

# Recommendations in the 2022 Revised Bioequivalence (BE) Statistical Guidance and BE Assessments

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SBIA: A Deep Dive - FDA Draft Guidance on Statistical Approaches  
to Establishing Bioequivalence  
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The 2022 Revised BE Statistical Guidance: *FDA Draft Guidance on Statistical Approaches to  
Establishing Bioequivalence (December 2022)*

# Outline

- BE Studies Assessed by the Office of Bioequivalence
- Some Recommendations in the BE Statistical Guidance and BE Assessments
  - Model Options
  - Group Analysis
  - Outliers
  - Modeling and Simulation Based Approach
- Summary

# BE Studies Assessed by the Office of Bioequivalence (OB)

- **Pharmacokinetic (PK) BE Studies**

e.g., Two-way Crossover Study, Partially Replicated Study, Fully Replicated Study, Narrow Therapeutic Index Drug Study, Parallel Study, Sparse Sampling Study, Abuse-deterrence Study

- **Pharmacodynamic (PD) BE Studies**

e.g., Vasoconstrictor study, Bronchoprovocation Study, Fecal Fat Excretion Study

- **In Vitro BE Studies**

e.g., Binding Study, In-vitro Release Test (IVRT), In-vitro Permeation Study (IVPT), Particle Size Distribution, Recovery, Spray Pattern, Plume Geometry, Comparative Dissolution

**OB conducts independent statistical analysis for BE studies above.**

# Model Options

Study Design or Models	Options in the 2022 BE Statistical Guidance
Two-way Crossover	GLM vs. Mixed
Sparse Sampling	Bootstrap vs. parametric method for estimation of SD and CI for the ratio of $AUC_{0-t}$
Dose-scaled Analysis	Resampling vs. NLME without resampling
Proc Mixed Procedure	Random Statement: TYPE=FA0(2) vs. CSH or UNR
Proc Mixed Procedure	Model Statement: DDFM=SATTERTH vs. DDFM=KR2

**Data driven post-hoc selection of the statistical model is not allowed.**

GLM: Generalized Linear Model; SD: Standard Deviation; CI: Confidence Interval; NLME: Nonlinear Mixed Effect;  
 FA0(2): No Diagonal Factor Analytic; CSH: Heterogenous Compound Symmetry;  
 UNR: Unstructured Corrs; DDFM: Denominator Degree of Freedom

# Group Analysis

- Statistical methods and models should be pre-specified in detail in the protocol or study analysis plan (SAP).
- BE should be determined based on the overall treatment effect in the whole study population. Appropriate group terms should be included in the statistical model.
- Subgroup analysis is only used as sensitivity analysis if there is a significant group effect.
- The significance of group effect is determined by the p value for the treatment-by-group interaction term in the average BE (ABE) analysis or the p value for the group term in the reference scaled ABE (RSABE) analysis.
- The reason for large heterogeneity among groups should be investigated.
- Pooling smaller groups into a larger group may be acceptable if justified and pre-specified. Sensitivity analysis on different pooling methods is recommended.

# Outliers

- In general, outlier data may only be removed from the BE statistical analysis if there is real-time documentation demonstrating a protocol violation.
- The existence of a subject outlier with no protocol violations and for which there are no bioanalytical errors could indicate product failure or subject-by-formulation interaction.
- All subject data should be submitted, with potential outliers flagged with appropriate documentation as part of the submission.

# Modeling and Simulation Based Approach

- The 2022 Revised BE Statistical Guidance states that modeling and simulation-based approaches may be utilized in some scenarios, such as
  - Sparse Sampling Studies
  - Missing Samples
- A modeling and simulation-based approach should be pre-specified. A post-hoc modeling and simulation-based approach cannot be used to salvage a failed BE study.

# Key Message

**Pre-Specify** Your Statistical  
Analysis Plan **in Detail!**



# Questions?

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