Institute for International Research
Generic Drug Summit 2008

The Past, Present and Possible Future of Proving Equivalency for Topical and Locally Acting Oral Generics

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Agenda for Today's Discussion

- Historically, topical and locally acting oral products have created more of a challenge than would be expected given the scientific methods employed by the agency.
- Goal is to provide an understanding of the FDA's methods and practices of determining bioequivalence for topical and locally acting oral generics
- Appreciate how the regulatory approval procedure has evolved and provide some insight regarding how the process may progress moving forward

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Overview

- **Products applied locally to the skin to treat diseases of the skin**
- **Types of products**
  - **Creams**
  - **Ointments**
  - **Gels**
  - **Solutions**
  - **Suspensions**
  - **Topical oils**
  - **NOT transdermals**

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Regulatory Requirements Over the Years

- Regulatory approaches to generic topicals
  - Pharmaceutical equivalents
    - Active ingredients
    - Qualitative excipients
  - Waivers of in vivo studies
- Evidence of non-therapeutically equivalent generic topical corticosteroid products
  - Stoughton, Arch Dermatol 1987;123:1312-4
- Change to in vivo BE testing
- Guidances
  - Topical Dermatologic Corticosteroids: In Vivo Bioequivalence – 2 June 1995

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Definition of Bioequivalence

- Pharmaceutical equivalents whose rate and extent of absorption are not statistically different when administered to patients or subjects at the same molar dose under similar experimental conditions.

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Purpose of Bioequivalence

- Therapeutic equivalence (TE)
- Bioequivalent products can be substituted for each other without any adjustment in dose or other additional therapeutic monitoring.
- The most efficient method of assuring TE is to assure that the formulations perform in an equivalent manner.

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Approaches to Determining Bioequivalence (21 CFR 320.24)

- In vivo measurement of active moiety or moieties in biologic fluid
- In vivo pharmacodynamic comparison
- In vivo limited clinical comparison
- In vitro comparison
- Any other approach deemed appropriate by FDA

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Topical Corticosteroids

- Guidance: Topical Dermatologic Corticosteroids: In Vivo Bioequivalence – 2 June 1995
- Pharmacodynamic measurement
- "Blanching" effect
- Dose controlled through duration of application (dose-duration)
- Dose-effect relationship established during each study

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Dermatopharmacokinetics

- Product placed on skin and removed at several timepoints
- "Skin stripping" with tape
- Kinetics of drug penetration into stratum corneum studied
- Problems
  - Studied only one "pathway"
  - Not proven to be related to drug availability at the site of activity
  - Different results from labs

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Special Considerations for BE of Topical Products

- Semi-solid topical products are complex dosage forms
- The skin is not a homogeneous "slab" of tissue
  - Several pathways through the skin into the body
    - Stratum corneum
    - Sweat glands
    - Hair follicles
    - Abraded skin

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Special Considerations for BE of Topical Products

- **Plasma concentrations are not an accurate measure of drug availability at the site of activity**
- **Surrogate measures may not always adequately reflect availability at the site of activity**
- **Clinical/PD measures for BE determination**
  - **Variable**
  - **May lack sensitivity**
  - **Limited ability to control dose**

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Current Case Study - Effudex

- Valeant Pharmaceuticals – Effudex
- Indications
  - Multiple actinic or solar keratosis
  - Superficial basal cell carcinomas
- Valeant filed Citizen Petition 2004P-0557 in Dec 04
  - Different sites of action for each indication – BE must be established at each site
  - BE must be established in the most difficult condition to treat
- FDA reviewed the CP and denied it, April 11, 2008
- April 11, 2008 – FDA approved an ANDA for Spear Pharmaceuticals – fluorouracil cream 5%

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Current Case Study - Effudex

- Dr. Janet Woodcock, · FDA had carefully considered Valeant's arguments, and decided to approve the Spear product, confirming that the Spear product is bioequivalent to Efudex(R) Cream
- " ... even when clinical trials are needed, it has not been the Agency's policy to require that bioequivalence be shown in every indication if drug release from the dosage form and appearance at the site or sites of activity has been demonstrated ...
- If a study demonstrated efficacy for a 5-FU formulation to treat AK, this would provide assurance that the formulation would penetrate the skin sufficiently to treat sBCC."
- The courts have expressly upheld FDA's regulatory implementation of the Act's bioequivalence requirements.
- Like thousands of generic drugs that have been approved over the years, the FDA approved the Spear product based on precedent and pursuant to its well established scientific, medical, and statistical review procedures for determining bioequivalence.

