PBPK Absorption Modeling and Virtual Bioequivalence to Support Generic Drug Development and Regulatory Decision Making for Oral Products

SBIA 2021: Advancing Generic Drug Development: Translating Science to Approval Date

Session 2: Considerations in Assessing Generic Drug Products of Oral Dosage Forms

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

Learning Objectives

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

2. To learn case examples on developing PBPK modeling and conducting virtual bioequivalence simulations for supporting regulatory decision making

PBPK: Physiologically-based Pharmacokinetic modeling

Outline of the Presentation

1. The Applications of PBPK Absorption Model
2. PBPK Guidances Supported by Regulatory Applications and Research
3. Highlights of PBPK Impacts in Office of Generic Drugs
4. Regulatory Review and Research of the PBPK Absorption Modeling and Simulation
5. Challenges and Opportunities
6. Conclusion

Submissions with 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, CMA 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

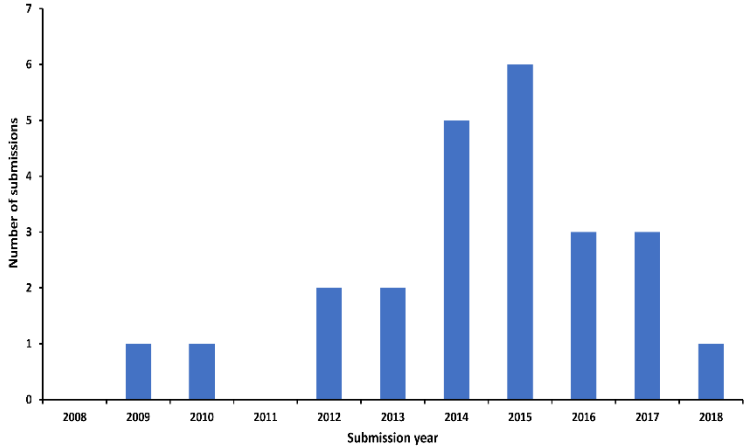


Figure. Number of New Drug Applications containing PBPK absorption modeling and simulations for biopharmaceutics assessment from January 2008 to December 2018 (Investigational New Drugs are not included)

