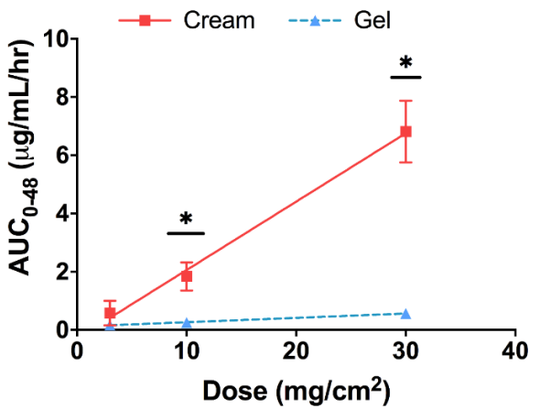
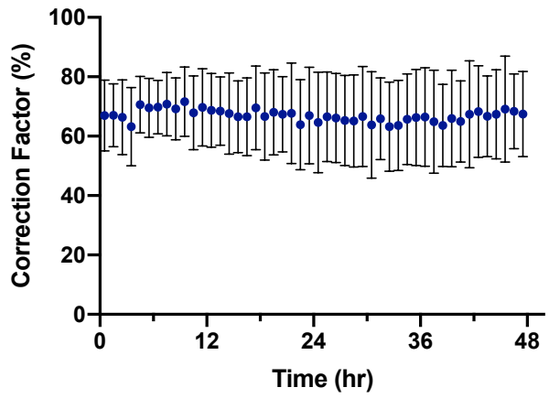
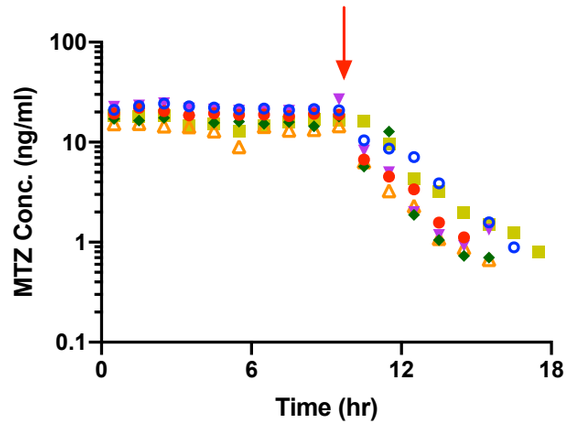
A Microdialysis Approach to Assess Dermal Pharmacokinetics of Topical Dermatological Drug Products







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Formulation Characterization and Cutaneous Pharmacokinetics to Facilitate Generic Topical Product Development

November 3rd, 2022

LIU Pharmacy

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Disclaimers

- The views and opinions presented here represent those of the speakers and should not be considered to represent advice or guidance on behalf of the **U.S. Food and Drug Administration**

- The views and opinions presented here do not represent views and opinions of **Vertex Pharmaceuticals Inc**.

Overview

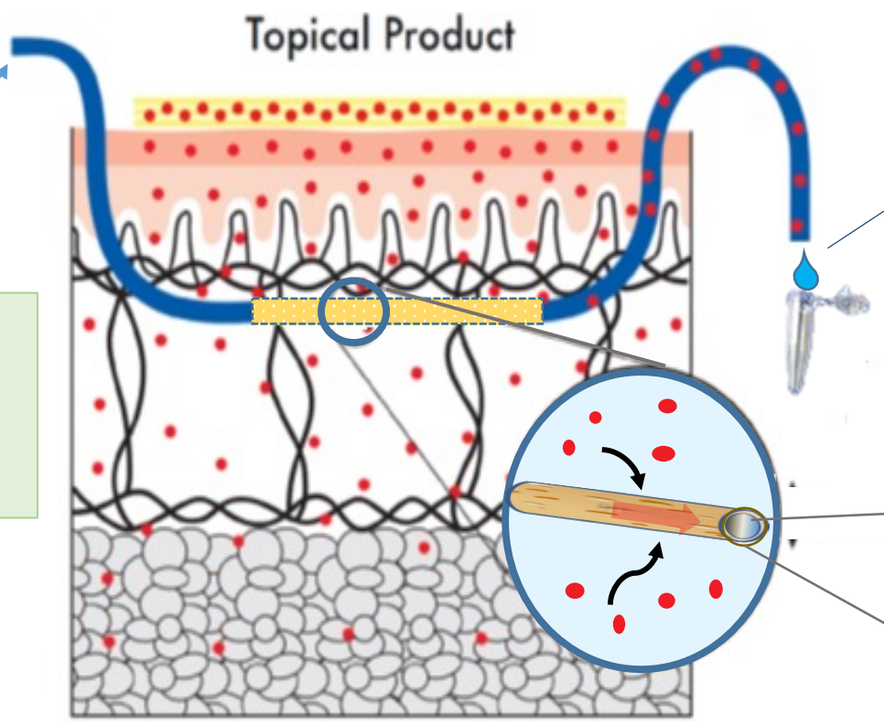
- Background on dermal microdialysis (dMD)
- Selection of dMD probe and considerations for in vitro dMD suitability
- Fundamental investigation of cutaneous pharmacokinetic principles in animal models
  - Local bioavailability (BA) of Metronidazole (MTZ) products
  - Formulation removal at specific dose durations
  - Exploratory bioequivalence (BE) in Rabbits

Background

- The goal of this proposal was to determine the suitability of the **microdialysis** technique to assess cutaneous BA/BE
- Several published reports have already explored the potential utility of dMD for BA/BE assessment, they also pointed out limitations:
  - Probe stability unknown
  - High variability in the results
  - Dermal concentrations too low to quantify
  - Study durations too brief for adequate cutaneous pharmacokinetic comparison of the products (*e.g.*, only 4-5 hours)
  - Extended immobilization of study participants
- **Here, we identify new strategies to overcome such limitations**

Dermal Microdialysis

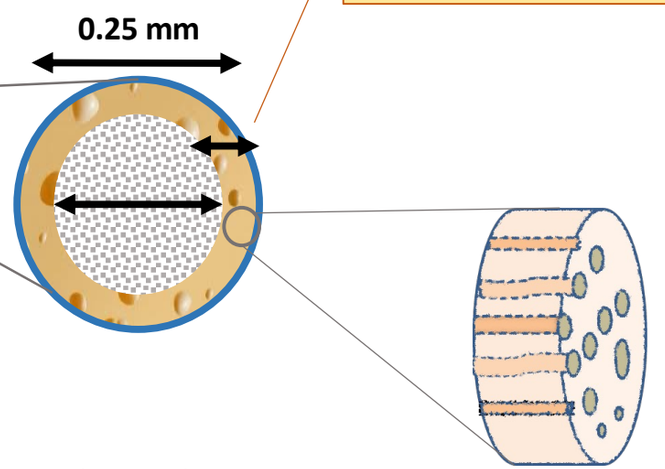
Isotonic fluid: **no net exchange of liquid volume**



