Using PBPK Model to Support Risk Assessment for Oral Products

Face to Face Seminar to Institute of Clinical Pharmacology and Pharmacometrics Office of Peking University Third Hospital

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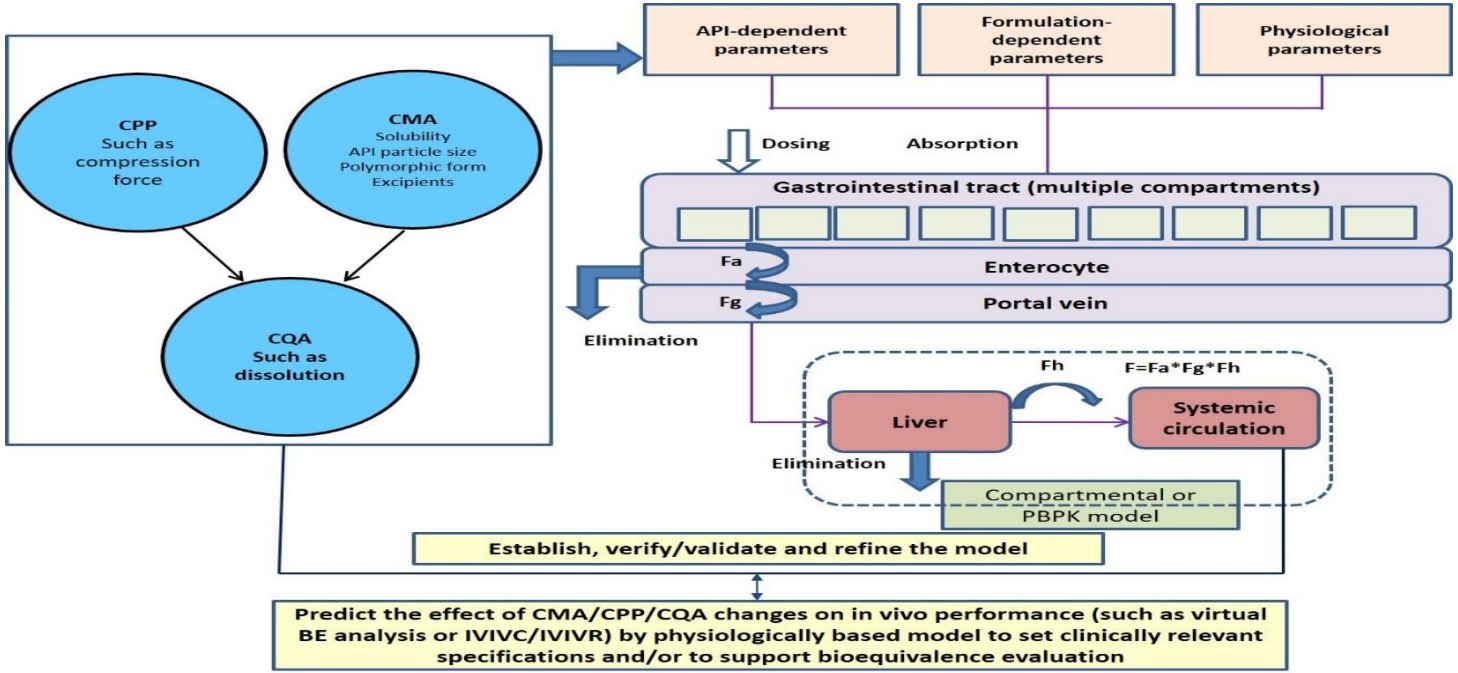
Outline of the Presentation

1. Regulatory questions that physiologically-based pharmacokinetic (PBPK) absorption modeling can help answer
2. Research highlight: using PBPK to evaluate the food impact on bioequivalence (BE)
3. Research highlight: using PBPK to evaluate the impact of gastric pH on BE
4. Research highlight: expanding Biopharmaceutics Classification System (BCS) class 3 waivers for generic drugs and using PBPK modeling to evaluate the impact of pharmaceutical excipients on absorption
5. Conclusion

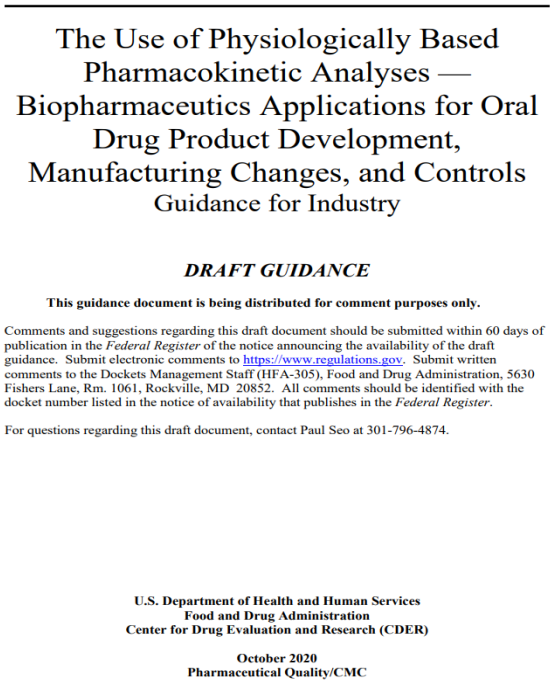
PBPK Absorption Model



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DRAFT GUIDANCE

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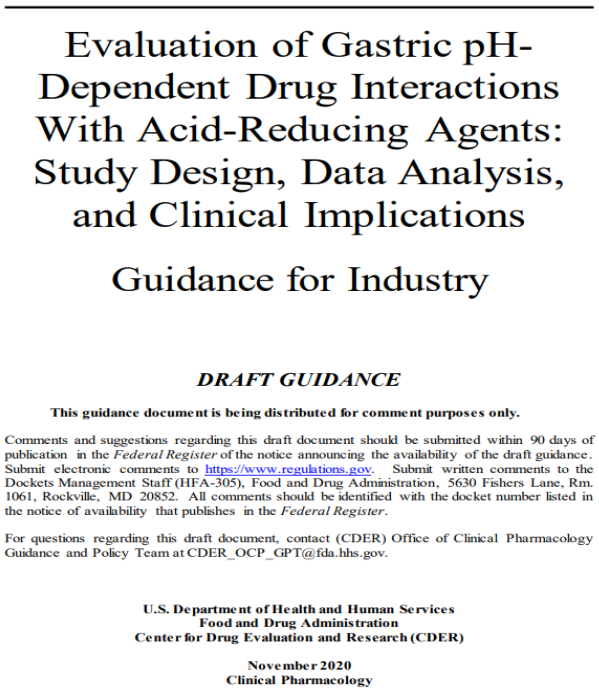
Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management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

