Assessing Food Impact on Bioequivalence Using Physiologically-Based Pharmacokinetic Modeling

2022 AAPS PharmSci 360

Session: Rapid Fire: Model Informed Drug Development (MIDD): Role in Dose Selection, Vulnerable Populations, and Biowaivers (BM)

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October 18, 2022

Disclaimer

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

Description and Objectives

- This presentation is to introduce the experiences, challenges and share views with the participants on how to apply in vitro and in silico approaches to evaluate the risk of food impact on bioequivalence (BE) and support decision making and regulatory assessment.

- This presentation will also introduce how to implement these approaches in assessing the impact of food on the bioequivalence of generic drugs, especially when the formulation of generic products may result in different BE with Reference Listed Drugs (RLD) under fed conditions.

Objectives of this presentation:

- Leverage knowledge learned in the rapid fire to help understand and identify cases that may have high risks of food impact on relative bioavailability and bioequivalence

- Learn the scientific advances in the use of Physiologically-Based Pharmacokinetic (PBPK) modeling approaches to quantitively predict the impact of food on relative bioavailability and bioequivalence

- Know challenges of implementing these approaches in assessing the impact of food on the relative bioavailability and bioequivalence for investigational drugs

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 10 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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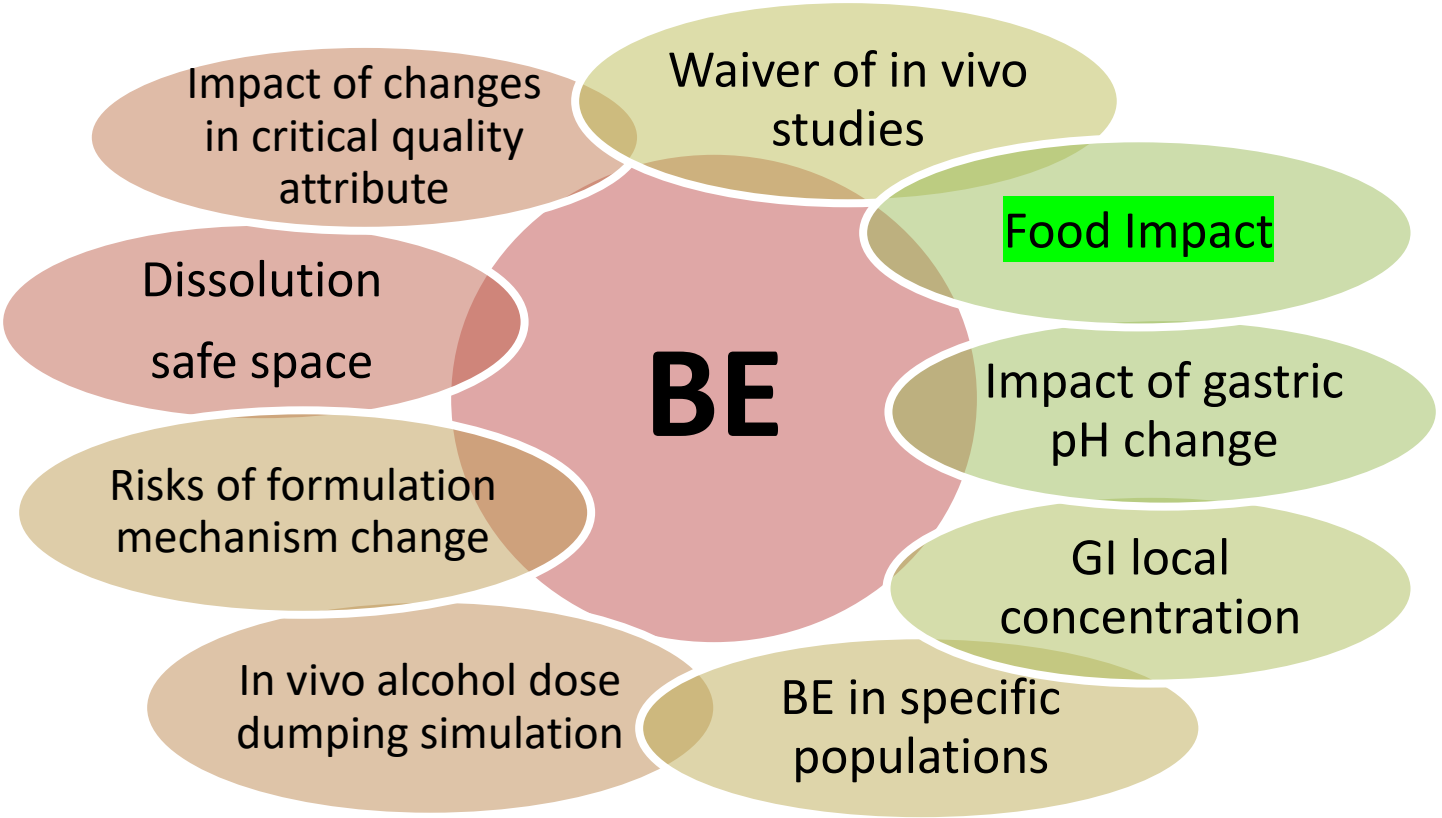
Regulatory Questions that PBPK Absorption Model can Help Answer



