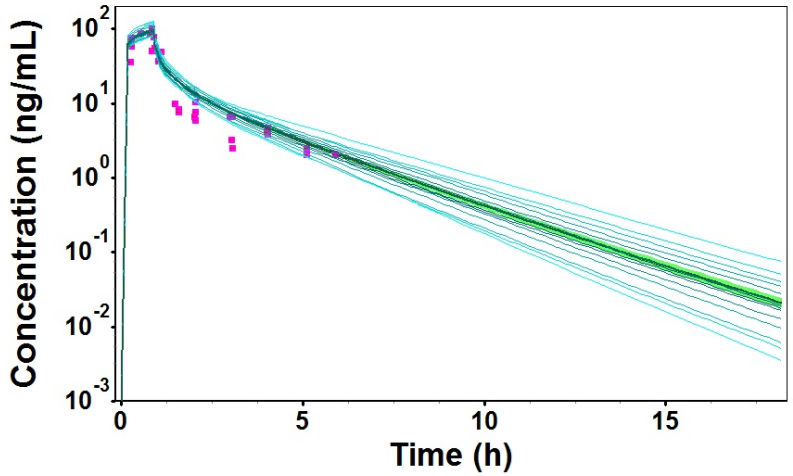


Miao L, Mousa YM, Zhao L, Raines K, Seo P, Wu F. Using a Physiologically Based Pharmacokinetic Absorption Model to Establish Dissolution Bioequivalence Safe Space for Oseltamivir in Adult and Pediatric Populations. AAPS J. 2020 Aug 10;22(5):107.