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U.S. Department of Health and Human Services
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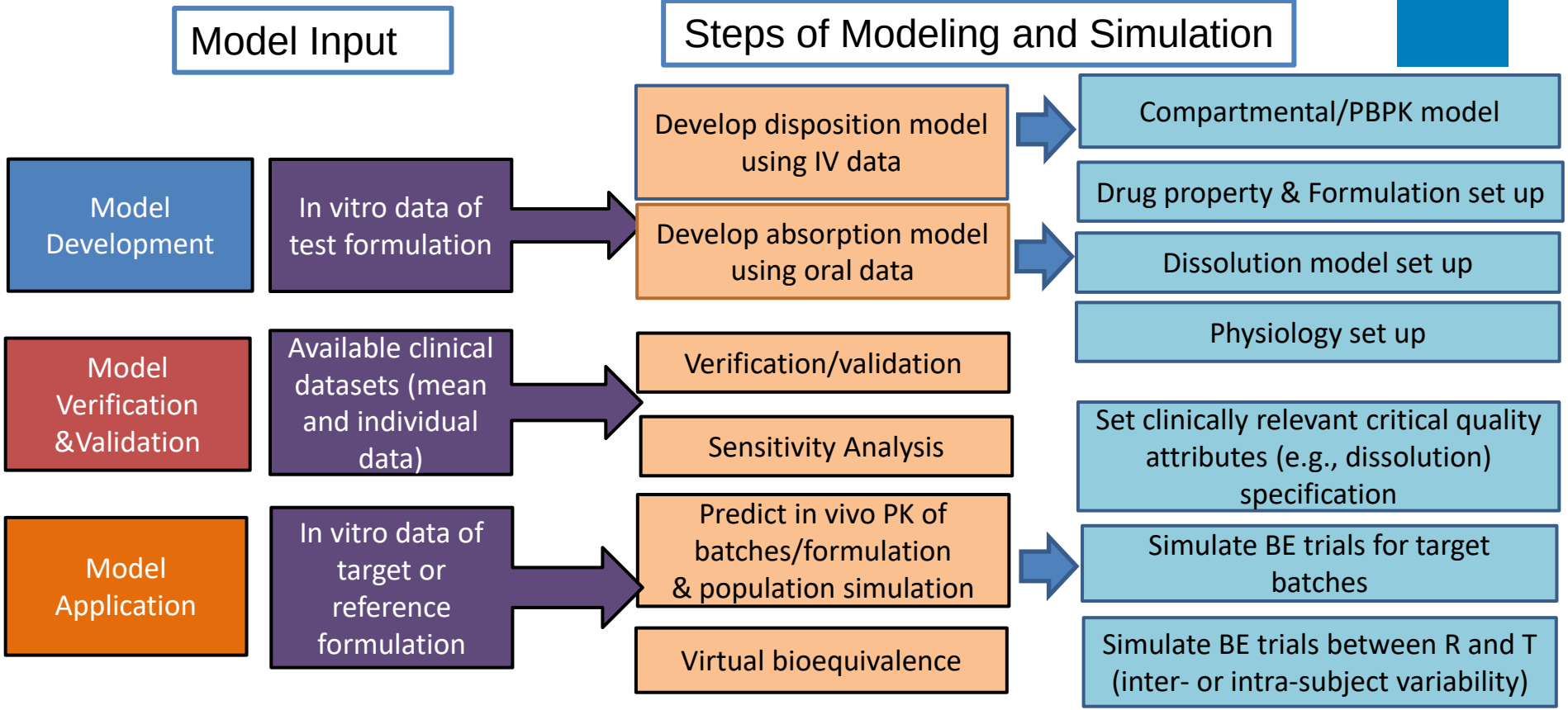
November 2020
Clinical Pharmacology

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

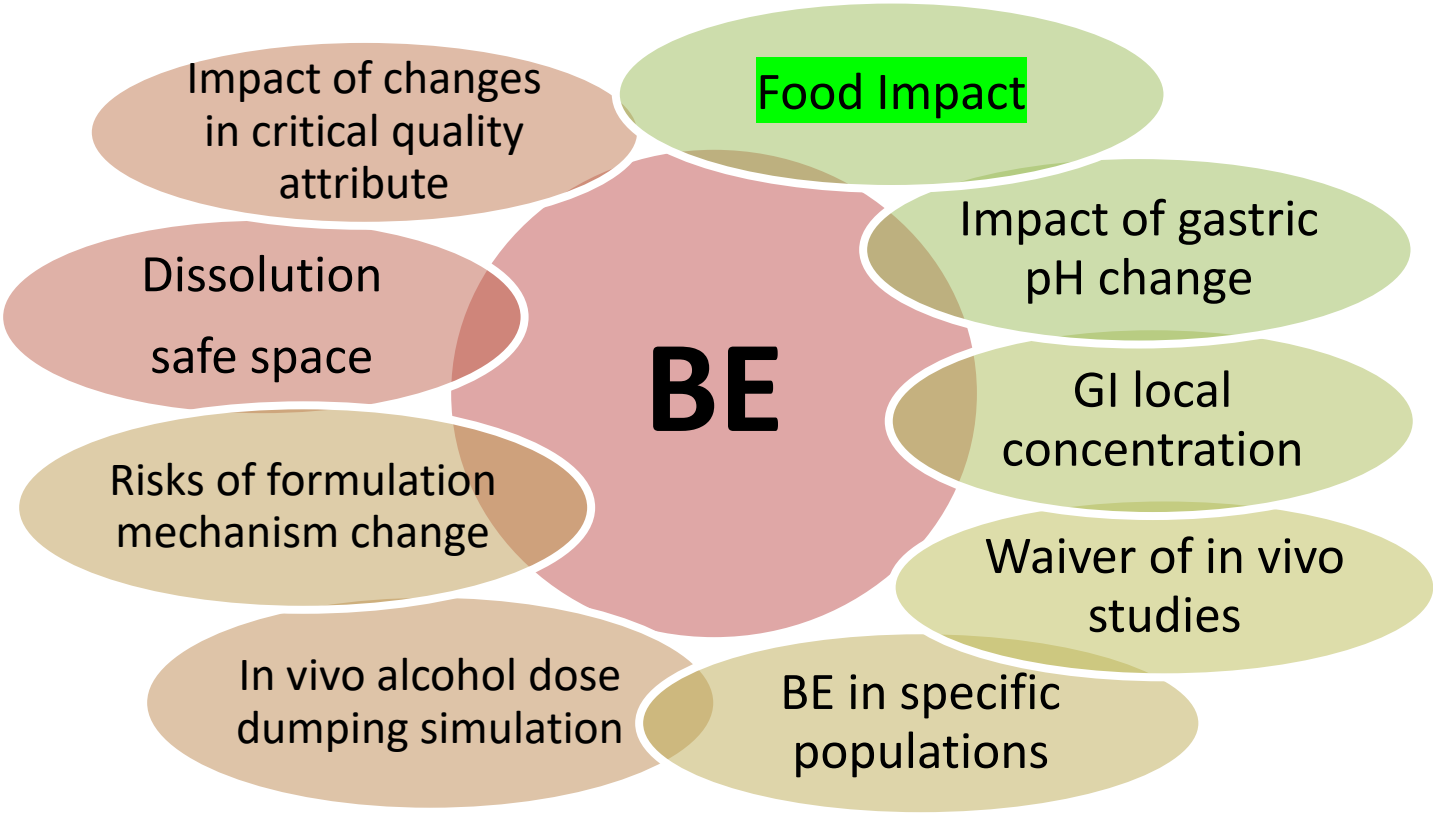
General PBPK Modeling Procedure in ANDA Submission



