OGD Perspectives on PBBM applications for generics

FDA/M-CERSI Physiologically Based Biopharmaceutics Modeling Workshop

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Office of Generic Drugs | CDER | U.S. FDA
August 31, 2023

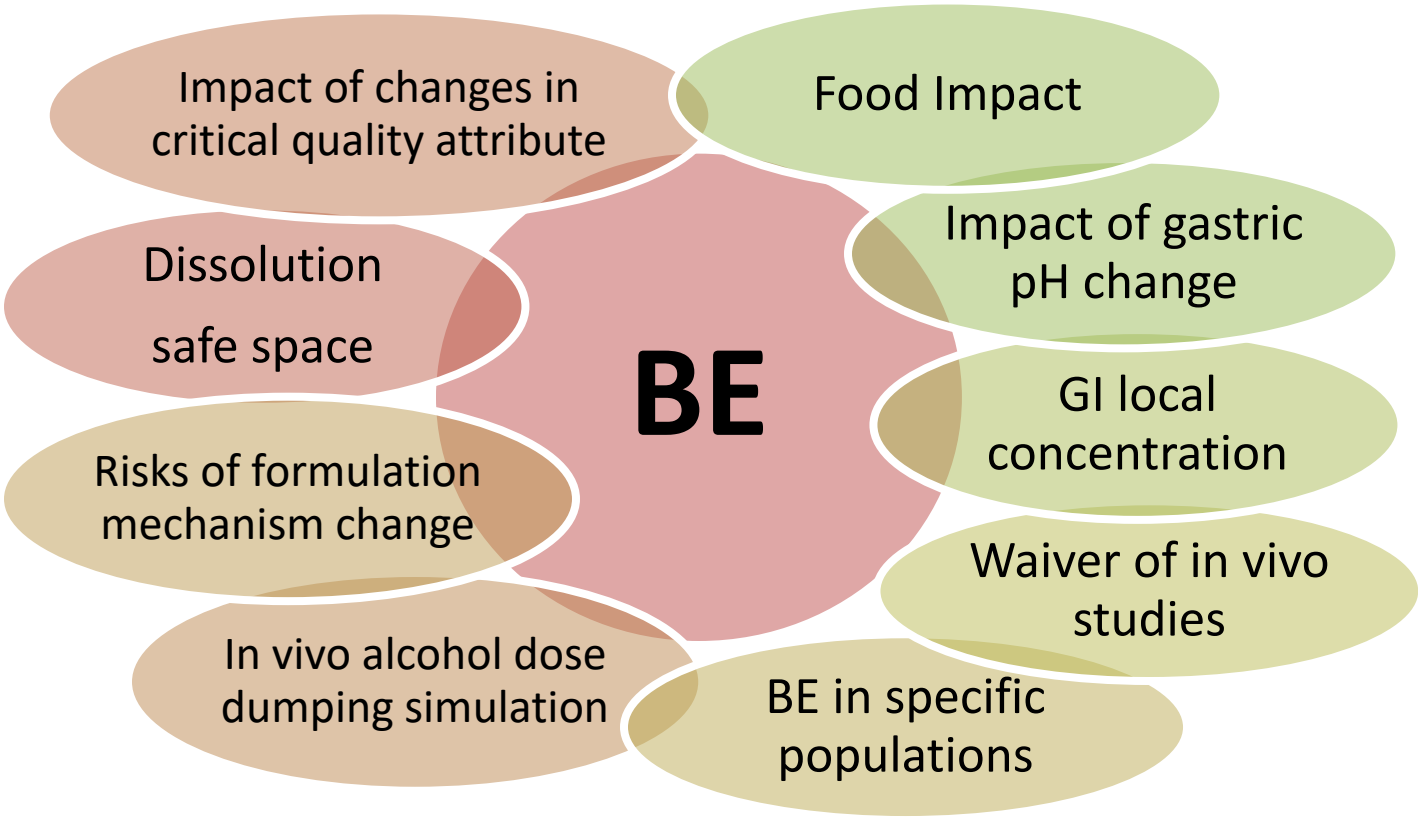
Disclaimer

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. Regulatory Questions that PBPK Absorption Model can Help Answer
2. General PBPK Modeling Procedure in ANDA Submission
3. PBPK Guidances Supported by Regulatory Applications and Research
4. Regulatory Case Examples of Using PBPK Absorption Modeling/PBBM in Office of Generic Drugs
5. Research of PBPK Absorption Modeling and Simulation
6. Conclusion

