A Generic Perspective on the Use of In Vitro Assessment Methods

Bridging Results from Maximum Use Trials with Sunscreen Reformulations

Topical Drug Development
Evolution of Science and Regulatory Policy
July 30th, 2019
University of Maryland School of Pharmacy, Baltimore, MD

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U.S. Food and Drug Administration, Office of Generic Drugs
Office of Research and Standards, Division of Therapeutic Performance
Disclaimer

• This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies.
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
Developing Rational BE Standards

• **A Modular Framework for In Vitro 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

• **A Scalable Framework for BE Evaluation**
  - **In Vivo** pharmacokinetic (PK) studies may be appropriate
  - **In Silico** computational modeling may be useful
Developing In Vitro BE Standards

• **Q1/Q2 Sameness** (components and composition of excipients)
  Mitigates the risk of known failure modes related to:
  • Irritation and sensitization
  • Formulation interaction with diseased skin
  • Stability, solubility, etc. of the drug
  • Vehicle contribution to efficacy
Formulations Can Alter Bioavailability

• It is widely understood that the formulation of a topical semisolid dosage form matters greatly.
• It is now increasingly clear how excipients exert their influence, by modulating the physicochemical and microstructural arrangement of matter in the dosage form.
• The resulting physical and structural characteristics of topical dosage forms, and their metamorphic properties on the skin, can directly influence topical bioavailability.
Developing In Vitro BE Standards

• **Q3 (Physical and Structural) Similarity**

  An evolving regulatory concept:

  - **Q1 Sameness**
    - Same Components as the RLD Product
  - **Q2 Sameness**
    - Same Components & Composition as the RLD Product ± 5%
  - **Q3 Similarity**
    - Same Components & Composition as the RLD Product ± 5%, and Similar Physical & Structural Properties
Effects of Q1/Q2/Q3 on Bioavailability

- Q1, Q2 or Q3 differences can affect:
  - The phase states and the arrangement of matter
  - Drug diffusion within the dosage form
  - Drug partitioning into the stratum corneum (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
  - Thermodynamic activity profile of the drug
    - Thermodynamic effects and heat effects are areas of active research for topical semisolid products and transdermal delivery systems
Developing In Vitro BE Standards

• **Q3 (Physical and Structural) Similarity**

  Mitigates the risk of potential failure modes related to:
  • Differences in Q1/Q2 sameness (± 5% tolerances)
  • Differences in pH that may sting or irritate diseased skin
  • Differences in the polymorphic form of the drug
  • Differences in rheology that alter the spreadability, retention, or surface area of contact with the diseased skin
  • Differences in entrapped air and drug amount per dose
  • Differences in phase states and diffusion, partitioning, etc.
  • Differences in metamorphosis and drying rates
Dosage Form Metamorphosis

- Solvent Activity of Q1/Q2 Identical Creams

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Quantity (%w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetostearyl Alcohol</td>
<td>12.5</td>
</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>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Manufacturing Conditions</th>
<th>Solvent Activity ($a_w$)</th>
</tr>
</thead>
<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>
</tbody>
</table>

Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi)  
FDA Award U01-FD005223
Dosage Form Metamorphosis

• Solvent Activity \( (a_s) = \frac{\rho}{\rho_0} \)
  - \( \rho \) = partial vapor pressure of Solvents in the product
  - \( \rho_0 \) = vapor pressure of pure Solvent system

Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) FDA Award U01-FD005223
Developing In Vitro BE Standards

• **IVPT (In Vitro Permeation Test): Cutaneous PK Study**
  Mitigates the risk of other unknown failure modes related to:
  • Differences in Q1 and/or Q2
  • Differences in physical and structural similarity
  • Differences that may not be identified by other tests
• IVPT is a sensitive, discriminating indicator of relative BA
• IVPT results can exhibit in vitro in vivo correlation (IVIVC)
• IVPT studies can compare the relative bioavailability of sunscreen actives (or other components of interest) between a test and reference formulation
IVPT Study Design

Donor 1  Donor 2  Donor 3  Donor 4  Donor 5  Donor n...