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

Reference: Adopted from: 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 Help Answer



PPI: proton pump inhibitor; GI: gastrointestinal

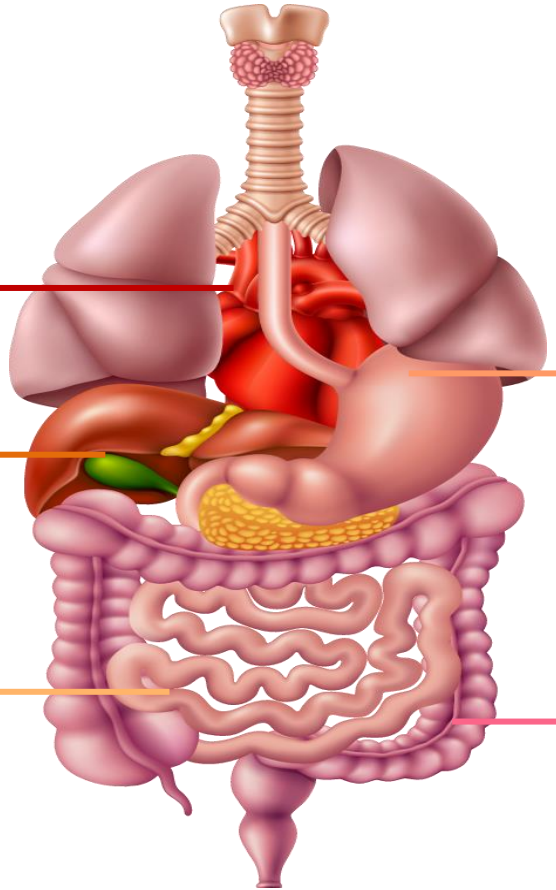
Reference: Adopted from Wu F. Application of PBPK Modeling in Regulatory Submission: FDA Experience on Generic Drugs. Podium Presentation, AAPS 360 Annual Conference, 2019

Effect of Food on Gastrointestinal Physiology

Blood Flow
- Increased Liver and Portal Vein Blood Flow

Gall Bladder
- Release of Bile Salt

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



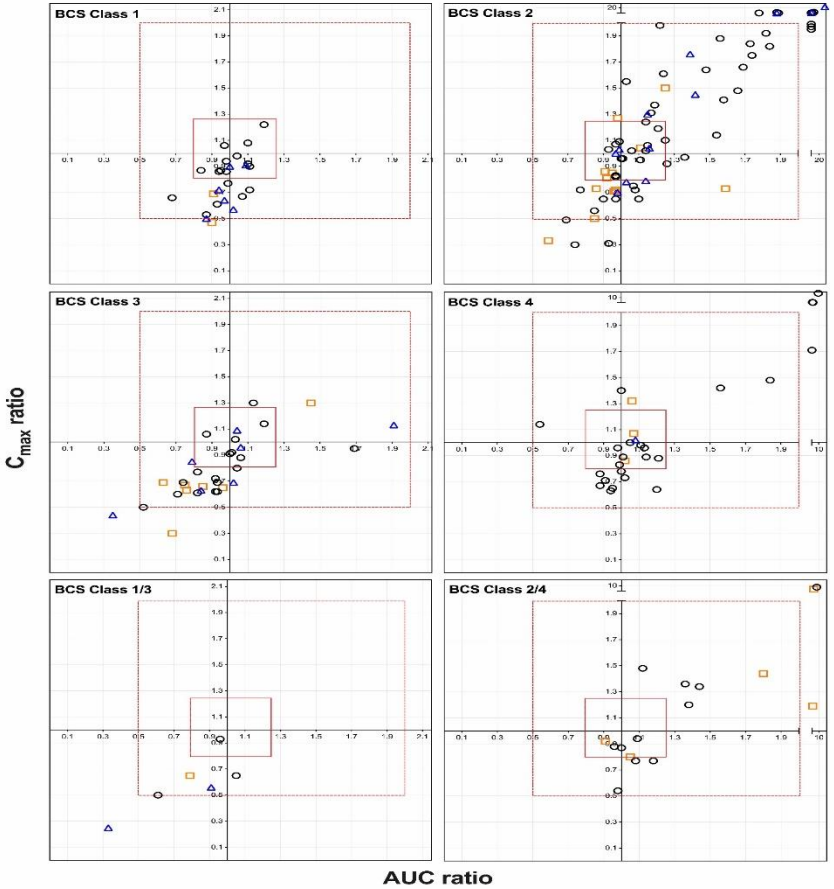
Stomach
- Increased pH
- Increased Motility
- Increased Acid Secretion
- Increased Volume
- Delayed Gastric Emptying

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 food effect studies, by BCS class

- Trends in food effect (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 Endpoints 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 waiver 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

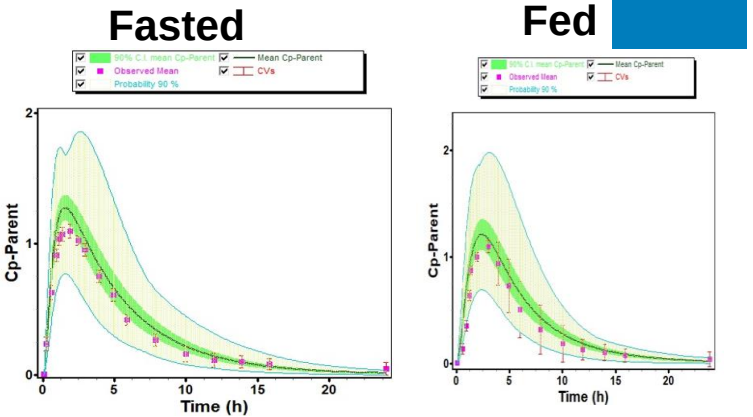


Figure. PBPK Model Simulation for Acyclovir IR Product 800 mg

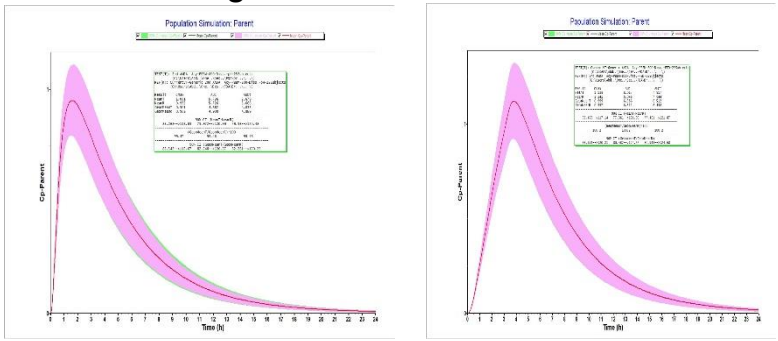


Figure. VBE of Acyclovir IR Product 800 mg

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

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 Cont. 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 reference listed drug (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 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.