PPI: proton pump inhibitor; GI: gastrointestinal

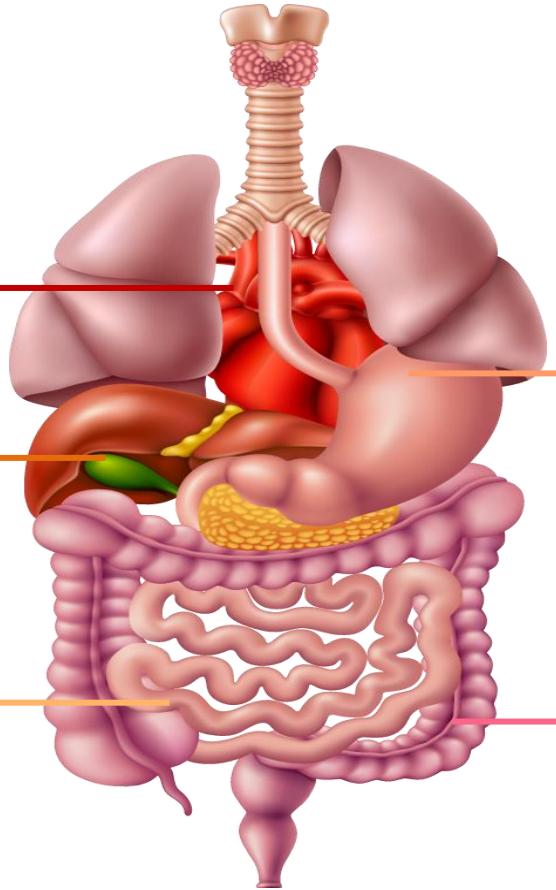
Reference: Adopted from Wu F. Application of PBPK Modeling in Regulatory Submission: FDA Experience on Generic Drugs. Podium Presentation, AAPS 360 Annual Conference, 2019

Effect of Food on Gastrointestinal Physiology

Blood Flow
- Increased Liver and Portal Blood Flow

Gall Bladder
- Release of Bile Salt

Small Intestine
- Increased Bile Salt Conc.
- Increased Mortality
- Increased Viscosity
- Increased Volume
- Decreased pH
- Change in Enzyme and Transporter's Activity



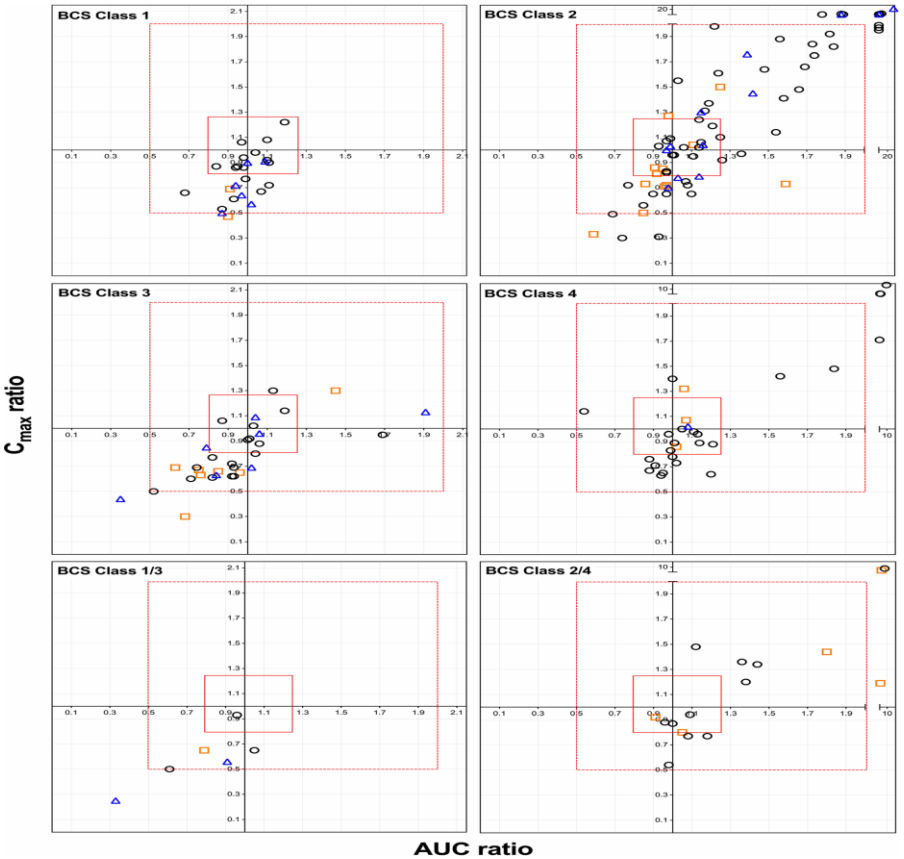
Stomach
- Increased pH
- Increased Mortality
- Increased Acid Secretion
- Increased Volume
- Delayed Gastric Emptying

