In Vivo Dermal Microperfusion & Microdialysis Bioequivalence Approaches

SBIA 2020: Advancing Innovative Science in Generic Drug Development Workshop

Session 3: Future Directions, Emerging Technology, and Current Thinking on Alternative BE Approaches

Topic 2: Topical Dermatologic Products

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Disclaimer

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

Learning Objectives

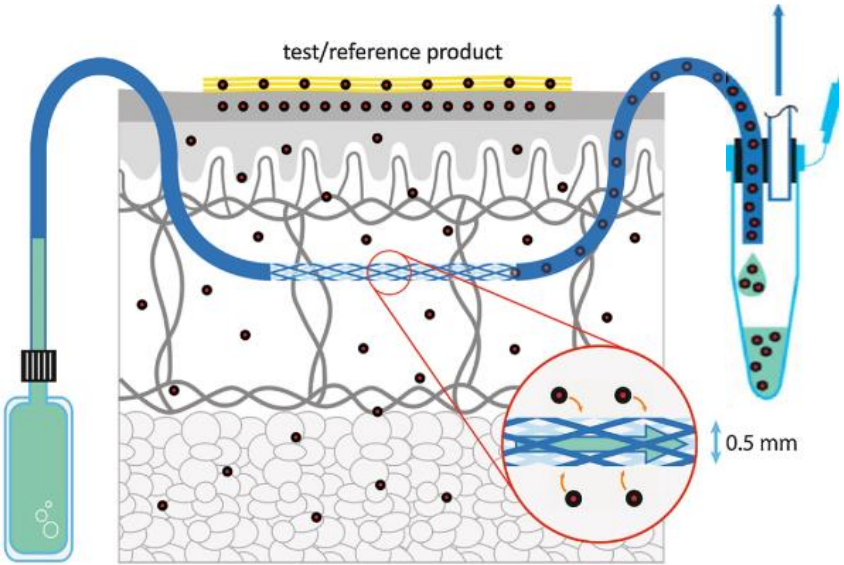
- Evaluate bioequivalence (BE) for topical dermatological drug products using in vivo pharmacokinetics (PK)-based approaches
- What are some advances in cutaneous PK methods by Generic Drug User Fee Amendments (GDUFA)-funded research?
- Design a BE study using in vivo cutaneous PK methods
  - Considerations related to method development/optimization
  - Considerations related to the pivotal BE study

Local PK-Based Approaches

- **Methodologies of Interest**
  - **In Vivo** Cutaneous PK Studies
    - ✓ Dermal Open Flow Microperfusion (dOFM)
    - ✓ Dermal Microdialysis (dMD)
    - ✓ Epidermal and/or Dermal Pharmacokinetic Tomography
- **Methodologies *Not of Interest***
  - **In Vivo** Cutaneous PK Studies
    - ✓ Tapestripping “Dermatopharmacokinetics” (DPK)

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.



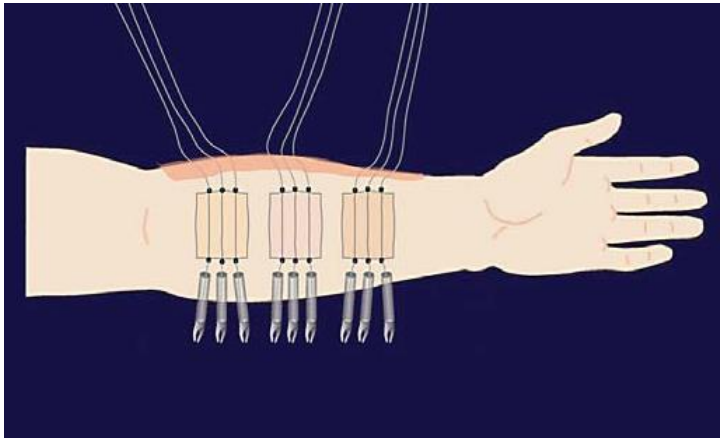


Image provided courtesy of Dr. Frank Sinner, Joanneum Research

Skin Pharmacol Physiol 2011;24:44–53

Cutaneous PK-Based Approaches

Traditional limitations and challenges

- Limited utility for certain classes of drugs
- High variability in the data
- Dermal drug concentrations too low to quantify
- 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 acceptance criteria for BE

