Translating Scientific Advances to Regulatory Methods Assessment of Cutaneous Pharmacokinetics

Innovations in Dermatological Sciences Conference
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CDER | U.S. FDA

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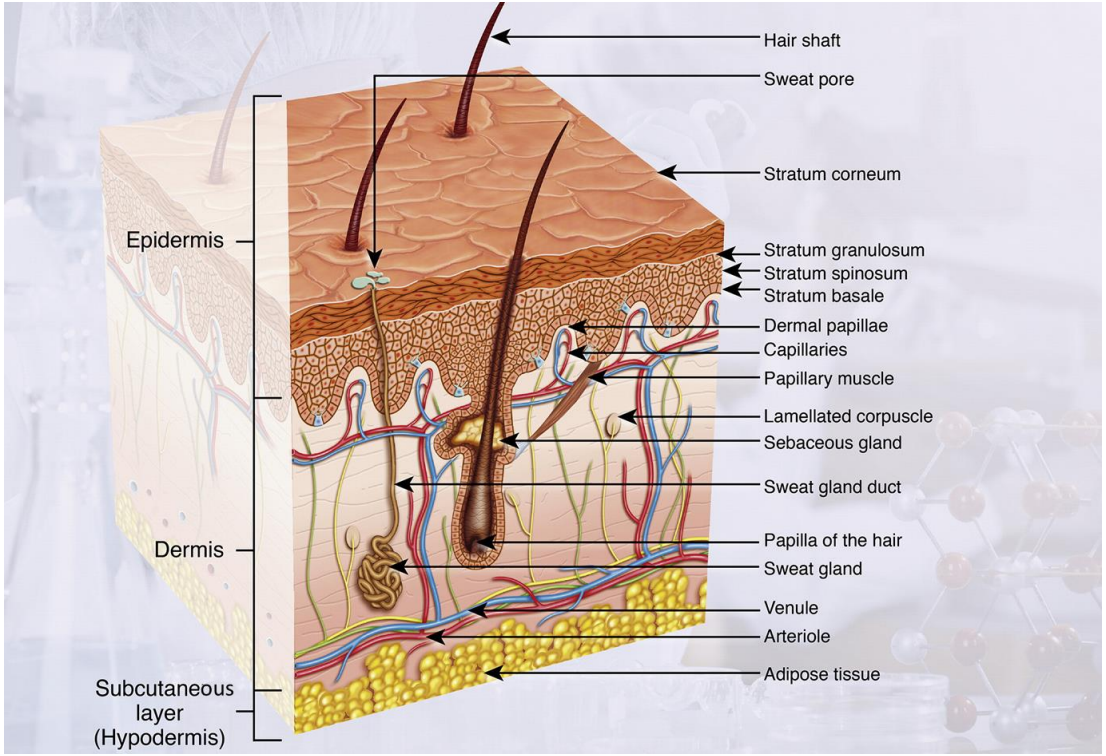
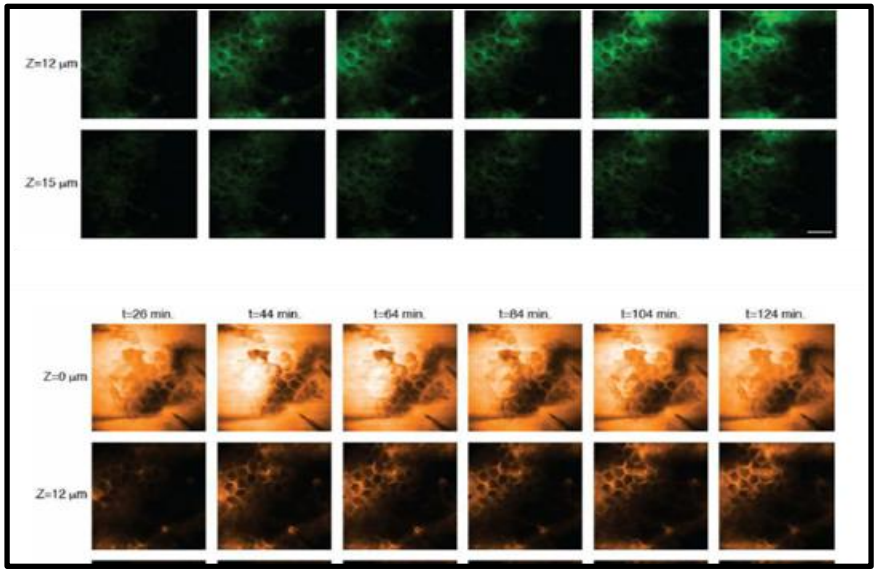
Skin Anatomy