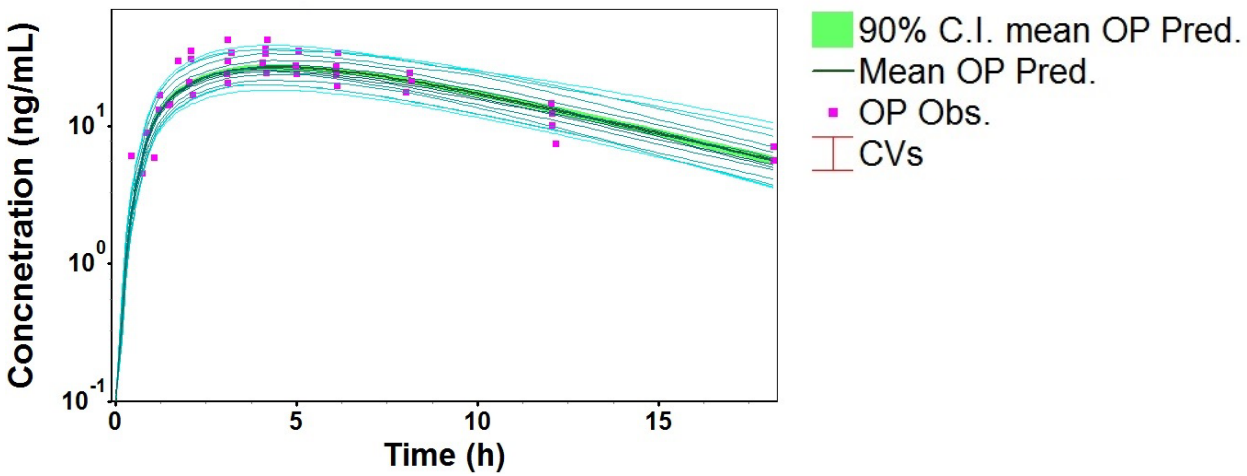
PBPK Model for Intravenous OP

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

OP



OC