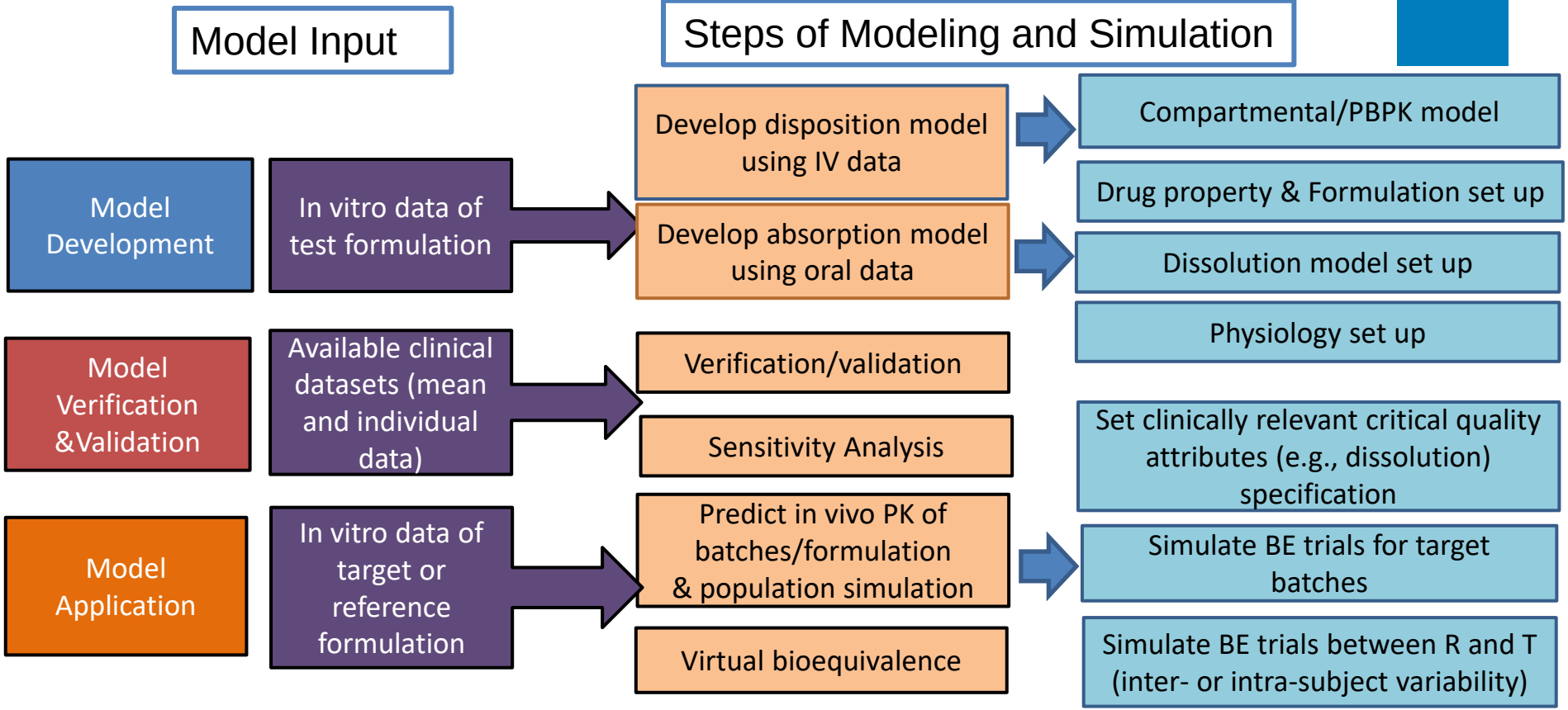
Regulatory Questions that PBPK Absorption Model can Help Answer



PPI: proton pump inhibitor; GI: gastrointestinal; BE: bioequivalence

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

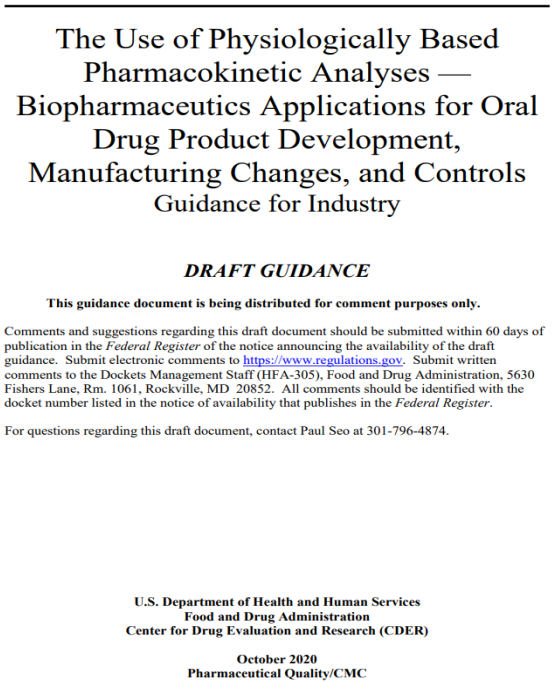
General PBPK Modeling Procedure in ANDA Submission



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

Guidances Supported by PBPK Regulatory Applications and Research



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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

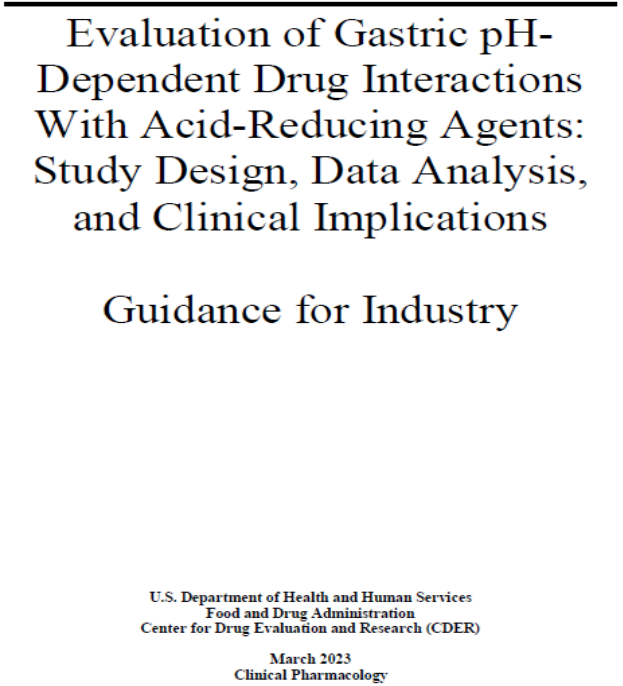
Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management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

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

March 2023
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

Highlights of PBPK Absorption Modeling Impacts on Regulatory Decision Making in OGD