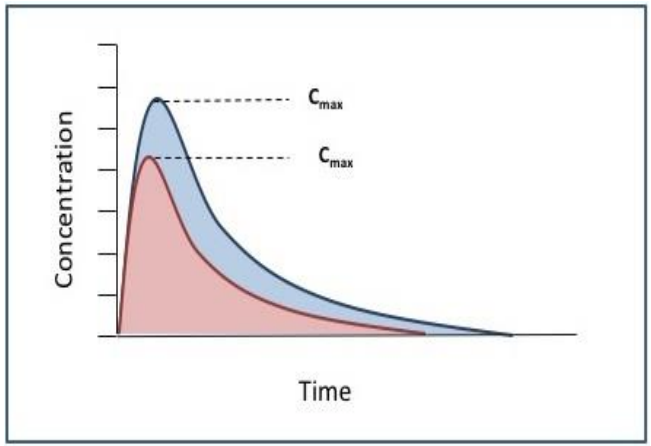


Mathes et al., *Adv Drug Deliv Rev.* **2014**, 69-70, 81-102

Potential of Cutaneous Pharmacokinetics (PK)

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



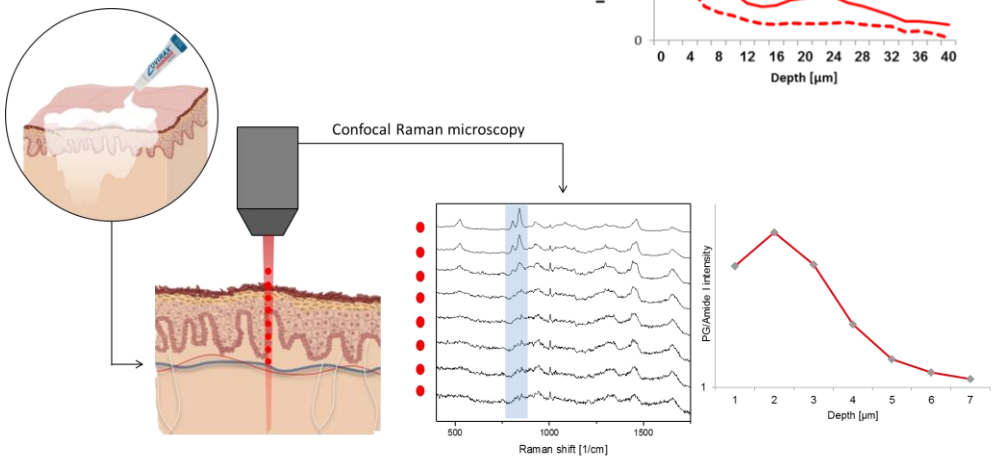


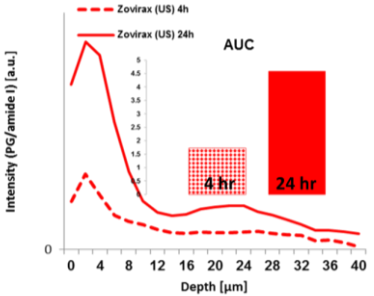
Saar Brian G. , Contreras-Rojas L. Rodrigo , Xie X. Sunney , and Guy Richard H. **Imaging Drug Delivery to Skin with Stimulated Raman Scattering Microscopy** Molecular Pharmaceutics **2011** 8 (3), 969-975

