Using Physiologically-Based Pharmacokinetic Absorption Modeling to Support Biopharmaceutics Classification System Class 3 Drug Waiver

SBIA 2020: Advancing Innovative Science in Generic Drug Development Workshop

Session 4: Practical Considerations in the Study Design and Data Evaluation Recommended in Product-Specific Guidances

Topic 1: Oral Products

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Office of Generic Drugs | CDER | U.S. FDA

September 30, 2020

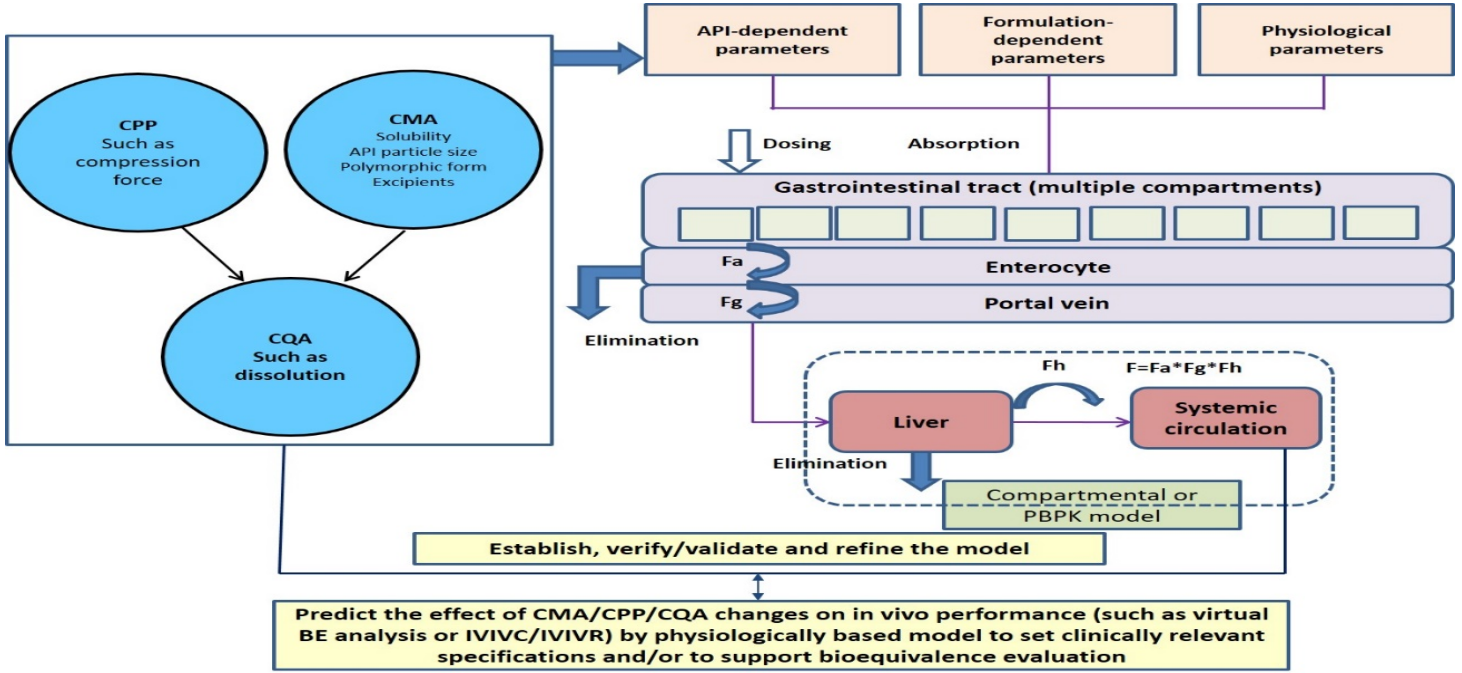
Learning Objectives

1. To understand PBPK absorption modeling and questions that PBPK models can help address to assist generic drug development

2. To learn strategies on developing PBPK modeling and conducting virtual bioequivalence simulations for potential use of PBPK modeling to support BCS Class 3 biowaiver

BCS: Biopharmaceutics Classification System; PBPK: Physiologically-based Pharmacokinetic Modeling

