Novel Approaches for Evaluating Bioavailability and Bioequivalence (BE) of Topical Drug Products

American Association of Pharmaceutical Scientists (AAPS)
Pharm Sci 360 Annual Meeting

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Office of Generic Drugs| CDER | U.S. FDA

October 18, 2022

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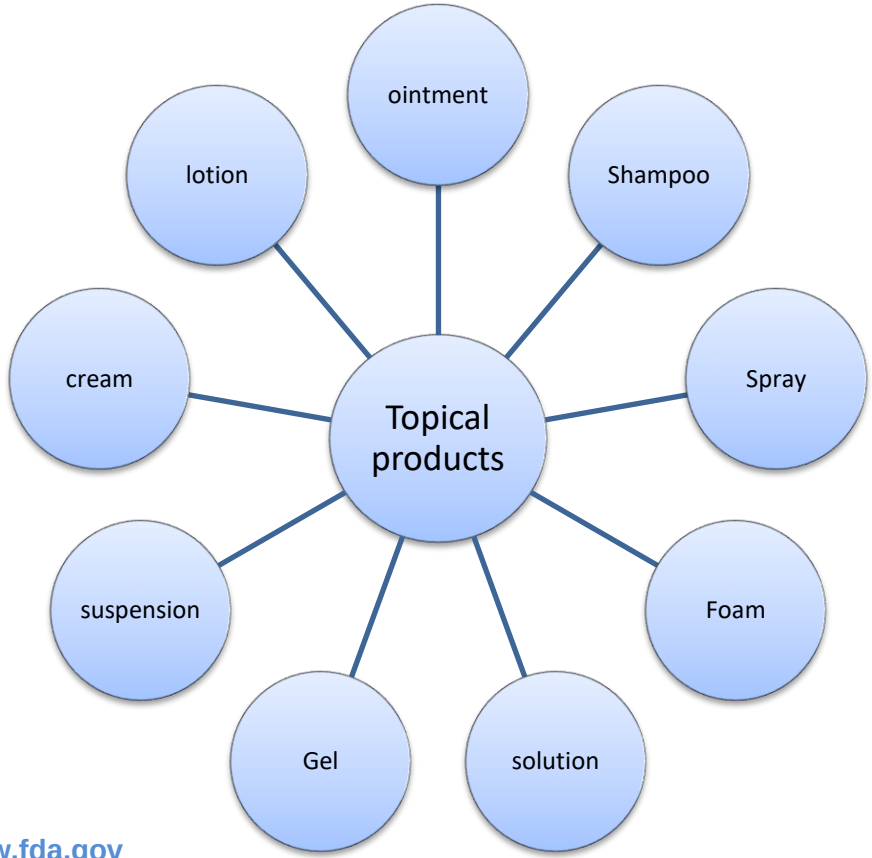
Topical Drug Products



www.fda.gov

https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm

BE for Topical Drug Products

Current approaches for establishing BE for complex topicals in product-specific guidances (PSGs):

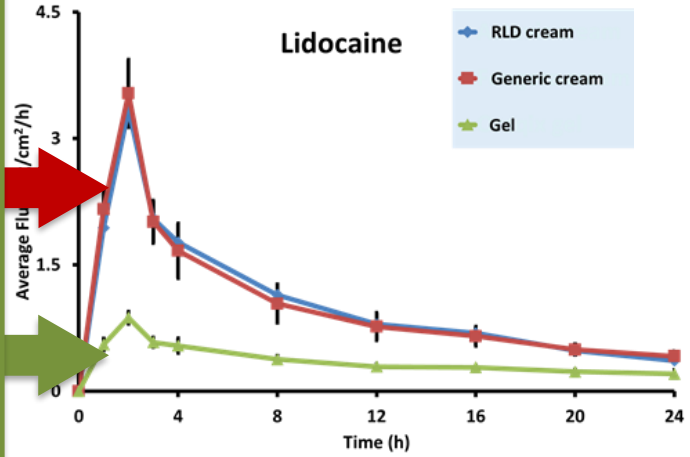
- Comparative in vivo BE studies
  - Clinical endpoint
  - Pharmacodynamic endpoint (e.g., vasoconstrictor (VC) studies)
- Efficient characterization-based BE studies
  - in vitro characterization and performance tests
  - in vivo pharmacokinetic (PK) studies

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

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

Rangappa et al. 2019 AAPS Poster, ***FDA award U01FD005233***

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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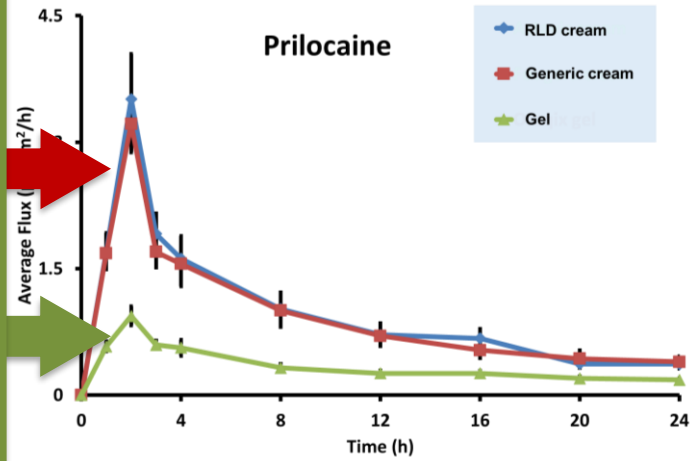


