Cutaneous Pharmacokinetics-Based Techniques: Translating Scientific Advances to Regulatory Methods

FDA Virtual Workshop: Formulation Characterization and Cutaneous Pharmacokinetics to Facilitate Topical Product Development

Session 2: Development of Cutaneous PK Based Approaches

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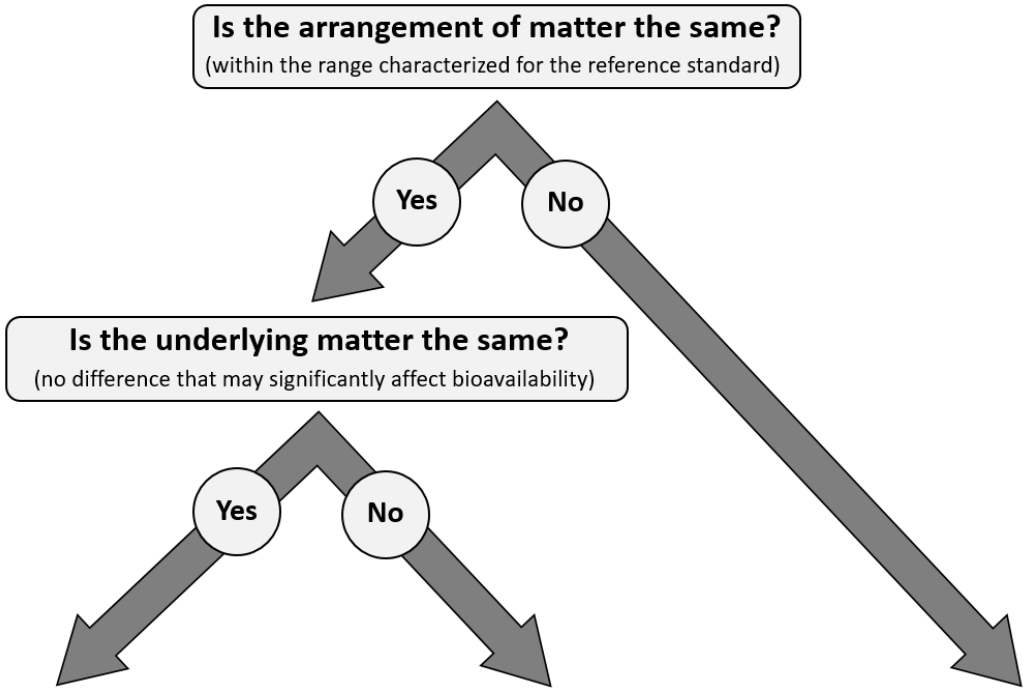
Bioequivalence (BE) for Topical Products