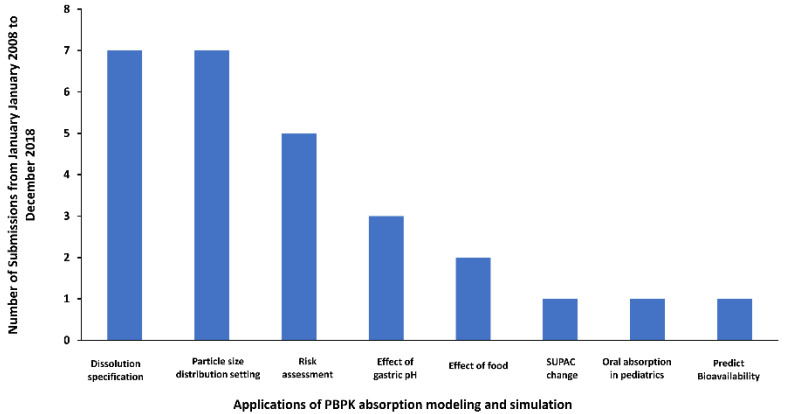
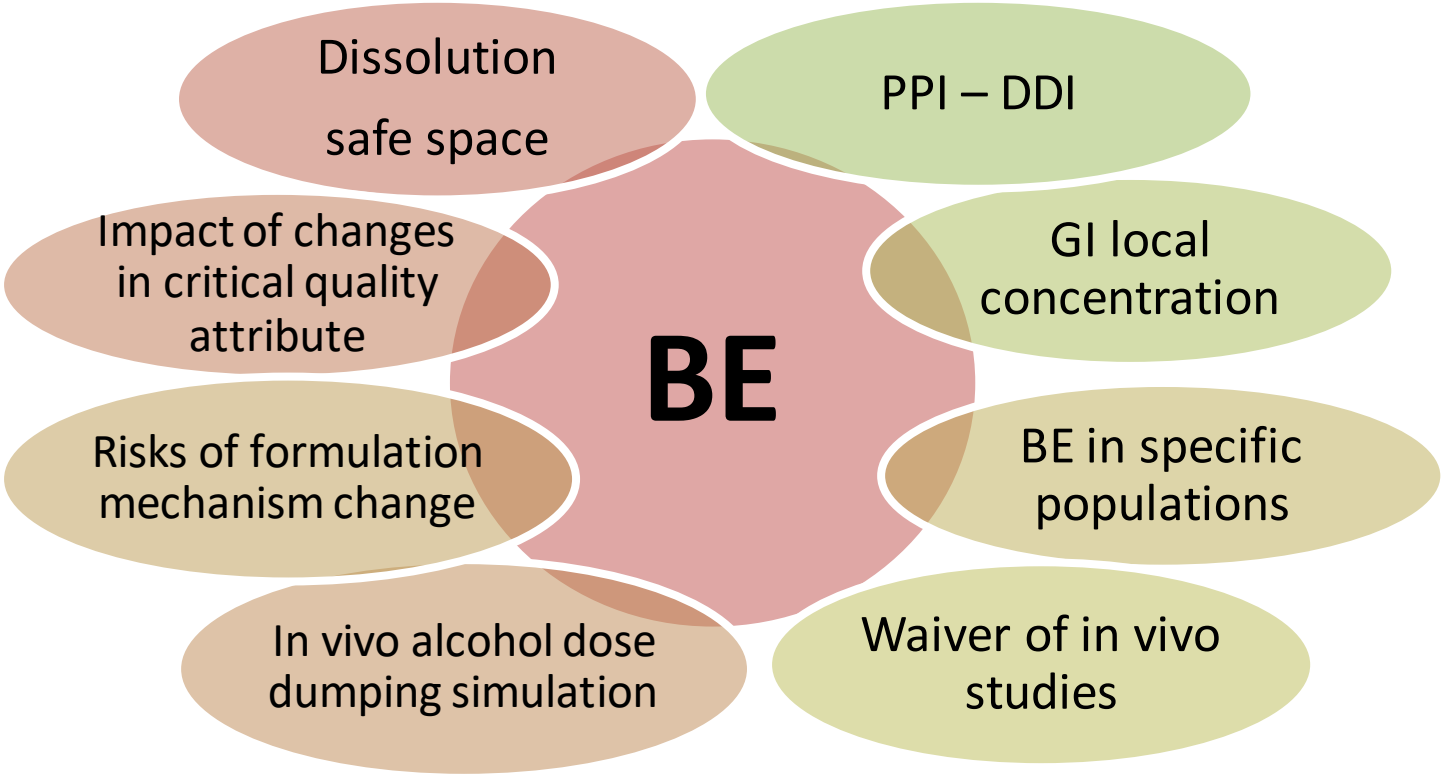


Figure. Applications of PBPK absorption modeling and simulations in the New Drug Applications submissions*. Abbreviations: SUPAC, Scale-Up and Post-Approval Changes

***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.

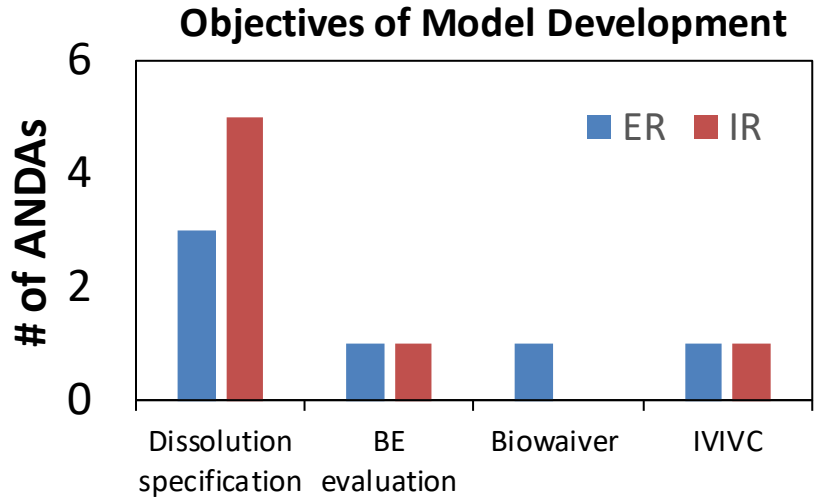
Regulatory Questions that PBPK Absorption Model can Answer