IVPT data suggested that bioavailability is correlated with Q3

Rangappa et al. 2019 AAPS Poster, ***FDA award U01FD005233***

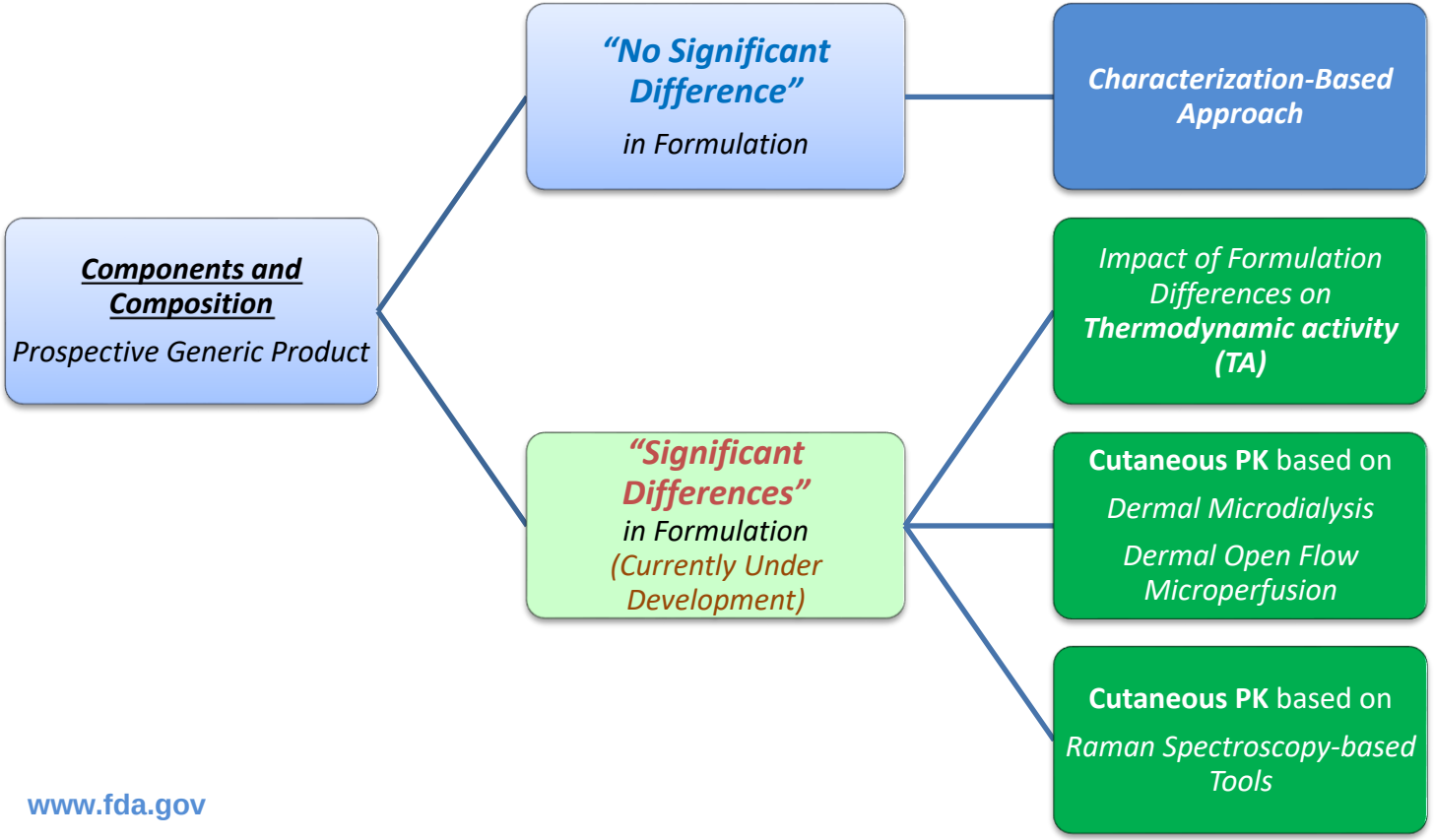
RLD = Reference Listed Drug

Characterization-Based BE Approach

A Modular and Scalable Approach to BE Evaluation that can include the following criteria/studies:

- 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

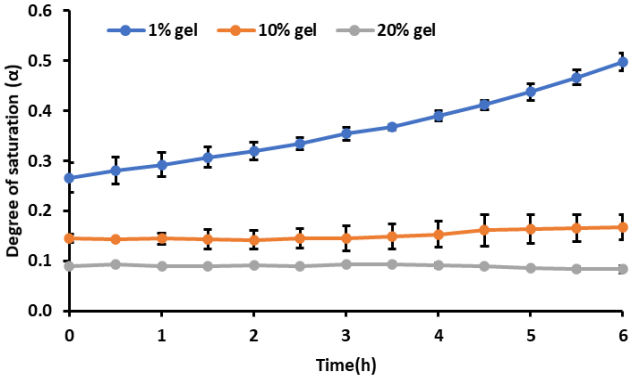
Potential Efficient Strategies for BE



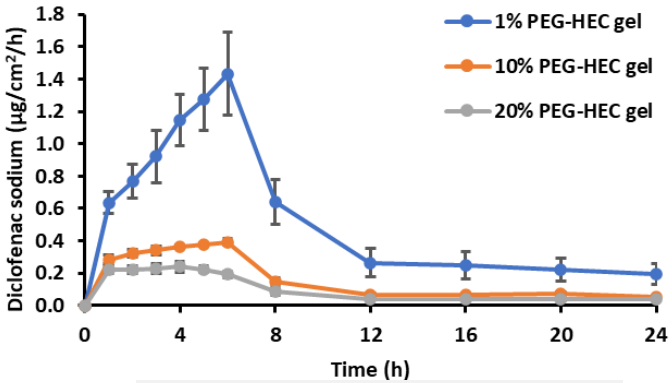
Compositional Differences and TA

Understanding the function of excipients and their impact on thermodynamic activity of the drug in the topical formulations.