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Current Case Study - Effudex

- Valeant sued FDA on April 25, 2008
- Requested TRO to suspend approval of Spear's ANDA
- FDA, Assoc. Commissioner for Policy and Planning issued an administrative order staying the approval of generic fluorouracil cream 5% until May 30, 2008 "because there are outstanding questions regarding this approval that the Agency must consider."
- Spear suspended all further sales and shipment
- However – no decision yet to date
- Spear is not currently marketing product
- Product remains listed in Electronic Orange Book

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Local Acting oral Drug Products – Case Studies

- Salix – Colazal · CP 2005P-1461
- Balsalazide is an orally administered – locally acting GI product
- Indications – reduce inflammation associated with ulcerative colitis – site of action – colon
- Requested FDA to:
  - Withdraw BE Guidance
  - Use ulcerative colitis patients in remission instead of normal health subjects
  - Measure specific analytes in adults and pediatrics
  - Fasting, Fed and sprinkling study
  - Specific in vitro requirements

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Local Acting oral Drug Products – Case Studies

- FDA denied the CP on December 28, 2007
- ANDAs approved on Dec 28, 2007
- Issues discussed in the denial of the CP
  - Characteristics of the product
    - Solubility
    - Mechanism of release
    - Ability to measure plasma concentrations and relation of plasma concentrations to release at the site of action
    - Sensitivity of clinical studies to detect differences in product performance
  - Clinical studies not required to establish BE
    - In vivo BE study (standard PK metrics)
    - Dissolution

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Local Acting oral Drug Products – Case Studies

- ViroPharma – correspondence 3/16/06 to FDA regarding Vancomycin Capsules
- Indications
  - Serious and life threatening infections of the GI tract caused by *Clostridium difficile* and *Staphylococcus aureus*
- In correspondence OGD stated that in vivo BE waivers can be requested on the basis on in vivo dissolution testing
- ViroPharma raised questions regarding impact of significant changes in the physiology of the GI tract – altered motility. pH, volume, presence of abnormal intraluminal constituents and inflammatory mediators

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Local Acting oral Drug Products – Case Studies

- Citizen Petition filed 3/17/06 – 2006P-0124 and supplements thereto
- Requesting for ANDAs and 505(b)(2) NDAs for Vancomycin Capsules
  - Studies should be required demonstrating rate and extent of drug release at the site of action
  - Stability
  - Generic is bioequivalent along the entire GI tract
  - Convene and advisory committee meeting
  - Validate with FDA Medical Policy and Biopharmaceutics Coordinating Committees the standards for approval of generics
  - Provide public review and comment on the standards for generic approval

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Local Acting oral Drug Products – Case Studies

- Risks to Individual patients and public health of waiving in vivo requirements
- Public comments regarding potential impact on the public health
- As of June 17, 2008
  - Petition is still pending
  - No ANDAs or 505(b)(2) NDAs approved by FDA

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HHS OIG Report on the FDA Generic Drug Review Process

- June 2008 report – examines ANDA reviews for 2006
- 96% of ANDAs are not approved in the first review cycle due to CMC deficiencies
- 46% of ANDAs – chemistry review exceeded 180 days (median was 217 days)
  - 0f 105 ANDAs that review >180 days – reviews for 69% did not even begin within 180 days
- Micro reviews most likely delayed – 76% > 1 year
- 58% of Bio reviews delayed – median review time of 287 days
- 56% of labeling reviews delayed – median review time of 277 days
- ANDA submissions have increased at more than double the rate of review resources over the last 5 years

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HHS OIG Report on the FDA Generic Drug Review Process

- Critical of the first in – first out review process
- Prioritization practices contribute to longer review times for ANDAs that are close to approval
- OIG Recommendations
  - Identify common ANDA deficiencies
  - Offer more guidance to the industry to decrease the % not approved
  - Increase the % of original ANDAs reviewed within 180 days
  - Identify new prioritization practices to reduce review times for ANDAs close to approval
- FDA is implementing process imporvements

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