

The Journey from Developing the Research Studies to Drafting a New Regulatory Standard

A Case Study with Acyclovir Cream

FDA Public Workshop

Topical Dermatological Generic Drug Products: Overcoming Barriers to Development and Improving Patient Access

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- The views expressed in this presentation do not reflect the official policies of the FDA, or the Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.
- I do not have any financial interest or conflict of interest with any pharmaceutical companies.



Our Commitments

- **Mission** of the Office of Generic Drugs
 - To make **high quality**, affordable medicines **available** to the public.
- **Vision** to support our commitments:
 - Product Quality Characterization (**high quality** medicines)
 - Efficient Bioequivalence (BE) Standards (make medicines **available**)

High Quality Drug Products



- What does “quality” mean for a drug product?

Fitness for Purpose

*“The totality of **features and characteristics of a product...** that bear on its ability to satisfy stated or implied needs”*

- International Organization for Standardization (ISO)

Control of Failure Modes

*“Good pharmaceutical quality represents **an acceptably low risk of failing** to achieve the desired clinical attributes.”*

- Dr. Janet Woodcock, Director, FDA CDER

Woodcock, J. (2004) The concept of pharmaceutical quality. Am Pharm Review 7(6):10-15

Available (and Affordable) Products



- Power of “efficient” BE standards

Overall Drug Products ¹

- **89%** of prescriptions dispensed in 2016 were for generics
- Efficient Pharmacokinetics (PK)-based methods available

Topical Drug Products ²

- Many topical products have no generics available
- Efficient Pharmacokinetics (PK)-based methods may be useful
- Efficient In Vitro Bioequivalence methods may be useful

Developing In Vitro BE Standards



- **A Rational Framework for In Vitro BE**
 - **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

Developing In Vitro BE Standards



- **Q1/Q2 Sameness** (components and composition of inactives)
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

Developing In Vitro BE Standards



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

Mitigates the risk of potential failure modes related to:

- Differences in Q1/Q2 sameness ($\pm 5\%$ 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, 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
- *Many of these Q3 concepts and the associated test methods had not been developed or standardized*

Developing In Vitro BE Standards

- **IVRT (In Vitro Release Test)**

Mitigates the risk of unknown failure modes related to:

- Differences in Q1/Q2 sameness ($\pm 5\%$ tolerances)
- Differences in physical and structural similarity
- Differences that may not be identified by quality tests
- IVRT is a sensitive, discriminating compendial method with established statistical analyses
- However, no In Vitro – In Vivo Correlation (IVIVC) is expected
- *Standard procedures for IVRT method development and validation had not been established*

Developing In Vitro BE Standards



- **IVPT (In Vitro Permeation Test): Cutaneous PK Study**

Mitigates the risk of unknown failure modes related to:

- Differences in Q1/Q2 sameness ($\pm 5\%$ tolerances)
- 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 IVIVC
- *Standard procedures for IVPT method development and validation had not been established*

Developing In Vitro BE Standards



- **IVPT Statistical Analysis of Bioequivalence**
 - The approach for Scaled Average Bio-Equivalence (SABE) analysis of highly variable drugs was modified for the IVPT study design
 - The mixed criterion uses the within-reference variability (σ_{WR}) as a cutoff point for bioequivalence analysis
 - When $\sigma_{WR} \leq 0.294$, Average Bio-Equivalence (ABE) is used
 - When $\sigma_{WR} > 0.294$, Scaled ABE (SABE) is used
- *Standard procedures for IVPT study statistical analysis of BE had not been established*

Acyclovir Cream, 5%: A Case Study



- Reference and Test Products Selected as Nominal Positive and Negative Controls for Bioequivalence

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		
Poloxamer 407	Poloxamer 407	Poloxamer 407		
	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



Comprehensive Research Strategy



• Physical & Structural Product Characterization

-  • FDA/CDER/OTS/DPQR (USA) Quality Tests
-  • University of Mississippi (USA) Quality Tests
-  • University of South Australia (Australia/Germany) Quality Tests



• In Vitro Release Test (IVRT)

-  • FDA/CDER/OTS/DPQR (USA) IVRT
-  • Joanneum Research (Austria) IVRT

• Cutaneous PK: In Vitro Permeation Test (IVPT)

-  • University of Mississippi (USA) IVPT
-  • University of Maryland (USA) IVPT
-  • University of South Australia (Australia) IVPT

