Common Bioequivalence Study Design Deficiencies and How to Avoid Them

Zhen Zhang, Ph.D.
Master Pharmacologist
Division of Bioequivalence I (DBI)
Office of Bioequivalence (OB)
Office of Generic Drugs (OGD)
CDER | US FDA

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Learning Objectives

- Understand study designs and relevant guidances
- Identify common deficiencies related to study design and analysis
- Identify unacceptable post-hoc modifications in BE studies
- Apply strategies to prevent common deficiencies and improve study success rate

Types of Bioequivalence (BE) Studies

- **In vivo BE Studies**
  - In vivo pharmacokinetic (PK) BE study
  - In vivo pharmacodynamic (PD) BE study
  - In vivo comparative clinical endpoint study
- **In vitro BE Studies**
  - In vitro release test
  - In vitro permeation test
  - Particle size distribution test
  - Single actuation content test
  - Many others

Approximately 50% of ANDAs submitted over the past 12 years included one or more PK BE studies

Guidances for in vivo PK BE Study Design

General Guidance

- FDA Guidance for Industry: Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (August 2021) [FDA PK BE Guidance]
- ICH M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms (October 2024) [ICH M13A]
- ICH M10 Bioanalytical Method Validation and Study Sample Analysis (November 2022) [ICH M10]
- FDA Guidance for Industry: Statistical Approaches to Establishing Bioequivalence (December 2022) [FDA BE Statistical Guidance]

Product Specific Guidance (PSG)

- 2407 PSGs as of 3/8/2026
- 61% PSGs with in vivo PK BE Study design recommendations

Components of A PK BE Study Protocol

- Study Objectives
- Study Design Type
- Study Population
- Dosing Conditions
- Washout Period
- Blood Sampling Schedule
- Bioanalytical Method
- Pharmacokinetic Analysis
- Statistical Analysis
- Safety Monitoring
- Others

Study Design: Add-on Study

- **Guidance Recommendations***: For BE studies, add-on subjects after the pre-specified number of subjects have been reached are generally not encouraged except in an adaptive study design with a pre-specified adaptation to add subjects and statistical methods to control the Type I error rate under the nominal level.
- **Common Deficiency Observed**: Applicant completed statistical analysis, and the study failed BE criteria. Additional subjects were enrolled after seeing the results to achieve passing outcomes. This post-hoc modification of study design and statistical analysis was not acceptable.
- **How to Avoid**:
  - Use a pre-specified adaptive design when uncertainty is high.
  - For non-adaptive designs, any sample size revision must be implemented before statistical analysis begins.

* FDA BE Statistical Guidance 2022

Study Design: Sample Size

- **Guidance Recommendations***: The total number of subjects in a study should be sufficient to provide adequate statistical power for a BE demonstration in the proposed study design.

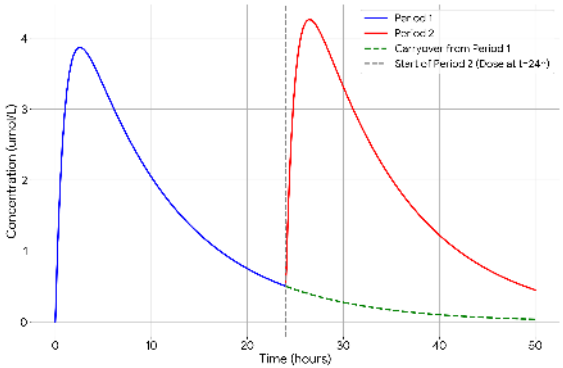
- **Common Deficiency Observed**: Inadequate sample size is one of the most common causes of failed BE studies and often results in major deficiencies.

- **How to Avoid**:
  - Develop a test product closely comparable to the reference listed drug or reference standard
  - Estimate a reasonable T/R ratio and variability
  - Account for a reasonable dropout rate in the sample size estimate
  - Conduct a pilot study, when appropriate
  - Use a pre-specified adaptive design when facing significant uncertainty

* FDA PK BE Guidance 2021

Washout: Carryover

- **Guidance Recommendations*** for Crossover BE Studies:
  - Use a sufficiently long washout period (e.g., at least 5 elimination half-lives, T_{half})
  - Exclude subjects based on the '5% C_{max} recommendation'
- **Common Deficiency Observed**: Inadequate washout resulted in a failed study due to exclusion of many subjects based on the '5% C_{max} recommendation'.



