Innovative Approaches to Evaluation of Topical Product Bioequivalence

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PQRI Workshop on the Evaluation of New and Generic Topical Drug Products - Current Challenges in Bioequivalence, Quality, and Novel Assessment Technologies
March 12, 2013

The views presented in this article are those of the authors and do not necessarily reflect official views of the Food and Drug Administration.
OGD Science Staff

- Use the best available **science** to make **high quality** generic products **available** to the American public
  - Respond to Citizen Petitions that challenge OGD science and policy
  - Develop new approaches for equivalence of complex and locally acting products
  - Ensure approved generics are therapeutically equivalent
  - Advance OGD modeling, simulation and data analysis
  - Implement GDUFA Regulatory Science commitments
  - Collaborate with external experts via contracts and grants
Guidance and Citizen Petitions

• Goal to identify alternatives to clinical endpoint bioequivalence studies when scientifically justified
• Communicated via individual product guidance but new approaches generate Citizen Petition challenges
• Examples from 2012-2013
  – Lidoderm
  – Acyclovir
Locally Acting Products

• Systemic Drugs

Drug Release from Product → Plasma Concentration → Site of Action → Effect

• Locally Acting Drugs

Drug Release from Product → Site of Action → Effect

Examples: Inhalation and Topical

Drug in plasma might not be detectable or might have multiple routes
Is There a Problem with Relying on Clinical Endpoints for BE?

• Barrier to generic competition
  – Consumer cost per year: millions

• Barrier to product improvement
  – Need to demonstrate BE after formulation change or in product development

• Clinical endpoints have high variability/low sensitivity
  – Inefficient detection of formulation differences

• Unnecessary human testing
  – Often 300-500 patients sometimes larger than original efficacy study
Regulatory Basis for Alternatives

• A 2003 addition to the Federal Food Drug and Cosmetic Act at Section 505(j)(8)(A)(ii) indicates that
  – “For a drug that is not intended to be absorbed into the bloodstream, the Secretary may assess bioavailability by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at the site of drug action”. 
Key Aspects of Bioequivalence

• Bioequivalence
  – Bioequivalence is about the formulation
  – Clinical effectiveness has already been established
  – Defined as no significant difference in rate and extent of absorption at site of action

• Many Steps Occur Before the Site of Action
  – Rate at which drug can leave the formulation
  – Rate at which drug can cross the skin
  – Rate at which drug diffuses in the skin
Why are Topical Products Complicated?

• Complexity
  – Semi-Solid dosage forms
  – Complex structure of skin
  – Product components affect skin
  – Disease state can change skin

• Failure Modes
  – Application
  – Formulation
  – Physiology

• Application
  – Different spreading on the skin
  – Different area/duration of exposure

• Formulation
  – Drug does not leave formulation
  – Thermodynamic activity is different (suspension v. dissolved drug)

• Physiology
  – Formulations have different effects on stratum corneum
  – One formulation prefers follicular pathway
BE Approaches for Locally Acting Products

- FDA has begun to make different recommendation for Q1 and Q2 formulations for other locally acting drugs: Vancomycin and Acarbose.
- For other locally acting products (inhalation products, GI acting) FDA has recommended “weight of evidence” or combined approaches:
  - PK, PD, in vitro for inhalation
  - Dissolution and PK for mesalamine
Q1 and Q2 Definitions

• Classify product similarity
  – Q1: Same components
  – Q2: Same components in same concentration
  – Q3: Same components in same concentration with the same arrangement of matter (microstructure)
Q1 and Q2 Identical

• Uncertainty Due to Differences in Manufacturing
  – Is the rheology the same?
  – Is the solubility of the drug in the formulation the same?
  – Are excipients released at same rate?
  – Is particle size the same? (suspensions)

• Potential Path Forward
  – In vitro tests are the best evaluation method for manufacturing process
    • Rheology
    • In vitro release (diffusion cell)
    • Particle Size (suspension)

• Precedent: Budesonide inhalation suspension (BE on particle size, no in vivo studies)
Application to Topical Products

• Acyclovir Ointment
  – In vitro approach for Q1 and Q2 formulations

• Lidocaine Topical Path
  – PK study for bioequivalence
  – Patch size (area) must be the same
  – Not a topical dermatological product
    • Local pain relief (different site of action)
Beyond Q1 and Q2

• Questions for Q1 identical
  – Excipient effect on skin barrier properties can be concentration-dependent
  – Thermodynamic activity could differ

• Questions for different inactive ingredients
  – In vivo test if composition differences in excipients could potentially alter either skin permeability or the solubility of drug in the formulation
  – Would in vitro release test answer this? Are there IVIVC
OGD Role in Innovation
ANDAs for Complex Products

