4th FDA/PQRI Conference on Advancing Product Quality Breakout Summaries

April 10, 2019

Hilton Rockville

PQRI
Product Quality Research Institute

FDA U.S. FOOD & DRUG ADMINISTRATION

TRACK 1:
NOVEL APPROACHES TO IMPROVE TREATMENT OUTCOME AND PATIENT SAFETY

Session 1: Complex Generics – Challenges and Opportunities

Moderator: Wenlei Jiang, FDA

Speakers: Daan Crommelin, Utrecht University

Katherine Tyner, FDA

Jeff Jiang, FDA

Presentations

1. Considerations for Biologics and Non-biological Complex Drugs

   Daan Crommelin, Utrecht University

2. An Overview of Complex Drug Substances and Complex Formulations – A Quality Perspective

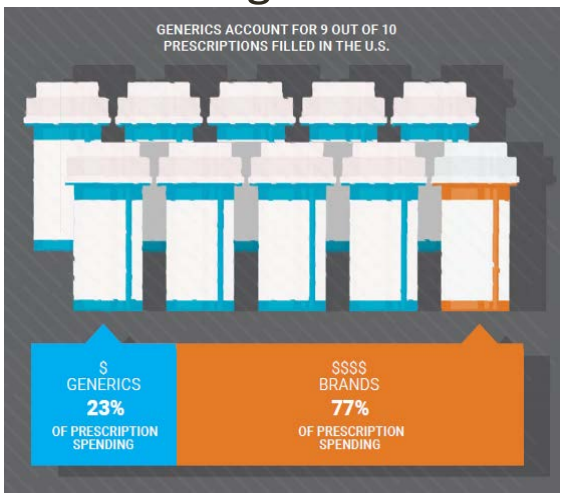
   Katherine Tyner, FDA

3. Overview of Complex Generics – Regulatory Perspective on Bioequivalence

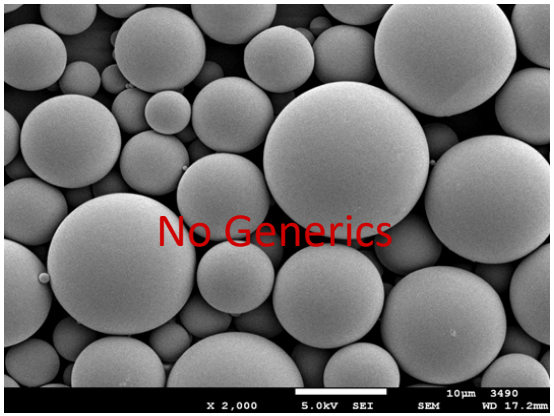
   Jeff Jiang, FDA

Session Background/Premise/Challenges

Overall Drug Products



However, limited generic availability for complex drugs



According to the GDUFA II commitment letter, **complex drug products** generally include products with

1) complex active pharmaceutical ingredients (APIs);

2) complex formulations;

3) complex routes of delivery;

4) complex dosage forms;

5) complex drug-device combination;

6) other products where there is complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement.

GDUFA: Generic Drug User Fee Amendments

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Key Points from Talk #1

Considerations for Biologics and Non-biological Complex Drugs

- The biosimilar concept has gained ground and is affecting (the economy of) the health care system (at least in EU; US to follow suit?).
- Critical Quality Attribute assessment should be based on a criticality analysis preferably including clinical performance data (cf. a-mab document and White Paper in AAPS J, 2018).
- Both biosimilars and non-biological complex drug (NBCD) products achieving similarity should be based on 'a stepwise approach and totality of evidence'.
- Are the present pathways for the approval of NBCD products adequate? Time for a new look at the Hatch Waxman act (cf. Gottlieb)*?

Gottlieb: Changes To Hatch-Waxman May Boost Complex Generic Market

April 04, 2019

Outgoing FDA chief Scott Gottlieb pinpointed complex generic and second-to-market novel drug development as two key areas in which he thinks the agency could have an effect in the drug pricing arena. During a House Appropriations subcommittee hearing on Wednesday (April 3), he told lawmakers they could contemplate changes to Hatch-Waxman that would allow the agency to look at small complements of clinical data when approving generics of complex drugs, and he highlighted that a lack of financial incentives are holding companies back from developing second-to-market novel drugs.

