Bioequivalence of Topical Products: Scientific Considerations

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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)

• The U.S. Government Accountability Office (GAO) Report in Aug 2016 analyzed a period spanning Q1 of 2010 through Q2 of 2015

• **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>
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</tr>
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<tbody>
<tr>
<td>Altabax, 15 g</td>
<td>I</td>
<td>92.50</td>
<td>106.18</td>
<td>168.75</td>
<td>196.86</td>
<td>104.36</td>
<td>112.82</td>
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<tr>
<td>Benzaclin, 50 g</td>
<td>A</td>
<td>166.79</td>
<td>205.80</td>
<td>451.29</td>
<td>503.85</td>
<td>337.06</td>
<td>202.08</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>
<td>2864.70</td>
<td>2705.30</td>
<td>1697.18</td>
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<tr>
<td>Clobex spray, 4 oz</td>
<td>S</td>
<td>389.57</td>
<td>500.29</td>
<td>827.11</td>
<td>958.01</td>
<td>568.44</td>
<td>145.91</td>
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<tr>
<td>Clofem cream, 30 g</td>
<td>S</td>
<td>96.47</td>
<td>132.92</td>
<td>220.75</td>
<td>360.02</td>
<td>263.55</td>
<td>273.19</td>
</tr>
<tr>
<td>Cultivate lotion 120 mL</td>
<td>S</td>
<td>305.00</td>
<td>493.92</td>
<td>918.63</td>
<td>1067.25</td>
<td>762.25</td>
<td>249.91</td>
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<tr>
<td>Derma-Smoothe FS oil, 4 oz</td>
<td>S</td>
<td>45.70</td>
<td>47.23</td>
<td>247.84</td>
<td>322.67</td>
<td>276.97</td>
<td>606.06</td>
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<tr>
<td>Finacea, 50 g</td>
<td>A</td>
<td>124.42</td>
<td>185.42</td>
<td>288.92</td>
<td>284.30</td>
<td>159.88</td>
<td>128.51</td>
</tr>
<tr>
<td>Ole-E foam, 100 g</td>
<td>S</td>
<td>307.58</td>
<td>382.79</td>
<td>750.79</td>
<td>841.76</td>
<td>534.18</td>
<td>173.67</td>
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<tr>
<td>Oracea, 40 mg (30 tablets)</td>
<td>A</td>
<td>439.01</td>
<td>416.09</td>
<td>632.80</td>
<td>702.46</td>
<td>263.45</td>
<td>60.01</td>
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<tr>
<td>Oxistat cream, 30 g</td>
<td>I</td>
<td>76.50</td>
<td>119.25</td>
<td>399.00</td>
<td>544.66</td>
<td>468.16</td>
<td>611.97</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>
<td>5204.31</td>
<td>3976.99</td>
<td>324.04</td>
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<tr>
<td>Retin-A Micro, 0.1%, 50 g</td>
<td>A</td>
<td>178.05</td>
<td>335.73</td>
<td>791.47</td>
<td>914.52</td>
<td>736.47</td>
<td>413.64</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>
<td>1883.98</td>
<td>1441.09</td>
<td>325.38</td>
</tr>
<tr>
<td>Soriatane, 25 mg (30 capsules)</td>
<td>P</td>
<td>757.75</td>
<td>958.50</td>
<td>1452.50</td>
<td>1595.27</td>
<td>837.52</td>
<td>110.53</td>
</tr>
<tr>
<td>Tazoroc cream, 60 g</td>
<td>P</td>
<td>465.99</td>
<td>522.58</td>
<td>848.21</td>
<td>962.90</td>
<td>496.91</td>
<td>106.64</td>
</tr>
<tr>
<td>Targretin gel, one 60-g tube</td>
<td>N</td>
<td>1686.78</td>
<td>1787.97</td>
<td>15708.40</td>
<td>30320.12</td>
<td>28633.34</td>
<td>1697.51</td>
</tr>
<tr>
<td>Tazoroc cream, 0.1%, 60 g</td>
<td>A</td>
<td>266.18</td>
<td>464.96</td>
<td>656.20</td>
<td>722.27</td>
<td>456.09</td>
<td>171.34</td>
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<tr>
<td>Xolegel, 30 g</td>
<td>I</td>
<td>212.50</td>
<td>278.00</td>
<td>389.25</td>
<td>641.96</td>
<td>429.46</td>
<td>202.10</td>
</tr>
</tbody>
</table>

