Using a Physiologically Based Pharmacokinetic Absorption Model to Establish Dissolution Bioequivalence Safe Space for Oseltamivir in Adult and Pediatric Populations

2021 AAPS Webinar for In-Vitro Release and Dissolution Testing (IVRDT) Community and the Society of Pharmaceutical Dissolution Science (SPDS-US)

Fang Wu, Ph.D.
Senior Pharmacologist, Scientific Lead for Oral PBPK
Division of Quantitative Methods and Modeling, Office of Research and Standard
Office of Generic Drugs | CDER | U.S. FDA
October 15, 2021

Disclaimer

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

Submissions with Physiologically Based Pharmacokinetic (PBPK) Absorption Modeling on New Drug Side

- New drug applications containing PBPK absorption modeling and simulation related to biopharmaceutics assessment is evolving with the increased knowledge, software availability and guidance publication.
- The applications cover the aspects including clinically relevant dissolution acceptance criterion, critical material attributes specifications, risk assessment, pH dependent drug-drug interaction, food effect, and biowaiver.

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.

Submissions with PBPK Absorption Modeling on New Drug Side

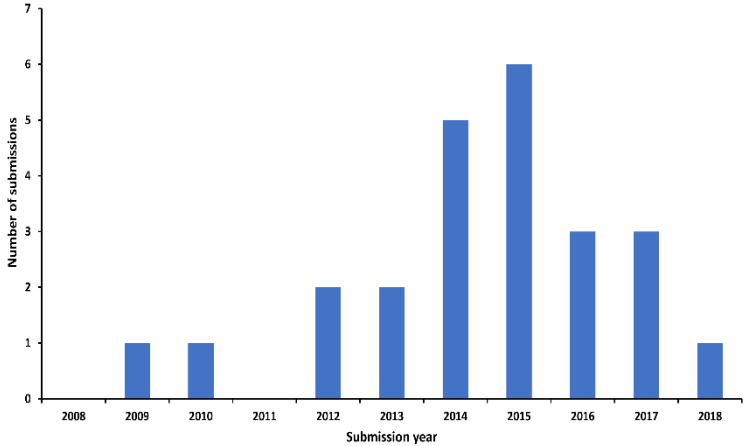


Figure. Number of New Drug Applications containing PBPK absorption modeling and simulations for biopharmaceutics assessment from January 2008 to December 2018 (Investigational New Drugs are not included)

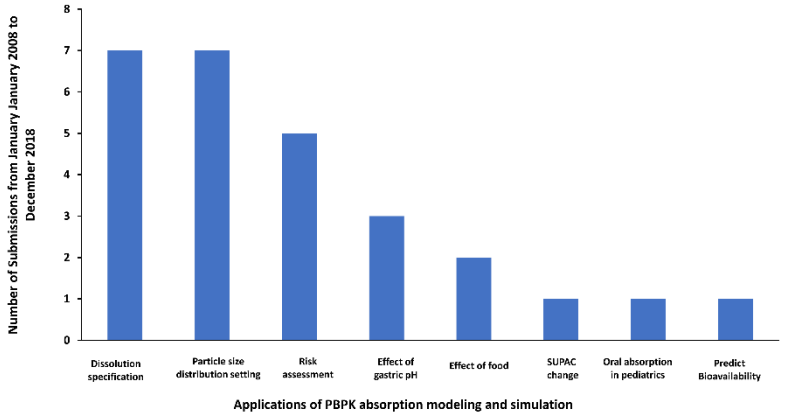
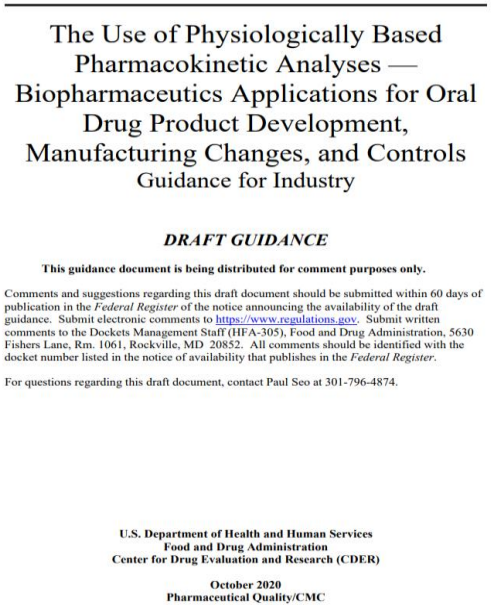


Figure. Applications of PBPK absorption modeling and simulations in the New Drug Applications submissions*. Abbreviations: SUPAC, Scale-Up and Post-Approval Changes

***Note that in some cases the same model was used for multiple purposes, e.g., setting of both particle size specification and dissolution acceptance criteria**

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.

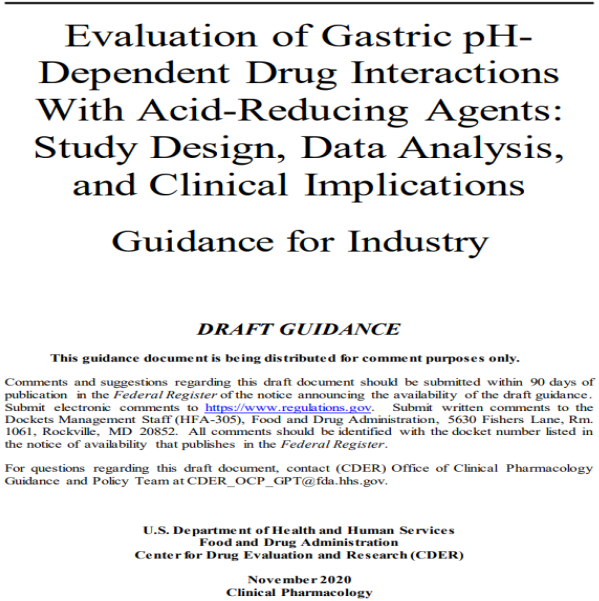
Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management 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

This guidance document is being distributed for comment purposes only.