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

Overview of PBPK Absorption Modeling and Simulation in ANDA Submission up to 2018



- Major objective is to support dissolution specification settings (8 out of 13 cases from 2012 to 2018)
- Second often objective is to support bioequivalence assessment (2 out of 13 cases)

ANDA: Abbreviated New Drug Applications; IR: Immediate Release; ER: Extended Release; BE: Bioequivalence

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

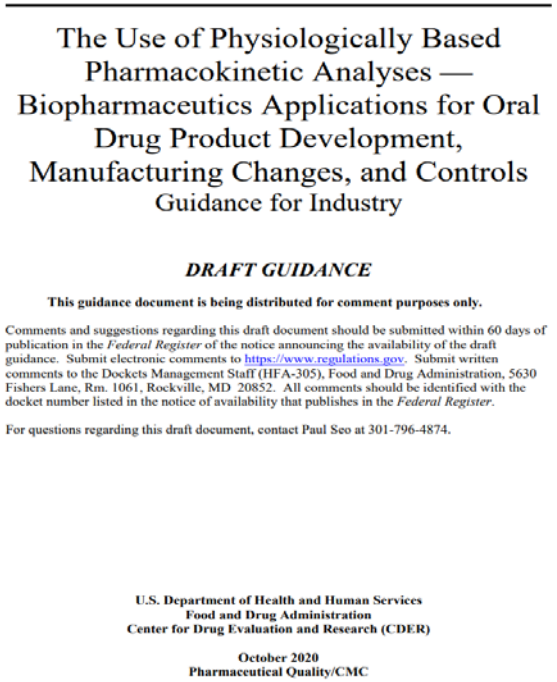
Highlights of PBPK Impacts in OGD

Category	Example Drug	Impact on regulatory decision making
Dissolution	Oxybutynin	Risk assessment for not conducting in vivo studies for lower strength generic products when bioequivalence has been established at higher strengths
Product quality	Prasugrel	Conclusion that less than 20% free base in prasugrel HCl product ensures in vivo BE of the generic product including subjects on PPI
Mechanism change risks	Venlafaxine	Model predicted that a delayed onset of venlafaxine release up to 4 h predicted to demonstrate BE for the openable matrix release mechanism against the osmotic pump based release mechanism
PPI effect	Several ER products	Risk assessment of changing drug release to a PH dependent mechanism
PK metrics determination	Mesalamine Suppositories	Determination of PK metrics for BE evaluation
Alcohol dose dumping	Metformin Hydrochloride ER	Assessment of alcohol dose dumping potential
Virtual simulation	Methylphenidate	Assessment of using PBPK model in combination with a two way crossover study to meet the guidance recommendation of a four way crossover study for BE

PPI: proton pump inhibitor; ER : extended release

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

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.

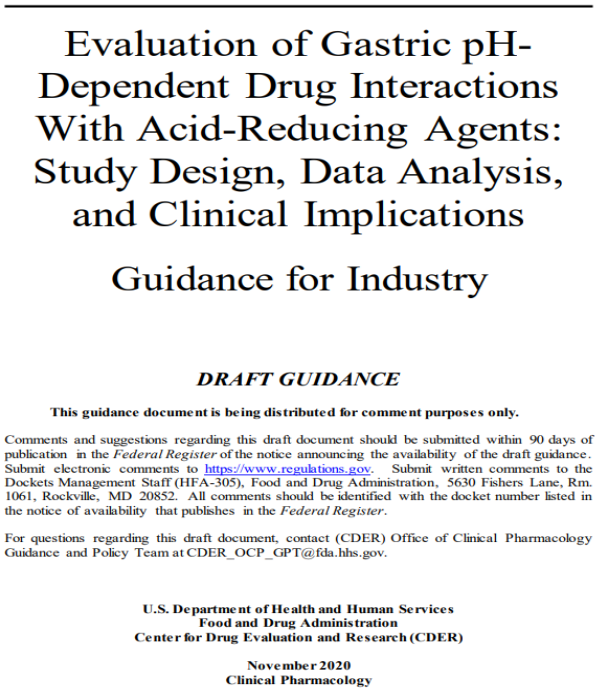
Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management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