Test
Reference

Skin
Membrane

Heater/
Circulator

Water Jacket

Sampling Port

Receptor
Chamber

Stirbar

Benzoic acid in Petrolatum

In Vitro Rate of Absorption

In Vivo Rate of Excretion

Source: Bronaugh and Franz (1986)
IVPT: *In Vitro In Vivo* Correlation

- Lehman et al., 2011 (92 IVIVC Data Sets)

*Fig. 1.* IVIV ratios of total absorption for all 92 data sets plotted on log-log scale. The IVIV ratios ranged from 0.18 to 19.7, with an overall mean of 1.6. Solid line: ideal 1:1 correlation. Dashed lines: ±3-fold difference from ideal.
IVPT: *In Vitro In Vivo* Correlation

- Lehman et al., 2011 (92 IVIVC Data Sets)

**Fig. 2.** IVIV ratios of total absorption for 11 fully harmonized data sets plotted on log-log scale. The IVIV ratios ranged from 0.58 to 1.28, with an overall mean of 0.96. Line: ideal 1:1 correlation.
IVPT: *In Vitro In Vivo* Correlation

- Shaw et al., 1975

“... *in vitro* accurately predicted the situation which pertains *in vivo*.”
IVPT: *In Vitro In Vivo* Correlation

- Venkateshwaran S, 1997
Nicotine TDS* Heat Effects Studies

* TDS = Transdermal Delivery System

<table>
<thead>
<tr>
<th>Nicotine TDDS 14 mg/24h</th>
<th>Patch size (cm²)</th>
<th>Rate/Area (µg/h/cm²)</th>
<th>Adhesive type</th>
<th>Other inactive ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicoderm CQ®</td>
<td>15.75</td>
<td>37</td>
<td>Polyisobutylene</td>
<td>Ethylene vinyl acetate-copolymer, polyethylene between pigmented and clear polyester backing</td>
</tr>
<tr>
<td>Aveva</td>
<td>20</td>
<td>29</td>
<td>Polyacrylate/Silicone</td>
<td>Polyester backing</td>
</tr>
</tbody>
</table>

Data provided courtesy of Prof. Audra Stinchcomb (University of Maryland) FDA Award U01-FD004955
Level A IVIVC/IVIVR for Nicotine TDS

• Approach I (prediction based upon in vitro data only)

Refer to Shin et al. (2018) In vitro-in vivo correlations for nicotine transdermal delivery systems evaluated by both in vitro skin permeation (IVPT) and in vivo serum pharmacokinetics under the influence of transient heat application. J Control Release. 270: 76-88. (Funded, in part, through FDA award U01FD004955 (Dr. Audra Stinchcomb; University of Maryland, Baltimore) and FDA award U01FD004942 (Dr. Kevin Li; University of Cincinnati))

• Approach II (including an in vivo-derived heat factor)
Refer to Shin et al. (2018) In vitro-in vivo correlations for nicotine transdermal delivery systems evaluated by both in vitro skin permeation (IVPT) and in vivo serum pharmacokinetics under the influence of transient heat application. J Control Release. 270: 76-88. (Funded, in part, through FDA award U01FD004955 (Dr. Audra Stinchcomb; University of Maryland, Baltimore) and FDA award U01FD004942 (Dr. Kevin Li; University of Cincinnati))
Comprehensive Research Strategy

• **Q3 Product Quality Characterization**
  - FDA/CDER/OTS/DPQR (USA)
  - University of Mississippi (USA)
  - University of South Australia (and Germany)

• **In Vitro Release Test (IVRT)**
  - FDA/CDER/OTS/DPQR (USA)
  - Joanneum Research (Austria)

• **Cutaneous PK: In Vitro Permeation Test (IVPT)**
  - University of Mississippi (USA)
  - University of Maryland (USA)
  - University of South Australia

• **Cutaneous PK: In Vivo Methods**
  - Joanneum Research (Austria)  dermal Open Flow Microperfusion (dOFM)
  - University of Maryland/Bath (USA/UK)  Tape Stripping
Coordinated Research Strategy

- Pharmaceutically Equivalent Acyclovir 5% Creams
- **Positive** and **Negative** Controls for BE