• Cutaneous PK: In Vivo Methods

-  • Joanneum Research (Austria) Dermal Open Flow Microperfusion (dOFM)
-  • Univ. of Maryland & Bath (U.K.) Tape Stripping

Physical and Structural Characterization

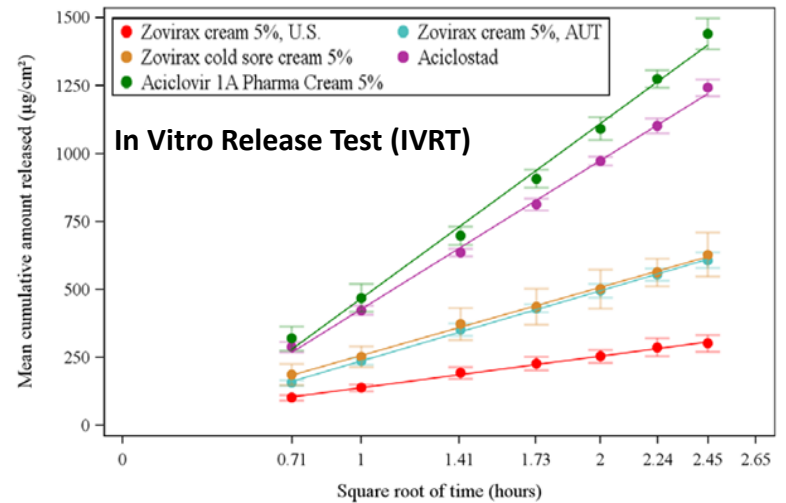
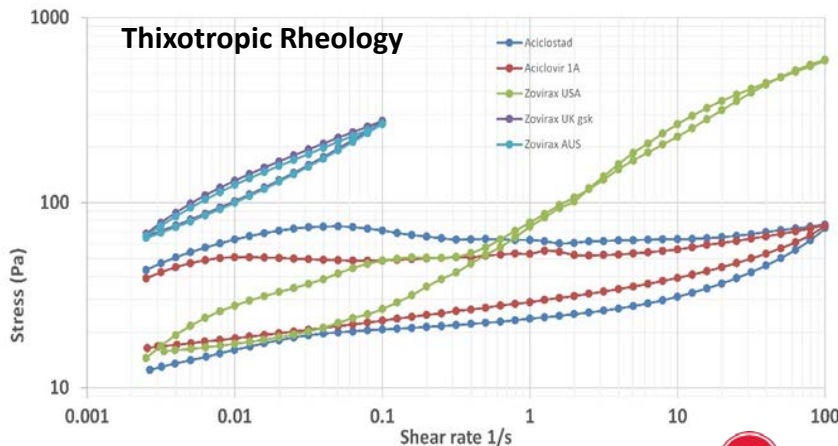
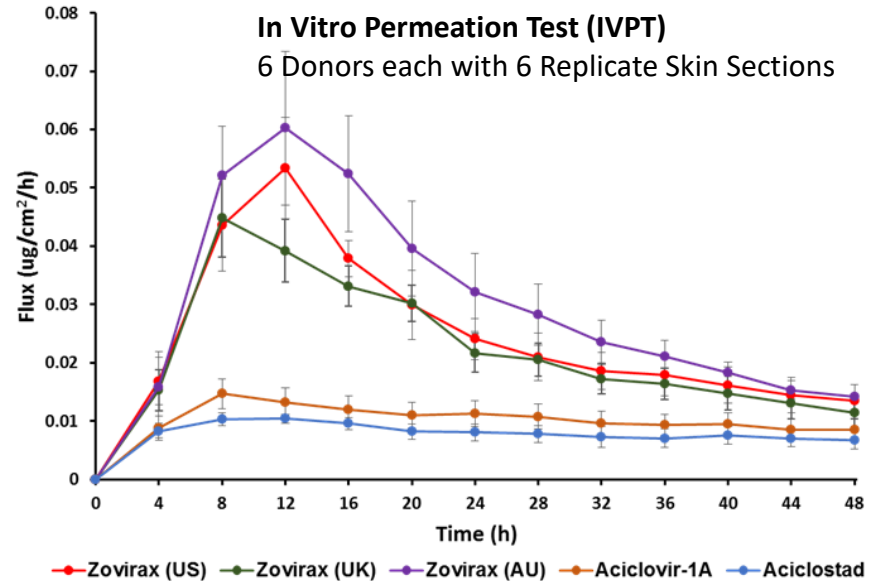


- Evaluating Complexity & Product Quality Attributes
 - Phase States and the Arrangement of Matter (globules/lamella)
 - Drug Amounts in Dissolved/Undissolved States in Drug Product
 - Drug Amount in Aqueous Phase
 - Drug Particle Size Distribution
 - Drug Polymorphic State
 - Drug Crystalline Habit
 - Texture Analysis
 - Water Activity
 - Drying Rate
 - Rheology
 - Density
 - pH
 - Etc.