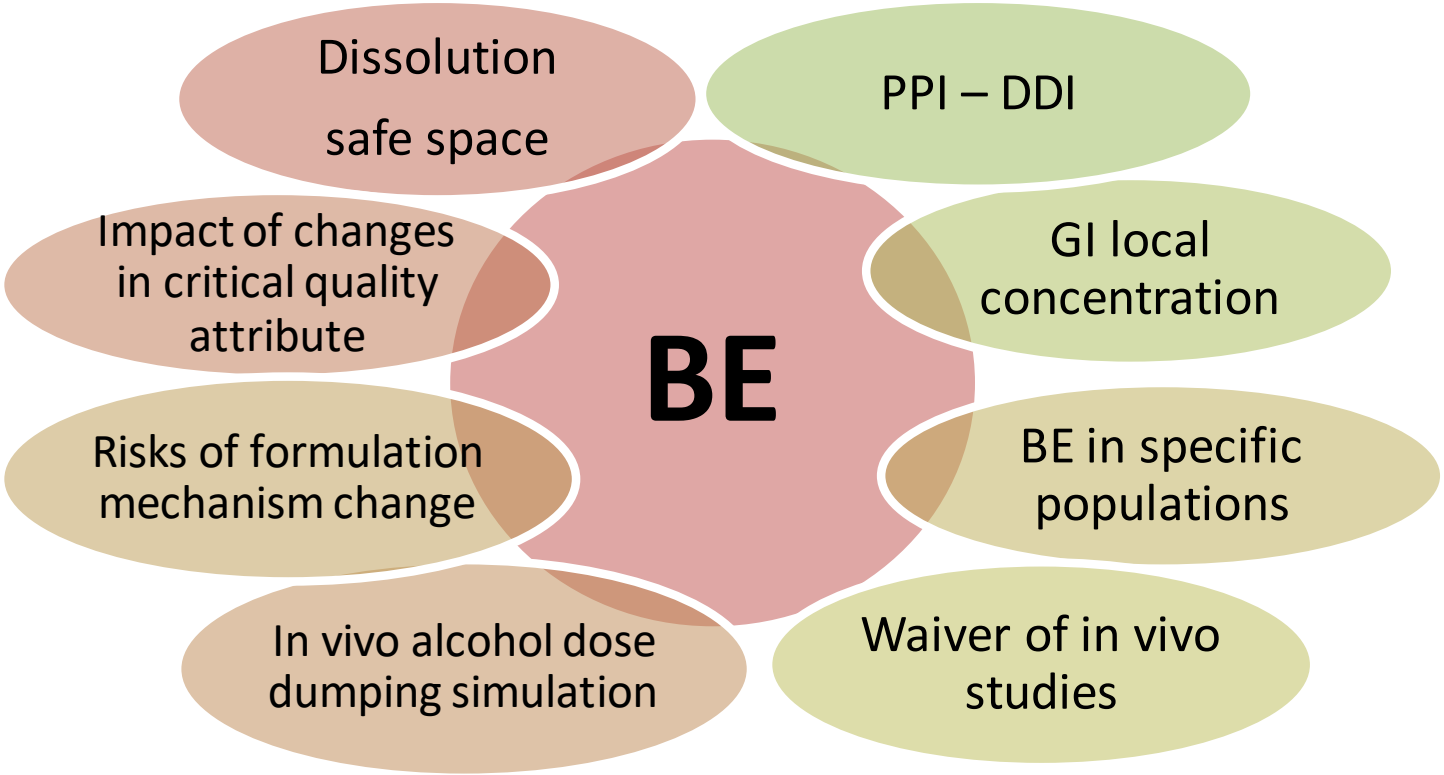
PBPK Absorption Model



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. 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 can Answer



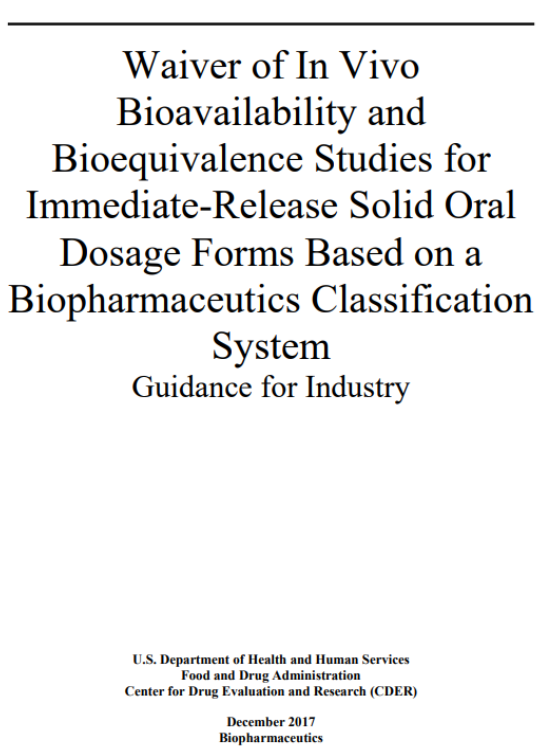
BE: bioequivalence; PPI: proton pump inhibitor; GI: gastrointestinal; DDI: drug-drug interaction

Courtesy of Dr. Liang Zhao

Guidance for BA/BE waivers (biowaivers) based on BCS

For BCS Class 3 drug products, the following should be demonstrated:

- The drug substance is highly soluble
- The drug product (test and reference) is very rapidly dissolving
- The test product formulation is qualitatively (Q1) the same and quantitatively (Q2) very similar

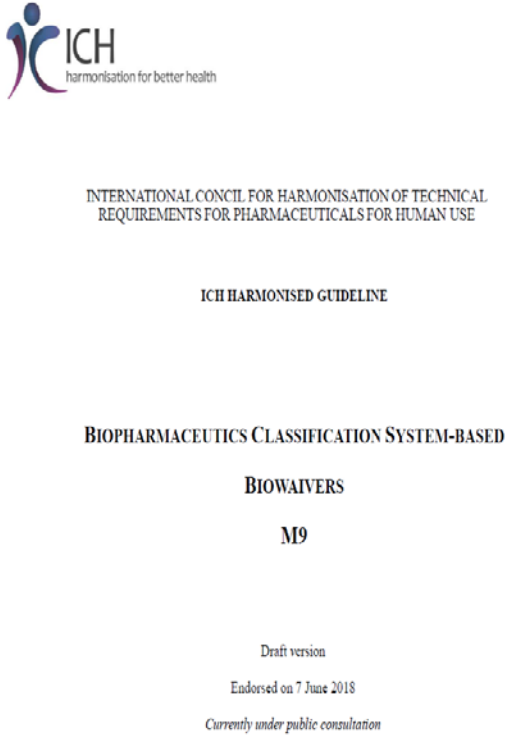

Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System

Guidance for Industry

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

December 2017
Biopharmaceutics

Link: https://www.fda.gov/media/70963/download


INTERNATIONAL CONCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

BIOPHARMACEUTICS CLASSIFICATION SYSTEM-BASED BIOWAIVERS

M9

Draft version

Endorsed on 7 June 2018

Currently under public consultation

Link: https://www.fda.gov/media/117974/download

www.fda.gov BA: Bioavailability

Biowaiver for BCS Class 3 Generic Drugs

PSG for Hydroxychloroquine Sulfate Oral Tablet

I. BCS Class 3-based biowaiver option

- "A waiver request of in vivo testing for this product may be considered provided that the appropriate documentation regarding high solubility, very rapid dissolution, and the test product formulation is qualitatively the same and quantitatively very similar"

