Alternative Model-Based Data Analysis Approach to Demonstrate Bioequivalence

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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The Disclaimer

- This presentation represents the views and perspectives of the speaker and does not necessarily reflect the views of the U.S. FDA.

Learning Objectives

- Recognize opportunities of using alternative model-integrated data analysis to demonstrate bioequivalence (BE)
- Review a case example of using population pharmacokinetic (PPK) modeling as an alternative analysis approach to demonstrate BE
- Learn key regulatory considerations when an alternative model-integrated approach is used

FDA Recognized Opportunities of Using Alternative Model-Integrated Approach to Demonstrate BE

- FDA recognizes the opportunities of using quantitative methods and modeling (e.g., model-integrated approach) to support demonstration of BE in the Product-specific guidance on paliperidone palmitate extended release suspension (2021)
- Opportunities of alternative model-integrated data analysis approach have been discussed at FY 2022 Generic Drug Science and Research Initiatives Workshop

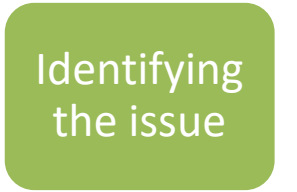
Examples of Model-Integrated Data Analysis Opportunities – addressing challenges in PK BE studies

- Use as an alternative data analysis approach for an interrupted BE study (e.g., pandemic interruption)
  - Missing data
- Develop alternative study designs or analysis methods for challenging drug products
  - Long-acting injectable and implantable products
  - Products for rare disease
  - Study with sparse PK samplings

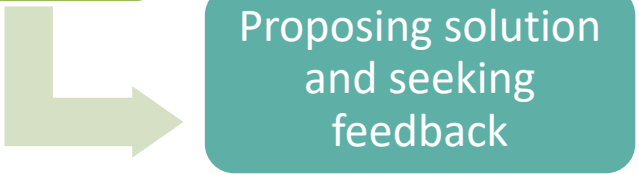
A Case Demonstration

-- An alternative model-integrated data analysis approach to demonstrate BE for an interrupted study

Process Can Be Used to Address An Interrupted BE Study



- The applicant identify the issue before unblinding data



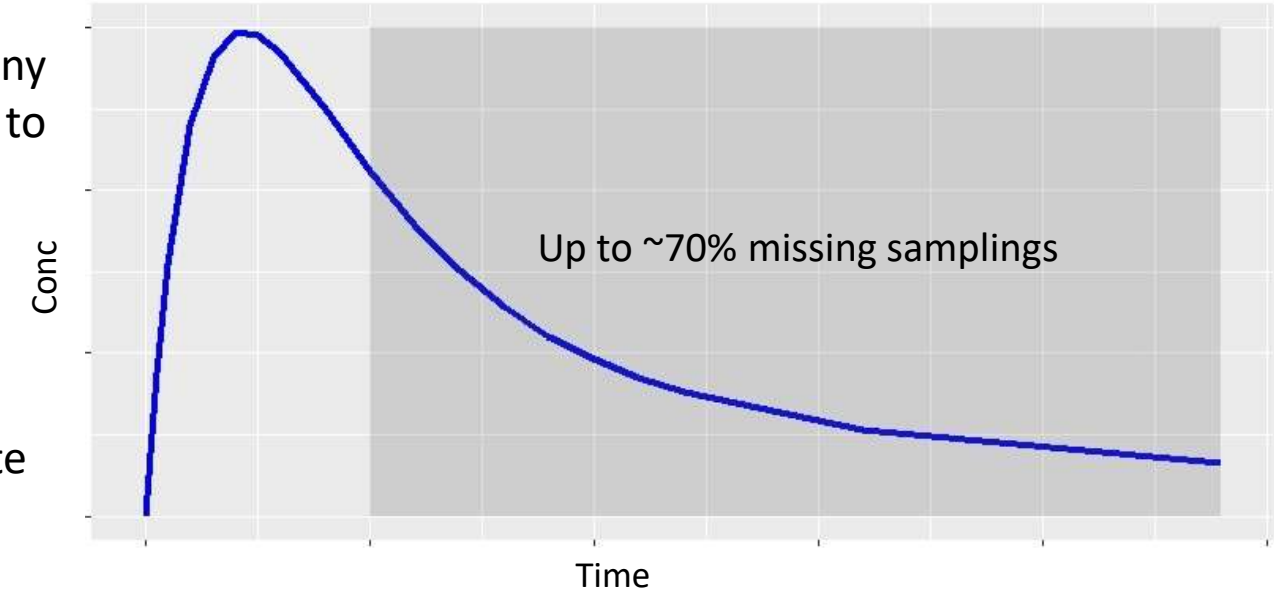
- The applicant may find and perform alternative analysis for interrupted studies and may discuss with FDA via pre-ANDA interactions

