U.S. FOOD & DRUG ADMINISTRATION

BIOEQUIVALENCE FUNDAMENTALS FOR GENERIC TOPICAL DERMATOLOGICAL DRUG PRODUCTS

Development and Harmonization of Current Regulatory Standards

Innovations in Dermatological Sciences

FDA: Development of Complex Generic Topical Products

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Topical Dermatological Drug Products

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

Complexity of Topical Products

- Topical drug products are typically complex, often in multiple ways (e.g., complex route of administration, complex dosage form)
- There are unique considerations impacting equivalence for complex generic topical products
- As the complexity of a formulation, dosage form, drug product, site of action and/or mechanism of action increases so do the potential failure modes for BE and therapeutic equivalence (TE)
- With a sufficient product and process understanding, relevant complexities can be identified and addressed systematically for the generic drug product

PSG's for Topical Dermatological Products

Potential ways to establish BE for complex topicals:

- Comparative clinical BE studies
  - Clinical (efficacy) endpoint
  - Pharmacodynamic endpoint (e.g., vasoconstrictor studies)
- *Efficient* characterization-based BE studies (e.g., in vitro)
  - in vitro
  - in vivo pharmacokinetic (PK) studies

PSG's for Topical Dermatological Products

A Modular and Scalable Approach to BE Evaluation

- Sameness of inactive ingredient components and quantitative composition e.g., qualitative **(Q1)** and quantitative **(Q2)** sameness
- **Q3** (Physical & Structural Characterization) as relevant to the nature of the product
- **IVRT** (In Vitro Release Test)
- **IVPT** (In Vitro Permeation Test) or another bio-relevant assay may be appropriate for some products
- In Vivo systemic **PK** studies may be appropriate for some products

Formulation of Topical Generics

- Sameness of excipient components and quantitative composition that may impact local or systemic bioavailability e.g., Q1/Q2 Sameness

Mitigates the risk of known failure modes related to:

- Irritation and sensitization
- Formulation interaction with diseased skin
- Vehicle contribution to efficacy
- Stability, solubility, etc., of the drug

Q1 sameness: Same components as the reference product
Q2 sameness: Same components and composition as the reference product ± 5%

PSG's for Topical Dermatological Products

- Formulation

The test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference product that may significantly affect the local or systemic availability of the active ingredient. For example, if the test and reference products are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the Guidance for Industry *ANDA Submissions – Refuse-to-Receive Standards*[1], the bioequivalence of the test product with respect to the reference product may be established using the in vitro option if the criteria below are also satisfied.

Q3 Similarity of Topical Generics

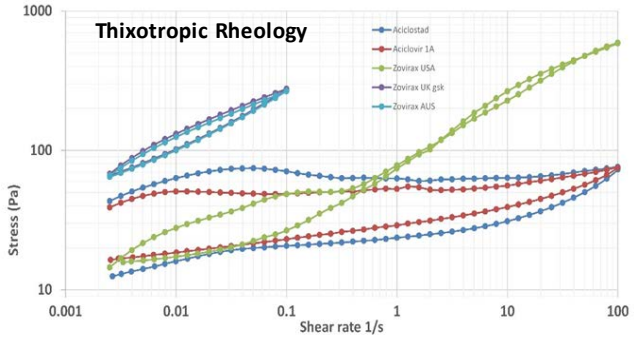
- Q3 Similarity (Arrangement of Matter)

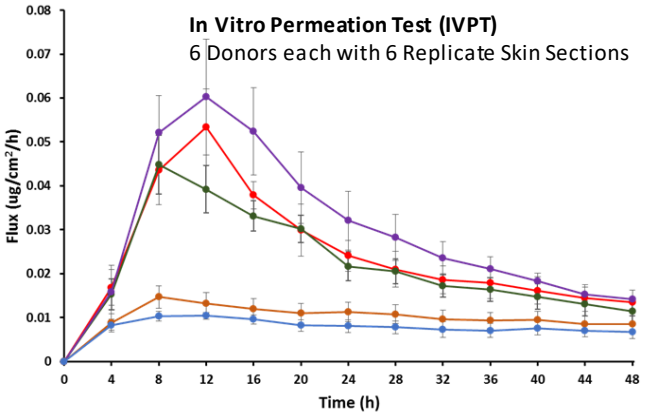
  Mitigates the risk of potential failure modes related to:

