Impact of Food and Formulation on Bioequivalence: A Generic Industry Perspective

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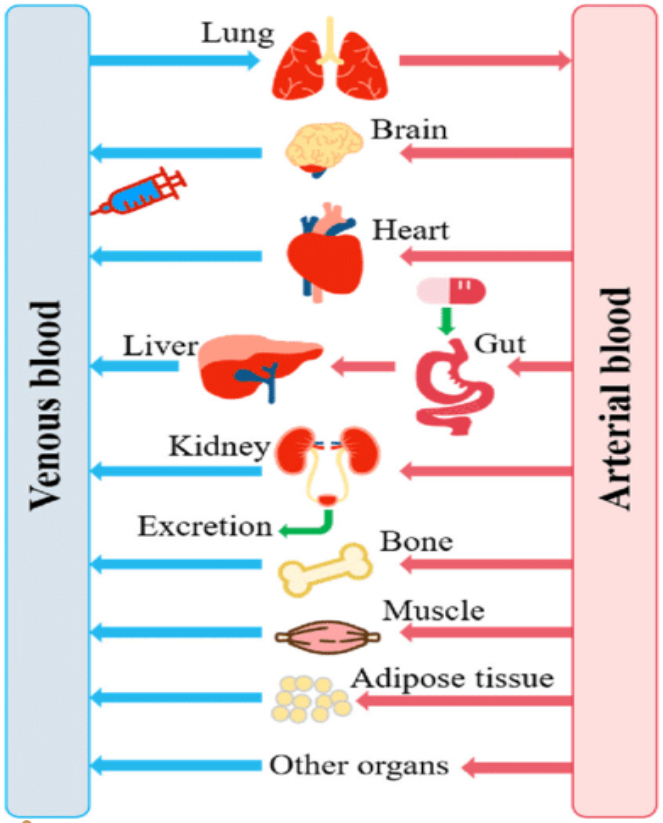
Oral PBPK Modeling and Simulation Applications for Generic Drug Development



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Proposed Advantages of PBPK Modeling in Generic Drug Development

- Aids in deeper understanding of the Drug and Reference Product
- Promotes Alternate BE Pathways requiring fewer In Vivo Studies
- Supports Bio Waivers of lower strengths in case of non proportional formulations
- Supports Robust Clinically Relevant Criteria for Performance Based Tests e.g. Dissolution
- Provides pathway for easier Post Approval Changes and effective Life Cycle Management

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1. Peng, Yaru, Zeneng Cheng, and Feifan Xie. *Metabolites* 11.2 (2021): 75

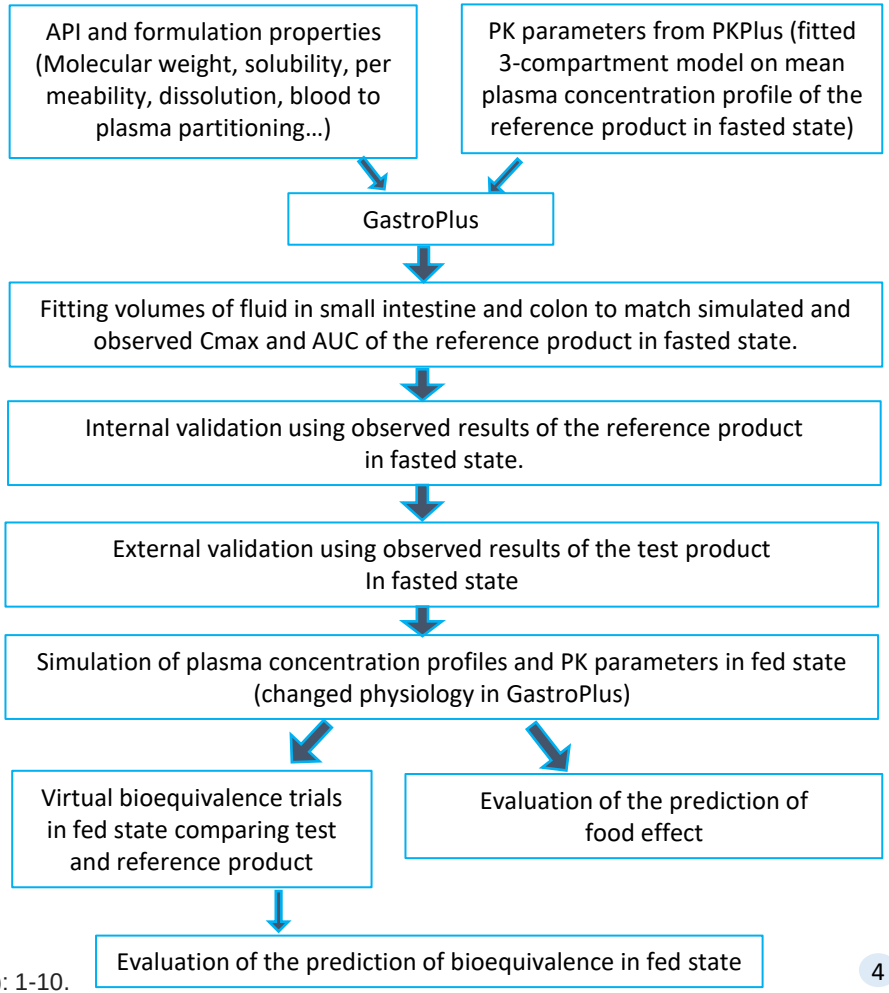
Optimal PBPK Modeling Workflow for Generic Industry