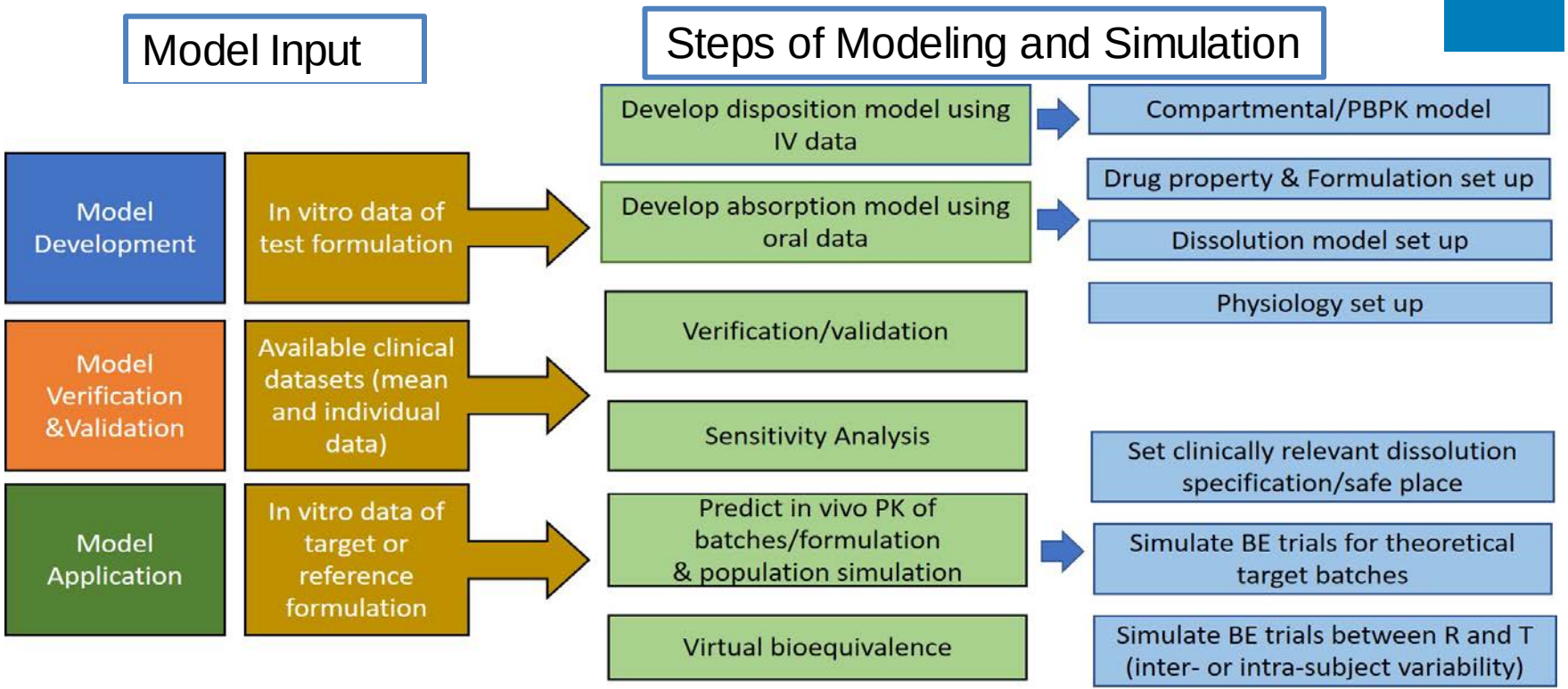
For questions regarding this draft document, contact (CDER) Office of Clinical Pharmacology Guidance and Policy Team at CDER_OCP_GPT@fda.hhs.gov.