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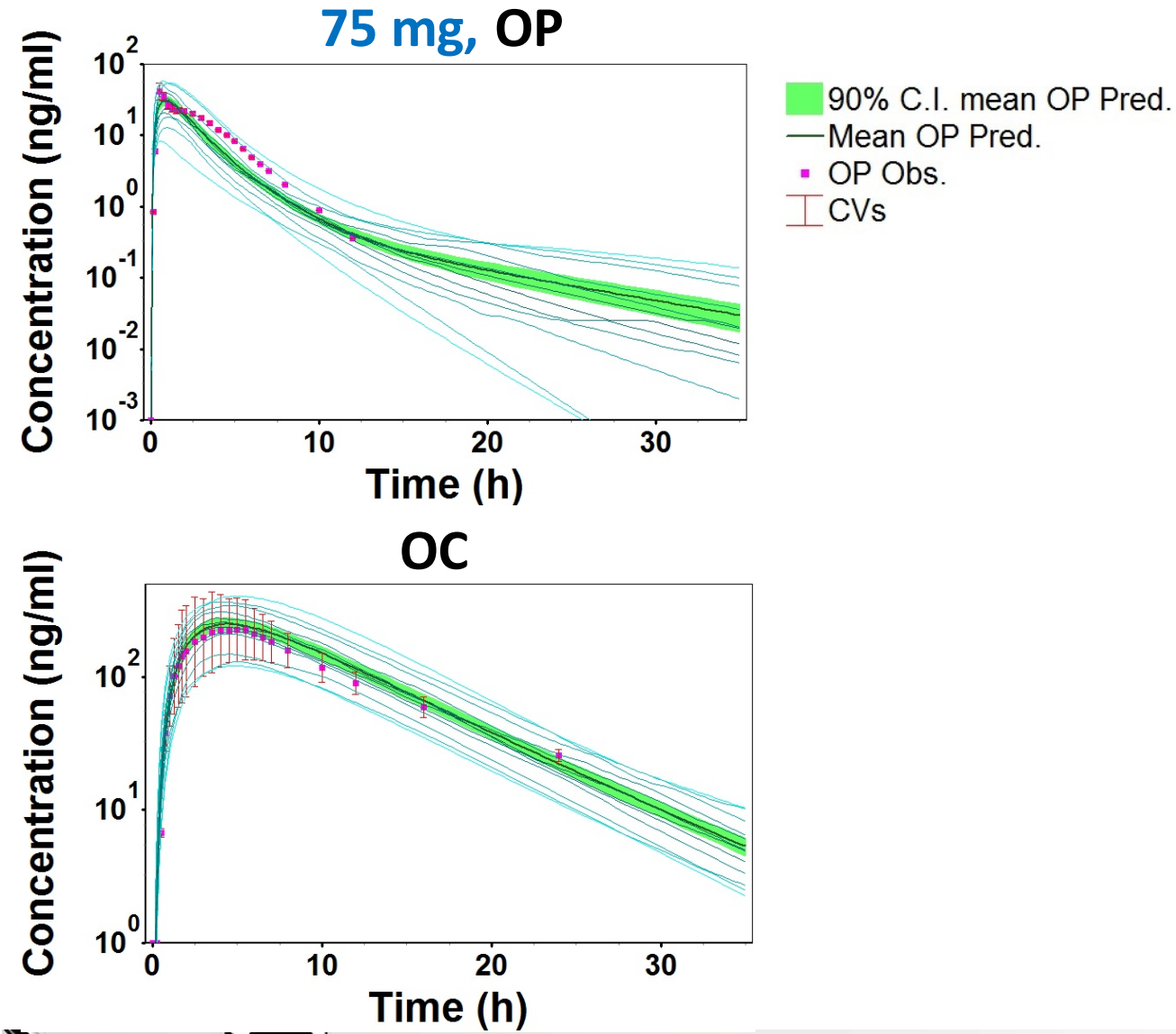
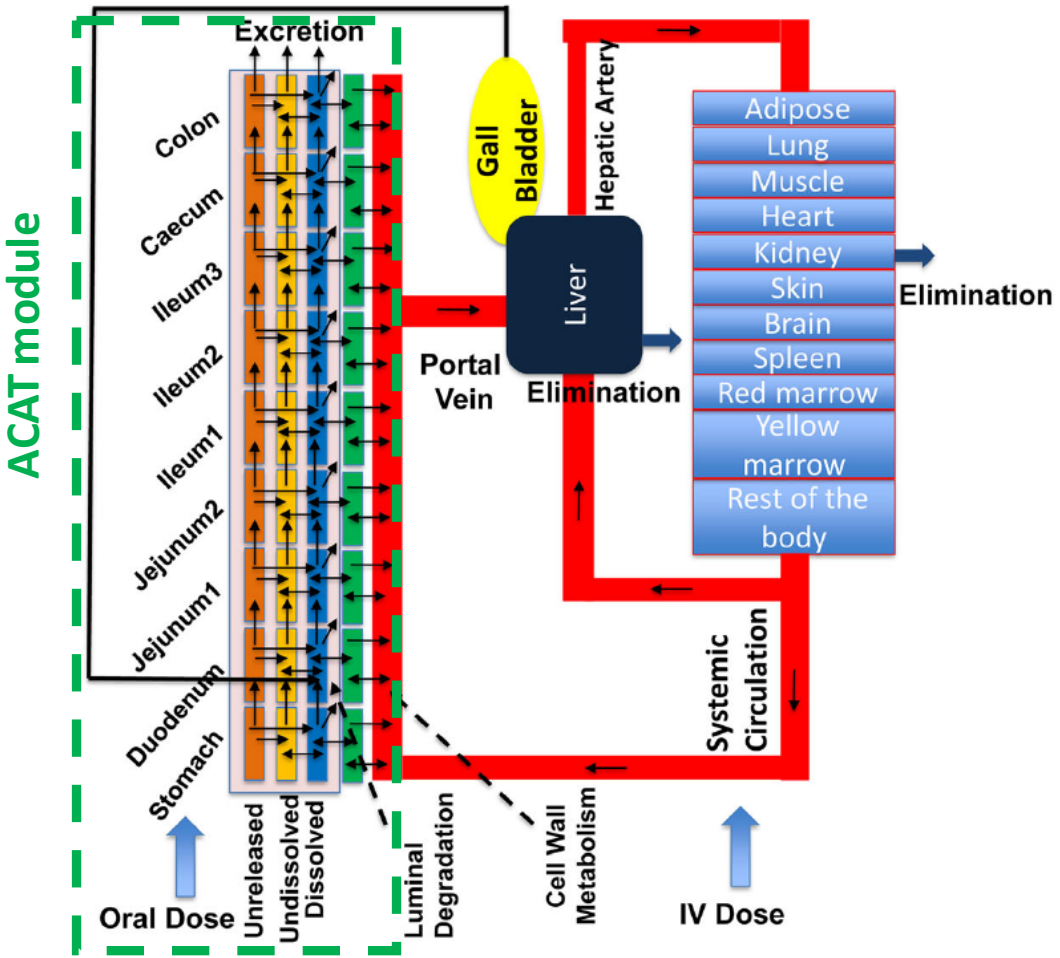
PBPK Model for Oral OP