Ideal drug candidates for PBPK Modeling

- Compounds with well characterized gastrointestinal absorption
- BCS Class I, II or III with linear PK across dose range
- Compounds without major transporter influence or saturable metabolism
- Compounds likely to demonstrate bio predictive dissolution

Limitations

- Compounds without published Intravenous PK data
- Compounds where absorption is limited by active transport
- Prodrugs and Compounds with GI Instability.
- Drugs showing high first pass/ hepatic metabolism
- Compounds with significant active metabolites
- Compounds demonstrating high in vivo variability
- Complex modified release systems with drugs of low solubility



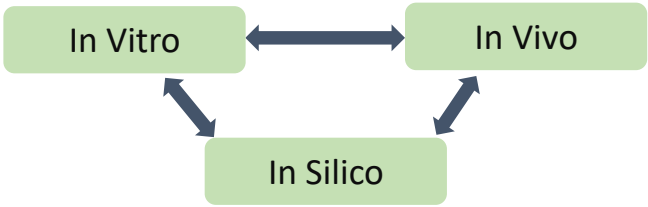
2. Rebeka, Jereb, et al. *AAPS PharmSciTech* 20.2 (2019): 1-10.

Effect of Food and Formulation on Bioavailability

Features	Postprandial State	Attribute affected	Impact
Gastric pH	Increased to pH 6-7	Drug solubility pH dependent stability and release	BCS Class II and IV Borderline Class III
Gastric Emptying time and motility	Increased gastric emptying time and increased motility	Absorption and Bioavailability Gastric stability	Delayed absorption for Class III and IV drugs Drugs with site specific absorption
Intestinal Fluid Composition and Volume	Addition of Bile Salts, Phospholipids Increased Volumes	Improved dissolution of Lipophilic drugs Enhanced absorption of poorly soluble drug by lipolysis of lipid vehicles Impaired solubility by precipitation	BCS Class II and IV Some poorly soluble drugs
Blood Flow	Increased splanchnic blood flow	Enhanced Clearance and Elimination	Drugs with High intrinsic extraction
Certain Formulation factors in FE	API	Particle Size and Polymorph	Class II and IV
	Excipients and Drug Product Design	Solubilizers, Absorption Enhancers Release controlling polymers	Eliminate/Modulate Food Effect

Assessing Food Effect : In Vitro, In Vivo or In Silico

Food has strongest impact on BCS Class II with minimal effects on Class I and reduced AUC for Class III



No Known Food Effect

- Mainly Class I drugs with high BA
- RLD and test should display similar dissolution in bio-relevant media
- Support BE filing with data through literature and PBPK simulation
- Is FED BE study relevant for Class III compounds?