www.fda.gov PSG: Product-Specific Guidance

Contains Nonbinding Recommendations

Guidance on Hydroxychloroquine Sulfate

This guidance represents the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient:	Hydroxychloroquine sulfate
Dosage Form; Route:	Tablet; oral
Recommended Studies:	Two options: Biopharmaceutics Classification System (BCS)-based biowaiver or in vivo study

I. BCS Class 3-based biowaiver option:

Link: https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_009768.pdf

Considerations for Biowaiver for BCS Class 3 Generic Drugs

Per PSG for Hydroxychloroquine Sulfate Oral Tablet

- The test product formulation should be qualitatively (Q1) the same and quantitatively (Q2) very similar

- In vitro characteristics meet the recommendation as indicated in the PSG (high solubility and very rapid dissolution)

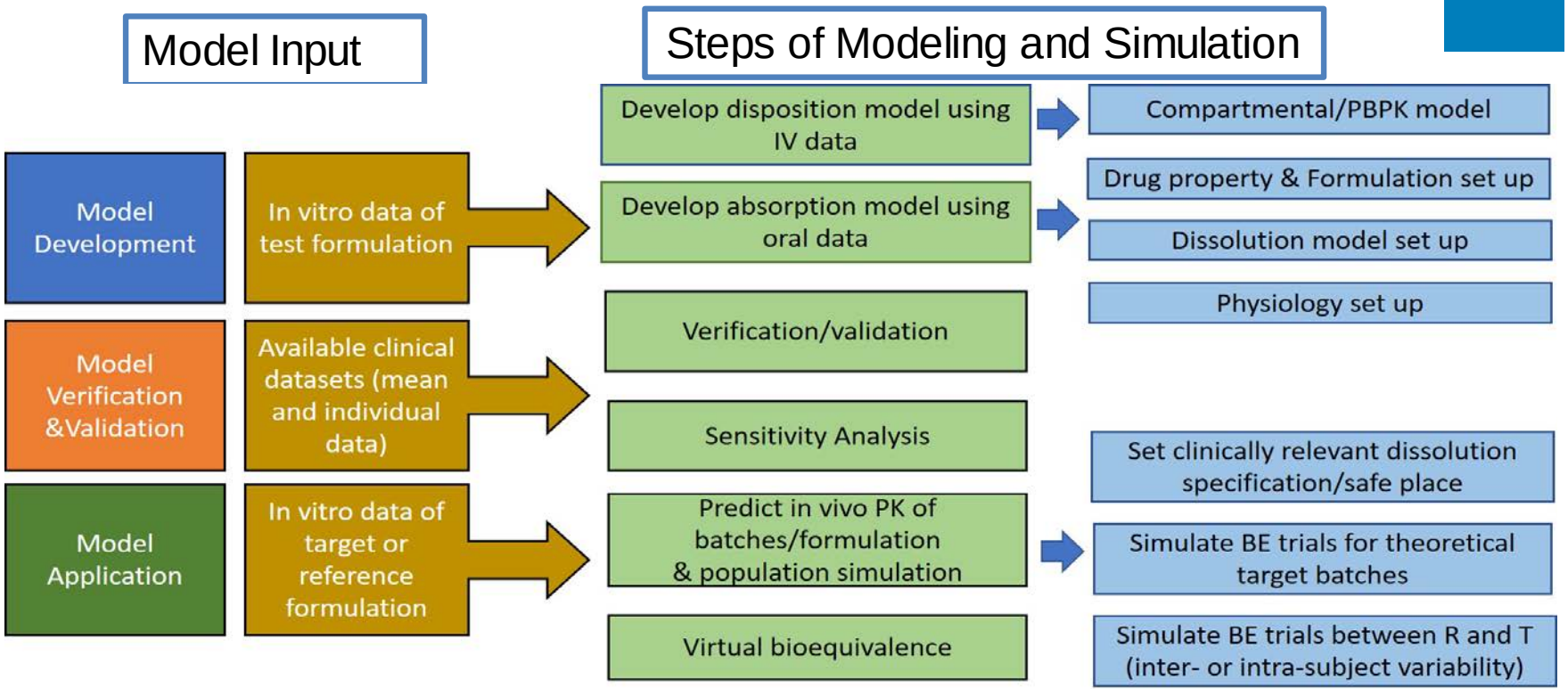
Expanding BCS Class 3 Biowaiver

- GDUFA-funded contract: *Expanding BCS Class 3 Waivers for Generic Drugs to Non-Q1/Q2* by Dr. Chris Bode from Absorption Systems Inc.
  - Use a novel in vitro product characterization tool to assess the impact of excipients on the dissolution and permeation of BCS Class 3 model drugs in solid oral dose forms
  - Improve confidence in the use of varying amounts of excipients, and potentially expand BCS Class 3 waivers for generic drugs to non-Q1/Q2 formulations
- Potential utility of PBPK modeling as an alternative BE approach to support biowaiver of non-Q1/Q2 BCS Class 3 drugs