- Statistical analysis plan changes should be made prior to data lock and unblinding
- The alternative analysis should be accompanied with adequate justifications and not lead to biased equivalence determination

An Interrupted PK BE Study

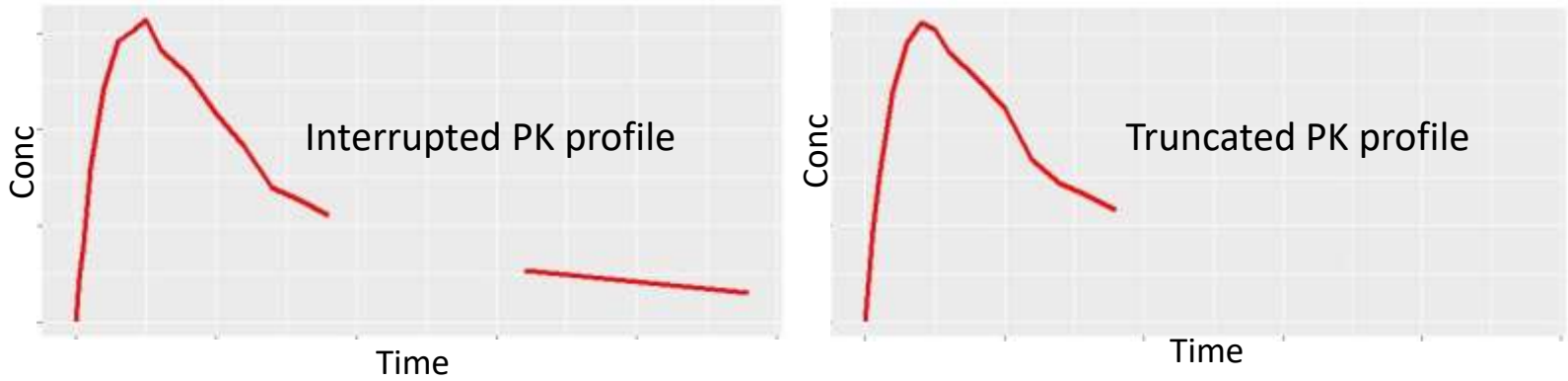
- An in vivo PK BE study with long study duration
- Due to the pandemic, many subjects could not return to the clinic to provide their PK blood samples
- This study experienced a high volume of **missing samples** in the mid- to late phase

A simulated time-concentration profile for demonstration purpose



Problems with Conventional NCA Approach

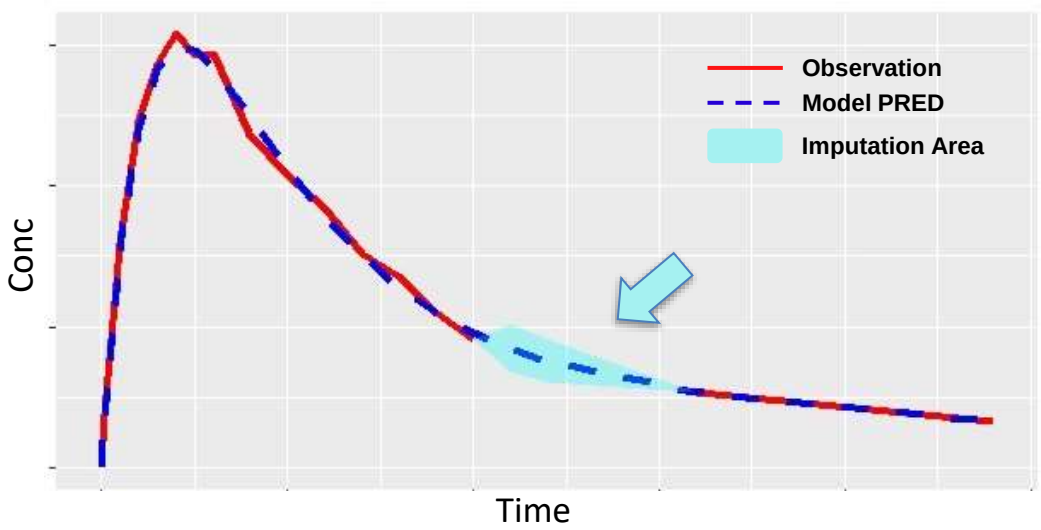
Simulated time-concentration profiles for demonstration purpose