Summary

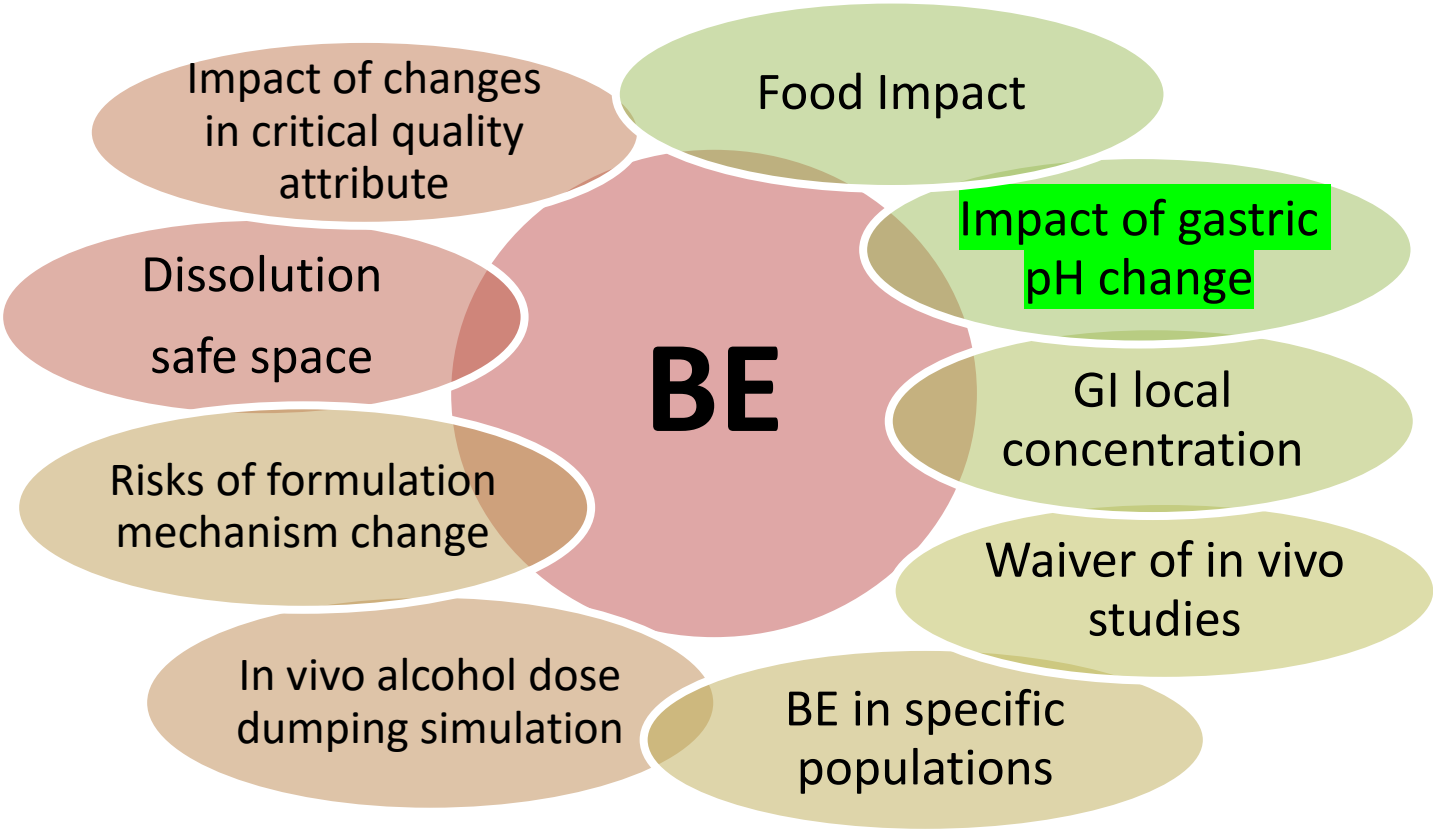
- Research projects and regulatory submission used PBPK modeling to assess risk of bio-inequivalence attributable to food intake and/or provide justifications of not conducting fed BE study

- To fill in existing knowledge gap and gain more experiences, 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

Regulatory Questions that PBPK Absorption Model can Help Answer



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Palbociclib Product Specific Guidance

Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Palbociclib

May 2022

This draft guidance, when finalized, will represent 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.

This guidance, which interprets the Agency's regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required.

This is a new draft product-specific guidance for industry on generic palbociclib.

Active Ingredient:	Palbociclib
Dosage Form; Route:	Tablet; oral
Recommended Studies:	Three in vivo bioequivalence studies with pharmacokinetic endpoints

Recommend three in vivo studies:

1. Type of study: Fasting

Design: Single-dose, two-treatment, two-period crossover in vivo

2. Type of study: Fed

Design: Single-dose, two-treatment, two-period, crossover in vivo

3. Type of study: Fasting, in presence of an acid-reducing agent

Design: Single-dose, two-treatment, two-period crossover in vivo

Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_212436.pdf

From New Drug Side: Evaluation of Gastric pH-Dependent Drug Interactions with Acid-Reducing Agents Guidelines

Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications

Guidance for Industry

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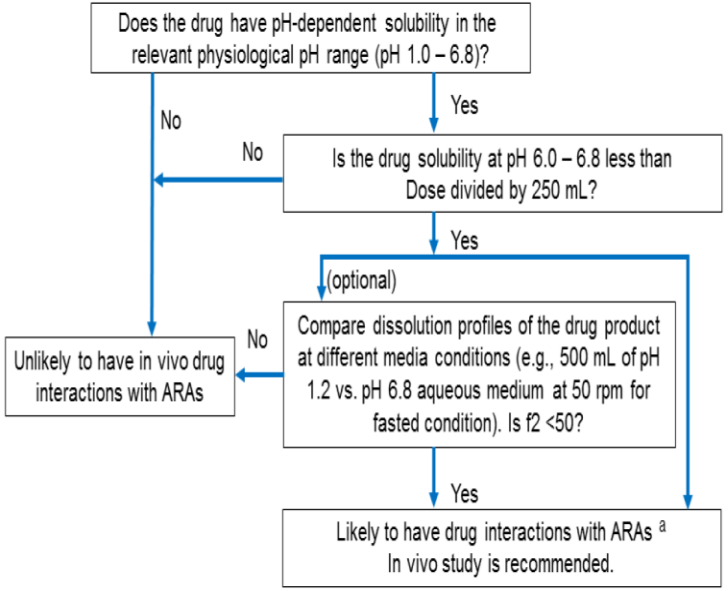


Figure 1. A Framework to Assess Clinical DDI Risk With ARAs for Immediate-Release Products of Weak-Base Drugs

In conjunction with the assessment framework outlined in Figure 1, physiologically based PK (PBPK) simulations can sometimes be used to further assess the potential for pH-dependent DDIs.