Positive Food Effect

- Multiple Mechanisms for Positive Food Effect
- API: Through increased solubility, increased absorption, enhanced site specific absorption
- Formulation: Alter dissolution by modified release, enhance availability through excipients, targeted lymphatic absorption

Negative Food Effect

- Caused by API precipitation in Fed state GI tract
- Augmented by micellar entrapment
- Caused by Enhanced intrinsic clearance of drug in presence of food
- Reduced Bioavailability due to delayed gastric emptying

Potential Applications of Oral PBPK Modeling in Generic Drug Development

Stage	Product Type	Relevant Domain	Potential application by Drug Class
Development	Immediate Release Products	API Attributes Excipient Attributes for Impact on BE	Class II: In Vitro + In Silico to Justify API Forms and PSD specifications Class III : In Silico for VBE/FE when excipients differ from Reference
		Effect of Solubility Enhancing Techniques	Class II: In Silico Modeling to evaluate Impact of improved Solubility on PK
	Modified Release Products	Design Pilot PK study designs	
		Evaluation of PK for multiple Prototypes	In Silico Modeling with VBE for Class 1 compounds with absorption dependent PK
		Evaluate prototypes for Complex PK metrics; pAUC or subject by formulation variability	In Silico for Products with robust Bio predictive dissolution profiles and absorption driven PK

Potential Applications of Oral PBPK Modeling in Generic Drug Development

Stage	Product Type	Relevant Domain	Potential application by Drug Class
Regulatory Incentives	Immediate Release	Alternate BE Pathway for drugs with Safety concerns, Oncology drugs, Immunosuppressants, some anti epileptics.	Class I: Via In Vitro BE Class II and III: A combination of In Vitro and In Silico Equivalency
		Extension of BE Waivers	Class III: By In Silico BE when excipients differ from Reference in quantity, or f2 does not meet due to very rapidly dissolving Test or reference.
		BE Waiver for Fed State	Class II: Predict food effect with In Vitro bio relevant dissolution and PBPK Modeling for Alternate Fed BE. Class III : Via In silico to demonstrate Fed state BE
	Modified Release	Support Clinically Relevant Dissolution Specifications	In Silico using MultiStage Dissolution testing for Products with robust Bio predictive dissolution.

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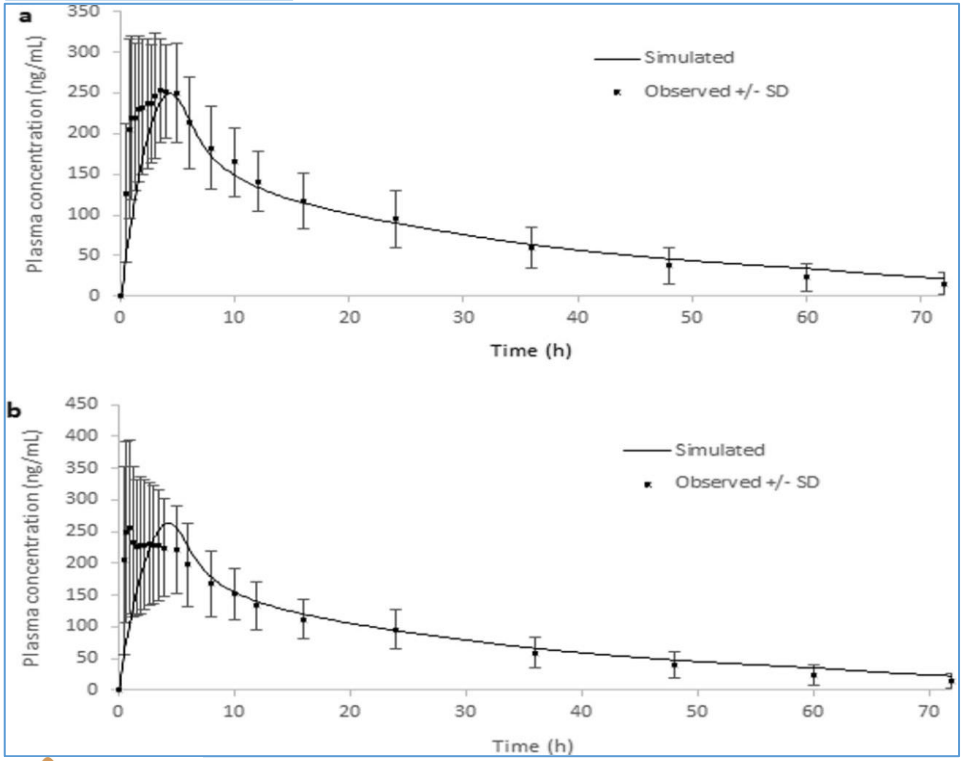
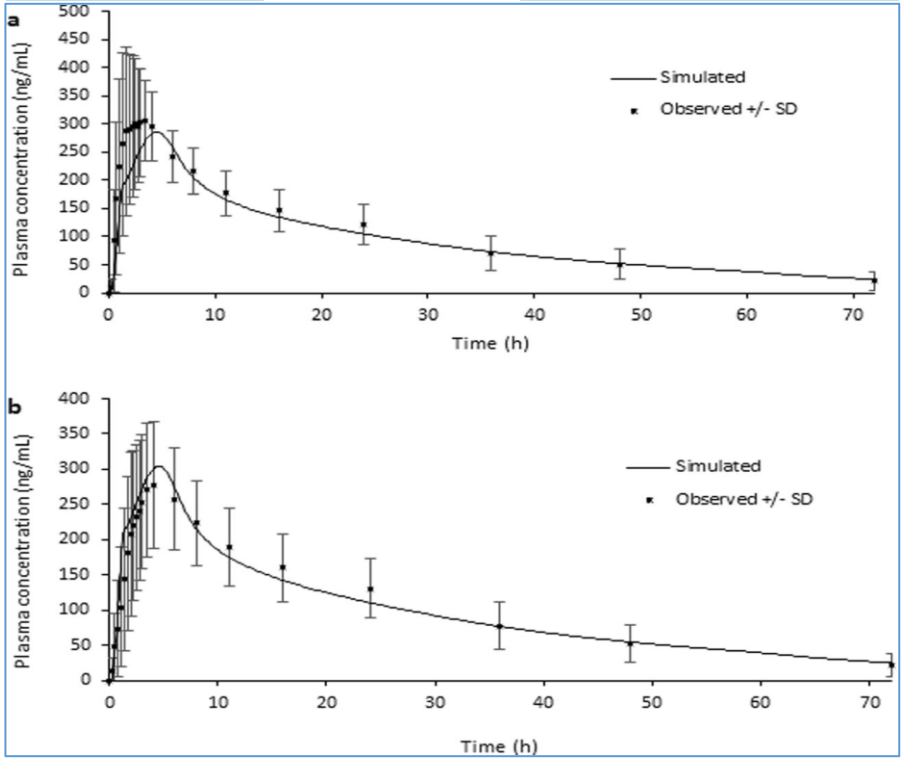
Case Study:
Food effect on Two Formulations with Crystalline (RLD) and Amorphous (Test) Forms[2]