Colon
- Increased Buffer Capacity
- Increased Osmolarity
- Decreased pH

Reference: Adopted from Abdullah, Al Shoyaib Presentation from FDA CRCG PBPK Workshop, 2021

AUC and Cmax ratios for drugs with FE studies, by BCS class

- Trends in FE data were investigated for 170 drugs with clinical FE studies from the literature and new drugs approved from 2013 to 2019 by U.S. FDA.
- The project found that drugs with significantly increased exposure FE (AUC ratio ≥2.0; N=14) were BCS Class II or IV, while drugs with significantly decreased exposure FE (AUC ratio ≤0.5; N=2) were BCS Class I/III or III



Reference: Owens et al, AAPS Journal, 2022, DOI: 10.1208/s12248-021-00667-w

Recapture of 2021 FDA CRCG PBPK Workshop Related to Risk Assessment of Food Impact

- Assigning confidence based on BCS classification may be an over-simplification. The driving mechanism of food effect can provide a perspective on the prediction confidence.
- From Innovation & Quality International Consortium, with high confidence:
  - BCS 1 and 3 compounds, where a significant contribution of transporter-mediated food effects can be ruled out (Note: low confidence on those with changes in hydrodynamics (viscosity) in presence of food)
  - A subset of BCS 2 and 4 compounds where the driving mechanism of food effect can be attributed to changes in solubility in the fed state related to changes in GI luminal physiology
- From Innovation & Quality International Consortium, with low confidence/high risk:
  - Main drivers for low confidence in predictions: Salt form, effect on microenvironment pH, changes in hydrodynamics (viscosity) in presence of food, buffer species and in vivo solubility
  - Where the mechanism of food effect is well-understood, but the in vitro to in vivo correlation is weak (e.g., compounds that undergo precipitation), a middle-out approach can be utilized with higher confidence using a clinical anchor study

Reference: Riedmaier, A.E. Presentation from FDA CRCG PBPK Workshop, 2021. https://complexgenerics.org/media/SOP/complexgenerics/pdf/Conference-Slides/D208%20Arian%20EmamiRiedmaier_PBPK_FoodEffect_WithAudio.pdf

Recapture of 2021 FDA CRCG PBPK Workshop Related to Risk Assessment of Food Impact (Cont')

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

Background: Based on FDA Draft Guidance (2021), "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 or when serious adverse events are anticipated with administration of the drug product under fed conditions.

Question: Can we use PBPK modeling to predict the impact of food on BE and support waive of in in vivo fed BE study at least in certain situations?

Regulatory Research:

- Potential utility of PBPK modeling to assess risk of bio-inequivalence attributable to food intake
- Virtual bioequivalence (VBE) indicated that food appears not to impact the bioequivalence results for this case