Courtesy of Dr. Frank Sinner

Collected sample concentration is proportional to the interstitial fluid concentration

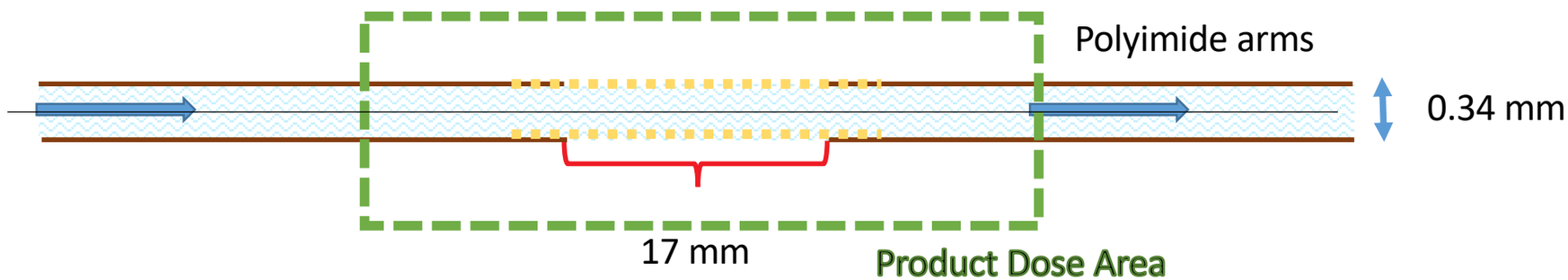
Tubular hollow dialysis fiber from an artificial kidney (Gambro AN69 – MWCO: 50 kDa)



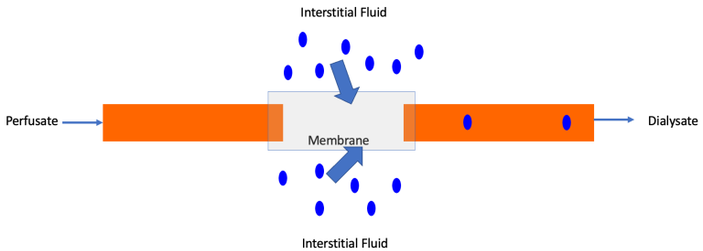
$$J = -D\frac{dC}{dx}$$

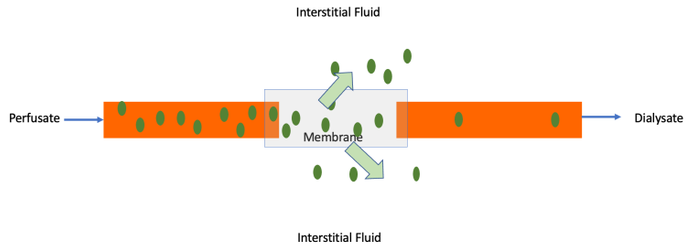
Selection of dMD probe

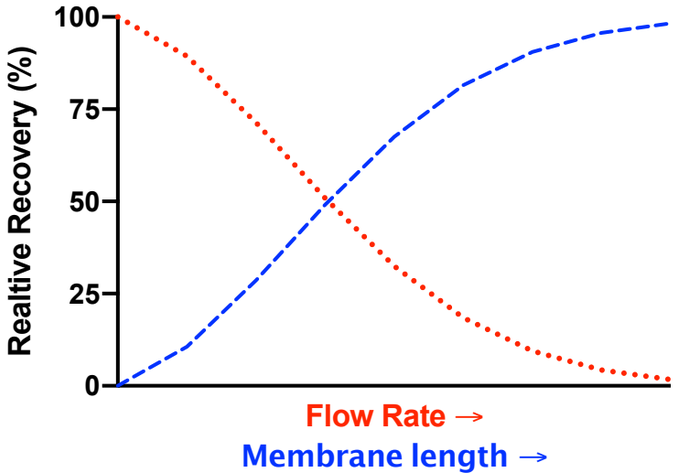
- After in vitro testing of commercial and in-house fabricated probes, we selected an in-house fabricated probe with the following characteristics:
  - Hollow dialysis membrane from Baxter PrismaFlex 100 (Gambro AN69) MWCO 50 kDa, 0.34 diameter (to allow a 25-gauge needle)
  - Window length: 17 mm (rigorously controlled)