<table>
<thead>
<tr>
<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>
</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>
<td>Cetyl alcohol</td>
</tr>
<tr>
<td>SLS</td>
<td>SLS</td>
<td>SLS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poloxamer 407</td>
<td>Poloxamer 407</td>
<td>Poloxamer 407</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimethicone 20</td>
<td>Dimethicone 20</td>
<td>Dimethicone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arlacel 165</td>
<td>Glyceryl Mono stearate</td>
<td>Glyceryl Mono stearate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arlacel 165</td>
<td>Polyoxyethylene stearate</td>
<td>Macrogol stearate</td>
<td></td>
<td>Polyoxyethylene stearate</td>
</tr>
</tbody>
</table>
Dosage Form Metamorphosis

- Solvent Activity and Drying Rate

Prof. Narasimha Murthy  FDA Award U01-FD005223

Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi)  FDA Award U01-FD005223
Product Quality and Performance

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

<table>
<thead>
<tr>
<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>
</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>
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<tr>
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<td>White Vaseline</td>
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<td>Cetostearyl alcohol</td>
<td>Cetyl alcohol</td>
<td>Cetyl alcohol</td>
</tr>
<tr>
<td>SLS</td>
<td>SLS</td>
<td>SLS</td>
<td>Dimethicone</td>
<td>Dimethicone</td>
</tr>
<tr>
<td>Poloxamer 407</td>
<td>Poloxamer 407</td>
<td>Poloxamer 407</td>
<td>Dimethicone 20</td>
<td>Dimethicone 20</td>
</tr>
<tr>
<td>Arlacel 165</td>
<td>Dimethicone 20</td>
<td>Dimethicone</td>
<td>Glycerol Mono Stearate</td>
<td>Glycerol Mono Stearate</td>
</tr>
<tr>
<td>Arlacel 165</td>
<td>Glycerol Mono Stearate</td>
<td>Glycerol Mono Stearate</td>
<td>Glycerol Mono Stearate</td>
<td>Glycerol Mono Stearate</td>
</tr>
<tr>
<td></td>
<td>Polyoxyethylene stearate</td>
<td>Macrogol stearate</td>
<td>Polyoxyethylene stearate</td>
<td>Polyoxyethylene stearate</td>
</tr>
</tbody>
</table>

- **Density (g/cc):**
  - Zovirax (USA): 1.02
  - Zovirax (UK): 1.02
  - Zovirax (Austria): 1.02
  - Aciclostad (Austria): 1.02
  - Aciclovir-1A (Austria): 1.01
- **Content Uniformity (%):**
  - Zovirax (USA): 97.9 ± 0.7
  - Zovirax (UK): 99.6 ± 1.4
  - Zovirax (Austria): 100 ± 2.2
  - Aciclostad (Austria): 99.7 ± 1.7
  - Aciclovir-1A (Austria): 98.3 ± 2.6
- **Polymorphic Form:**
  - Zovirax (USA): 2,3 hydrate
  - Zovirax (UK): 2,3 hydrate
  - Zovirax (Austria): 2,3 hydrate
  - Aciclostad (Austria): 2,3 hydrate
  - Aciclovir-1A (Austria): 2,3 hydrate
- **Crystalline Habit:**
  - Zovirax (USA): Rectangular
  - Zovirax (UK): Rectangular
  - Zovirax (Austria): Rectangular
  - Aciclostad (Austria): Ovoid
  - Aciclovir-1A (Austria): Ovoid
- **Particle size (d50) (µm):**
  - Zovirax (USA): 3.8
  - Zovirax (UK): 2.5
  - Zovirax (Austria): 3.4
  - Aciclostad (Austria): 6.8
  - Aciclovir-1A (Austria): 6
- **pH:**
  - Zovirax (USA): 7.74
  - Zovirax (UK): 7.96
  - Zovirax (Austria): 7.54
  - Aciclostad (Austria): 4.58
  - Aciclovir-1A (Austria): 6.05
- **Work of Adhesion:**
  - Zovirax (USA): 59
  - Zovirax (UK): 81
  - Zovirax (Austria): 60
  - Aciclostad (Austria): 17
  - Aciclovir-1A (Austria): 18
- **Drug in Aq (mg/g):**
  - Zovirax (USA): 0.49
  - Zovirax (UK): 0.64
  - Zovirax (Austria): 0.49
  - Aciclostad (Austria): 0.37
  - Aciclovir-1A (Austria): 0.26
- **Drying Rate (T-30%):**
  - Zovirax (USA): >12h ~8h
  - Zovirax (UK): ~7h <1h
  - Zovirax (Austria): <1h
  - Aciclostad (Austria): <1h
  - Aciclovir-1A (Austria): <1h
- **Water Activity:**
  - Zovirax (USA): 0.75
  - Zovirax (UK): 0.73
  - Zovirax (Austria): 0.74
  - Aciclostad (Austria): 0.95
  - Aciclovir-1A (Austria): 0.95