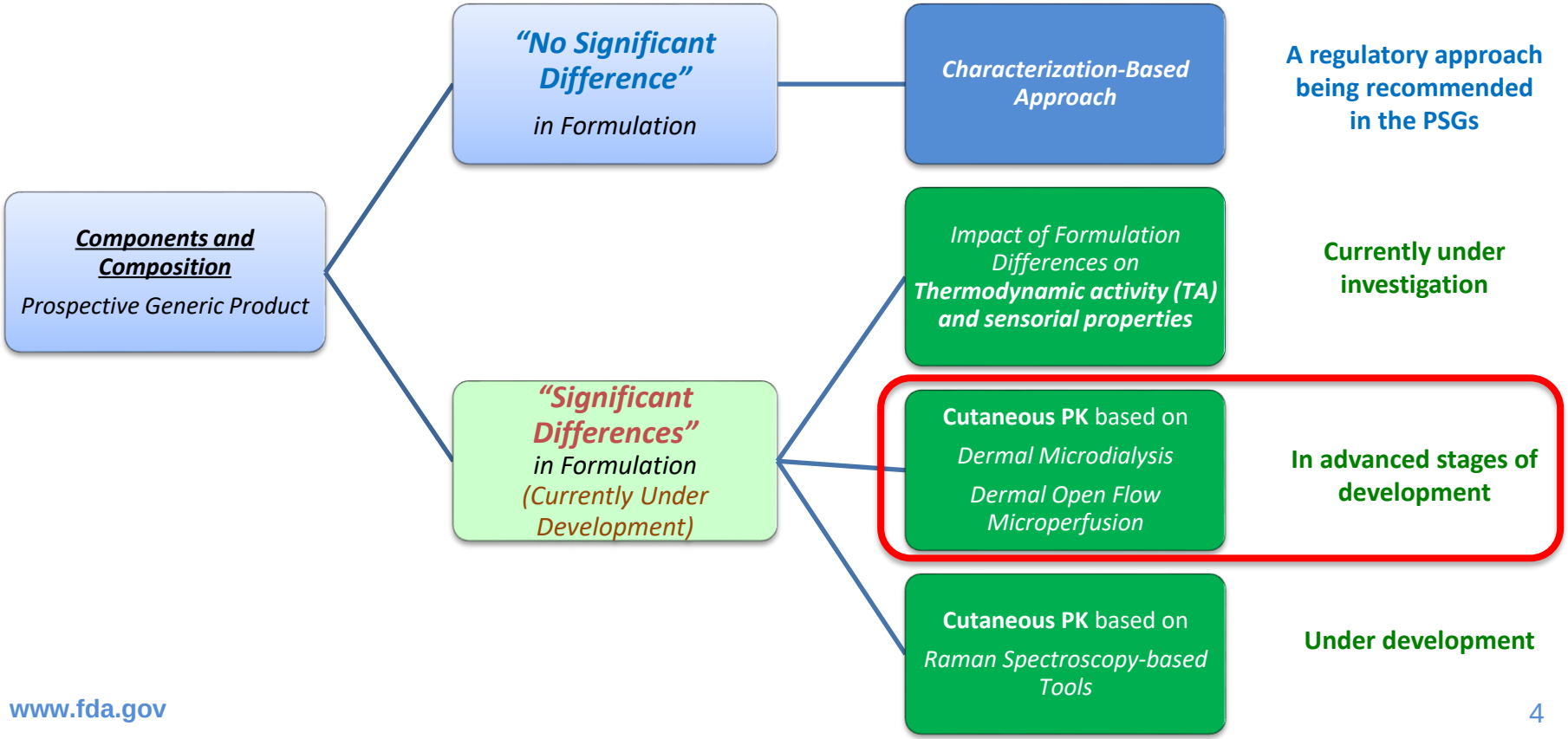
Generally eligible for characterization-based bioequivalence approaches in current PSGs

In vivo cutaneous PK dOFM/dMD BE studies?

Generally eligible for traditional in vivo bioequivalence approaches in current PSGs

Adapted from Guidance for Industry: Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs (October 2022)

Potential Efficient Strategies for BE



GDUFA-Funded Research Awards

Novel methodologies (dermal microdialysis (dMD) and dermal open flow microperfusion (dOFM)) to assess the bioavailability (BA) and BE of topical dermatological drug products:

- Joanneum Research
  - U01FD004946, 2013-2016
  - U01FD005861, 2016-2022
  - U01FD007669, 2022
- Long Island University (LIU)
  - U01FD005862, 2016-2020
  - U01FD006930, 2020

https://www.fda.gov/drugs/generic-drugs/generic-drug-research-priorities-projects

