Advancing Regulatory Science Through Innovative Bioequivalence Approaches

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Outline: Closing the gap on Regulatory Research

1) Impact of Food on Bioequivalence (BE)
2) Biopharmaceutics Classification System (BCS) Class 3 Waiver
3) Biowaiver for Lower Strengths
4) Novel in vivo BE designs

Understanding the Impact of Food on Bioequivalence

Background: Based on FDA Draft Guidance (2013), "Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA", generally, both fasting and fed in vivo BE study are recommended for immediate release (IR) product. However, only fasting study is recommended for BE evaluations for other agencies.

Question: Can we identify opportunities for harmonization such that only fasting BE studies are recommended for the establishment of BE at least in certain situations?

Regulatory Research:

Meta-analysis of food effect on PK; Leveraging PBPK modeling to assess risk of bio-inequivalence attributable to food intake

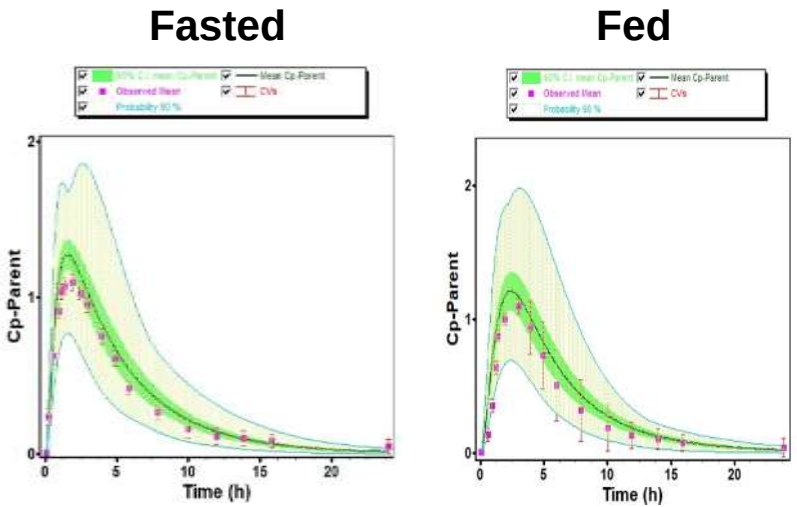


Figure. PBPK Model Simulation for Drug X IR product

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

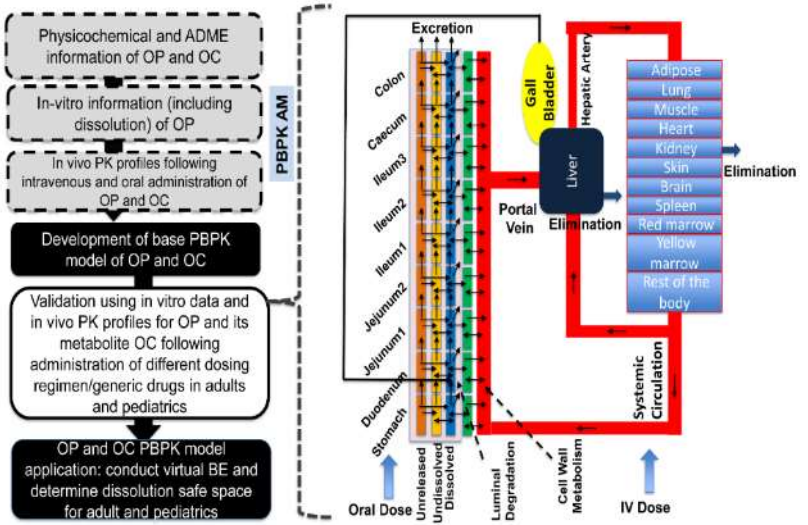
Challenges and Opportunities to Support BCS Class 3 Drug Waiver

Background: Based on FDA Guidance (2021) M9 Biopharmaceutics Classification System-Based (BCS) Biowaivers, for BCS class 3 drug products, the test product formulation should be qualitatively (Q1) the same and quantitatively (Q2) very similar.

Question: Whether and how we can expand BCS Class 3 biowaiver to non Q1/Q2 product?

Regulatory Research:

Potential utility of PBPK modeling as an alternative BE approach to support biowaiver of non-Q1/Q2 BCS Class 3 drugs.



Flowchart: Develop a PBPK model for a putative BCS Class 1/3 drug, oseltamivir phosphate (OP) and its metabolite oseltamivir carboxylate (OC) in both adults and pediatrics and conduct virtual BE

Reference: Miao L, Mousa Y, Zhao L , Raines K, Seo P, Wu F. AAPS Journal, 2020. DOI : 10.1208/s12248-020-00493-6

Biowaivers for Lower Strengths

- We recommend applicants demonstrate proportionality between non-biostudy and biostudy strengths to support biowaiver requests
- Deviations in proportionality can be supported by increased knowledge of the impact of excipients on characteristics of the API and on gut wall transporters and enzymes
- Deviations in dissolution similarity can be addressed through an identification of a dissolution “safe-space”
- Establishment of bio-predictive dissolution methods and the use of PBPK/PBBM techniques may allow for biowaivers in the absence of dissolution profiles and formulation proportionality

Novel in Vivo BE Evaluation Pathways

Background: Lagging generic drug approvals for long acting injectables and oncology products due to cost and challenges when conducting in vivo clinical studies

Question: Can we adopt novel study designs to reduce the regulatory burden?

Regulatory research:

Mechanistic IVIVCs and model informed study designs that can significantly reduce regulatory burden; a case for model integrated evidence for generic drug approval.

Designs to reduce study sample size and/or duration

Evidence generation using sufficiently validated and verified model

Weight of evidence approach by leveraging clinically relevant in vitro testing results

Summary

- Ongoing and future research provides enormous opportunities to fundamentally change some of our current regulatory bioequivalence approaches and requirements:
  - Granting Biowaivers and avoiding duplicative and scientifically unnecessary studies
  - Using novel BE designs, advanced in-vitro characterization and novel modeling and simulation approaches to advance and accelerate generic drug approvals

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