PBPK Absorption Modeling to Support Risk Assessment and Biowaiver for Generic Oral Products

PBPK 2021: Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches

Day 2 Session 1: Oral PBPK as alternative BE approach, risk assessment/biowaiver

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Disclaimer

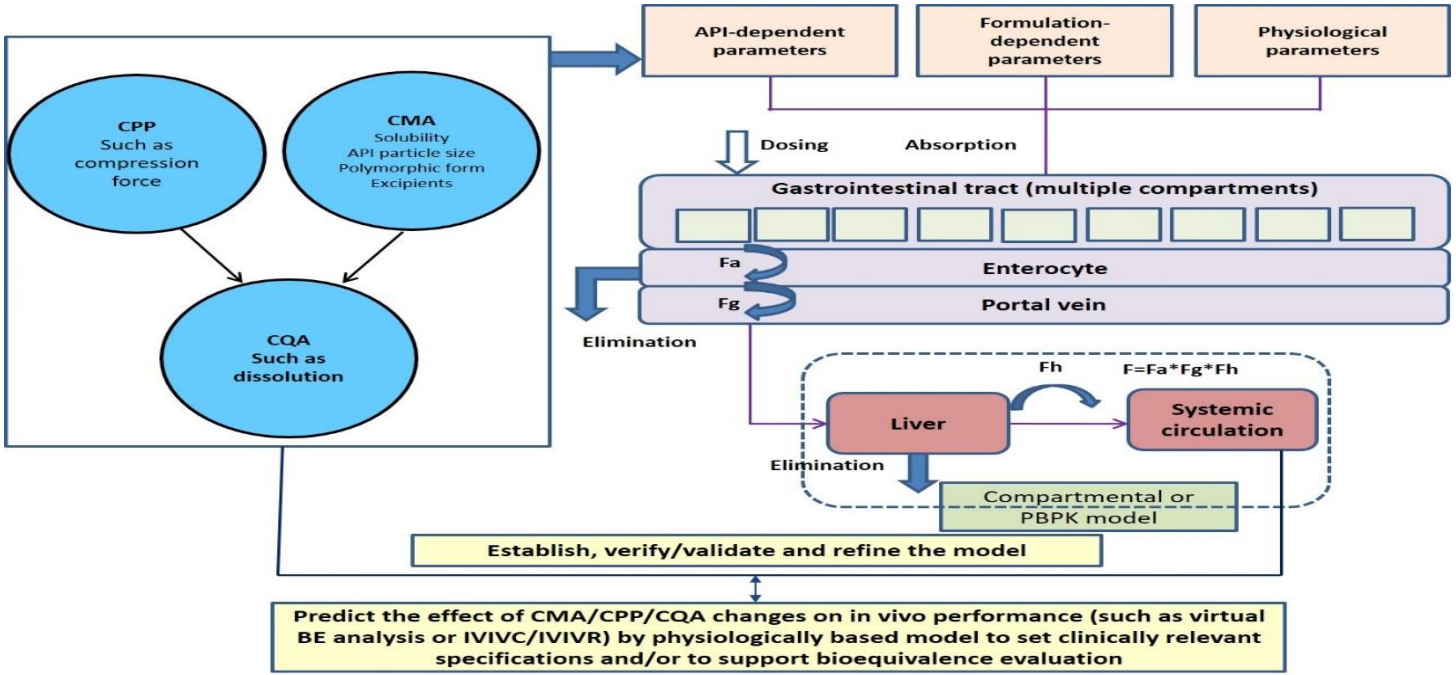
This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies

Outline of the Presentation

1. PBPK Absorption Model and its Applications
2. Highlights of Recent Oral PBPK Impacts on Regulatory Decision Making in OGD
3. Highlights of Oral PBPK Research to Support Biowaiver and Risk Assessment
4. Conclusion

PBPK: Physiologically-based pharmacokinetic modeling; OGD: Office of Generic Drugs