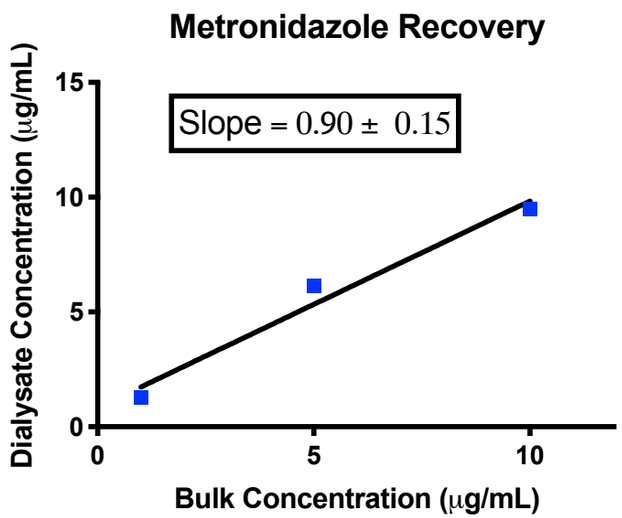
dMD In Vitro System Suitability

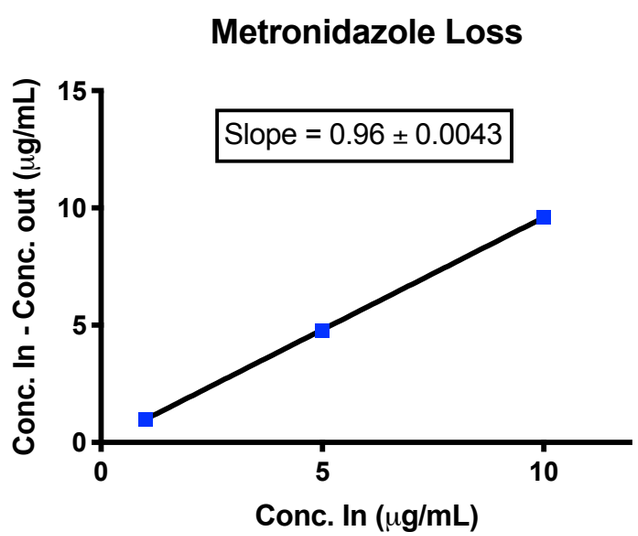






Optimized Parameters
Flow rate: 0.5 uL/min
Membrane length: 1.7 cm



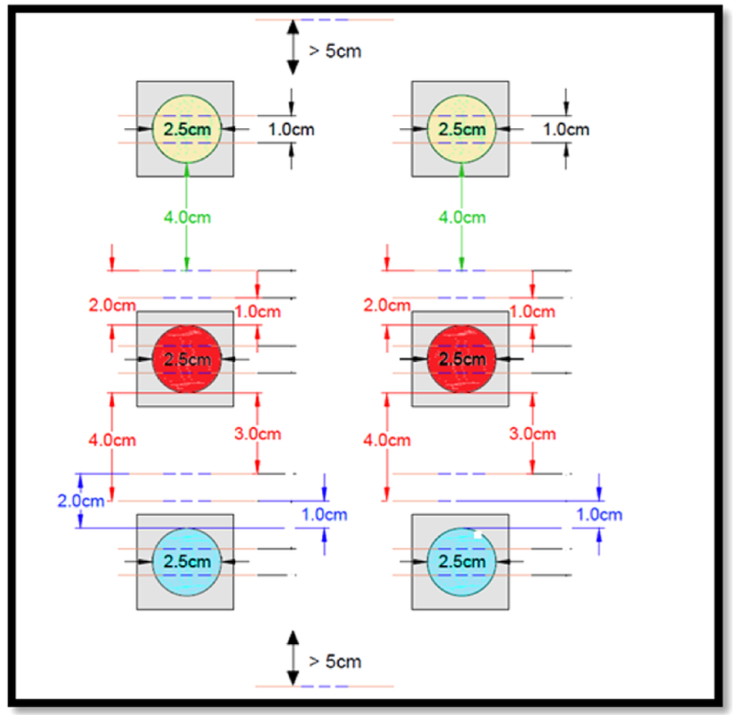


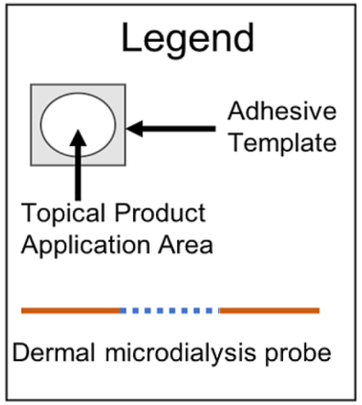
In vitro recovery ~ 90%
In vitro retrodialysis ~ 96%

✓ dMD set-up suitable for Metronidazole

Local BA of Metronidazole (MTZ) In Yucatan Minipig

- Two MTZ formulations (a gel and a cream) applied at 3, 10, and 30 mg/cm^2
  - Is the dMD probe **sensitive** to different local BA from two products and escalating product doses?
- Two application sites/experiment; two probes under each formulation
  - How reproducible (or consistent) is the measured dermal PK?
- Lateral diffusion probes at 1, 2, 3, 4 cm from the edge of the application site
  - Is there a potential for cross contamination between application sites?
- Two redistribution probes
  - **Systemic redistribution**: Is the MTZ absorbed systemically interfering with that measured at the application site?
- 48 hours sampling to characterize the entire PK profile
  - Is the probe recovery **stable** for 48 hours?





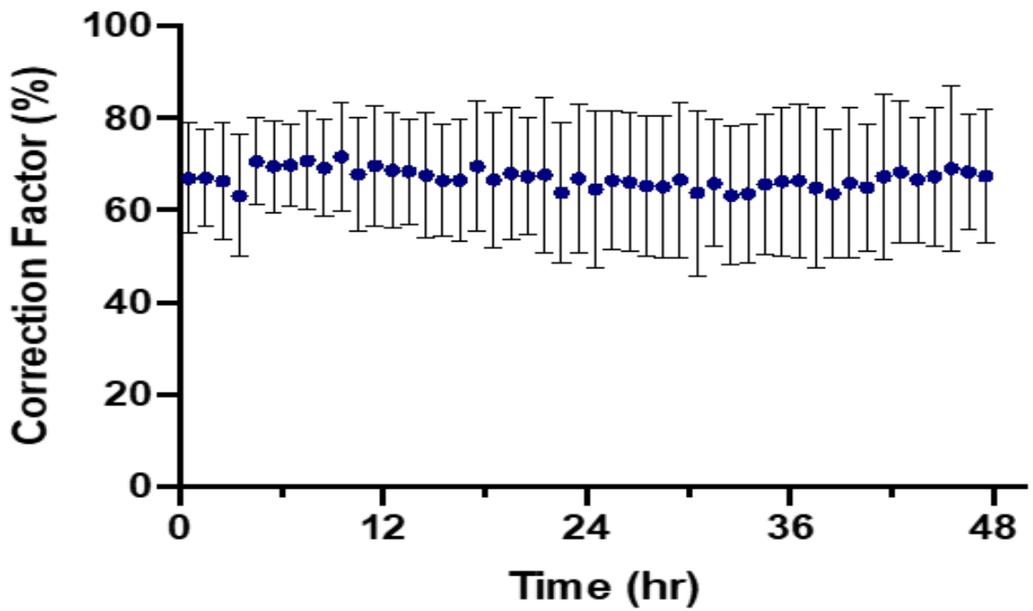
Yucatan mini-pig

TEWL and probe depth were measured to investigate their effect on dermal exposure

Kuzma, B. A., Senemar, S., Ramezanli, T., Ghosh, P., Raney, S. G., & Stagni, G. (2021). Evaluation of local bioavailability of metronidazole from topical formulations using dermal microdialysis: Preliminary study in a Yucatan mini-pig model. *Eur J Pharm Sci, 159*, 105741. doi:10.1016/j.ejps.2021.105741

Probe Stable For The Entire 48-hr Sampling

- Correction factor data was used to assess probe stability over time
- Changes in dialysate concentrations are reflective of the environment surrounding the probe rather than any technical issues with the probe (*i.e.*, **no probe fouling**)

