Challenges of Assessing Bioequivalence of Topical Pharmaceutical Products

Robert Lionberger
OGD Science Staff

PQRI Workshop on the Evaluation of New and Generic Topical Drug Products - Current Challenges in Bioequivalence, Quality, and Novel Assessment Technologies
March 13, 2013
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Outline

• Introduction to Generic Drugs
• GDUFA Update
• OGD Topical Drug Overview
  – Access to generics
  – Equivalence of approved generics
• Future Approaches
Therapeutic Equivalence

• Approved generics must have Therapeutic Equivalence
  – Have the same clinical efficacy and safety profiles when administered to patients under conditions specified in the labeling.
  – Can be substituted for each other without any adjustment in dose or other additional monitoring
Determinants of Therapeutic Equivalence

- Product Design and Performance
- Labeled Indications
- Patient Attributes and Use

What OGD Evaluates

- Bioequivalence Studies

The Goal

- Therapeutic Equivalence
Therapeutic Equivalence of Topical Products

• **Challenge**: to align recommended bioequivalence studies as part of therapeutic equivalence evaluation

• **Challenge**: evolve pharmaceutical equivalence evaluation from *is this a cream* to performance measures that matter to patients and successful generic substitution
Bioequivalence Studies

Past

All risks of product inequivalence must be managed by design of bioequivalence study

Minimal evaluation of pharmaceutical equivalence: dosage form, strength
Design of bioequivalence study complements equivalence in design and performance. Fewer inequivalence risks are managed by BE study.

QbD informed evaluation of pharmaceutical equivalence: dosage form, strength, product design and product performance.
Generic Drug Volume

• Volume increases in generic drug prescriptions 1984-2012
  – In 1984: 14%
  – In 2006: 66%
  – In 2012: >80%

• Cost of generic drugs
  – estimated 30-80% in medication savings for health care systems

• Cumulative savings related to generic drug program for Americans over last decade estimated ~ $1 T (NHEA)
Steady Interest in ANDAs

ANPA Receipts

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<th>Fiscal Year</th>
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As of December 2012
Each Year Fewer Approvals than Submissions

ANDA Original & Tentative Approvals

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As of December 2012
An Increasing Backlog

Office of Generic Drugs Pending Applications

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As of December 2012
Generic Drug User Fee Act

• $299 Million/year for FDA’s generic drug programs
  – Fees on applications and sites
• Resources come with accountability
  – 10 month review time goal for new applications phased in over the first 5 years
  – Clear backlog over 5 years
• 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
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
OGD Topical Overview

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

Total $18.3 Billion in 2008
US topical anti-acne market in 2007

- Retin-A (J&J/generics) $180m
- Differin (Galderma) $199m
- BenzaClin (Dermik/Sanofi-Aventis) $216m
- Topical antibiotics $85m
- Duac (GSK/Steifel) $134m
- Ziana (Medicis) $35m
- Others $179m
- Benzoyl peroxide $14m
Current Generic Competition

Fragmented Market

Retin-A: 6 forms; 7 total generics
Retin-A Micro: No generics

0.1 %Gel: 2 generics
Cream: 1 generic
0.3% Gel: 1 generic
Lotion: no generic

1 generic
Reasons for Limited Generic Competition

• Most topical dermatological drugs have < $50 million in yearly sales before generic competition

• High cost of equivalence studies
  – Need one per dosage form/strength
  • (few waivers for lower strength)

• Complexity of semi-solid formulations
Benefits of Efficient Bioequivalence Studies

• For topical corticosteroids there is an establish PD bioequivalence study
  – 0.5% betamethasone cream: 5 generics
  – 0.1% mometasone cream: 5 generics
  – 0.1% mometasone ointment: 6 generics
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
Dermatological Products

• Currently, FDA often relies on clinical endpoints for bioequivalence
  – Fallback when we cannot identify an alternative measure of drug release

• Study design
  – Test, reference and placebo arms
  – Compare test and reference clinical outcomes
  – Both test and reference must be superior to placebo
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
Recent Innovations

• Lidoderm Patch
  – PK based equivalence for a topical product

• Acyclovir Ointment
  – Characterization based equivalence for formulations with same concentrations of same inactive ingredients

• Dermal Microdialysis
  – Research underway into direct measure of drug in dermis
OGD Topical Overview

• Goals of OGD Regulatory Science
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  – Equivalence of approved generics
Equivalence Assurance

• Clinical endpoint point BE studies may not be sensitive to formulation differences
  – ANDA sponsors may be asked for additional data when formulation/mechanisms differ
    • Microsphere formulations (see draft guidance)
    • Excipients with retentive properties not found in RLD
    • PK + clinical for diclofenac
Complexity of Topical Dosage Forms = Need for QbD

- Labeled Use Safety and Efficacy
- Define Quality Target Product Profile
- Product Design and Understanding
- Process Design and Understanding
- Control Strategy
- Continual Improvement

TARGET → DESIGN and UNDERSTANDING → IMPLEMENTATION
Define QTPP

• Analysis of the reference listed drug (RLD) product
  – RLD labeling
    • Dosage form, Strength, Route of administration
    • Clinical Pharmacology
    • Indication and Usage
    • Precautions/ Adverse Reactions
    • Dosage and Administration
    • How supplied (container closure system and storage)
  – Comprehensive testing
    • Physical Attributes: appearance, color, odor, pH, rheological behavior (consistency, viscosity), drug particle size, oil globule size, spreadability etc.
    • Identification of inactive ingredients including preservative and antioxidant etc.
    • Assay, homogeneity, and tube uniformity
    • Impurity profile: RLD near expiration
    • In Vitro Release Test \((\text{Flux assay using porcine ear/synthetic membrane/cadaver skin})\)

• Other resources
  – Scientific literature/Patents
  – FOI requests
  – FDA database for dissolution / bioequivalence recommendation

• Begin with the end in mind: pharmaceutical equivalence and bioequivalence
Value of QbD Oriented Development

in vitro flux studies in skin target equivalence to RLD

Drug Deposition using Human Skin

Cumulative permeated amount (μmol/cm²)

Time (h)

Percent Applied Dose

Epidermis
Dermis
Receptor

RLD
Formulation 1
Formulation 2
RLD
Our Deliverables and Goals

• Generics of highest quality
• Generics that are completely and reliably interchangeable with brand products
• Generics across all therapeutic classes
Finally: Form Follows Function

• Organizational changes planned at CDER
• OGD elevated to Super Office status on par with Office of New Drugs
• Planning for a new Office of Pharmaceutical Quality
  – Integrated regulatory paradigm for review and surveillance
  – Supporting both new and generic drugs
Thank you!