Risk Assessment and Management for Formulation Change Using Model Integrated Approach

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Patient Centric Dissolution Testing: Biopharmaceutics Risk Framework - Collaboration Session

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Disclaimer

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

The presenter is offering his perspective based upon his experiences during regulatory decision-making

The Convergence between Product Quality and Bioequivalence (BE)

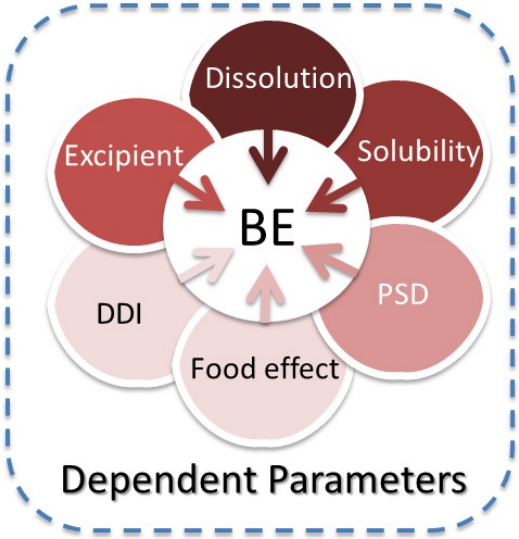
- Generally, difficult to establish a relationship between the in vitro test and in vivo performance for immediate release solid dosage forms
- Clinical relevancy of quality attribute is important both for quality control and BE assessment
- BE space for in vitro parameters including in vitro release testing (IVRT) standard can be of great reference value to quality management
- Modeling is an integration of knowledge, experience, and data
- Model-integrated approach will shed light on the connections between product quality and BE

Highlights of Recent Oral Physiologically based Pharmacokinetics (PBPK) Impacts on Regulatory Decision Making in OGD

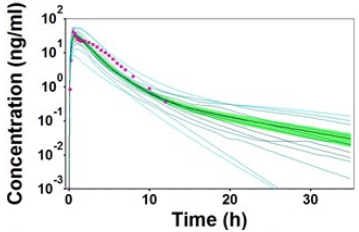
Category	Impact on regulatory decision making
Drug quality (risk assessment)	Evaluate the impact of Particle Size Distribution (PSD) on BE and support setting a clinically relevant 3-tier PSD specification
Drug quality (risk assessment)	Risk assessment of the impact of dissolution rate at different pH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

Zhang et al, CPT:PSP 2017 Aug;6(8):523-531

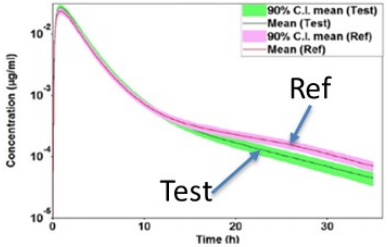
Application of PBPK Modeling in Regulatory for Generic Submissions



