FACILITATING PATIENT ACCESS TO HIGH QUALITY GENERICS:

A Case Study in Regulatory Science

American Academy of Dermatology Forum on FDA Hot Topics:
The Evolving Regulatory Landscape
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Disclaimer

- 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.

Mission of the Office of Generic Drugs

- The mission of the Office of Generic Drugs is to make **high quality**, **affordable** medicines **available** to the public.
- Key initiatives to support the mission
  - High Quality generics (**product quality characterization**)
  - Availability of generics (**efficient bioequivalence standards**)
- How can regulatory science positively impact both these initiatives?

High Quality Generic 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

High Quality Generic Drug Products

- Product qualities (attributes) that we must consider
  - The composition of matter in the product
  - The states of matter in the product
  - The arrangement of matter in the product
  - 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, burning or cooling (patient perceptions)
  - Metamorphosis of the dosage form on the skin
  - Bioavailability (BA) and Bioequivalence (BE)

High Quality Generic Drug Products

- We must consider how failure modes for therapeutic performance arise from and convolute among multiple product quality attributes
- We must consider how the risk of all such therapeutic performance failure modes can be mitigated
- We must understand what product quality attributes to characterize, what characterization techniques to use, and how to interpret the collective results

Available (and Affordable) Products

- What is the impact of "efficient" BE standards?

Overall Drug Products [1]

- **89%** of prescriptions dispensed in 2015 were for generics
- $1.46 trillion saved in healthcare costs 2006-2015

Topical Drug Products [2]

- **37.7%** of all topical drug products have generics available
- **76.7%** of topical **steroid** products have generics available, illustrating the impact of more efficient BE standards[3]

[1] GPhA 2016 Generic Drug Savings & Access in the United States Report
[2] Office of Generic Drugs Topical & Transdermal Products Database
[3] Excludes products for which generics cannot yet be made available

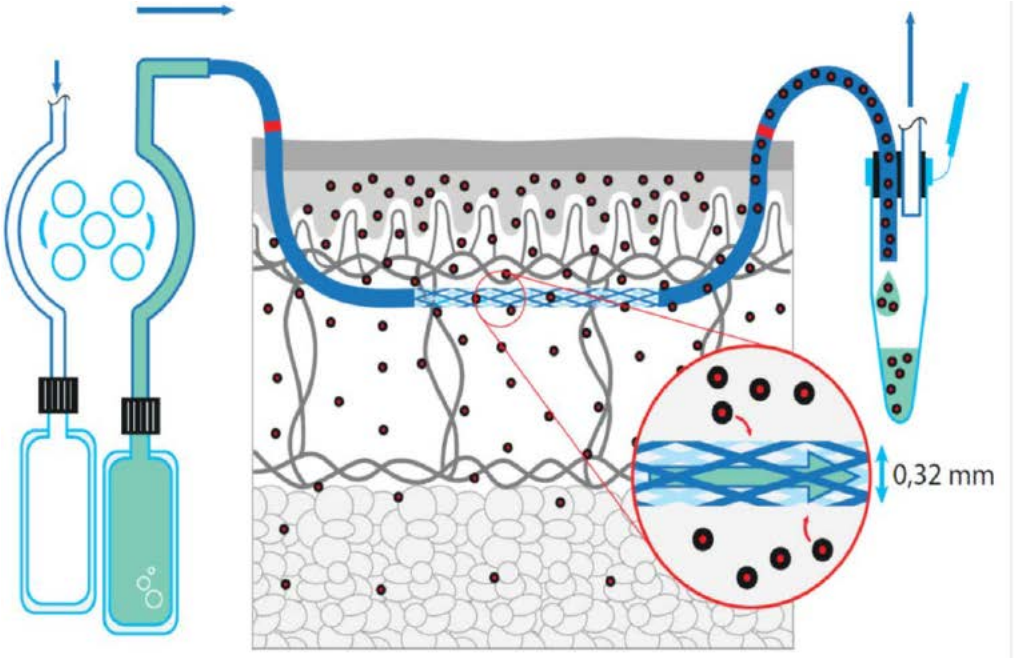
Cutaneous Pharmacokinetics

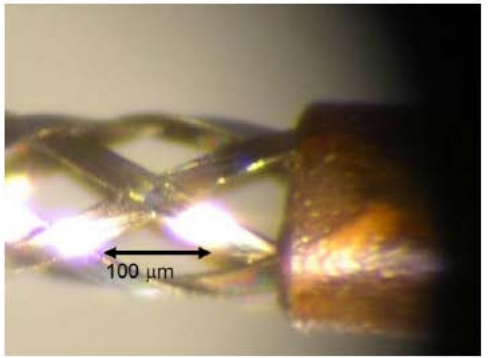
- Could cutaneous **pharmacokinetic methods** support the development of more **efficient** pathways for approval of topical drug products?