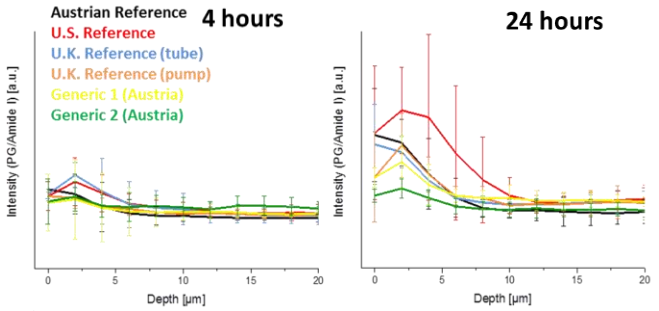
Cutaneous PK Techniques

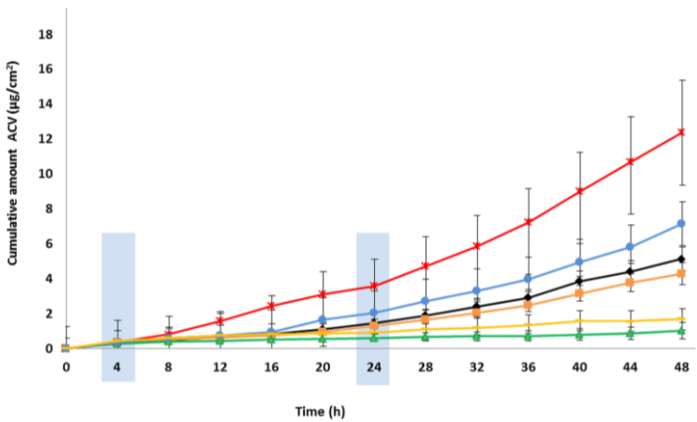
- Epidermal PK
  - Tapestripping “Dermatopharmacokinetics” (DPK)
  - In vitro Permeation Testing (IVPT)
  - Epidermal and/or Dermal Pharmacokinetic Tomography e.g., Raman based methods
- Dermal PK
  - Dermal Open Flow Microperfusion (dOFM)
  - Dermal Microdialysis (dMD)

Epidermal PK







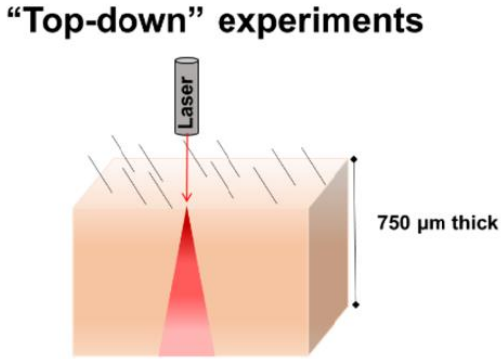


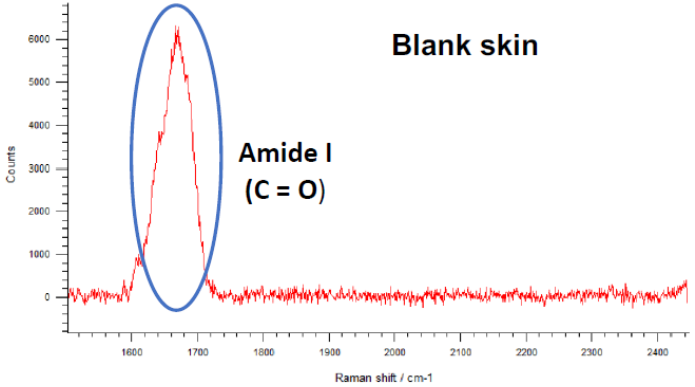
Challenges with Imaging-based tools

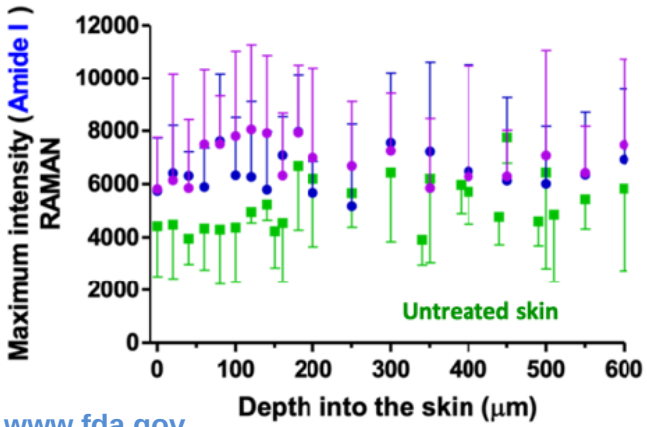
Examples of Historical limitations

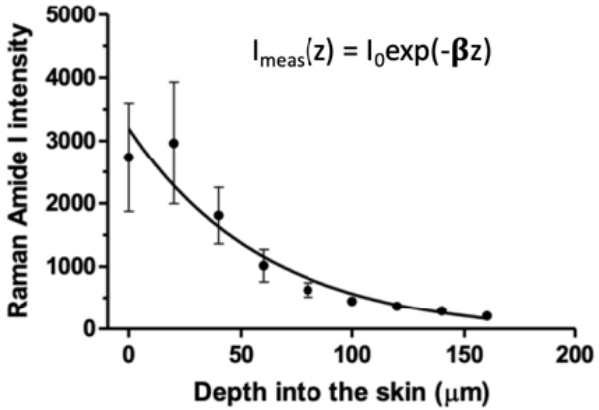
- *Challenges with detection of molecule in the skin*
- *Challenges related to signal attenuation within the skin*
- *Challenges related to utility of tool as a semi-quantitative evaluation technique*
- *Challenges associated with limited utility, applicable for molecules with unique Raman signal*
-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