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

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

PBPK absorption model in Assessing the Impact of Particle Size Distribution (PSD) on BE

A Capsule Product: efficacy related to systemic drug exposure

Background: PK parameters, e.g., Cmax and AUC are found to be sensitive to changes in mean particle size of Drug X under fasting condition. The Applicant submitted a mechanistic absorption model to link PSD with in vivo PK data.

Question: What is the impact of PSD on bioequivalence?

Solution: PBPK modeling and simulation suggested that the test vs reference PK metrics showed a low risk of non-BE when D90 changed over a wide range with a certain fixed value of D50 for all strengths.

Regulatory Impact: The modeling results support a satisfactory BE assessment of this ANDA and setting a clinically relevant 3 tier PSD specification.

Formu-lation	D10	D50	D90	Test/Reference Ratios			BE
				Cmax	AUCt	AUC inf	
Reference	X10	X50	X90				
Test 1	X10--	X50	X90--	107	105	106	Pass
Test 2	X10-	X50	X90-	1	98.3	98.2	Pass
Test 3	X10+	X50	X90+	81.2	81.5	81.3	Pass
Test 4	X10++	X50	X90++	80.3	79.8	80.3	Fail

Simulation results with fixed D50 and changed D10 and D90 using the reference upper bound PSD

Using PBPK Absorption Modeling to Support Waiver for Lower Strength with in vitro Testing Deviations

Background: Waiver of lower strength can be dependent on 1. formulation proportionality; 2 dissolution similarity; 3. bioequivalence on other strength. However, there are cases that have dissimilar dissolution profiles for lower strength of the Test product

Question: What is the impact of dissolution dissimilarity on the in vivo performance of the lower strength for Test product?

Review and Impact:

- PBPK/PBBM modeling was used for predicting the impact of faster release of lower strength on the bioequivalence under fasting and fed conditions.

Deficiencies identified on the submitted PBPK/PBBM model:

-Validate the model for the intended purpose using different strengths or using data from formulations with different release rate.

-Demonstrate prediction performance for pharmacokinetic data of bio-strength under fed condition.

-When these deficiencies are addressed, the developed PBPK/PBBM model can be used in assessing the impact of dissolution differences on in vivo performance/Bioequivalence.

PBBM: Physiologically-based Biopharmaceutics Modeling

Using PBPK Absorption Modeling to Evaluate the Impact of Food on Bioequivalence

Background: Based on FDA Draft Guidance (2013), "Bioequivalence Studies with Pharmacokinetic Endpoint for Drugs Submitted under an ANDA", generally, both fasting and fed in vivo bioequivalence (BE) study are recommended for immediate release (IR) product unless the product should be taken only on an empty stomach. However, only fasting study is recommended for BE evaluations for other agencies.

Question: Can we identify opportunities for harmonization such that only fasting studies are recommended for the establishment of BE at least in certain situations?

Regulatory Research:

- Potential utility of PBPK modeling to assess risk of bio-inequivalence attributable to food intake

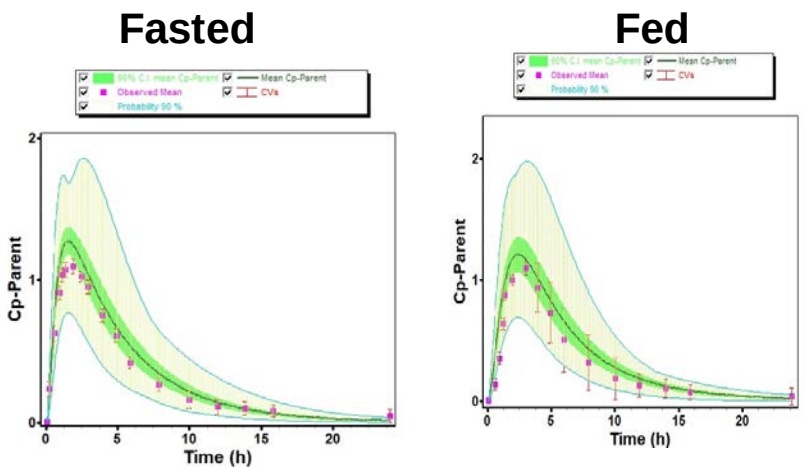


Figure. PBPK Model Simulation for Drug Y IR product

Parameter	Observed		Predicted		Observed	Predicted
	Fasted	Fed	Fasted	Fed	Ratio (Fed/Fasted)	Ratio (Fed/Fasted)
C_{max}	1.097	1.096	1.181	1.071	0.99	0.90
$AUC_{(0-Inf)}$	7.567	7.588	7.24	7.951	1.002	1.09
$AUC_{(0-t)}$	6.892	6.982	7.117	7.802	1.01	1.09