Acyclovir Cream, 5% In Vitro BE

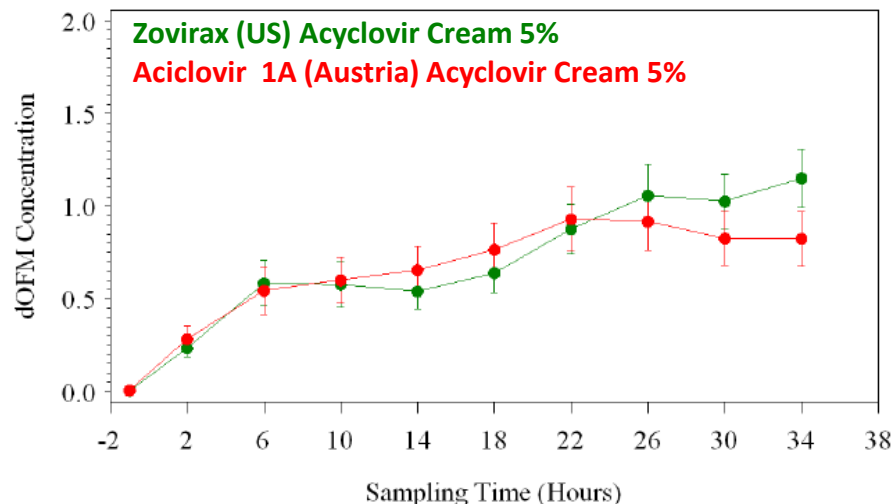
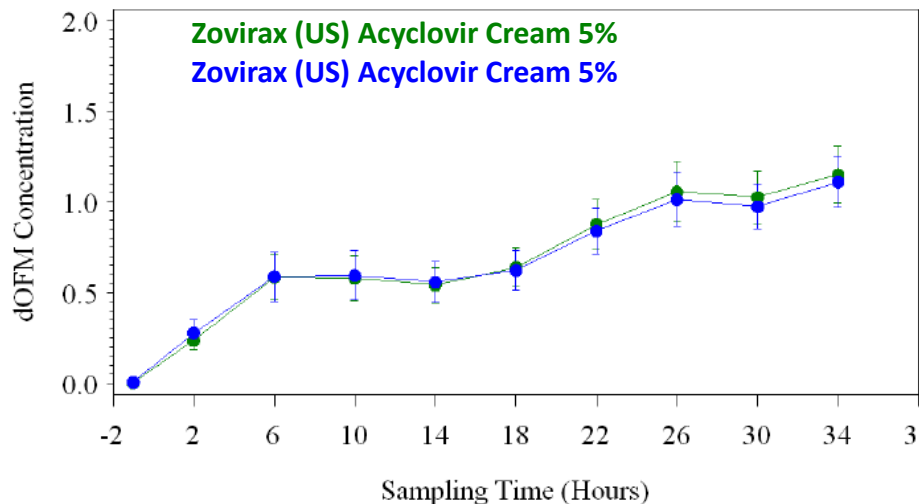


	Zovirax (USA)	Zovirax (UK)	Zovirax (Austria)	Aciclostad (Austria)	Aciclovir-1A (Austria)
Water	Water	Water	Purified water	Water	Water
Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol
Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
White petrolatum	White soft paraffin	White Vaseline	White Vaseline	White Vaseline	White Vaseline
Cetostearyl alcohol	Cetostearyl alcohol	Cetostearyl alcohol	Cetyl alcohol	Cetyl alcohol	Cetyl alcohol
SLS	SLS	SLS			
Poloxamer 407	Poloxamer 407	Poloxamer 407			
	Dimethicone 20	Dimethicone 20	Dimethicone	Dimethicone	Dimethicone
	Arlacel 165	Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate
	Arlacel 165	Polyoxyethylene stearate	Macrogol stearate	Polyoxyethylene 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
Crystalline 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