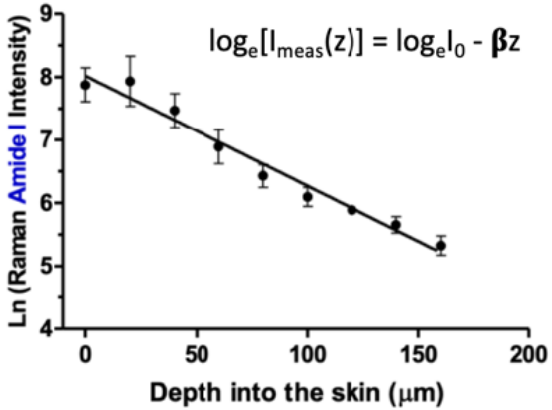
Strategies to Correct for Signal Attenuation





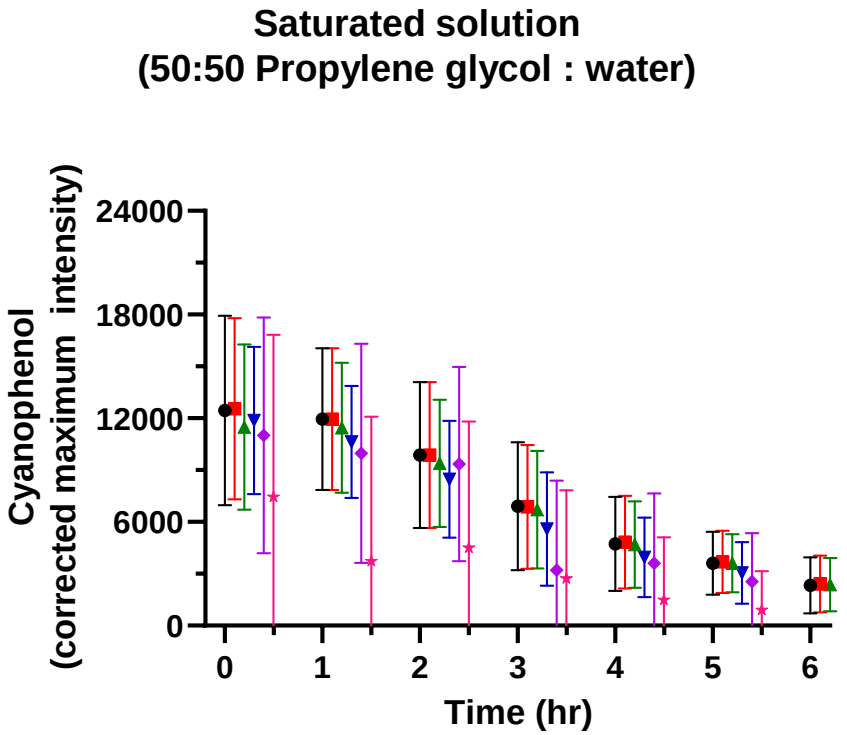


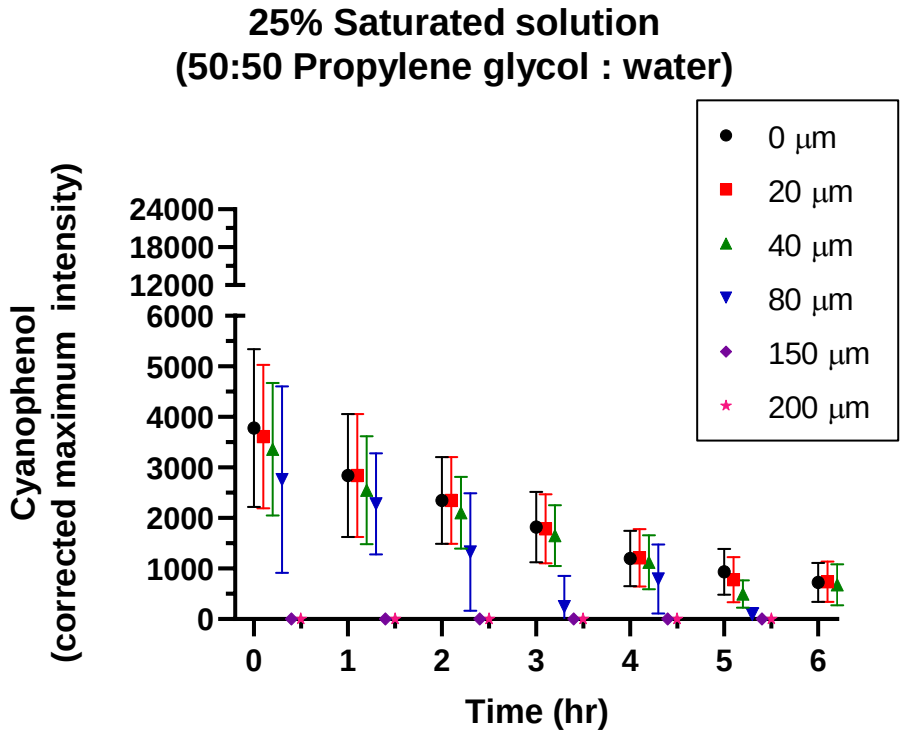




Prof. Richard Guy FDA Award U01-FD006533

Evaluation of Epidermal PK





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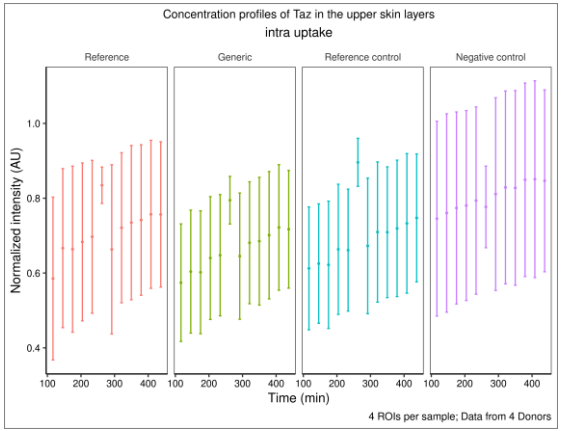