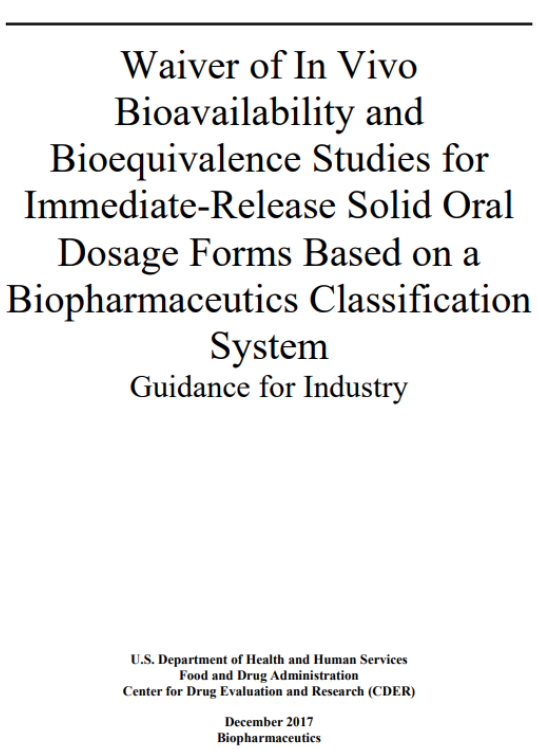
Table. PK Parameters of Drug Y under Fed & Fasted Conditions

Reference: Shoyaib A., Wu F. OGD internal research

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

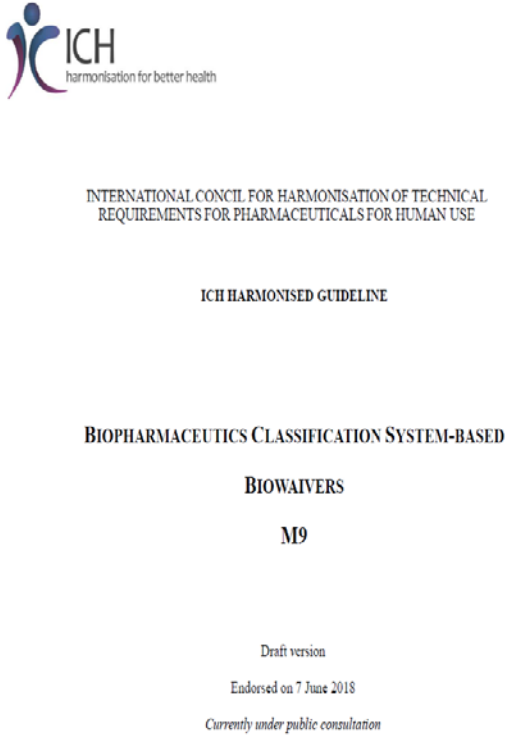

Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System

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

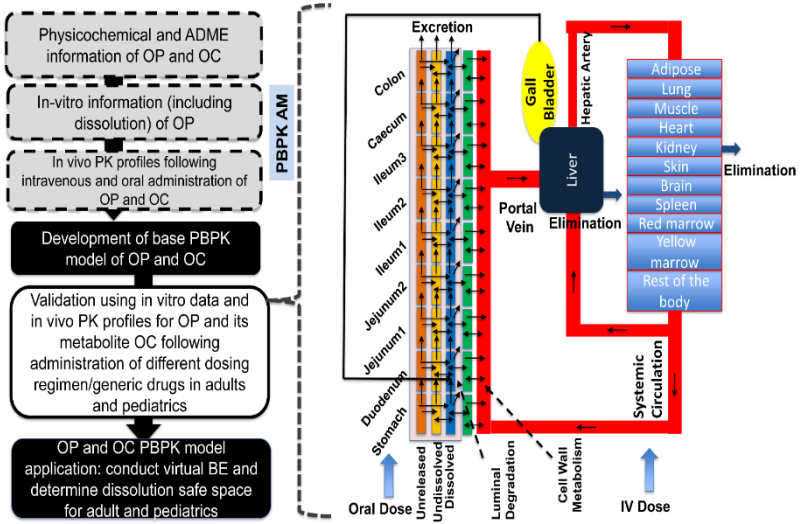
Using PBPK Absorption Modeling to Support BCS Class 3 Drug Waiver