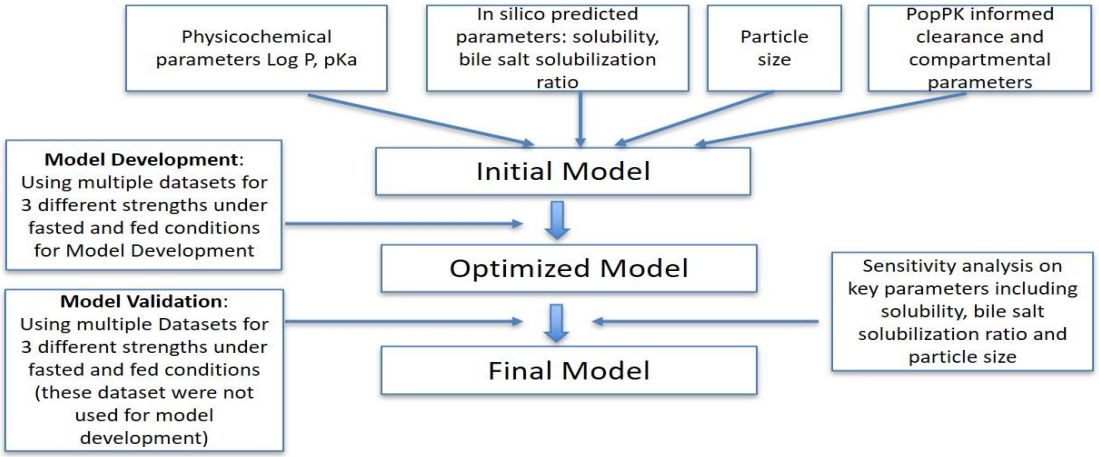
Category	Impact on regulatory decision making
Risk assessment of the impact of Particle Size Distribution (PSD) on BE	Evaluate the impact of PSD on BE and support setting a clinically relevant 3 tier PSD specification
Risk assessment of deviation of dissolution profiles on BE	Using IVIVC and PBPK absorption 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 non-comparable dissolution on BE	IVIVC/PBPK absorption modeling to assess the impact of non-comparable dissolution profiles of extended release (ER) tablets on in vivo performance
Identify biopredictive dissolution and support BE evaluation	PBPK absorption modeling to help identify biopredictive dissolution and support BE evaluation for a gastrointestinal (GI) locally acting product

IVIVC: In vitro in vivo correlation

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 A 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: PBPK absorption model in Assessing the Impact of PSD on BE

- **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

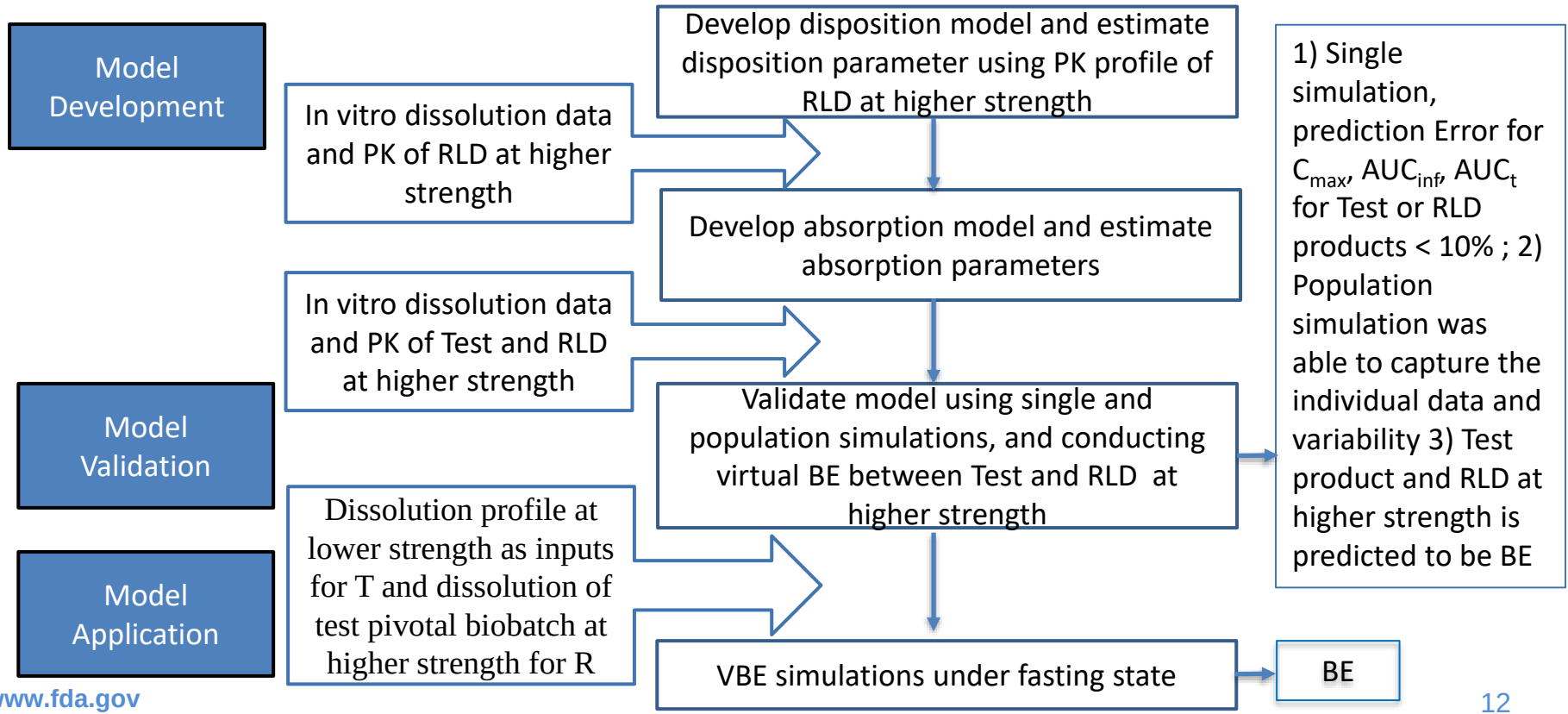
- PBPK modeling and simulation suggested that the test vs reference PK metrics showed a low risk of non-BE when D90 changed over a wide range with a certain fixed value of D50 for all strengths.
- The modeling results support a satisfactory BE assessment of this ANDA and setting a clinically relevant 3 tier PSD specification.