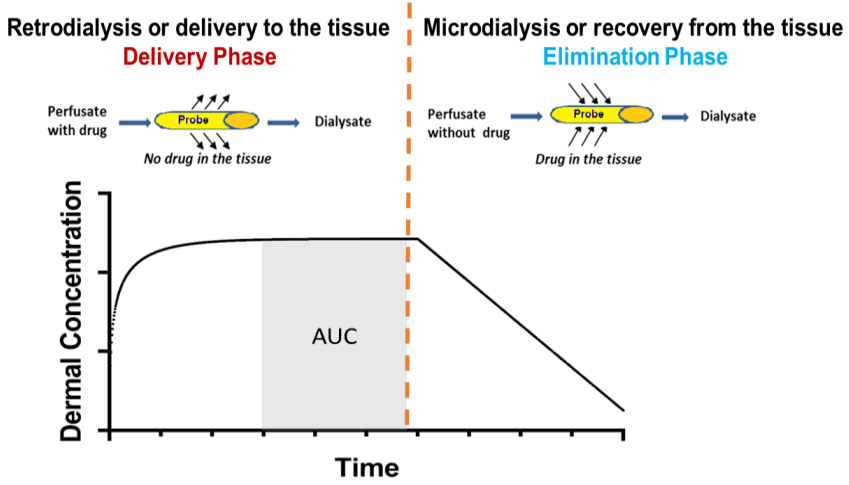
Overview of the Studies

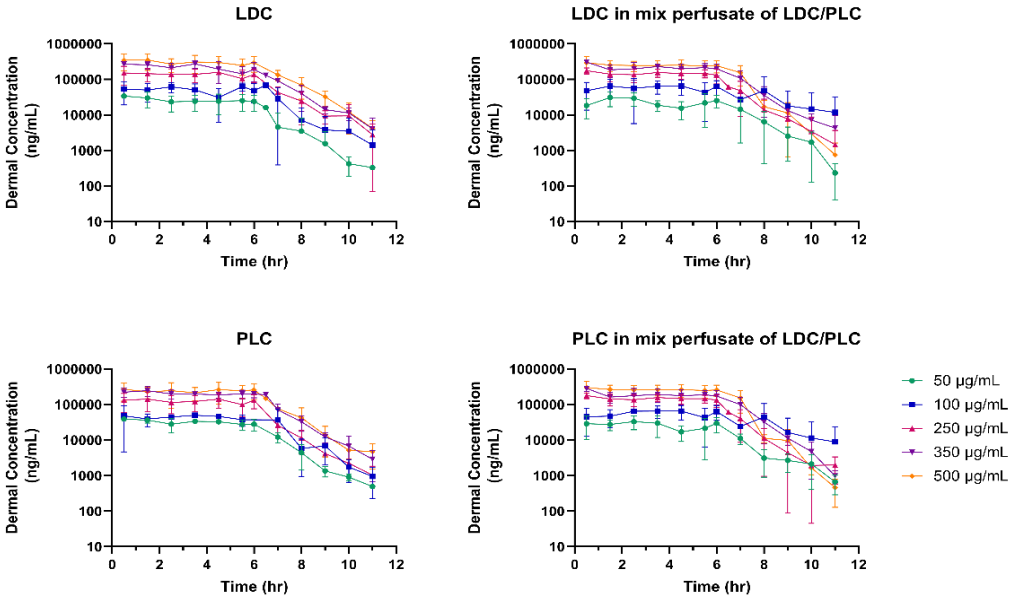
Technique	Drug products	Drug characteristics	Model	Outcome
dOFM	Acyclovir creams	Hydrophilic, minimally protein bound	Human	Optimization of the study design and conclusive assessment of BE
dOFM	Lidocaine prilocaine creams and gel	Relatively lipophilic, protein bound	Human	Optimization of the study design, statistical analysis and conclusive assessment of BE
dMD	Metronidazole gels and creams	Hydrophilic, minimally protein bound	Pig Rabbit	Method development and qualification, testing different study designs, and BE assessment
dOFM and dMD	Lidocaine prilocaine creams	Relatively lipophilic, protein bound	Human	Systemic cross talk at high dose, performance of dMD vs dOFM
dOFM	Diclofenac sodium gel and solution	Relatively lipophilic, highly protein bound	Human	Optimization of the study design and data analysis is under review
dMD	Lidocaine prilocaine	Relatively lipophilic, highly protein bound	Rabbit	Assessment of dermal disposition independent of absorption

Sensitivity and Applicability

- Can dMD be used for lipophilic drug molecules?
- Can dMD and dOFM measure and distinguish bioavailability of two similarly structured drug molecules?
- A closer look at the dermal disposition of topical drugs