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*.

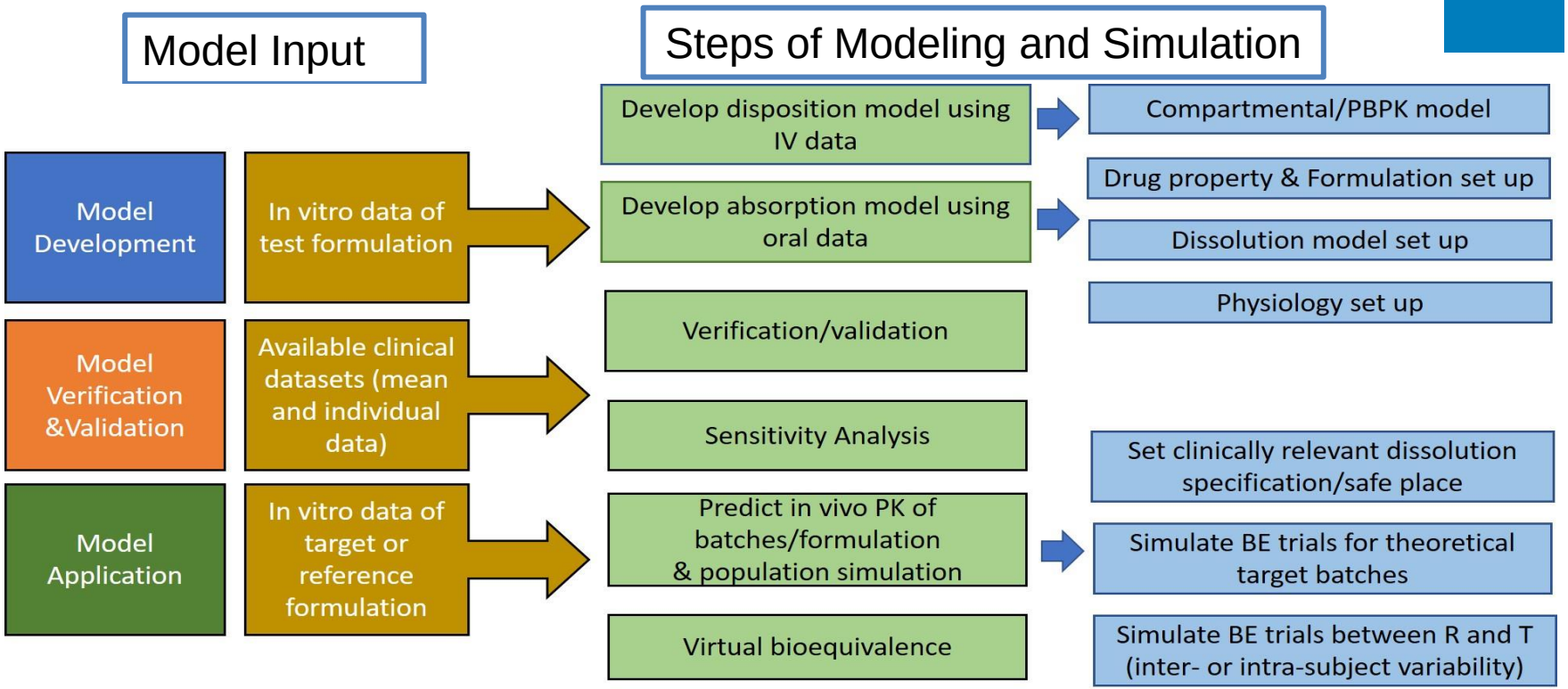
For questions regarding this draft document, contact (CDER) Office of Clinical Pharmacology Guidance and Policy Team at CDER_OCP_GPT@fda.hhs.gov.