GDUFA: Generic Drug User Fee Amendments

Link: https://www.fda.gov/drugs/generic-drugs/generic-drug-research-priorities-projects

General PBPK Modeling Procedure in ANDA Submission



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

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

Case Study 1: Using PBPK Modeling to Predict Pharmacokinetics for Saxagliptin

Purpose:

- Develop a PBPK model for a putative BCS Class 3 drug, saxagliptin

- Predict the impact of acid reducing agents (ARAs) on in vivo exposure of saxagliptin

Reference: Dong Z, Li J, Wu F, Zhao P, Lee SC, Zhang L, Seo P, Zhang L. Application of Physiologically-based Pharmacokinetic Modeling to Predict Gastric pH-dependent Drug-drug Interactions for Weak Base Drugs. CPT Pharmacometrics Syst Pharmacol. 2020. DOI: 10.1002/psp4.12541

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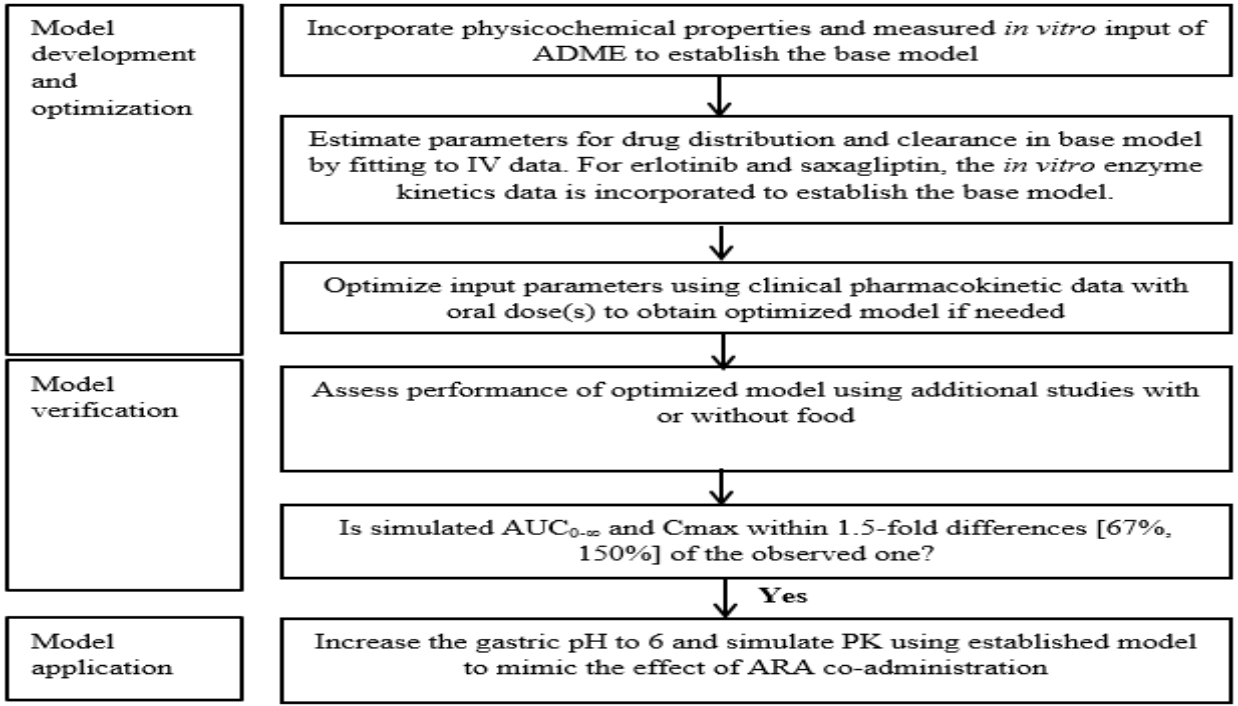
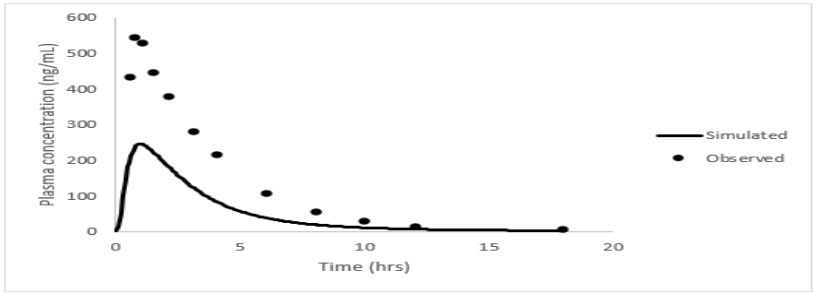


Figure: Flow diagram of model development and verification process.

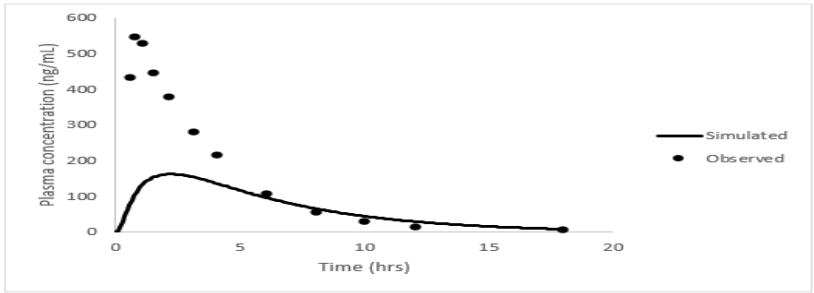
Reference: Dong Z , Li J, Wu F, Zhao P, Lee SC, Zhang L, Seo P, Zhang L. CPT Pharmacometrics Syst Pharmacol. 2020. DOI: 10.1002/psp4.12541

