Characterization Based Approaches for Establishing Bioequivalence Locally Acting Drug Products Applied to the Skin

Session III

The Global Bioequivalence Harmonisation Initiative

September 29, 2022

Priyanka Ghosh, PhD & Markham Luke, MD PhD

Office of Research and Standards (ORS), Office of Generic Drugs (OGD)

CDER | U.S. FDA

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This presentation reflects the views of the authors and should not be construed to represent FDA's views or policies.

Characterization-based BE Approach

- The components and composition of a topical product (and how it is manufactured) can modulate its physicochemical and structural (Q3) arrangement of matter
- These Q3 characteristics influence molecular interactions that control the rate and extent of topical bioavailability
- One approach to developing generic topical products is to:
  - Characterize the complexity of the reference standard
  - Match the formulation and Q3 characteristics of the reference standard
  - Understand product performance compared to the reference standard

Characterization-based BE Approach

A Modular and Scalable Approach to BE Evaluation

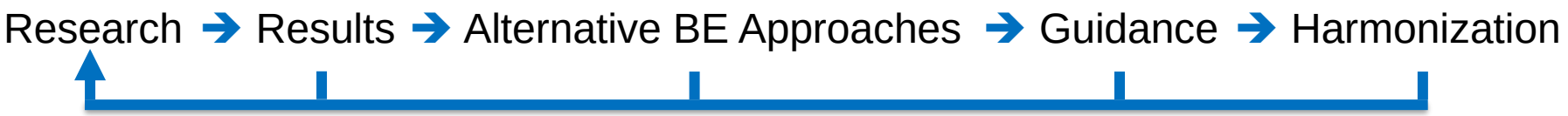
- Sameness of inactive ingredient components and quantitative composition, e.g., qualitative **(Q1)** and quantitative **(Q2)** sameness
- **Q3** (Physicochemical & Structural Characterization) as relevant to the nature of the product
- **IVRT** (In Vitro Release Test)
- **IVPT** (In Vitro Permeation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

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_020126.pdf

GDUFA Research Program

Enhance patient access to generic drug products

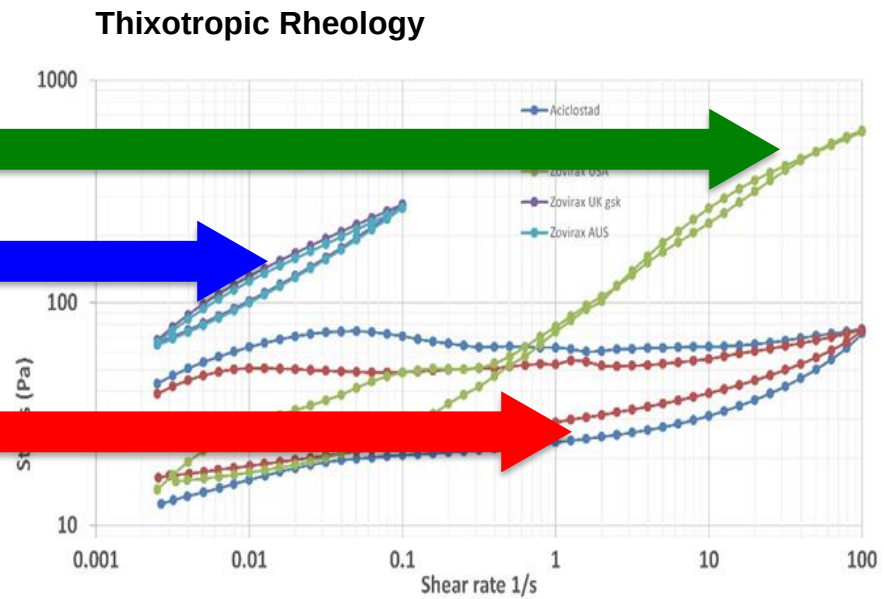
- Overcome barriers limiting generic drug development
- Utilize scientific evidence to establish efficient, modern BE standards
- Continually study, learn, evolve, refine, and harmonize



https://www.fda.gov/drugs/generic-drugs/science-research

In Vitro Characterization (Acyclovir)

	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				
	Cetostearyl alcohol	Cetostearyl alcohol	Cetostearyl alcohol	Cetyl alcohol	Cetyl alcohol
	SLS	SLS	SLS		
	Poloxamer 407	Poloxamer 407	Poloxamer 407		
		Dimethicone 20	Dimethicone 20		
		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



Rheological data were found to be very sensitive to formulation changes

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

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	Mineral oil	iquid Paraffin	Liquid Paraffin	iquid Paraffin	Viscous Paraffin
	White petrolatum	/hite soft paraffin	White Vaseline	/hite Vaseline	White Vaseline
	Cetostearyl alcoh	etostearyl alcohol	Cetostearyl alcoh	etyl alcohol	Cetyl alcohol
	SLS	LS	SLS		
	Poloxamer 407	oloxamer 407	Poloxamer 407		
		imethicone 20	Dimethicone 20	imethicone	Dimethicone
		rlacel 165	Glyceryl Mono Stearate	lyceryl Mono tearate	Glyceryl Mono Stearate
		rlacel 165	Polyoxyethylene stearate	/lacrogol tearate	Polyoxyethylene stearate
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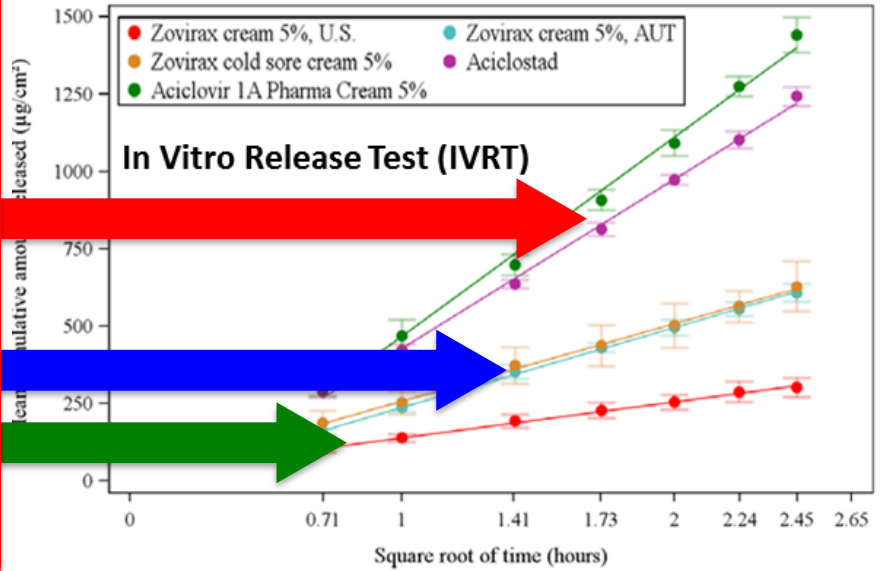

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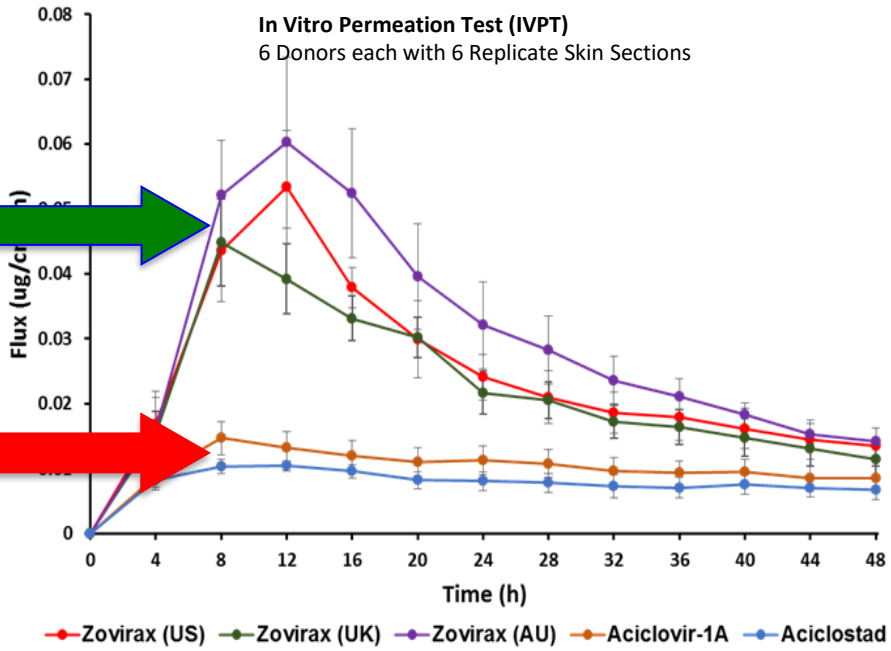
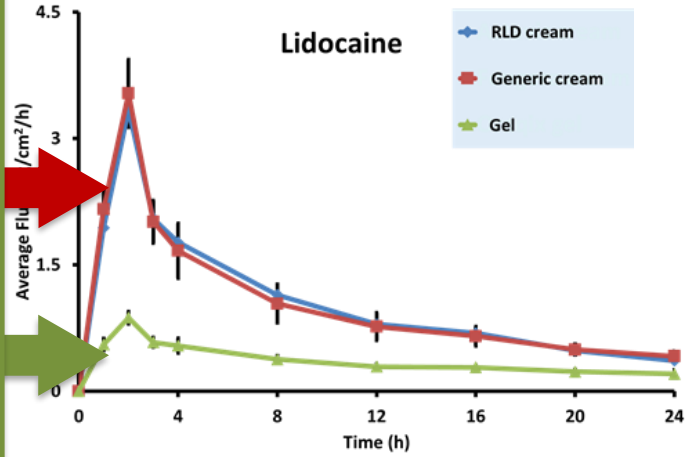