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

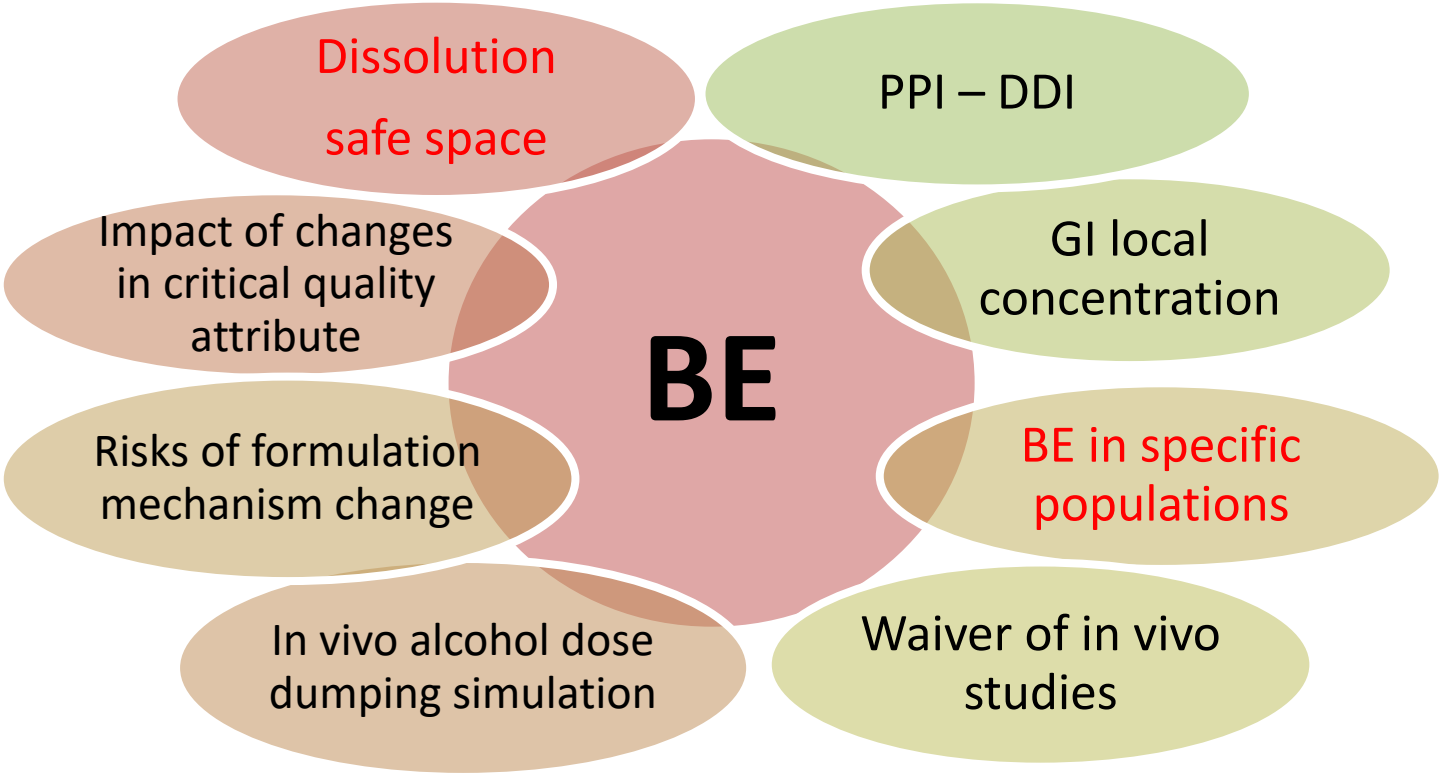
General PBPK Modeling Procedure in ANDA Submission



PK: pharmacokinetic; IV: intravenous; T: test product; R: reference product; BE: bioequivalence

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

Regulatory Questions that PBPK Absorption Model may Answer



ADME

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

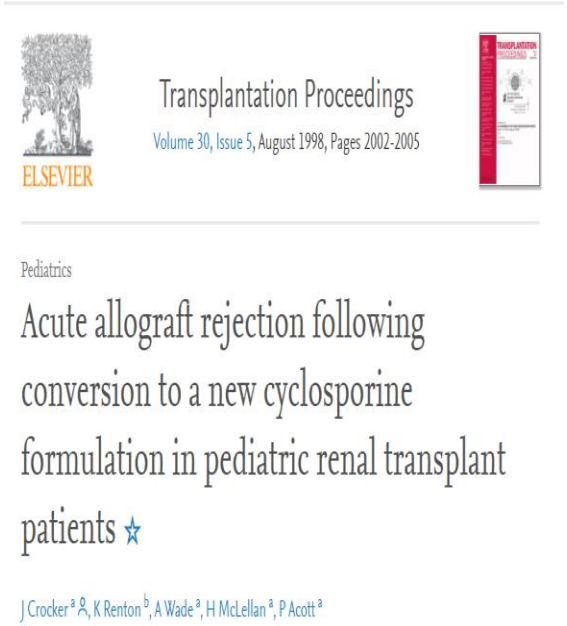
	Putative risk factors	Number of studies identified
Physiological factors (ADME effect)	Age-related absorption effects (e.g., GI motility, GI fluid volume or composition, and GI transit time)	28
	Age-related distribution effects (e.g., protein binding)	2
	Age-related metabolism or clearance effects	15
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: BAA #HHSF223201810112C, 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*

Physiological Risk Factors
ADME Effect



ELSEVIER

Transplantation Proceedings

Volume 30, Issue 5, August 1998, Pages 2002-2005

Pediatrics

Acute allograft rejection following conversion to a new cyclosporine formulation in pediatric renal transplant patients ☆

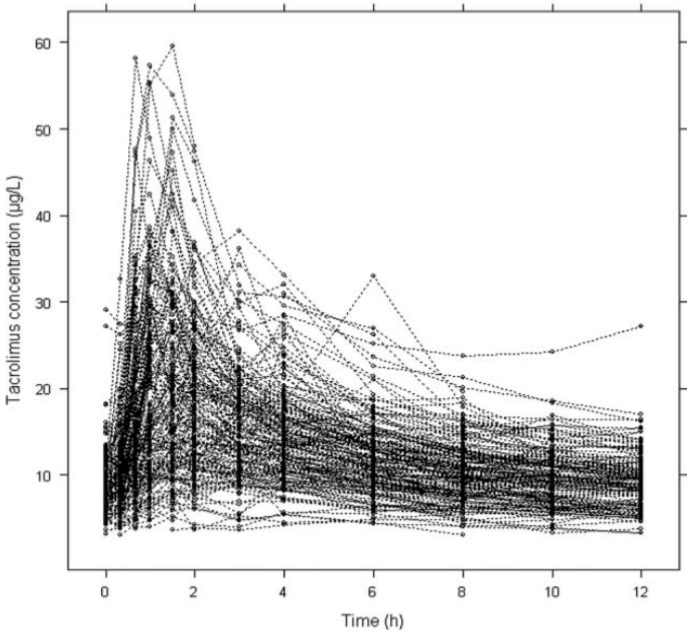
J Crocker [a] [Q], K Renton [b], A Wade [a], H McLellan [a], P Acott [a]