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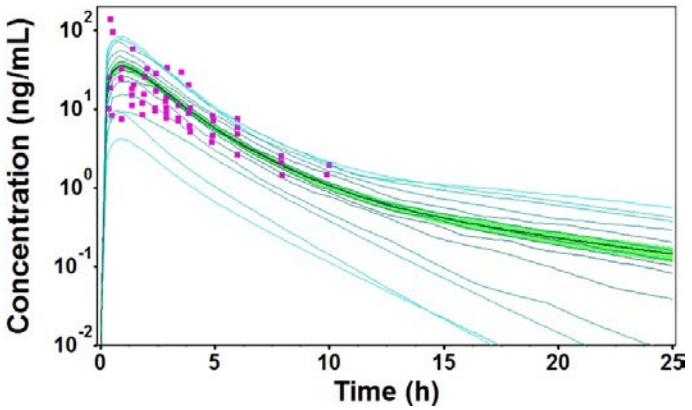
Validation of PBPK Model for Oral OP

100 mg, OP



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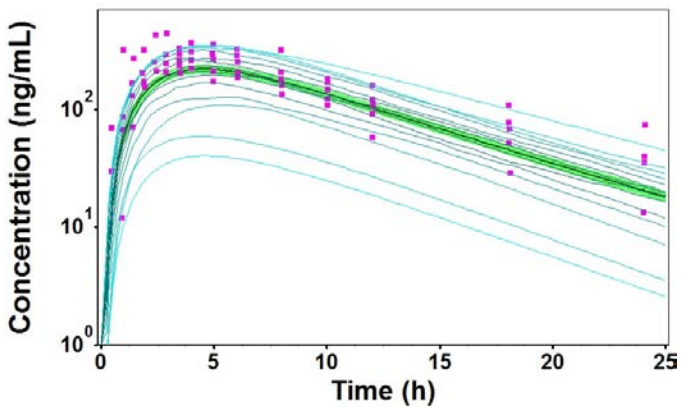
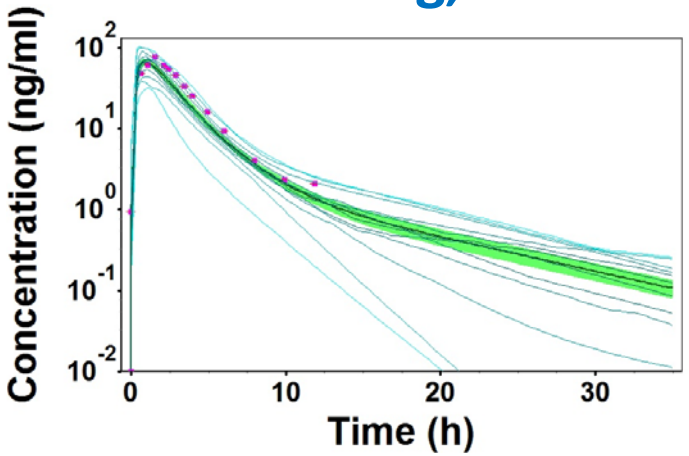
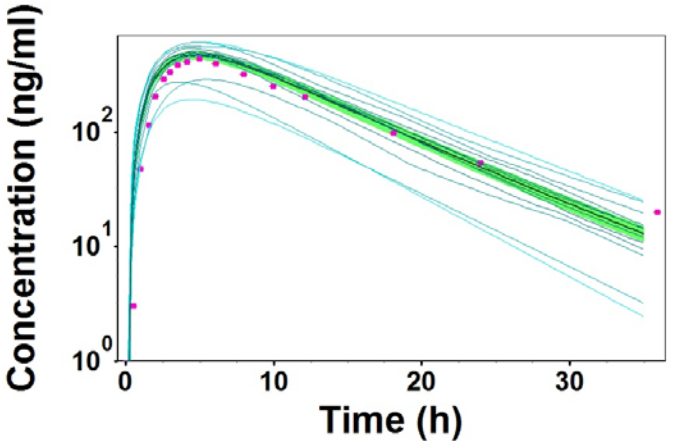