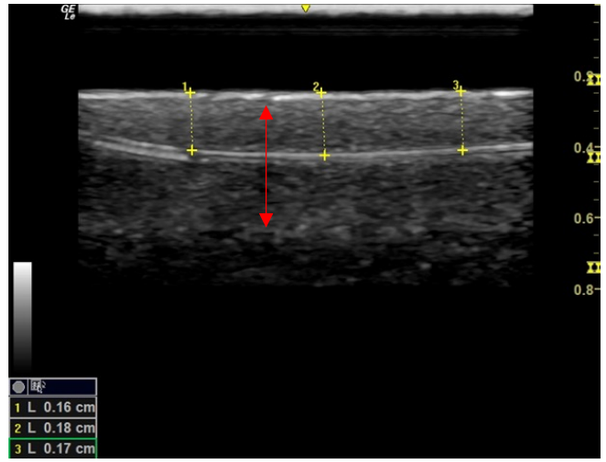


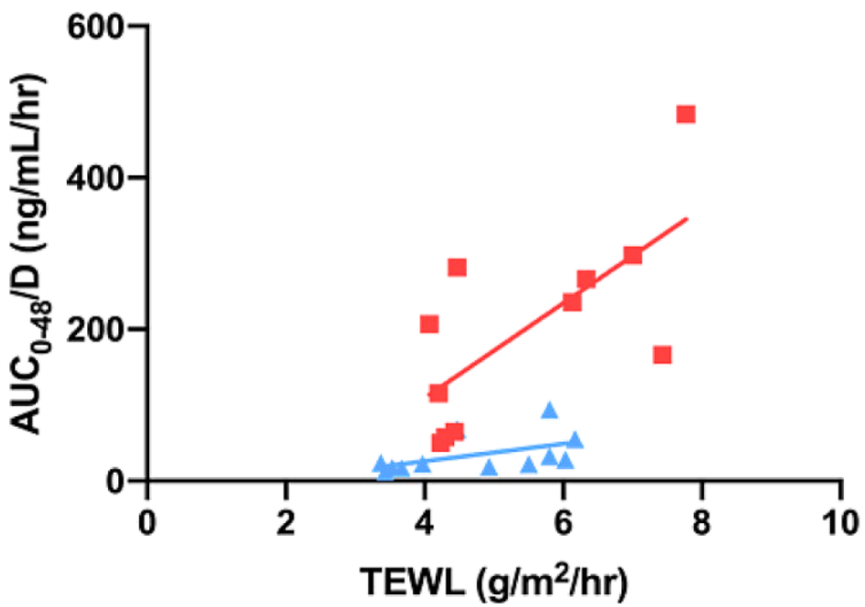
$$Correction\ Factor = 1 - \frac{[D_3 - MTZ]_{dialysate}}{[D_3 - MTZ]_{perfusate}}$$

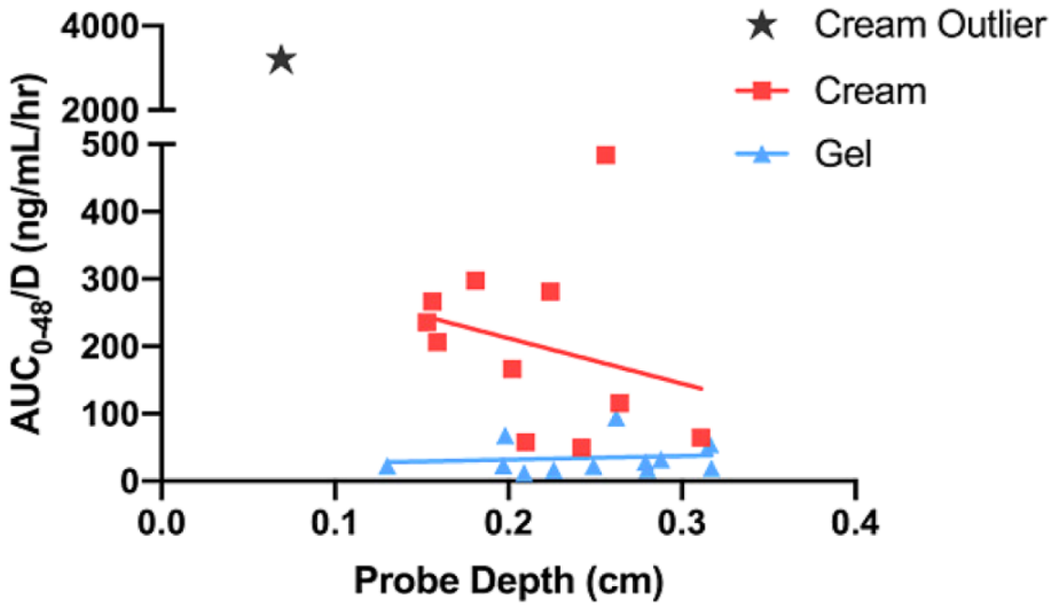
$$[MTZ]_{dISF} = \frac{[MTZ]_{dialysate}}{Correction\ Factor}$$

Kuzma, Benjamin A., et al. *European Journal of Pharmaceutical Sciences* 159 (2021): 105741.