- Could such pathways facilitate the availability of affordable, high quality topical generic drug products?

Cutaneous Pharmacokinetics

- Dermal Open Flow Microperfusion (dOFM)





CE-certified for clinical use

Images provided courtesy of Dr. Frank Sinner, Joanneum Research, Austria

Cutaneous Pharmacokinetics

- dOFM System Validation and Study Controls

Data/Images provided courtesy of Dr. Frank Sinner, Joanneum Research, Austria

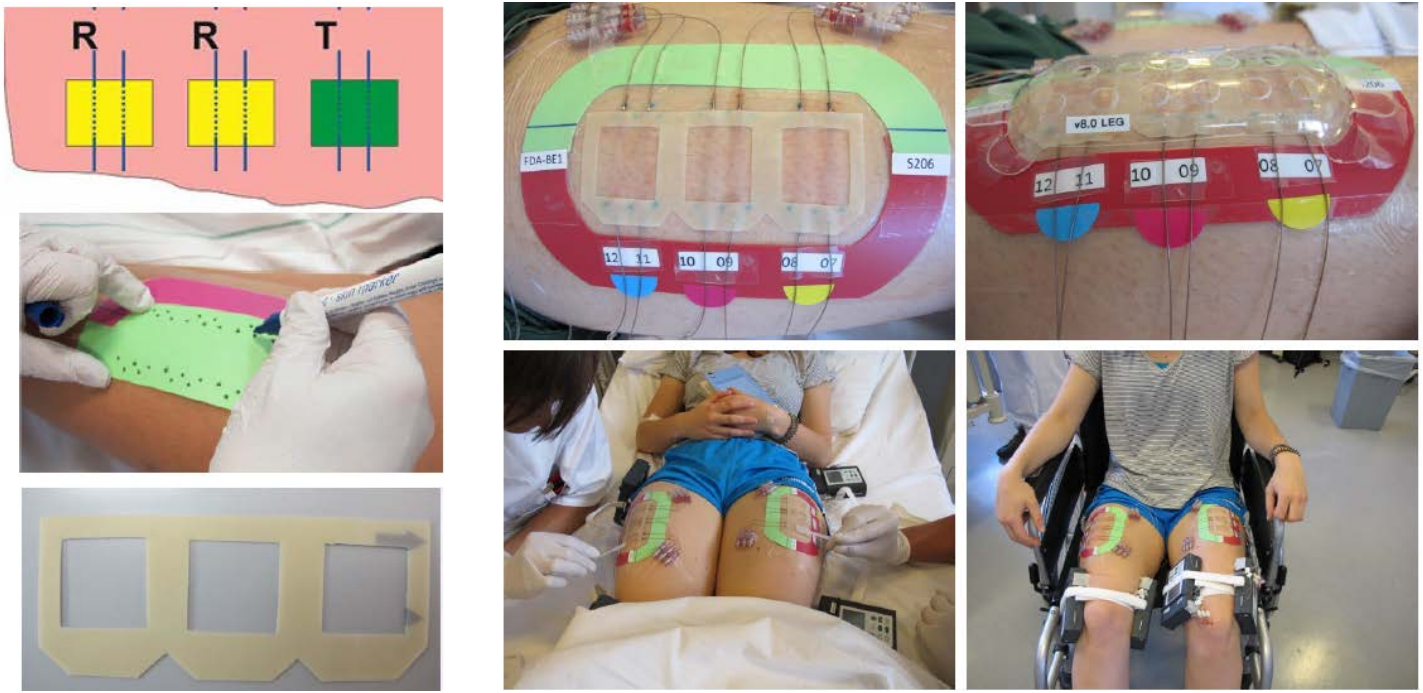
Pharmaceutically Equivalent Creams

- 5 Pharmaceutically Equivalent Acyclovir 5% Creams

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]	[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