150 mg, OP



OC



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

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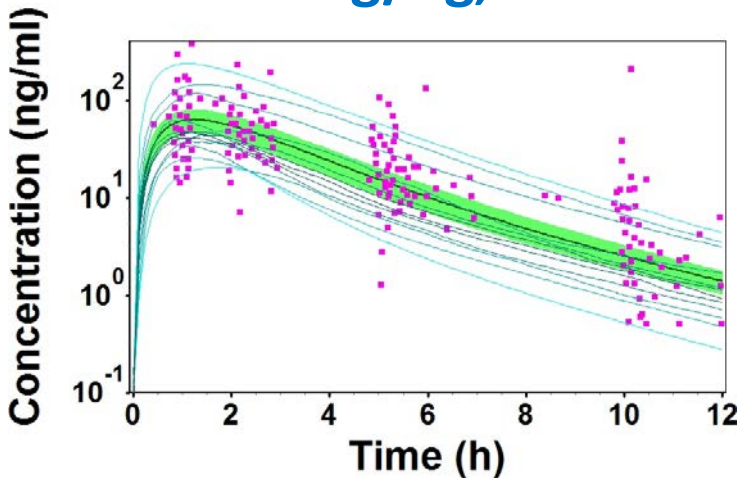
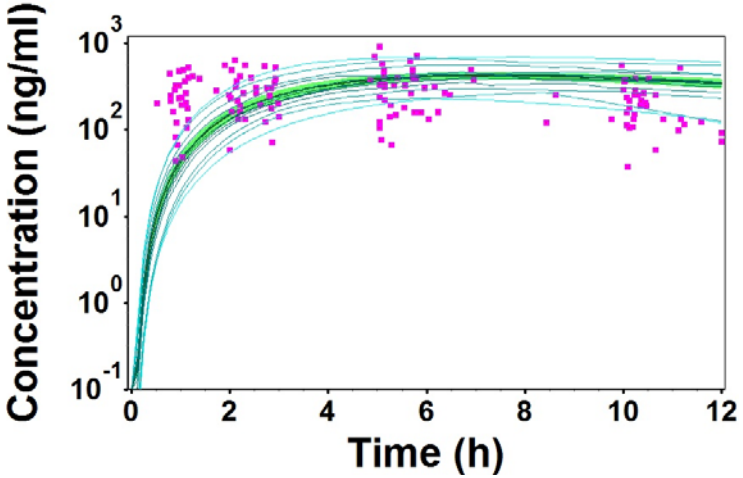
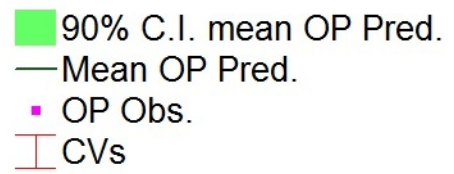
Predicting the PK Profiles in Pediatric