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Key Points from Talk #2

An Overview of Complex Drug Substances and Complex Formulations – A Quality Perspective

- Complexity in drug products can translate to complexity in identifying, establishing, and maintaining quality
- A suite of analytical techniques is often needed in order to adequately demonstrate product quality (sometimes multiple techniques for the same CQA)
- There are multiple ways to interact with FDA during the development of complex products (Pre-ANDA, Emerging Technology Program, Standards, Extramural funding)

Key Points from Talk #3

Overview of Complex Generics – Regulatory Perspective on Bioequivalence

- Approved generic drugs are therapeutically equivalent to the referenced list drug product and can be substituted freely
- Therapeutic equivalents are approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated
- There are different challenges for demonstrating bioequivalence of different complex generic drug products
- Constraining formulation variation by Q1/Q2 (i.e., qualitatively and quantitatively controlling inactive ingredients) is a foundation for bioequivalence approaches of most complex generic drug products
- Based on formulation Q1/Q2, in vitro bioequivalence approaches were recommended for certain complex generic drug products

Panel Discussion and Q&As

1. Which category of complex drug product is most challenging for generic development?

Each category of complex drug product has its unique complexity. Drug-device combination products targeting for local delivery certainly present multiple development challenges.

2. How does Pre-ANDA program and discussion with ETT differ from each other?

Pre-ANDA program applies to generic application only while discussion with ETT applies for both innovator and generic products. Discussion with ETT focuses on innovative product technology (e.g., dosage form or packaging such as a container and closure system); manufacturing process (e.g., design, scale-up or lifecycle approaches); and/or control strategy. Pre-ANDA focuses on alternative equivalence approaches.

Panel Discussion and Q&As

3. Complex drug impossible to be fully characterized or challenging to be characterized?

There are approved complex generics on the US and EU market. Some complex generics on the EU market did not demonstrate the same safety and efficacy.

4. EU experiences with the approval of complex generic drugs

- 2 out of 85 approved via centralized procedure
- Different national agencies may not hold consistent approval standards

5. How confident do patients feel about approved complex generic drugs?

- Post-approval monitoring
- Example with anti-epileptic drugs

6. Develop USP monograph for complex generic drug products

Overall Conclusions

- Lay foundation for the follow on sessions in this track (complex injectable and implantable, topical, inhalation products, and others)
- Provide overview of complex drug quality considerations and bioequivalence approaches
- Complex drug products present challenges but also great opportunities for generic development.
- FDA strives to remove scientific and regulatory hurdles and promote complex drug development
  - Regulator research
  - Guidance and review practice
  - Opportunities for face-to-face interactions between FDA and industry

Session 2: Developments in Biopharm Characterization of Injectable and Implantable Products

Moderator: Nan Zheng, FDA

Speakers: Jeffrey Clogston, Nanotechnology Characterization Laboratory

Karl Malcolm, Queen's University Belfast

Wenlei Jiang, FDA

Presentations

1. Physicochemical Characterization of Nanomedicines

   Jeffrey Clogston, Nanotechnology Characterization Laboratory

2. Challenges and Considerations in the Development and Validation of In Vitro Drug Release Testing for Intravaginal Rings

   Karl Malcolm, Queen's University Belfast

3. Complex Injectable and Implantable Drug Products: Bioequivalence Considerations

   Wenlei Jiang, FDA

Session Background/Premise/Challenges

- Complex injectable and implantable products improve clinical outcome and patient safety.
  - Improved delivery efficiency
  - Reduced off-site toxicity
- Biopharmaceutical characterization of complex injectable and implantable products can be challenging.
  - Identify critical attributes based on product specific design features
  - Lack of standardization of the evaluation of critical attributes: method and specification
- Advances in biopharmaceutical characterization improves quality control and equivalence evaluation of complex injectable/implantable products.

