Development of Efficient Alternative Bioequivalence Approaches for Topical Dermatological Drug Products

Innovations in Dermatological Sciences Conference

FDA Regulatory Updates for Topical Drug Products

Tannaz Ramezanli, PharmD, PhD

Pharmacologist

ORS/OGD

CDER | U.S. FDA

September 28/29, 2021

Disclaimer

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

Complexity of Topical Products

- Topical drug products are typically complex, often in multiple ways (e.g., complex route of administration, complex dosage form)
- 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 bioequivalence (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

Evaluation of BE for Topical Products

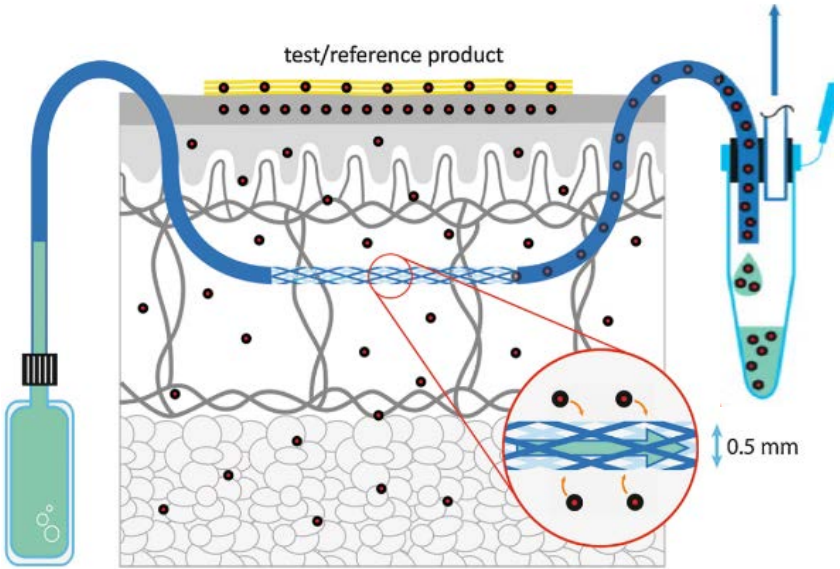
- A Modular Framework for Characterization-Based BE
  - **No Difference in the formulation** compared to the reference product (e.g., **Qualitative (Q1) and Quantitative (Q2)** sameness)
  - **Physical and Structural (Q3)** characterization
  - **IVRT** (In Vitro Release Test)
  - **IVPT** (In Vitro Permeation Test)
- Evidence to Support a Demonstration of BE
  - **In Vivo Pharmacokinetic (PK)** Studies
  - **In Vivo Pharmacodynamic** (e.g., Vasoconstrictor) Studies
  - **In Vivo Comparative Clinical Endpoint BE** Studies
  - **In Silico** Quantitative Methods, Modeling and Simulation

Cutaneous PK Techniques

- Techniques explored in the past
  - **In Vivo** Stratum Corneum Sampling Studies
    - Tapestripping "Dermatopharmacokinetics" (DPK)
- Techniques that are currently being developed/utilized
  - **In Vitro** Cutaneous Pharmacokinetic Studies
    - In Vitro Permeation Testing (IVPT)
  - **In Vivo** Cutaneous Pharmacokinetic Studies
    - Dermal Open Flow Microperfusion (dOFM)
    - Dermal Microdialysis (dMD)
- Techniques that we hope to develop
  - **In Vivo** Cutaneous Pharmacokinetic Studies
    - Epidermal and/or Dermal Pharmacokinetic Tomography, e.g., Raman-based methods

Cutaneous PK-Based Approaches

- dMD and dOFM directly measure the in vivo rate and extent of drug bioavailability at/near the site of action in the skin.