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


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Patient Access to Topical Products

• The vast majority (approximately 80%) of topical dermatological drug products have fewer than three generic competitors, and in many cases, have no approved generics at all. This may have been attributable to the historical barriers to the development of topical dermatological drug products, possibly including
  • Comparative clinical endpoint bioequivalence (BE) studies
  • The complex nature of topical formulations
  • The relatively small market capitalization for some products
Available (and Affordable) Products

• Power of “efficient” BE standards

Overall Drug Products
• In 2017, 9 out of every 10 prescriptions in the U.S. were dispensed using generic drugs.
• Efficient Pharmacokinetics (PK)-based methods available

Topical Drug Products
Most topical products have few or no generics available
• Efficient Local and Systemic PK-based methods may be useful
• Efficient In Vitro BE standards may be useful
• Efficient BE approaches supported by a collective weight of evidence from in silico, in vitro and/or in vivo studies?

1 AAM 2018 Generic Drug Access & Savings in the United States Report
Developing Rational BE Standards

• As the complexity of a formulation, dosage form, drug product, route of administration, site of action and/or the mechanism of action increases so do the potential failure modes for bioequivalence and therapeutic equivalence

• With a sufficient product and process understanding, relevant complexities can be identified and addressed systematically for the generic drug product
Developing Rational BE Standards

- **A Modular and Scalable Approach to BE Evaluation**
  - Q1/Q2 sameness of inactive ingredient components and quantitative composition
  - Q3 (Physical & Structural Characterization) as relevant to the nature of the product
  - IVRT (In Vitro Release Test) for moderately complex products
  - IVPT (In Vitro Permeation Test) or another bio-relevant assay for more complex drug products
  - In Vivo systemic PK studies may be appropriate
  - In Silico computational modeling may be useful
Developing Rational BE Standards

- **Other Methodologies of Interest**
  - **In Vivo** Cutaneous PK Studies
    - ✔ Dermal Open Flow Microperfusion (dOFM)
    - ✔ Dermal Microdialysis (dMD)
    - ✔ Epidermal and/or Dermal Pharmacokinetic Tomography

- **Other Methodologies *Not of Interest***
  - **In Vivo** Cutaneous PK Studies
    - ✔ Tapestripping “Dermatopharmacokinetics” (DPK)
Product Quality and Performance

In Vitro Permeation Test (IVPT)
6 Donors each with 6 Replicate Skin Sections

<table>
<thead>
<tr>
<th>Product</th>
<th>Zovirax (USA)</th>
<th>Zovirax (UK)</th>
<th>Zovirax (Austria)</th>
<th>Aciclostad (Austria)</th>
<th>Aciclovir-1A (Austria)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>Water</td>
<td>Purified water</td>
<td>Water</td>
<td>Water</td>
<td>Water</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>Propylene glycol</td>
<td>Propylene glycol</td>
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<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>
<td></td>
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<tr>
<td>White petrolatum</td>
<td>White soft paraffin</td>
<td>White Vaseline</td>
<td>White Vaseline</td>
<td></td>
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<tr>
<td>Cetostearyl alcohol</td>
<td>Cetostearyl alcohol</td>
<td>Cetyl alcohol</td>
<td>Cetyl alcohol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLS</td>
<td>SLS</td>
<td>SLS</td>
<td></td>
<td></td>
<td></td>
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<table>
<thead>
<tr>
<th>Poloxamer 407</th>
<th>Poloxamer 407</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Dimethicone 20</td>
<td>Dimethicone 20</td>
<td>Dimethicone</td>
</tr>
<tr>
<td>Glycerin Mono Stearate</td>
<td>Glycerin Mono Stearate</td>
<td>Glycerin Mono Stearate</td>
</tr>
<tr>
<td>Arelac 165</td>
<td>Polyoxethylene stearate</td>
<td>Polyoxethylene stearate</td>
</tr>
</tbody>
</table>

