Advances in Topical Bioequivalence Assessments: Characterization-Based Approaches

Topical Drug Development - Evolution of Science and Regulatory Policy II
Challenges in Topical Drug Development – Harnessing In Vitro Methods

University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI)
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Division of Therapeutic Performance, Office Research and Standards
Office of Generic Drugs
CDER | U.S. FDA
Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies.
The GAO Report (GAO-16-706)

- 57% of the topical drug products experienced an extraordinary price increase in that period
- The average price of topical generic drugs was 276% higher by the end of the period analyzed
- Manufacturers and other stakeholders reported that market competition, influenced by various factors, drives generic drug prices
The GAO Report (GAO-16-706)

Source: GAO analysis of Medicare Part D prescription drug event data. | GAO-16-706
# Retail Prices for Dermatologic Drugs

<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Altabax, 15 g</td>
<td>I</td>
<td>92.50</td>
<td>106.18</td>
<td>168.75</td>
</tr>
<tr>
<td>Benzaclin, 50 g</td>
<td>A</td>
<td>166.79</td>
<td>205.80</td>
<td>451.29</td>
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<tr>
<td>Carac cream, 30 g</td>
<td>N</td>
<td>159.40</td>
<td>227.16</td>
<td>2939.68</td>
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<tr>
<td>Clorex spray, 4 oz</td>
<td>S</td>
<td>389.57</td>
<td>500.29</td>
<td>827.11</td>
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<tr>
<td>Clofiderm, 30 g</td>
<td>S</td>
<td>96.47</td>
<td>132.92</td>
<td>220.75</td>
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<tr>
<td>Cultivate lotion 120 mL</td>
<td>S</td>
<td>305.00</td>
<td>493.92</td>
<td>918.63</td>
</tr>
<tr>
<td>Derma-Smoothe FS oil, 4 oz</td>
<td>S</td>
<td>45.70</td>
<td>47.23</td>
<td>247.84</td>
</tr>
<tr>
<td>Finacea, 50 g</td>
<td>A</td>
<td>124.42</td>
<td>185.42</td>
<td>288.92</td>
</tr>
<tr>
<td>Olux-E foam, 100 g</td>
<td>S</td>
<td>307.58</td>
<td>382.79</td>
<td>750.79</td>
</tr>
<tr>
<td>Oracea, 40 mg (30 tablets)</td>
<td>A</td>
<td>439.01</td>
<td>416.09</td>
<td>632.80</td>
</tr>
<tr>
<td>Oxsitet cream, 30 g</td>
<td>I</td>
<td>76.50</td>
<td>119.25</td>
<td>399.00</td>
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<tr>
<td>Oxsoralen-Ultra, 10 mg (50 capsules)</td>
<td>P</td>
<td>1227.32</td>
<td>2150.49</td>
<td>4568.54</td>
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<tr>
<td>Retin-A Micro, 0.1%, 50 g</td>
<td>A</td>
<td>178.05</td>
<td>353.73</td>
<td>791.47</td>
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<tr>
<td>Solaraze gel, 100 g</td>
<td>N</td>
<td>442.89</td>
<td>618.56</td>
<td>1738.91</td>
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<tr>
<td>Soritane, 25 mg (30 capsules)</td>
<td>P</td>
<td>757.75</td>
<td>958.50</td>
<td>1452.50</td>
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<tr>
<td>Taconex, 60 g</td>
<td>P</td>
<td>465.99</td>
<td>522.58</td>
<td>848.21</td>
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<tr>
<td>Targretin gel, one 60-g tube</td>
<td>N</td>
<td>1686.78</td>
<td>1787.97</td>
<td>15708.40</td>
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<tr>
<td>Tazorac cream, 0.1%, 60 g</td>
<td>A</td>
<td>266.18</td>
<td>464.96</td>
<td>656.20</td>
</tr>
<tr>
<td>Xolegel, 30 g</td>
<td>I</td>
<td>212.50</td>
<td>278.00</td>
<td>389.25</td>
</tr>
</tbody>
</table>

Abbreviations: A, acne and rosacea; I, antiinfective; N, antineoplastic; P, psoriasis; S, corticosteroid.