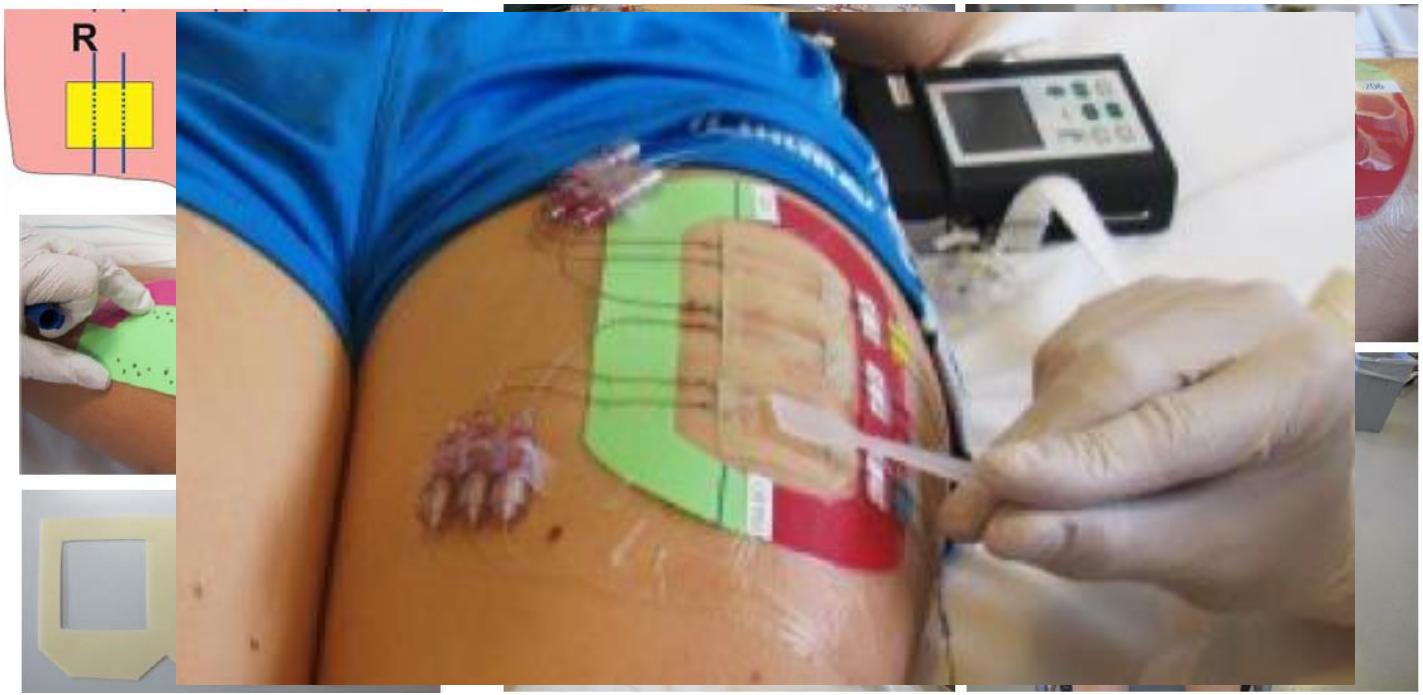
GDUFA-Funded Research Awards

Novel methodologies (dOFM and dMD) to assess the BE of topical dermatological drug products:

- Joanneum Research
  - U01FD004946
  - U01FD005861
- Long Island University (LIU)
  - U01FD005862
  - U01FD006930

Cutaneous PK Studies With dOFM

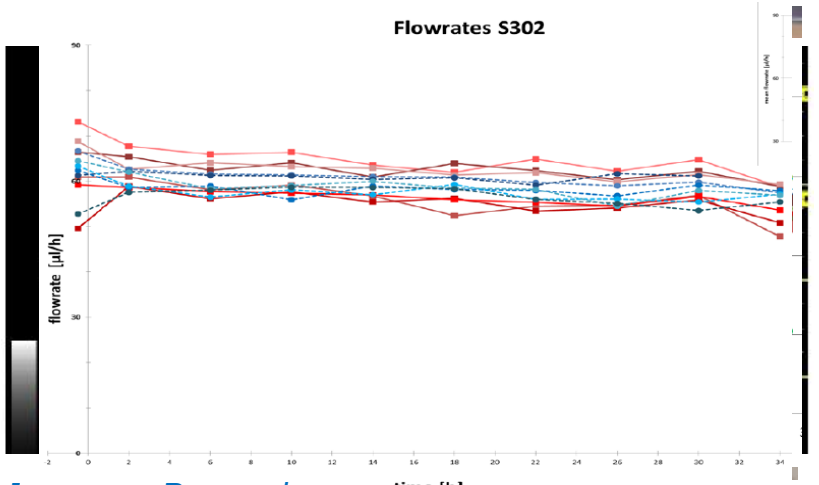
- Testing Positive and Negative Controls for BE