Diclofenac sodium gels with different amounts of polyethylene glycol (PEG) 200



Change in DS of the diclofenac sodium in the gels over time



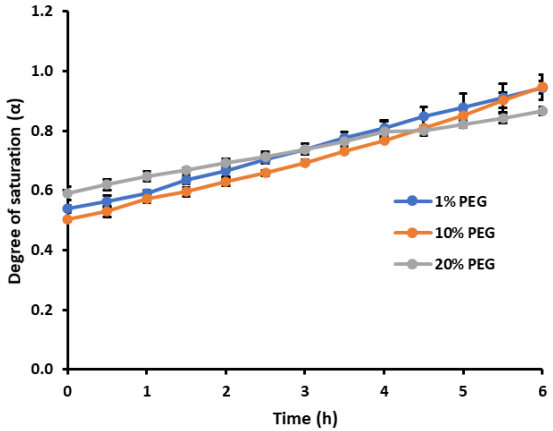
Permeation profile of diclofenac from diclofenac sodium gels

Rangappa et al. 2021 AAPS Poster, FDA Award U01FD006507

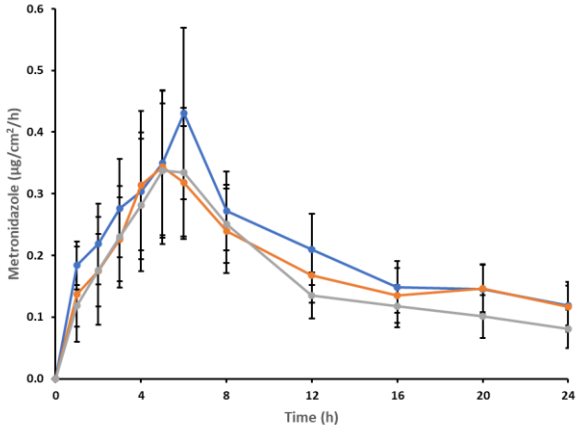
Compositional Differences & Bioavailability

Understanding the function of excipients and their impact on thermodynamic activity of the drug in the topical formulations.

Metronidazole gels with different amounts of PEG 200



Fractional solubility of metronidazole gels

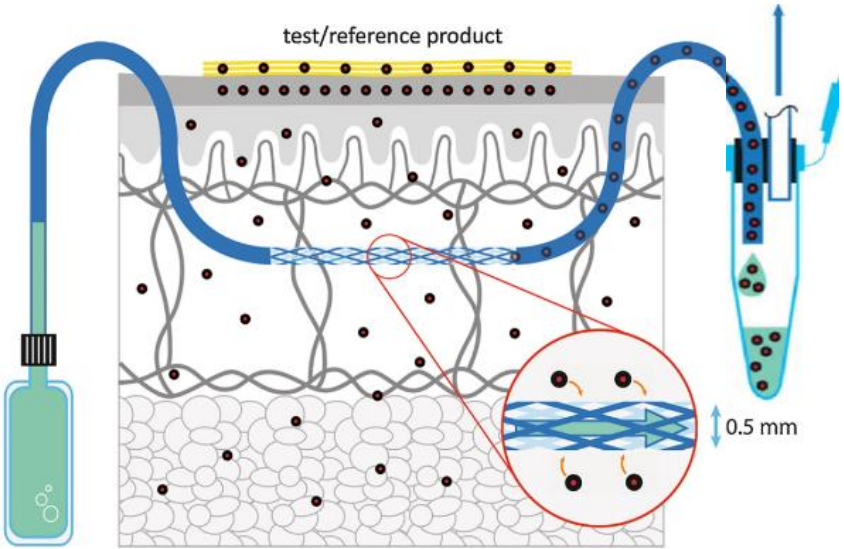


: Flux profiles of metronidazole gels using a semi-infinite dose (n=6 replicates per skin donor; 3 skin donors; data presented as mean of 3 donor data ± SEM)

Rangappa et al. 2022 AAPS Poster, FDA Award U01FD006507

Cutaneous PK: Dermal Sampling Techniques

- 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.