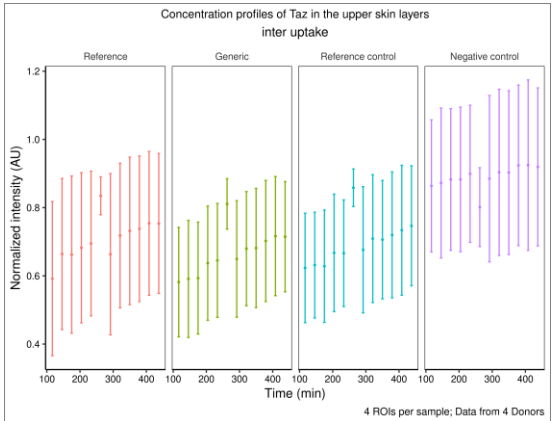
Evaluation of Epidermal PK

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



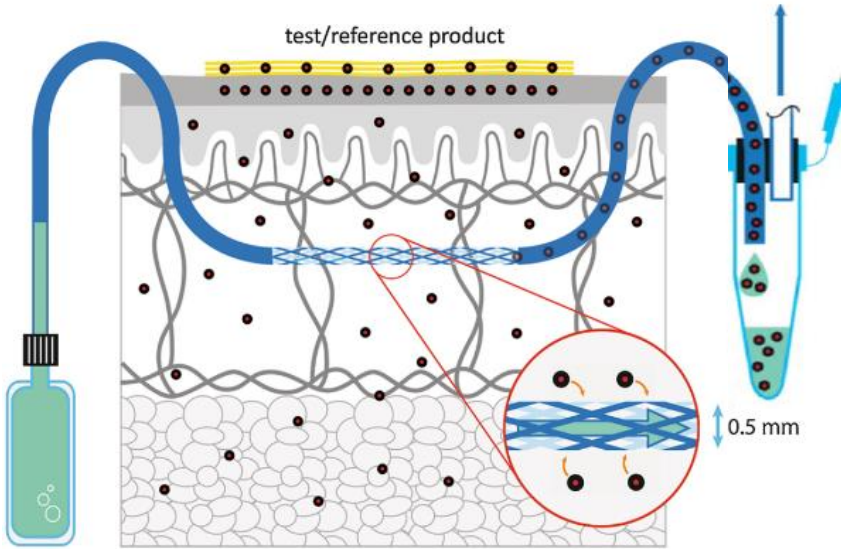
Prof. Conor Evans FDA Award U01-FD006698

Current State 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.