Cutaneous Pharmacokinetics

- dOFM: Testing Positive and Negative Controls for BE



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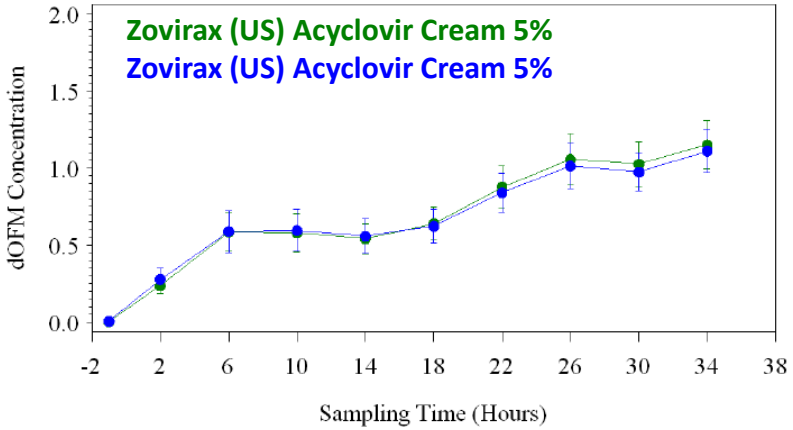
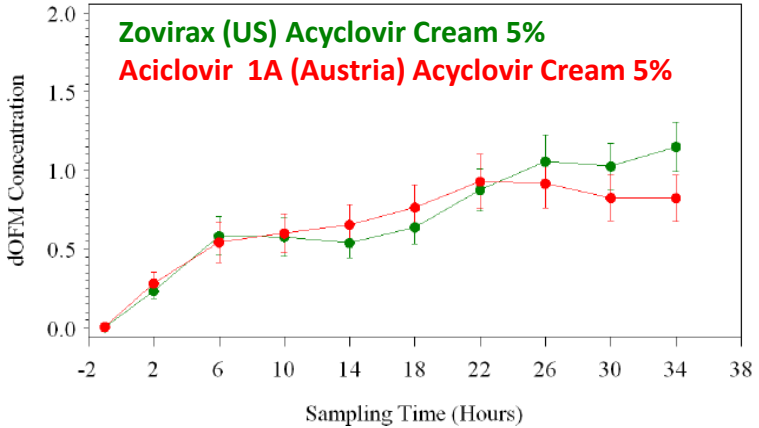
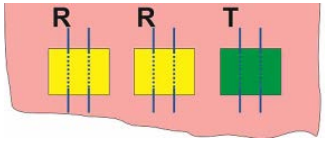
Dermal Pharmacokinetics by dOFM





Outcome variable	$CI_{90\%}$
log(AUC0-36h)	[-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(AUC0-36h)	[-0.369 ; 0.050] or [69.1 % ; 105.2 %]
log(C_{max})	[-0.498 ; 0.022] or [60.8 % ; 102.2%]

Data provided courtesy of Dr. Frank Sinner, Joanneum Research, Austria

Bodenlenz et al. (2017) Open Flow Microperfusion as a Dermal Pharmacokinetic Approach to Evaluate Topical Bioequivalence. Clin Pharmacokinet. 2017 Jan;56(1):91-98. doi: 10.1007/s40262-016-0442-z (FREE Full Text Article)

Pharmaceutically Equivalent Creams

- 5 Pharmaceutically Equivalent Acyclovir Creams

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
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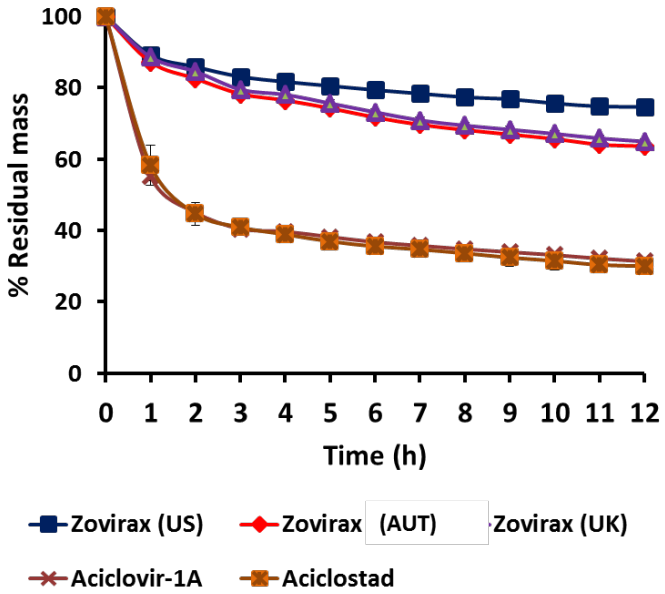
In Vitro BA/BE Assessment Methods