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

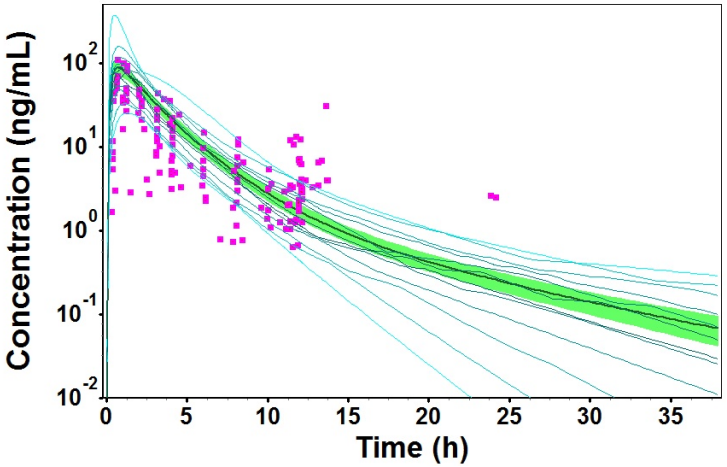
0 – 2 months

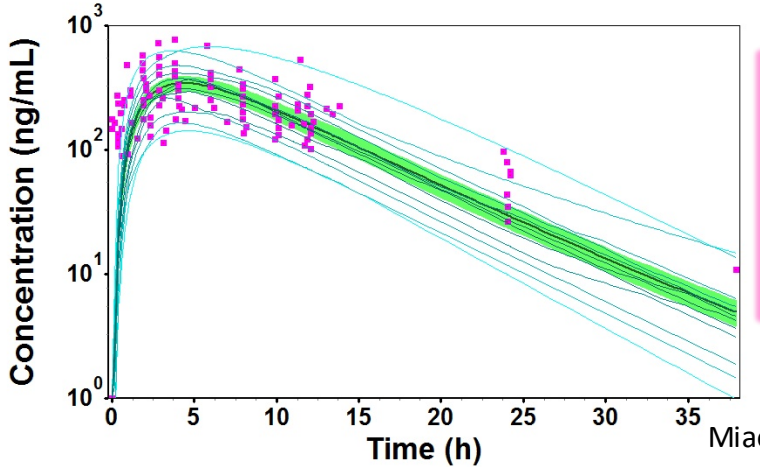






9 – 18 years





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

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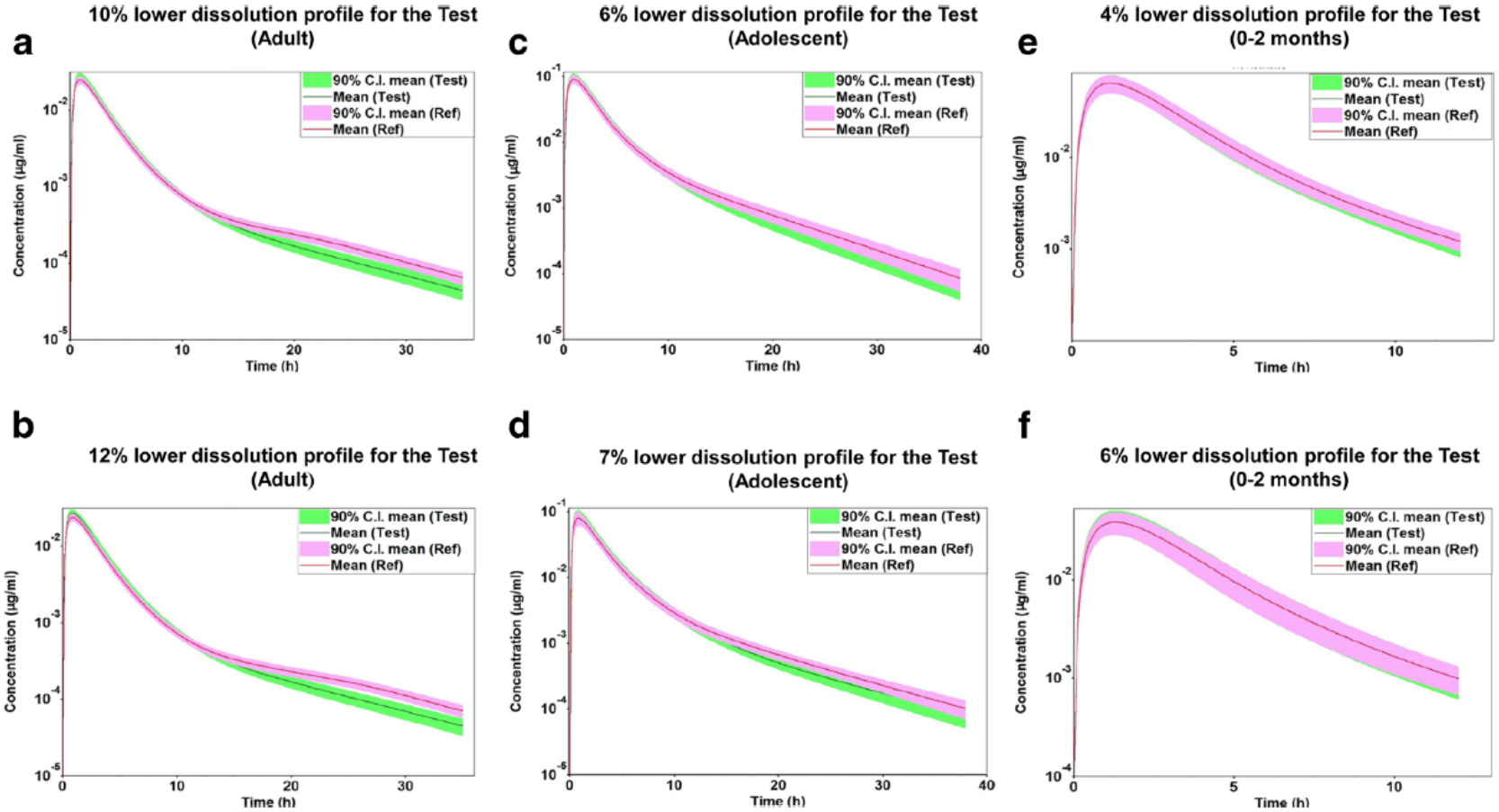
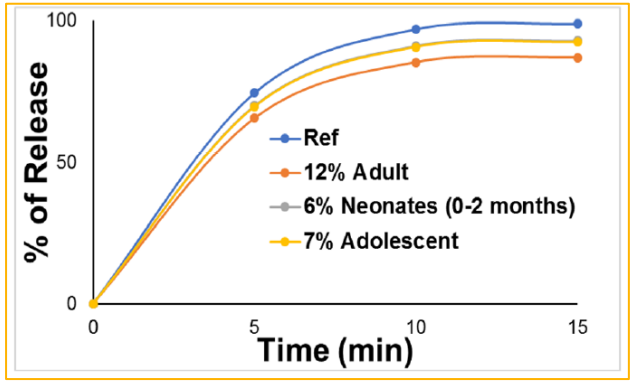
Virtual BE Simulation and Analysis for the Reference and Test OP Products in Adults and Pediatrics to Determine BE Dissolution Safe Space for OP