In children Neoral was rapidly absorbed and produced a high peak level of within 1 to 2 hours after dosing; Unique to pediatric patients, who generally have **increased GI motility**, and may be a feature unique to drugs like CyA with its dependence on metabolism in the GI tract

ADME: Absorption, distribution, metabolism and excretion

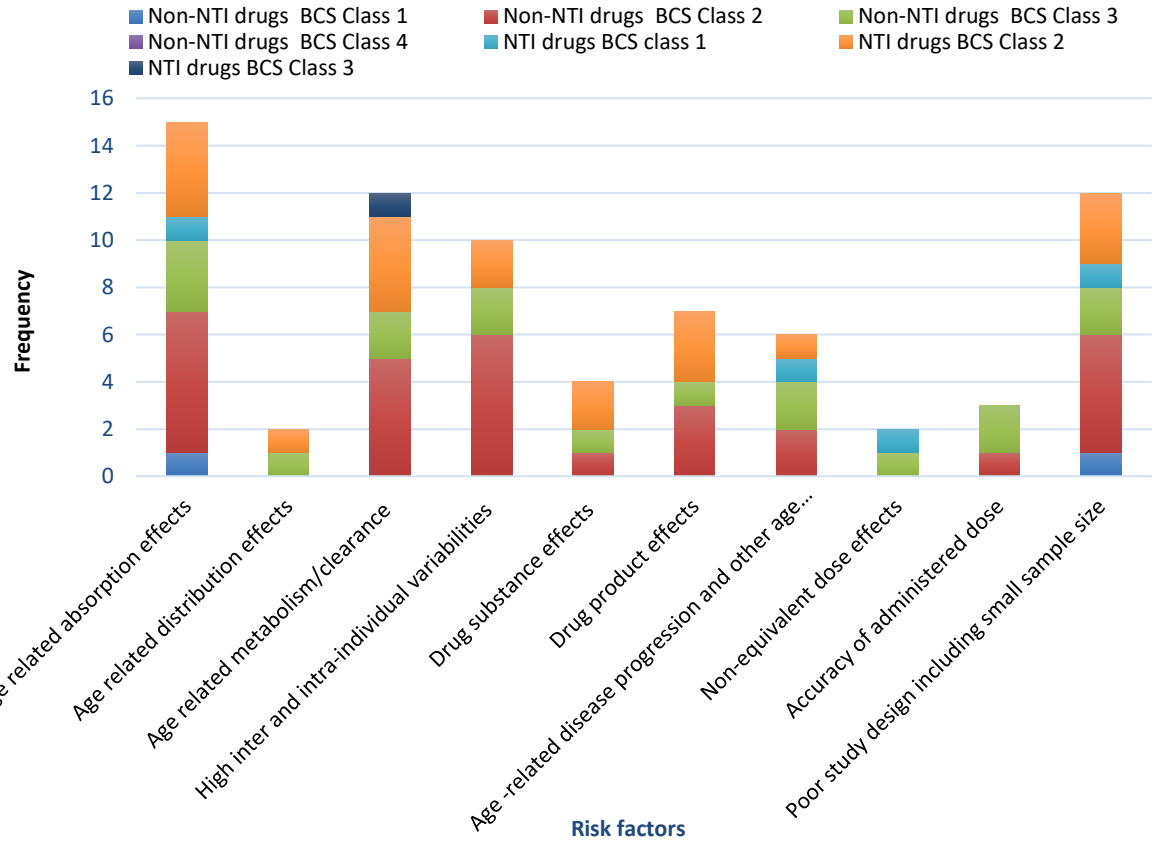
Pediatric Population Characteristics

- High inter-individual variability was reported in several studies
- Children are inherently variable due to different stages of maturation between individuals
- Typically, clinical studies conducted in children are not conducted in a “healthy” population
- Examples of genetic polymorphism within the population



Sikma MA et al., AM J Transplant, 2015, DOI: 10.1111/ajt.13309

Summary of Risk Factors



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:

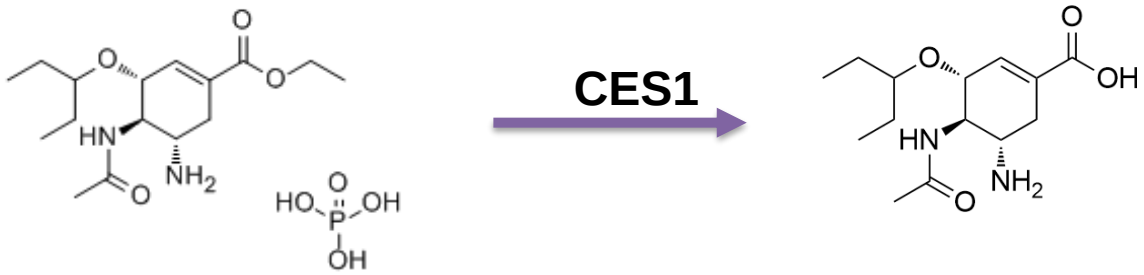
- Develop a PBPK model for a putative BCS Class 1/3 drug, oseltamivir phosphate (OP) and its metabolite oseltamivir carboxylate (OC) in both adults and pediatrics
- Conduct virtual BE simulations to establish BE dissolution safe space for OP in both adults and pediatrics

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)