Case Example 2: PBPK Absorption Modeling to Support Waiver for Lower Strength of an Oral Tablet Product

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.
- Lower Strength of drug B has a faster dissolution profile compared to bio-strength (higher strength).
- Per RLD label, the administration of drug B with a low-fat or a high-fat meal increased drug exposure by approximately 3-5 fold, compared to fasting condition.
- Per RLD label, the drug product should be taken with a meal.
- The Applicant used a mechanistic absorption model to predict whether the faster dissolution of lower strength has significant impact on the in vivo performance under fasting condition but not under fed condition.

Case Example 2: PBPK Absorption Modeling to Support Waiver for Lower Strength of an Oral Tablet Product



Case Example 2: PBPK Absorption Modeling to Support Waiver for Lower Strength of an Oral Tablet Product

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.

Summary for Case Example 2

- PBPK/PBBM modeling and simulation was used to evaluate the impact of faster dissolution profile of lower strength compared to higher strength on in vivo performance.

- The model should be sufficiently validated before being used to evaluate such impact.

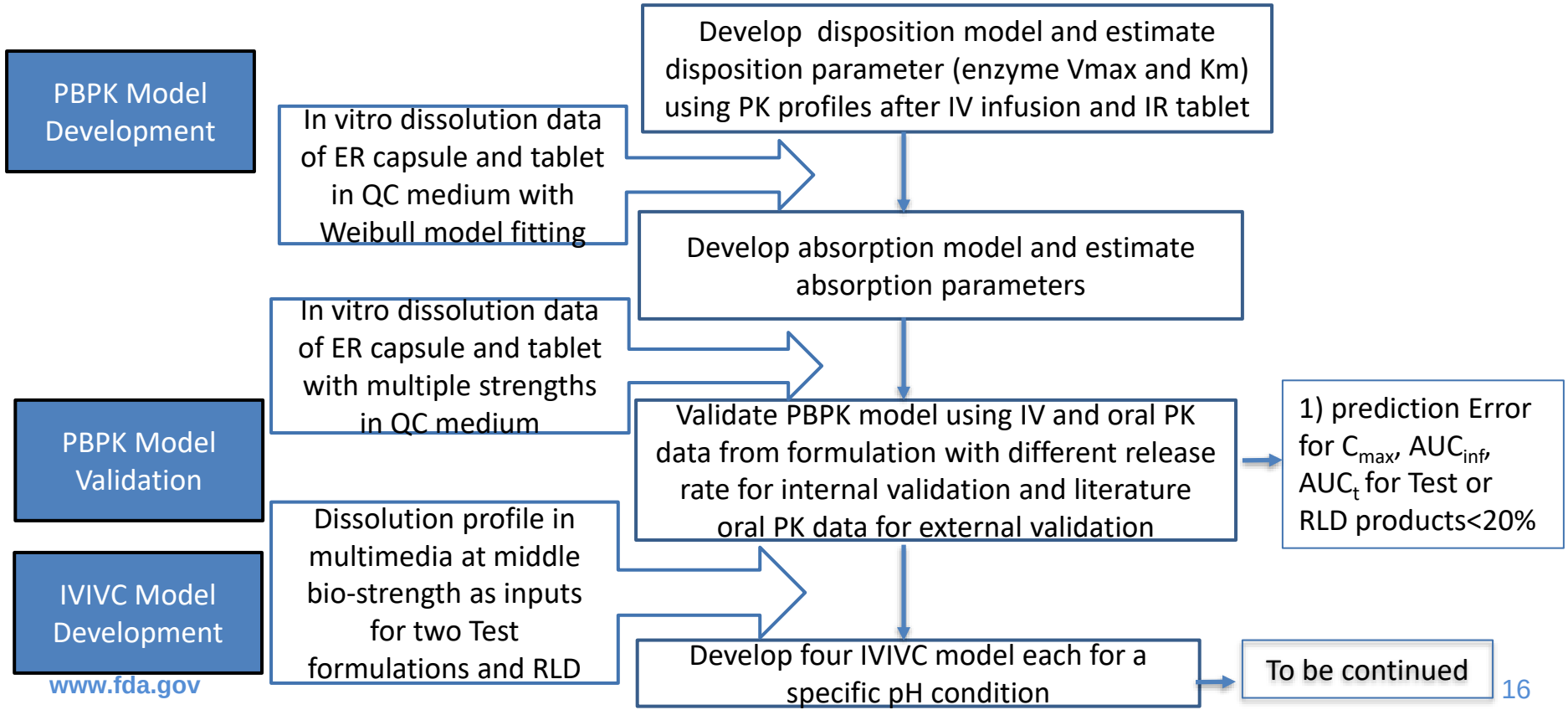
Case Example 3: PBPK Absorption Modeling/IVIVC to Assess the Impact of Non-comparable Dissolution Profiles of ER Tablets on In vivo Performance