PBPK absorption model



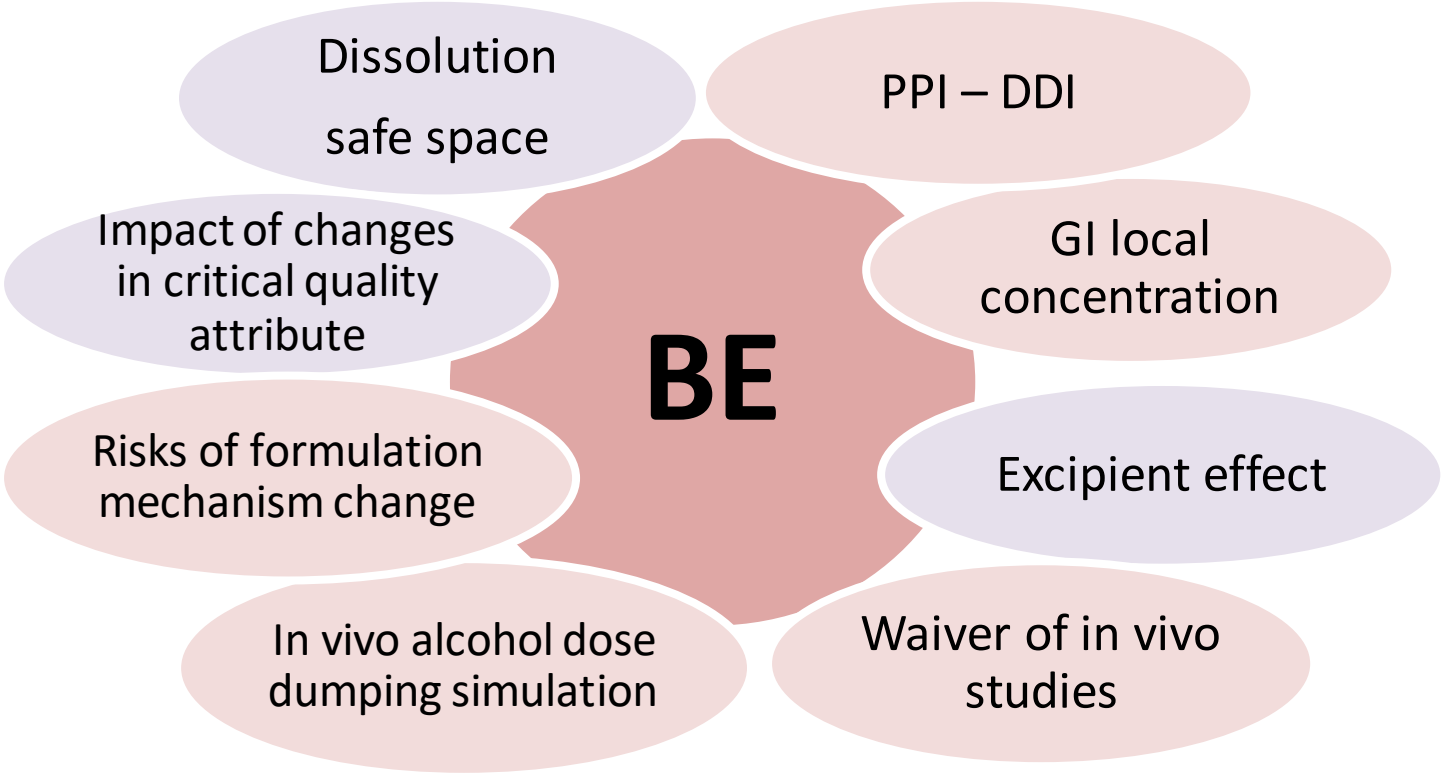
Fitting the model to reference PK data



Virtual BE between test and reference with cross-over population and incorporated variability

BE: bioequivalence; **DDI**: drug-drug interaction; **PSD**: particle size distribution

Regulatory Utilities of PBPK Absorption Model



PBPK: Physiologically based PK; BE: bioequivalence; PPI: proton pump inhibitor; GI: gastrointestinal; DDI: drug-drug interaction

Case I: PBPK Absorption Model in Assessing the Impact of Particle Size Distribution (PSD) on BE

A Capsule Product: efficacy related to systemic drug exposure.

Background: PK parameters, e.g., Cmax and AUC are found to be sensitive to changes in mean particle size of the active pharmaceutical ingredient under fasting condition. There is a PSD deviation in terms of D90 between test and reference product.

Question: What is the effect of PSD deviation on bioequivalence?

Modeling approach: PBPK modeling and simulation by the FDA assessor suggested that the test vs reference PK metrics showed a low risk of non-BE when D90 varied over a wide range with a certain fixed value of D50 for all strengths.

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

Formulation	D10	D50	D90	Test/Reference Ratios			BE
				Cmax	AUCt	AUCinf	
Refence	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

Simulation results with fixed D50 and changed D10 and D90 using the reference upper bound PSD

Case 2: Assessing the Impact of Pharmaceutical Excipients on Absorption

Background: Drug solubility, effective permeability, and intestinal metabolism and transport are parameters that govern bioavailability.

Question: What would be the effects of excipients on the systemic bioavailability of a drug by altering these parameters.

Modeling approach:

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

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

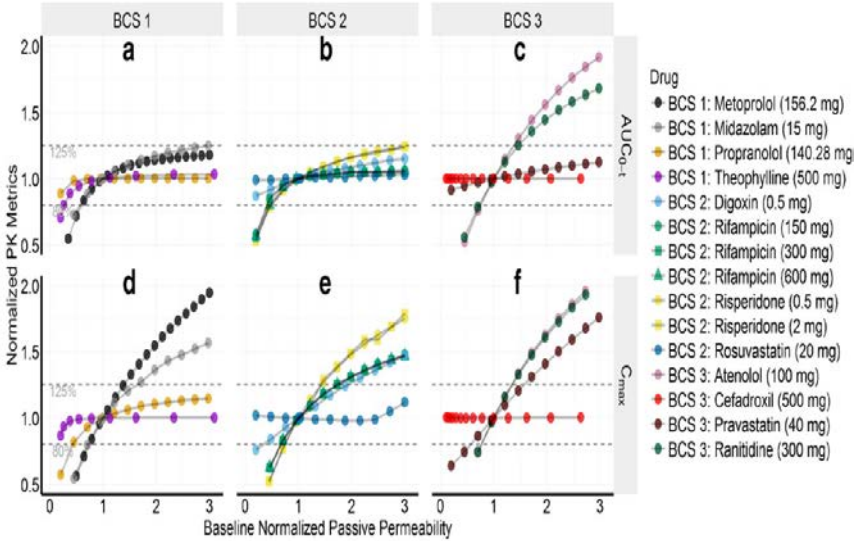


Figure: The effect of changes in passive permeability on Cmax and AUC0-t parameter changes for BCS class 1 (a, d), 2 (b, e) and 3 (atenolol, cefadroxil, pravastatin, and ranitidine) (c, f) drug IR products.