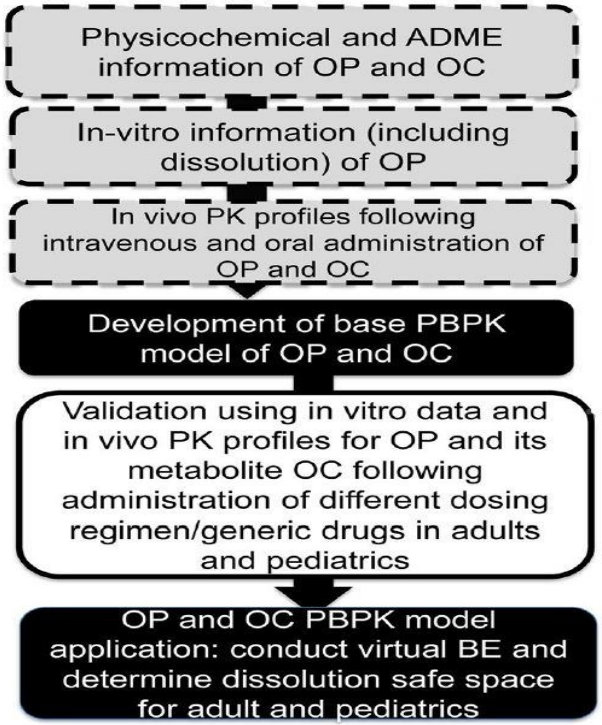
- Antiviral medication, for influenza A and B
- A pro-drug of the active metabolite Oseltamivir Carboxylate (OC)



OP **OC**

PBPK Model Development

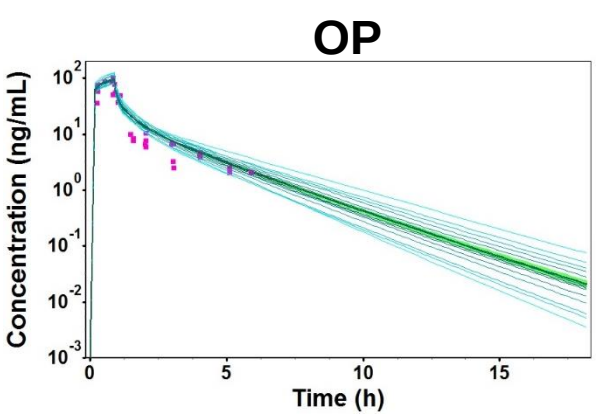
Properties	Value
LogP (OP/OC)	0.36/− 2.1
Molecular weight (OP/OC)	312/284
pKa (OP/OC)	7.70/8.2
Distribution	
Human blood to plasma ratio (OP/OC)	1/0.6
Fraction unbound in plasma (OP/OC)	58%/97%
Elimination	
CL_{renal} (L/h) (OP/OC)	4.2/18.8 (adults, for i.v. and oral)
V_{max} (mg/s/mg-CES1)*	0.52 (adults, 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)	$1.01*10^{-4}$

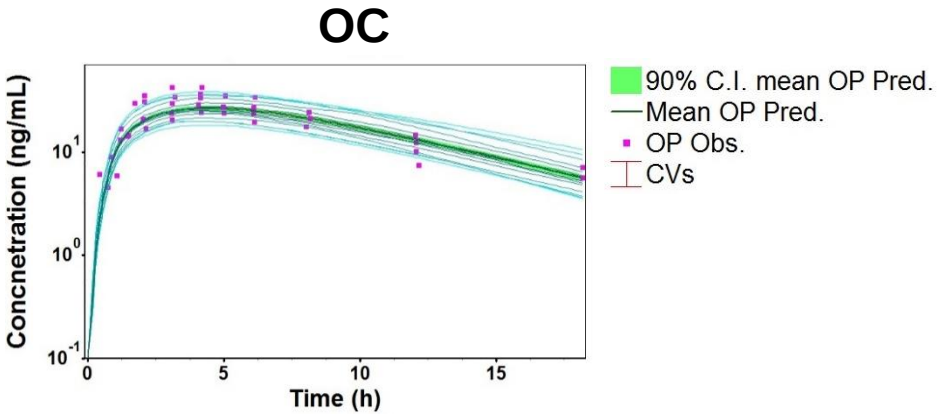


Miao L, Mousa YM, Zhao L, Raines K, Seo P, Wu F. Using a Physiologically Based Pharmacokinetic Absorption Model to Establish Dissolution Bioequivalence Safe Space for Oseltamivir in Adult and Pediatric Populations. AAPS J. 2020 Aug 10;22(5):107.

PBPK Model for Intravenous OP

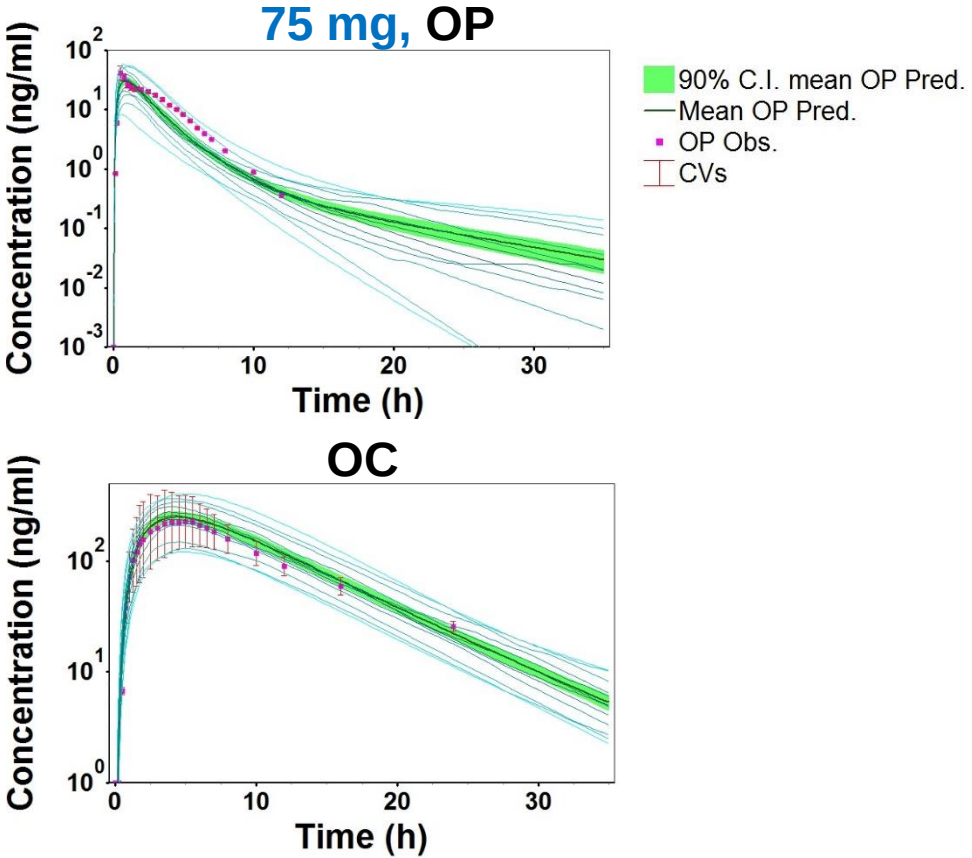
- GastroPlus™ with PBPKPlus™ module was used for modeling and simulation
- **15 mg intravenous OP**

