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Innovative Approaches for Complex Generics

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What is Bioequivalence?

- Approved generic drug products are therapeutic equivalents
  - They can be substituted for the brand product
- FDA ensures generic drugs are pharmaceutical equivalents
  - Same active ingredient, Same dosage form, Same strength
  - We generally do not use statistics for this
- FDA ensures generic drugs are bioequivalent
  - No significant difference in rate and extent of drug at **site of action**
  - We do use statistical analysis for bioequivalence (BE) studies

What are Complex Generics?

- "Complex Product" is a defined term in the GDUFA II Commitment Letter.
  - products with complex active ingredients, formulations, routes of delivery or dosage forms
  - complex drug-device combinations
  - other products where complexity or uncertainty concerning the approval pathway or other alternative approach would benefit from early scientific engagement

What are Complex Generics?

- Non complex
  - Tablets, capsules, solutions and suspension for oral administration and systemic delivery
    - Solid oral MR dosage forms are non-complex
  - Solutions for topical or parenteral administration
- Complex
  - Complex actives including larger peptides
  - Other dosage forms
  - All locally acting drugs
  - Drug device combinations with user interface considerations
  - Abuse deterrent formulations

Key Issue for Access to Complex Generics

- When the “site of drug action” is systemic we use pharmacokinetic studies to establish BE
- When drugs are delivered directly to the site of action we need to develop new methods
  - Comparative clinical endpoint bioequivalence studies
  - Characterization-based approaches (Q3)
  - Weight of evidence
    - Combined in vitro and in vivo performance measures

Innovative Approaches to BE with Statistical Components

- Reference product batch to batch variability
- Statistical methods for profile comparisons (EMD, PBE)
- Statistical methods for in vitro comparisons (IVPT, PBE)
- Adhesion and irritation analysis for transdermal products
- Sparse sample BE studies
- Dose scale analysis
- Model based BE designs

What is the Role of Statistical Analysis for Complex Generics?

- Develop new statistical methods that are appropriate to new problems
- Evaluate new approaches by quantitative analysis of the proposed new approach
  - This includes but is not limited to the statistical analysis

Interface Between Statistics and Equivalence Decisions

- Generic drug program is based on the idea that the generic drug is the same as the reference product
  - The generic drug evaluation is done in the context of information about the reference product
  - We don’t repeat safety and efficacy studies but we conclude that generic products are safe and effective
  - How do we incorporate this idea into our thinking about complex generics?

Batch to Batch Variability

- Most bioequivalence studies are conducted on a single batch of test and reference products
  - Statistical analysis (90% CI of T/R within 80-125%) is very useful in drawing a conclusion about the significance of the result of this study
- What if different batches of the reference product will give different results in the BE study?

Batch to Batch Variability: Possible Approaches

- Statistical Perspective
  - Include many batches in the BE study and try to conclude that the means over all batches are the same
- Pharmaceutical Perspective
  - Ensure through pharmaceutical science that the batches in the BE study are representative
- Clinical Perspective
  - Widen BE acceptance limits to recognize that larger variations are not clinically significant

Model-Based Bioequivalence

- Traditional approach to analyzing bioequivalence studies is to use Non-compartment analysis (NCA)
  - Calculate AUC and Cmax based only on observed data
- Model-Based Bioequivalence
  - Fit observed data to a pre-specified model
  - Perform BE analysis on the model output
- Considerations (Topics of current OGD research)
  - Can amplify the decisional power
  - Introduces the potential for bias

Applications of Model-Based Bioequivalence

- Cases where current designs are not optimal
  - Sparse sample PK studies, Long-acting injectable, PD studies
- Ongoing research collaborations
  - HHSF223201610110C with France Metre
  - HHSF223201710015C with Andrew Hooker

Conclusion

- There is the opportunity to develop innovative bioequivalence methods that address some of the challenges related to complex generics
- Efficient decision making is essential to the success of the generic drug program
  - Any time proposed equivalence studies are larger than the original safety and efficacy studies is an opportunity for a multi-disciplinary collaboration to understand where we are not leveraging prior knowledge