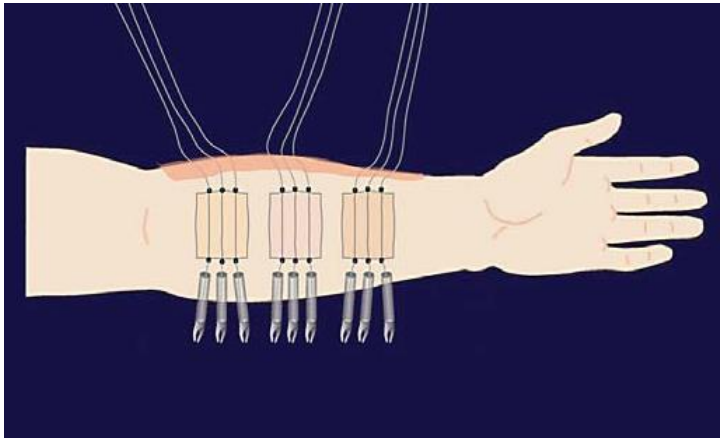


Image provided courtesy of Dr. Frank Sinner, Joanneum Research

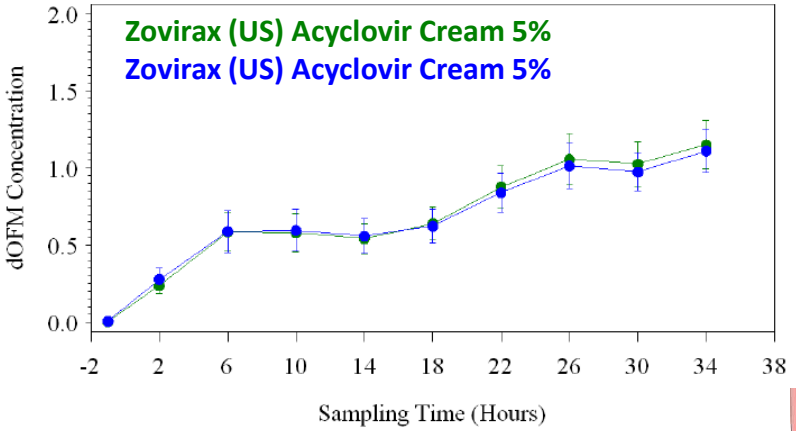
Skin Pharmacol Physiol 2011;24:44–53

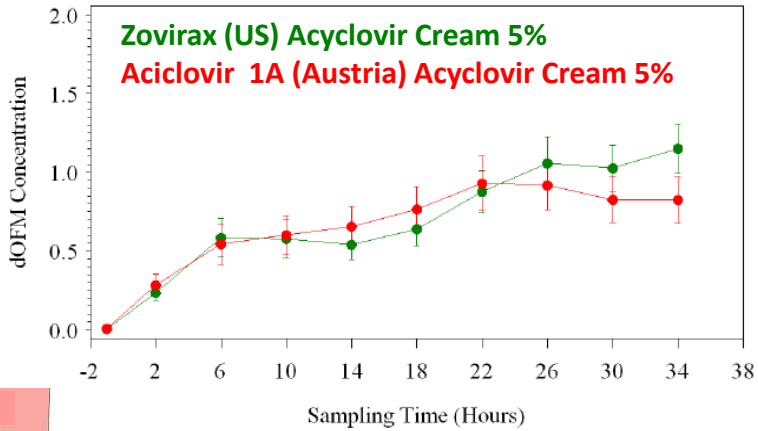
Dermal PK

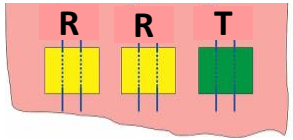
Examples of Historical limitations

- 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





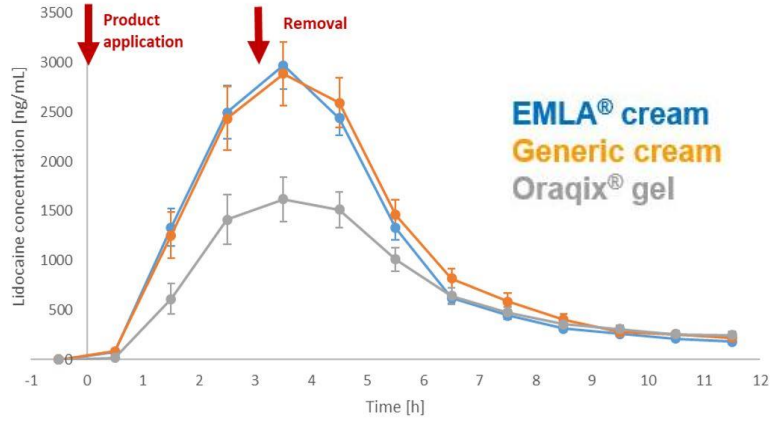


Outcome variable	$CI_{90\%}$	BE-limits	BE