- **How to Avoid**:
  - Consider a parallel study design, when appropriate
  - Do not base washout duration solely on the <u>mean</u> T_{half}; account for variability of T_{half}
  - Pre-specify alternative approaches in the protocol (e.g., subtraction, population PK analysis) with scientific justification.

* 1) FDA PK BE Guidance 2021; 2) ICH M13A 2024

Sampling Time: First Point C_{max}

- **Guidance Recommends***: For drug products with rapid absorption, collection of blood samples at an early time point, between 5 and 15 minutes after dosing, followed by additional sample collections, e.g., two to five samples in the first hour after dosing, is usually sufficient to assess peak drug concentrations.
- **Common Deficiency Observed**: A large proportion of subjects had C_{max} at the first post-dose sampling time point (0.5 hour), indicating that peak concentrations were not adequately captured.
- **How to Avoid**:
  - Thoroughly understand the PK properties of the drug product
  - Conduct a pilot study, if necessary, to optimize the sampling schedule

* 1) FDA PK BE Guidance 2021; 2) ICH M13A 2024

PK Analysis

- **Guidance Recommends*:**
  - For single-dose studies, C_{max}, AUC_{0-t}, AUC_{0-inf}
  - For steady-state studies, C_{max}, AUC_{0-tau}
  - Additional PK parameters: Partial AUC (pAUC), T_{max}, etc.
- **Common Deficiency Observed:**
  - In a fasting PK BE study, subjects with missing samples right next to C_{max} were included in the BE analysis. The inclusion of these subjects was unacceptable.
  - In a steady-state PK BE study, subjects who completed the study were excluded from the BE analysis because AUC_{0-tau} could not be estimated for these subjects due to software limitations. The exclusion of these subjects was unacceptable.
- **How to Avoid:**
  - Pre-specify scientifically sound methods for calculating PK parameters in the protocol
  - Pre-specify inclusion and exclusion criteria related to PK analysis
  - Minimize deviations in blood sampling, particularly at critical time points

* 1) FDA PK BE Guidance 2021; 2) ICH M13A 2024

Statistics: Covariates in Parallel Study Statistical Model

- **Guidance Recommendations***: The applicant may also consider pre-specifying inclusion of important demographic and baseline prognostic covariates in the statistical model for parallel studies.
- **Common Deficiency Observed**: The study failed using the pre-specified statistical model without covariates. Covariates were subsequently added post hoc to obtain passing results. This post-hoc statistical analysis was unacceptable.
- **How to Avoid**:
  - Pre-specify covariates in the statistical model, if appropriate, for parallel studies
  - If model revision is necessary, revise the statistical protocol before conducting the statistical analysis

* 1) FDA BE Statistical Guidance 2022; 2) ICH M13A 2024

Statistics: Group Analysis

- **Guidance Recommendations***: The statistical model should take into account the multi-group nature of the BE study, e.g., by using a model including terms for group, sequence, sequence x group, subject within sequence x group, period within group and formulation.
- **Common Deficiency Observed**: The applicant didn't include group-related terms in the statistical model. When the appropriate group terms were included, the study failed to demonstrate BE.
- **How to Avoid**:
  - Avoid using multiple groups, if feasible
  - If multiple groups are necessary, include group-related terms (group, sequence, sequence x group, subject within sequence x group, period within group) in addition to other terms in the final statistical model

* 1) FDA BE Statistical Guidance 2022; 2) ICH M13A 2024

Summary

- Reviewed key regulatory recommendations for PK BE studies
- Highlighted common deficiencies in PK BE study design and analysis
- Emphasized that many failed studies resulted from inadequate planning
- Stressed the importance of pre-specified, scientifically and statistically sound protocols
- Encouraged proactive strategies to prevent deficiencies and improve BE study success rate

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