Dermal Infusion Followed by Microdialysis



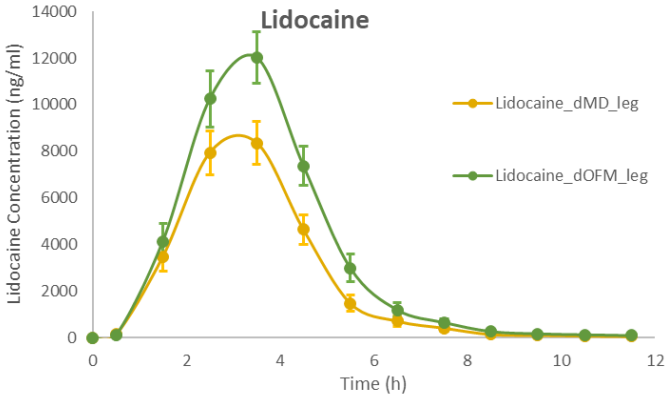


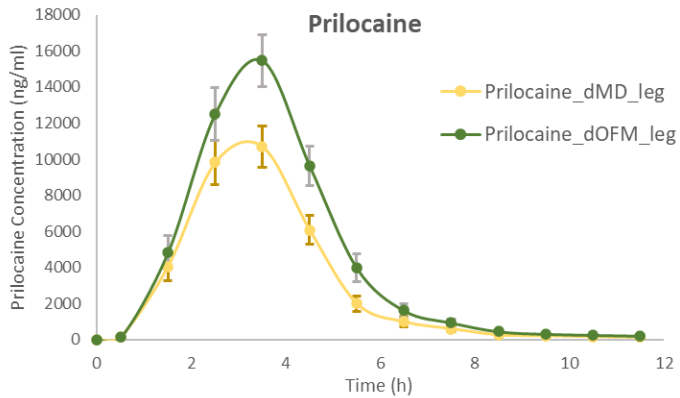
(mean ± SD, 4 rabbits)

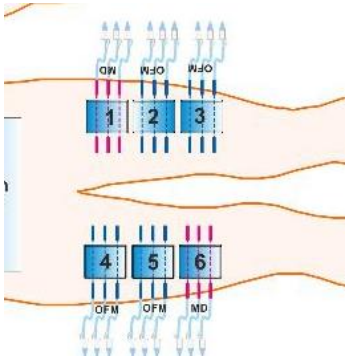
The dermal infusion approach demonstrates that the dermal disposition of lidocaine (LDC) and prilocaine (PLC) is independent of the dose delivered directly to the dermis over a range of therapeutically relevant concentrations.

dOFM vs. dMD

In a study performed by Joanneum Research, in 20 subjects both dOFM and dMD were able to capture PK profiles for lidocaine and prilocaine from EMLA® cream.



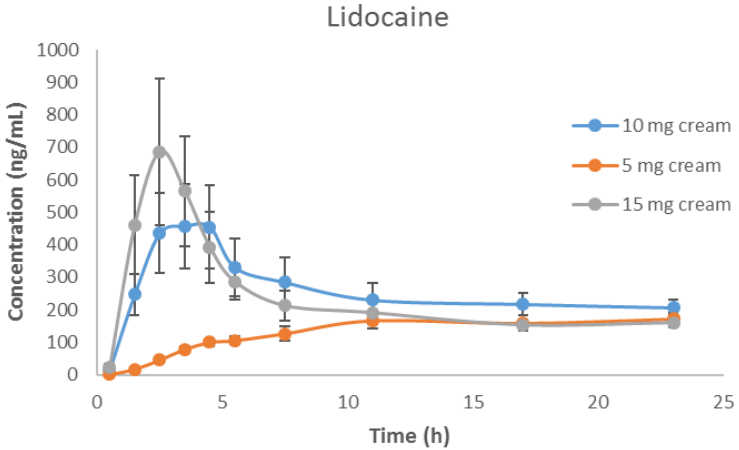


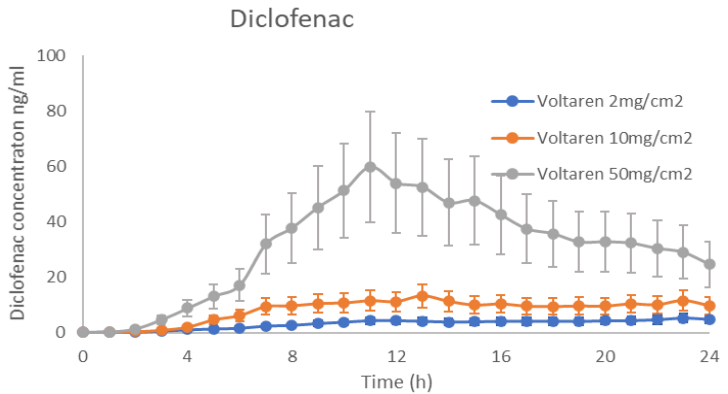


(mean ± SE, 20 subjects)

