

Challenges and Opportunities when Using Oral PBPK to Support Risk Assessment and Biowaiver in Regulatory Submissions

*SBIA 2022: Advancing Generic Drug Development:
Translating Science to Approval*

Day (2), Session (7): (Quantitative Methods – Study Design, Model-integrated BE Approaches)

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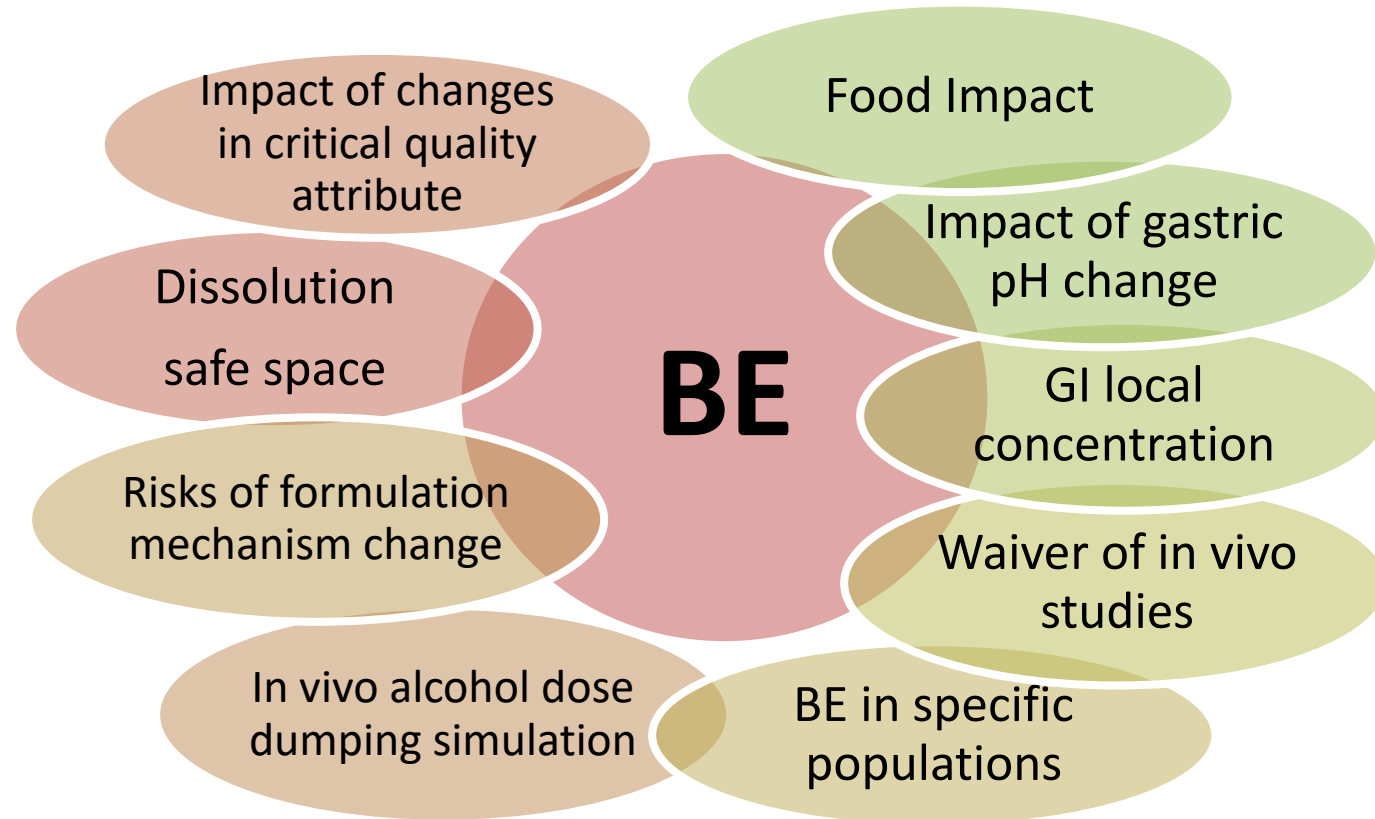
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Learning Objectives

1. Understand regulatory questions that physiologically-based - pharmacokinetic modeling (PBPK) absorption model can help answer in generic drug development
2. To learn recent case examples on developing PBPK modeling and conducting virtual bioequivalence simulations for supporting regulatory decision making

Regulatory Questions that PBPK Absorption Model can Help Answer



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

General PBPK Modeling Procedure in ANDA Submission

Model Input

Steps of Modeling and Simulation

Model Development

In vitro data of test formulation

Develop disposition model using IV data

Develop absorption model using oral data

Compartmental/PBPK model

Drug property & Formulation set up

Dissolution model set up

Physiology set up

Model Verification & Validation

Available clinical datasets (mean and individual data)

Verification/validation

Sensitivity Analysis

Set clinically relevant critical quality attributes (e.g., dissolution) specification

Model Application

In vitro data of target or reference formulation

Predict in vivo PK of batches/formulation & population simulation

Virtual bioequivalence

Simulate BE trials for target batches

Simulate BE trials between R and T (inter- or intra-subject variability)

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

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)

Case Example 1: PBPK absorption model to Evaluate the Impact of Drug Degradation at pH 1.2 on BE



Background: Drug degradation was observed in the in vitro dissolution studies at pH 1.2 for an oral tablet product. The Applicant submitted a PBPK model to address whether the observed drug degradation would impact drug plasma time-concentrations profile as well as BE under fasted and fed conditions

Question: What is the impact of observed drug degradation at pH 1.2 on bioequivalence?