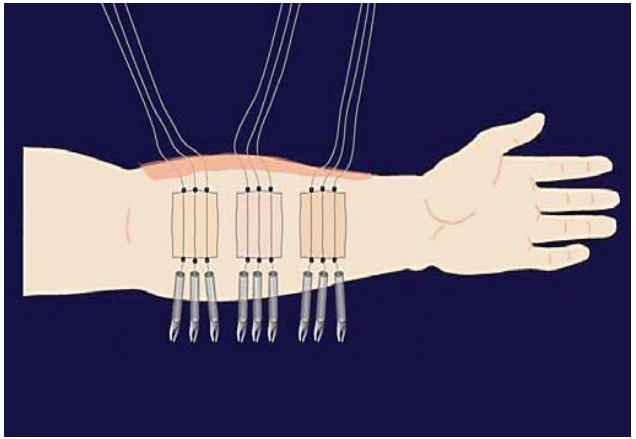
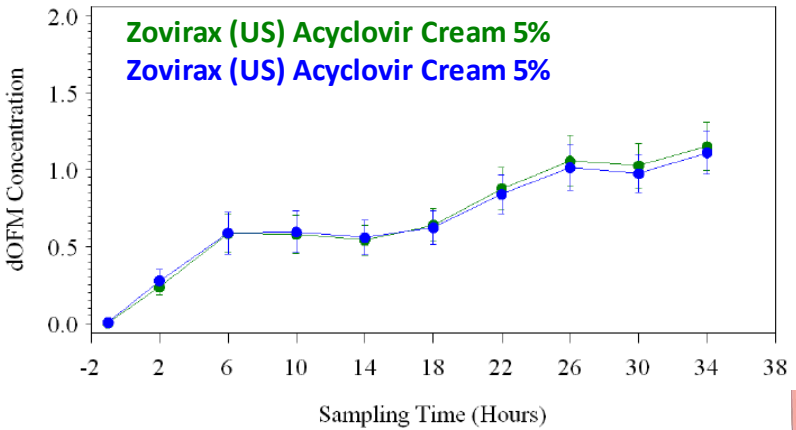
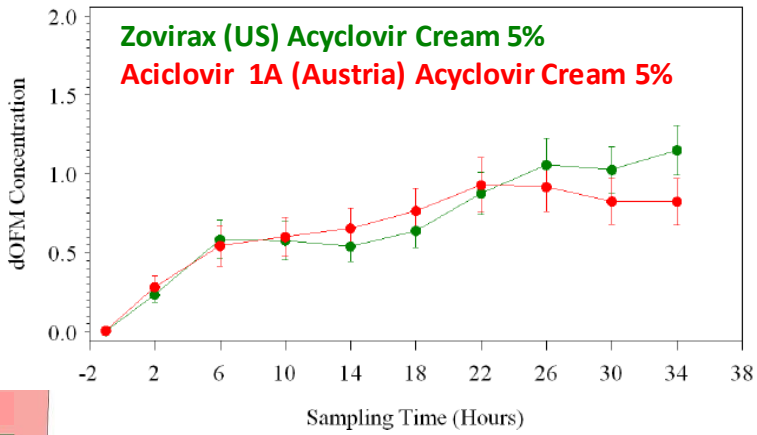
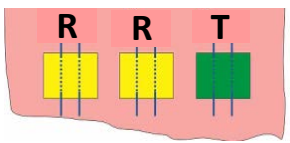


Image provided courtesy of Dr. Frank Sinner, Joanneum Research
Skin Pharmacol Physiol 2011;24:44–53

Pivotal BE Study for Acyclovir Cream







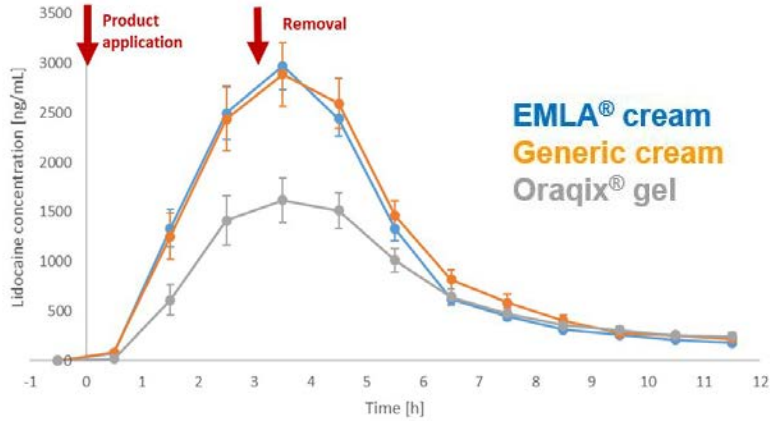
Outcome variable	$CI_{90\%}$	BE-limits	BE
$\log(AUC_{0\text{-}36h})$	[-0.148 ; 0.162] or [86.2 % ; 117.5 %]	[-0.223 ; 0.223] or [80% ; 125%]	passed
$\log(C_{max})$	[-0.155 ; 0.190] or [85.7 % ; 120.9%]		passed