Background: Based on Biopharmaceutics Classification System (BCS) Biowaiver Guidance, for BCS class 3 drug products, the test product formulation should be qualitatively (Q1) the same and quantitatively (Q2) very similar.

Question: Whether and how we can expand BCS Class 3 biowaiver to non Q1/Q2 product?

Regulatory Research:

- Potential utility of PBPK modeling as an alternative BE approach to support biowaiver of non-Q1/Q2 BCS Class 3 drugs



Flowchart: 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 and conduct virtual BE

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

Challenges and Opportunities (When Using PBPK Absorption Model)

Current status

- Gastrointestinal (GI) physiology could be incorporated in PBPK model and more understanding is on the upper part of GI tract
- Drug substance and product attributes such as solubility, permeability, dissolution profiles and particle size are used as model inputs

Further Improvement

- Need further understanding of physiology in the lower small part of GI tract, such as colon for the drug which will be absorbed in colon
- Consistent and adequate approach of generating (biorelevant) solubility, dissolution profiles (QC vs biorelevant), permeability and particle size changes during the possible precipitation process is needed

Challenges and Opportunities (When Using PBPK Absorption Model)

Current status

- Some drug/formulation dependent or system dependent parameters are used as model inputs with assumptions
- Validation/verification of PBPK model is conducted before the application of the model

Further Improvement

- Uncertain drug/formulation dependent or system dependent parameters need adequate justification
- Sufficient purpose-dependent model validation/verification is needed

Relevant Grant/Contract

- Contract BAA "Better Understanding Risk Mitigation in the Evaluation of Relative Bioavailability of Pediatric Generic Products" to Dr. Hannah Batchelor from University of Birmingham
- Contract BAA: "Expanding BCS Class 3 Waivers for Generic Drugs to Non-Q1/Q2" to Dr. Chris Bode from Absorption Systems Inc.
- PBPK modeling research grant: "Physiologically Based Pharmacokinetic (PBPK) Models of Oral Absorption to Simulate the Results of Bioequivalence Studies"

BAA: Broad Agency Announcement

Link: https://www.fda.gov/drugs/generic-drugs/generic-drug-research-priorities-projects
Link: https://grants.nih.gov/grants/guide/rfa-files/RFA-FD-21-012.html

Recent Publications Supported by 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

Conclusion

- Currently, modeling and simulation tools e.g., PBPK absorption modeling and simulation (M&S) has been increasingly used in generic drug applications.
- With continuous improvement along with more submissions and research, PBPK absorption M&S would aid in:
  - Setting clinically relevant specification, conducting risk assessment on the impact of Critical Quality Attributes
  - Evaluating the impact of excipients and food on bioequivalence
  - Supporting (alternative) bioequivalence approach design
  - Supporting high impact applications such as alternative bioequivalence approach and biowaiver

Challenge Question

PBPK Absorption Modeling can be used for:

A. Assessing the Impact of Particle Size Distribution (PSD) on BE

B. Supporting BCS Class 3 Drug Waiver

C. Risk assessment of bio-inequivalence attributable to food intake

D. All of the above

Challenge Question

PBPK Absorption Modeling can be used for:

A. Assessing the Impact of Particle Size Distribution (PSD) on BE

B. Supporting BCS Class 3 Drug Waiver

C. Risk assessment of bio-inequivalence attributable to food intake

D. All of the above

Acknowledgement

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Drs Andrew Babinski, Miyoung Yoon

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

FDA/OPQ/ONDP/Division of Biopharmaceutics

Drs Paul Seo, Kimberly Raines

Publication Co-authors


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