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SBIA: A Deep Dive - FDA Draft Guidance on Statistical Approaches to Establishing Bioequivalence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The 2022 Revised BE Statistical Guidance: *FDA Draft Guidance on Statistical Approaches to Establishing Bioequivalence (December 2022)*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

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Questions?

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