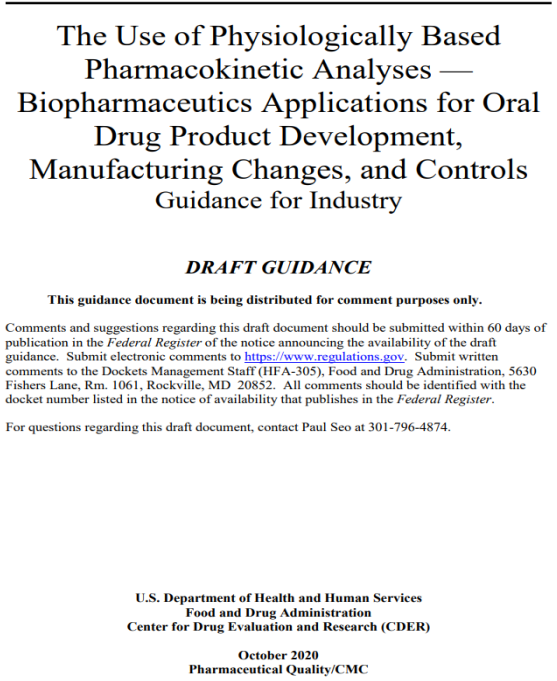
PBPK Absorption Model



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 Research and 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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

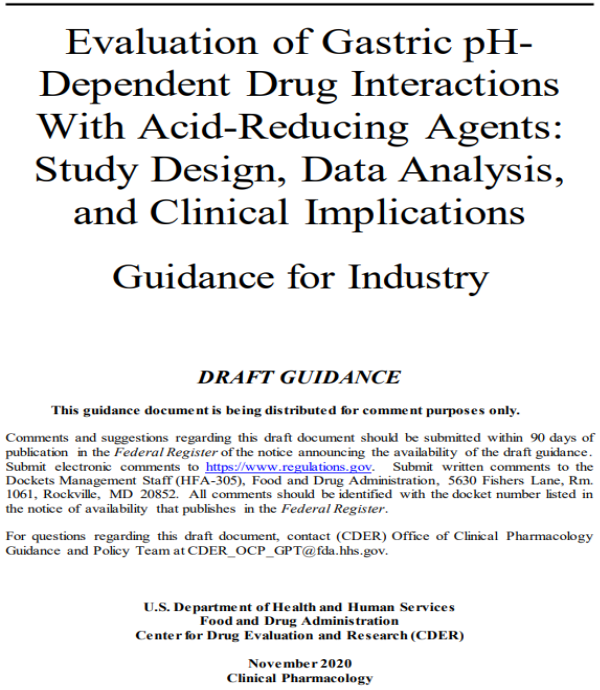
Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management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