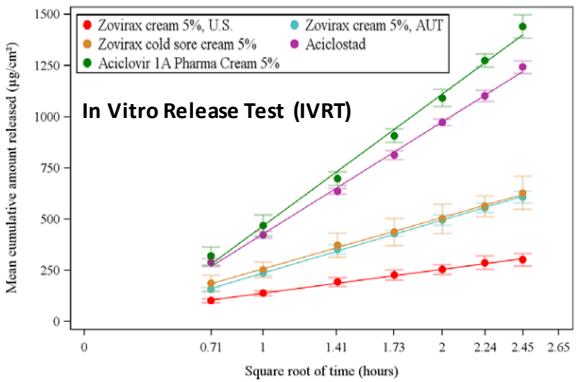
  - Differences in formulation
  - Differences in pH that may sting or irritate diseased skin
  - Differences in the polymorphic form of the drug
  - Differences in rheology that alter the spreadability, retention, etc.
  - Differences in entrapped air and drug amount per dose
  - Differences in phase states and diffusion, partitioning, etc.
  - Differences in metamorphosis and drying rates

Q3 and Performance

	Zovirax (USA)	Zovirax (UK)	Zovirax (Austria)	Aciclostad (Austria)	Aciclovir-1A (Austria)
	Water	Water	Purified water	Water	Water
	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol
	Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
	White petrolatum	White soft paraffin	White Vaseline	White Vaseline	White Vaseline
	Cetostearyl alcohol	Cetostearyl alcohol	Cetostearyl alcohol	Cetyl alcohol	Cetyl alcohol
	SLS	SLS	SLS	[redacted]	
	Poloxamer 407	Poloxamer 407	Poloxamer 407		
	[redacted]	Dimethicone 20	Dimethicone 20	Dimethicone	Dimethicone
		Arlacel 165	Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate
		Arlacel 165	Polyoxyethylene stearate	Macrogol stearate	Polyoxyethylene stearate
Density (g/cc)	1.02	1.02	1.02	1.02	1.01
Content Uniformity (%)	97.9 ± 0.7	99.6 ± 1.4	100 ± 2.2	99.7 ± 1.7	98.3 ± 2.6
Polymorphic Form	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate
Crystilline Habit	Rectangular	Rectangular	Rectangular	Ovoid	Ovoid
Particle size (d50) (µm)	3.8	2.5	3.4	6.8	6
pH	7.74	7.96	7.54	4.58	6.05
Work of Adhesion	59	81	60	17	18
Drug in Aq (mg/g)	0.49	0.64	0.49	0.37	0.26
Drying Rate (T-30%)	>12h	~8h	~7h	<1h	<1h
Water Activity	0.75	0.73	0.74	0.95	0.95