Research Highlight: Solubility and Dissolution Comparison for Prediction of Gastric pH-Mediated Drug-Drug Interactions

Background: Coadministration of acid-reducing agents (ARAs) can directly increase gastric pH, leading to potential alterations in the absorption of victim drugs, particularly those whose solubility is affected by the elevation of gastric pH, including weak base and weak acid drugs.

Question: How solubility and dissolution profile comparisons under different pH conditions can be used to predict gastric pH-mediated drug-drug interaction (DDI) potential?

Research Analysis:

67 NMEs with solubility under different pHs and dissolution profiles generated in pH 1.2, 4.5, and 6.8 aqueous media were included for analysis. Similarity factor (f2) was used to compare dissolution profiles at different pHs for pH-mediated DDI prediction (e.g., f2<50 predicts positive DDI). Prediction accuracy was calculated based on the outcome comparison between predicted and observed DDIs.

Drugs	Food status	Prediction by	TP *N*(%)	TN *N*(%)	FP *N*(%)	FN *N*(%)	Prediction accuracy
WBDs (*N* = 49)	Fasted	Dissolution	23 (57.5%)	6 (15%)	11 (27.5%)	0 (0%)	29/40 (72.5%)
	Fed	Dissoultion	5 (41.6%)	3 (25%)	3 (25%)	1 (8.3%)	8/12 (66.7%)
	Fasted	Solubility	23 (57.5%)	9 (22.5%)	8 (20%)	0 (0%)	32/40 (80%)
	Fed	Solubility	6(50%)	2 (16.6%)	4 (33.3%)	0 (0%)	8/12 (66.7%)

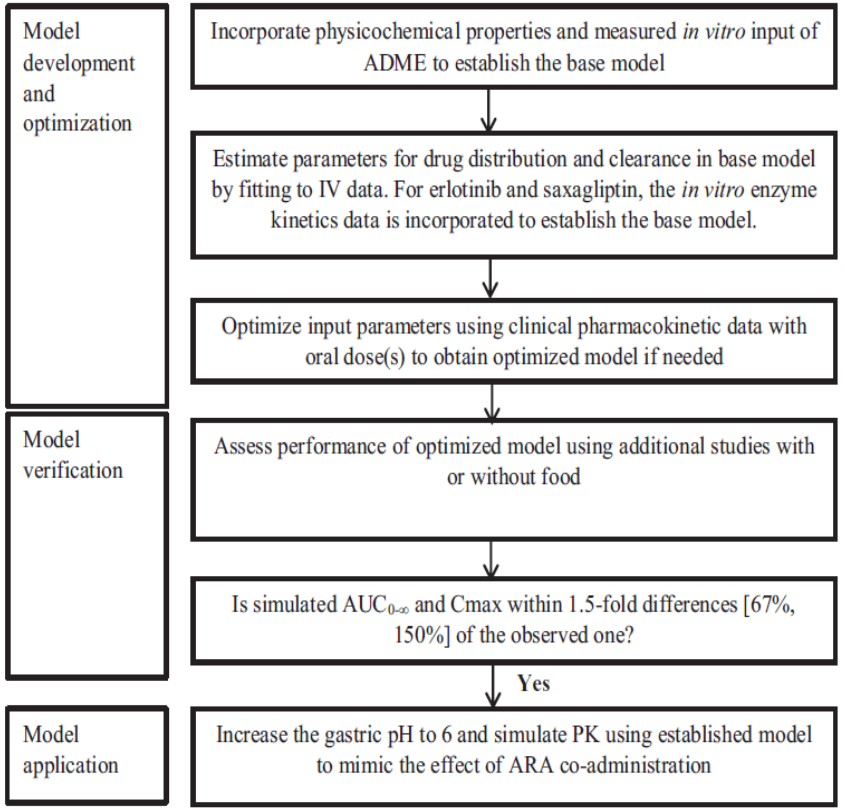
Table. Prediction summary of pH-dependent DDIs for all NMEs and WBDs (from 2003 to 2019) using dissolution profile comparison and solubility and clinical dose approach.

Note: Comparable prediction accuracy under both fasted and fed conditions when compared to the prediction using solubility and clinical dose.

Reference: Miao et al. The AAPS Journal (2022) 24:35
DOI: 10.1208/s12248-022-00684-3

Research Highlight: Application of PBPK Modeling to Predict Gastric pH-Dependent Drug–Drug Interactions for Weak-Base Drugs

- **Background**: Weak-base drugs are susceptible to drug–drug interactions (DDIs) when coadministered with gastric acid–reducing agents (ARAs)
- **Objective**: Investigate whether PBPK modeling can be used to evaluate the potential of such pH-dependent DDIs for four weak-base drugs
- **Method:** PBPK models of four model drugs (tapentadol, darunavir, erlotinib, and saxagliptin) were optimized using pharmacokinetic data following oral administration without ARAs, which were then verified with data from additional PK studies in the presence and absence of food. The models were subsequently used to predict the extent of DDIs with ARA coadministration.



Reference: Dong Z et al. CPT Pharmacometrics Syst. Pharmacol. (2020) 9, 456–465; doi:10.1002/psp4.12541

Research Highlight: Application of PBPK Modeling to Predict Gastric pH-Dependent Drug–Drug Interactions for Weak-Base Drugs