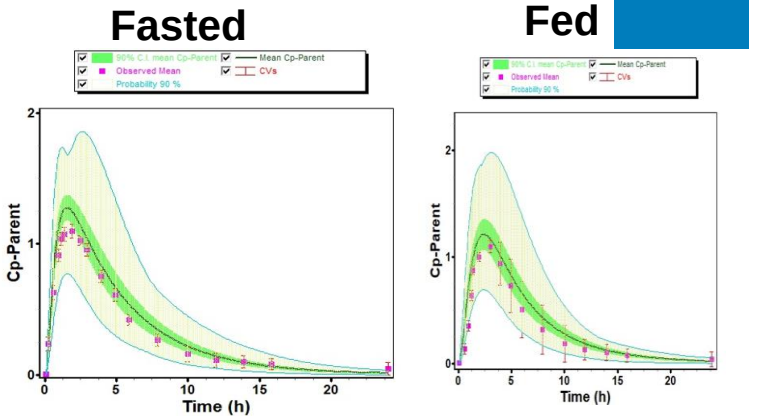


Figure. PBPK Model Simulation for Acyclovir IR Product 800 mg

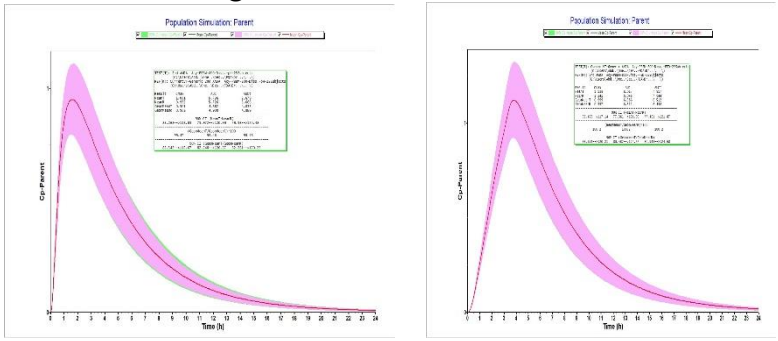


Figure. VBE of Acyclovir IR Product 800 mg

Reference: Shoyaib A., Fang L, Zhao L, Wu F. Internal Research and Poster Presentation in 2022 AAPS PharmSci360, **M1130-11-64**

Considerations When Using PBPK to Evaluate Food Impact

Current status

- The in-vitro dissolution data generated using bio-predictive dissolution media is preferable for incorporation into PBPK model to predict plasma profile under fed condition. However, dissolution data generated using quality control (QC) dissolution media may also be acceptable if the applicant can demonstrate that the dissolution data is capable of predicting the plasma profile under fed condition using a validated PBPK model under fed condition

Further Improvement

- The role of pH and bile salts on dissolution rate and extent of drug release need to be taken into consideration while deciding if a bio-relevant dissolution media would be advantageous over QC dissolution media
- Further research is needed to assess the probable role of dissolution apparatus and mechanical set up (e.g., apparatus type, paddle speed) used in generating bio-relevant dissolution data to mimic fed condition

Reference: FDA CRCG PBPK Workshop, 2021, https://complexgenerics.org/PBPK2021/

Considerations When Using PBPK to Evaluate Food Impact

Current status

- The role of food on intestinal transporter is an important matter for consideration during food effect prediction using PBPK. There is a lack of available data, both in-vitro and in-vivo clinical data, related to the impact of food on transporters.
- Default between subject variability (BSV) available in PBPK platforms are used as a starting point during the virtual bioequivalence (VBE) trials runs.

Further Improvement

- Relevant research is needed in order to leverage the full potential of PBPK model in food effect prediction
- Default BSV variabilities may be modified if proper justification and data related to the modified variability are available. For highly variable drugs, BSV may need to be incorporated according to the clinical data

Reference: FDA CRCG PBPK Workshop, 2021

Considerations When Using PBPK to Evaluate Food Impact

Current status

- When food effects of orally administered drugs are mediated by the gastric emptying, gastrointestinal pH, PBPK models may predict the impact of food intake more accurately compared to more complex mechanisms, such as transporter, metabolism, food-drug complex formation, and formulation mediated food effect.
- For selecting the type of food to be used in PBPK model, attention should be paid towards the aim of the study, e.g., whether the aim is to assess the fed BE or to assess the pH DDI in fed condition.

Further Improvement

- Relevant research is needed on understanding mechanism associated with food impact on pharmacokinetics, e.g., food impact on transporter, metabolism, food-drug complex formation and formulation mediated food effect.
- Further research is needed to understand and develop mechanistic relationship between types of meal and their impact on the mechanism of oral absorption.

DDI: Drug Drug Interaction

Reference: FDA CRCG PBPK Workshop, 2021

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

Category	Impact on regulatory decision making
Risk assessment of drug degradation	Using PBPK modeling and simulations to evaluate the impact of drug degradation at pH 1.2 on BE
Risk assessment of deviation of dissolution profiles	Using IVIVC and PBPK absorption model to evaluate the impact of non-comparable dissolution profiles of the Test and RLD products for lower strengths in multi-media (pH 1.2, pH 4.5 and pH 6.8 buffers) on their in vivo performance
Risk assessment of impact of food on BE and biowaiver	Based on in vivo fasted and pilot fed BE study, using PBPK absorption modeling and simulation to evaluate the impact of food on BE
Virtual BE simulations with other study design	Using PBPK modeling for conducting virtual trial for a BE study with more subjects and fully replicated study design (in combination with in vivo pilot BE studies)

IVIVC: In vitro in vivo correlation

Reference: Wu F, Presentation at FDA SBIA Workshop, 2022

Regulatory Case Example: Using PBPK Absorption Modeling to Evaluate the Food Impact on BE

Background: Drug X oral tablets include API with amorphous solid dispersion (ASD) form. A mechanistic absorption model for oral tablet was developed based on literature data and results from pilot BE studies (using another two batches of different formulations) in the fasted and fed state and pivotal BE study in the fasted state, comparing the Test formulations and the RLD.