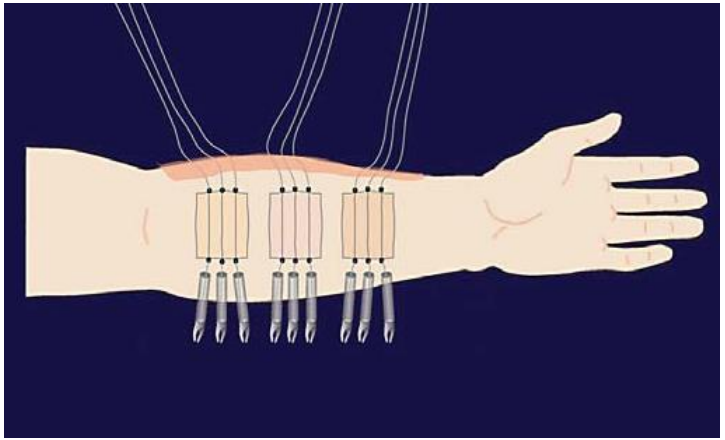


Image provided courtesy of Dr. Frank Sinner, Joanneum Research

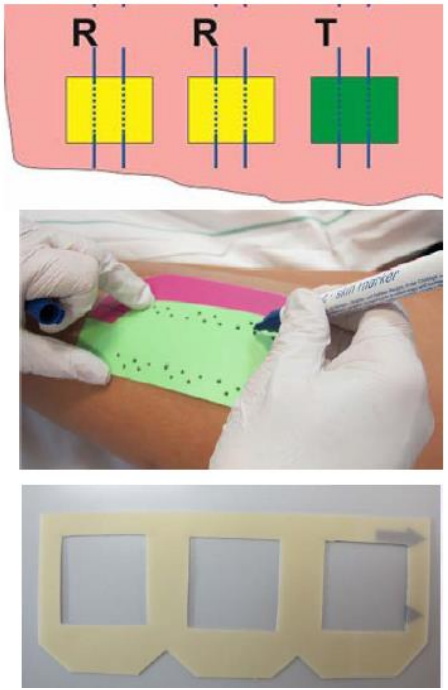
Skin Pharmacol Physiol 2011;24:44–53

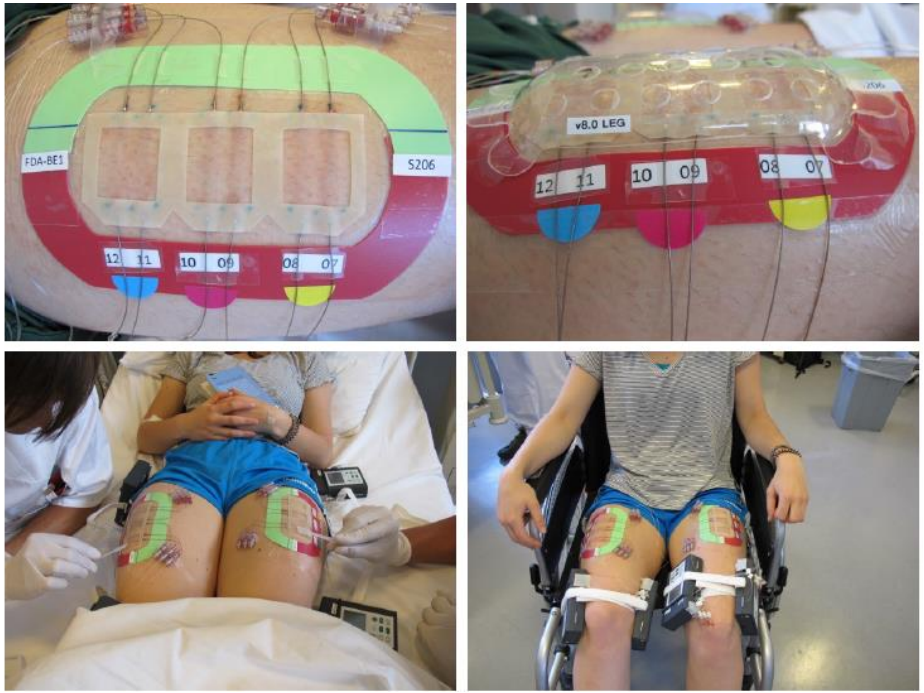
Dermal Sampling Techniques

Examples of Traditional limitations and challenges:

- Limited utility for certain classes of drugs
- High variability in the data
- Immobilization of study participants while connected to pumps and tubing
- Study durations too brief (e.g., 4-5h) for adequate comparison of the products
- Establishing BE criteria