$log(AUC_{0-36h})$	[-0.148 ; 0.162] or [86.2 % ; 117.5 %]	[-0.223 ; 0.223] or [80% ; 125%]	passed
$log(C_{max})$	[-0.155 ; 0.190] or [85.7 % ; 120.9%]		passed

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

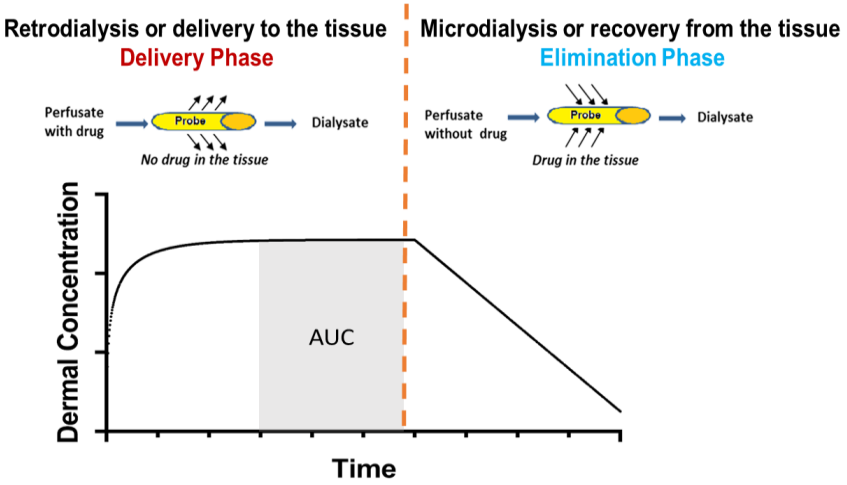


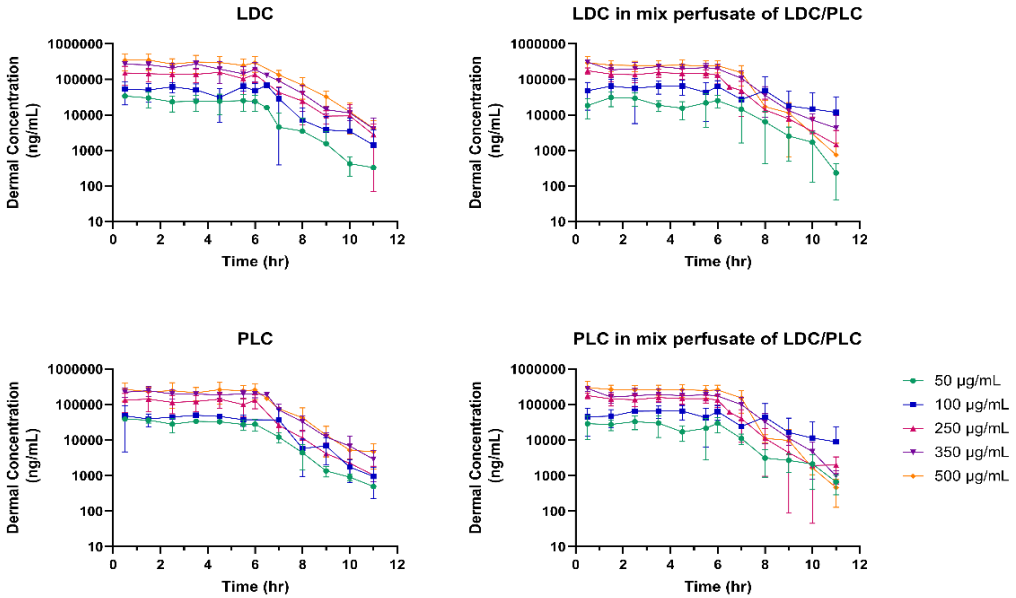
R: EMLA® (lidocaine; prilocaine) topical cream, 2.5%; 2.5 %
$T_{generic}$: generic lidocaine; prilocaine cream, 2.5%; 2.5%
$T_{non\text{-}equ}$: Oraqix®(lidocaine; prilocaine) dental gel, 2.5%; 2.5%