Images provided courtesy of Dr. Frank Sinner, Joanneum Research

Study Controls

- Application site: controlled by application template
- Probe depth: monitored by ultrasound
- Barrier integrity test: transepidermal water loss (TEWL)
- Local blood flow
- Flow rates



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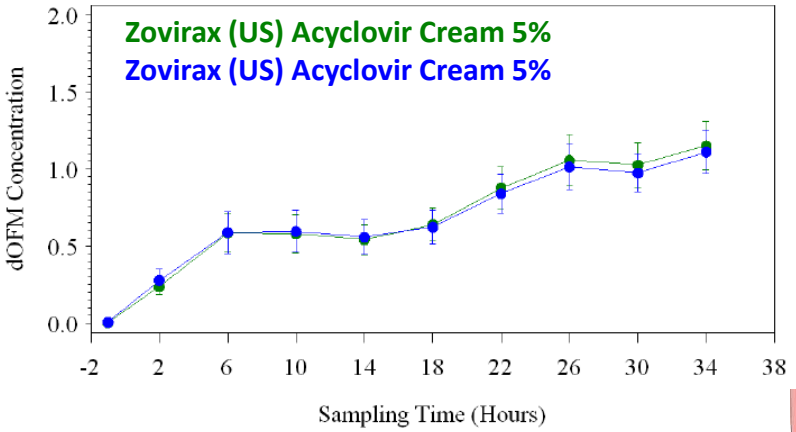
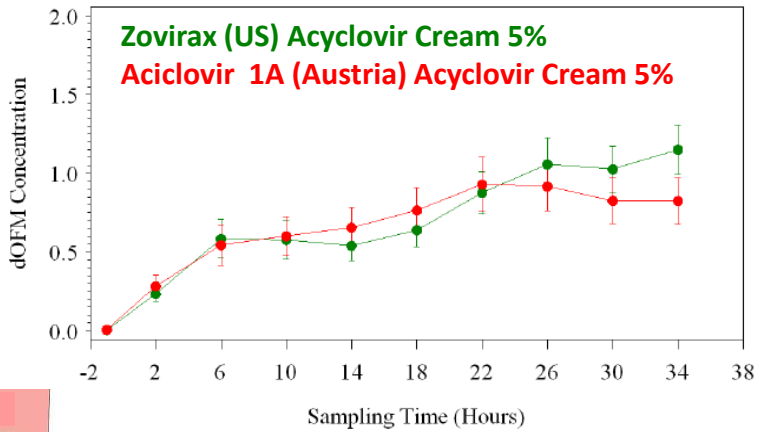
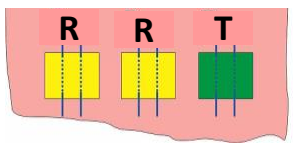
Pivotal BE Study for Acyclovir Cream







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

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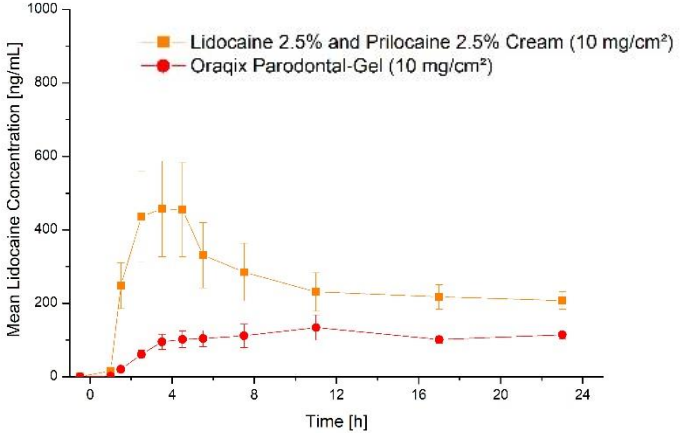
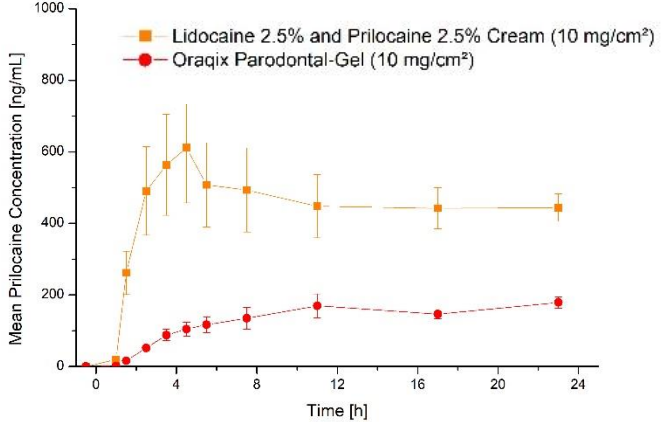
Pilot BE Study for EMLA® vs Oraqix®