IVPT data suggested that bioavailability is correlated with Q3

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

In Vitro Characterization (Lidocaine)

Q3 Attribute	Lidocaine2.5%, Prilocaine2.5% RLD Cream		Lidocaine-2.5%, Prilocaine-2.5% Generic Cream		Lidocaine-2.5%, Prilocaine-2.5% Gel
pH	9.22 ± 0.08		8.92 ± 0.03		7.76 ± 0.05
Density (g/cc)	1.0142 ± 0.0002		1.0148 ± 0.0002		1.0374 ± 0.0001
WOA (g.sec)	59.427 ± 0.338		65.893 ± 0.614		3.186 ± 0.207
Particle Size of API (µm)	Lidocaine and Prilocaine completely dissolved				the formulation
Globule Size, d50 (µm)	3.30		3.00		
Drug in Aqueous Phase (µg/g)	Lidocaine	1.64 ± 0.06	Lidocaine	1.74 ± 0.12	---
	Prilocaine	1.99 ± 0.06	Prilocaine	2.11 ± 0.15	
Drug in Oil Phase (µg/g)	Lidocaine	23.45 ± 0.36	Lidocaine	23.21 ± 0.18	---
	Prilocaine	23.47 ± 0.18	Prilocaine	23.12 ± 0.2	
Water Activity	1.003 ± 0.002		1.004 ± 0.007		1.002 ± 0.005
Drying,T50 (min)	3.37 ± 0.15		3.82 ± 0.73		7.9 ± 0.46
Rheology Yield Stress(Pa)	36.7 ± 1.2		35.7 ± 0.6		15.7 ± 2.3



IVPT data suggested that bioavailability is correlated with Q3

Data provided courtesy of Prof. Narasimha Murthy associated with FDA funding for award U01FD0005233
RLD = Reference Listed Drug

In Vitro Characterization (Prilocaine)

Q3 Attribute	Lidocaine2.5%, Prilocaine2.5% RLD Cream		Lidocaine-2.5%, Prilocaine-2.5% Generic Cream		Lidocaine-2.5%, Prilocaine-2.5% Gel
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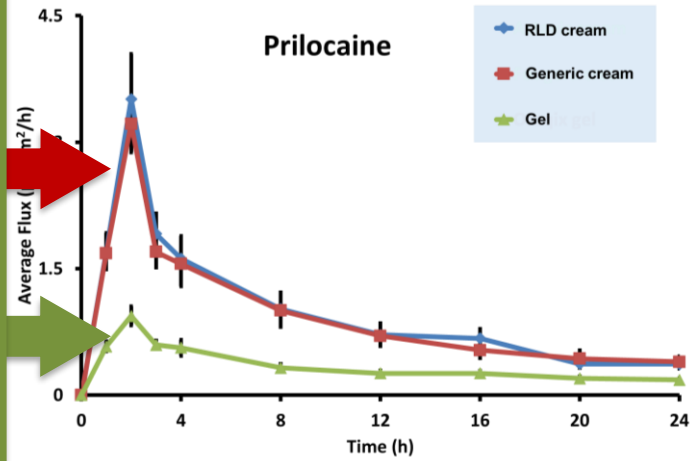

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Characterization-based BE Approach

A Modular and Scalable Approach to BE Evaluation

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- In vivo systemic **PK** studies may be appropriate for some products

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Acceptability of a Test Formulation

- Name of each ingredient in the formulation and information on ingredient grade are highly recommended
- Quantitative nominal amount for each (and every) ingredient in the composition table
- Quantitative nominal amount specified to same number of decimal places (at least two)

Ingredients	Function	% W/W
Tanasone, USP	Active ingredient	0.10
Ardamethacin, USP	Active ingredient	0.50
White Petrolatum, USP	emollient, oil phase	15.00
Mineral Oil, USP	emollient, oil phase	2.00
Cetyl alcohol plus stearyl alcohol (Stenol® I665)	stiffening agent, emulsifier	12.00
Propylene Glycol, USP	solvent, humectant	10.00
Ceteareth-30 (EUMULGIN® B 3)	Emulsifier	1.77
Sodium Phosphate Monobasic Dihydrate, USP	buffering agent	0.35
Sodium Hydroxide, NF	pH adjuster	0.003^
Phosphoric Acid, NF	pH adjuster	0.006^
Benzyl alcohol, NF	preservative	1.00
Purified Water, USP	Vehicle	58.00

^ QS to pH 5.5

Identification of Relevant Q3

*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)

Identification of Relevant Q3

*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

IVRT Studies

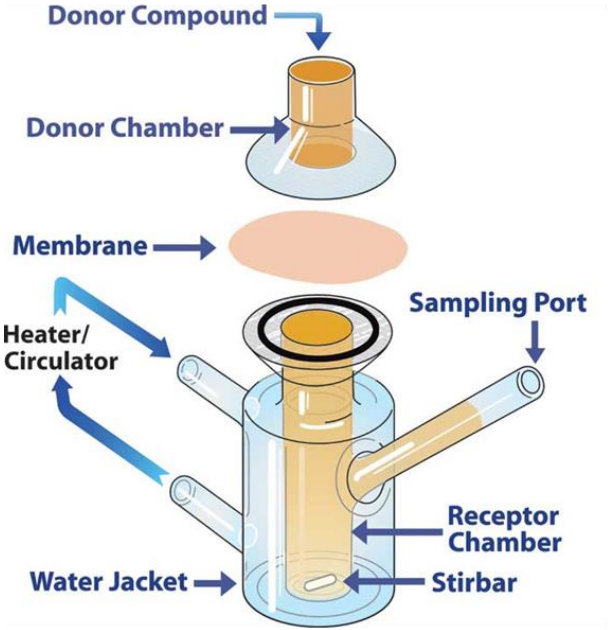
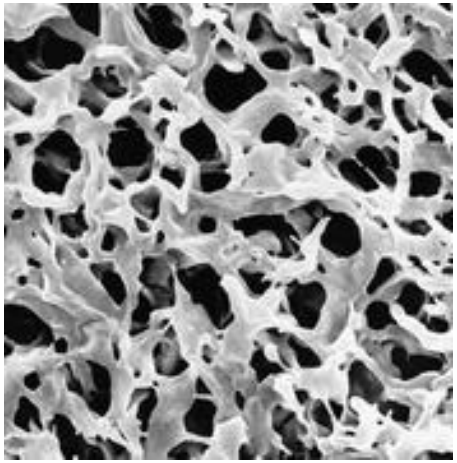
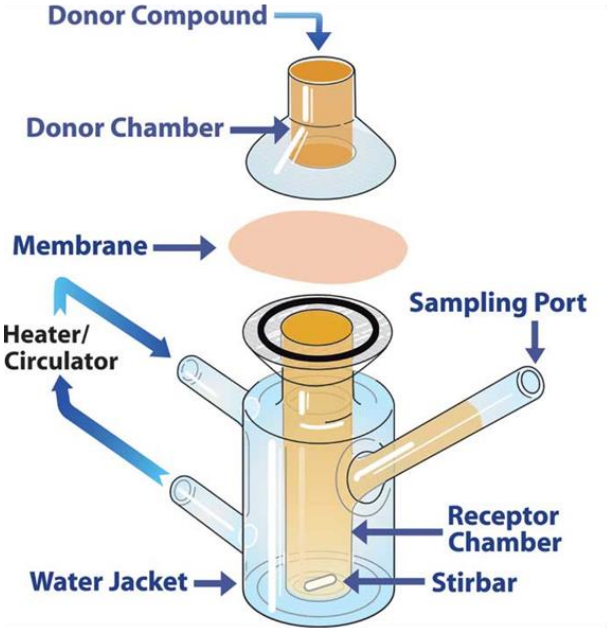