No significant effect of covariates on dermal exposure







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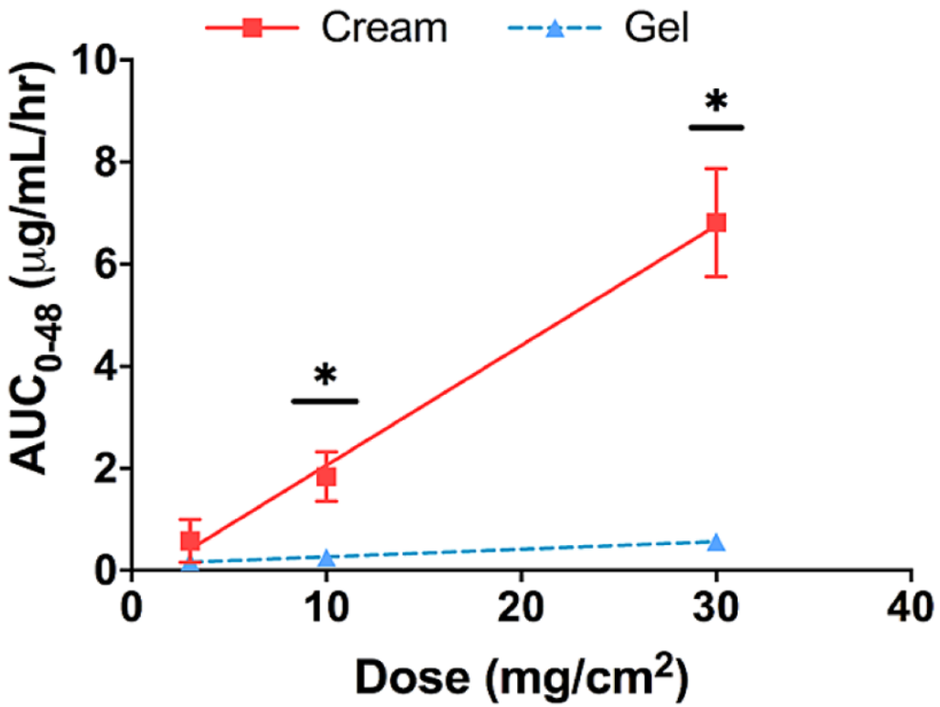
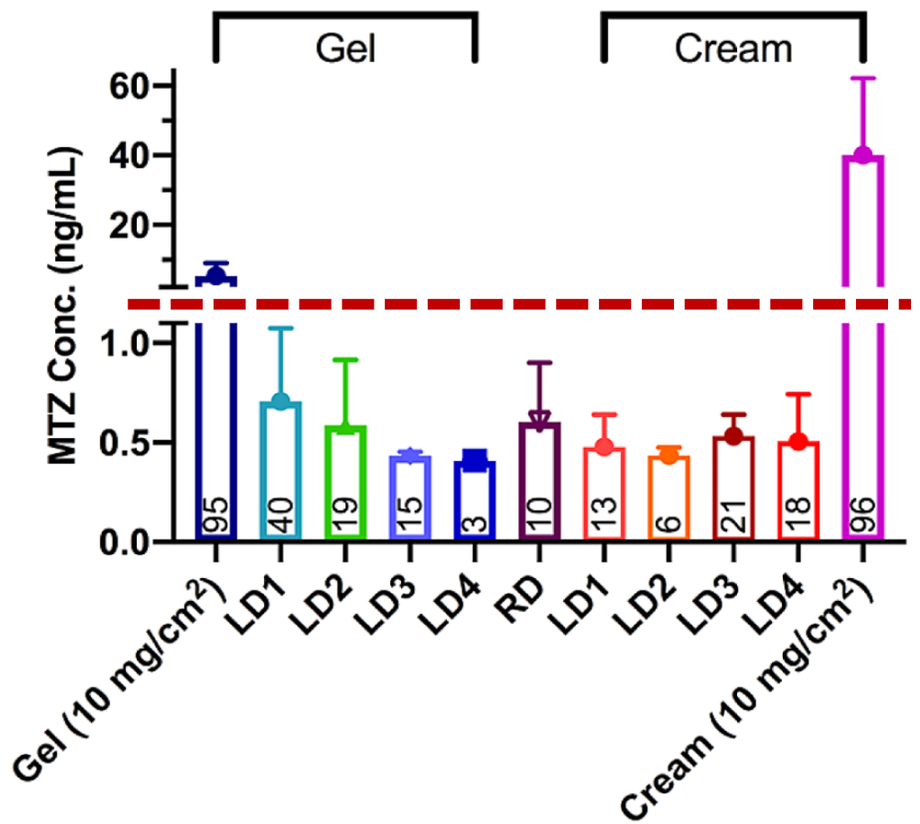
Linear Dose-Response and Negligible Lateral Diffusion





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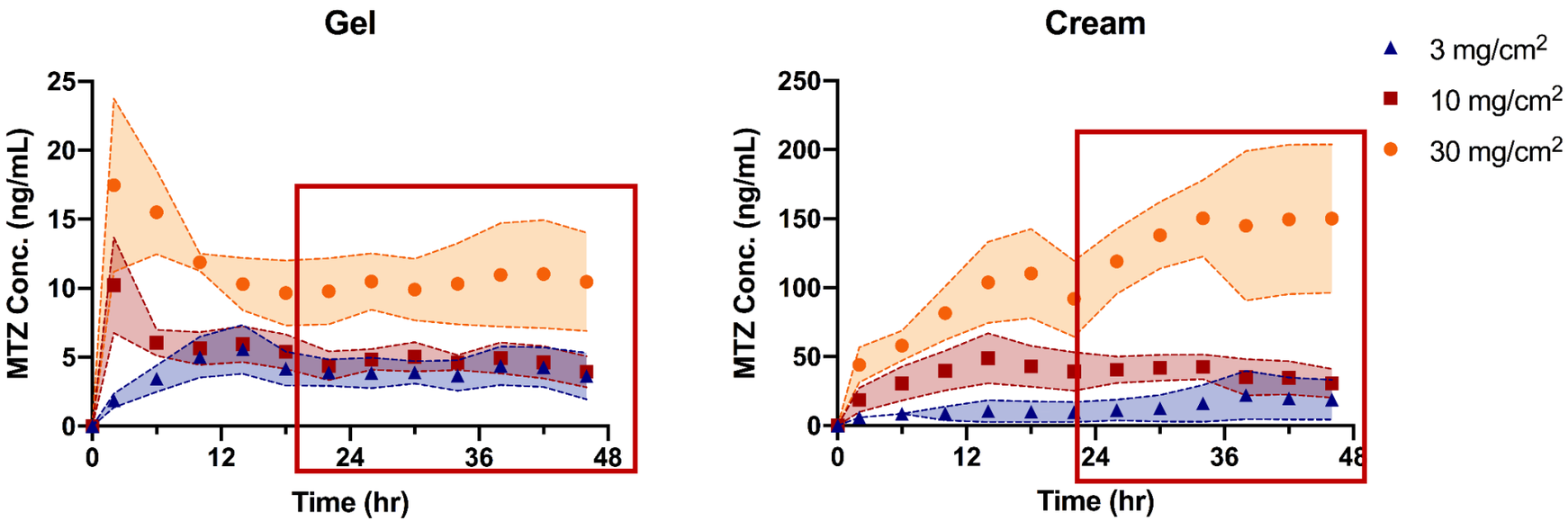
Lack of Terminal Phase

- ✕ Unable to get reliable estimate of C_{max}
- ✕ Concentrations continue to either level off or increase after 24-hr



- The concentrations are plotted as the average of 4 time points with the corresponding averaged time midpoints.