Thixotropic Rheology

In Vitro Release Test (IVRT)

Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) **FDA Award U01-FD005223** and Dr. Frank Sinner (Joanneum Research **FDA Award U01-FD004946**
# Product Quality and Performance

Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) [FDA Award U01-FD005223](https://www.fda.gov)

<table>
<thead>
<tr>
<th>Quality Attribute</th>
<th>Metrocream®</th>
<th>Generic Cream (Fougera)</th>
<th>Metrogel®</th>
<th>Generic Gel (Tolmar)</th>
<th>Generic Gel (Taro)</th>
</tr>
</thead>
<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 (μm)</td>
<td></td>
<td></td>
<td>Active ingredient is completely dissolved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug in Aq (mg/g)</td>
<td>4.20</td>
<td>2.92</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<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>

![Graph showing metronidazole flux over time](image1.png)

![Graph showing stress-strain relationship](image2.png)

Dose 10 mg/cm²

![Graph showing product remaining over time](image3.png)
IVPT Results for Different Products

Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) FDA Award U01-FD005223
IVPT Results: Acyclovir Cream, 5%

- Cutaneous Pharmacokinetics by IVPT

Negative Controls for Bioequivalence

<table>
<thead>
<tr>
<th>University of Mississippi</th>
<th>University of Maryland</th>
<th>University of South Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>15 mg/cm²</td>
<td></td>
</tr>
<tr>
<td>Dosing technique</td>
<td>Dispensed-Spatula</td>
<td>Dispensed and dispersed- Positive displacement pipette</td>
</tr>
<tr>
<td></td>
<td>Dispensed-glass rod</td>
<td>Dispensed- Pipette</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dispersed- Syringe plunger</td>
</tr>
<tr>
<td>Skin type</td>
<td>Torso</td>
<td>Abdomen</td>
</tr>
<tr>
<td></td>
<td>Dermatomed</td>
<td>Dermatomed</td>
</tr>
<tr>
<td></td>
<td>Heat separated epidermis</td>
<td></td>
</tr>
<tr>
<td>Instrument</td>
<td>Franz diffusion cell (2 cm²)</td>
<td>In-Line Flow through cell (0.95 cm²)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Franz diffusion cell (1.3 cm²)</td>
</tr>
<tr>
<td>Skin Integrity</td>
<td>Electrical Resistance</td>
<td>Trans Epidermal Water Loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Electrical resistance</td>
</tr>
</tbody>
</table>

Data provided courtesy of
Prof. Narasimha Murthy (University of Mississippi) **FDA Award U01-FD005223**,
Prof. Audra Stinchcomb (University of Maryland) **FDA Award U01-FD004947**, and
Prof. Michael Roberts (University of South Australia) **FDA Award U01-FD005226**
Influence of Quality on Performance

• Influence of Dose Application on Bioavailability

![Graph showing flux vs. time for U.S. and U.K. Zovirax](chart.png)

Data provided courtesy of Prof. Audra Stinchcomb (University of Maryland) FDA Award U01-FD004947
Influence of Quality on Performance

• Influence of Dose Dispensing on Bioavailability

Data provided courtesy of
Prof. Narasimha Murthy (University of Mississippi) FDA Award U01-FD005223,
Prof. Audra Stinchcomb (University of Maryland) FDA Award U01-FD004947, and
Prof. Michael Roberts (University of South Australia) FDA Award U01-FD005226
Influence of Dispensing Stress on Q3