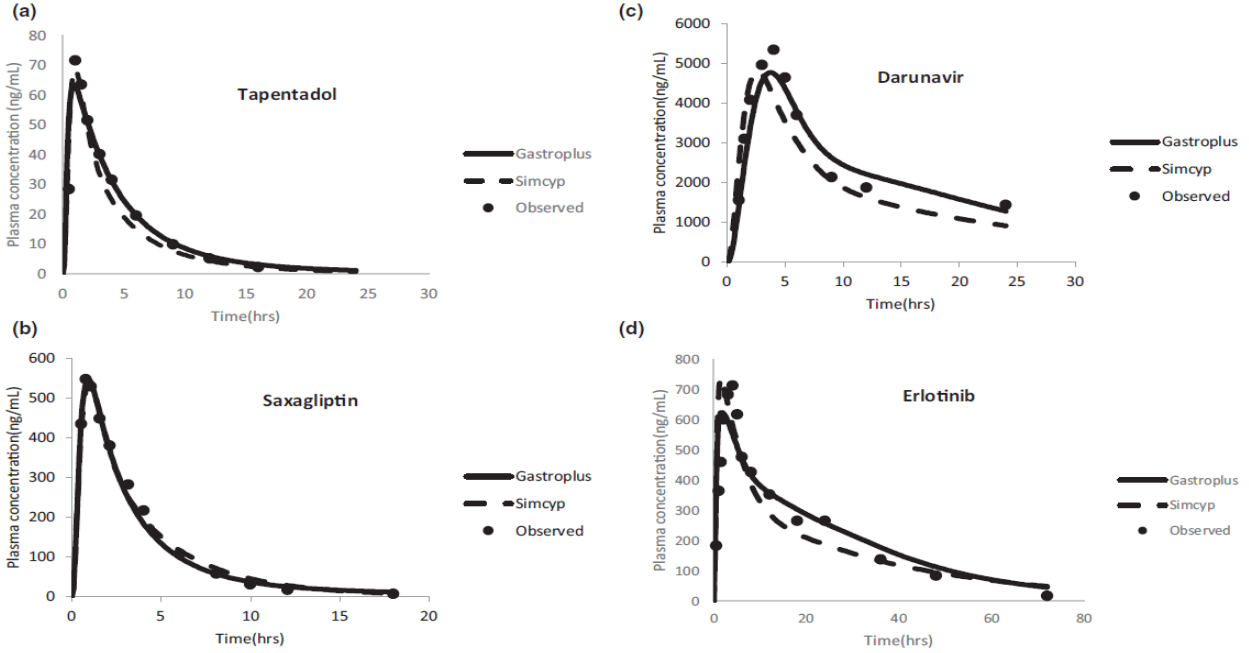


Figure. Representative base model verification prediction results. Simulation of plasma concentrations followed by a single oral dose of (a) 80 mg tapentadol, (b) 100 mg saxagliptin, (c) 600 mg darunavir with 100 mg ritonavir under the fed condition, and (d) 150 mg erlotinib using both Gastroplus and Simcyp physiologically-based pharmacokinetic platforms.

Reference: Dong Z et al. CPT Pharmacometrics Syst. Pharmacol. (2020) 9, 456–465; doi:10.1002/psp4.12541

Prediction performance of PBPK Model

Table Prediction performance of the established models on drug exposure (Cmax and AUC) and pH-dependent DDI following a single dose administration with and without concomitant omeprazole

Drug	Platform	C_{max} (predicted/observed)[a]		Predicted C_{max} ratio[b]	Observed C_{max} ratio[c]	*R* value (C_{max})[d]	AUC (predicted/observed)[a,e]		Predicted AUC ratio[b,e]	Observed AUC ratio[c,e]	*R* value (AUC)[d,e]
		Alone	With omeprazole				Alone	With omeprazole			
Tapentadol, 80 mg	Gastroplus	0.81	0.89	1.00	0.91	1.10	1.01	1.00	1.00	1.01	0.99
	Simcyp	0.91	0.96	0.95	0.91	1.05	0.85	0.84	1.00	1.01	0.99
Saxagliptin, 10 mg	Gastroplus	1.00	1.00	0.98	0.98	1.00	1.17	0.99	0.95	1.12	0.85
	Simcyp	1.18	1.20	1.00	0.98	1.02	1.32	1.18	1.00	1.12	0.89
Darunavir, 400 mg	Gastroplus	1.07	1.04	1.00	1.03	0.97	1.15	1.10	1.00	1.05	0.95
	Simcyp	1.05	0.93	0.91	1.03	0.89	1.00	0.90	0.95	1.05	0.90
Erlotinib, 150 mg	Gastroplus	0.85	1.19	0.54	0.39	1.40	1.17	1.70	0.79	0.54	1.45
	Simcyp	0.85	1.19	0.55	0.39	1.40	0.96	1.19	0.67	0.54	1.24

AUC, area under the concentration-time curve; $AUC_{0-\infty}$, area under the concentration-time curve from time zero to infinity; $AUC_{96-108h}$, area under the concentration-time curve from 96 to 108 hour; C_{max}, maximum concentration; DDI, drug–drug interaction.

[a]The value represents the ratio of predicted and observed C_{max} or AUC alone or in the presence of omeprazole. Refer to Table 1 for reference information on the pH-dependent DDI study.

[b]The value represents the model predicted ratio of C_{max} or AUC in the presence and absence of acid-reducing agents.

[c]The value represents the observed ratio of C_{max} or AUC in the presence and absence of acid-reducing agents. Refer to Table 1 for reference information on the pH-dependent DDI study.

[d]*R* value is calculated according to Eq. 1 as described in the Methods section, which represents the ratio of predicted C_{max} or AUC ratio over the observed ratio. Refer to Table 1 for reference information on the pH-dependent DDI study.

[e]$AUC_{0-\infty}$ for tapentadol, erlotinib, and saxagliptin and $AUC_{96-108h}$ for darunavir.

Reference: Dong Z et al. CPT Pharmacometrics Syst. Pharmacol. (2020) 9, 456–465; doi:10.1002/psp4.12541