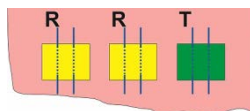


Acyclovir Cream, 5% In Vivo BE

- Dermal Pharmacokinetics by dOFM (20 subjects)



Outcome variable	CI _{90%}
log(AUC _{0-36h})	[-0.148 ; 0.162] or [86.2 % ; 117.5 %]
log(C _{max})	[-0.155 ; 0.190] or [85.7 % ; 120.9%]



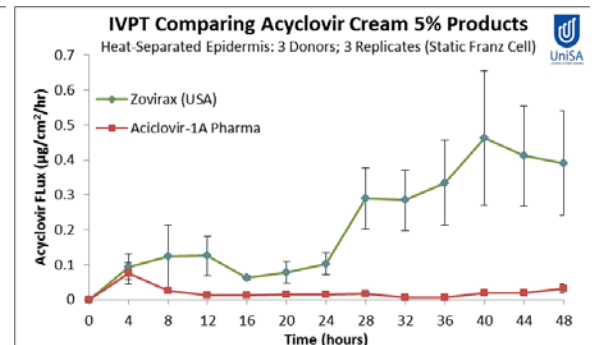
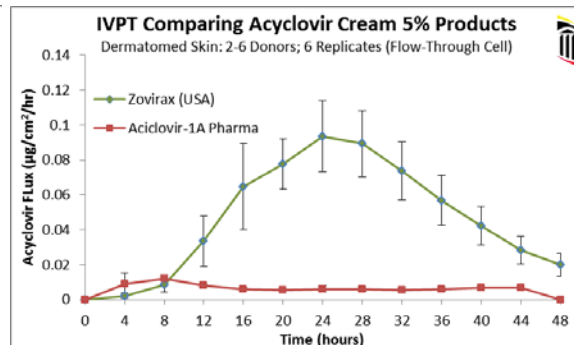
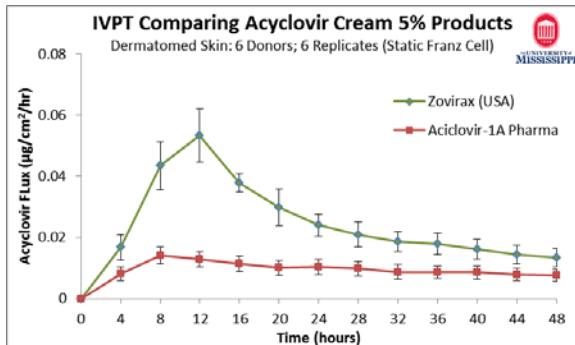
Outcome variable	CI _{90%}
log(AUC _{0-36h})	[-0.369 ; 0.050] or [69.1 % ; 105.2 %]
log(C _{max})	[-0.498 ; 0.022] or [60.8 % ; 102.2%]

Acyclovir Cream, 5% In Vitro BE



- Dermal Pharmacokinetics by IVPT (15 Donors)
Negative Controls for Bioequivalence