Background

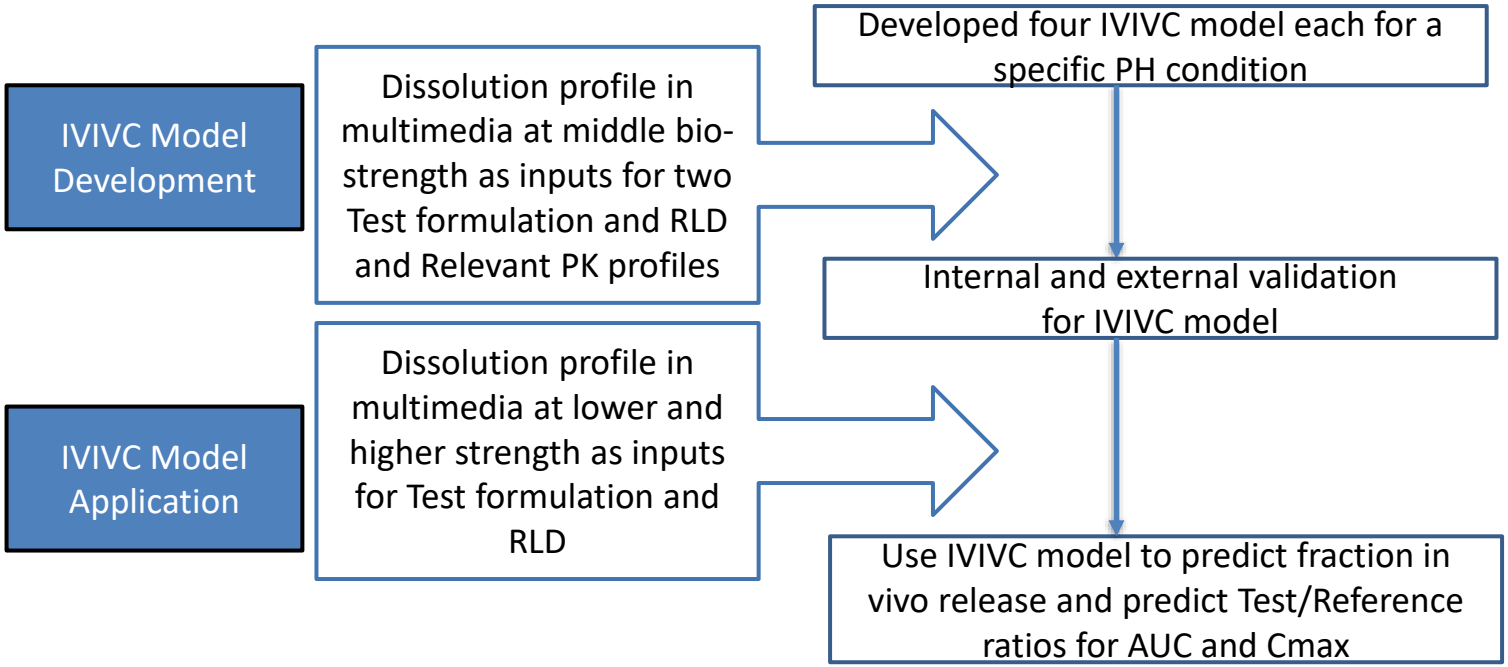
- Both RLD and Test products use osmotic pressure to deliver drug C at a controlled rate. The controlled rate of drug delivery into the gastrointestinal lumen is independent of pH or gastrointestinal motility.
- Per RLD label, the drug product should be taken with a meal.
- The dissolution profiles of the lower and higher strengths of the Test product are comparable to that of the bio-batch (middle strength) of Test product in both QC and multi-pH media conditions (pH 1.2, 4.5 and 6.8 buffer) (f2>50), but not comparable to those of corresponding strength of RLD.
- The Applicant developed both mechanistic absorption model and IVIVC to justify that T/R ratios for Cmax and AUCt of all strengths remain within the 80%-125% acceptance limit.

ER: Extended release

Case Example 3: PBPK Absorption Modeling/IVIVC to Evaluate BE for ER Tablets



Case Example 3: PBPK Absorption Modeling/IVIVC to Evaluate BE for ER Tablets



Case Example 3: PBPK Absorption Modeling/IVIVC to Evaluate BE for ER Tablets

For IVIVC

- As the middle bio-strength has similar dissolution for T and R in QC medium and multi-pH medium, the applicant's IVIVC models were not developed based on formulations with different release rates, hence not considered acceptable.
- Even based on applicant's IVIVC model predictions, predicted T/R ratios for Cmax for lower and higher strengths in multi-pH media falls outside 0.8-1.25 BE limit, which indicates the applicant's IVIVC model failed to support that generic product is BE to RLD.

Case Example 3: PBPK Absorption Modeling/IVIVC to Evaluate BE for ER Tablets

Deficiencies identified on the submitted PBPK/IVIVC model

For PBPK

- There is a lack of non-BE batch to challenge the PBPK model. The Applicant is recommended to use available or theoretical non-BE batch/formulation to evaluate the sensitivity and demonstrate the bio-discriminating capability of the model.
- The developed mechanistic PBPK absorption modeling with further sufficient validation together with virtual BE simulations may be used to provide risk assessment and support the justification for the non-comparable dissolution of both higher and lower strengths of Test and RLD products in multi-pH media.