Refinement of the PBPK Model for Saxagliptin

a)

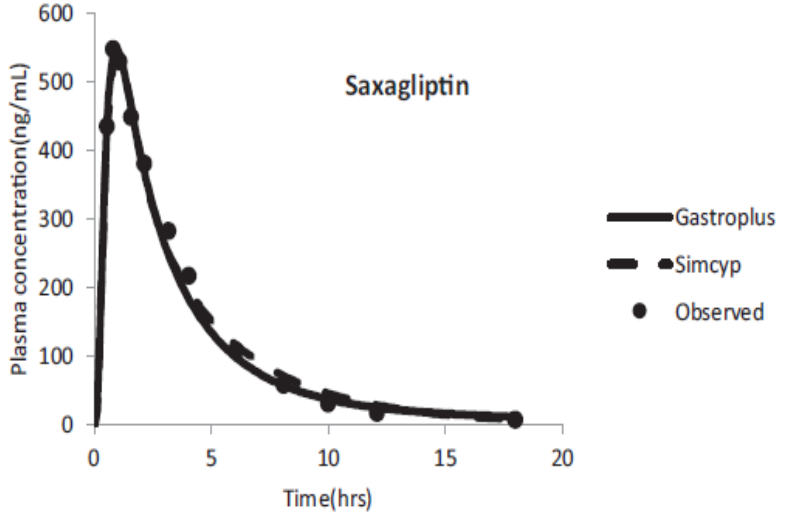


b)



Simulation of plasma concentrations followed by single oral of 100 mg saxagliptin with base model a) in Gastroplus and b) in SimCYP

After optimization of permeability and Intersystem Extrapolation Factor (ISEF)



Representative base model verification results. Simulation of plasma concentrations followed by a single oral dose of 100 mg saxagliptin

Reference: Dong Z , Li J, Wu F, Zhao P, Lee SC, Zhang L, Seo P, Zhang L. CPT Pharmacometrics Syst Pharmacol. 2020. DOI: 10.1002/psp4.12541

Sensitivity Analysis on Absorption-related Parameters

- Sensitivity analysis on absorption-related parameters suggested that **permeability** and **ISEF** has a significant impact on area under curve (AUC) comparing with other factors

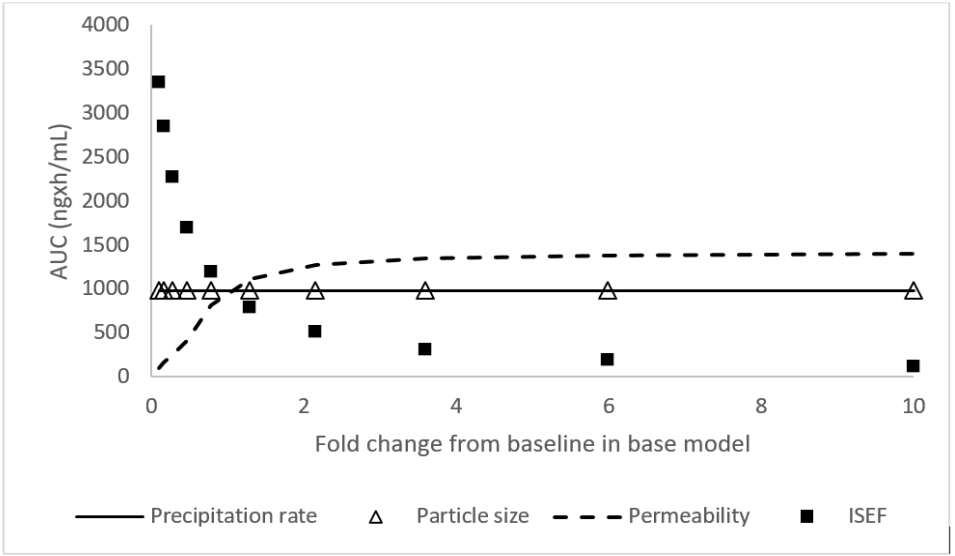
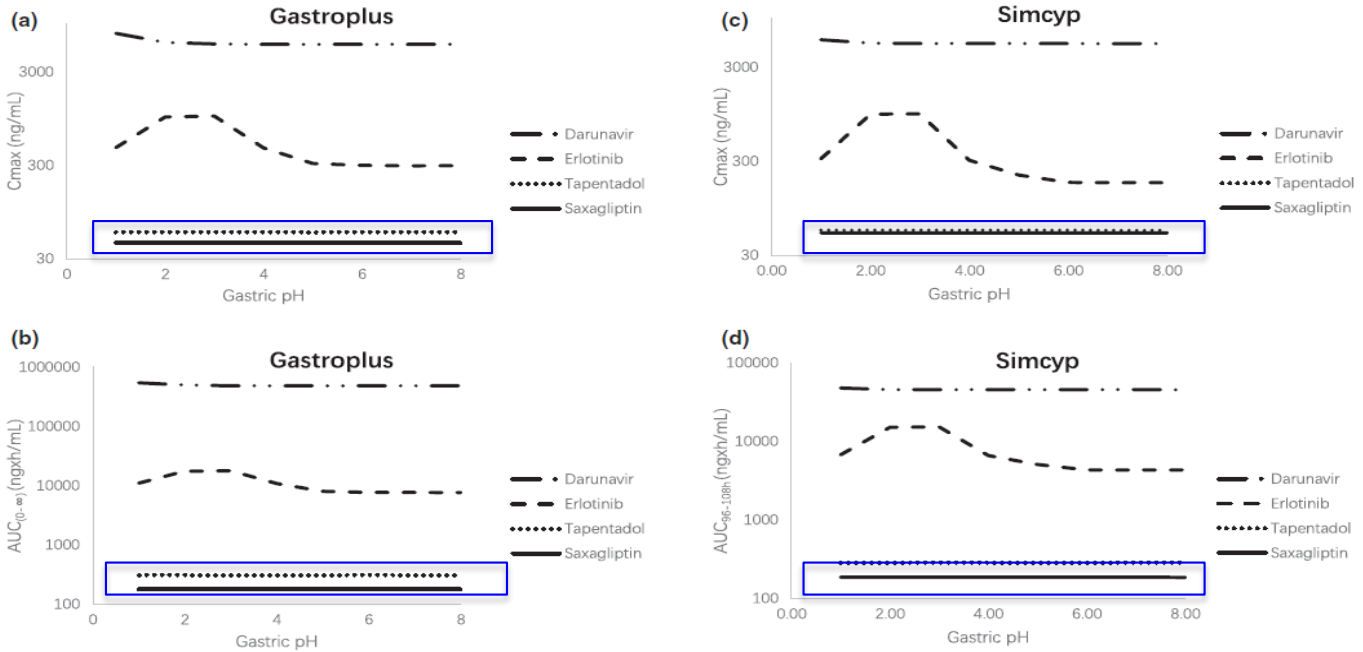