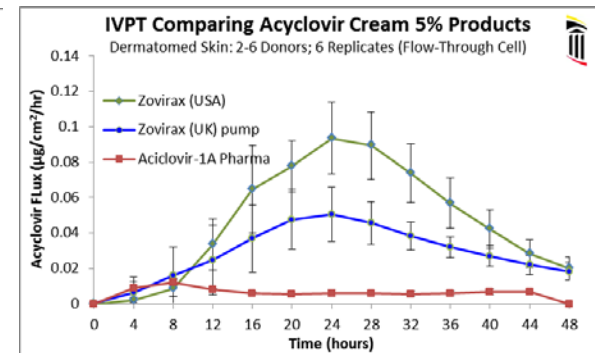
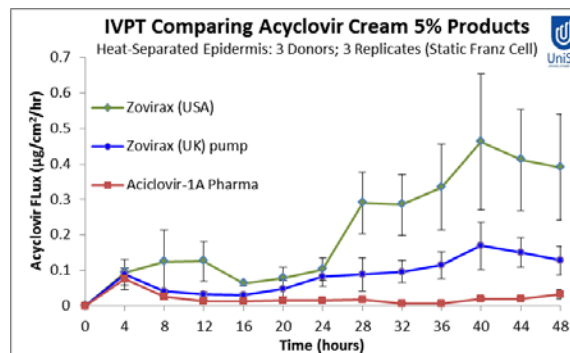
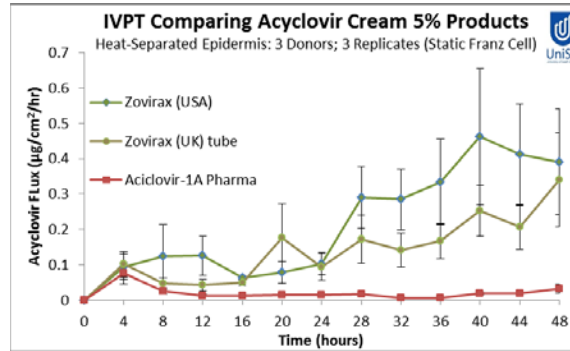
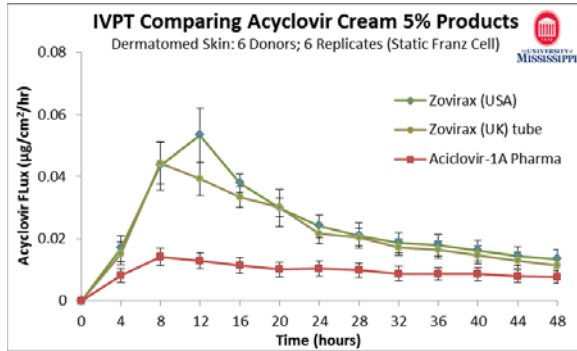
	University of Mississippi	University of Maryland	University of South Australia
Dose	15 mg/cm ²		
Dosing technique	Dispensed-Spatula Dispersed-glass rod	Dispensed and dispersed- Positive displacement pipette	Dispensed- Pipette Dispersed- Syringe plunger
Skin type	Torso	Abdomen	Abdomen
Thickness	Dermatomed	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



Influence of Quality on Performance



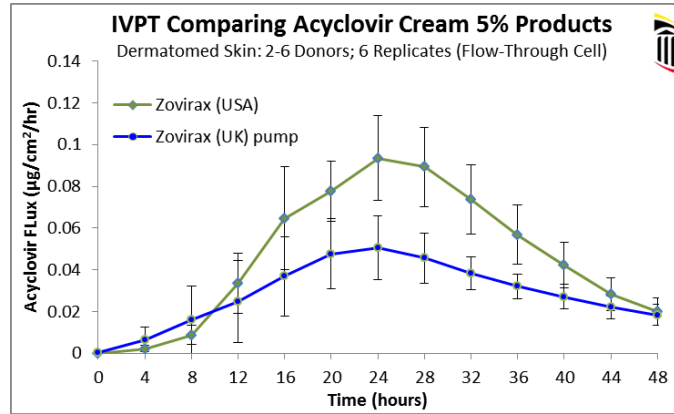
- Influence of Dose Dispensing on Bioavailability