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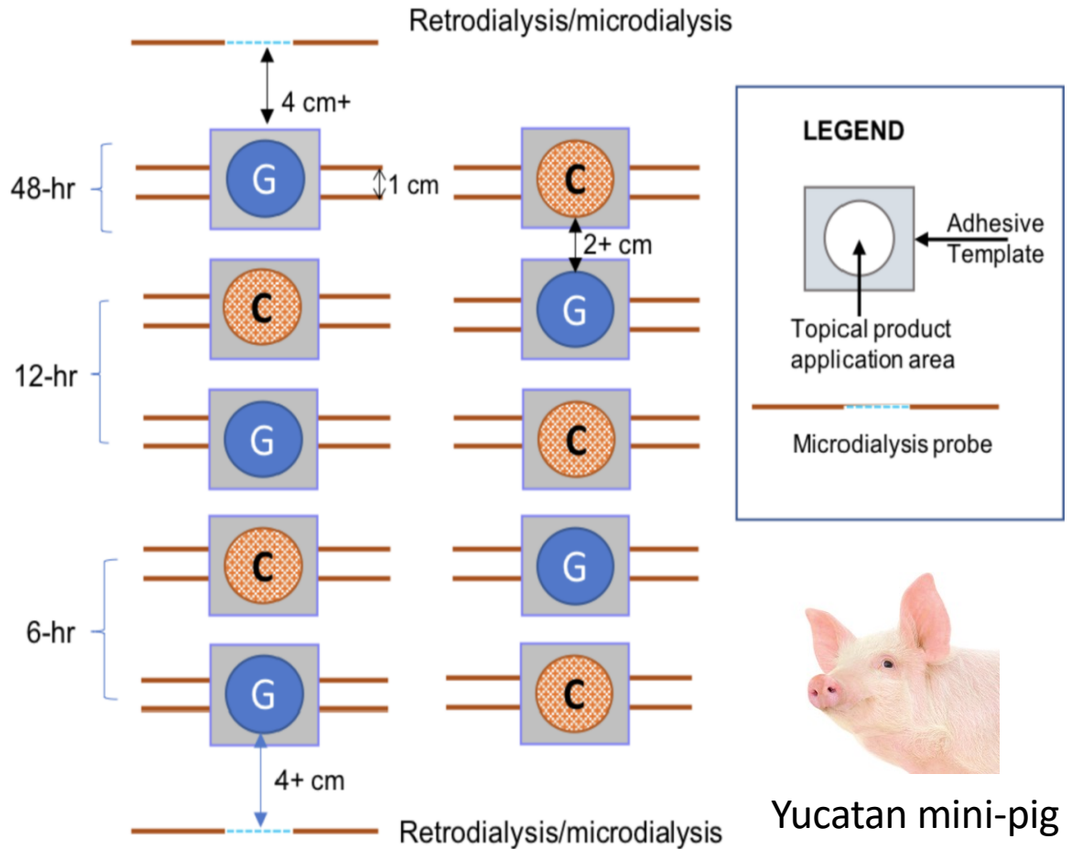
Dose Duration Effect On Dermal MTZ BA

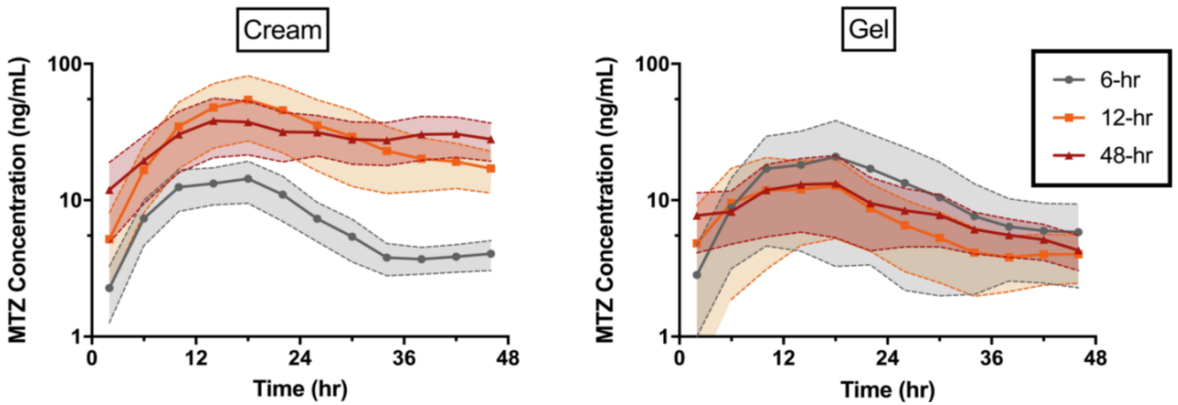
- Two products: a generic MTZ gel and a generic cream
- Product-dose: 10 mg/cm^2
- Three dose durations (DD): 6, 12, 48 hr
  - Rigorously controlled wipe-off procedure
- Two additional probes to assess dermal elimination
- **All other procedures were identical to the previous study**, apart from a slight modification in the anesthesia protocol to improve the vital parameters of the animals

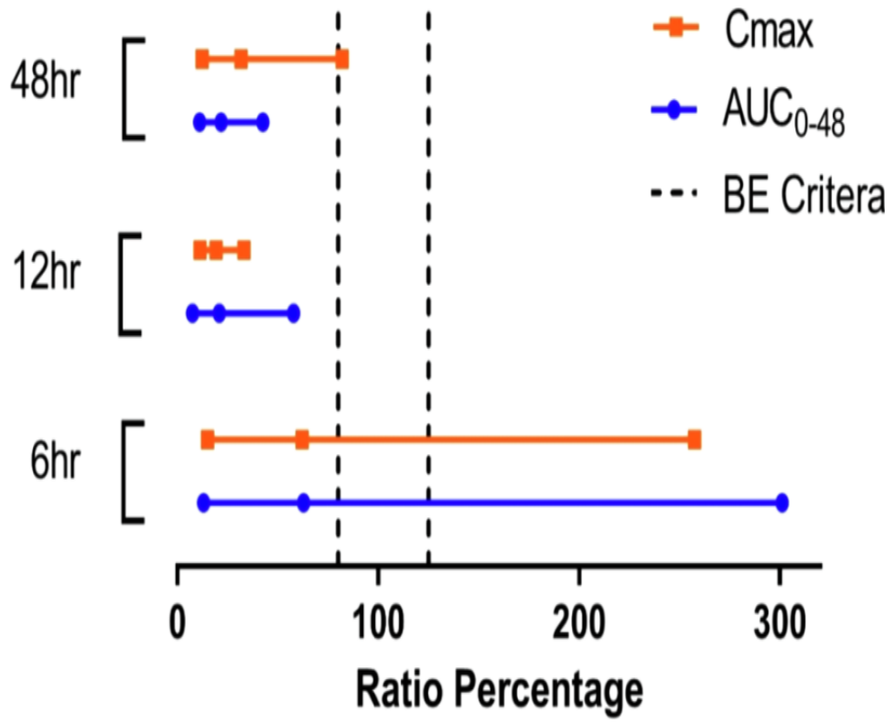


Yucatan mini-pig

Kuzma, B. A., Senemar, S., Ramezanli, T., Ghosh, P., Raney, S. G., & Stagni, G. (2022). The dose-duration effect on cutaneous pharmacokinetics of metronidazole from topical dermatological formulations in Yucatan mini-pigs. *Eur J Pharm Biopharm, 175*, 43-52. doi:10.1016/j.ejpb.2022.05.001