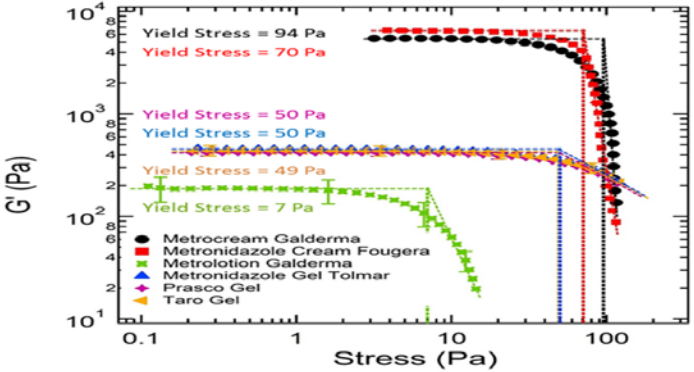


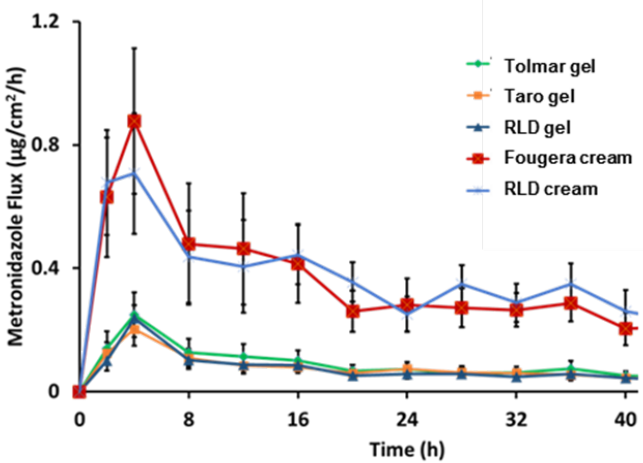


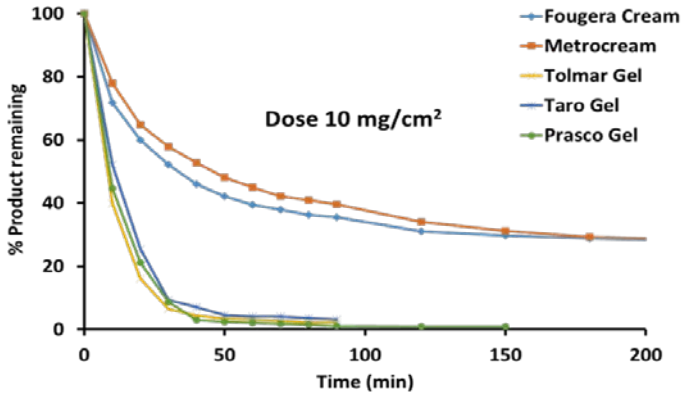
Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) FDA Award U01-FD005223 & Dr. Frank Sinner (Joanneum Research) FDA Award U01-FD004946

Q3 and Performance

Quality Attribute	Metrocream®	Generic Cream (Fougera)	Metrogel®	Generic Gel (Tolmar)	Generic Gel (Taro)
pH	4.8	5.1	5.2	5.0	5.4
Density (g/cc)	1.02	1.02	1.01	1.02	1.02
WOA (g.sec)	57.6	63.9	39.4	43.9	42.0
Particle size (µm)	Active ingredient is completely dissolved				
Drug in Aq (mg/g)	4.20	2.92	---	---	---
Drug in Oil (mg/g)	2.58	3.94	---	---	---
Solvent Activity	0.977	0.974	0.992	0.994	1.002
Globule size, d_{50} (µm)	2.8	2.2	---	---	---
Drying, T_{30}(min)	17	11.4	5.5	4.7	6.5







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

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
- Additional performance tests (e.g., IVPT) may be required

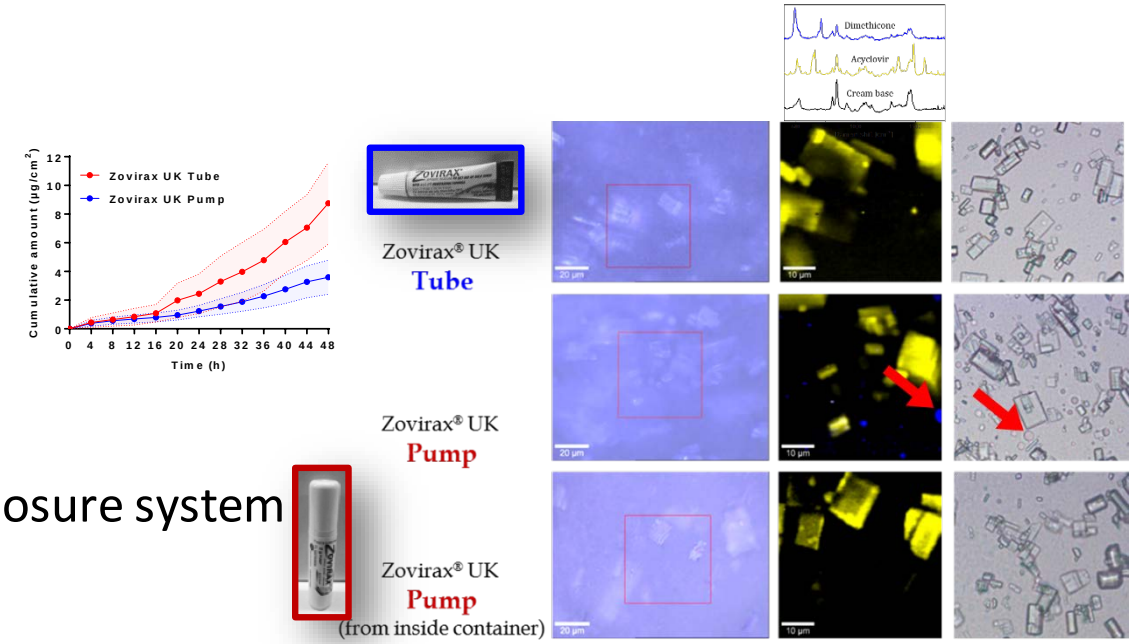
Note: The packaging configuration itself may impact bioavailability