IVPT Bioequivalence Limits

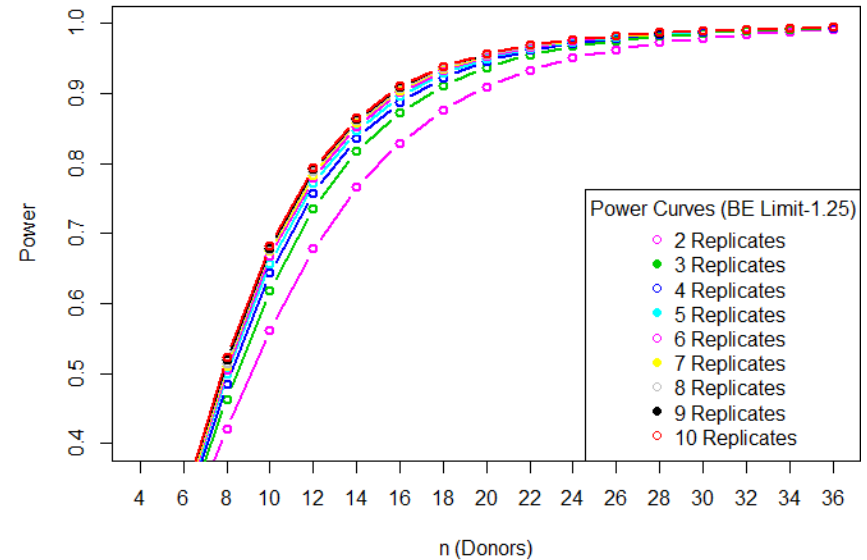
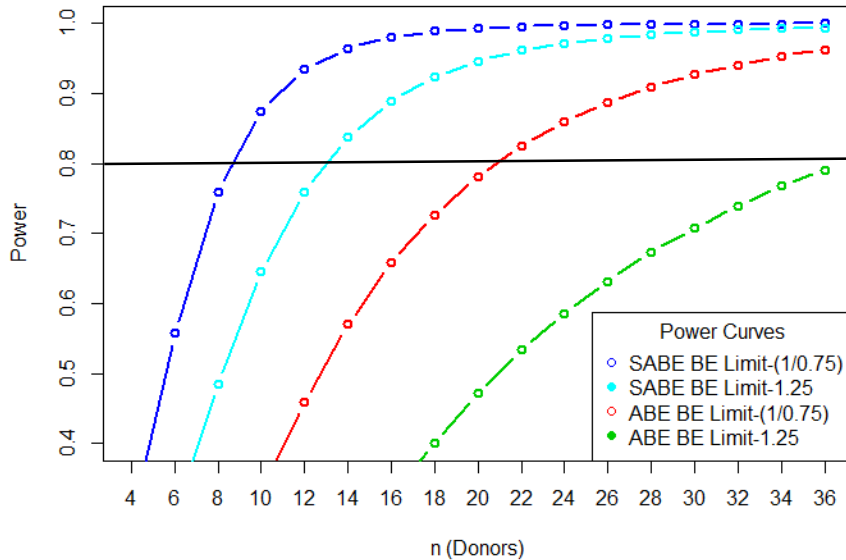


- Bioequivalence Limits, Study Power and Study Size



UK-US Jmax

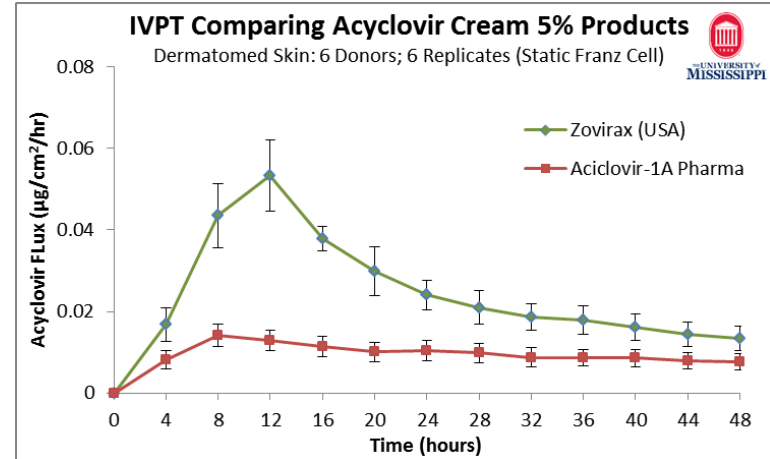
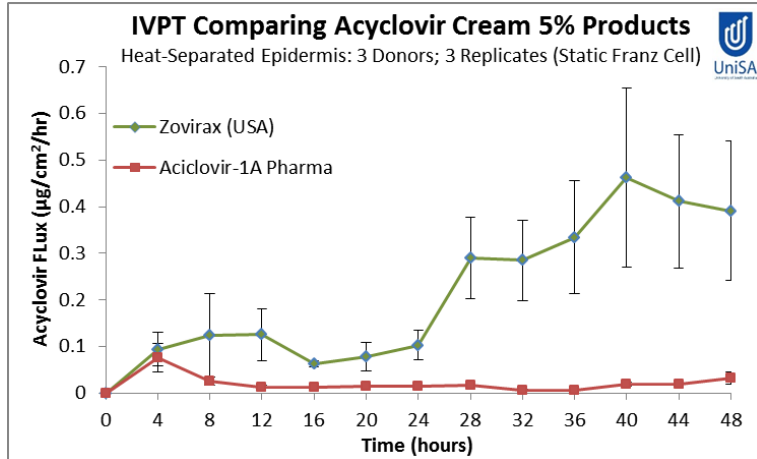
UK-US Jmax



Mixed Criterion (S)ABE: Acyclovir Cream, 5%



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



Aciclovir-1A[®] (T) vs. Zovirax[®] US (R)