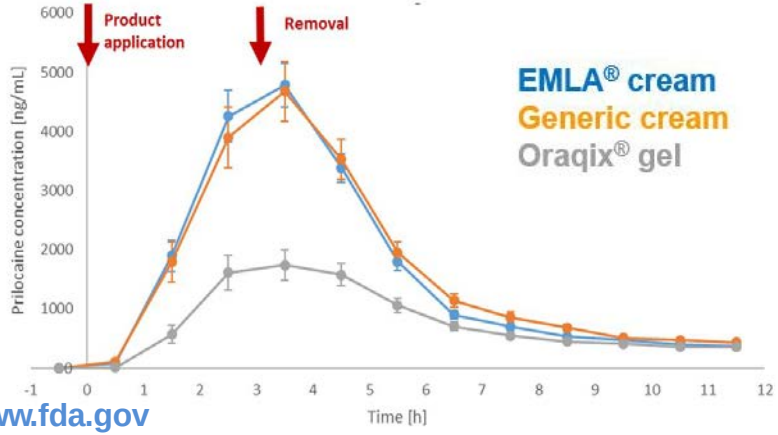
Outcome variable	$CI_{90\%}$	BE-limits	BE
$\log(AUC_{0\text{-}36h})$	[-0.369 ; 0.050] or [69.1 % ; 105.2 %]	[-0.223 ; 0.223] or [80% ; 125%]	x Failed
$\log(C_{max})$	[-0.498 ; 0.022] or [60.8 % ; 102.2%]		x Failed

www.fda.gov

Clinical pharmacokinetics vol. 56,1 (2017): 91-98

BE Study for Lidocaine Prilocaine Cream

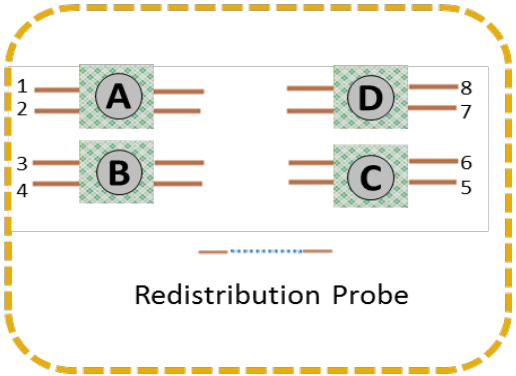




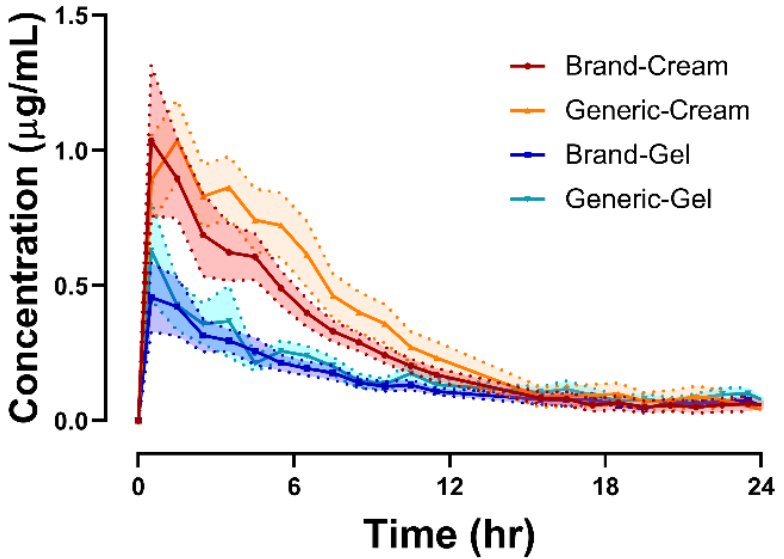
R: EMLA® (lidocaine; prilocaine) topical cream, 2.5%; 2.5 %
$T_{generic}$: generic lidocaine; prilocaine cream, 2.5%; 2.5%
$T_{non\text{-}equ}$: Oraqix®(lidocaine; prilocaine) dental gel, 2.5%; 2.5%

	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	

Cutaneous PK of Metronidazole Products



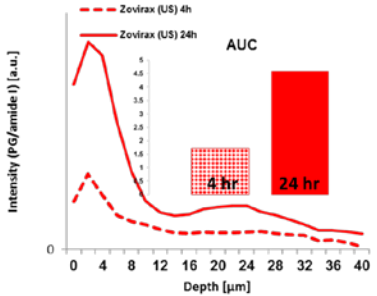
- MetroGel® topical gel, 0.75% “Brand Gel”
- Metronidazole topical gel, 0.75% “Generic Gel”
- MetroCream® topical cream, 0.75% “Brand Cream”
- Metronidazole topical cream, 0.75% “Generic Cream”