Summary

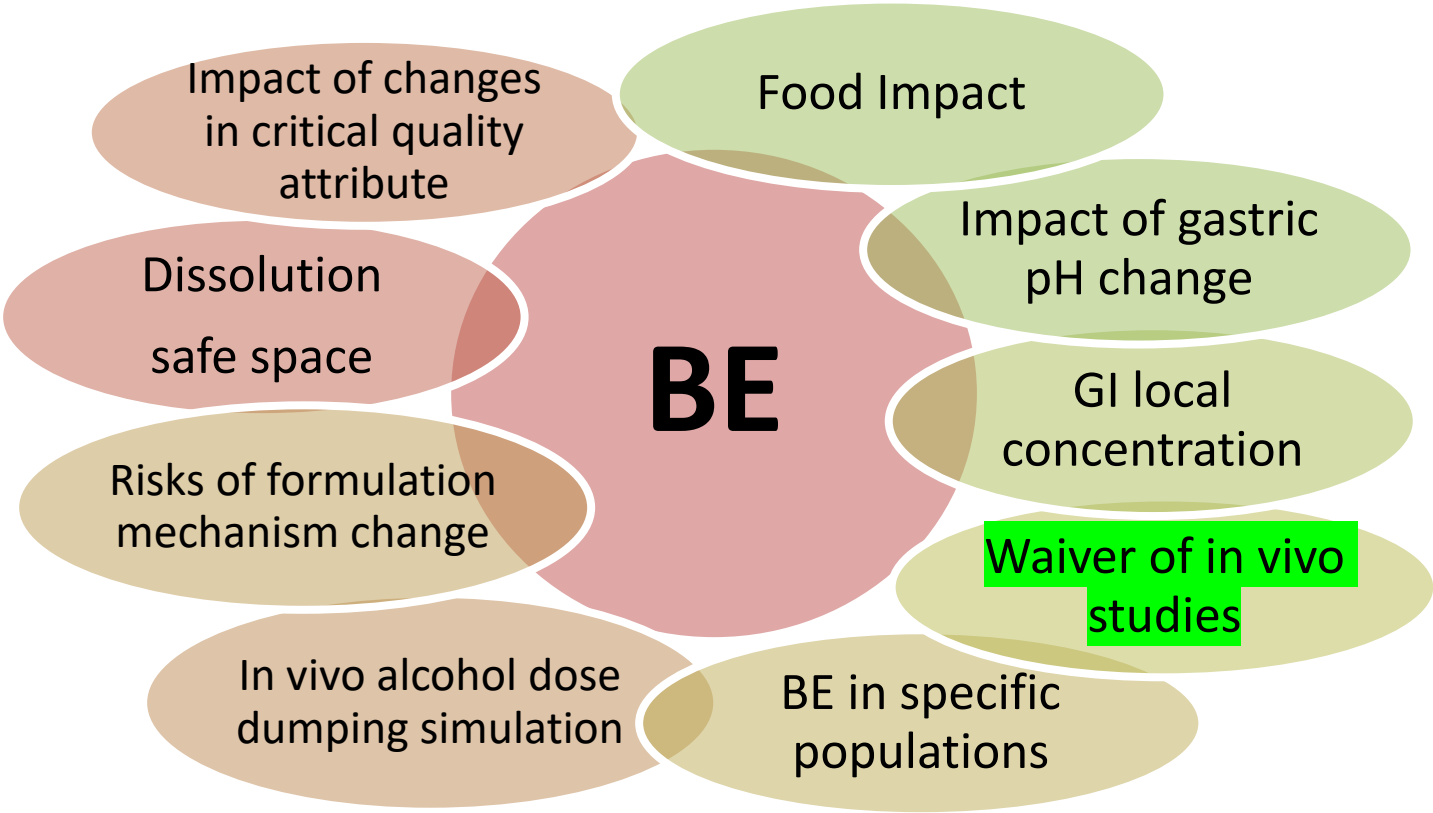
- The results suggested that the PBPK models developed could adequately describe the lack of the effect of ARA on the PK of tapentadol, darunavir, and saxagliptin and could qualitatively predict the effect of ARA in reducing the absorption of erlotinib.

- Using solubility, dissolution, and modeling approaches can help evaluate the impact of gastric pH on drug exposure or bioavailability.

Considerations on Evaluating the Impact of Gastric pH on Bioequivalence

- For generic drugs, additional BE studies (e.g., in subjects with altered gastric pH) may be needed when there are formulation dependent gastric pH mediated DDI.
- The risk is high under certain situations, e.g., when test products and comparator products contain different levels of pH stabilizing/modifying excipients.
- PBPK models to predict PPI based DDI is an important step towards identifying formulation dependent DDI.
- Scientific justifications, e.g., pH-solubility profile, comparative dissolution testing at multiple pHs and modelling may be used to demonstrate that a BE study in a gastric pH-altered situation may not be needed.

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

Research for Supporting Expand 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

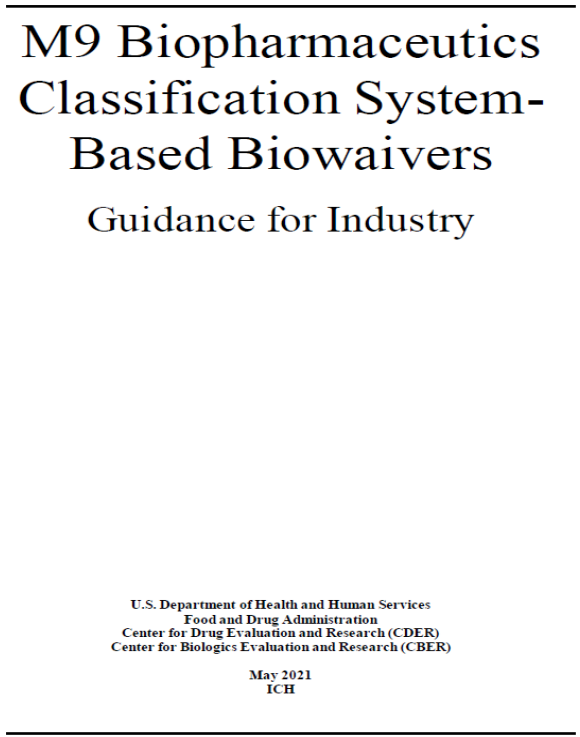
GDUFA: Generic Drug User Fee Amendments

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

Guidance for BCS-based Biowaivers

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 (≥85% for the mean percent dissolved in ≤15 minutes)
- All of the excipients should be qualitatively (Q1) the same and quantitatively (Q2) similar.


M9 Biopharmaceutics Classification System-Based Biowaivers

Guidance for Industry

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

May 2021
ICH

Link: M9 Biopharmaceutics Classification System-Based Biowaivers | FDA

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

Challenges: What if the test product is not qualitatively the same or not quantitively very similar?

Testing Methods Used in GDUFA-funded Contract Project

Project "Expanding BCS Class 3 Waivers for Generic Drugs to Non-Q1/Q2"

- Five model drugs:
  - Acyclovir (Class 3, clinical data on excipient effects)
  - Cimetidine (Class 3, clinical data on excipient effects)
  - Ranitidine (Class 3, clinical data on excipient effects)
  - Atenolol (Class 3, cell monolayer integrity marker)
  - Minoxidil (Class 1)
- Used In-vitro Dissolution Absorption System (IDAS) to evaluate the permeation of the pre-dissolved model drugs in the absence and presence of 15 excipients

Reference: Adopted from: Bode C. Expanding BCS Class 3 Waivers for Generic Drugs to Non-Q1/Q2 Products Podium Presentation, CRCG PBPK Workshop, 2021

Test Excipients

Excipient	Concentration (mg/mL)		
	Low	Mid	High*
Povidone K30	0.0500	0.200	0.800
Hydroxypropyl methylcellulose 2910 (4000 mPa·s)	0.0125	0.0500	0.210
Hydroxypropyl methylcellulose 2910 (15 mPa·s)	0.0125	0.0500	0.210
Sodium lauryl sulfate(SLS)	0.0375	0.150	0.300
PEG-400	0.260	1.11	4.23
Lactose monohydrate	0.500	2.00	8.00
Microcrystalline cellulose	0.390	1.55	6.21
Magnesium stearate	0.100	0.400	1.60
Croscarmellose sodium	0.0450	0.180	0.720
Sorbitol	1.25	5.00	20.0
Dibasic calcium phosphate dihydrate	0.160	0.640	2.54
Silicon dioxide	0.0400	0.160	0.640
Pregelatinized starch	0.113	0.453	1.81
Talc	0.0400	0.400	4.00
Mannitol	0.170	0.682	2.73