IVPT PK Endpoint	Maximum Flux (Jmax)	Total Bioavailability (AUC)
Point Estimate	0.172	0.104
S _{Within Reference}	0.521	0.551
SABE [0.80, 1.25]	4.433 (Non-BE)	7.236 (Non-BE)
N for [0.80, 1.25] with 3 Replicates	6	8



Aciclovir-1A[®] (T) vs. Zovirax[®] US (R)

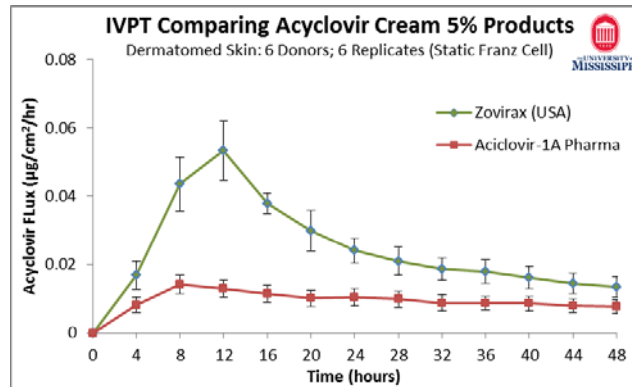
IVPT PK Endpoint	Maximum Flux (Jmax)	Total Bioavailability (AUC)
Point Estimate	0.290	0.366
S _{Within Reference}	0.575	0.419
SABE [0.80, 1.25]	2.383 (Non-BE)	1.884 (Non-BE)
N for [0.80, 1.25] with 6 Replicates	8	20



Mixed Criterion (S)ABE: Acyclovir Cream, 5%



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



Aciclovir-1A[®] (T) vs. Aciclovir-1A[®] (R)

IVPT PK Endpoint	Maximum Flux (Jmax)	Total Bioavailability (AUC)
Point Estimate	0.983	0.958
S Within Reference	0.303	0.318
SABE [0.80, 1.25]	-0.026 (BE)	-0.041 (BE)
N for [0.80, 1.25] with 4 Replicates	26+	15
N for [0.80, 1.25] with 3 Replicates	26+	15

Zovirax[®] US (T) vs. Zovirax[®] US (R)

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



BE Standards for Topical Products



Topical drug products can be complex in multiple ways:

- Complex compositions of matter in the product
 - Immiscible mixtures of several “inactive” ingredients
- Complex states of matter in the product
 - Partially dissolved, partially dispersed drug(s)
- Complex arrangements of matter in the product
 - Multiple phases/components in the drug product
- Complex drug diffusion within the dosage form
 - Potentially complex and dynamic distribution of drug(s)
- Complex device and/or patient interactions
 - Potentially influencing bioavailability at target site of action

BE Standards for Topical Products

- 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
- Product specific guidances (PSGs) are developed to be appropriate to the nature and complexity of the relevant drug product

Solution-Based Topical Drug Products



- Less “complex” solution-based topical products
 - Waivers for simple Q1/Q2 topical solutions: *21 CFR 320.22(b)(3)*
 - In vitro comparative physicochemical characterization mitigates the risk of potential failure modes for BE
 - Examples of Product Specific Guidances (PSGs)
 - **Draft Guidance on Ciclopirox** (*Topical Solution*)
“Since the resin imparts important characteristics to the formulation and hence the nail coat, it is important that data be provided showing the polymeric resin has similar physicochemical properties as the RLD.”
 - **Draft Guidance on Erythromycin** (*Topical Swab*)
“...adequate information must be provided to ensure that the composition of the pledgets will not affect the performance of the product.”

Solution-Based Topical Drug Products



- Less “complex” solution-based foam aerosols
 - In Vitro evidence to support a waiver of in vivo evidence of BA or BE per 21 CFR 320.22(b)(3), or a clinical endpoint BE study
 - Comparative physicochemical characterizations:
 - Microscopic Birefringence Analysis (do crystals form upon dispensing?)
 - Time to Break Analysis (conducted at 30°C, 33°C, 35°C & 40°C)
 - Weight per Volume of un-collapsed foam aerosol
 - Examples of PSGs
 - **Draft Guidance on Minoxidil** (*Foam Aerosol*)
 - **Draft Guidance on Clobetasol Propionate** (*Foam Aerosol*)
 - **Draft Guidance on Clindamycin Phosphate** (*Foam Aerosol*)
 - **Draft Guidance on Ketoconazole** (*Foam Aerosol*)
 - **Draft Guidance on Betamethasone Valerate** (*Foam Aerosol*)