Summary for Case Example 3

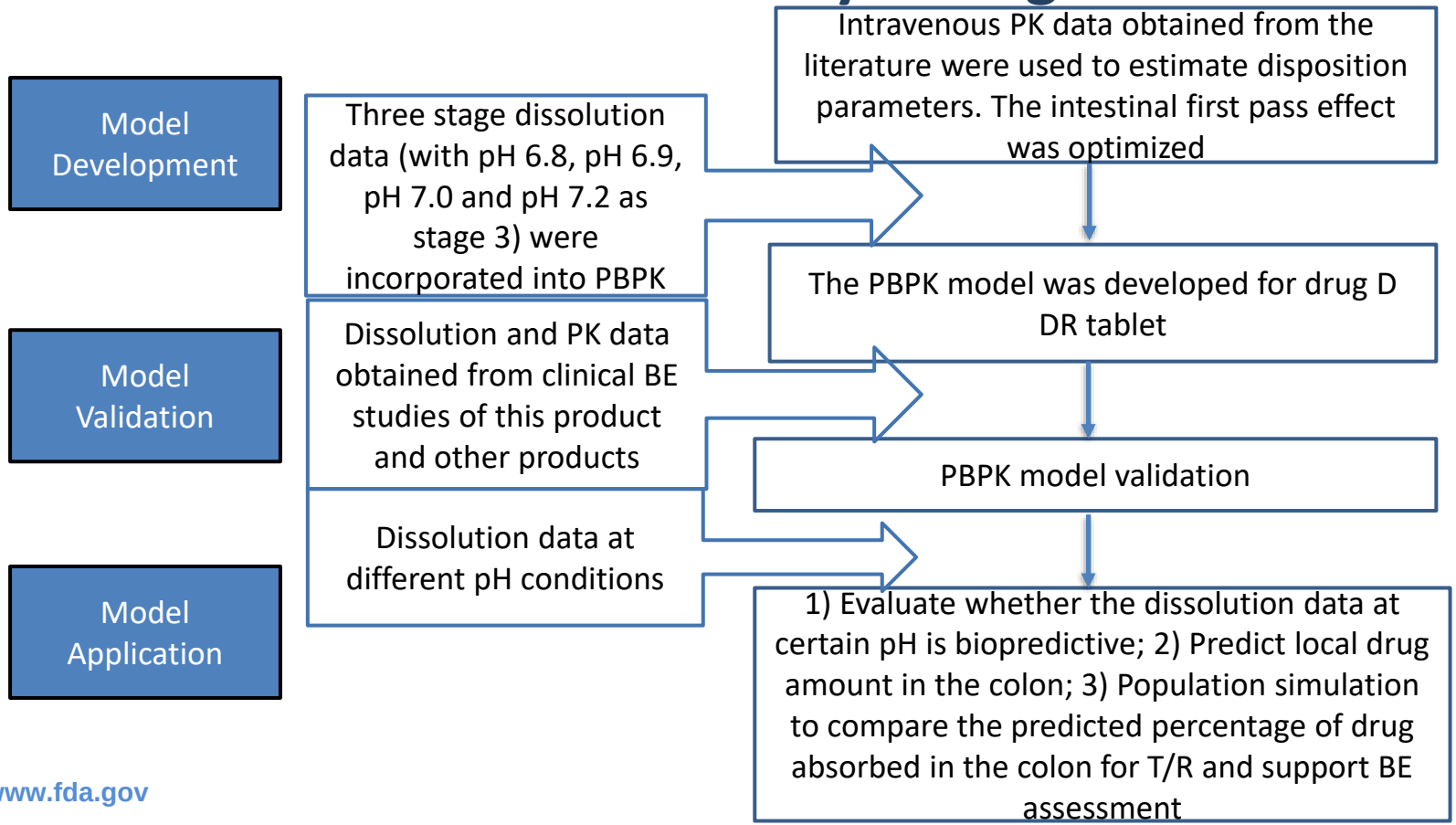
- PBPK/IVIVC modeling was used to support the justification for the non-comparable dissolution of both higher and lower strengths of Test and RLD products in multi-pH media.
- IVIVC models were not developed based on formulations with different release rates, this limitation restricts its utility to evaluate the effect of non-comparable dissolution.
- The developed mechanistic PBPK absorption modeling with further sufficient validation together with virtual BE simulations may be used to provide risk assessment.

Case Example 4: PBPK Modeling to Support BE Evaluation of a GI Locally Acting Product

Background

- Drug D delayed release (DR) tablet is indicated for mildly to moderately active ulcerative colitis
- The product-specific guidance for this product recommends a fasting PK BE study, and a fed PK BE study and comparative dissolution studies at four different pHs (6.5, 6.8, 7.2, and 7.5)
- f2 values for dissolution profile comparison between test and RLD were <50 at pH 6.8 and 6.9 buffer condition
- The two products were found to be bioequivalent for systemic PK under both fasting and fed conditions
- PBPK absorption modeling was developed and used by the reviewers to predict local drug amount in the colon by incorporating dissolution data at different pH conditions

Case Example 4: PBPK Absorption Modeling to Support BE Evaluation of a GI Locally Acting Product



Case Example 4: PBPK Absorption Modeling to Support BE Evaluation of a GI Locally Acting Product

Results

- Dissolution profiles at both pH 7.0 and pH 7.2 (as stage 3) is biorelevant/biopredictive to the PK profiles with PE%<22%.
- Population simulations (n=25) showed that the percentage of drug absorbed in the colon is similar between the RLD and test product with the 90% CI of the T/R ratio falling within 80-125%.

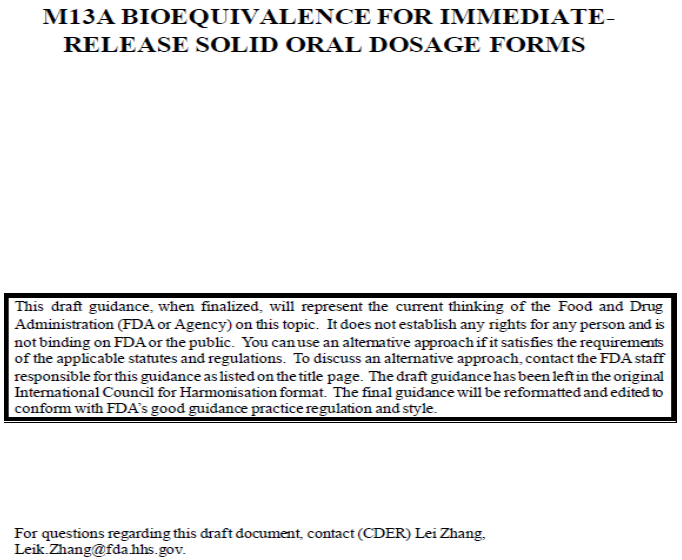
pH at Stage 3 Dissolution	PK Parameter	Predicted for Colon for RLD	Predicted for Colon for Test
7.2	Cmax	157.7	152.4
	AUCt	2592	2609
7	Cmax	156.6	153.6
	AUCt	2580	2567
6.9	Cmax	157	153.2
	AUCt	2521	2422

Table: Predicted PK parameters Cmax (mg) and AUCt (mg*h) for amount of drug in colon

Summary for Case Example 4

- PBPK model suggested that the three-stage dissolution profiles at both pH 7.0 and pH 7.2 (as stage 3) may be biopredictive/biorelevant to the local and systemic exposure.
- The PBPK model can be used to predict that the percentage of drug absorbed in the colon is similar between the RLD and test product.