PSG's for Topical Dermatological Products

- Q3
  - Example of Q3 recommended for single phase systems
    - Appearance
    - Microscopy
    - pH
    - Specific gravity
    - Rheology
    - Particle size
    - Polymorphic form
    - Weight loss (drying rate)
    - Etc.

PSG's for Topical Dermatological Products

- Q3
  - Example of Q3 recommended for multi phase systems
    - Appearance
    - Microscopy
    - pH
    - Specific gravity
    - Rheology
    - Particle size
    - Polymorphic form
    - Globule size
    - Water activity
    - Impact of container closure system
    - Etc.



Data provided courtesy of Prof. Michael Roberts and Prof. M.Windberg

PSG's for Topical Dermatological Products

- IVRT

> The test and RLD products have an equivalent rate of acyclovir release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one lot each of the test and RLD products using an appropriately validated IVRT method.

  - IVRT method development
  - IVRT method validation
  - IVRT pivotal study

- If a test product is being developed for packaging in multiple container closure systems (CCS), IVRT may need to be conducted using dispensed product from each CCS compared to product dispensed from the corresponding packaging configuration of the reference product

For additional information, please see the draft guidance for industry on Acyclovir Topical Cream, 5%, https://www.accessdata.fda.gov/drugsatfda_docs/psg/Acyclovir_topical%20cream_RLD%2021478_RV12-16.pdf

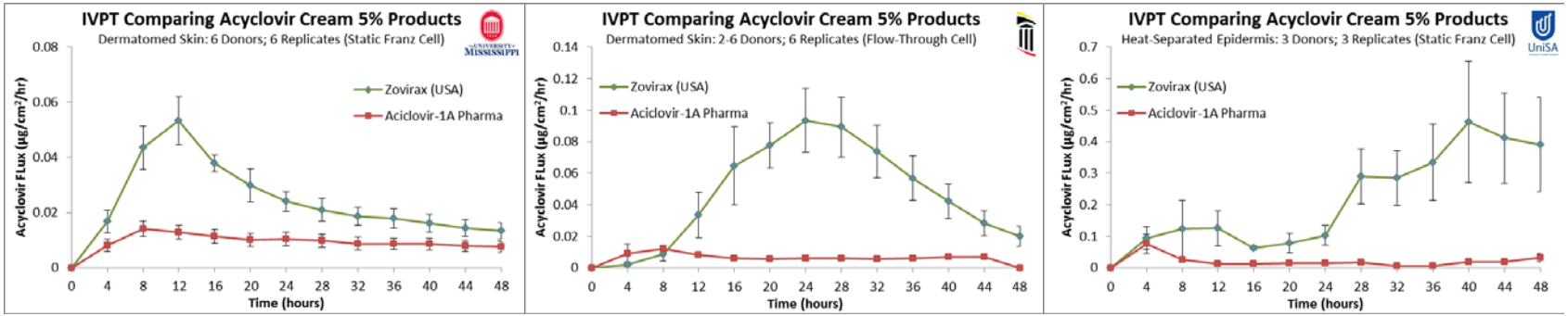
PSG's for Topical Dermatological Products

- IVPT

The test and RLD products are bioequivalent based upon an acceptable in vitro permeation test (IVPT) comparing the rate and extent of acyclovir permeation through excised human skin from a minimum of one lot each of the test and RLD products using an appropriately validated IVPT method.