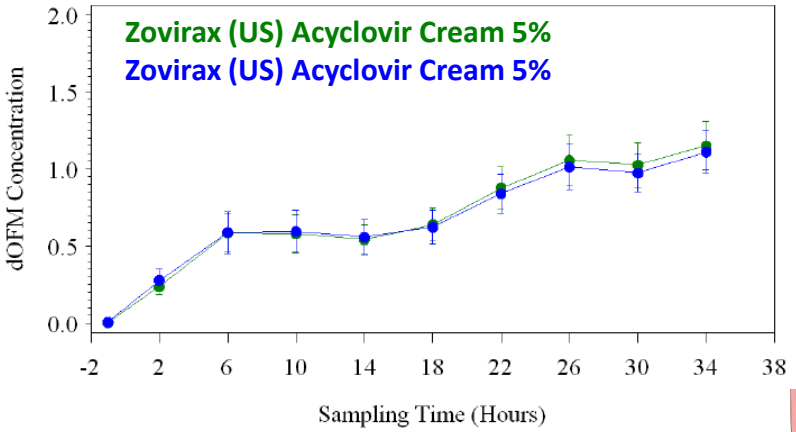
dOFM Study Set UP

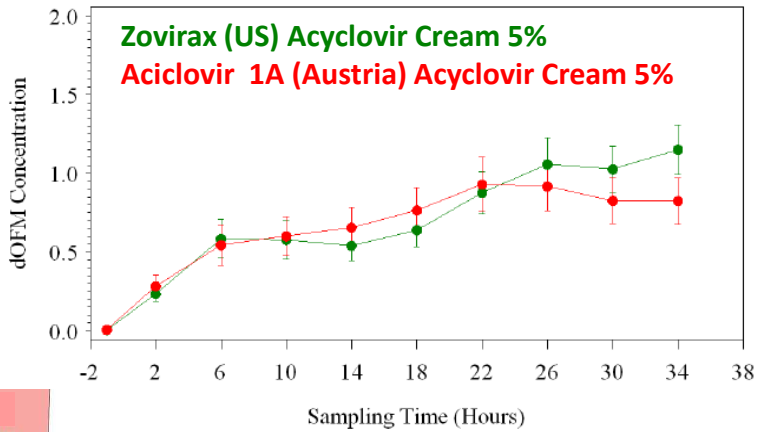


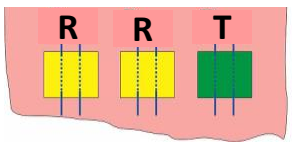


Images provided courtesy of Dr. Frank Sinner (Joanneum Research) ***FDA Award U01FD004946***

BE Study for Acyclovir Cream





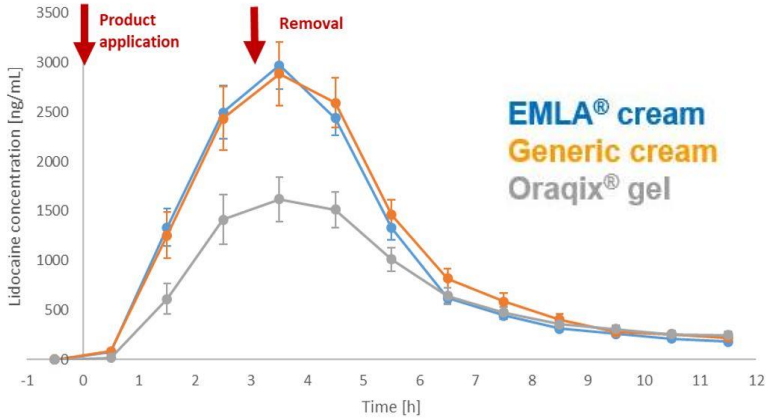


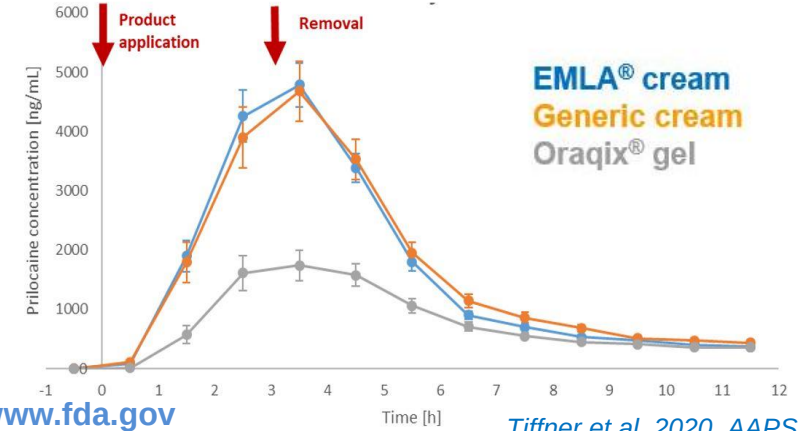
Outcome variable	$CI_{90\%}$	BE-limits	BE
$\log(AUC_{0\text{-}36h})$	[-0.148 ; 0.162] or [86.2 % ; 117.5 %]	[-0.223 ; 0.223] or [80% ; 125%]	passed
$\log(C_{max})$	[-0.155 ; 0.190] or [85.7 % ; 120.9%]		passed

Outcome variable	$CI_{90\%}$	BE-limits	BE
$\log(AUC_{0\text{-}36h})$	[-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

Clinical pharmacokinetics vol. 56,1 (2017): 91-98 ***FDA Award U01FD004946***

BE Study for Lidocaine Prilocaine Cream



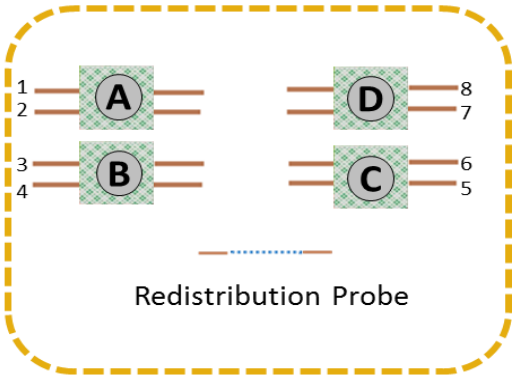


R: EMLA® (lidocaine; prilocaine) topical cream, 2.5%; 2.5 %
$T_{generic}$: generic lidocaine; prilocaine cream, 2.5%; 2.5%
$T_{non\text{-}equ}$: Oraqix®(lidocaine; prilocaine) dental gel, 2.5%; 2.5%