• Influence of Dose Dispensing on Product Quality

Prof. Michael Roberts FDA Award U01-FD005226

Data provided courtesy of Prof. Michael Roberts (University of South Australia) FDA Award U01-FD005226
Influence of Dispensing Stress on Q3

- Influence of Dose Dispensing on Product Quality

Prof. Michael Roberts  FDA Award U01-FD005226

Comparison Zovirax UK pump and tube
**IVPT Statistical Analysis**

- **Negative Controls** for BE: Aciclovir-1A® vs. Zovirax® US

<table>
<thead>
<tr>
<th>Aciclovir-1A® (T) vs. Zovirax® US (R)</th>
<th>PK Endpoint</th>
<th>Maximum Flux ((J_{\text{max}}))</th>
<th>Total Bioavailability ((AUC))</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVPT</td>
<td>Point Estimate</td>
<td>0.172</td>
<td>0.104</td>
</tr>
<tr>
<td></td>
<td>S Within Reference</td>
<td>0.521</td>
<td>0.551</td>
</tr>
<tr>
<td></td>
<td>SABE [0.80, 1.25]</td>
<td>4.433 (Non-BE)</td>
<td>7.236 (Non-BE)</td>
</tr>
<tr>
<td></td>
<td>N for [0.80, 1.25] with 3 Replicates</td>
<td>6</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aciclovir-1A® (T) vs. Zovirax® US (R)</th>
<th>PK Endpoint</th>
<th>Maximum Flux ((J_{\text{max}}))</th>
<th>Total Bioavailability ((AUC))</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVPT</td>
<td>Point Estimate</td>
<td>0.290</td>
<td>0.366</td>
</tr>
<tr>
<td></td>
<td>S Within Reference</td>
<td>0.575</td>
<td>0.419</td>
</tr>
<tr>
<td></td>
<td>SABE [0.80, 1.25]</td>
<td>2.383 (Non-BE)</td>
<td>1.884 (Non-BE)</td>
</tr>
<tr>
<td></td>
<td>N for [0.80, 1.25] with 6 Replicates</td>
<td>8</td>
<td>20</td>
</tr>
</tbody>
</table>

Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) FDA Award U01-FD005223, and Prof. Michael Roberts (University of South Australia) FDA Award U01-FD005226
**IVPT Statistical Analysis**

- **Positive Controls** for BE: Aciclovir-1A® and Zovirax® US

### Comparison to Self by dividing up 6 replicates

#### Aciclovir-1A® (T) vs. Aciclovir-1A® (R)

<table>
<thead>
<tr>
<th>IVPT PK Endpoint</th>
<th>Maximum Flux (Jmax)</th>
<th>Total Bioavailability (AUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Point Estimate</td>
<td>0.983</td>
<td>0.958</td>
</tr>
<tr>
<td>$S$ Within Reference</td>
<td>0.303</td>
<td>0.318</td>
</tr>
<tr>
<td>SABE [0.80, 1.25]</td>
<td>-0.026 (BE)</td>
<td>-0.041 (BE)</td>
</tr>
<tr>
<td>N for [0.80, 1.25] with 4 Replicates</td>
<td>26+</td>
<td>15</td>
</tr>
<tr>
<td>N for [0.80, 1.25] with 3 Replicates</td>
<td>26+</td>
<td>15</td>
</tr>
</tbody>
</table>

#### Zovirax® US (T) vs. Zovirax® US (R)

<table>
<thead>
<tr>
<th>IVPT PK Endpoint</th>
<th>Maximum Flux (Jmax)</th>
<th>Total Bioavailability (AUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Point Estimate</td>
<td>0.962</td>
<td>1.101</td>
</tr>
<tr>
<td>$S$ Within Reference</td>
<td>0.697</td>
<td>0.469</td>
</tr>
<tr>
<td>SABE [0.80, 1.25]</td>
<td>-0.214 (BE)</td>
<td>-0.020 (BE)</td>
</tr>
<tr>
<td>N for [0.80, 1.25] with 4 Replicates</td>
<td>12+</td>
<td>14</td>
</tr>
<tr>
<td>N for [0.80, 1.25] with 3 Replicates</td>
<td>14</td>
<td>15+</td>
</tr>
</tbody>
</table>

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