Adequate Characterization of Dermal PK





Drying time impacts dermal BA

- Removal of drug product before:
  - Lower BA (Cream – 6hr)
- Removal of drug product after:
  - Unaffected dermal BA (Gel – 6hr)

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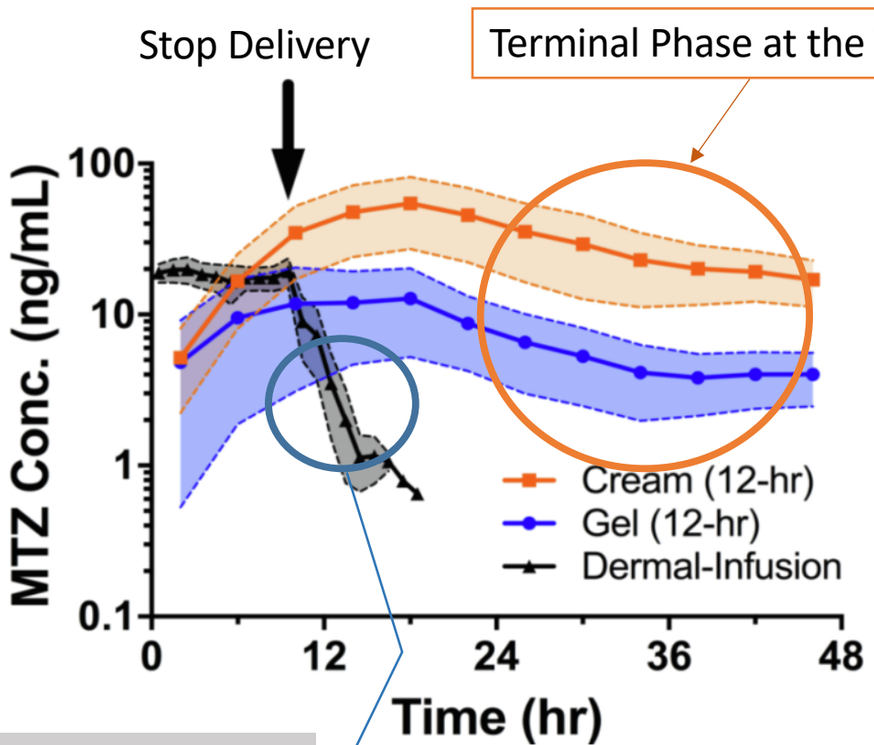
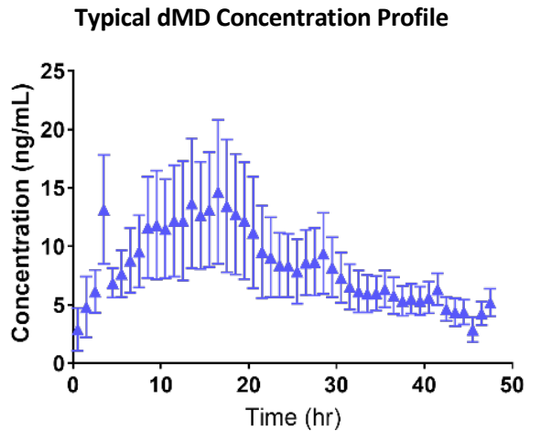
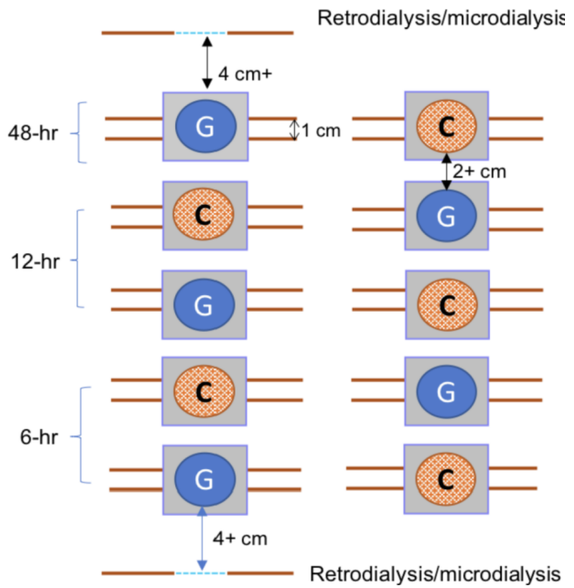
Flip/Flop Cutaneous PK