Other Guidance Supported by PBPK Regulatory Applications and Research



M13A BIOEQUIVALENCE FOR IMMEDIATE-RELEASE SOLID ORAL DOSAGE FORMS

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or 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 FDA staff responsible for this guidance as listed on the title page. The draft guidance has been left in the original International Council for Harmonisation format. The final guidance will be reformatted and edited to conform with FDA's good guidance practice regulation and style.

For questions regarding this draft document, contact (CDER) Lei Zhang, Leik.Zhang@fda.hhs.gov.

2.1.5 Fasting and Fed Study Conditions

The design of a BE study with regard to the use of fasting and/or fed conditions depends on the dosing instructions of the comparator product as well as the properties of the drug substance and product formulation.…The rationale can be supported by modelling, e.g., appropriately validated/qualified physiologically-based pharmacokinetic (PBPK) modelling or semi-mechanistic absorption models.

Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m13a-bioequivalence-immediate-release-solid-oral-dosage-forms (Issued Jan 2023)

PBPK Modeling for Risk Assessment of Food Impact

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

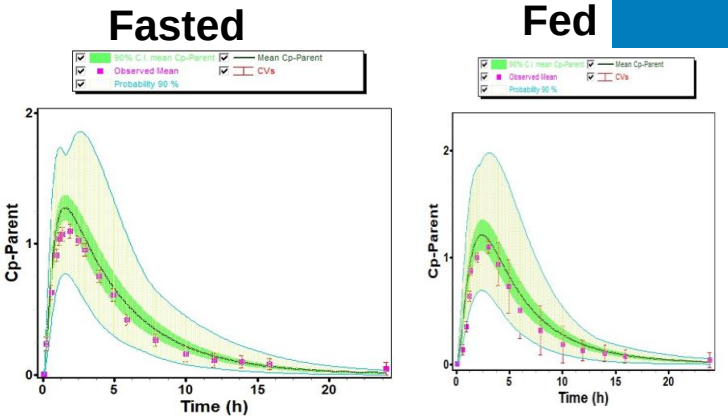


Figure. PBPK Model Simulation for Acyclovir IR Product 800 mg

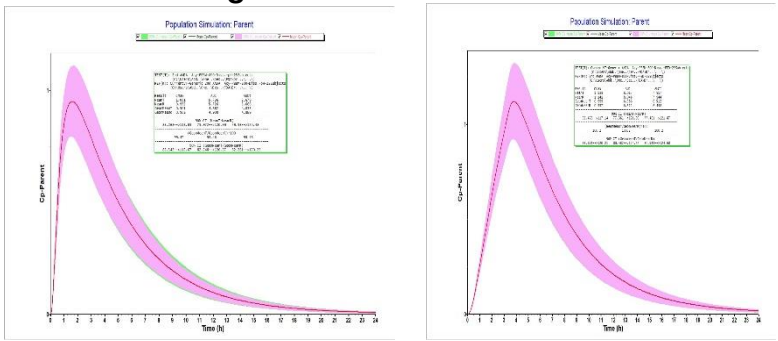
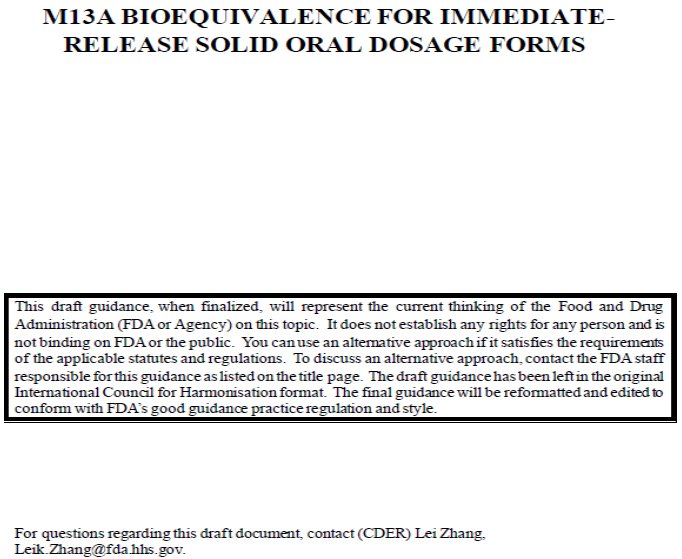


Figure. VBE of Acyclovir IR Product 800 mg

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

Other Guidance Supported by PBPK Regulatory Applications and Research



M13A BIOEQUIVALENCE FOR IMMEDIATE-RELEASE SOLID ORAL DOSAGE FORMS

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For questions regarding this draft document, contact (CDER) Lei Zhang, Leik.Zhang@fda.hhs.gov.

3.4 pH-Dependency

Modelling, e.g., appropriately validated/qualified PBPK modelling or semi-mechanistic absorption models, and virtual BE simulation may be used to further assess the risk of bioinequivalence.

Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m13a-bioequivalence-immediate-release-solid-oral-dosage-forms (Issued Jan 2023)

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

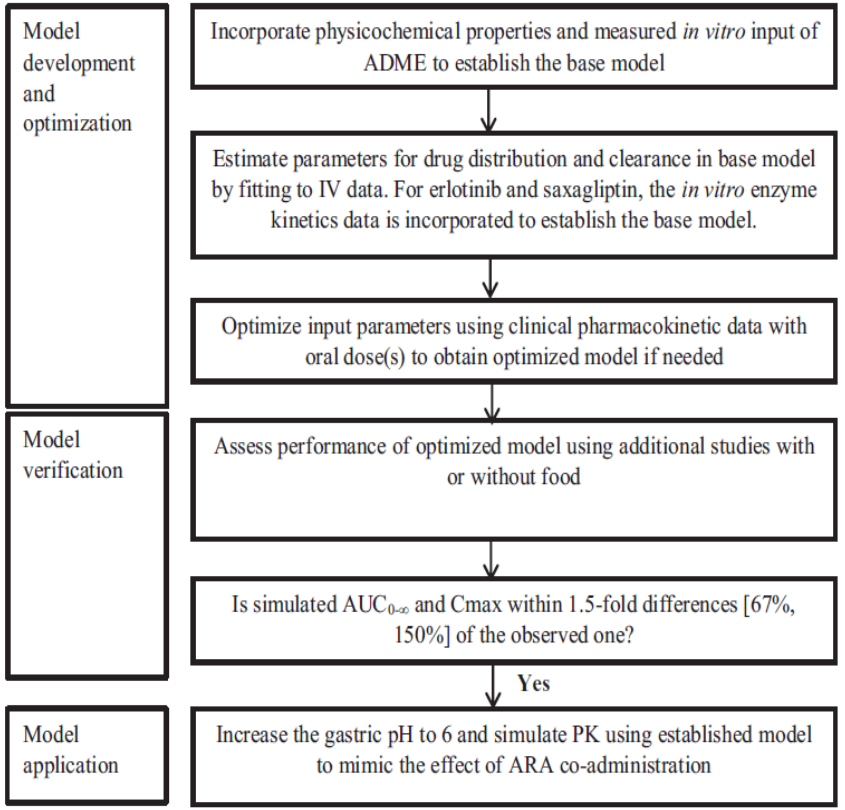
3. Type of study: Fasting, in presence of an acid-reducing agent

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

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

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

- **Method:** PBPK models of four model drugs (tapentadol, darunavir, erlotinib, and saxagliptin) were optimized using pharmacokinetic data following oral administration without Acid Reducing Agent (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.
- **Results:** Model simulations 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



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

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 RLD 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.

Recent Publications Supported by Internal and External Research

Received: 18 September 2022 | Revised: 27 November 2022 | Accepted: 13 December 2022
DOI: 10.1002/psp4.12907

REVIEW

Regulatory utility of physiologically-based pharmacokinetic modeling to support alternative bioequivalence approaches and risk assessment: A workshop summary report

Fang Wu[1] | Youssef Mousa[1] | Kimberly Raines[2] | Chris Bode[3] | Yu Chung Tsang[4] | Rodrigo Cristofoletti[5] | Hongling Zhang[6] | Tycho Heimbach[7] | Lanyan Fang[1] | Filippos Kesisoglou[7] | Amitava Mitra[8] | James Polli[9] | Myong-Jin Kim[1] | Jianghong Fan[10] | Banu S. Zolnik[2] | Duxin Sun[11] | Yi Zhang[1] | Liang Zhao[1]

Received: 16 September 2022 | Revised: 4 December 2022 | Accepted: 16 December 2022
DOI: 10.1002/psp4.12913

MINI REVIEW

Regulatory utility of physiologically based pharmacokinetic modeling for assessing food impact in bioequivalence studies: A workshop summary report

Abdullah Al Shoyaib[1] | Arian Emami Riedmaier[2] | Anita Kumar[3] | Partha Roy[4] | Neil John Parrott[5] | Lanyan Fang[1] | Nilufer Tampal[4] | Yuching Yang[6] | Rebeka Jereb[7] | Liang Zhao[1] | Fang Wu[1,†]

www.fda.gov

The AAPS Journal (2023) 25:67
https://doi.org/10.1208/s12248-023-00826-1

RESEARCH ARTICLE

Integration of Biorelevant Pediatric Dissolution Methodology into PBPK Modeling to Predict *In Vivo* Performance and Bioequivalence of Generic Drugs in Pediatric Populations: a Carbamazepine Case Study

Gopal Pawar[1] · Fang Wu[2] · Liang Zhao[2] · Lanyan Fang[2] · Gilbert J. Burckart[3] · Kairui Feng[2] · Youssef M. Mousa[2] · Abdullah Al Shoyaib[2] · Marie-Christine Jones[1] · Hannah K. Batchelor[4]

Received: 12 October 2022 | Revised: 21 December 2022 | Accepted: 2 January 2023
DOI: 10.1002/psp4.12920

MINI REVIEW

Regulatory utility of mechanistic modeling to support alternative bioequivalence approaches: A workshop overview

Andrew Babiskin[1] | Fang Wu[1] | Youssef Mousa[1] | Ming-Liang Tan[1] | Eleftheria Tsakalozou[1] | Ross L. Walenga[1] | Miyoung Yoon[1] | Sam G. Raney[2] | James E. Polli[3] | Anna Schwendeman[4] | Vishalakshi Krishnan[4] | Lanyan Fang[1] | Liang Zhao[1]

Received: 2 December 2022 | Revised: 5 January 2023 | Accepted: 6 January 2023
DOI: 10.1002/psp4.12930

PERSPECTIVE

Increasing impact of quantitative methods and modeling in establishment of bioequivalence and characterization of drug delivery

Miyoung Yoon[1] | Andrew Babiskin[1] | Meng Hu[1] | Fang Wu[1] | Sam G. Raney[2] | Lanyan Fang[1] | Liang Zhao[1]

Recent Publications Supported by Internal and External Research

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

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Conclusion

- Currently, modeling and simulation tool, e.g., PBPK absorption modeling and simulation (M&S) has been increasingly used in generic drug applications.
- Case examples of PBPK absorption modeling to evaluate the impact of critical quality attributes on BE include:
  - Evaluate the impact of PSD on BE and support setting a clinically relevant PSD specification
  - Conduct risk assessment on the impact of non-comparable dissolution profiles of the Test and RLD products on in vivo performance
  - PBPK absorption modeling to help identify biopredictive dissolution and support BE evaluation of a gastrointestinal (GI) locally acting product

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