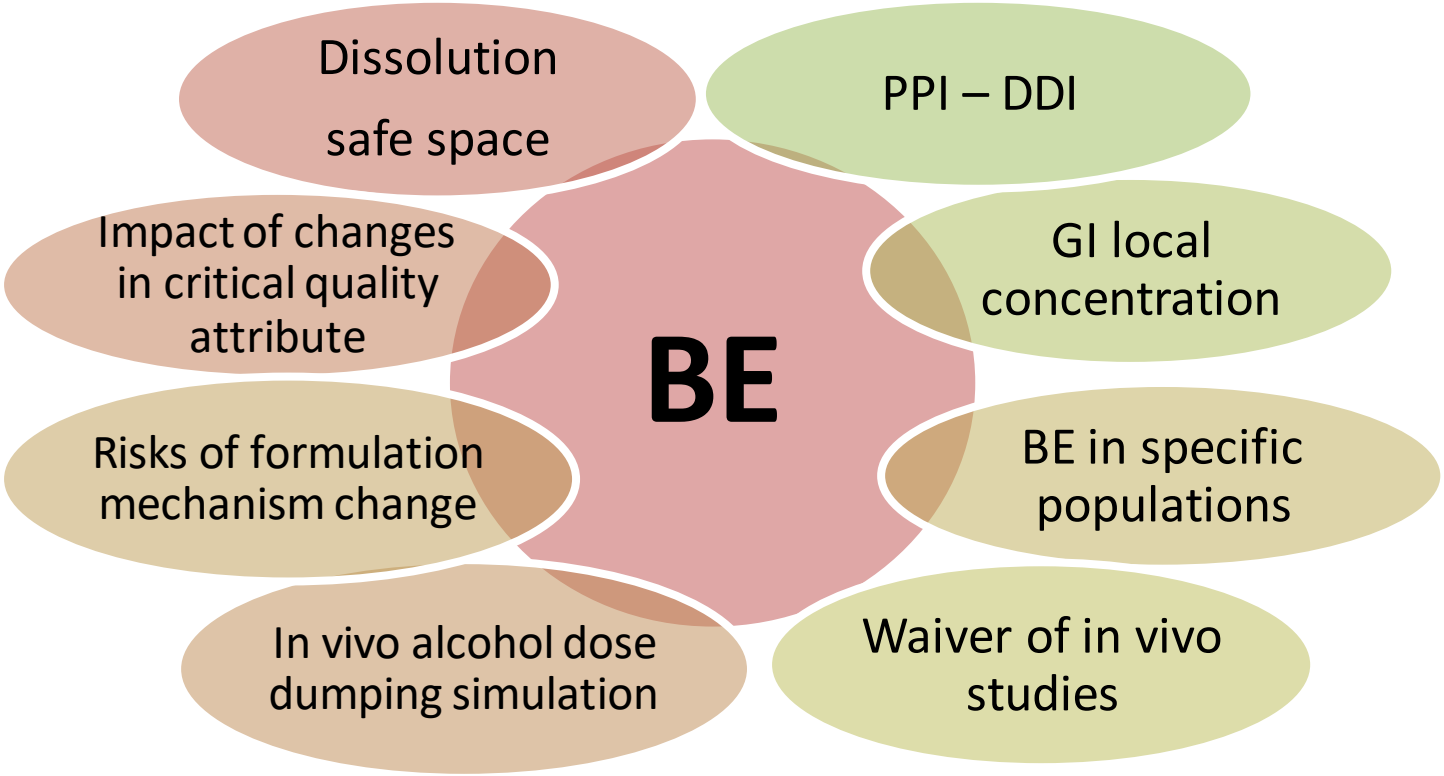
For questions regarding this draft document, contact (CDER) Office of Clinical Pharmacology Guidance and Policy Team at CDER_OCP_GPT@fda.hhs.gov.

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

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

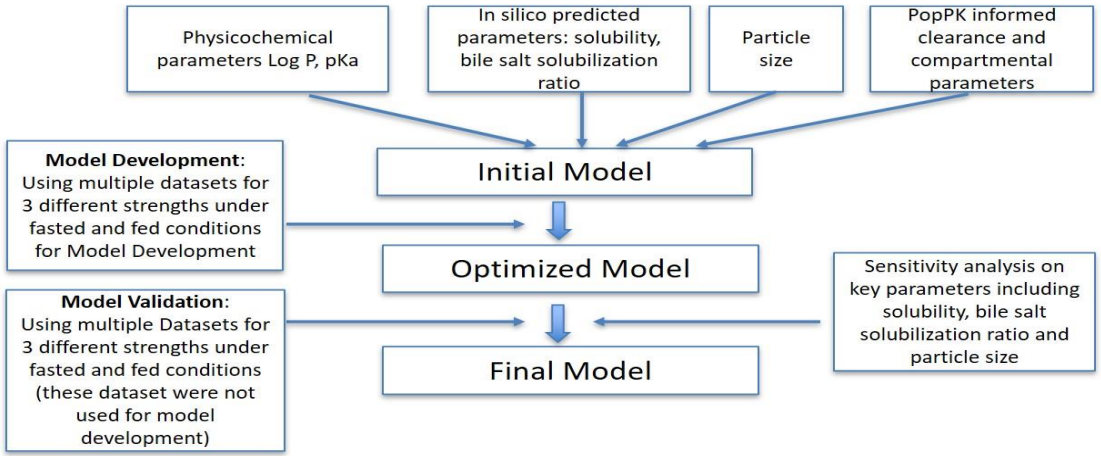
Highlights of Recent Oral PBPK Impacts on Regulatory Decision Making in OGD

Category	Impact on regulatory decision making
Drug quality (risk assessment)	Evaluate the impact of Particle Size Distribution (PSD) on BE and support setting a clinically relevant 3 tier PSD specification
Drug quality (risk assessment)	Risk assessment of the impact of dissolution rate at different pH on the drug exposure
Drug quality (risk assessment)	Evaluate the acceptable range of free base content in prasugrel HCl product
Biowaiver	Evaluate the impact of faster dissolution profile of lower strength (deviation of dissolution) on in vivo bioequivalence and support biowaiver

Case Example 1: PBPK absorption model in Assessing the Impact of Particle Size Distribution (PSD) on BE

- **Background**: For a capsule product, 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.