Image courtesy of PermeGear



IVPT Studies



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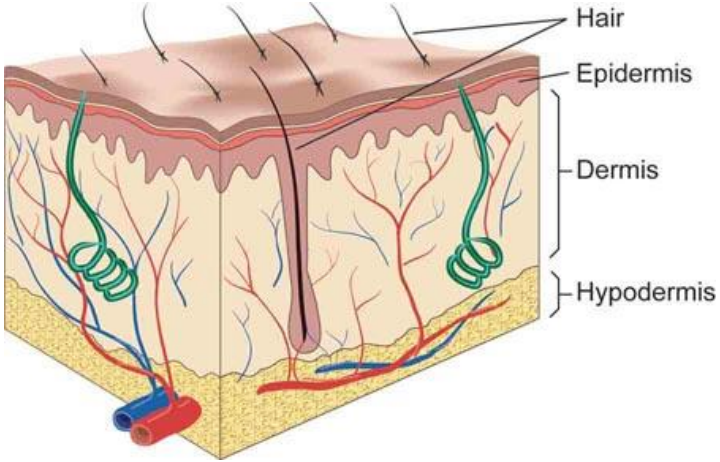
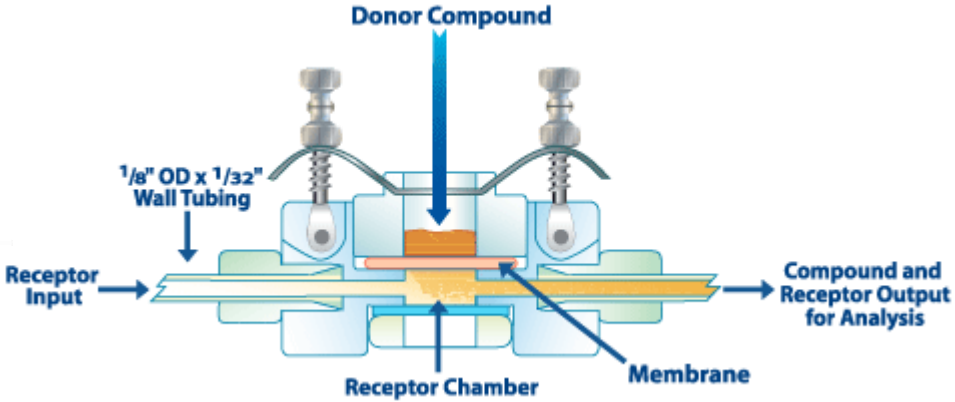
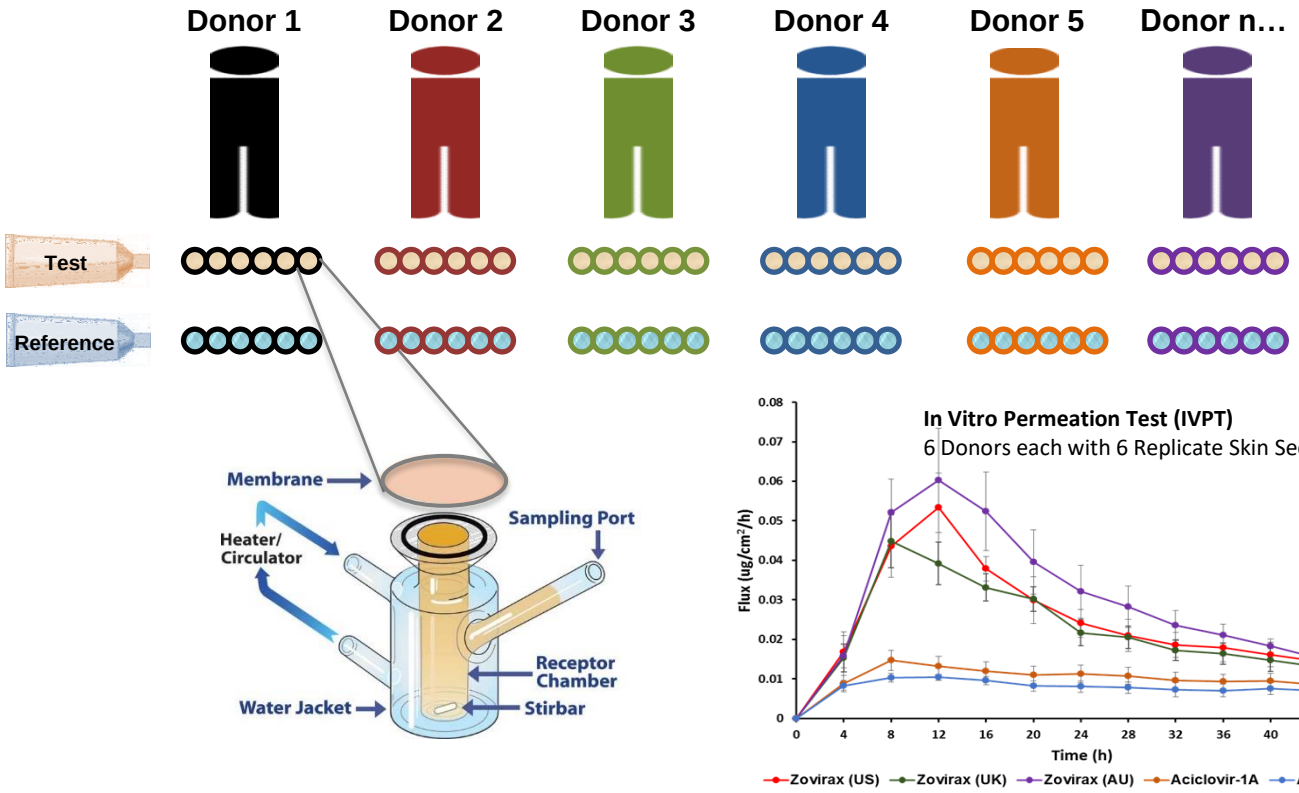




IVPT Study Design



Strategic Considerations for Establishing BE

Components and Composition

Prospective Generic Product

"No Significant Difference" in Formulation
(Characterization Based Approach)

- *Characterization of the Physical and Structural Properties **(Q3)***
- ***IVRT** (In Vitro Release Test)*
- ***IVPT** (In Vitro Permeation Test)*
- *In vivo systemic pharmacokinetic **(PK)** studies*
- *In ***silico**-based tools (Modeling and Simulation)*

"Differences" in Formulation
(Currently Under Development)

- *Impact of Formulation Differences on **Thermodynamic** Potential*
- ***Cutaneous PK** Approaches*
  - *Dermal Microdialysis*
  - *Dermal Open Flow Microperfusion*
  - *Raman Spectroscopy-based Tools*
- *Comparative Clinical Endpoint Studies*

Research Collaborations

- *Impact of Formulation Composition on the Structure and Performance Attributes of Topical Products with Sathyanarayana Murthy at Topical Products Testing LLC.*
- *Bioequivalence of Topical Products: Elucidating the Thermodynamic and Functional Characteristics of Compositionally Different Topical Formulations with Michael Roberts at University of South Australia*
- *Elucidating Sensorial and Functional Characteristics of Topical Formulations with Yousuf Mohammed at University of Queensland*
- *Characterization of Key System Parameters of Mechanistic Dermal PBPK Models in Various Skin Diseases and Performance Verification of the Model Using Observed Local and Systemic Concentrations with Sebastian Polak at Simcyp, Ltd.*
- *Formulation Drug Product Quality Attributes in Dermal Physiologically-Based Pharmacokinetic Models for Topical Dermatological Drug Products and Transdermal Delivery Systems with Michael Roberts at University of Queensland*
- *Assessment of Transdermal Drug Product Quality and Performance Attributes via Enhanced Virtual Bioequivalence Simulations with Jessica Spires at Simulations Plus, Inc*

https://www.fda.gov/media/146749/download#page=122

Summary

- Topical drug products applied to the skin are generally complex dosage forms
- Understanding the microstructure of a given formulation, in situ and during metamorphosis, is critical for an assessment of BE of the active ingredient(s) from the drug product
- Characterization based approaches, that are currently reflected in product-specific guidances (PSGs), can serve as an efficient mechanism for evaluation of BE
- Such approaches are designed to develop high quality generic products that are well matched with the reference standard
- Goal of the GDUFA regulatory science research program is to facilitate the development of such tools that can be utilized for establishing BE and thereby enhance the availability of generic topical drug products