Key Points from Talk #1

Physicochemical Characterization of Nanomedicines

- The Nanotechnology Characterization Lab (NCL) facilitates the translation of nanotech into drugs and diagnostics with its expertise in nanoparticle characterization.
  - Novel orthogonal method for drug loading using elemental analyzer and combustion analysis
  - New method developed with reverse-phase HPLC to increase efficiency and accuracy in the assessment of lipid composition and stability
  - Novel method to examine size and charge on a per particle basis by Tunable Resistive Pulse Sensing
  - AF4-MALS/DLS method developed to assess protein binding to liposomes
  - Novel stable isotope tracer method to measure free drug fractions

Key Points from Talk #2

Challenges and Considerations in the Development and Validation of In Vitro Drug Release Testing for Intravaginal Rings

- Vaginal rings are available with different materials, manufacturing processes, ring types, and in vivo release kinetics
- In vitro release assays are usually conducted in shaking incubator with a selected release medium and shaking speed to mimic in vivo release
- Challenges and opportunities:
  - Need for compendial apparatus and methods
  - Selection of release medium for very poorly water soluble drugs
  - Evaluating variation in in vitro release testing methods
  - Need for accelerated in vitro release assay with good discriminatory ability

Key Points from Talk #3

Complex Injectable and Implantable Drug Products: Bioequivalence Considerations

- Complex injectable and implantable drug products have unique complexity and challenges for generic development
- Product-specific bioequivalence guidance are developed based on product complexity, in vivo performance, and scientific and regulatory advances in product characterization
  - In vitro release testing method development
  - Statistic method development for particle size profile comparison
  - Model-based bioequivalence method
  - Excipient sameness consideration
  - IVIVC development

Panel Discussion and Q&As

- Biopharmaceutical characterization and in vitro drug release test of vaginal ring
  - Gaps in vitro/in vivo drug release:
    differences in time frame; limited reports in IVIVC
  - Selection of release medium and assay condition: presence of sink condition
  - Complexity in release kinetics: reservoir vs matrix ring
- Current status on generic approval of complex parenteral products
  - Endeavors to remove hurdles in scientific evaluation
  - Encourage communications at pre-ANDA meetings
- Application of standard physicochemical characterization in NCL
  - Standard protocols for metabolite identification and impurities using LC-MS
- Environmental concerns with vaginal rings
  - Challenging for non-thermoplastic rings due to high drug load after use and a lack of capability to recycle the rings

Overall Conclusions

- Advances in biopharmaceutical characterization facilitates the development and regulatory review of nanomedicine therapies.
- In vitro release testing of intravaginal rings is challenging due to a lack of compendial apparatus, methods, and standards for evaluation of viabilities. There is tremendous interest in the development of accelerated in vitro release testing method that is discriminative and predictive of in vivo performance.
- Complex injectable and implantable products have unique complexity and challenges.
- Regulatory research activities in product characterization are in progress to alleviate scientific hurdles in the bioequivalence evaluation of complex injectable and implantable products.

Session 3: A Novel Approach for Overcoming Barriers to Improve Patient Access for Topical Drugs