Model Development and Validation workflow



Case Example 1: Simulations to evaluate the impact of PSD

- **Model application**: Simulation using PBPK model with fixed D50 and changed D10 and D90

Formulation	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

Summary for Case Example 1

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

Case Example 2: 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; and 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.

PBBM: Physiologically-based biopharmaceutics modeling

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 conditions.

-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.

Highlights of Oral PBPK Research to Support Biowaiver and Risk Assessment

Category	Topic
Contract BAA (active)	Expanding BCS Class 3 Waivers for Generic Drugs to Non-Q1/Q2
Contract BAA (active)	Better Understanding Risk Mitigation in the Evaluation of Relative Bioavailability of Pediatric Generic Products
Grant (completed)	Design, Development, Implementation and Validation of a Mechanistic Physiologically-based Pharmacokinetic (PBPK) Framework for the Prediction of the In Vivo Behaviour of Supersaturating Drug Products
New Grant	Physiologically Based Pharmacokinetic (PBPK) Models of Oral Absorption to Simulate the Results of Bioequivalence Studies
Internal Research	Best Practices for Using Oral Physiologically Based Pharmacokinetic (PBPK) Modeling to Support Generic Drug Development

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

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"

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

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

Case Example 3: Using PBPK Modeling to Evaluate the Impact of Pharmaceutical Excipients on Absorption

Background: Drug solubility, effective permeability, and intestinal metabolism and transport are parameters that govern bioavailability. Excipients may affect the systemic bioavailability of a drug by altering these parameters.

Regulatory Research:

Parameter sensitivity analyses using PBPK models were performed to examine the potential impact of excipients on absorption of different BCS class drugs.

Results: It demonstrated the potential capability of PBPK model to ascertain the potential impact of excipients on drug absorption and bioavailability.

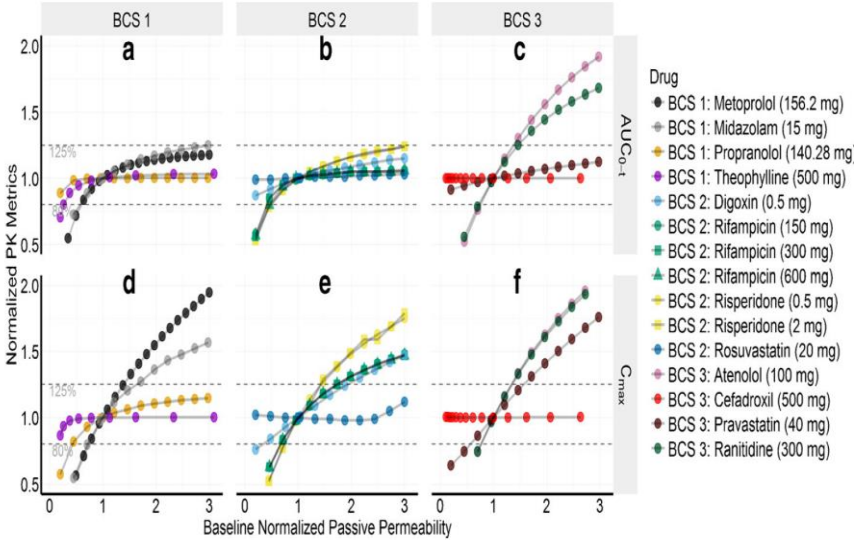


Figure: The effect of changes in passive permeability on Cmax and AUC0-t parameter changes for BCS class 1 (a, d), 2 (b, e) and 3 (atenolol, cefadroxil, pravastatin, and ranitidine) (c, f) drug IR products.

