Regulatory Approaches for Generic Drugs: BE of Topical Drug Products

Barbara M. Davit, Ph.D., J.D.
Director, Division of Bioequivalence II
Office of Generic Drugs, CDER, FDA

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Evaluation of New and Generic Topical Drug Products
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Agenda

• Bioequivalence issues unique to topical drug products
• Pharmacokinetic (PK) approach
• Pharmacodynamic (PD) approach
• Clinical approach
• In vitro approach
• Waiver of BE requirement (biowaiver)
• Summary and conclusions
Why do bioequivalence (BE) studies of topical products present unique regulatory issues?
Why are BE studies necessary for proposed new generic products?

• The US Code and FDA’s regulations require that a generic drug product be bioequivalent to its corresponding reference listed drug (RLD) product for marketing approval.

• It is not necessary to demonstrate safety and efficacy for the new generic.
  – Relies on RLD safety and efficacy data.

• If certain criteria are met, FDA may grant a biowaiver.
Objective of BE studies in generic drug approval process

• In an acceptable BE study, the generic and reference product should not show a significant difference in the rate and extent of availability at the site of action

• FDA’s regulations list suitable BE approaches ranked by sensitivity, accuracy, reproducibility

• For each new generic topical drug product, FDA must consider
  – The optimal BE approach; or
  – Whether a biowaiver is appropriate
BE approaches, ordered by accuracy, sensitivity, reproducibility

• PK
• PD
• Clinical endpoint
• In vitro
• Any other approach deemed suitable by FDA
Considerations in selecting BE approach for a generic topical drug

Choice of BE study design depends on ability to compare drug delivered by generic & RLD at site of action.

- Site of action
- Mechanism of action
- Sensitivity of approach
- Feasibility of approach
- RLD formulation
Some definitions applied in comparing generic and RLD topical formulations

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Abbr.</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Qualitatively the same</td>
<td>Q1</td>
<td>Generic and RLD products contain the same active and inactive ingredients</td>
</tr>
<tr>
<td>Quantitatively the same</td>
<td>Q2</td>
<td>Generic and RLD products contain the same amounts of active and inactive ingredients</td>
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<tr>
<td>Physicochemical attributes of a topical dosage form</td>
<td>Q3</td>
<td>Generic and RLD products have the same physicochemical properties</td>
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Several case studies illustrate how FDA determines an appropriate BE approach for a generic topical product
Application of PK approach: lidocaine topical patch 5%
Application of PK approach:
lidocaine topical patch 5%

<table>
<thead>
<tr>
<th>Drug substance</th>
<th>Indication</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>• An amide-type local anesthetic agent</td>
<td>• Relief of pain associated with post-herpetic neuralgia</td>
<td>• Lidocaine acts on nerves in dermal tissue</td>
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</table>
**Application of PK approach: lidocaine topical patch 5%**

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<tr>
<th>Site of action</th>
<th>RLD formulation</th>
<th>Sensitivity, feasibility</th>
</tr>
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<td>• Lidocaine penetrates beneath the stratum corneum to reach the site of action in dermal tissue</td>
<td>• An adhesive material containing 5% lidocaine, to be applied to the skin</td>
<td>• Lidocaine in plasma is proportional to its presence at site of action</td>
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<tr>
<td></td>
<td></td>
<td>• Measuring lidocaine in plasma is feasible</td>
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</table>
Application of PD approach: fluocinolone acetonide 0.01% topical body oil
Application of PD approach: fluocinolone acetonide topical oil

**Drug substance**
- Low-to-medium range potency corticosteroid

**Indication**
- Topical treatment of atopic dermatitis

**Mechanism of action**
- Has anti-inflammatory, antipruritic, & vasoconstrictive properties
Application of PD approach: fluocinolone acetonide topical oil

Site of action
- Absorbed percutaneously; not intended to be systemically absorbed

RLD formulation
- A solution of fluocinolone acetonide in a blend of oils

Sensitivity, feasibility
- The PD vasoconstrictr assay can accurately detect rate and extent of availability in skin
Fluocinolone acetonide topical oil: additional considerations for BE

Is the generic fluocinolone acetonide 0.01% topical oil formulated to be Q1/Q2 the same as the RLD?