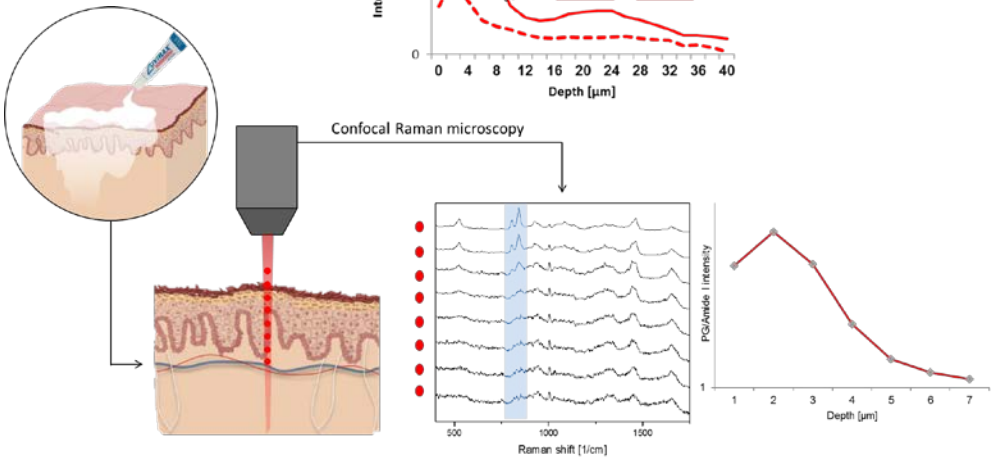


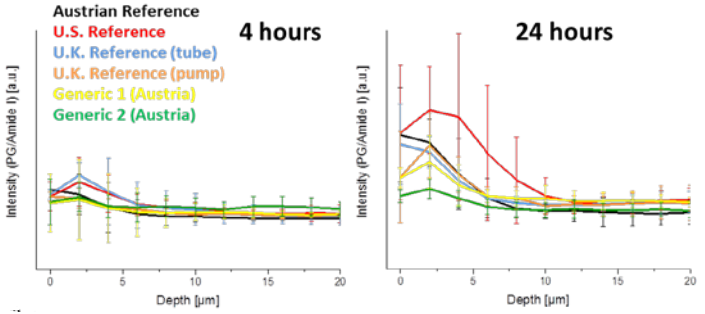
*Average dermal concentration profiles using **dMD**, (mean ± SEM, n=7), in rabbits*

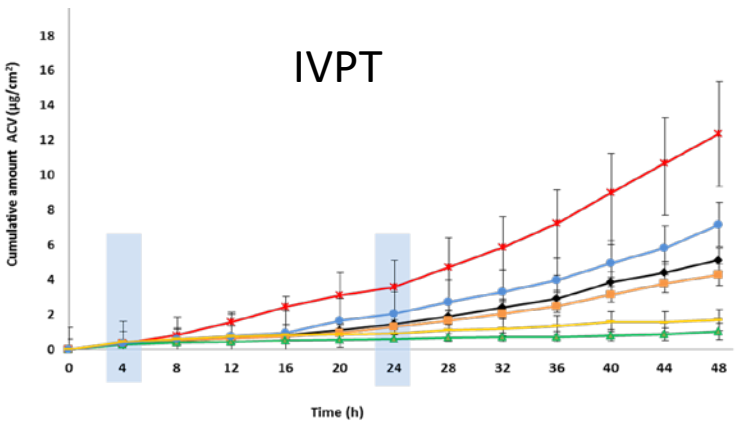
Data/images provided courtesy of Dr. Grazia Stagni, Long Island University

Cutaneous PK: Non-Invasive Techniques









3 donors, 3 replicates

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

Summary

- 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 dermatological products).
- FDA is exploring cutaneous PK-based techniques to assess BE of topical drug products.
- Efficient in vivo 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.
- FDA has funded research studies to assess the feasibility of Confocal Raman Spectroscopy-based techniques for evaluation of cutaneous PK.

Acknowledgements

U.S. FDA

- Priyanka Ghosh, PhD
- Sam Raney, PhD
- Markham Luke, MD, PhD
- Eleftheria Tsakalozou, PhD
- Ying Jiang, PhD
- Robert Lionberger, PhD

Research Collaborators

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

GDUFA Award U01FD004946

GDUFA Award U01FD005861

- **Dr. Frank Sinner, Joanneum Research**

GDUFA Award U01FD006533

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

GDUFA Award U01-FD005226

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

GDUFA Award U01FD005862

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


FDA
U.S. FOOD & DRUG
ADMINISTRATION