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- Sam Raney, PhD
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- Ahmed Zidan, PhD
- Pahala Simamora, PhD
- Bing Cai, PhD
- Robert Lionberger, PhD

Research Collaborators

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Cutaneous Pharmacokinetic Based Approaches for Establishing Bioequivalence
Locally Acting Drug Products Applied to the Skin

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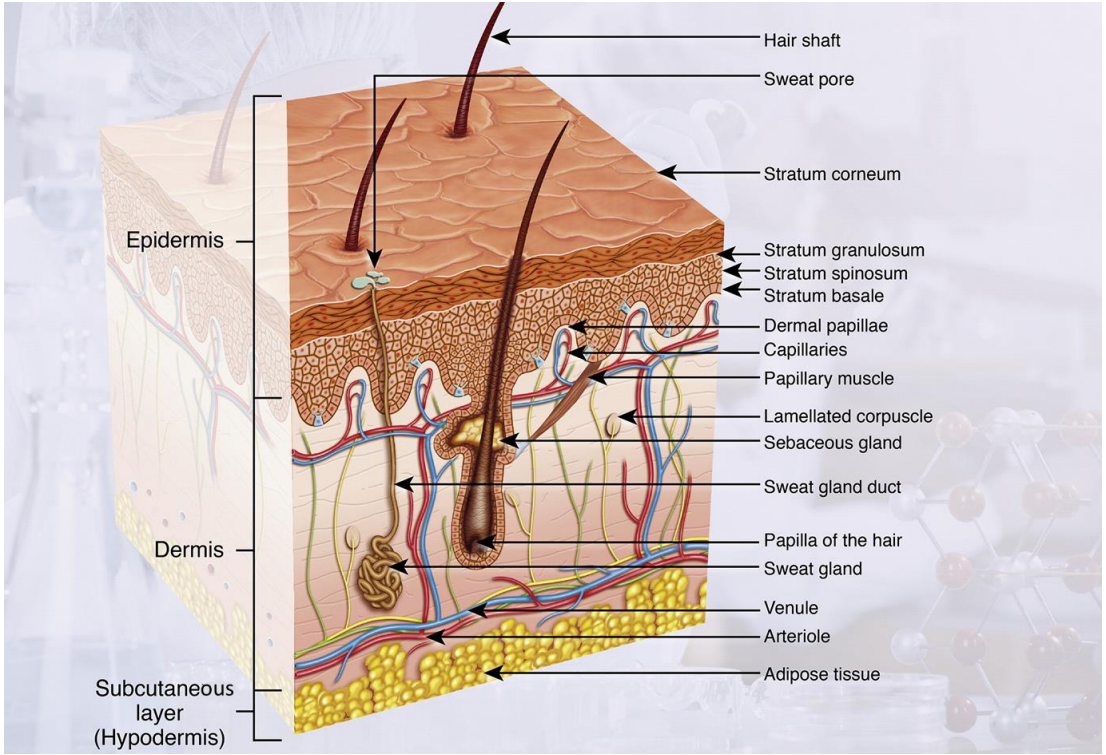
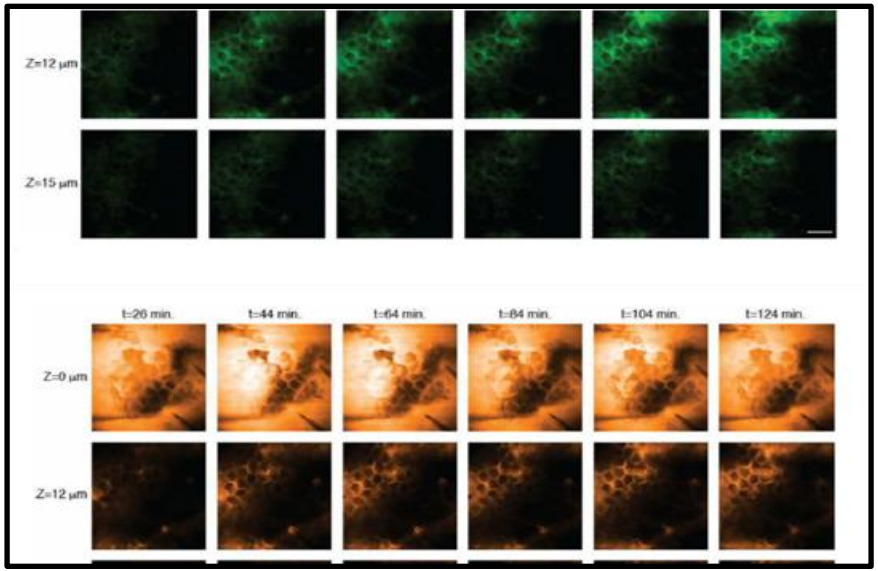
From Anatomy to Pharmacology

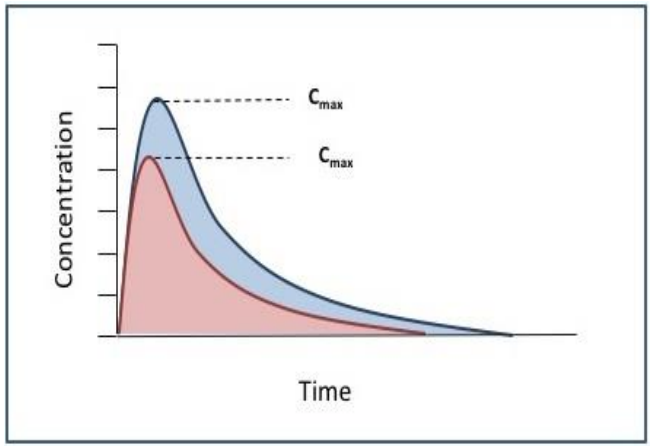


Mathes et al., *Adv Drug Deliv Rev.* **2014**, 69-70, 81-102

Potential of Cutaneous PK

Can we develop **cutaneous PK** based methods to quantify drugs in **“real time”** at or near the **site of action** in the skin?



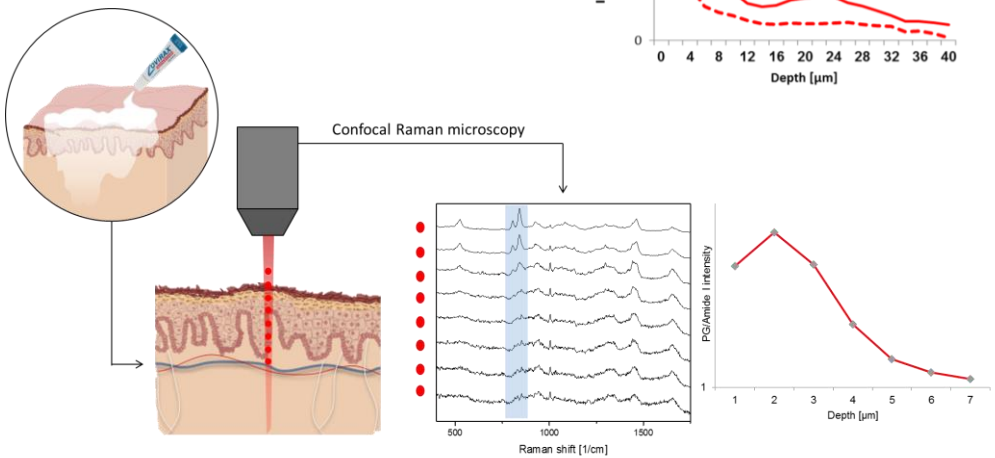


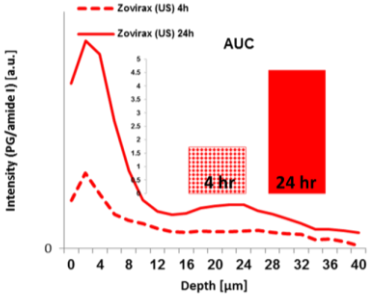
Saar Brian G. , Contreras-Rojas L. Rodrigo , Xie X. Sunney , and Guy Richard H. **Imaging Drug Delivery to Skin with Stimulated Raman Scattering Microscopy** Molecular Pharmaceutics **2011** 8 (3), 969-975