- Arrangement of Matter
- Particle Size Analysis
- Texture Analysis
- **Water Activity**
- **Drying Rate**
- Rheology
- Density
- pH
- Etc.



Product	Solvent Activity (a_w)
Zovirax (US)	0.753 ± 0.002
Zovirax (AUT)	0.735 ± 0.000
Zovirax (UK)	0.732± 0.002
Aciclovir 1A	0.948 ± 0.001
Aciclostad	0.948 ± 0.003

Data provided courtesy of Prof. Narasimha Murthy, University of Mississippi

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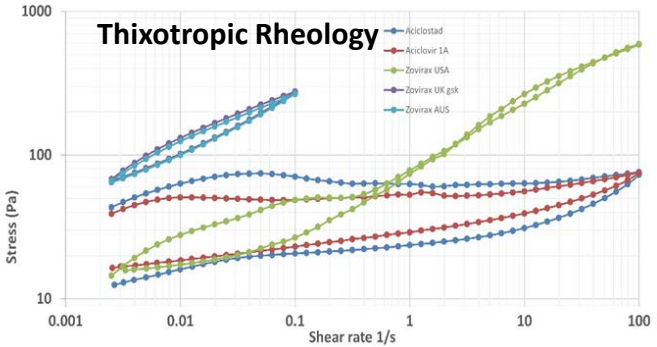
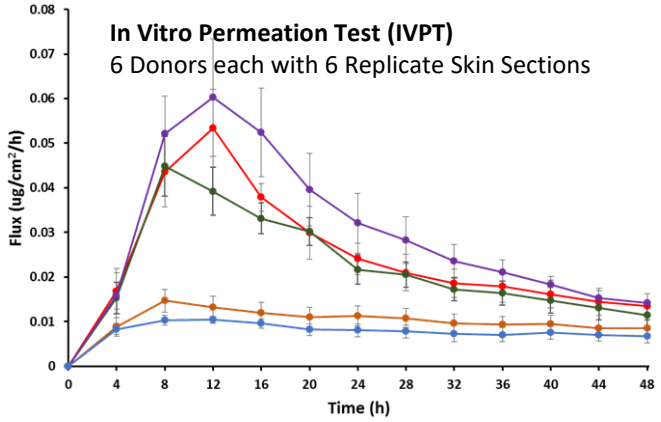
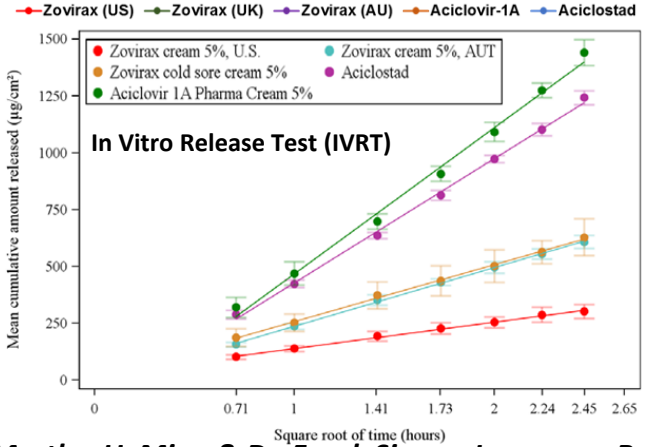
		Arlacel 165	Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate
		Arlacel 165	Polyoxyethylene stearate	Macrogol stearate	Polyoxyethylene stearate
Density (g/cc)	1.02	1.02	1.02	1.02	1.01
Content Uniformity (%)	97.9 ± 0.7	99.6 ± 1.4	100 ± 2.2	99.7 ± 1.7	98.3 ± 2.6
Polymorphic Form	2,3 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