Thixotropic Rheology

In Vitro Release Test (IVRT)

Data provided courtesy of Prof. Narasimha Murthy & Dr. Frank Sinner
Enhancing the Availability of Generics

• The *Proposed* Topical Classification System (TCS)\(^2,^3\)
  • Modeled on the Biopharmaceutics Classification System (BCS)
  • By the TCS scheme, topical formulations that pass an in vitro release test (IVRT) would be eligible for a biowaiver
  • It may be an *efficient* way to develop topical generics, and it has generated some interest in the field, so let’s explore it…

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The TCS Proposed by Shah et al.

Scientific Issue: TCS suggests that IVRT ≈ Q3

- “Based on composition and IVR similarity, the compared dosage forms are classified as TCS class 1, 2, 3 and 4. ...TCS class 1 and TCS class 3 dosage forms are eligible for biowaiver”

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Figure Source: Shah, VP et al. Int J Pharmaceut 509 (2016) 35–40
The Arrangement of Matter (Q3)

- Physicochemical & Structural Properties Affect:
  - 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 SC
  - Alteration of skin structure and chemistry
  - Drug diffusion within the skin itself
  - Drug delivery & bioavailability at the target site
  - Skin (de)hydration, irritation or damage
  - Metamorphosis of the dosage form on the skin
Tests of the Arrangement of Matter

• Quality Tests to Study the Arrangement of Matter
  • Microscopic Analyses of Microstructure (e.g., Globules)
  • Dissolved vs. Undissolved Amounts of the Drug
  • Concentration of Drug in the Continuous Phase
  • Size Distribution of Globules/Particles
  • Drug Polymorphic State (Raman, XRD, etc.)
  • Solvent/Water Activity (Drying Rate)
  • Density
  • pH
  • Etc.

• The tests themselves are not the arrangement of matter
• No single test characterizes all the arrangement matter
• The collective results from all the tests help us to infer various details about the underlying arrangement of matter
The Proposed TCS

Scientific Issue: TCS suggests that IVRT ≈ Q3

- “Based on composition and IVR similarity, the compared dosage forms are classified as TCS class 1, 2, 3 and 4. ...TCS class 1 and TCS class 3 dosage forms are eligible for biowaiver”

- “The proposed topical drug classification system is based on qualitative and quantitative equivalence of composition (Q1 and Q2) and on the similarity of IVR rates (as estimator of microstructural sameness, Q3) between two compared formulations, a generic product and RLD.”

- “If the product is Q1 and Q2, and if it meets IVR (Q3) comparison criteria and confidence intervals identified in SUPAC-SS, a biowaiver can be provided”

- “The IVR (Q3) reflects the microstructure, arrangement of the matter and the state of aggregation of the dosage form.”

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IVRT *Can* Discriminate Some Things

- IVRT *did discriminate* 8 formulations made with Petrolatum, USP from different sources

![Bar chart showing rate of release for different formulations](chart.png)

Data provided courtesy of Paul A. Lehman and Dr. Thomas J. Franz
**IVRT Cannot Discriminate Some Things**

- **IVRT did not discriminate** 14 formulations with substantial variations in particle size

IVRT Release Rate is not Biorelevant

- As long as IVRT indicates that the drug release rate is the same, isn’t that all that matters?

The release rate measured by an IVRT is **arbitrary**

- It can be modulated by IVRT method parameters like the choice of receptor solution or membrane.
IVRT Release Rate is not Biorelevant

The ‘release rate’ in an IVRT is **not biorelevant**

- IVRT pseudo-infinite, occluded dose *artificially* provides a steady-state release rate.
- This is not representative of the drug release kinetics from a finite dose (thin film) of an un-occluded topical product that dries on the skin.