Moderator: Filippos Kesisoglou, Merck

Speakers: Vinod Shah, Pharmaceutical Consultant

Flavian Rădulescu, Carol Davila University of Medicine and Pharmacy

Tannaz Ramezanli, FDA

Presentations

1. In Vitro Release and Q3 Measurements for Semisolid Drug Products

   Flavian Rădulescu, Carol Davila University of Medicine and Pharmacy

2. The Premise of a Topical Drug Classification System as an Alternative to Clinical Endpoint Bioequivalence Studies

   Vinod Shah, Pharmaceutical Consultant

3. Bioequivalence of Topical Products: Scientific Considerations

   Tannaz Ramezanli, FDA

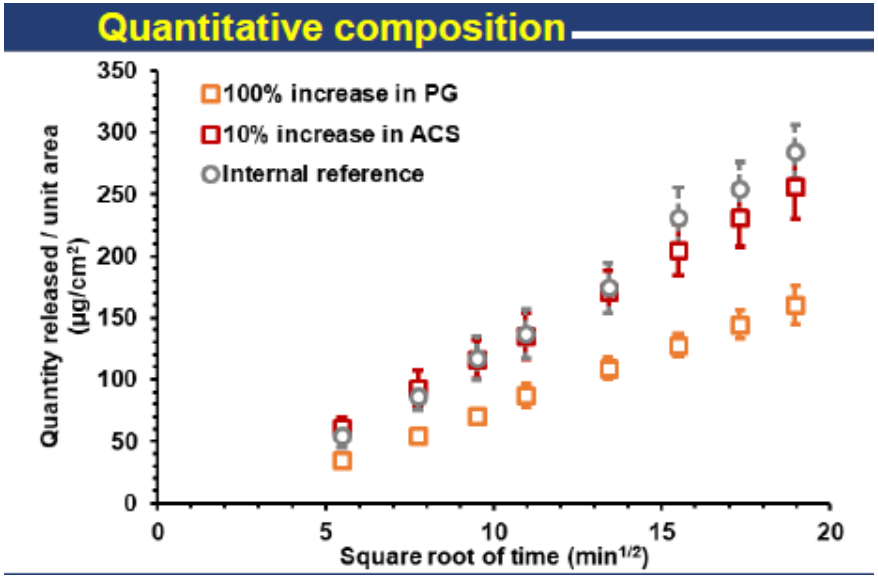
Session Background/Premise/Challenges

- Topical drug products are considered complex drug products
- As such the current gold standard for demonstration bioequivalence are clinical endpoint equivalence studies
- The Topical Classification System has been proposed as an alternative approach to enabling demonstration of equivalence between formulations
- PQIR has been a co-sponsor of a project towards TCS validation.

Key Points from Talk #1

In Vitro Release and Q3 Measurements for Semisolid Drug Products

- In Vitro Release (IVR) test is a comparative, steady state release measurement performed in well-defined conditions (validated method)
- IVR is a good indicator of the combined influence of composition and microstructural characteristics.
- IVR provides an objective measurement of similarity.
- Adequate interpretation of IVR requires details on role, type and quantities of excipients.
- IVR non-similarity indicates risks of non-equivalent in vivo performance.



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Key Points from Talk #2

The Premise of a Topical Drug Classification System as an Alternative to Clinical Endpoint Bioequivalence Studies

- TCS is a framework for classifying topical drug product based on Q1/Q2 similarity, role of inactive ingredients, microstructure arrangement of matter (Q3) and IVRT
- TCS 1 and 3 products may be eligible for biowaivers
- TCS validation project ongoing. Preliminary in vitro and in vivo results with acyclovir cream indicate only TCS1 formulation exhibits ratio of mean >0.8.

Q1, Q2 Same **Q3 Same** **TCS class 1**	**Q1, Q2 Same** **Q3 Different** **TCS class 2**
Q1, Q2 Different **Q3 Same** **TCS class 3**	**Q1, Q2 Different** **Q3 Different** **TCS class 4**

Comparison	Ratio of means	Lower limit, 90%CI	Upper limit, 90%CI
F4 vs. F0	0.8419	0.7287	0.9726
F5 vs. F0	0.7576	0.6558	0.8753
F9 vs. F0	0.6997	0.6057	0.8084

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Key Points from Talk #3

Bioequivalence of Topical Products: Scientific Considerations

- Topical drug products have very few generic alternatives
- Development of efficient BE standards based on efficient local/systemic PK methods and efficient in vitro BE may be useful
- The two main concerns around TCS is the translatability of IVR to Q3 similarity and it's biorelevance
- Due to the complexities associated with topical products, demonstration of comprehensive understanding of the product complexities and manufacturing issues is critical.

Panel Discussion and Q&As

- Audience pointed out the differential view of the TCS approach in the different presentations
- It is acknowledged that IVR is method dependent. The goal is to provide a comparison between formulations, not to predict in vivo release (as it doesn't employ skin). If IVR differences are seen, Q3 differences are likely.
- An IVR method does need to go through a validation procedure.
- Proving Q3 similarity based on properties is not straightforward. What exact measurements to make and how to interpret differences may not be clear.

Overall Conclusions

- Demonstration of bioequivalence for topical drug products is challenging
- Challenge is related to complexity of formulation and challenges with assessment of delivery impact
- Adoption and validation of alternative in vitro BE methods is of interest
- TCS has been proposed as an alternative to clinical evaluation
- The first data on TCS “validation” with acyclovir are available and additional data with two more compounds will be generated
- Additional dialogue and debate is needed to understand applicability of in vitro tests (IVR) to assessing similarity in the context of “biowaivers”