Figure: Impact of absorption-related parameters and ISEF on AUC for saxagliptin. X-axis represents the fold change from the baseline that was used in base model for each parameter. Y-axis represents the AUC following 5 mg single dose of saxagliptin.

Reference: Dong Z , Li J, Wu F, Zhao P, Lee SC, Zhang L, Seo P, Zhang L. CPT Pharmacometrics Syst Pharmacol. 2020. DOI: 10.1002/psp4.12541

Impact of Gastric pH on Drug Exposure



Impact of gastric pH on maximum plasma concentration (Cmax) and AUC for weak base drugs including saxagliptin (BCS Class 3) using the verified physiologically-based pharmacokinetic model

Reference: Dong Z , Li J, Wu F, Zhao P, Lee SC, Zhang L, Seo P, Zhang L. CPT Pharmacometrics Syst Pharmacol. 2020. DOI: 10.1002/psp4.12541

Case Study 1 Summary

- PBPK model was developed for the putative BCS Class 3 drug, saxagliptin.

- PBPK model could adequately describe the lack of the effect of ARAs on the drug exposure of weak base drugs including saxagliptin.

Reference: Dong Z , Li J, Wu F, Zhao P, Lee SC, Zhang L, Seo P, Zhang L. CPT Pharmacometrics Syst Pharmacol. 2020. DOI: 10.1002/psp4.12541

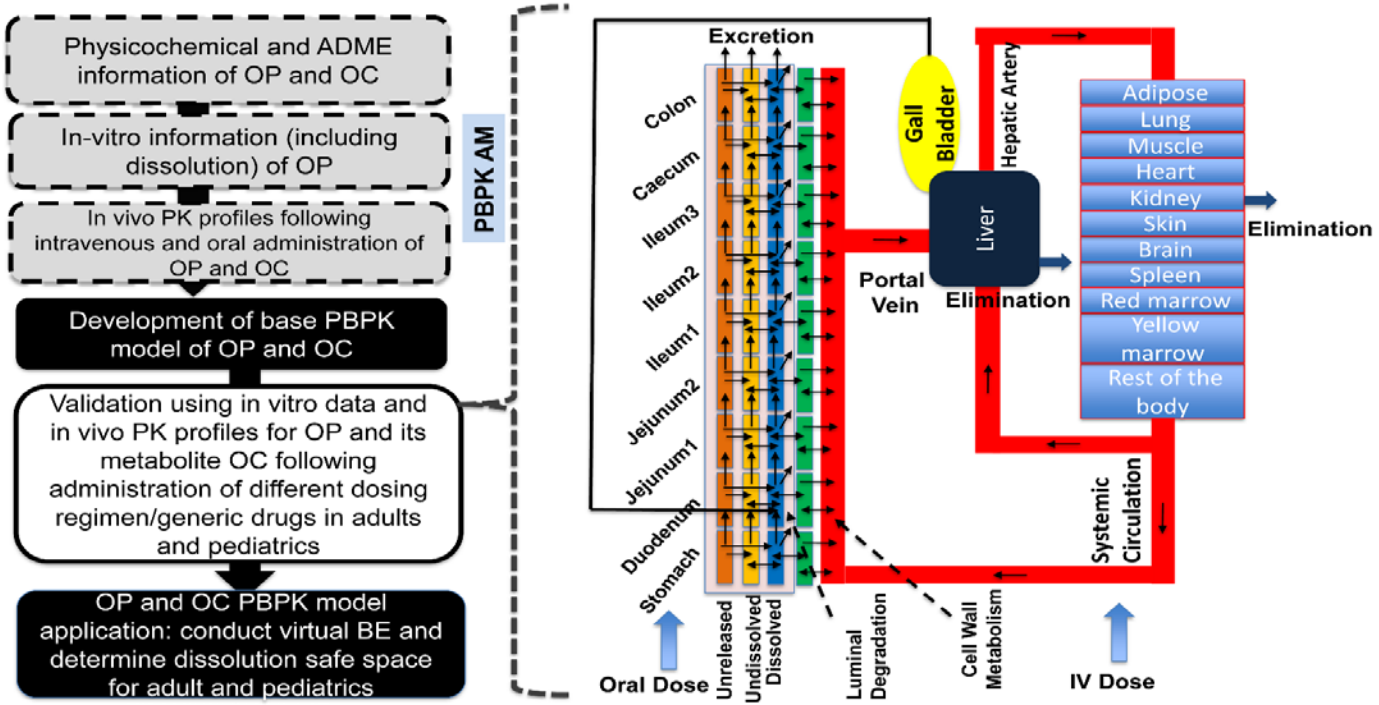
Case Study 2: Using PBPK Modeling to Establish Bioequivalence Dissolution Safe Space for Oseltamivir