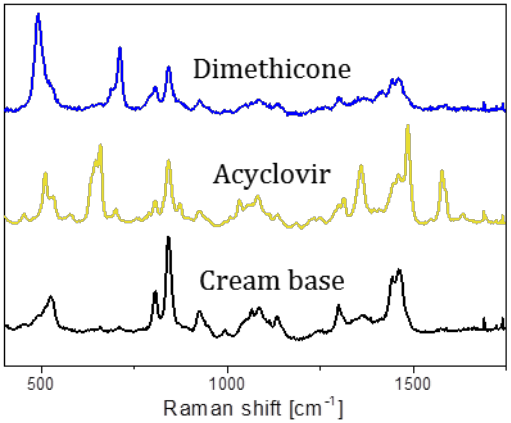


Data provided courtesy of Prof. Narasimha Murthy, U. Miss. & Dr. Frank Sinner, Joanneum Research

In Vitro BA/BE Assessment Methods

- Influence of Dose Dispensing on Product Quality

Prof. Michael Roberts FDA Award U01-FD005226



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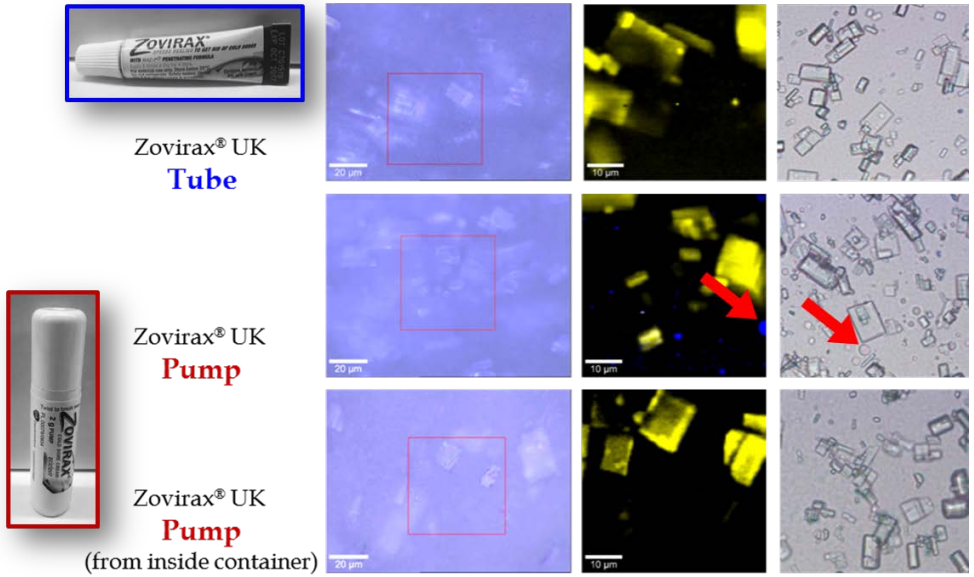

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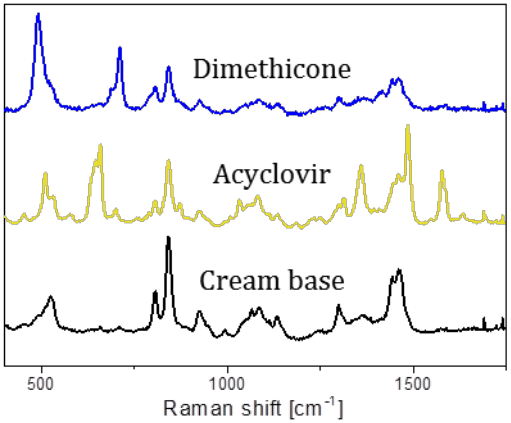