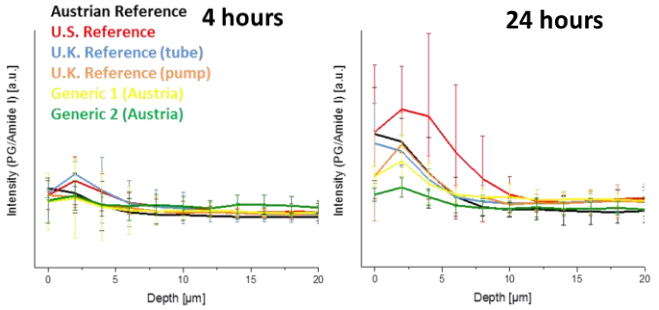
Cutaneous PK Techniques

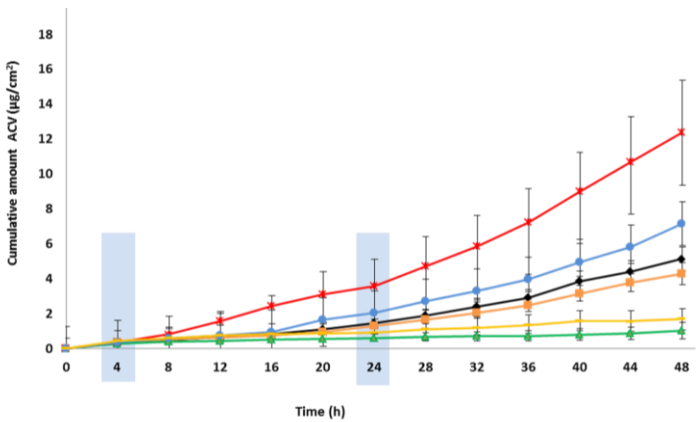
- Epidermal PK
  - Tapestripping “Dermatopharmacokinetics” (DPK)
  - In vitro Permeation Testing (IVPT)
  - Epidermal and/or Dermal Pharmacokinetic Tomography e.g., Raman based methods
- Dermal PK
  - Dermal Open Flow Microperfusion (dOFM)
  - Dermal Microdialysis (dMD)

Epidermal PK







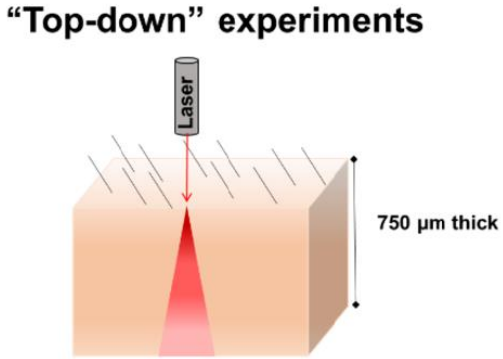


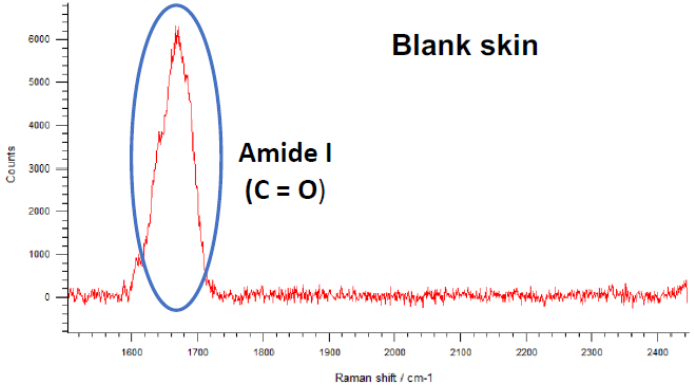
Challenges with imaging-based tools

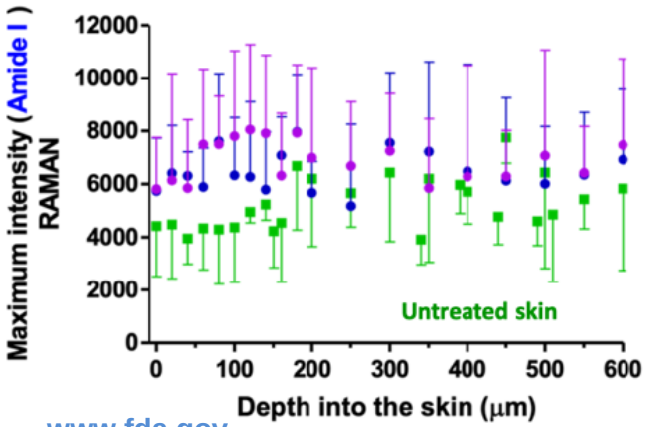
Historical limitations

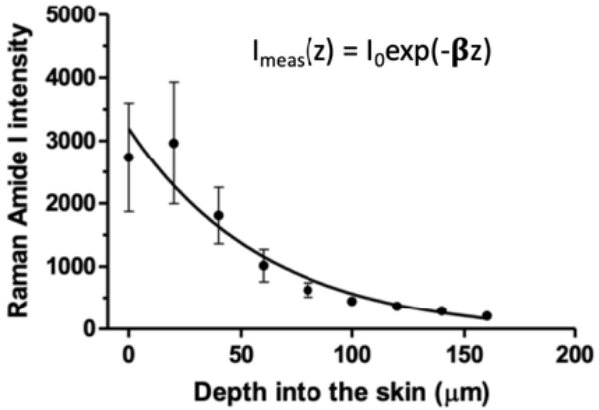
- *Challenges with detection of molecule in the skin*
- *Challenges related to signal attenuation within the skin*
- *Challenges related to utility of tool as a semi-quantitative evaluation technique*
- *Challenges associated with limited utility, applicable for molecules with unique Raman signal*
- *Challenges related to data collection and data analysis of spectroscopic data*
- *Development of validation strategies for utilization of method in a regulatory setting*

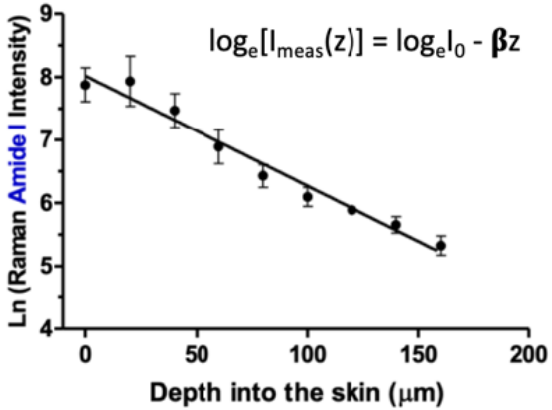
Strategies to Correct for Signal Attenuation