Patient Access to Topical Products

- Approximately 80% of topical dermatological drug products have fewer than three generic competitors; for many products no generics are available at all.
- This may have been attributable to the historical barriers to the development of topical dermatological drug products, possibly including:
  - Difficulty/issues with comparative clinical endpoint bioequivalence (BE) studies.
  - The complex nature of topical formulations.
Topical Dermatological Formulations

- The formulation of a topical product matters greatly.

- The components and composition modulate the physical and structural arrangement of matter.

- The resulting topical product characteristics can influence metamorphosis and bioavailability.
Topical Dermatological Formulations

• Components, composition, physical and structural properties of a topical product can influence:
  • The drug state(s) and phase(s) of the dosage form
  • The distribution of the drug in the dosage form
  • Drug diffusion within the dosage form
  • Drug partitioning from the dosage form into the skin barrier
  • The structure and chemistry of the skin barrier
  • Drug diffusion within the skin itself
  • Drug delivery and bioavailability at the target site
  • Skin (de)hydration, irritation, or damage
  • The metamorphosis of the dosage form on the skin
Failure Modes (BE) – Drug Substance

Is the Drug Substance **Dissolved** in the Formulation?

- Isomers of the drug
- pKa(s) of the drug
- pH of the formulation

Is the Drug Substance **Suspended** in the Formulation?

In addition to the potential failure modes identified on the left....

- Polymorphic forms of the drug
- Particle size distribution of the drug (and crystalline habit)
Failure Modes (BE) – Dosage Form

Is the Formulation a **Single Phase** System? *e.g., solution, gel*

- Excipient differences
- Viscosity/Rheology
- pH

Is the Formulation a **Multi Phase** System? *e.g., lotion, cream*

In addition to the potential failure modes identified on the left....

- Phases and arrangement of matter
- Distribution/localization of drug

Note: The packaging configuration itself may impact bioavailability
Mechanism and/or Site of Action

Is the Mechanism/Site of Action Well Understood?

- Acyclovir Topical Cream
- Benzyl Alcohol Topical Solution

An in vitro characterization based approach may be recommended

Is the Mechanism/Site of Action Not Well Understood?

- Dapsone Topical Gel
- Ivermectin Topical Cream

If the mechanism and/or site of action may be (partially) systemic, an in vivo PK study may also be recommended
Formulation of Topical Generics

- Sameness or *‘No Difference’* in the topical formulation **Q1** (components) and **Q2** (composition)

Mitigates the risk of failure modes related to:
- Irritation and sensitization
- Formulation interaction with diseased skin
- Stability, solubility, etc., of the drug
- Vehicle contribution to efficacy
Formulation of Topical Generics

• Q3 Similarity (Arrangement of Matter)

Mitigates the risk of failure modes related to differences in:
• Q1/Q2 sameness (± 5% tolerances)
• pH that may sting or irritate diseased skin
• Polymorphic form of the drug
• Rheology that alter the spreadability, retention, etc.
• Entrapped air and drug amount per dose
• Phase states and diffusion, partitioning, etc.
• Metamorphosis and drying rates
Q3 Sameness for Topical Products

- An evolving concept for topical dermatological products

Q3 Sameness
Same Components & Composition as the Reference Product ± 5%, and Same Physical & Structural Properties

Q2 Sameness
Same Components & Composition as the Reference Product ± 5%

Q1 Sameness
Same Components as the Reference Product

Generally allowing for variability within the range characterized for batches of the reference product

Potentially allowing for a difference in the nominal amount of a pH adjusting agent to match the reference product

Generally allowing for variations in an ingredient that comply with the relevant compendial standard

www.fda.gov
Evaluation of BE for Topical Products

• A Modular Framework for In Vitro BE Evaluation
  • Qualitative (Q1) and Quantitative (Q2) Sameness or ‘No Difference’
  • Physical and Structural (Q3) Sameness/Similarity
  • IVRT (In Vitro Release Test)
  • IVPT (In Vitro Permeation Test)

• Multiple Approaches for BE Evaluation
  • In Vivo Pharmacokinetic Studies
  • In Vivo Pharmacodynamic (Vasoconstrictor) Studies
  • In Vivo Comparative Clinical Endpoint BE Studies
  • In Silico Quantitative Methods, Modeling and Simulation
# Metronidazole, 0.75% In Vitro Data