IVPT Results: Acyclovir Cream, 5%

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



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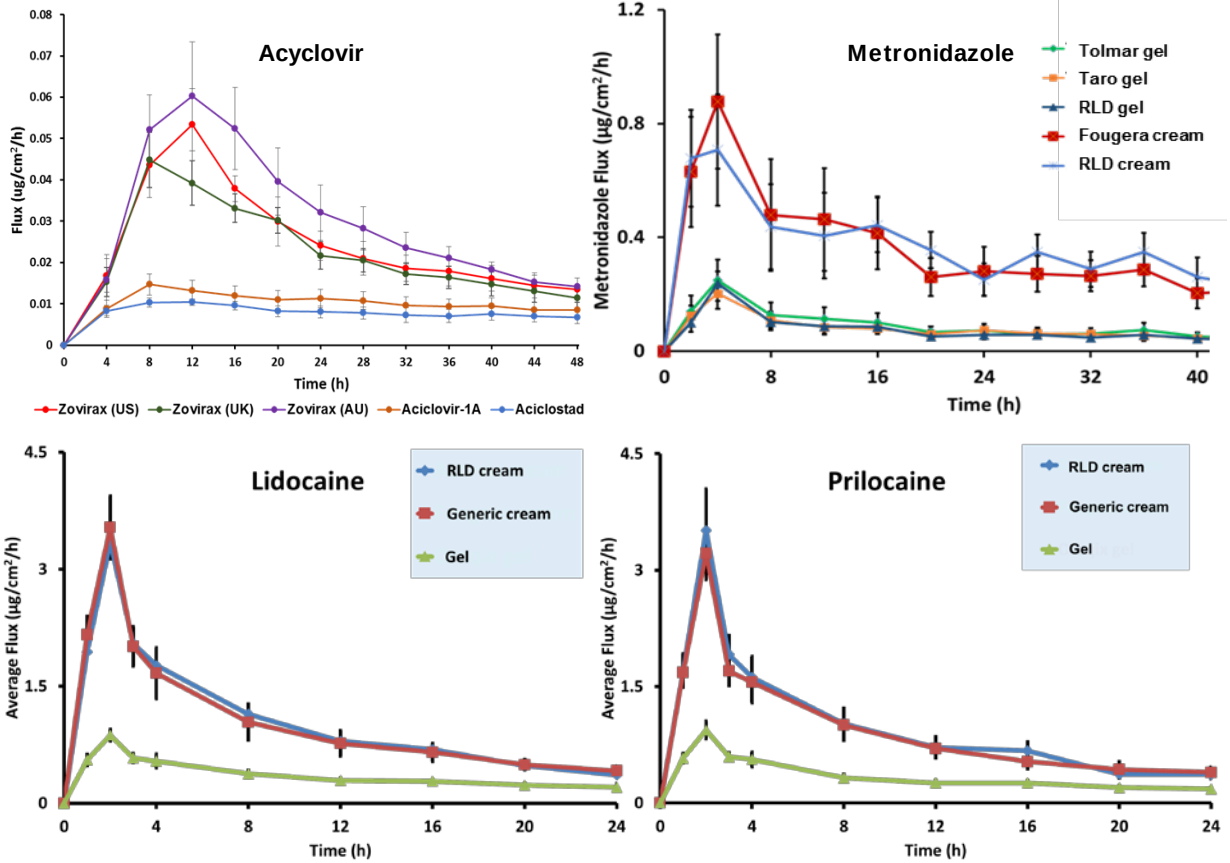
Prof. Michael Roberts (University of South Australia) FDA Award U01-FD005226

IVPT Results for Different Products



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PSG's for Topical Dermatological Products

- IVPT

> The test and RLD products are bioequivalent based upon an acceptable in vitro permeation test (IVPT) comparing the rate and extent of acyclovir permeation through excised human skin from a minimum of one lot each of the test and RLD products using an appropriately validated IVPT method.