Data provided courtesy of Dr. Frank Sinner, ***Award U01FD005861***

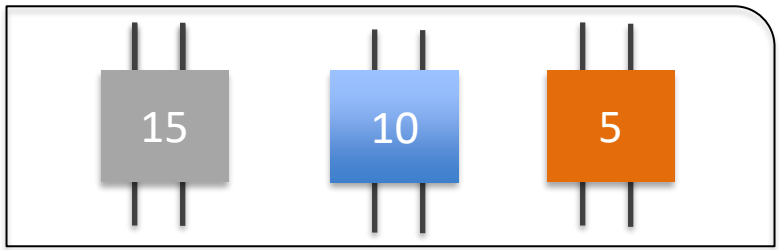
Discrimination Capability



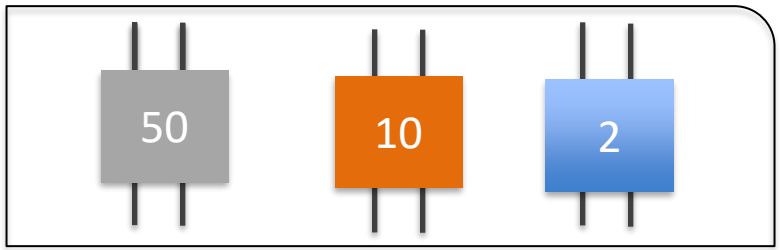


(mean ± SE, 6 subjects)