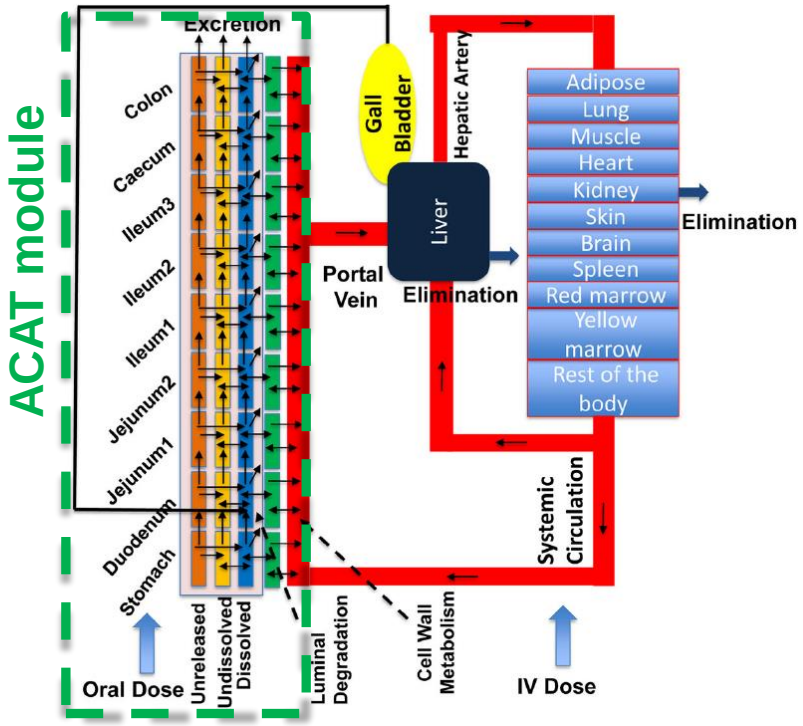




Miao L et al. AAPS J. 2020 Aug 10;22(5):107

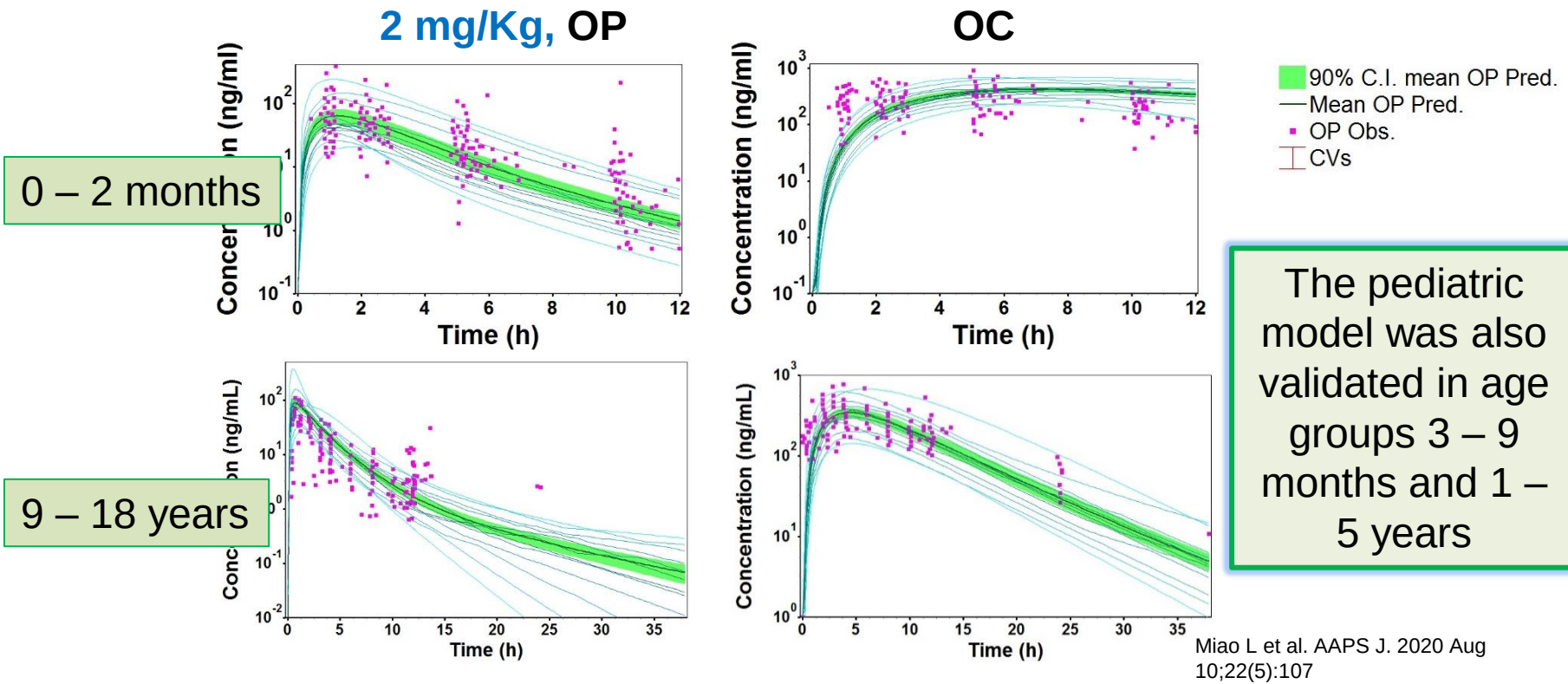