![Graph showing cumulative penetration and flux over time for different formulations.](image)
Tests of the Arrangement of Matter

- **Performance** Tests to Study the Arrangement of Matter
  - The IVRT (United States Pharmacopeia <1724>) and other tests

- The arrangement of matter, taken all together, defines the rheology, drying rate, release rate (IVRT), etc.
- But, the converse cannot be assumed
- No single test describes all the arrangement of matter
- IVRT does not describe all the arrangement of matter

www.fda.gov
The *Proposed TCS*

**Scientific Issues:**

- **IVRT Equivalence ≠ Q3 Similarity**
  - Scientifically wrong to assume that IVRT ≈ Q3
  - IVRT alone *cannot* assure Q3 similarity

- **IVRT Equivalence ≠ Similar Bioavailability**

- Putting IVRT aside for a moment, are the failure modes for bioequivalence adequately mitigated by Q1 and Q2 sameness?
Differences with Q1/Q2 Creams

• Solvent Activity of Q1/Q2 Identical Creams

Prof. Narasimha Murthy  FDA Award U01-FD005223

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Quantity (%w/w)</th>
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<tbody>
<tr>
<td>Cetostearyl Alcohol</td>
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</tr>
<tr>
<td>White Wax</td>
<td>12</td>
</tr>
<tr>
<td>Mineral Oil</td>
<td>56</td>
</tr>
<tr>
<td>Sodium Borate</td>
<td>0.5</td>
</tr>
<tr>
<td>Water</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
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<table>
<thead>
<tr>
<th>Manufacturing Conditions</th>
<th>Solvent Activity ($a_w$)</th>
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<tbody>
<tr>
<td>3500 RPM (15 min)</td>
<td>0.931 ± 0.002</td>
</tr>
<tr>
<td>7000 RPM (45 min)</td>
<td>0.875 ± 0.006</td>
</tr>
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</table>

Data provided courtesy of Prof. Narasimha Murthy
The *Proposed TCS*

**TCS Class 1: for a “biowaiver”**
- Q1 and Q2 Sameness
- IVRT Equivalence

**Scientific Issue:**
- Failure modes for bioequivalence are not necessarily mitigated by Q1 and Q2 sameness alone, and the addition of IVRT still may not ensure bioequivalence because the IVRT cannot ensure similar Q3, obscures metamorphosis, and cannot ensure similar bioavailability.
The *Proposed TCS*

- **TCS Class 3: for a “biowaiver”**
  - Q1 and/or Q2 Difference*
  - IVRT Equivalence

* “…essential to evaluate the properties of the excipients with respect to safety and efficacy, as well as how excipients affect both the thermodynamic activity of the active pharmaceutical ingredient and the skin permeability. ...If the excipients are inert and IVR turns out to be the same ...then the dosage form can be provided with a biowaiver”*  

**Scientific Issue:**

- The (placebo) vehicle often contributes to efficacy
- It is unclear what evidence would establish that the “excipients are inert”

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The *Proposed TCS*

- **TCS Class 2**: for a bioequivalence study
  - Q1 and Q2 Sameness
  - IVRT *Difference*

- **TCS Class 4**: for a bioequivalence study
  - Q1 and Q2 *Difference*
  - IVRT *Difference*

**Scientific Issues:**

- It is unclear what bioequivalence studies would be involved, and whether they would be *efficient*
Conclusions (What To Do)

• Developers of complex topical dermatological drug products can ensure that the products are of high quality and can bring greater predictability and timeliness to the review of generic drug applications by
  • Demonstrating a comprehensive understanding of the product complexities and manufacturing issues
  • Providing information that mitigates risks of potential failure modes for therapeutic equivalence
  • Initiating pre-ANDA communication with the FDA during product and program development, if necessary

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