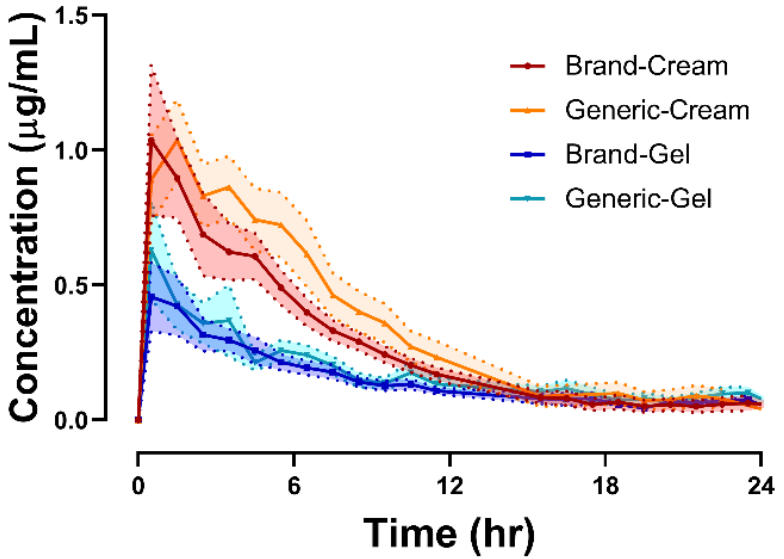
	PK endpoint	Drug	95% upper confidence bound	BE - criterion satisfied	Result
T_{gen} vs. R_1	$AUC_{0\text{-}12}$	lidocaine	-0.053	Yes	The generic cream is **bioequivalent** to the reference cream.
	C_{MAX}		-0.055	Yes	
	$AUC_{0\text{-}12}$	prilocaine	-0.051	Yes	
	C_{MAX}		-0.043	Yes	
$T_{non\text{-}equ}$ 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	

Tiffner et al. 2020, AAPS poster, ***FDA Award U01FD005861***

Cutaneous PK of Metronidazole Products



- 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”



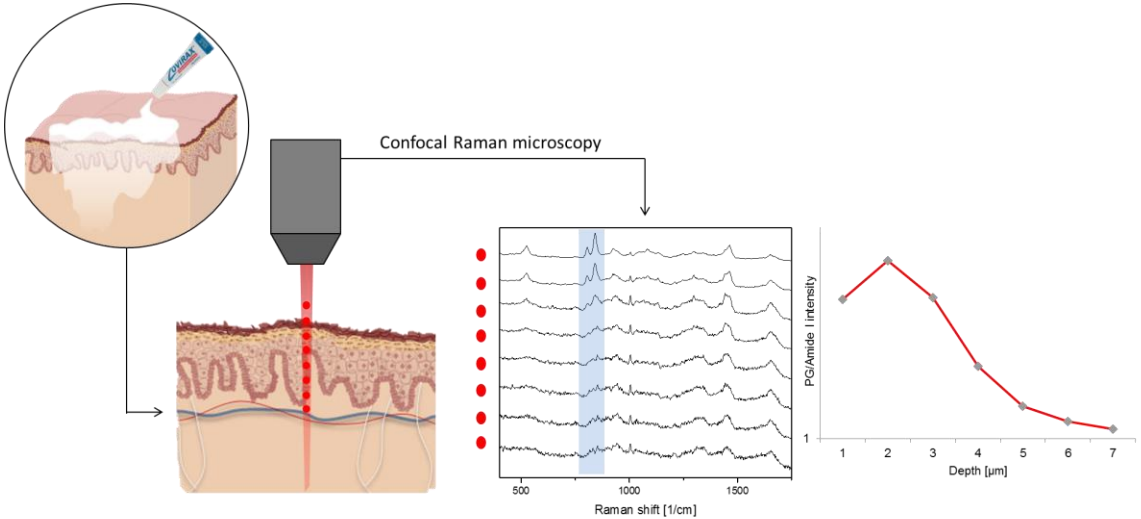
*Average dermal concentration profiles using **dMD**, (mean ± SEM, n=7), in rabbits*

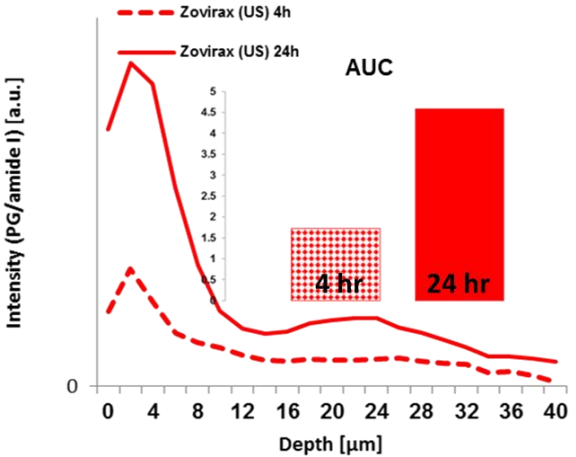
*Senemar et al. 2019 AAPS poster, **FDA Award U01FD005862***

Overcoming the Limitations

- Use of portable pumps
- Control and reduce the variabilities:
  - Study controls: application site, dose, application technique, probe depth, barrier integrity, flow rates
- Development of data analysis strategies
- Method development and validation strategies

Cutaneous PK- Confocal Raman





Characterizing drug concentration gradient in upper layers of skin (epidermis)

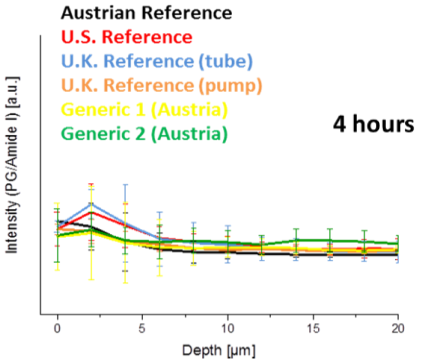
Data/images provided courtesy of Prof. Michael Roberts, UniSA