• OGD Science and Review priority to open the ANDA pathway
• Pre-ANDA meeting requests may be granted for new approaches
• Correspondence responses are prioritized
Advance Modeling and Simulation

• To design products for intended performance
• To assess risks related to policy decisions
  – Need better models
    • Of the physiology (IVIVC)
    • Of the product
    • Of the process
• To efficiently review and monitor quality
  • Data from marketed batches
  • Data from patient usage of generic drugs
Modeling Lidocaine

![Diagram of modeling with labeled compartments and equations]

- **Dermis**
- **Plasma**

- **Equations:**
  - $k_1$
  - $k_{21}$
  - $k_2$
  - $k_{32}$
  - $k_3$
  - $k_{43}$
  - $Q$
  - $k_p$
  - $k_{cp}$
  - $k_e$

- **Plots:**
  - **Dermis** concentration over time (ng/mL)
  - **Plasma** concentration over time (ng/mL)
  - **Lidocaine Conc (mg/mL)**

- **Simsing the RLD Data in A202346**

- **Graphs:**
  - Time (hr)
  - Lidocaine Conc (ng/mL)

**Graphs:**

- Time (hr): 0, 6, 12, 18, 24, 30, 36
- Lidocaine Conc (ng/mL): 0, 5, 10, 15, 20, 25, 30, 35, 40
External Research Collaborations

- University of Bath
  - QbD for DPI
- University of Michigan
  - PK for GI acting drugs
- National Jewish
  - Inhalation PD eNO
- University of Maryland
  - BCS class 3 waivers
  - AED patient study
- Cincinnati/Rochester/JHU
  - AED patient study
- University of Florida
  - Dermal Microdialysis
  - Inhalation PK
- University of Colorado
  - Ophthalmic IVIVC
- University of Cincinnati
  - Immunosuppressant PK
- VCU
  - CFD for inhalation
Communications of Results

• Citizen Petition Responses
  – About 30 per year

• Individual Product BE Guidances
  – About 40 per year have science staff input

• Scientific Meetings and Workshops
  – ~10 AAPS posters

• Publications (13 2012 publications)
  – On pAUC, DPI device performance, profile comparison, modeling and simulation, therapeutic equivalence
GDUFA Benefits For Innovation

• Faster review times
• Timelines for correspondence responses on new regulatory approach
• GDUFA is the only user fee to directly support regulatory science
  – Why? Market failure for innovation investments
Market Failure for Innovation

• For new drugs, innovation rewarded by product exclusivity
• For generic drugs, innovation rewarded by market access for other generic firms
• GDUFA support for Regulatory Science indicates
  – There is a public benefit to innovative generics
  – There is a benefit to industry as a whole
GDUFA Regulatory Science

• GDUFA Funds will support regulatory science focused on
  – Therapeutic Equivalence
  – Opening the ANDA pathway

• GDUFA mandates a new collaboration
  – FDA “will convene a working group and consider suggestions from industry and other stakeholders to develop an annual list of regulatory science initiatives for review by CDER Director.”
Upcoming RFP

• Grant (Cooperative Agreement) to support innovation in bioequivalence method development for topical products
  – $500,000 potentially available
  – Also a separate grant opportunity for TDDS

• Past Support for Innovation
  – Annette Bunge: Improvement of skin stripping
  – Audra Stinchcomb: NIR for topical drug assay
  – Hartmut Derendorf: Microdialysis
Future Regulatory Science Input

• Current list of projects (FY 2013) was attached to the GDUFA letter

• June 19, 2013 public meeting
  – OGD will open a Docket for public comment

• Encourage this group to provide input through the public process to support keeping topical bioequivalence on the GDUFA list
Pathway to New BE Methods

• Technology Established
  – Used in research/development
  – Publications
  – Commercial Availability?

• Submitted to FDA (Supportive Information)
  – Pharmaceutical Development
  – Bioavailability

• Future use as primary BE method?
Diffusion Cell Examples

• Submitted in an NDA to compare clinical to commercial (new site)
• Submitted in an NDA to identify significance of particle size
• Submitted in an ANDA to support waivers for topical solution with small difference in excipients
Pathway to New BE Method

• For product which are known to be equivalent
  – Approved generics via clinical endpoints
  – Do proposed new BE methods confirm this
  – New method may be more sensitive

• For products which are known to be different
  – Deliberate manufacture of trial formulations
  – Alternate dosage forms
  – Do proposed new BE methods distinguish them
Summary

• Goals of OGD Regulatory Science
  – Access to Generics
  – Equivalence of approved generics

• Recent Progress
  – Acyclovir, Lidocaine

• Future Regulatory Science Support