Changes in cutaneous bioavailability with different dose amounts



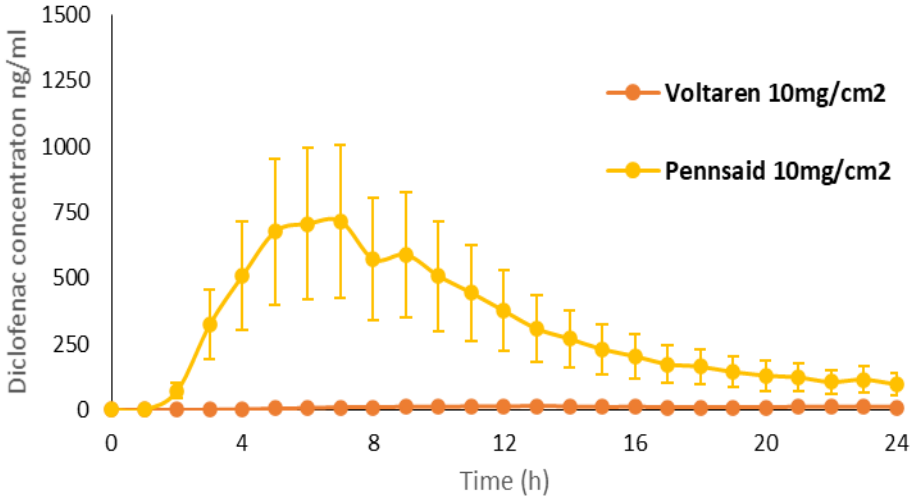
Target dose

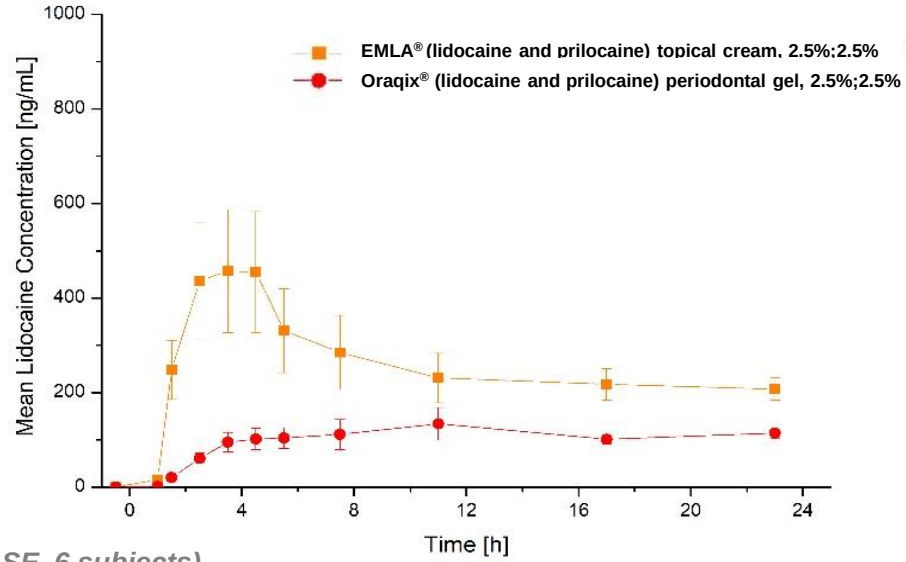


*Data provided courtesy of Dr. Frank Sinner, **Award U01FD005861***

Discrimination Capability

Changes in cutaneous bioavailability by using an altered formulation

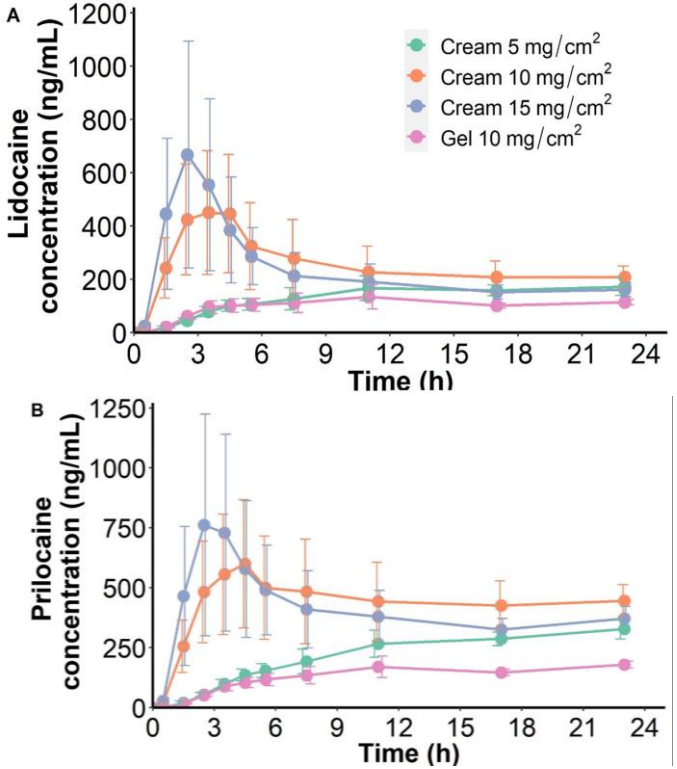




(mean ± SE, 6 subjects)

Data provided courtesy of Dr. Frank Sinner, ***Award U01FD005861***

Quantitative Assessment of Pilot Studies



(mean ± SE, 6 subjects)

The 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.

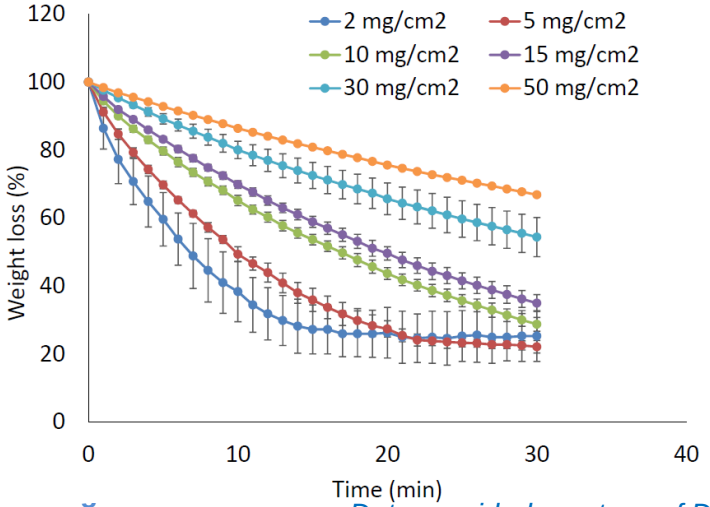
Dose vs Cream 10 mg/cm²	Point Estimate				Bootstrap (n=1000)			
	Percent conc profile		Percent AUC profile		Percent conc profile		Percent AUC profile	
	Lidocaine	Prilocaine	Lidocaine	Prilocaine	Lidocaine	Prilocaine	Lidocaine	Prilocaine
f_1								
Cream 5 mg/cm² (n=12)	65.5	63.4	64.6	63.1	63.1 (48.7 – 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)