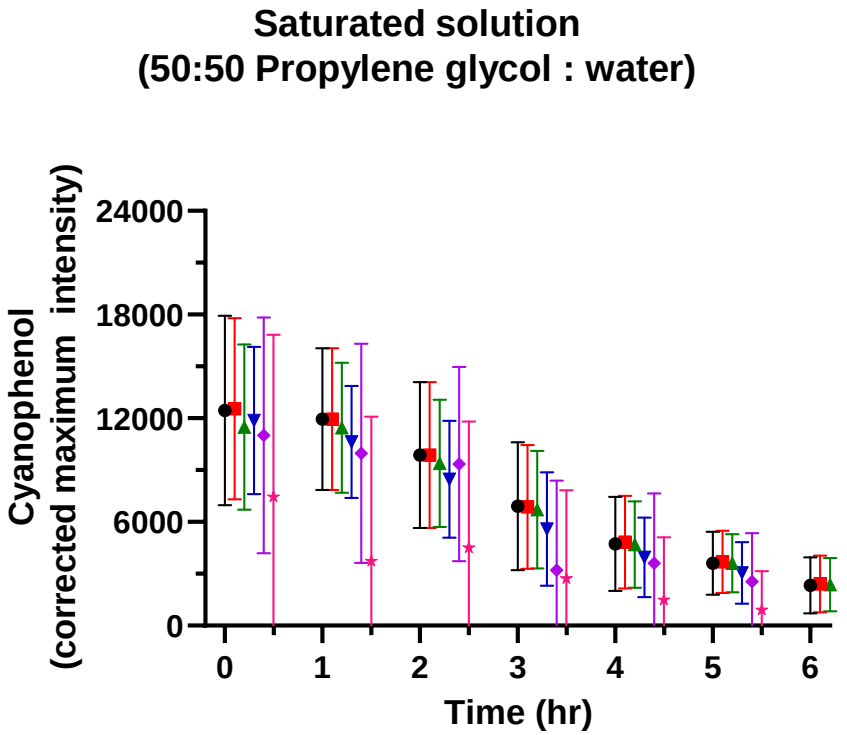


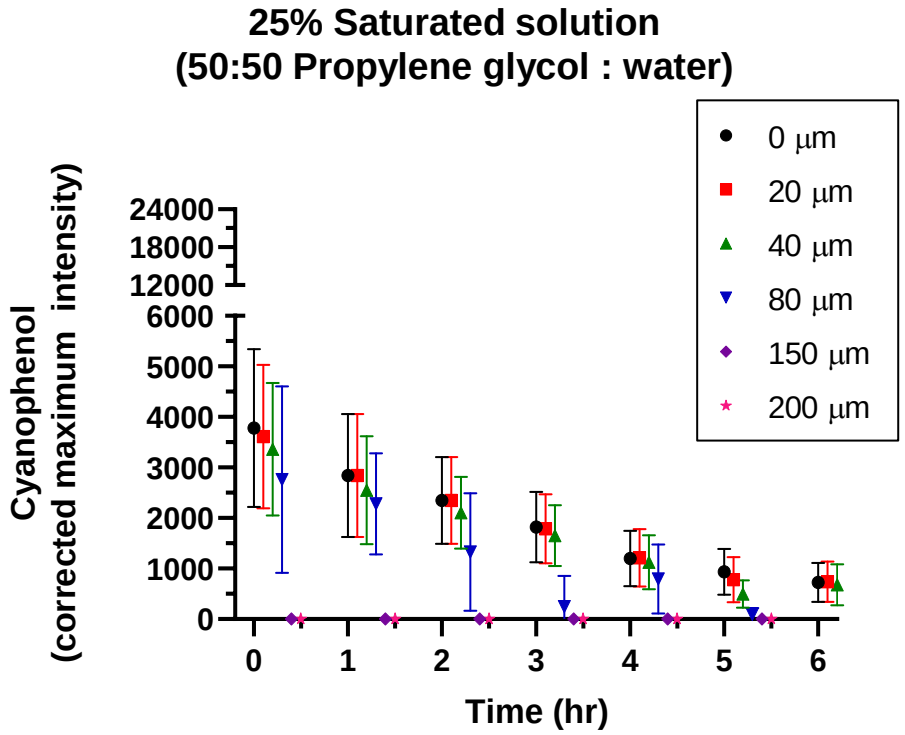




Prof. Richard Guy FDA Award U01-FD006533

Evaluation of Epidermal PK



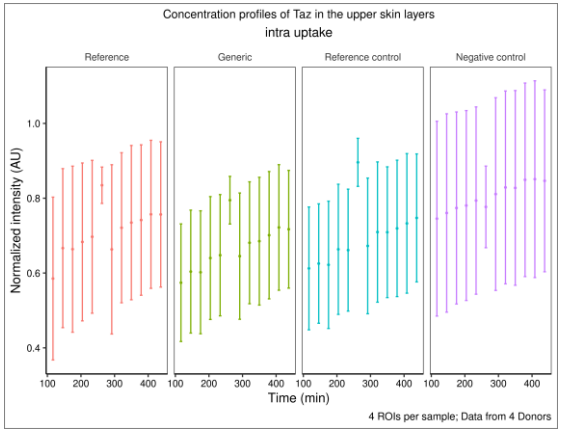


Prof. Richard Guy FDA Award U01-FD006533

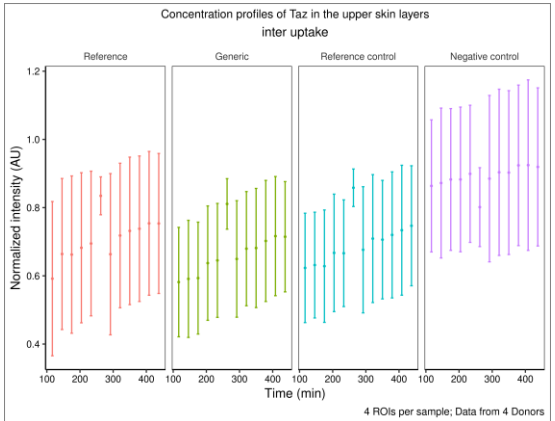
Evaluation of Epidermal PK

Reference product: Tazorac® cream (x2) **Test product**: Generic tazarotene cream **Alternate formulation**: Tazorac® gel **Alternate formulation**: Lab made tazarotene solution in PEG	
Number of skin samples & regions of interest (ROIs)	4 donors 4 replicates per formulation 4 ROIs per skin sample
Depth stack	Step size: 8 µm; final depth at 64 µm
Study duration	~6.5 hours of imaging (15 cycles)
Skin uptake conditions	Finite dose (5 µL); Occlusive; 32°C

Within Lipid-Rich Skin Regions



Within Lipid-Poor Skin Regions



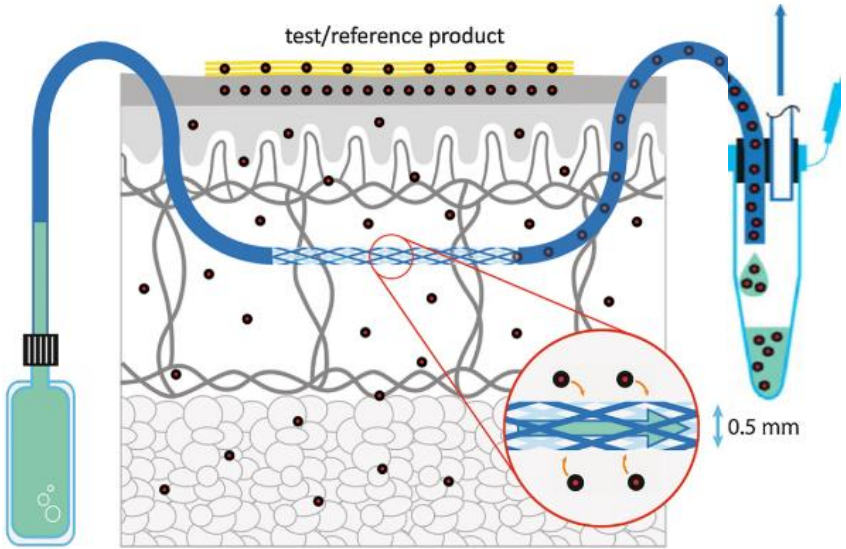
Prof. Conor Evans FDA Award U01-FD006698

Current Thinking and Next Steps

- *Detection of molecule in the skin*
  - *We can detect certain active ingredients in formulations; however, we are exploring advanced techniques e.g., Sparse Spectral Sampling Stimulated Raman Scattering*
- *Utility of tool as a semi-quantitative evaluation technique*
  - *Preliminary in vitro data with multiple molecules suggests that comparison of cutaneous PK is feasible using the technique*
- *Data collection and data analysis of spectroscopic data*
  - *Multiple approaches including Deep Learning utilized to automate data collection and processing*
- *Development of validation strategies for utilization of method in a regulatory setting*
  - *Currently we are utilizing available data to identify relevant parameters for assessment of cutaneous PK data*
  - *Future scope of work would include development of method validation strategies*

Dermal PK

- Microdialysis (dMD) and Open Flow Microperfusion (dOFM) directly measure the in vivo rate and extent of drug bioavailability at/near the site of action in the skin.