Fasted State



Fed State

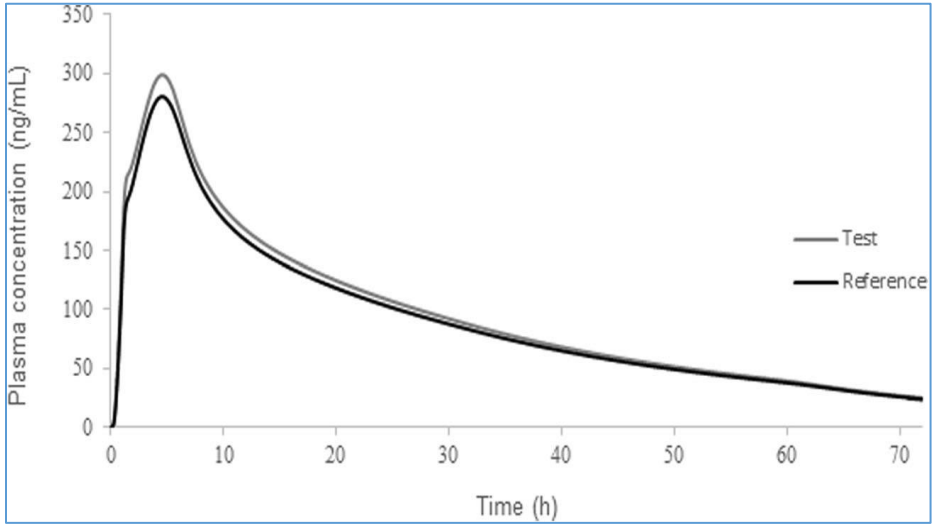
(a) Reference, (b) Test



2. Rebeka, Jereb, et al. "PBPK absorption modeling of food effect and bioequivalence in fed state for two formulations with crystall ine and amorphous forms of BCS 2 class drug in generic drug development." *AAPS PharmSciTech* 20.2 (2019): 1-10.