Shukla et al. 2022 ASCPT poster

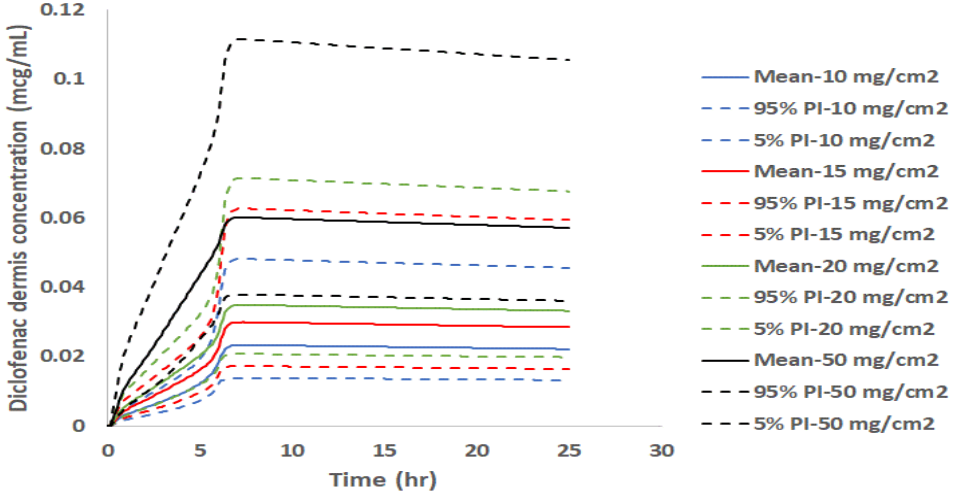
Considerations for the Study Design

- Product dose
  - Case study for diclofenac sodium topical gel, 1%

Evaluating the metamorphosis of different dose amounts



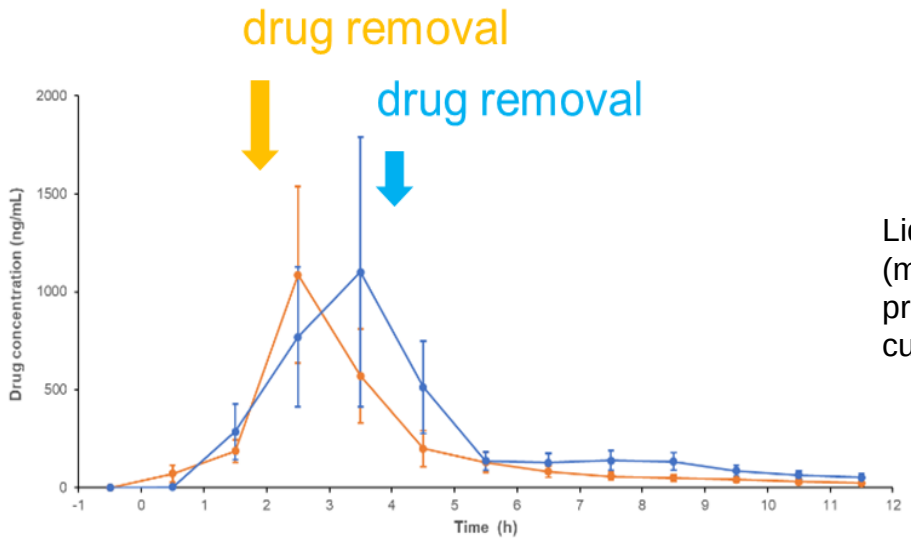
Predicting the bioavailability of different dose amounts using modeling and simulation



Data provided courtesy of Dr. Ahmed Zidan and Dr. Eleftheria Tsakalozou

Considerations for the Study Design

- Study duration and application duration
  - Case study for lidocaine prilocaine topical cream, 2.5%;2.5%

