Breakout Session Summary

IN VITRO BIOEQUIVALENCE METHODS

SUBSESSIONS

- Orally inhaled and nasal complex drugs
- Ophthalmic and parenteral complex drugs
- Topical dermatological complex drugs

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Panelists

- **Bryan Newman, PhD**
  Acting Team Leader, Division of Therapeutic Performance
  Office of Research and Standards, OGD
- **Denise Conti, PhD**
  Staff Fellow, Division of Therapeutic Performance
  Office of Research and Standards, OGD
- **Ross Walenga, PhD**
  Chemical Engineer, Division of Quantitative Methods and Modeling
  Office of Research and Standards, OGD
- **Changning Guo, PhD**
  Research Chemist, Division of Complex Drug Analysis
  Office of Testing and Research, OPQ
- **Bhagwant Rege, PhD**
  Director, Division of Immediate and Modified Release Products III
  Office of Lifecycle Drug Products, OPQ
- **Michael Spagnola, MD**
  Lead Physician, Division of Clinical Review
  Office of Bioequivalence, OGD
- **Bing Li, PhD**
  Acting Director
  Office of Bioequivalence, OGD
- **Andrew Cooper, PhD**
  Head of Analytical and Materials Science
  Mylan Global Respiratory Group, Mylan

Orally Inhaled and Nasal Complex Drugs

What are the scientific gaps for extending in vitro option to complex inhalation formulations and dosage forms?

- "In vitro approaches as alternative to clinical studies for OINDPs", Andrew Cooper (Mylan Global Respiratory Group, UK)
  - Understanding relevance of additional physical characterization techniques for *in-vivo* performance is important
  - In-vitro dissolution is a key technique for low solubility compounds: evidence of rate of absorption at the site of action
    - ✓ Greater understanding and standardization of dissolution techniques is required
    - ✓ Use of *in-vitro* dissolution data in mechanistic *in-vivo* models is potentially valuable
    - ✓ "i-BCS" classification of molecules for inhaled delivery needed to inform guidance development

Summary of Discussion

- Complexities for establishing bioequivalence for inhalation products arise from the site of action where the product performance depends on factors contributing to the regional drug deposition and distribution.
- As we scale up the complexity of the product, additional factors have to be considered in order to address the equivalence of local drug delivery in lieu of comparative clinical study.
  - For solution formulations formulation sameness (Q1 and Q2 sameness) and device similarity are most critical factors that affect the performance.
  - For suspension formulations along with the formulation and device sameness, additional factor relating to API particle size may be considered.
  - For DPI products, in addition to the in vitro studies like SAC and APSD, predictive API particle size should consider agglomeration and deagglomeration, which may result in differences in how the drug is deposited. Other factors that may be important are static charge and dissolution of the delivered particles.

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- **Yan Wang, PhD**
  Acting Team Leader, Division of Therapeutic Performance, Office of Research and Standards, OGD

- **Darby Kozak, PhD**
  Acting Deputy Director, Division of Therapeutic Performance, Office of Research and Standards, OGD

- **Xiaoming Xu, PhD**
  Senior Chemist, Division of Product Quality and Research, Office of Testing and Research, OPQ

- **Theofanis Mantourlias, PhD**
  Head of Formulation Development, BU Generic and Complex Formulations, Fresenium Kabi

- **Mark Shiyao Liu**
  Senior Director, Clinical R&D, Mylan Inc.

Ophthalmic and Parenteral Complex Drugs

- Physicochemical characterization for supporting bioequivalence: particle size measurement and related data analysis

- Challenges for developing complex generic long acting injectable products

- Emerging technologies for supporting bioequivalence of complex drugs

Ophthalmic and Parenteral Complex Drugs

Particle size measurement and related data analysis

- "In vitro population bioequivalence (PBE) parameters for particle size distribution (PSD)", Mark Liu (Mylan Global Pharmacokinetics, USA)
  - ✓ Z-average/PDI vs D50/SPAN: pros and cons
  - ✓ Since less variability for disparity is beneficial, if PDI or Span represent distribution width variability, could it be a one-sides test?
  - ✓ Whether it is necessary to require PBE for in vitro particle size, then in vivo BE is required? Can it be supportive?

Ophthalmic and Parenteral Complex Drugs

Challenges for developing complex generic long acting drugs

- "Complex formulations – Main considerations: the way forward for complex formulations", Theofanis Mantourlias(FRESENIUS KABI)
  - ✓ Is the provided guidance enough?
  - ✓ Why generic cannot find their way through?
  - ✓ How about manufacturing process and its importance to achieve bioequivalence?
  - ✓ What is the way forward?

Ophthalmic and Parenteral Complex Drugs

Emerging technologies for supporting bioequivalence of complex drugs

- "Image-based microstructure bioequivalence evaluation", Shawn Zhang (DigiM Solution LLC)
  - ✓ Where do novel analytical techniques like focused ion beam-scanning electron microscope (FIB-SEM) fit in with ophthalmic and parenteral complex products and establishing BE?

Take Home Messages

- ✓ Each particle size technique has its own limitations and the most appropriate reporting parameters.
- ✓ Be aware of new analytical technologies for particle size measurement and explore what is the most appropriate ways to report and analyze the data for supporting equivalence.
- ✓ More general information/guidance for PLGA characterization is needed
- ✓ Each PLGA product is a different case and its performance is governed by different attributes. Therefore, case by case understanding of what really affects the release profile.
- ✓ More research on the impact of manufacturing process as it plays a huge role on release performance. Minor differences in manufacturing process can significantly alter the release profile.
- ✓ Developing in vitro BE approach for complex drugs is an collaborative effort. We are open to new technologies for supporting bioequivalence of complex drugs

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Topical Dermatological Complex Products

FDA Panelists

- Hiren Patel, PhD — Office of Bioequivalence
- Elena Rantou, PhD — Office of Biostatistics
- Pahala Simamora, PhD — Office of Pharmaceutical Quality
- Sam Raney, PhD — Office of Research and Standards

Topical Dermatological Complex Products

Research Questions on IVPT Method Development & Validation

- Can we predict or reduce the incidence of an aberrant flux profile from a cell?
- Are there barrier function tests (for a specific drug) that can be developed?
- What are the principles for utilizing aliquot or partial vs. full volume sampling?
- When is a shorter (4-6 hr) dose duration with a wipe-off suitable for a BE study?
- What are the principles for evaluating IVPT sensitivity with a wipe-off study design?

Research Questions on Challenges with Q3 Characterization

- How should generic developers adapt to variability among batches of the R product?
  - As a function of batch-to-batch variation in the R product
  - As a function of age-related trends in Q3, IVRT and/or IVPT for the R product

Topical Dermatological Complex Products

Research Questions on IVPT Data Analysis

- Do anomalous flux profiles impact the sensitivity/outcome of a BE Study?
- Can IVPT BE Studies be performed using multiple lots of R and T product ?
- Can pilot study data define outlier cutoffs at x standard deviations?
- What pre-specified criteria can objectively define an outlier (aberrant flux profile)?
- Should donors that do not exhibit a complete absorption phase be in the BE analysis?
- What are suitable ways to deal with missing data (e.g., a weighted average)?
- What are suitable ways to deal with zero-data for PK endpoints?
- Which of the multiple methods for outlier detection is best suited for IVPT?
- Could an ANOVA suited for replicate data assess BE without inflating Type I error?
- Can population modeling be helpful to assess aberrant or outlier flux profiles?


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