Lidocaine



Prilocaine

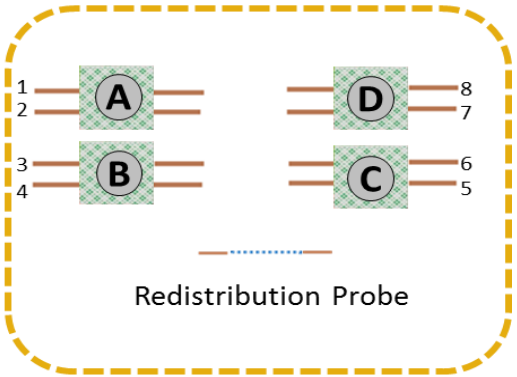


BE-Results – **EMLA® (lidocaine;prilocaine) topical cream, 2.5:2.5%** versus **Oraqix® (lidocaine;prilocaine) dental gel, 2.5:2.5%**

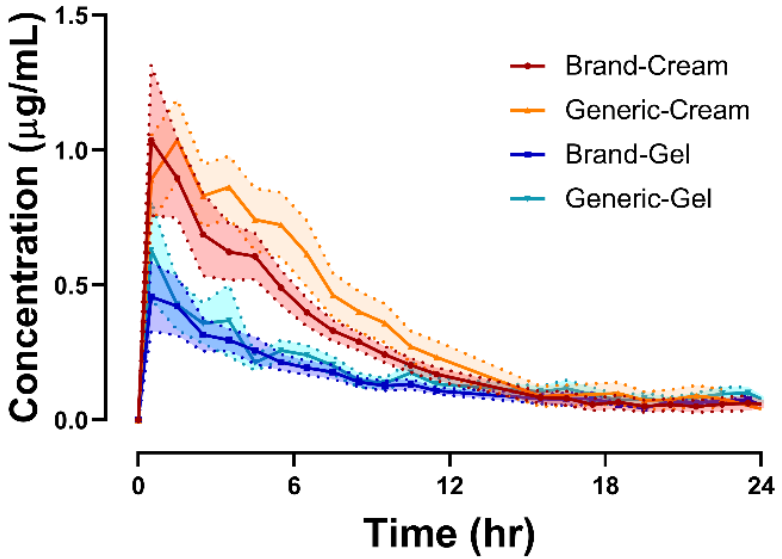
Drug	PK endpoint	Estimate	Lower Limit	Upper Limit	BE-evaluations
Lidocaine	AUC_{0-24}	2.00	1.51	2.65	Not BE
	C_{MAX}	2.79	1.75	3.21	Not BE
Prilocaine	AUC_{0-24}	2.37	2.14	3.63	Not BE
	C_{MAX}	2.75	2.15	3.51	Not BE

Data/images provided courtesy of Dr. Frank Sinner, Joanneum Research

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, LIU

PK-Based Methods for Topical BE

- Alternative BE approaches to comparative clinical endpoint BE studies may be possible by
  - Efficient **In Vitro BE** methods (characterization-based approaches)

    Particularly for prospective generic products which have '***No Difference***' in components (Q1), composition (Q2), or physical and structural characteristics (Q3) relative to the reference product.

  - Efficient **In Vivo BE** methods (cutaneous PK-based approaches)

    Particularly for prospective generic products which have '***Similar***' components (Q1), composition (Q2), or physical and structural characteristics (Q3) relative to the reference product.