PBPK Model for Oral OP





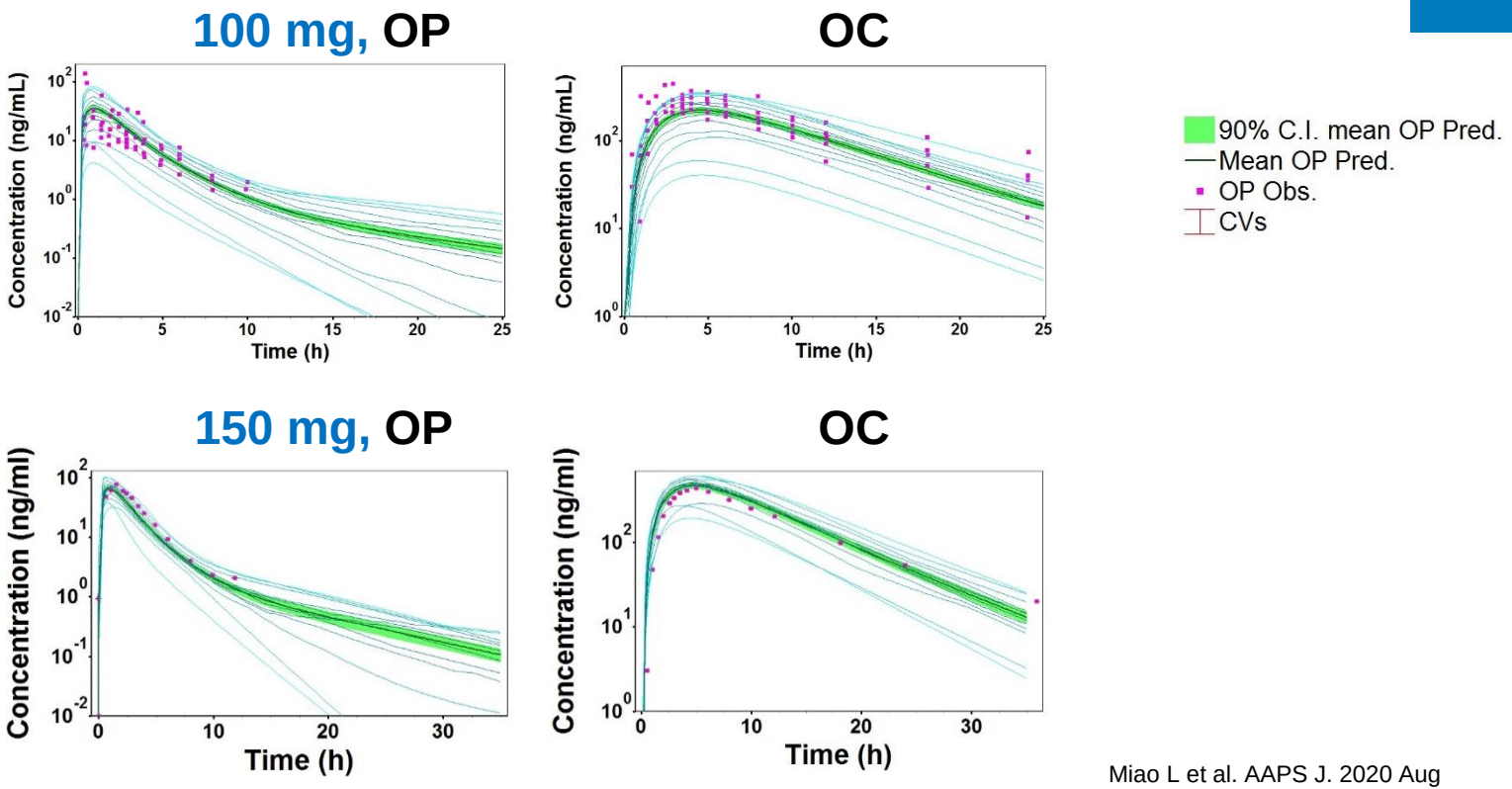
Miao L et al. AAPS J. 2020 Aug 10;22(5):107