Challenges with Imaging-Based Tools

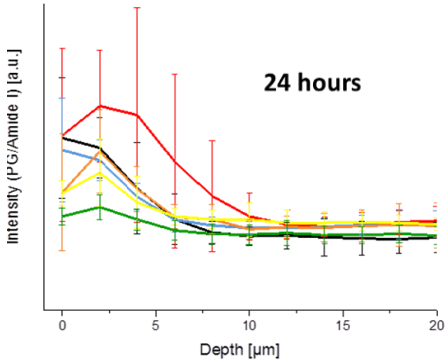
Examples of historical limitations

- 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

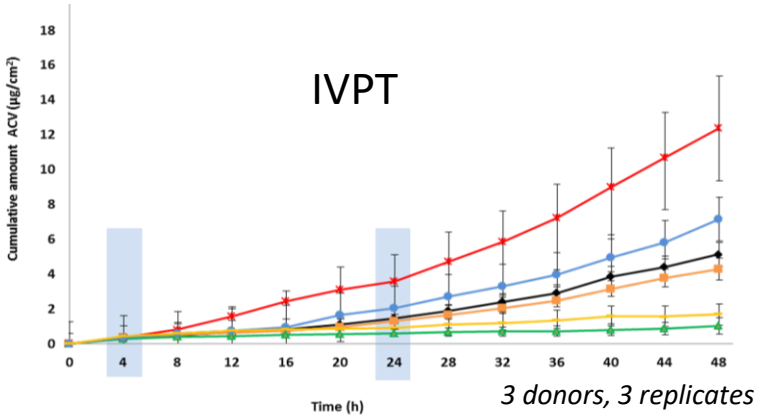
Cutaneous PK of Acyclovir Creams



Raman



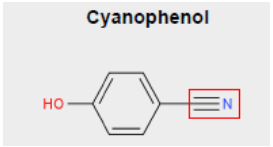
IVPT



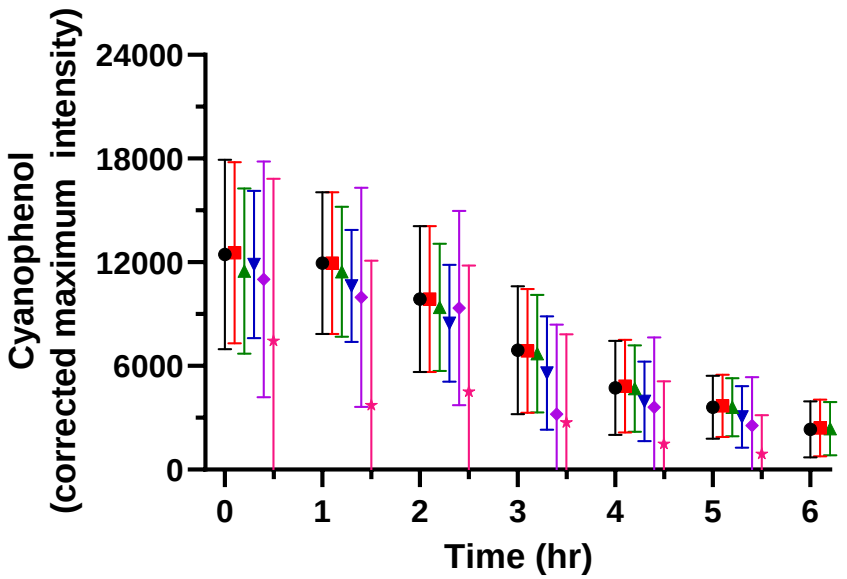
3 donors, 3 replicates

Pharm Res 2022 May;39(5):935-948 ***FDA Award U01FD005226***

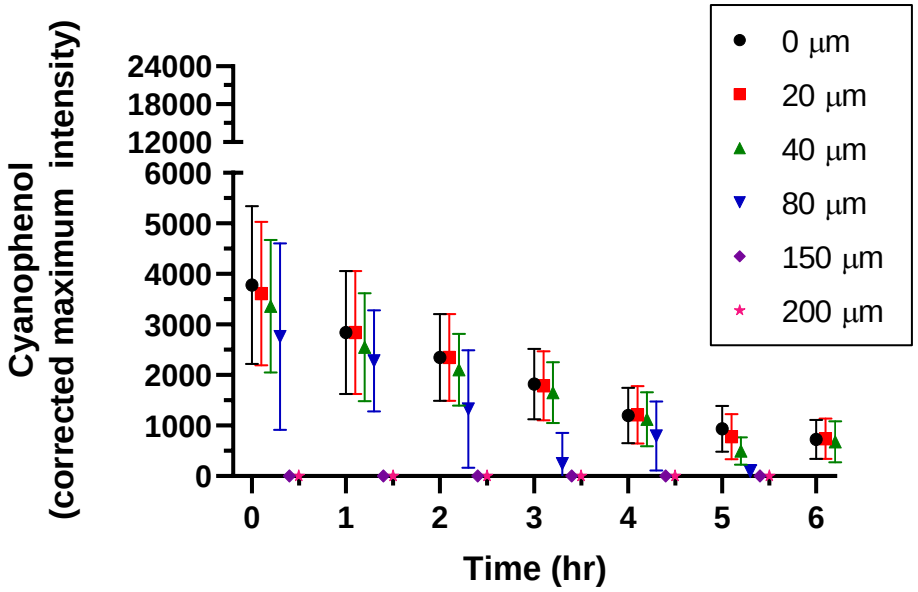
Cutaneous PK of Cyanophenol



Saturated solution
(50:50 Propylene glycol : water)