Reference: Chow EC, Talattof A, Tsakalozou E, Fan J, Zhao L, Zhang X. AAPS Journal, 2016. DOI : doi: 10.1208/s12248-016-9964-4.

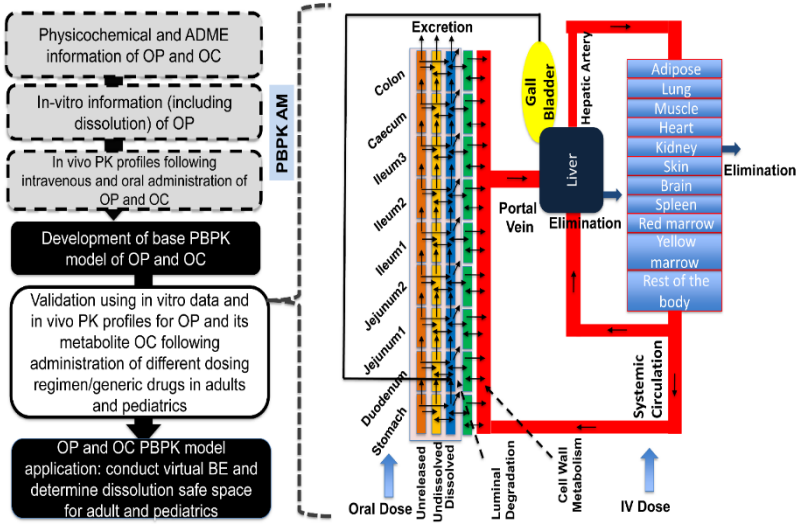
Case Example 4: Using PBPK Absorption Modeling to Support BCS Class 3 Drug Waiver

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

Considerations When Using PBPK to Support Biowaiver

Current status

- Investigators is trying to establishing correlations between the in vitro characteristics and observed or estimated pharmacokinetics (In vitro in vivo correlation, IVIVC). Dissolution method may not be bio-predictive. For poorly permeable drugs, the IVIVC may become non-linear.
- The potential impact of physiological variability on the dissolution rate may not be captured.

Further Improvement

- Establish a biopredictive dissolution test
- Modeling in vitro dissolution profiles, the combination of drug- (e.g., solubility and bile micelle: water partition coefficient) and formulation-specific properties (e.g., product-specific particle size distribution) with Gastrointestinal (GI) variability (e.g., intraluminal pH, intestinal fluid volume and bile salts concentration).

Reference: Wu F, Cristofoletti R, Zhao L, Rostami-Hodjegan A. Scientific considerations to move towards biowaiver for biopharmaceutical classification system class III drugs: How modeling and simulation can help. Biopharm Drug Dispos. 2021 Apr;42(4):118-127. doi: 10.1002/bdd.2274.

Considerations When Using PBPK to Support Biowaiver

Current status

- GI physiology related to absorption of BCS III drugs includes permeation. The impact of the formulation/excipients on permeation is not fully considered.
- Virtual BE simulations have considered interindividual (between subjects) variability in the GI tract

Further Improvement

- Interplay of the formulation and drug with physiology of the gut needs to be considered (e.g., the impact of excipients on efflux transport and transit time).
- Need to inform the models with correct estimates of within subject variability (obtain from previous replicated study or include in the system parameters)
- Accommodate IVIVC for various in vivo conditions (e.g., stratified population)

Reference: Wu F, Cristofoletti R, Zhao L, Rostami-Hodjegan A. Scientific considerations to move towards biowaiver for biopharmaceutical classification system class III drugs: How modeling and simulation can help. Biopharm Drug Dispos. 2021 Apr;42(4):118-127. doi: 10.1002/bdd.2274.

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

With continuous improvement along with more submissions and research, PBPK absorption modeling and simulations can be used in the following areas:

- Setting clinically relevant specification, conducting risk assessment on the impact of critical quality attributes
- Supporting high impact applications such as alternative bioequivalence approach and biowaiver
- Evaluating the impact of excipients and food on bioequivalence

Acknowledgement

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Dr. Andrew Babinski, Miyoung Yoon

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