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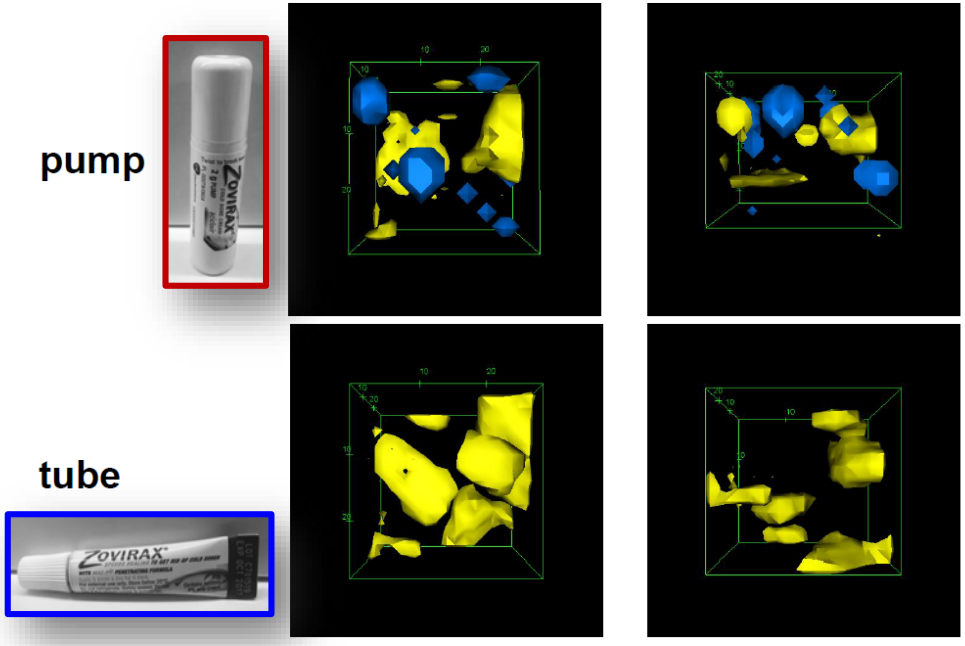

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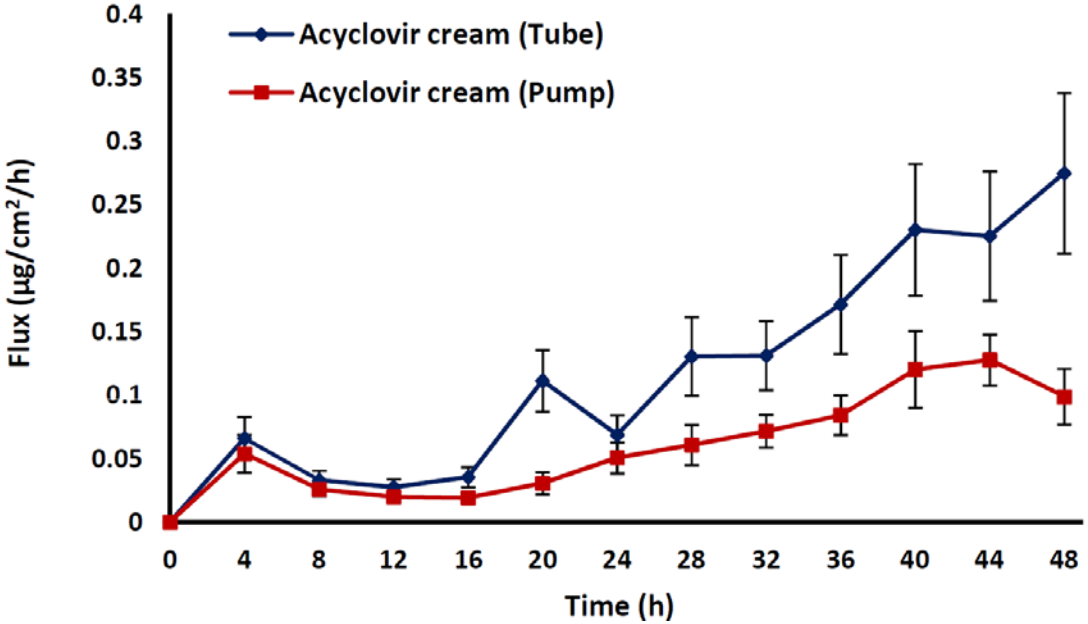

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Summary

- OGD is developing novel, sensitive and efficient in vivo and in vitro approaches to evaluate local BA and BE for complex semisolid topical drug products
- Sophisticated product characterizations systematically mitigate the risk of failure modes for therapeutic equivalence, ensuring bioequivalence by design
- These initiatives can now facilitate the availability of high quality topical drug products for patients who may not have previously had access to the medicine

Draft Guidance on Acyclovir Published!

- Docket Open for Comment

Contains Nonbinding Recommendations

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

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- **Frank Sinner, PhD**