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 bioequivalence (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

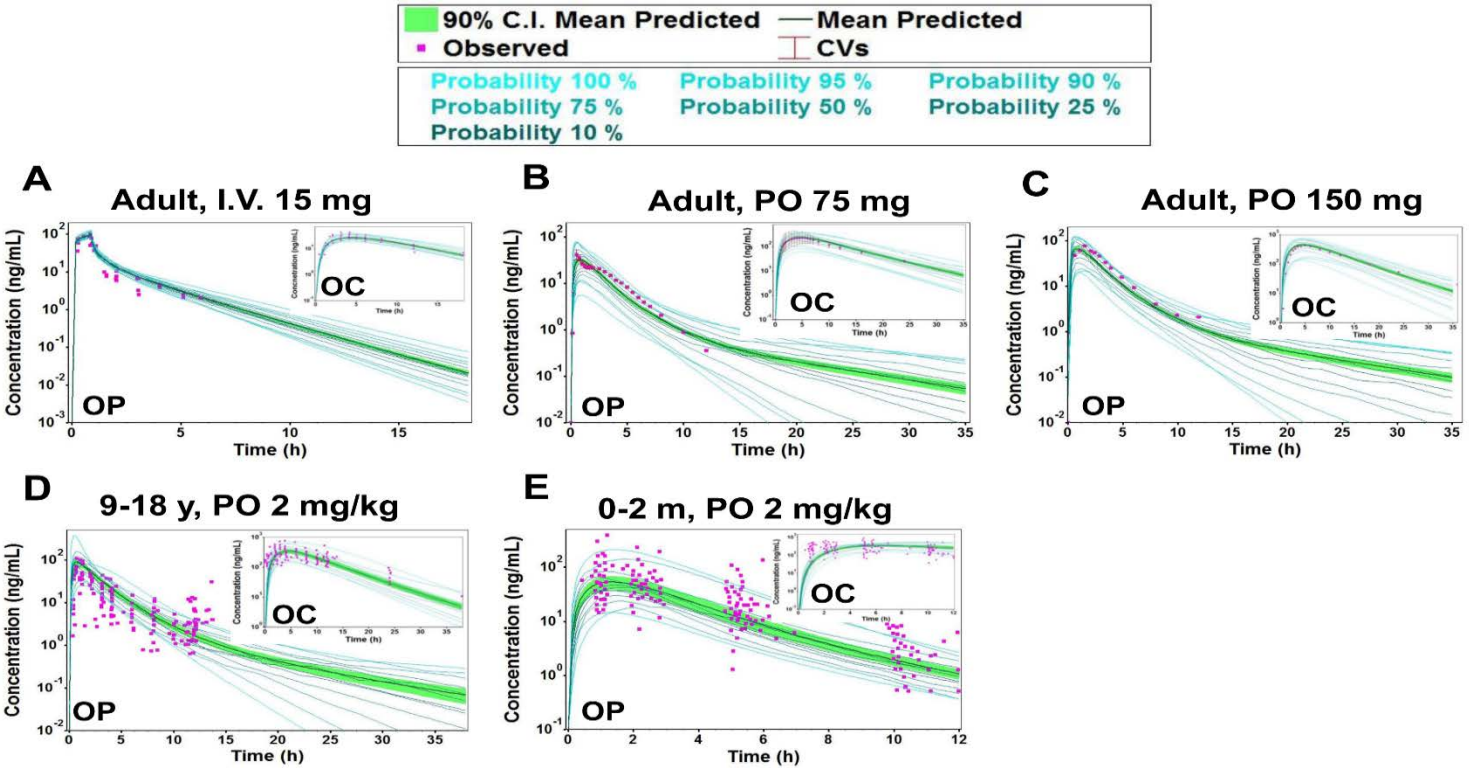
Case Study 2: Using PBPK Modeling to Establish BE Dissolution Safe Space for Oseltamivir



OP: oseltamivir phosphate; OC: oseltamivir carboxylate; RLD: reference listed drug

Reference: Miao L, Mousa Y, Zhao L , Raines K, Seo P, Wu F. AAPS Journal, 2020. DOI : 10.1208/s12248-020-00493-6