Predicting the PK Profiles in Pediatrics



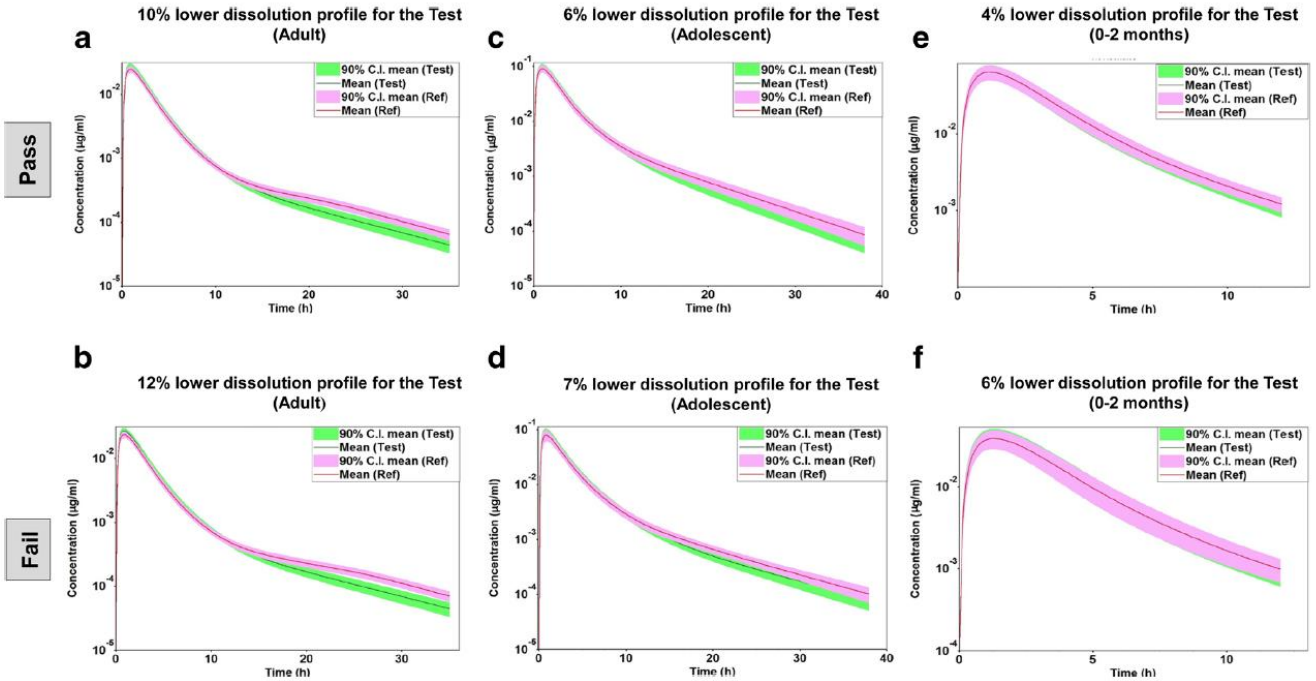
Miao L et al. AAPS J. 2020 Aug 10;22(5):107

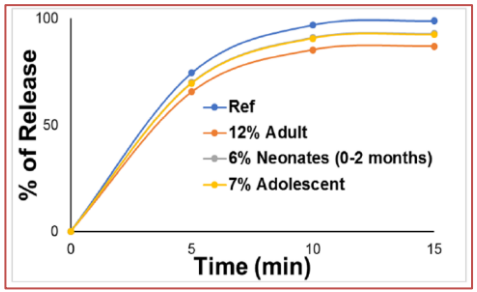
Validation of PBPK Model for Oral OP



Miao L et al. AAPS J. 2020 Aug 10;22(5):107

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

Miao L et al. AAPS J. 2020 Aug 10;22(5):107

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 to 18-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 to the models along with additional research and applied regulatory experiences, 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
- The Agency encourages applicants to submit modeling and simulation data and communicate at an early stage, e.g., via pre-ANDA meeting or controlled correspondence

Recent Publications Supported by Our Internal and External Research

The AAPS Journal (2021) 23: 31
DOI: 10.1208/s12248-021-00564-2

Commentary

Biopharmaceutics Applications of Physiologically Based Pharmacokinetic Absorption Modeling and Simulation in Regulatory Submissions to the U.S. Food and Drug Administration for New Drugs

Fang Wu,[1,2,9] Heta Shah,[3] Min Li,[1] Peng Duan,[3] Ping Zhao,[4,5] Sandra Suarez,[3] Kimberly Raines,[1] Yang Zhao,[1,6] Meng Wang,[1,7] Ho-pi Lin,[1] John Duan,[3] Lawrence Yu,[8] and Paul Seo[1,9]

The AAPS Journal (2020) 22: 107
DOI: 10.1208/s12248-020-00493-6

Research Article

Using a Physiologically Based Pharmacokinetic Absorption Model to Establish Dissolution Bioequivalence Safe Space for Oseltamivir in Adult and Pediatric Populations

Lei Miao,[1] Youssef M. Mousa,[1] Liang Zhao,[1] Kimberly Raines,[2] Paul Seo,[2] and Fang Wu[1,3]

Biopharmaceutics & Drug Disposition

INVITED REVIEW

Scientific considerations to move towards biowaiver for biopharmaceutical classification system class III drugs: How modeling and simulation can help

Fang Wu, Rodrigo Cristofoletti, Liang Zhao , Amin Rostami-Hodjegan

CPT: Pharmacometrics & Systems Pharmacology

Article | Open Access

Application of Physiologically-Based Pharmacokinetic Modeling to Predict Gastric pH-Dependent Drug–Drug Interactions for Weak Base Drugs

Zhongqi Dong, Jia Li, Fang Wu, Ping Zhao, Sue-Chih Lee, Lillian Zhang, Paul Seo, Lei Zhang

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Dr. Liang Zhao, Dr. Lucy Fang

University of Birmingham

Dr. Gopal Pawar, Dr. Hannah Batchelor

FDA/CDER/OTS/OCP

Dr. Gilbert J. Burckart

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