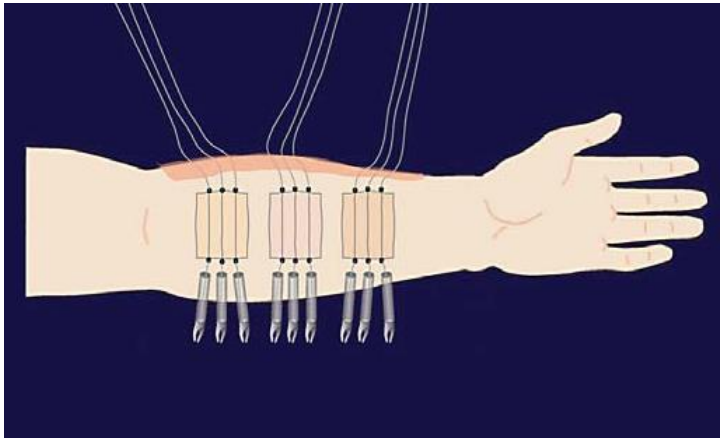


Image provided courtesy of Dr. Frank Sinner, Joanneum Research

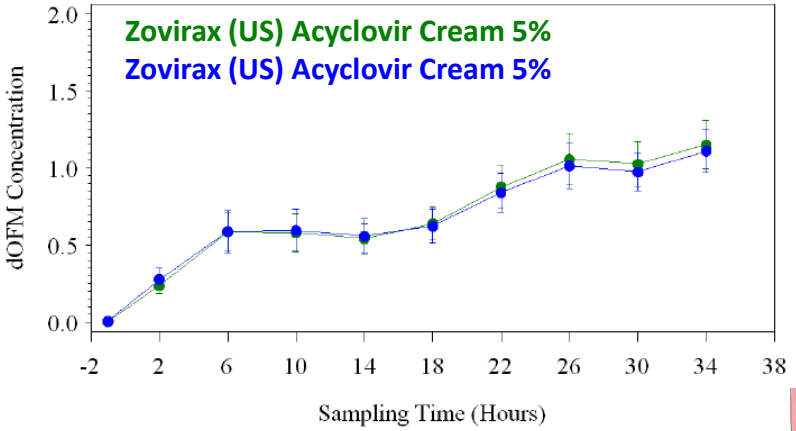
Skin Pharmacol Physiol 2011;24:44–53

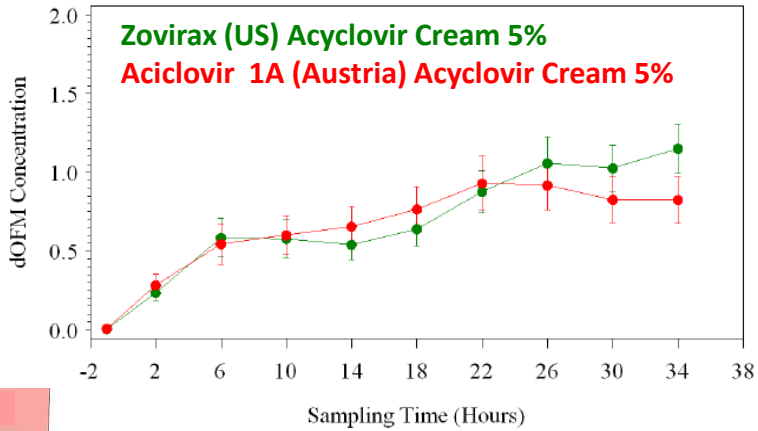
Dermal PK

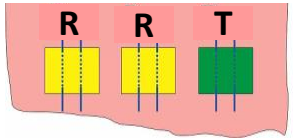
Historical limitations

- Analytical limitations/High variability in the data
- Study controls: Application site, dose, application technique, probe depth, barrier integrity, flow rates
- Development of data analysis strategies
- Development method validation strategies

Dermal PK - dOFM





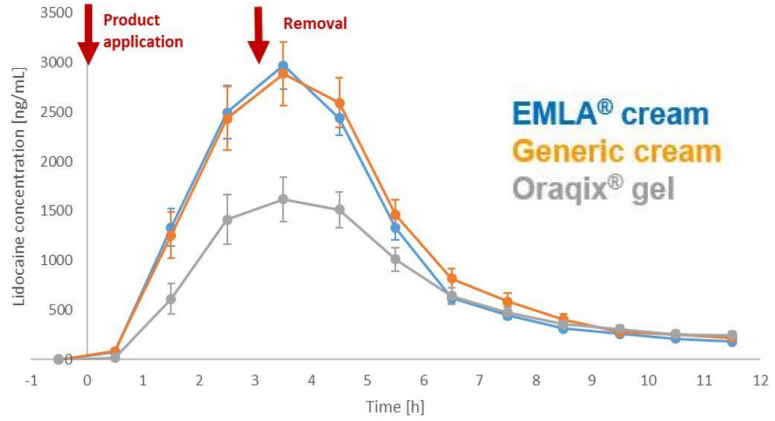


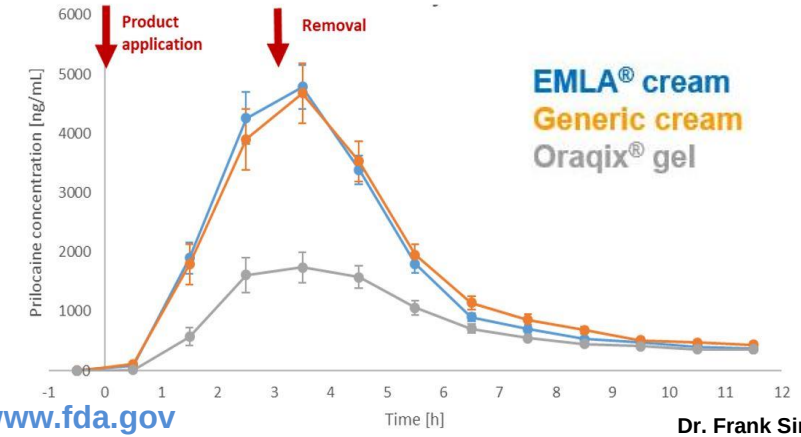
Outcome variable	$CI_{90\%}$	BE-limits	BE
$log(AUC_{0-36h})$	[-0.148 ; 0.162] or [86.2 % ; 117.5 %]	[-0.223 ; 0.223] or [80% ; 125%]	passed
$log(C_{max})$	[-0.155 ; 0.190] or [85.7 % ; 120.9%]		passed

Outcome variable	$CI_{90\%}$	BE-limits	BE
$log(AUC_{0-36h})$	[-0.369 ; 0.050] or [69.1 % ; 105.2 %]	[-0.223 ; 0.223] or [80% ; 125%]	x Failed
$log(C_{max})$	[-0.498 ; 0.022] or [60.8 % ; 102.2%]		x Failed

Bodenlenz M, et al. **Open Flow Microperfusion as a Dermal Pharmacokinetic Approach to Evaluate Topical Bioequivalence.** Clin Pharmacokinet. 2017 Jan;56(1):91-98.

Dermal PK - dOFM



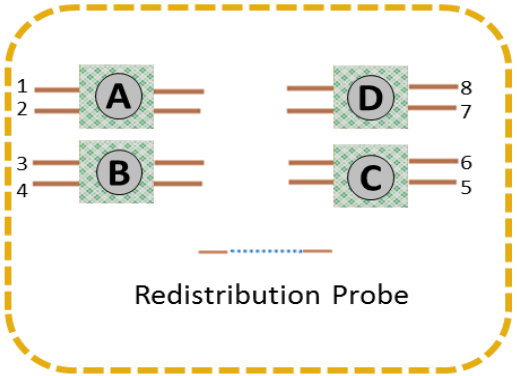


R: EMLA® (lidocaine; prilocaine) topical cream, 2.5%; 2.5 %
$T_{generic}$: generic lidocaine; prilocaine cream, 2.5%; 2.5%
$T_{non\text{-}equ}$: Oraqix®(lidocaine; prilocaine) dental gel, 2.5%; 2.5%