Semisolid Topical Drug Products



- Moderately “complex” semisolid topical products
 - Examples of PSGs
 - **Draft Guidance on Acyclovir** (*Topical Ointment*)
 - *Q1/Q2 sameness of the test and RLD formulations*
 - *Comparative physicochemical characterization of test and RLD products*
 - *Equivalent acyclovir release from test and RLD products evaluated by IVRT*
 - NOTE: A clinical endpoint BE study is recommended as an alternative
 - **Draft Guidance on Silver Sulfadiazine** (*Topical Cream*)
 - *Q1/Q2 sameness of the test and RLD formulations*
 - *Physically and structural similarity based upon an acceptable comparative physicochemical characterization of appearance, polymorphic form of the drug, globule and/or particle size distribution and crystal habit, rheological behavior, specific gravity, and pH...*
 - *Equivalent silver sulfadiazine release from test and RLD products evaluated by IVRT*

Semisolid Topical Drug Products

- “Complex” semisolid topical products

- Example of a PSG

- **Draft Guidance on Acyclovir** (*Topical Cream*)

“To qualify for the in vitro option for this drug product the following criteria should be met:

A. *The test and Reference Listed Drug (RLD) products are qualitatively (Q1) and quantitatively (Q2) the same...*

B. *The test and RLD products are physically and structurally similar...*

C. *The test and RLD products have an equivalent rate of acyclovir release based upon an acceptable in vitro release test (IVRT)... using an appropriately validated IVRT method*

D. *The test and RLD products are bioequivalent based upon an acceptable in vitro permeation test (IVPT)... using an appropriately validated IVPT method”*

Semisolid Topical Drug Products

- “Complex” semisolid topical products

- Example of a PSG

- **Draft Guidance on Benzyl Alcohol** (*Topical Lotion*)

- “i. Equivalent comparative qualitative and quantitative (Q1/Q2) characterization.

- ii. Equivalent comparative physicochemical and microstructural characterization of comparable pH, specific gravity, emulsion globule size distribution ...and viscosity profiles...

- iii. Equivalent comparative dosage form performance characterization in vitro, using the USP compendial In Vitro Release Test (IVRT) method. We recommend that the IVRT method be validated...

- iv. Equivalent comparative dosage form performance characterization ex vivo in *Pediculus humanus capitis* (head lice), using an appropriate pediculicide hair tuft assay with relevant controls...”

Semisolid Topical Drug Products

- “Complex” semisolid topical products with multiple potential mechanisms/sites of action
 - Examples of a PSGs
 - **Draft Guidances on Dapsone** (*Topical Gels*)
 - **Draft Guidance on Ivermectin** (*Topical Cream*)
 - 1) *Q1/Q2 sameness*
 - 2) *Q3 (physical and structural) similarity*
 - 3) *IVRT equivalence*
 - 4) *in vitro BE study with local (cutaneous) PK endpoints (IVPT)*
 - 5) *In vivo BE study with systemic (plasma) PK endpoints*

Conclusions

- For products across a range of complexity, consider how failure modes for product performance arise from and convolute among multiple potential critical quality attributes (CQAs)
- Consider how the risk of failure modes can be mitigated once the associated (individual and collective) quality attributes are designed into the product and controlled within a well-characterized design space
- Consider which product quality and performance attributes to characterize in order to identify CQAs, what measurement techniques to use, and how to interpret the results

Conclusions

- How does the FDA
 - ensure that complex topical generic drug products are of high quality
 - bring greater predictability and timeliness to the review of generic drug applications
- The FDA
 - Develops science-based regulatory standards that address product complexities and manufacturing issues
 - Develops guidance indicating what evidence would be acceptable to support a demonstration of BE
 - Initiates pre-ANDA communication with Industry during product and program development, as appropriate

Conclusions

- How can complex generic product developers
 - ensure that complex generic topical drug products are of high quality
 - bring greater predictability and timeliness to the review of generic drug applications
- Complex generic product developers can
 - Demonstrate a comprehensive understanding of the product complexities and manufacturing issues
 - Provide information that mitigates risks of potential failure modes for therapeutic equivalence
 - Initiate pre-ANDA communication with the FDA during product and program development, if necessary

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