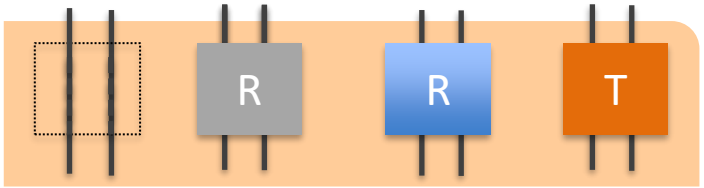


Lidocaine concentration-time profiles (mean ± SE, 3 subjects) for drug product removal after 2 hours (orange curve) and after 4 hours (blue curve)

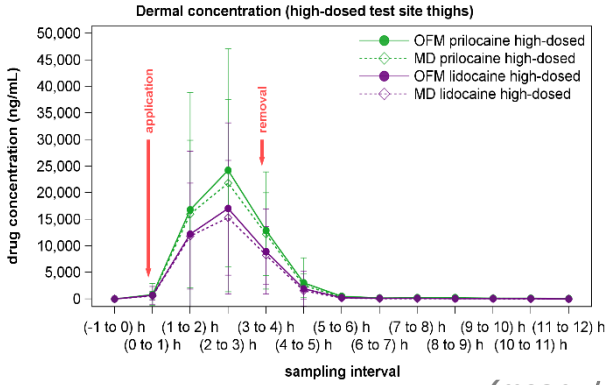
Data provided courtesy of Dr. Frank Sinner, ***Award U01FD005861***

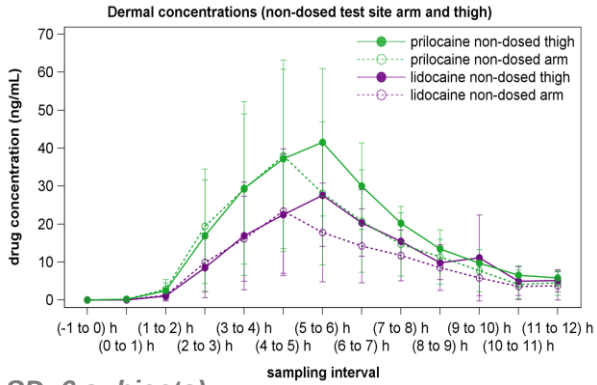
Considerations for the Study Design

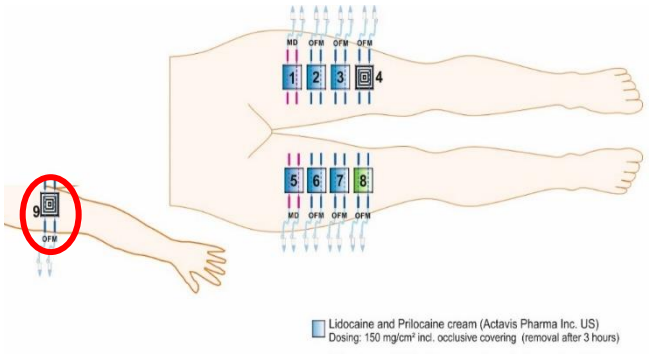
- Lateral diffusion



- Systemic absorption and systemic redistribution







(mean ± SD, 6 subjects)

Tiffner et al. 2019 AAPS poster, ***Award U01FD005861***

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
- Method development and validation strategies
- Optimizing the BE study design
- Development of data analysis strategies

What We Have Learned/Demonstrated

- dMD and dOFM can detect differences in dermal drug concentration.
- dMD and dOFM may be used for evaluating BA and BE of hydrophilic and hydrophobic topical drugs.
- dMD and dOFM were both capable of assessing the BA of lidocaine and prilocaine.
- In our dMD and dOFM studies the lateral diffusion and systemic redistribution have been minimal compared to the drug concentrations detected at the topical applicate sites.
- A pilot study can be conducted to assist with optimization of the BE study design (e.g., selection of dose, sampling duration, application duration, and estimation of subject number)

Potential Challenges to Address

- *Access to the techniques and expertise*
- *Bioanalytical method validation*
- *Availability of standardized methodologies for qualification*
- *Appropriate analysis of the data*
- *Cost*

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.
- 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.
- The design of the pivotal BE study using dOFM and dMD can be informed by conducting a pilot study supported by in vitro/in silico data.
- To propose an alternative BE approach for a prospective generic topical product using a dermal sampling methodology, you can submit a pre-ANDA product development meeting request to the Office of Generic Drugs.

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- **Dr. Grazia Stagni**

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