Consecutive missing samples in elimination phase impact AUC calculations when perform the conventional noncompartmental analysis (NCA)

- Interrupted and truncated AUC profiles
- Issues in estimating terminal rate constant (λz)

Use PK Modeling to Impute Missing Values



Simulated time-concentration profiles for demonstration purpose

- Data imputation is conducted at an individual level
- A PPK model is developed from the impacted study
- Missing points are filled by values estimated from the PPK model with uncertainties estimated (presented as the imputation area)

BE Establishment with Alternative Model-Integrated Data Analysis Approach

Develop PPK model using data from the impacted BE study

- Structure model development using data from the reference product
- Inclusion of covariates
- Inclusion of formulation dependent parameters for prediction accuracy on different formulations

Validate PPK model

- Goodness-of-fit plots, Visual Predictive Checks (VPCs), etc.
- Guidance for Industry Population Pharmacokinetics (2022)

Impute data for missed visits for individual PK profile

- To account for uncertainty from the residual variability, 1000 imputations are conducted to calculate the passing rate

BE establishment

- Model-imputed data are used for BE establishment
- Observed data with conventional NCA approach are used as supportive information

BE Results

- BE was demonstrated for all parameters (C_{max}, AUC_{0-t}, AUC_{0-inf}) based on the model imputed data.
- Data imputation were conducted for 1000 times to account for uncertainty from the residual variability. The passing rate from 1000 imputations was 100%.

Summary of the Case Example

- Due to the high volumes of consecutive missing samples in the elimination phase, the conventional NCA approach may be insufficient to demonstrate BE.
- Alternative model-integrated data analysis approach could support BE demonstrate for a pandemic-interrupted study.
- A PPK model developed using actual clinical data, with sufficient validation, can be used for data imputation at an individual level to mitigate the impact of missing data points.
- Before unblinding the clinical data, the applicant is expected to determine, and pre-specify analyses plan.

Key Components in Alternative Model-Integrated Analysis Approach

- The alternative model-integrated data analysis approach should be accompanied with adequate scientific justifications:
  - Include sufficient model verification and validation for the intended regulatory use
  - Demonstrate it is capable to discern formulation difference and comparable to the conventional approach
  - Demonstrate it would not lead to biased equivalence determination
  - Properly characterize the uncertainty and the impact on BE determination
- The proposed alternative approach can be discussed with FDA via pre-ANDA programs
- Alternative model-integrated approach should be pre-specified in statistical analysis plan and be made prior to data lock and unblinding

Challenge Question #1

Which of the following scenarios does NOT belong to alternative model-integrated data analysis approaches to demonstrate BE ?

A. Use population PK model for data imputation for an interrupted BE study

B. Use noncompartmental analysis (NCA) to calculate PK metrics (AUC)

C. Use modeling approaches to develop alternative study designs or analysis method for challenging drug products

Challenge Question #2

An alternative model-integrated data analysis approach should:

A. Be accompanied with adequate scientific justifications

B. Not lead to biased equivalence determination

C. Be pre-specified before seeing study results

D. All of the above

Resources

- *Zhao et al.* Generating Model Integrated Evidence for Generic Drug Development and Assessment
- *Sharan et al.* Model-Informed Drug Development for Long-Acting Injectable Products: Summary of American College of Clinical Pharmacology Symposium
- Guidance for Industry Population Pharmacokinetics (2022)
- FDA Draft Product Specific Guidance on paliperidone palmitate extended release suspension (2021)
- FY 2022 Generic Drug Science and Research Initiatives Workshop
- FDA-CRCG Workshop: Establishing the Suitability of Model-Integrated Evidence to Demonstrate Bioequivalence for Long-Acting Injectable and Implantable Drug Products (2021)

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Questions?

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Closing Thought

Quantitative methods and modeling has been increasingly applied to facilitating generic drug development/review and play a critical role in the modernization of bioequivalence assessment.

Adapted from *Zhao et al.* Clin Pharmacol Ther, 2019


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