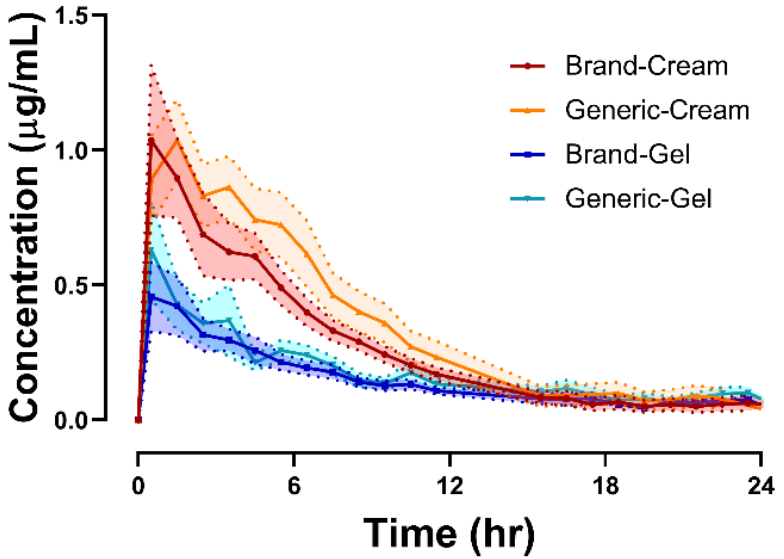
	PK endpoint	Drug	95% upper confidence bound	BE - criterion satisfied	Result
T_{gen} vs. R_1	$AUC_{0\text{-}12}$	lidocaine	-0.053	Yes	The generic cream is **bioequivalent** to the reference cream.
	C_{MAX}		-0.055	Yes	
	$AUC_{0\text{-}12}$	prilocaine	-0.051	Yes	
	C_{MAX}		-0.043	Yes	
$T_{non\text{-}equ}$ vs. R_2	$AUC_{0\text{-}12}$	lidocaine	0.330	No	The gel is **not bioequivalent** to the reference cream.
	C_{MAX}		0.623	No	
	$AUC_{0\text{-}12}$	prilocaine	0.703	No	
	C_{MAX}		1.174	No	

Dr. Frank Sinner FDA Award U01-FD005861

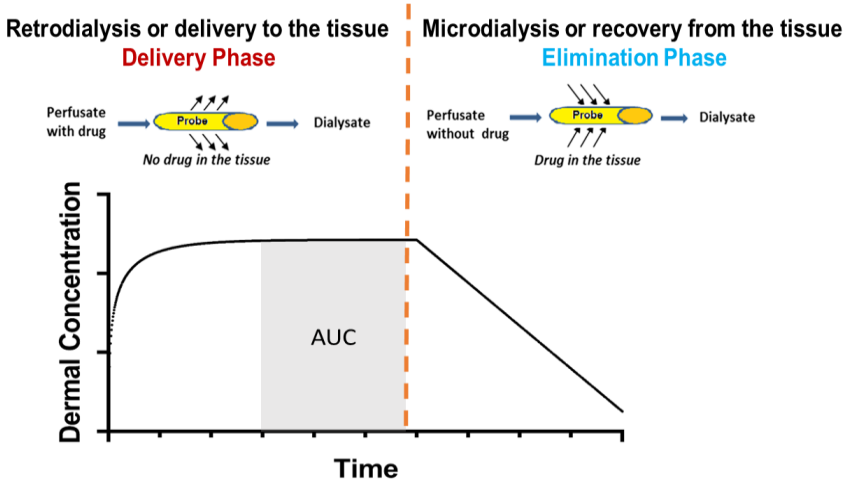
Dermal PK - Microdialysis

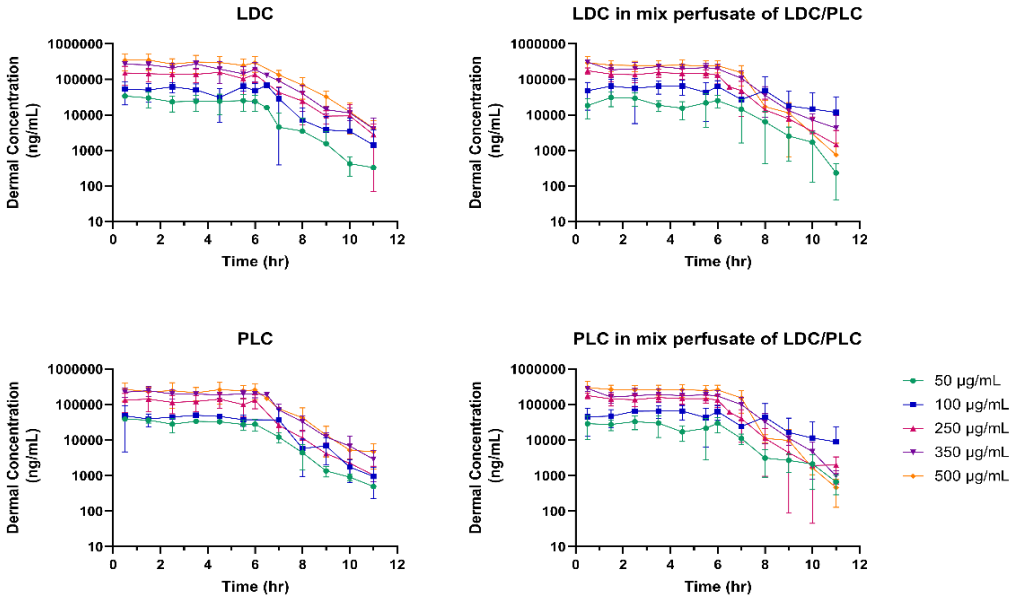


- MetroGel® topical gel, 0.75% “Brand Gel”
- Metronidazole topical gel, 0.75% “Generic Gel”
- MetroCream® topical cream, 0.75% “Brand Cream”
- Metronidazole topical cream, 0.75% “Generic Cream”



Dermal PK - Microdialysis





Prof. Grazia Stagni FDA Award U01-FD005862

Current Thinking and Next Steps

- *Analytical limitations/High variability in the data*
  - *We can reliably detect and compare active ingredients(s) in the dermis following topical application, approximately 20 subjects were used for the BE assessment*
- *Study controls: Application site, dose, application technique, probe depth, barrier integrity, flow rates*
  - *Relevant study controls have been identified and implemented*
- *Development of validation strategies for utilization of method in a regulatory setting*
  - *Currently we are utilizing available data to identify relevant parameters for assessment of cutaneous PK data*
  - *Equipment and method validation strategies*
  - *How we can use dermal PK data in conjunction with other available information/strategies (e.g., formulation information, modeling and simulation-based approaches) to support generic product development*

Research Collaborations

- *Novel methodologies and IVIVC approaches to assess BE of topical drugs with Frank Sinner at Joanneum Research*
- *Development of a Universal Bioequivalence Test Method for Topical Drugs Using dOFM with Frank Sinner at Joanneum Research*
- *Benchmark of Dermis Microdialysis to Assess Bioequivalence of Dermatological Topical Products with Grazia Stagni at Long Island University.*
- *Elucidating Fundamental Principles of Dermal Pharmacokinetics via Microdialysis with Grazia Stagni at Long Island University*
- *Assessing the Skin Pharmacokinetics of Topical Drugs, and the Bio(in)equivalence of Topical Drug Products, Using Non-Invasive Techniques with Richard Guy at University of Bath*
- *U01FD006698 Pharmacokinetic Tomography for the Measurement of Topical Drug Product Bioequivalence with Conor Lee Evans at Massachusetts General Hospital/Harvard Medical School*

https://www.fda.gov/media/146749/download#page=122

Summary

- Cutaneous PK techniques can be utilized to develop efficient strategies for evaluation of bioavailability for topical products applied to the skin
- Epidermal PK based methods appear to be promising, however they are currently in the early stages of development
- dOFM and dMD methods have the potential to support a demonstration of BE when the proposed method is optimized and controlled to be adequately discriminating and reproducible
- Goal of the Generic Drug User Fee Amendments (GDUFA)-funded research program is to develop efficient BE approaches for complex generic drug products including topical products applied to the skin

Relevant Resources

- **General guidances**
  - Topical Dermatologic Corticosteroids: in Vivo Bioequivalence https://www.fda.gov/media/70931/download
  - Bioequivalence studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA" for the design and conduct of the PK BE study https://www.fda.gov/media/87219/download
  - Assessing Adhesion with Transdermal Delivery Systems and Topical Patches for ANDAs https://www.fda.gov/media/98634/download
  - Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs https://www.fda.gov/media/117569/download
  - Transdermal and Topical Delivery Systems – Product Development and Quality Considerations https://www.fda.gov/media/132674/download
- **Product-Specific Guidances for Generic Drug Development** https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances- generic-drug-development

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Research Collaborators

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GDUFA Award U01-FD005226

- **Dr. Michael Roberts, University of South Australia**

GDUFA Award U01FD005862

GDUFA Award U01FD006930

- **Dr. Grazia Stagni, Long Island University**

GDUFA Award U01FD006533

- **Dr. Richard Guy, University of Bath**

GDUFA Award U01FD006698

- **Dr. Conor Lee Evans at Massachusetts General Hospital/Harvard Medical School**

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