Retrodialysis/Microdialysis Terminal phase

Flip/flop pharmacokinetics





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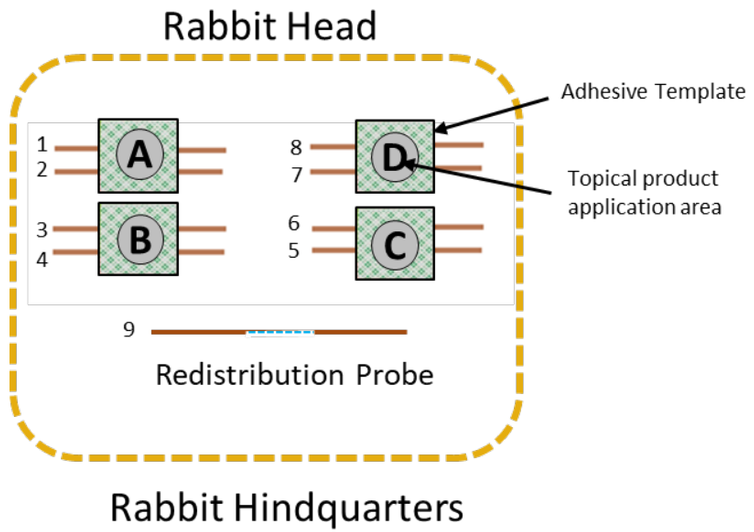
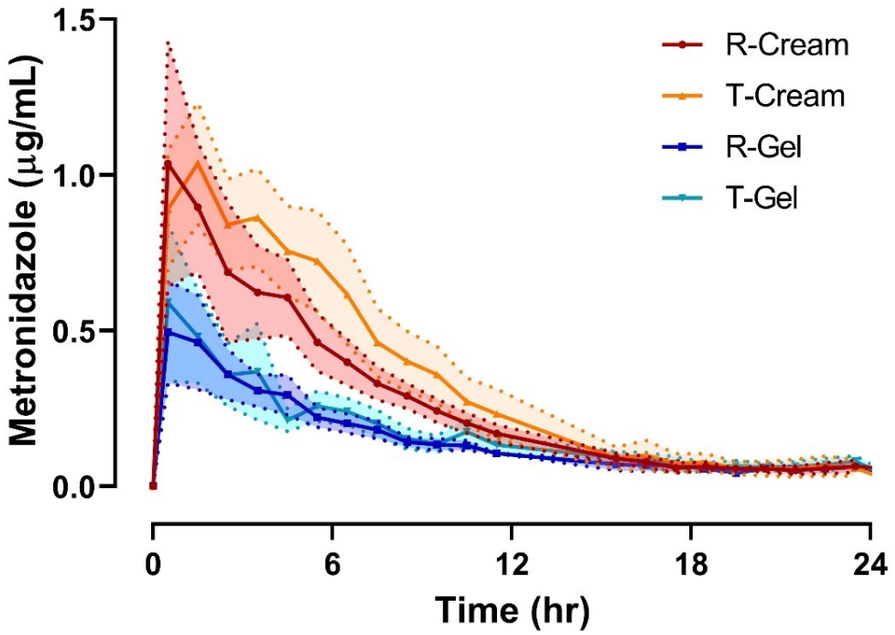
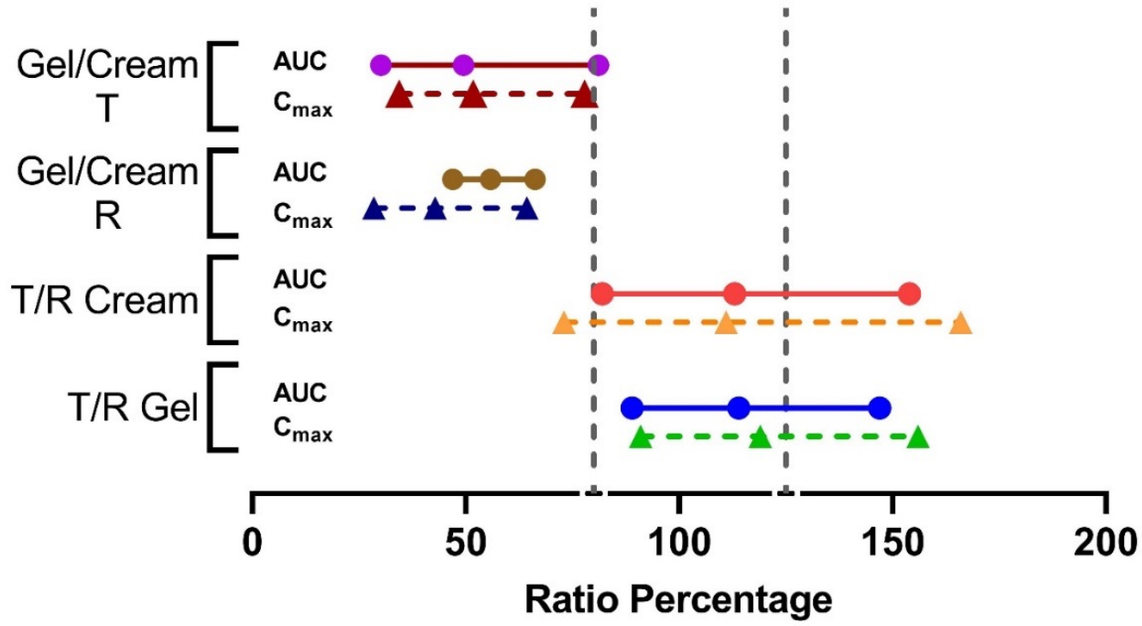
Bioequivalence Evaluation of Topical MTZ Products using Dermal Microdialysis in New Zealand Rabbits

- Four products:
  - FDA approved gel generic (T) and reference gel (R)
  - FDA approved cream generic (T) and reference cream (R)
- Product-dose: 10 mg/cm^2
- One additional probe to assess redistribution
- 7 New Zealand Rabbits
- Study duration: 24 hours
- Probe performance marker: acetaminophen
- All other procedures were identical to the previous mini-pig studies



Adequate cutaneous PK characterization



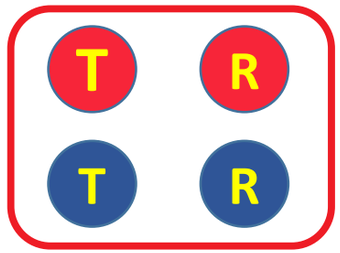


BE Power Analysis

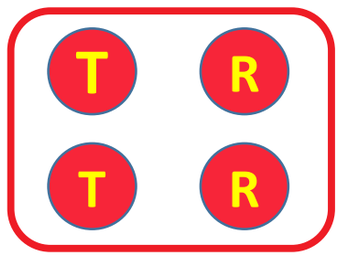
Number of rabbits required to achieve statistical power of 80% per comparison and endpoint

Study Design		A	B
		N-rabbits	
T vs. R gel*	$Ln(AUC_{0-24})$	11	5
(RSABE)	$Ln(C_{max})$	10	4
T vs. R. cream**	$Ln(AUC_{0-24})$	21	10
(ABE)	$Ln(C_{max})$	20	9

A: reference formulation and test formulation for both cream and gel are applied on each rabbit with two probes per formulation (same design used in this study);



B: reference and test formulations of the same dose form (e.g., cream) were considered be applied at two application sites each per rabbit with two probes per application site.



Summary

- The dMD study design and protocol utilized here showed:
  - Probe **stability**
  - Ability to differentiate between two product types (cream vs. gel) as well as increasing product doses
  - Confidence in no lateral diffusion or systemic redistribution
- Study design considerations such as distance between applications, the product dose duration, product dose, and sampling frequency for adequate temporal resolution to be chosen with rationale
- The retrodialysis/ microdialysis approach allowed for the identification of flip/flop dermal PK
- The exploratory BE study indicated the point estimates within the 80-125% boundaries for BE, yet more rabbits were needed to power the study
- The animal models utilized here were useful to address fundamental in vivo cutaneous PK principles

Next Steps: Clinical Translation

- Challenges:
  - Find a dermatologist/nurse's team in an accredited research facility willing to collaborate in the translation
  - Address the issue of probe sterilization for human use
  - Find a probe performance marker suitable for human use
  - Study design must maximize comfort of participants while obtaining high quality data:
    - Number of probes
    - Number of sites
    - Study duration
    - Continuous versus intermittent sampling

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Dr. Elena Rantou

U01FD005862 (2016)"Benchmark of dermis microdialysis to assess bioequivalence of dermatological topical products" (PI – Grazia Stagni)