  - IVPT method development
  - IVPT method validation
  - IVPT pilot study
  - IVPT pivotal study

- Clearly outline all data analysis including the statistical analysis plan within the study protocol

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

Solution-Based Topical Products

- Waivers for generic topical solutions that contain no differences in inactive ingredients compared to the reference product: *21 CFR 320.22(b)(3)*
- Product characterization may be recommended to mitigate unique concerns

- **Draft Guidance on Tavaborole** *(Topical Solution)*

  "relevant quality and performance attributes of the test and reference formulations should include appearance, specific gravity, viscosity, evaporation (drying) rate, surface tension, and any other potentially relevant physical and chemical properties…"

Semisolid Topicals (Single-Phase Systems)

- **Draft Guidance on Acyclovir** *(Topical Ointment)*
  - *Formulation sameness of the generic and reference formulations*
  - *Comparative physicochemical characterization of the generic and reference products*
  - *Equivalent acyclovir release from the generic and reference products evaluated by IVRT*

- **Draft Guidance on Clindamycin phosphate** *(Topical Gel)*
  - *Formulation sameness of the generic and reference formulations*
  - *Physically and structural similarity based upon an acceptable comparative physicochemical characterization of appearance, rheological behavior, specific gravity, and pH…*
  - *Equivalent drug release from the generic and reference products evaluated by IVRT*

Topical Products (Multi-Phase Systems)

Draft Guidance on Acyclovir *(Topical Cream)*

- *Formulation sameness of the generic and reference formulations*
- *The generic and reference products are physically and structurally similar based upon an acceptable comparative physicochemical characterization… Assessment of appearance, polymorphic form, particle size distribution and crystal habit, pH, specific gravity, water activity and rheological behavior*
- *The generic and reference products have an equivalent rate of acyclovir release based upon an acceptable in vitro release test (IVRT)… using an appropriately validated IVRT method*
- *The generic and reference products are bioequivalent based upon an acceptable in vitro permeation test (IVPT)… using an appropriately validated IVPT method*

Topical Products (Multi-Phase Systems)

Multiple potential mechanisms/sites of action

Draft Guidance on Ivermectin *(Topical Cream)*

Draft Guidance on Doxepin hydrochloride *(Topical Cream)*

- *Formulation sameness*
- *Comparative physicochemical characterization (Q3 similarity): Appearance, pH, specific gravity, emulsion globule size distribution …and rheological behavior and viscosity profiles…*
- *IVRT equivalence*
- *In vitro BE assessment with local (cutaneous) PK endpoints (IVPT)*
- *In vivo BE study with systemic (plasma) PK endpoints*

Generic Topical Product Development

- 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 currently of Interest*
  - **In Vivo** Stratum Corneum Sampling Studies
    - × Tapestripping "Dermatopharmacokinetics" (DPK)

Ongoing Research

- **In Vitro** Characterization and Prediction of Product Behavior
  Elucidating the Thermodynamic and Functional/Sensorial Characteristics of Variously Complex and Compositionally Different Topical & Transdermal Products
- **In Vivo** Characterization of Cutaneous Pharmacokinetics
  Evaluating the Cutaneous Pharmacokinetics of Topical Drug Products by Pharmacokinetic Tomography and/or Dermal Microperfusion/Microdialysis
- **In Silico** Modeling and Simulation to Support Bioequivalence Assessments
  Developing & Verifying Models Integrate the Product, the Skin & Local Tissues, and the Systemic Circulation to Predict Drug Concentrations at a Site of Action

Generic Topical Product Development

- If a PSG is available
  - Follow the recommendation in the PSG to establish BE
  - Submit a pre-ANDA meeting request when you propose an alternative BE approach
  - Submit controlled correspondence (CC) for questions related to appropriateness of a formulation for a specific BE approach, etc.

- If PSG is unavailable

  Steps toward the development of a generic topical product
  - Identify the reference product
  - Identify the studies proposed to support a demonstration of BE appropriate to the complexity of the dosage form

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Guidance Development Teams

Transdermal and Topical Dermatological Guidance Development Teams

- Office of Generic Drugs
  - Office of Research and Standards
  - Office of Bioequivalence
  - Office of Generic Drug Policy
- Office of Pharmaceutical Quality
  - Office of Lifecycle Drug Products


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