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

Case 3: Using PBPK Absorption Modeling to Support Waiver for Lower Strength with in vitro Testing Deviations

Background: Waiver of lower strength can be dependent on 1) formulation proportionality; 2) dissolution similarity; and 3) bioequivalence on other strength. However, there are cases that have dissimilar dissolution profiles for lower strength of the Test product

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

Modeling Assessment and Impact:

PBPK/PBBM modeling was used for predicting the impact of faster release of lower strength on the bioequivalence under fasting and fed conditions. Deficiencies were developed accordingly.

PBBM: Physiologically-based biopharmaceutics modeling

Deficiencies identified on the submitted PBPK/PBBM model:

-Validate the model for the intended purpose using different strengths or using data from formulations with different release rate.

-Demonstrate prediction performance for pharmacokinetic data of bio-strength under fed conditions.

-When these deficiencies are addressed, the developed PBPK/PBBM model can be used in assessing the impact of dissolution differences on in vivo performance/bioequivalence.

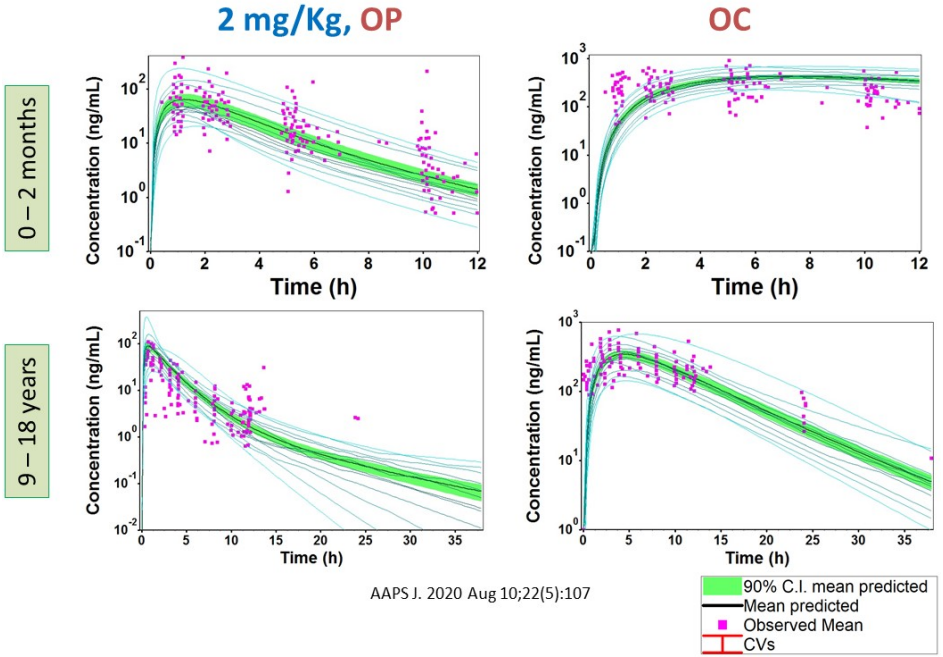
Case 4: Using PBPK Modeling to Identify Dissolution BE Space for Oseltamivir Phosphate (OP)

Background: Antiviral medication is used for influenza A and B. OP is a pro-drug of the active metabolite Oseltamivir Carboxylate. Pediatric BE is extrapolated from BE established in the adult population.

Question: What will be an appropriate dissolution BE space for the pediatric formulation?

Modeling Approach: The pediatric PBPK model was established from the adult PBPK by changing the physiological parameters, predicted using population estimates of age-related physiology.

Impact: BE Dissolution Safe Space for OP was determined for pediatric population divided into different age groups.



AAPS J. 2020 Aug 10;22(5):107

The pediatric model was also validated in age groups 3 - 9 months and 1 - 5 years

Miao L et. at. AAPS J. 2020 Aug 10;22(5):107.

Take Home Message

- Quantitative methods and modeling is an integration of knowledge, experience, and data
- Model-integrated approach can serve as a key method to assess and mitigate biopharmaceutics and BE risks including but not limited to
  - Dissolution profiles
  - Excipient changes
  - Deviations in critical quality attributes
  - Others

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