	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

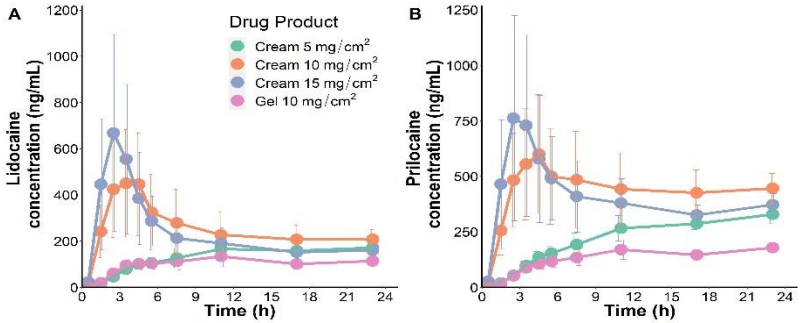
Dermal PK - Microdialysis

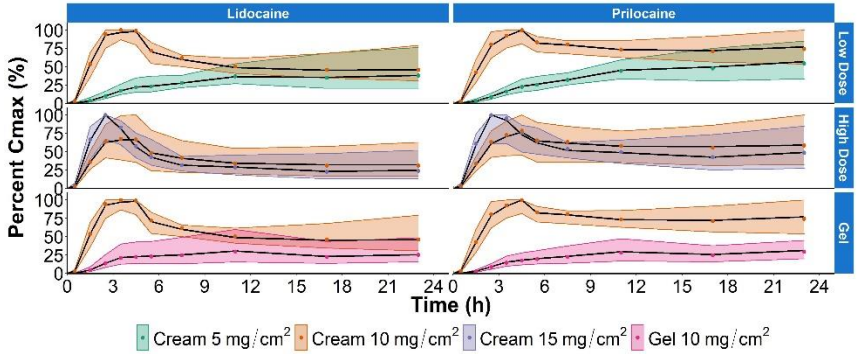




Prof. Grazia Stagni FDA Award U01-FD005862

Cutaneous PK – Data Analysis





Dose vs Cream 10 mg/cm²	Point Estimate				Bootstrap (n=1000)			
	Percent conc profile		Percent AUC profile		Percent conc profile		Percent AUC profile	
	Lidocaine	Prilocaine	Lidocaine	Prilocaine	Lidocaine	Prilocaine	Lidocaine	Prilocaine
f_1								
Cream 5 mg/cm² (n=12)	65.5	63.4	64.6	63.1	63.1 (48.7 – 74.2)	61.3 (47.3 – 72.4)	62.1 (47.1 – 73.0)	61.0 (47.3 – 71.8)
Cream 15 mg/cm² (n=12)	30.5	24.1	14.6	13.3	39.4 (21.6 – 73.4)	33.2 (17.4 – 62.2)	30.3 (11.4 – 68.0)	25.7 (10.1 – 56.4)
Gel 10 mg/cm² (n=6)	70.2	76.0	69.4	75.7	67.2 (49.0 – 80.6)	74.2 (61.9 – 83.0)	65.7 (43.4 – 80.6)	73.5 (60.0 – 84.2)
f_2								
Cream 5 mg/cm² (n=12)	15.6	15.7	27.6	29.8	16.8 (14.8 – 19.9)	16.6 (13.9 – 22.7)	29.0 (23.6 – 37.5)	31.0 (25.8 – 38.4)
Cream 15 mg/cm² (n=12)	39.6	38.8	60.7	65.7	35.2 (27.9 – 42.3)	35.2 (27.2 – 43.9)	48.7 (33.1 – 65.1)	53.7 (38.2 – 70.2)
Gel 10 mg/cm² (n=6)	15.5	13.0	25.3	24.6	17.0 (14.0 – 22.3)	13.6 (11.0 – 18.6)	27.3 (20.9 – 38.2)	25.5 (21.6 – 31.1)

For the purpose of this study, cutaneous PK profiles were considered to be discriminated if **f_1 > 15 or f_2 < 50** and with bootstrap analysis when the 90% confidence interval (CI) for f_1 > 15 or for f_2 < 50

Current State 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 bioequivalence (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*

Potential Challenges with Implementation

- *Access to the techniques*
- *Expertise*
- *Cost*
- *Availability of standardized methodologies*

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

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