Review and Impact: The agency further developed PBPK model showed that the observed in vitro drug degradation is not expected to significantly impact the plasma time-concentrations profile and drug exposure under fasted and fed conditions using virtual BE simulations. This is likely due to the long degradation half-life (>10 hours) as compared to the relatively short gastric transit time (~15 min). Similarly, gastric pH changes did not affect in vivo PK parameters as simulated using agency developed PBPK model.

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Major limitations identified on the submitted PBPK model:

-The Applicant used in vitro dissolution rather than solubility profiles to calculate drug degradation rate, which is not appropriate. There could be other formulation factors and/or dissolution conditions that led to slower drug release at pH 1.2.

-The model developed by the Applicant could not replicate the findings from in vivo bioavailability (BA) study that evaluated the impact of gastric pH change (i.e., administration of drug with and without proton pump inhibitor) on drug PK profile.

Case Example 2: Using IVIVC/PBPK Absorption Modeling to Assess the Impact of Non-comparable Dissolution Profiles on In vivo Performance



Background: Non-comparable dissolution of the Test and RLD products in quality control (QC) media and multi-pH media for lower strengths of Drug X ER tablets were observed.

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

Review and Impact:

- IVIVC and PBPK mechanistic absorption modeling were used for predicting the impact of non-comparable dissolution profiles of lower strength on the in vivo performance.

Major limitations identified on the submitted IVIVC model:

-The applicant's IVIVC model was not established and validated using formulations with different release rates as recommended by the IVIVC guidance.

- The applicant did not use PK data from intravenous or immediate release oral formulations as reference to predict the disposition parameters.

-Using dissolution testing data conducted in quality control medium in IVIVC analysis is not sufficient to address the 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).

Case Example 3: Using PBPK Absorption Modeling to Evaluate the Food Impact on BE



Background: Drug Y oral tablets include API with amorphous solid dispersion (ASD) form. A mechanistic absorption model was developed for oral tablet 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 developed PBPK model were identified.

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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 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.

Challenges and Opportunities (When Using PBPK Absorption Model)



Challenges

- The model inputs, including solubility, permeability, dissolution profiles need to be biorelevant/biopredictive
- PBPK model needs to be sufficiently validated for its intended purpose/context of use
- Insufficient in vivo PK datasets for the development and validation of the model (e.g., lack of human IV data to estimate the drug disposition parameters)

Further Improvement

- Consistent and adequate approach of generating and incorporating (biorelevant/biopredictive) solubility, dissolution profiles (QC vs biorelevant), and permeability is needed
- Using all available datasets to validate the model for its intended purpose
- Using dataset from IV or oral solution data with complete absorption and appropriate approach to estimate the disposition parameters.

Challenges and Opportunities (When Using PBPK Absorption Model)

Challenges

- The model needs to be challenged 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

Further Improvement

- Formulation variations included in model verification need to be wide enough to avoid extrapolation outside of the tested space of the formulation variations
- Consider assessing type 1 error for BE assessment when using modeling (e.g., large number of virtual BE studies may be conducted with an appropriate number of subjects using a series of fold differences between your test product and RLD and report the virtual BE results and BE passing rate)



Research Updates 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

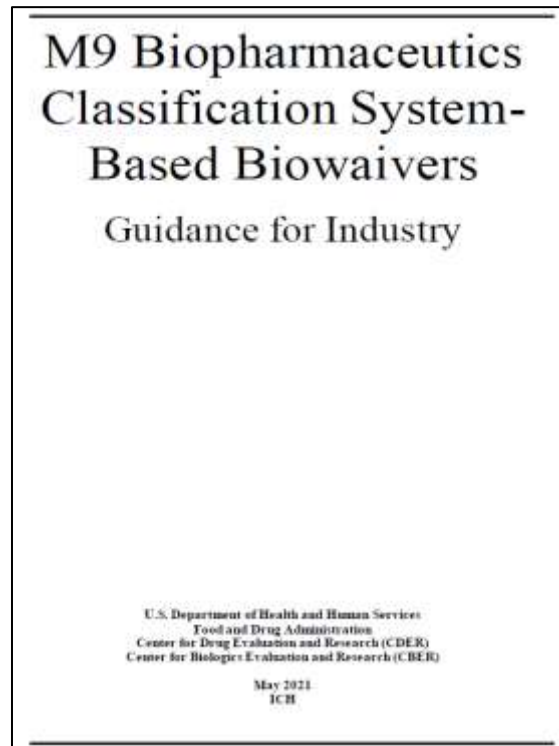
GDUFA: Generic Drug User Fee Amendments

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



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 quantitatively 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