Question: Can PBPK model be used to evaluate the BE of proposed generic product and RLD in the fed state using virtual BE simulation?

Review and Impact:

- PBPK modeling was used for predicting the bioequivalence under fed conditions. The risk and complexity of the formulation of the proposed product were evaluated and major concerns/limitations of the proposed PBPK model were identified.

Major limitations identified on the developed PBPK model:

-Lack of supporting information related to formulation design, manufacturing process, API characteristics (e.g., particle size or percentage of amorphous form vs crystallization form), excipients and quality attributes of the drug product that may significantly impact the in vivo dissolution and bioavailability of drug.

-There is lack of correlation between generated in vitro dissolution profiles and in vivo dissolution/release

-The model validation step is based on bioavailability/BE studies which demonstrated BE among the batches tested. Challenging the model with (in vitro and in vivo) data which showed lack of BE and/or batches with different release rate to support the robustness of the established PBPK model is recommended.

Relevant Grant and Contract are Funded by GDUFA

- Active Grant: “Development and validation of a best practices framework for PBPK analysis for biopharmaceutic applications in support of model-informed biowaivers of fed state BE studies for BCS class II drugs” with Dr. Rodrigo Cristofoletti at University of Florida

- Active Contract BAA: “Disintegration and Dissolution of Solid Dosage Forms and Influence of Food Induced Viscosity on Its Kinetics, Tools and Methodologies for Bioequivalence and Substitutability Evaluation” with Peter Langguth at Johannes Gutenberg University

Relevant Publications Supported by Internal and External Research

Citation: CPT Pharmacometrics Syst. Pharmacol. (2020) 9, 456–465; doi:10.1002/psp4.12541

The AAPS Journal (2022) 24:16
DOI: 10.1208/s12248-021-00667-w

Research Article

Exploring the Relationship of Drug BCS Classification, Food Effect, and Gastric pH-Dependent Drug Interactions

Katie Owens,[1,4] Sophie Argon,[1] Jingjing Yu,[1] Xinning Yang,[2] Fang Wu,[3] Sue-Chih Lee,[3] Wei-Jhe Sun,[3] Anuradha Ramamoorthy,[2] Lei Zhang,[3] and Isabelle Ragueneau-Majlessi[1]

ARTICLE

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

Zhongqi Dong[1,4], Jia Li[1,5], Fang Wu[2,6], Ping Zhao[1,7], Sue-Chih Lee[1,6], Lillian Zhang[3], Paul Seo[2] and Lei Zhang[1,6,*]

The AAPS Journal (2022) 24:35
DOI: 10.1208/s12248-022-00684-3

Research Article

Application of Solubility and Dissolution Profile Comparison for Prediction of Gastric pH-Mediated Drug-Drug Interactions

Lei Miao,[1] Fang Wu,[1,4] Xinning Yang,[2] Youssef M Mousa,[1] Anuradha Ramamoorthy,[2] Sue-Chih Lee,[1] Kimberly Raines,[3] Lei Zhang,[1] and Paul Seo[3]

Conclusion

- PBPK is evolving rapidly in this area and modeling has a great potential in generic drug development for assessing the impact of food on bioequivalence.
- Research projects and regulatory submission increase the understanding of using PBPK modeling to assess the risk of bio-inequivalence attributable to food intake and/or provide justifications of not conducting fed BE study.
- The success of PBPK modeling for assessing food impact may depend on the mechanisms by which food affects the absorption of orally administered drugs.
- Industry can take the advantage of pre-ANDA meetings for discussion with the Agency regarding the suitability of their proposed PBPK models for food effect assessment.

Acknowledgement

OGD/ORS/Division of Quantitative Methods and Modeling

Oral PBPK group: Drs. Abdullah Shoyaib, Youssef Mousa, Yi-Hsien Cheng

Drs. Liang Zhao, Lucy Fang

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

FDA/OTS/OCP: Xinning Yang

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FDA CRCG 2021 PBPK Workshop D2S2 Faculties

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U.S. FOOD & DRUG ADMINISTRATION

Questions?

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