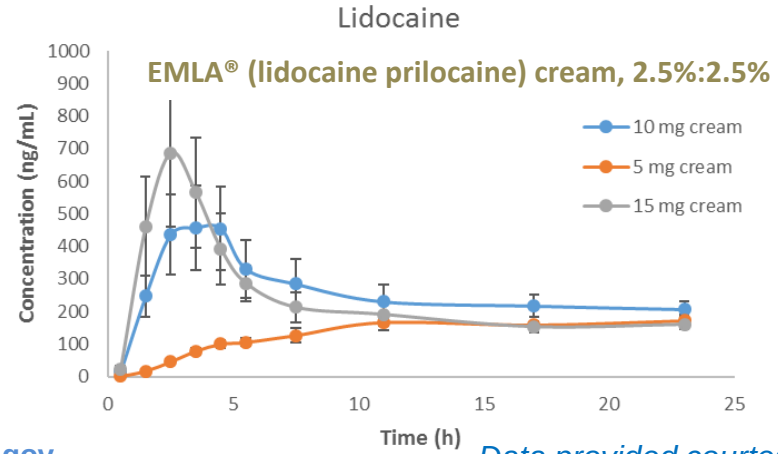
BE Studies Using dMD/dOFM

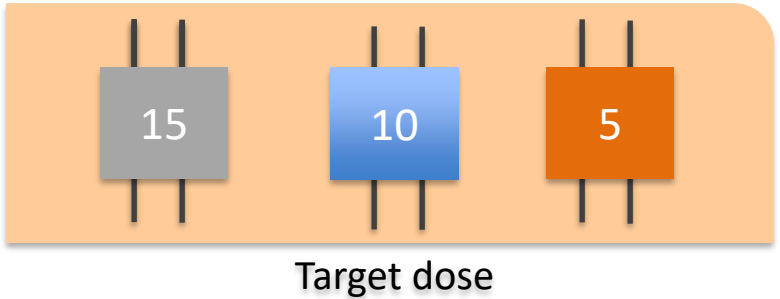
- Study Controls
- Method Development/Optimization
- Pilot Study
- Pivotal Study

Method Development/Optimization

Considerations for the study design: dose selection

- The sampling technique should demonstrate changes in the dermal bioavailability for <u>different dose amounts.</u>



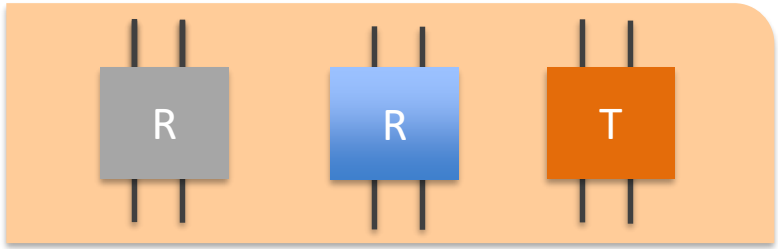


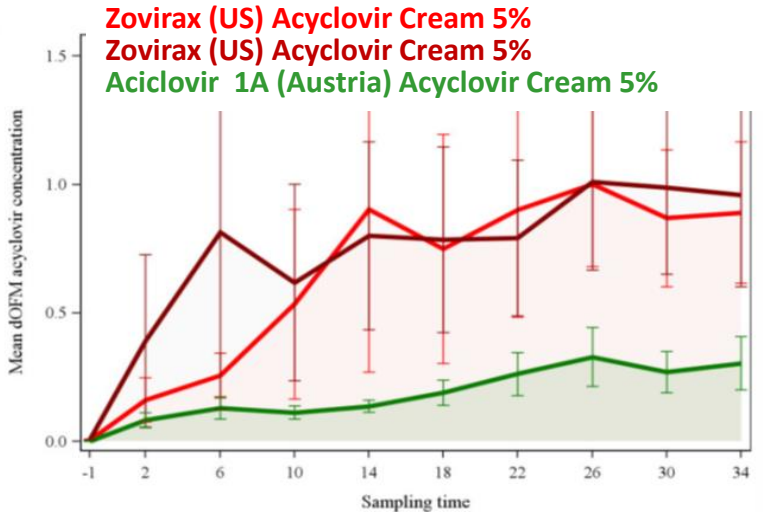
Data provided courtesy of Dr. Frank Sinner, Joanneum Research

Method Development/Optimization

Considerations for the study design:

- The sampling technique should demonstrate changes in the dermal bioavailability by <u>inclusion of positive and negative controls for BE.</u>