Case Study:
Food effect on Two Formulations with Crystalline (RLD) and Amorphous (Test) Forms[2]

Simulated plasma profiles in Fed state



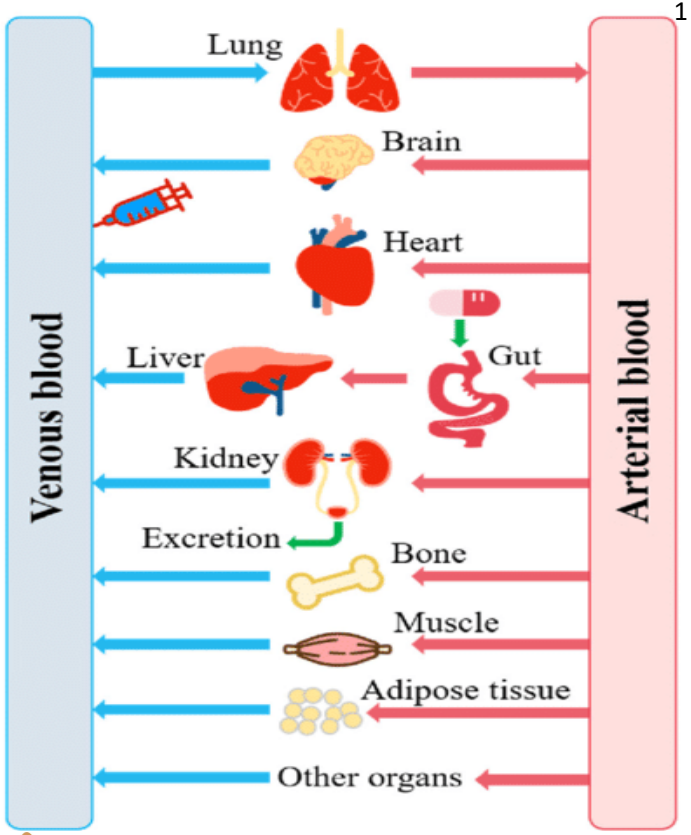
Prediction of Food Effect

	Observed ratios fed/fasted	Simulated ratios fed/fasted	% PE
	Test formulation		
C_{max}	1.08	1.16	−6.9
AUC_t	1.28	1.18	7.9
AUC_{inf}	1.31	1.17	10.3
	Reference formulation		
C_{max}	1.21	1.15	5.3
AUC_t	1.23	1.16	5.1
AUC_{inf}	1.23	1.16	5.4

- Model was able to predict the food effect for Reference and Test products
- Model predicted Fed BE for Test against Reference.
- PE values for prediction of Food effect up to 10%

2. Rebeka, Jereb, et al. "PBPK absorption modeling of food effect and bioequivalence in fed state for two formulations with crystalline and amorphous forms of BCS 2 class drug in generic drug development." *AAPS PharmSciTech* 20.2 (2019): 1-10.

Oral PBPK Modeling and Simulation
Quantitative Modeling for Generic Drug Development



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Challenges for Quantitative Modeling in Current State:

- Empirical uncertainty in modeling strategy, model input parameters, method of data generation, subjective optimization processes and robustness.
- Resource Intensive Process requiring Initial investment without visibility of concrete returns.
- Requires timely Regulator participation and agreement for model acceptability and conclusions.
- Lack of guidelines to establish Predictive ability of Model for intended use.
- Broad applicability is constrained by Drug ADME disposition and Drug product design.
- Challenges in determining bio relevant dissolution profile/method(s) for complex systems.
- Challenges to incorporate Inter and Intra subject variabilities to mimic In Vivo performance.

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References

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2. Jereb Rebeka, *et al*. "*PBPK absorption modeling of food effect and bioequivalence in fed state for two formula tions with crystalline and amorphous forms of BCS 2 class drug in generic drug development*." *AAPS PharmSci Tech* 20.2 (2019): 1-10.

3. Tistaert C., *et al*. "*Food Effect Projections via PBPK Modeling: Predictive Case Studies*" . J. Pharm. Sci. (2019)10 8:592-602.

4. Tao, Z., *et al*. "*A Review of Current Methods for Food Effect Prediction during Drug Development*". Current Pha rmacology Reports 6(4): 1-13.

5. Guidance for Industry; M9 Biopharmaceutics Classificaton System Based Biowaivers , FDA: May 2021

Thank you