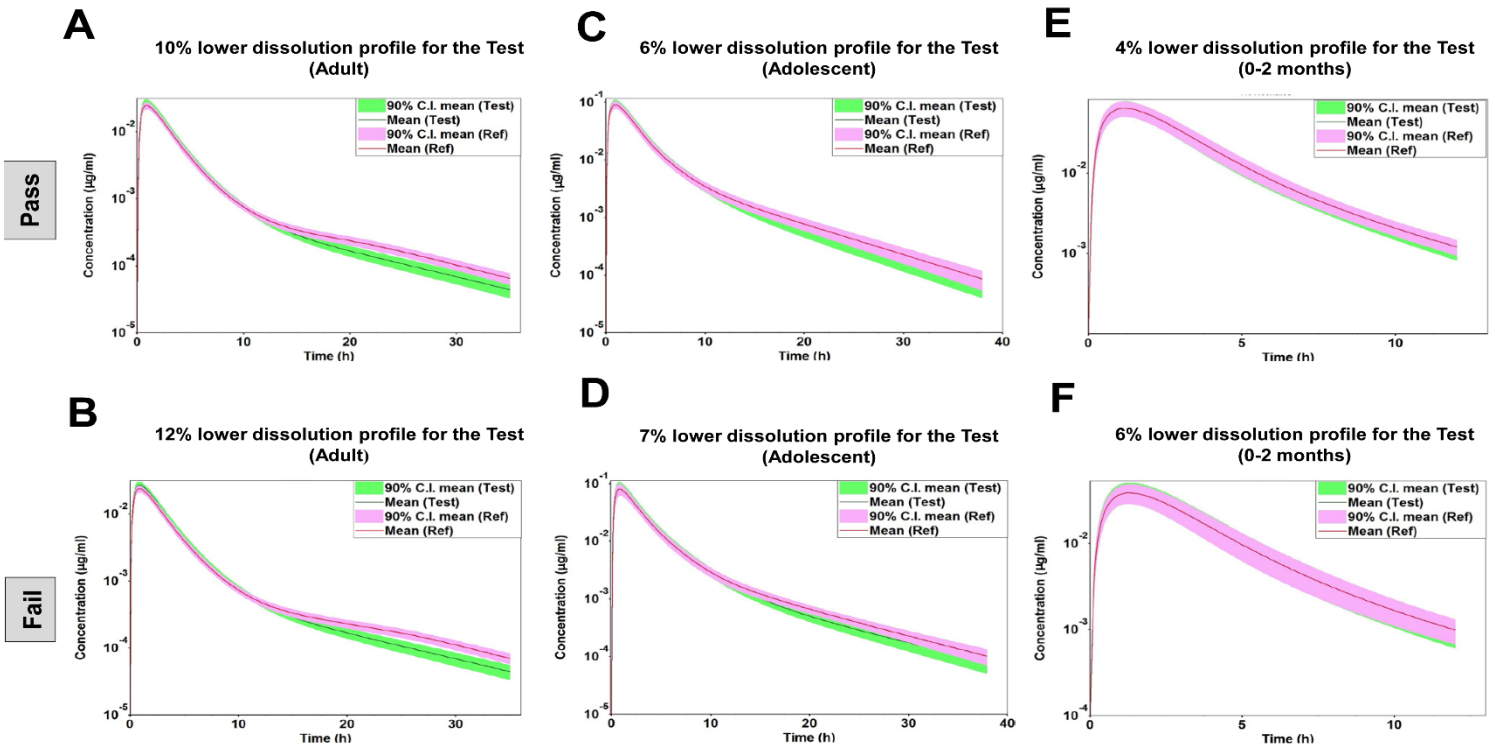
Simulated and Observed Concentration-Time Profiles for OP and OC in Adults and Pediatrics



OP: oseltamivir; OC: oseltamivir carboxylate; RLD: reference listed drug; PO: per oral

Reference: Miao L, Mousa Y, Zhao L , Raines K, Seo P, Wu F. AAPS Journal, 2020. DOI : 10.1208/s12248-020-00493-6

Population and Virtual BE Analysis between Test and Reference Product in Adults and Pediatrics to Determine BE Dissolution "Safe Space" for OP



OP: oseltamivir; OC: oseltamivir carboxylate; RLD: reference listed drug

Reference: Miao L, Mousa Y, Zhao L , Raines K, Seo P, Wu F. AAPS Journal, 2020. DOI : 10.1208/s12248-020-00493-6

Case Study 2 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 RLD in adults.
- In contrast, a stringent trend of dissolution boundary (safe space) was observed for pediatrics (6% slower for 8-18-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.

Reference: Miao L, Mousa Y, Zhao L , Raines K, Seo P, Wu F. AAPS Journal. 2020. DOI : 10.1208/s12248-020-00493-6

Conclusion

- These cases demonstrated the utility of PBPK absorption modeling and simulation (M&S) to support the pharmacokinetic evaluation for BCS Class 3 Drugs.
- PBPK absorption M&S could be used as an alternative BE approach and aid more regulatory decision making in generic drug areas to ensure safe and effective use of drug products.
- The FDA/Agency encourages submitting alternative BE proposals with modeling and simulation data.
- Communicating with the Agency at an early stage, e.g., via controlled correspondences or pre-ANDA meetings, is encouraged.

Challenge Question

PBPK Absorption Modeling can be used for:

A. Predicting the impact of gastric pH on the pharmacokinetics of weak base drugs

B. Serving as an alternative BE approach for waiving the in vivo BE studies

C. Setting bioequivalence dissolution safe space for special populations

D. All of the above

Challenge Question

PBPK Absorption Modeling can be used for:

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C. Setting bioequivalence dissolution safe space for special populations

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Acknowledgement

FDA/OGD/ORS/Division of Quantitative Methods and Modeling

Dr. Liang Zhao, Dr. Lucy Fang

Dr. Lei Miao, Dr. Youssef Mousa

Dr. Andrew Babinski, Dr. Zhanglin Ni

Colleagues from ORS/DQMM/Quantitative Clinical Pharmacology Team

FDA/OGD/ORS: Dr. Robert Lionberger, Dr. Lei Zhang

Colleagues from OCP and OPQ who are involved in the publications

FDA Critical Path and MCMi Funding Support


FDA
U.S. FOOD & DRUG
ADMINISTRATION