Yes

FDA will consider granting a biowaiver

No

Applicant must show BE via the vasoconstrictor assay
Application of clinical endpoint approach: 5-flourouracil (5-FU) cream 5%
**Application of clinical approach: 5-FU cream 5%**

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| - A fluoro-pyrimidinedione which is cytotoxic | - Topical treatment of actinic keratoses (AK)  
- Treatment of superficial basal cell carcinomas (sBCC) | - Creates a thymine deficiency, provoking unbalanced growth in rapidly-growing cells, such as carcinomas |
Application of clinical approach:
5-FU cream 5%

Site of action
• Acts on AK and sBCC lesions in the epidermis and dermis

RLD formulation
• Cream contains 5-FU in a vanishing cream base comprised of several inactive ingredients

Sensitivity, feasibility
• AK treatment is considered more sensitive to formulation performance than sBCC treatment
• It is feasible to perform a clinical endpoint BE study in AK patients
Clinical endpoint BE studies of 5-FU: additional considerations

• Primary endpoint is proportion of subjects with treatment success at study week 6
• Success is defined as 100% clearance of all AK lesions within the treatment area
• A placebo control arm is recommended to
  – Demonstrate that the generic and RLD are active;
  – As a parameter to show that study is sufficiently sensitive to detect differences between products
Application of in vitro approach: acyclovir ointment 5%
An in vitro approach can be used for acyclovir ointment 5%

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| • A synthetic nucleotide analogue active against herpes viruses | • Initial outbreaks of genital herpes  
• Treat certain types of lesions caused by Herpes simplex virus | • Converted to acyclovir triphosphate intracellularly  
• Acyclovir triphosphate stops replication of herpes viral DNA |
An in vitro approach can be used for acyclovir ointment 5%

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| • Acyclovir delivered by the ointment functions in the upper layer of the skin | • Considerably less complex than a cream  
• Consists of one active ingredient suspended in a polyethylene glycol base | • An in vitro BE approach more sensitive than a clinical endpoint BE study  
• Due to low potency of ointment, a clinical endpoint BE study may not be feasible or reliable |
BE of acyclovir ointment 5%: additional considerations

- The generic and RLD products must be Q1/Q2.
- To show that generic and RLD are also Q3, conduct in vitro tests to compare:
  - Release rates
  - Particle size, viscosity, morphic form, PEG molecular weight distribution
- If not Q1/Q2, conduct clinical endpoint study.
For the diclofenac sodium gel 1%, FDA recommends a PK endpoint study and a clinical endpoint study to demonstrate BE.
For diclofenac sodium gel 1%, FDA recommends two in vivo BE studies

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<td>• Non-steroidal anti-inflammatory</td>
<td>• Relief of the pain of osteoarthritis</td>
<td>• Inhibits cyclooxygenase, resulting in decreased synthesis of molecules associated with inflammatory response</td>
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For diclofenac sodium gel 1%, FDA recommends two in vivo BE studies

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| • The joint or local soft tissue  
• Diclofenac penetrates the soft tissue  
• Diclofenac is also well-absorbed  
• Unclear if effects are due solely to local delivery or if systemic delivery contributes | • A gel comprised of several different inactive ingredients | • A PK study is most sensitive, accurate, reproducible but may be unsuitable if drug acts mainly by local action  
• As there is evidence that drug may be locally-acting, an in vivo study with clinical endpoints should also be conducted |
The FDA will consider granting biowaivers for topical products provided certain criteria are met.
Criteria for granting a biowaiver for a topical solution

• Formulation is a solution for application to skin;

• Generic and RLD contain the same active ingredient in the same concentration and dosage form;

• The generic contains no inactive ingredient or other change in formulation from the RLD that might significantly affect availability
  – e.g., FDA may request in vivo and/or in vitro BE studies if generic and RLD have differences in penetration enhancers
Biowaivers for products coded “AT” in FDA’s Orange Book

- Applies to very few topical formulations approved prior to 1962
- Underwent review by the Drug Efficacy Study Implementation (DESI) panels of experts
- Generic and RLD must contain same active ingredient and be of same dosage form
- Examples
  - Erythromycin topical gel
  - Hydrocortisone topical cream
Summary and conclusions

- FDA determines the optimal BE approach for each proposed generic topical formulation on a case-by-case basis

- Approach may be PK, PD, clinical, in vitro

- In determining the optimal BE approach for each product, FDA considers
  - Drug mechanism of action, site of action
  - Complexity of RLD formulation
  - Feasibility, sensitivity of an approach
References

  - Voltaren® gel, NDA 22122
  - Electronic Orange Book
  - Bioequivalence Recommendations Guidance for the diclofenac sodium topical gel, 1% strength
- [http://www.regulations.gov](http://www.regulations.gov)
  - Acyclovir ointment 5%, Docket No. FDA-2012-P-0779
  - Fluocinolone acetonide topical oil 0.01%, Docket No. FDA-2004-P-0215
  - Fluorouracil cream, Docket No. 2004P-0557/CP1
  - Lidocaine patch 5%, Docket No. FDA-2006-P-0356
  - 21 CFR Section 320.22 (biowaivers)
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Thank you for your attention!