* In general (with some exceptions), the High test concentration is equal to the highest amount of a given excipient in an immediate-release solid oral dose form (according to the FDA Inactive Ingredients Database), dissolved in 250 mL; the Mid concentration is generally 25% of the High; and the Low concentration is generally 25% of the Mid

Reference: Adopted from: Bode C. Expanding BCS Class 3 Waivers for Generic Drugs to Non-Q1/Q2 Products Podium Presentation, CRCG PBPK Workshop, 2021

Results with Class 3 Model Drugs

Effects	Excipients	Change in Permeation
None	Hydroxypropyl methylcellulose (two viscosities), microcrystalline cellulose, croscarmellose sodium, talc, mannitol, silicon dioxide	No effects on permeation of any model drugs
Have some effect on one or two model drugs	Povidone K30	Decrease in permeation of acyclovir and ranitidine
	Magnesium stearate	Decrease in permeation of acyclovir
	Lactose, calcium phosphate, pregelatinized starch, PEG-400	Increase in permeation of cimetidine and ranitidine
Inconsistent effect	Sorbitol	Have effects on permeation of all model drugs, but different directions in two tests
Consistent effect	Sodium lauryl sulfate (SLS)	Dose-dependent increase in permeation of all model drugs

Reference: Adopted from: Bode C. Expanding BCS Class 3 Waivers for Generic Drugs to Non-Q1/Q2 Products Podium Presentation, CRCG PBPK Workshop, 2021

Research Project Summary

- Most of the excipients tested had little or no effect on the permeation of Class 3 drugs
- The project suggests expanding biowaivers to non-Q1/Q2 formulations within a certain range for a Class 3 drug may be possible.
- PBPK models may be used to assess the impact of excipients on BE

Using PBPK Modeling to Evaluate the Impact of Pharmaceutical Excipients on Absorption

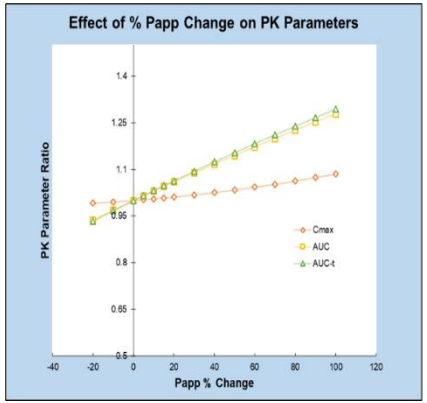
Background: As a proof of concept, we have utilized an oral PBPK model of acyclovir immediate release (IR) tablet for assessing the impact of excipient and food intake on the BE of generic acyclovir IR tablet using virtual healthy subjects and virtual bioequivalence (VBE) trials.

Regulatory Research:

Parameter sensitivity analyses and VBE using PBPK models were performed to examine the potential impact of Papp (apparent permeability) on PK and BE of BCS class III drugs.

Results: The VBE results suggested that more than 30% change of Papp value for test product due to presence of certain excipient may result in failed BE of acyclovir 800 mg IR tablet under both fasted and fed conditions

(A)



(B)

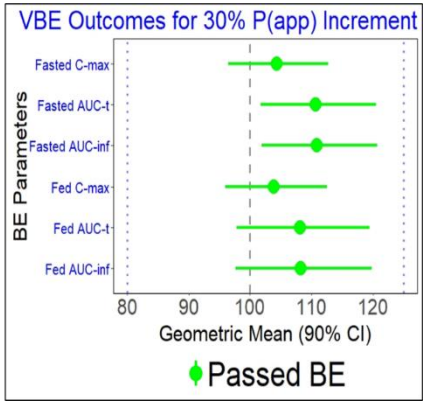


Figure: **(A) Impact of excipient-mediated apparent intestinal permeability (Papp) changes on the PK parameters predicted using single subject simulation and acyclovir oral PBPK model. (B) VBE trials show that the test and reference acyclovir 800 mg IR tablets are BE under fasted and fed condition for up to 30% Papp value increment in the test product.**

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

Recent Publications Supported by Internal and External Research

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

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

Check for updates

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]

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

Check for updates

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]

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

Recent Publications Supported by Internal and External Research (Continued)

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]

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]

www.fda.gov

molecular pharmaceutics
pubs.acs.org/molecularpharmaceutics Article

Phase Behavior and Crystallization Kinetics of a Poorly Water-Soluble Weakly Basic Drug as a Function of Supersaturation and Media Composition

Tu Van Duong, Zhanglin Ni, and Lynne S. Taylor*

Cite This: *Mol. Pharmaceutics* 2022, 19, 1146–1159 Read Online

REVIEW ARTICLE

Theme: The Biological Effect of Pharmaceutical Excipients

A Critical Overview of the Biological Effects of Excipients (Part I): Impact on Gastrointestinal Absorption

Marilyn N. Martinez[1] · Balint Sinko[2] · Fang Wu[3] · Talia Flanagan[4] · Enikő Borbás[5] · Eleftheria Tsakalozou[3] · Kathleen M. Giacomini[6]

The AAPS Journal (2022) 24: 61
https://doi.org/10.1208/s12248-022-00713-1

REVIEW ARTICLE

Theme: The Biological Effect of Pharmaceutical Excipients

A Critical Overview of the Biological Effects of Excipients (Part II): Scientific Considerations and Tools for Oral Product Development

Marilyn N. Martinez[1] · Fang Wu[2] · Balint Sinko[3] · David J. Brayden[4] · Michael Grass[5] · Filippos Kesisoglou[6] · Aaron Stewart[5,7] · Kiyohiko Sugano[8]

Conclusion

- Currently, modeling and simulation tools e.g., PBPK absorption modeling and simulation has been increasingly used in generic drug applications.
- PBPK modeling has been used to assess the risk of bio-inequivalence attributable to food intake.
- Solubility, dissolution characteristics and PBPK modeling can be used to predict the impact of gastric pH on drug exposure. Further investigations is warranted to demonstrate that PBPK modelling can be used to assess whether a BE study in a gastric pH-altered situation is needed.
- PBPK modeling can be used to predict the impact of excipient on drug absorption.
- GDUFA funded research projects support to fill the knowledge gap.

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Oral PBPK group: Drs. Youssef Mousa, Abdullah Shoyaib, Yi-Hsien Cheng, Lei Miao (previous fellow)

Drs. Liang Zhao, Lucy Fang

OCP: Drs. Xinning Yang, Zhongqi Dong (previous fellow)

University of Washington: Katie Owens

Absorption Systems: Dr. Chris Bode

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

FDA CRCG 2021 PBPK Workshop D2S2 Faculties

Publication Co-authors


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