## Quality Attributes

<table>
<thead>
<tr>
<th>Quality Attribute</th>
<th>Metrocream® (Fougera)</th>
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<tbody>
<tr>
<td>pH</td>
<td>4.8</td>
<td>5.1</td>
<td>5.2</td>
<td>5.0</td>
<td>5.4</td>
</tr>
<tr>
<td>Density (g/cc)</td>
<td>1.02</td>
<td>1.02</td>
<td>1.01</td>
<td>1.02</td>
<td>1.02</td>
</tr>
<tr>
<td>WOA (g/sec)</td>
<td>57.6</td>
<td>63.9</td>
<td>39.4</td>
<td>43.9</td>
<td>42.0</td>
</tr>
<tr>
<td>Particle size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(µm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug in Aq (mg/g)</td>
<td>4.20</td>
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<tr>
<td>Drug in Oil (mg/g)</td>
<td>2.58</td>
<td>3.94</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Solvent Activity</td>
<td>0.977</td>
<td>0.974</td>
<td>0.992</td>
<td>0.994</td>
<td>1.002</td>
</tr>
<tr>
<td>Globule size, d50 (µm)</td>
<td>2.8</td>
<td>2.2</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Drying, T30(min)</td>
<td>17</td>
<td>11.4</td>
<td>5.5</td>
<td>4.7</td>
<td>6.5</td>
</tr>
</tbody>
</table>

## Rheology

![Rheology Graph](https://via.placeholder.com/150)

- Yield Stress = 94 Pa
- Yield Stress = 70 Pa
- Yield Stress = 50 Pa
- Yield Stress = 49 Pa
- Yield Stress = 7 Pa

Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi)

FDA Award U01-FD005223

[www.fda.gov](http://www.fda.gov)
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<tr>
<td>Particle size (µm)</td>
<td>Active ingredient is completely dissolved</td>
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</table>

## In Vitro Permeation Test

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www.fda.gov
# Product Quality and Performance

**In Vitro Permeation Test (IVPT)**

<table>
<thead>
<tr>
<th>Product</th>
<th>USA</th>
<th>UK</th>
<th>Austria</th>
<th>Austria</th>
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<tbody>
<tr>
<td>Water</td>
<td>Water</td>
<td>Purified water</td>
<td>Water</td>
<td>Water</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>Propylene glycol</td>
<td>Propylene glycol</td>
<td>Propylene glycol</td>
<td>Propylene glycol</td>
</tr>
<tr>
<td>Mineral oil</td>
<td>Liquid Paraffin</td>
<td>Liquid Paraffin</td>
<td>Liquid Paraffin</td>
<td>Viscous Paraffin</td>
</tr>
<tr>
<td>White petrolatum</td>
<td>White soft paraffin</td>
<td>White Vaseline</td>
<td>White Vaseline</td>
<td>White Vaseline</td>
</tr>
<tr>
<td>Cetostearyl alcohol</td>
<td>Cetostearyl alcohol</td>
<td>Cetostearyl alcohol</td>
<td>Cetyl alcohol</td>
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</tbody>
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**Table Data**

<table>
<thead>
<tr>
<th>Donor</th>
<th>Poloxamer 407</th>
<th>Poloxamer 407</th>
<th>Poloxamer 407</th>
<th>Dimethicone 20</th>
<th>Dimethicone 20</th>
<th>Arlacel 165</th>
<th>Glyceryl Mono Stearate</th>
<th>Polyoxyethylene Stearate</th>
<th>Arlacel 165</th>
<th>Glyceryl Mono Stearate</th>
<th>Polyoxyethylene Stearate</th>
<th>Density (g/cc)</th>
<th>Content Uniformity (%)</th>
<th>Polymorphic Form</th>
<th>Crystalline Habit</th>
<th>Particle size (d50) (µm)</th>
<th>pH</th>
<th>Work of Adhesion</th>
<th>Drug in Aq (mg/g)</th>
<th>Drying Rate (T-30%)</th>
<th>Water Activity</th>
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<tr>
<td>1</td>
<td>1.02</td>
<td>1.02</td>
<td>1.02</td>
<td>97.9 ± 0.7</td>
<td>99.6 ± 1.4</td>
<td>100 ± 2.2</td>
<td>2,3 hydrate</td>
<td>2,3 hydrate</td>
<td>2,3 hydrate</td>
<td>2,3 hydrate</td>
<td>2,3 hydrate</td>
<td>3.8</td>
<td>97.9 ± 0.7</td>
<td>Rectangular</td>
<td>Rectangular</td>
<td>3.4</td>
<td>7.74</td>
<td>59</td>
<td>0.49</td>
<td>&gt;12h</td>
<td>0.75</td>
</tr>
<tr>
<td>2</td>
<td>1.02</td>
<td>1.02</td>
<td>1.02</td>
<td>99.7 ± 1.7</td>
<td>98.3 ± 2.6</td>
<td>1.02</td>
<td>2,3 hydrate</td>
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<td>2,3 hydrate</td>
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<tr>
<td>3</td>
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Product Quality and Performance