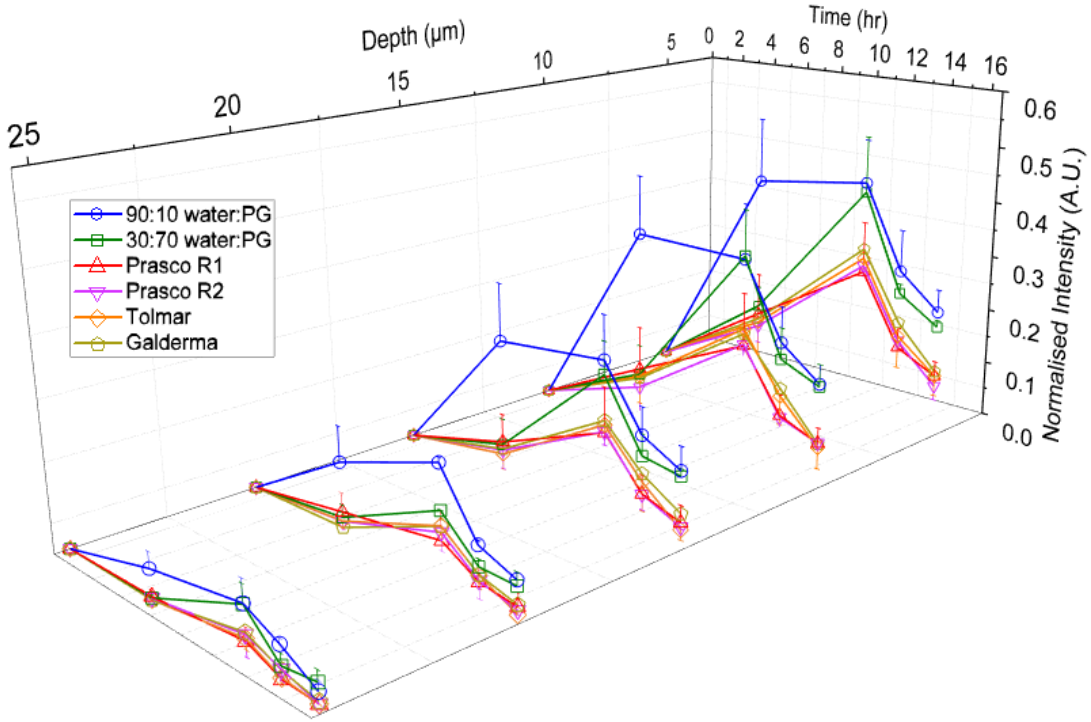


25% Saturated solution
(50:50 Propylene glycol : water)



Vitry et al. 2020 AAPS Poster, ***FDA Award U01FD006533***

Cutaneous PK of Metronidazole



Normalized Metronidazole Raman signal intensities, as functions of depth and time following 6 and 12 hr application of three commercial gels and two laboratory-made (solution) formulations on pig skin. Experiments with the reference gel Data plotted as Mean ± SD (n = 12)

Overcoming the Limitations

- 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*

Summary and Conclusions

- FDA is investigating novel alternative, scientifically valid methods, including in vitro and in vivo approaches, to support the assessment of BE for topical drug products that have compositional differences compared to the reference standard.
- Research is ongoing to understand the influence of compositional differences on drug thermodynamic activity and bioavailability in complex topical formulations.
- Cutaneous PK-based approaches using dOFM and dMD have the potential to support a demonstration of BE when the proposed method is optimized and controlled to be adequately discriminating and reproducible.
- Cutaneous PK-based approaches using the spectroscopic and imaging-based techniques appear to be promising; however, these are currently in the early stages of development.

https://complexgenerics.org/topical-formulation-characterization-cutaneous-PK

Opportunities with FDA

Looking for a post-doctoral opportunity?
https://www.zintellect.com/Opportunity/Details/FDA-CDER-2022-0791

Looking for funding for generic drug research?
https://www.fda.gov/drugs/generic-drugs/generic-drug-research-collaboration-opportunities

Acknowledgements

U.S. Food & Drug Administration

- Sam Raney, PhD
- Priyanka Ghosh, PhD
- Ying Jiang, PhD
- Sagar Shukla, PharmD, PhD
- Markham Luke, MD PhD
- Robert Lionberger, PhD

Research Collaborators

Funding for research projects was made possible, in part, by the U.S. FDA through:

GDUFA Award U01FD006507, University of Mississippi/TPT

GDUFA Award U01FD005233, University of Mississippi

- **Dr. S Narasimha Murthy**

GDUFA Award U01FD004946, Joanneum Research
GDUFA Award U01FD005861, Joanneum Research

- **Dr. Frank Sinner**

GDUFA Award U01FD005226, University of South Australia

- **Dr. Michael Roberts**

GDUFA Award U01FD005862, Long Island University
GDUFA Award U01FD006930, Long Island University

- **Dr. Grazia Stagni**

GDUFA Award U01FD006533, University of Bath

- **Dr. Richard Guy**

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