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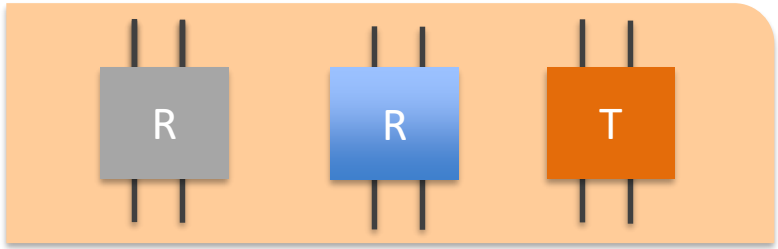

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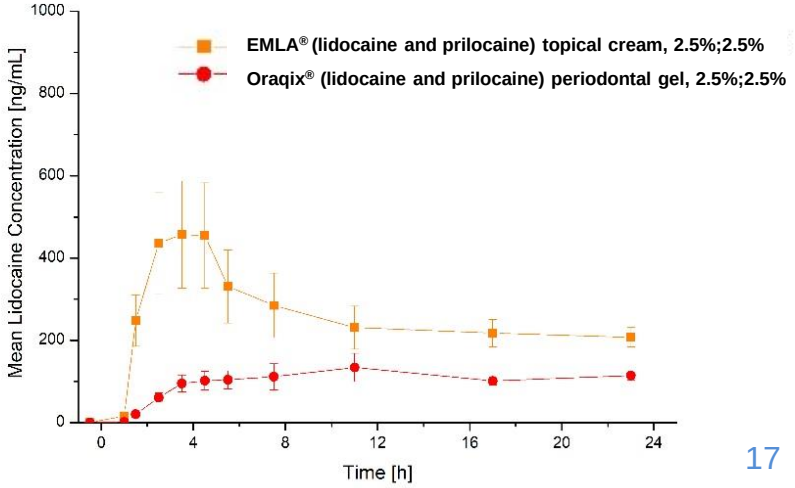
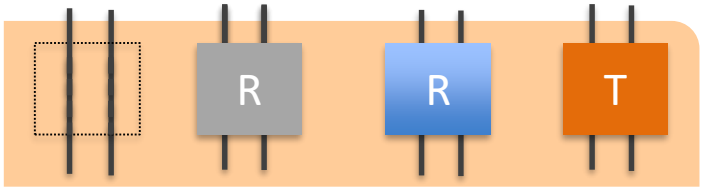
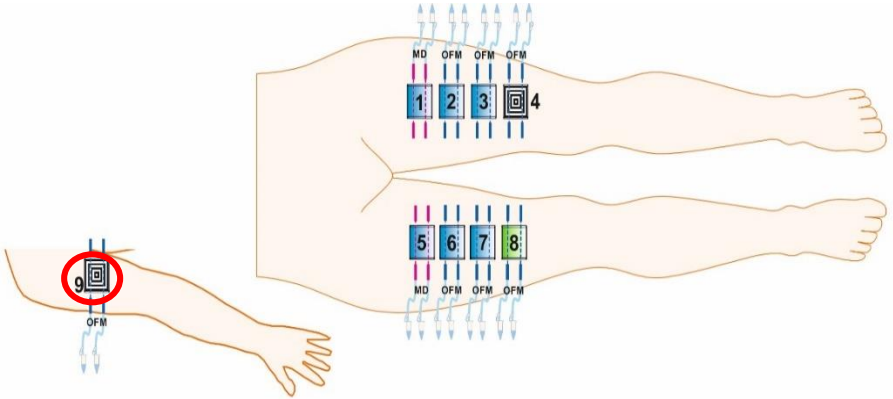


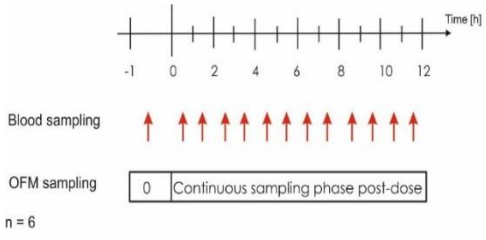
Method Development/Optimization

Considerations for the study design:

- Lateral diffusion
- Systemic absorption and systemic redistribution







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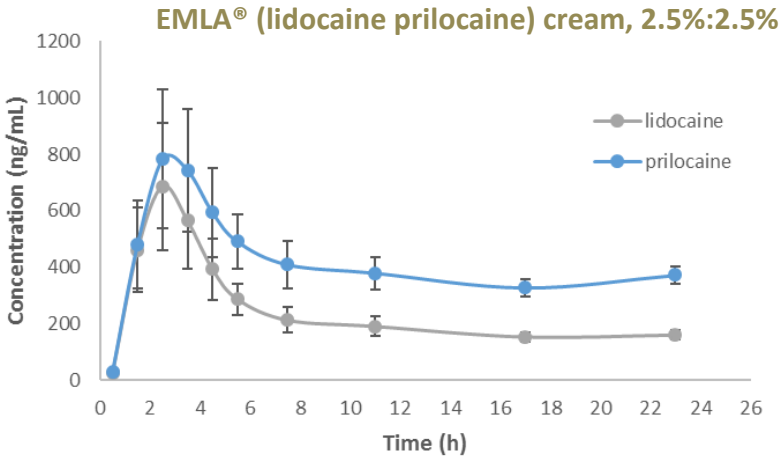
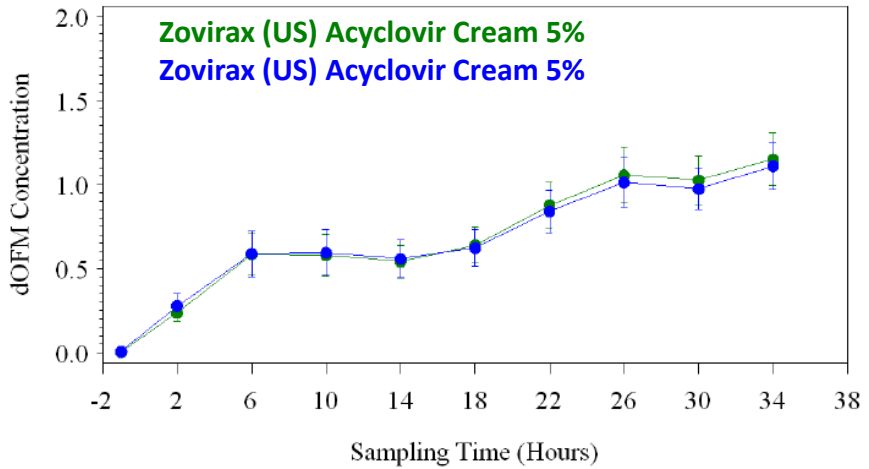
Method Development/Optimization

Considerations for the study design:

- Dose duration and sampling duration





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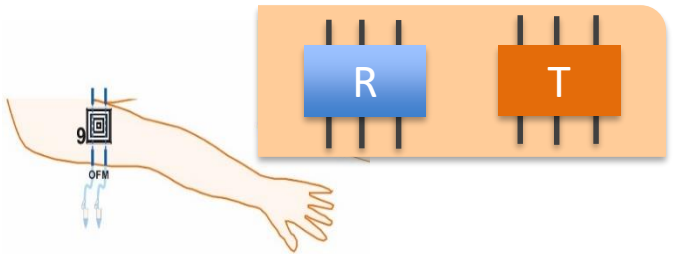
BE Study Design Considerations

- Number of test and reference sites per subject
- Number of replicate probes per application site
- Non-dosed sites to assess lateral diffusion and/or systemic redistribution
- Duration of the study



Conclusions

- 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.
- Efficient in vivo dOFM and dMD based BE studies may be particularly useful for prospective generic products which have ‘similar’ components (Q1), composition (Q2), or physical and structural characteristics (Q3) relative to the reference product.
- The results from the method development/optimization and pilot studies may be suitable to support a demonstration that a dOFM study in human subjects (at the selected dose) would be able to differentiate changes/differences in the rate and extent to which drugs become available in the dermis.
- To propose this alternative BE approach for a topical product, you can submit a pre-ANDA product development meeting request to the Office of Generic Drugs.

Acknowledgements

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Research Collaborators

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GDUFA Award U01FD005861

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

GDUFA Award U01FD005862

- **Dr. Grazia Stagni, LIU**

Challenge Question

Which of the following statements is NOT true about developing an in vivo dOFM/dMD PK- based method?

The method development/optimization study(ies) are expected:

A. To show that an appropriate dose is selected for the pivotal BE study

B. To support that the proposed method is able to discriminate an increase in the rate and extent to which a topical product may deliver a drug into the skin

C. To be adequately powered

D. To support that an appropriate dose/study duration is selected for the pivotal BE study

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