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Acyclovir

Metronidazole

Lidocaine

Prilocaine

Q3 Concept?

Q3 Concept?

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Q3 Concept?

Q3 Concept?

Not necessarily Q1 & Q2 the same

~

No significant impact on bioavailability
Q3 Sameness vs. Similarity

- **An evolving concept** for topical dermatological products

**Q3 Sameness**
- Same Components & Composition as the Reference Product ± 5%, and
- Same Physical & Structural Properties

**Q2 Sameness**
- Same Components & Composition as the Reference Product ± 5%

**Q1 Sameness**
- Same Components as the Reference Product

**Q3 Similarity**
- Similar Components & Composition to the Reference Product, and
- Similar Physical & Structural Properties

- No Difference in inactive ingredients or other aspects of the formulation relative to the reference product
- that may significantly affect local or systemic bioavailability (e.g., Q1/Q2 sameness, but not necessarily)
Alternative BE Approaches

• Certain BE approaches may **generally** be alternatives for topical dermatological drug products
  – In vitro (characterization-based) BE approach
  – In vivo (comparative clinical endpoint) BE approach

• Product-specific guidances may state:

> Applicants intending to propose an alternative approach by which to demonstrate bioequivalence should refer to the guidance for industry Controlled Correspondence Related to Generic Drug Development and the guidance for industry Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA for additional information describing the procedures on how to clarify regulatory expectations regarding your individual drug development program.
FDA Product-Specific Guidance (PSG)

- Product-Specific Guidances for Generic Drug Development (*Searchable*)
FDA Acyclovir Cream PSG

- Draft Guidance on Acyclovir (*Recommended Dec 2014; Revised Dec 2016*)
  
  [https://www.accessdata.fda.gov/drugsatfda_docs/psg/Acyclovir_topical%20cream_RLD%20201478_RV12-16.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/psg/Acyclovir_topical%20cream_RLD%20201478_RV12-16.pdf)

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**Draft Guidance on Acyclovir**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

- **Active Ingredient:** Acyclovir
- **Dosage Form; Route:** Cream; topical
- **Recommended Studies:** Two options: in vitro or in vivo study
Next Steps

• **Q3 Characterization**
  
  Developing compendial methods for Q3 characterization
  
  • What instrumentation to utilize (e.g., for polymorphs)
  
  • How many samples to analyze (e.g., number of particles)
  
  • How many replicates to use (e.g., rheological measurements)
  
  • How to report results (e.g., viscosity at low/mid/high shear)
  
  • Other considerations
Next Steps

• **IVRT Studies**
  
  Improving general understanding of IVRT principles and practices
  • Pseudo-infinite dose kinetics
  • Steady state release rate for a suitably sustained duration
  • Appropriate linearity of steady state region
  • Misconceptions surrounding a dose depletion exceeding 30%
  • Issues related to specific apparatus and/or metamorphosis
  • Issues related to studies with certain synthetic membranes
Next Steps

• **IVPT Studies**
  Improving general understanding of IVPT principles and practices
  • Finite dose kinetics, dose depletion, and metamorphosis
  • Diffusion cell apparatus and sampling of the receptor solution
  • Considerations relating to skin type, preparation, and storage
  • Barrier integrity assumptions, testing, and acceptance criteria
  • Study designs and data analyses (appropriate to context of use)
    • Dose duration vs. study duration; number of donors vs. replicates
    • Questions/Issues related to “outlier” or aberrant data
Future Research & Discussion

• Further develop standard (compendial) test methods for:
  – Q3 Characterization

• Enhance the overall level of investigator experience with principles and technical considerations for:
  – IVRT Studies

• Evolve/Establish best practices, study designs, qualified apparatus, and compendial methods for:
  – IVPT Studies
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