

# 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

Identifying the issue

- The applicant identify the issue before unblinding data



Proposing solution and seeking feedback

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



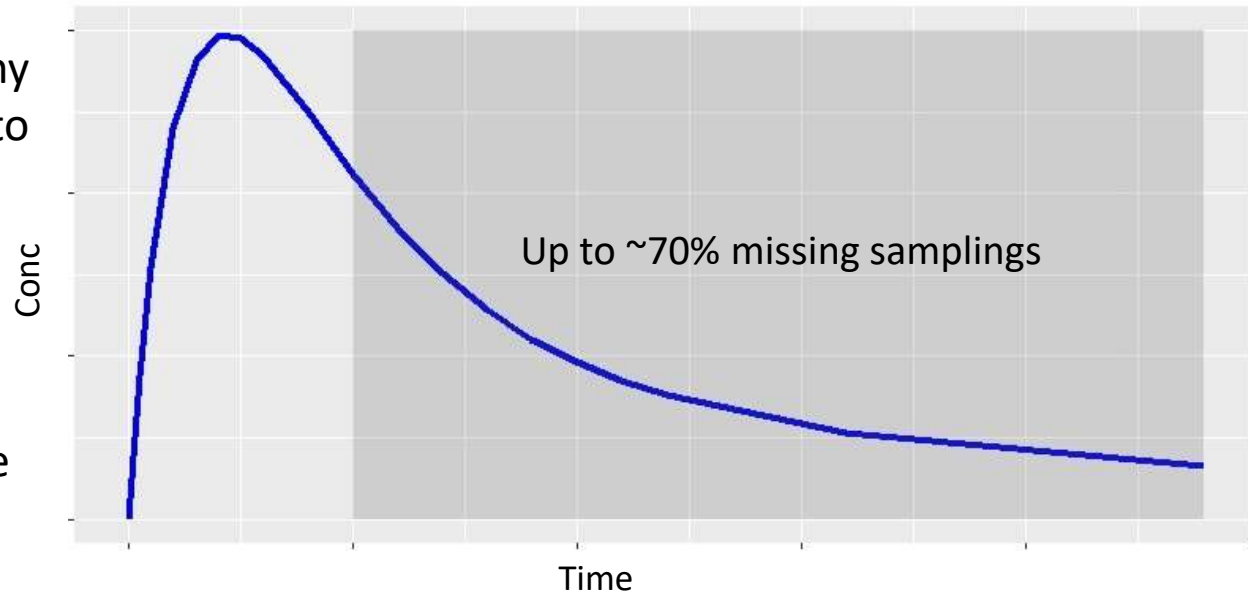
ANDA Submission

- 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

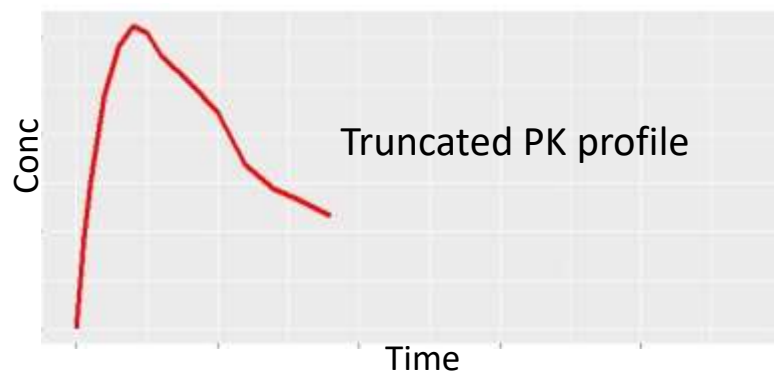
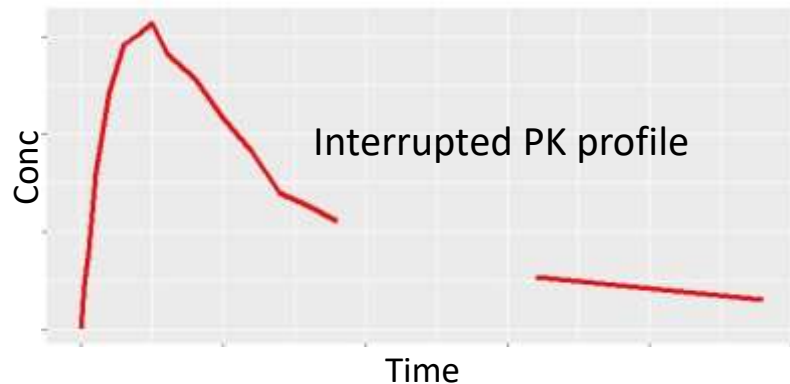




# Problems with Conventional NCA Approach



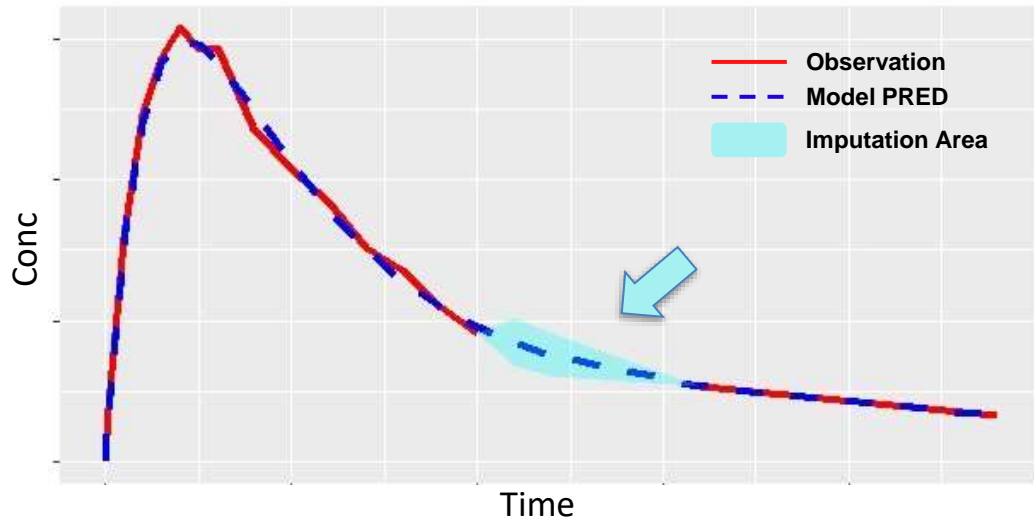
Simulated time-concentration profiles for demonstration purpose



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 ( $\lambda_z$ )

# 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



Validate PPK model



Impute data for missed visits for individual PK profile



BE establishment

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

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

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

- 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.