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 PBPB 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



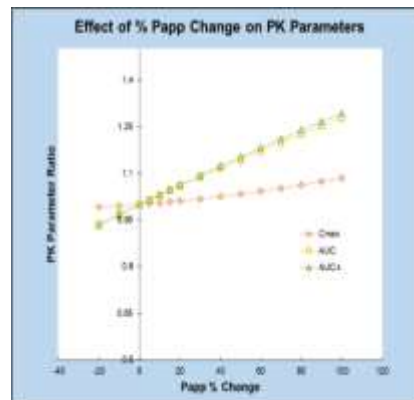
Background: As a proof of concept, we have utilized an oral PBPK model of acyclovir immediate release (IR) tablet for assessing the impact of excipient and food intake on the BE of generic acyclovir IR tablet using virtual healthy subjects and virtual bioequivalence (VBE) trials.

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)

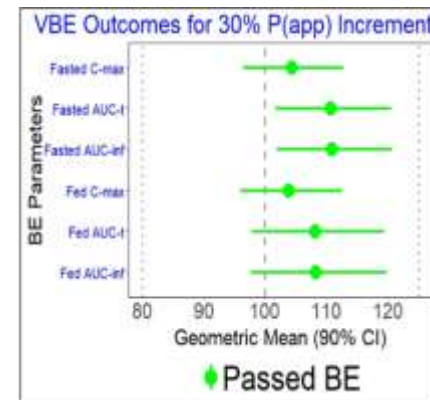


Figure: (A) Impact of excipient-mediated apparent intestinal permeability (Papp) changes on the PK parameters predicted using single subject simulation and acyclovir oral PBPK model. (B) VBE trials show that the test and reference acyclovir 800 mg IR tablets are BE under fasted and fed condition for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

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

Relevant Grant/Contract

- Completed Contract BAA: “Expanding BCS Class 3 Waivers for Generic Drugs to Non-Q1/Q2” with Dr. Chris Bode from Absorption Systems Inc.
- Completed Contract BAA “Better Understanding Risk Mitigation in the Evaluation of Relative Bioavailability of Pediatric Generic Products” with Dr. Hannah Batchelor from University of Birmingham
- Active Grant: “Development and validation of a best practices framework for PBPK analysis for biopharmaceutical applications in support of model-informed biowaivers of fed state BE studies for BCS class II drugs” with Dr. Rodrigo Cristofolletti 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

BAA: Broad Agency Announcement

Link:

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

<https://www.fda.gov/drugs/generic-drugs/fy-2021-gdufa-science-and-research-report>

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 Ruines,³ Lei Zhang,¹ and Paul Seo³

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 Rugueneau-Majlessi³

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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



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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. Martinez¹ · Balint Sinko² · Fang Wu³ · Talia Flanagan⁴ · Enikő Borbás⁵ · Eleftheria Tsakalozou⁴ · Kathleen M. Giacomini[®]

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. Martinez¹ · Fang Wu² · Balint Sinko³ · David J. Brayden⁴ · Michael Grass⁵ · Filippos Kesisoglou⁶ · Aaron Stewart^{5,7} · Kiyohiko Sugano⁸

Conclusion



- Currently, modeling and simulation tools e.g., PBPK absorption modeling and simulation (M&S) has been increasingly used in generic drug applications.
- GDUFA funded research projects support to fill the knowledge gap.
- Recent Oral PBPK Impacts on Regulatory Decision Making include:
 - Evaluate the impact of drug degradation at pH 1.2 on BE
 - Conduct risk assessment on the impact of non-comparable dissolution profiles of the Test and RLD products on in vivo performance
 - Conduct risk assessment on the impact of food on bioequivalence
 - Assess a BE study with more subjects and another study design in combination with in vivo pilot BE study



Challenge Question #1

For BCS Class 3-based biowaiver, which of the following statements is NOT true?

- A. The drug substance is highly soluble
- B. The drug product (test and reference) is very rapidly dissolving ($\geq 85\%$ for the mean percent dissolved in ≤ 15 minutes)
- C. All of the excipients should be qualitatively (Q1) the same and quantitatively (Q2) similar.
- D. There is no possibility of expanding biowaivers to non-Q1/Q2 formulations within a certain range

Challenge Question #2

PBPK Absorption Modeling can be used for:

- A. Evaluate the impact of drug degradation at pH 1.2 on BE
- B. Risk assessment of the impact of deviation of dissolution profiles on BE
- C. Risk assessment of bio-inequivalence attributable to food intake
- D. All of the above



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Absorption Systems: Dr. Chris Bode

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