Pass

Fail





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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Case Example Summary

- The virtual BE analysis indicated that drug products with the dissolution boundary at 10% slower than dissolution profile of pivotal bio-batch could maintain BE to the reference listed drug in adults.

- In contrast, a stringent trend of dissolution boundary (safe space) was observed for pediatrics (6% slower for 8 to18-year-old adolescents, 4% slower for neonates).

- This study highlights the utility of PBPK absorption modeling and simulation in prediction of BE and providing a quantitative basis for setting clinically relevant specifications for dissolution for OP in both adults and pediatric populations.

Challenges and Opportunities (Developing and applying PBPK absorption Models for Pediatrics)

Current status

- Drug substance and product attributes such as solubility, permeability, dissolution profiles, and particle size are used as pediatric model inputs
- Some system-dependent parameters, e.g., gastrointestinal (GI) pH, transit times, fluid volume, surface area and length, and enzyme/transporter localization and abundance are used as pediatric model inputs with assumptions

Further Improvement

- Consistent and adequate approach of generating (biorelevant) solubility, dissolution profiles, permeability, and particle size changes during the possible precipitation process is needed
- Uncertain system-dependent parameters need adequate justifications

Challenges and Opportunities (Developing and applying PBPK absorption Models for Pediatrics)

Current status

- Population predictions with generalized variabilities are used in PBPK model
- Validation/verification of PBPK model is conducted before the application of the model
- Limited application of PBPK modeling for pediatric products

Further Improvement

- Subject variabilities in pediatric population should be considered when needed
- Sufficient purpose-dependent model validation/verification is needed
- Application of PBPK modeling for pediatrics products can be used for BE or relative bioavailability assessment when appropriate

Conclusion

- For high-risk scenarios, e.g., NTI drugs or drugs with low solubility, PBPK modeling and simulations may be used as supportive evidence, e.g., by conducting virtual BE assessment in pediatrics
- With continuous improvement along with more submissions and research, PBPK absorption modeling and simulations would aid in mitigating the risk of bioinequivalence or undesired relative bioavailability to ensure safe and effective use of drug products in pediatrics.
- Submit modeling and simulation data and communicate with the Agency at an early stage, e.g., via pre-ANDA meeting, is encouraged.

Acknowledgments

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University of Birmingham

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FDA/CDER/OTS/OCP

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Questions

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