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General Overview: The Use of Quantitative Methods and Modeling to Facilitate Generic Drug Development and Regulatory Assessment

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Outline

- Modeling and simulation for new and generics drugs
- Current utilities of Quantitative Clinical Pharmacology (QCP) and Physiologically-based Pharmacokinetic (PBPK) models
- Case introductions

Quantitative Methods and Modeling in New and Generic Drug Approvals

- The use of advanced quantitative methods and computational modeling has become part of modern drug development and assessment
- New Drug: Model Informed Drug Development
- Generic Drug: MIDD + MIE?

MIDD: Model informed drug development
MIE: Model integrated evidence

What is Model Informed Drug Development?

- A powerful tool to guide drug development and can support development and review decision making
- Its scope of application is closely related to data sufficiency and the extent of existing knowledge that can be used to interpret data and extrapolate results
- Modeling and simulation generated data cannot always substitute for the required basic level of clinical evidence in the new drug application (NDA) stage

https://www.fda.gov/drugs/development-resources/model-informed-drug-development-pilot-program

Jain et al. CPT Pharmacometrics Syst. Pharmacol. (2019) 8, 5–8

What is Model Integrated Evidence?

- Using MIE such as the VBE study results not just to plan a pivotal study but to serve as pivotal evidence
  - product approval
  - in combination with relevant *in vitro* bioequivalence (BE) testings, support alternatives to otherwise recommended conventional *in vivo* studies
- An integration of knowledge and predictive performance of the model for the intended modeling purpose
- Only information that is a combination of science and knowledge, and is sufficiently supported, validated, and verified by prior data, can be classified as MIE for regulatory decision making

Zhao et al. Clin Pharmacol Ther. 2019 Feb;105(2):338-349

What is a Virtual BE Study?

- Use of model to compare test and reference formulations
- Model must have a formulation variable that can be adjusted to represent the difference between T and R
- Model generates a population for BE study, compares T and R in that population
  - Simulate many studies to estimate probability of success or failure

BE: bioequivalence; T: test product; R: reference product

Quantitative Clinical Pharmacology (QCP)

- BE study design and data analysis
  - Pharmacokinetic (PK) endpoints
    - Sparse PK sampling: model-informed optimal BE study design and model-based BE analysis
    - Endogenous baseline correction: appropriate BE metrics and criteria
    - Patient PK study: long-acting injectables
  - Pharmacodynamic (PD) endpoints
    - Dose-scale analysis
    - Endpoint sensitivity assessment
    - Alternative study design
  - Comparative clinical endpoints
    - Clinical trial simulation platform
- PK/PD analysis to support BE recommendations and analysis
    - Narrow therapeutic index (NTI) classification and BE criteria
    - Partial AUC (area under the curve) as additional BE metric
    - Model-based BE assessment

PBPK for Systemically and Locally Acting Products

- Identification of critical quality attribute and bio-predictive dissolution method
- Determine appropriate systemic PK BE metrics to ensure equivalence on local drug delivery at the site of action
- Justify differences in quality attributes and in vitro testing results from reference listed drug (RLD)
- Simulate virtual BE studies to evaluate effects of formulation difference on systemic and action site drug exposure
    - For locally acting products, PBPK modeling package can potentially be used to support not conducting comparative clinical endpoint (CE) or PD endpoint studies as currently recommended in product specific guidances (PSGs)
- Advance in vitro approaches to BE for locally-acting products
    - Guide selection of clinically-relevant in vitro tests for BE

Cases Today

- PK-PD based PSG Development, Research and ANDA Assessment
  - PK/PD Meta-analysis of Abuse Deterrent Opioid Drug Products (Presenter: Lucy Fang)
  - Regulatory Considerations on Dose-scale Analysis in Assessing Pharmacodynamic Equivalence (Presenter: Xiajing (Jean) Gong)
  - Application of Quantitative Clinical Pharmacology (QCP) in Development of Long Acting Injectable Products (Presenter: Satish Sharan)

- PBPK models to support not conducting comparative clinical endpoint or PD endpoint studies
  - PBPK Modeling and Simulation Approaches: Best Practices for Regulatory Applications Related to Locally-acting Generic Drugs (Presenter: Eleftheria Tsakalozou)
  - Credibility Establishment for Computational Fluid Dynamics Models of Complex Generic Drug Delivery (Presenter: Ross Walenga)

ANDA: Abbreviated new drug application

Quantitative Methods and Modeling in the Future

- Support alternative generics development program:
  - E.g., in vitro testing + (PK?) + in silico study simulations for complex products
- Identify and prioritize research areas for regulatory science program by quantitatively integrate drug, physiology, and pharmacology information and dynamics

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