Public comment

Improved stratum corneum sampling *in vivo* delivers added value for topical bioequivalence assessment

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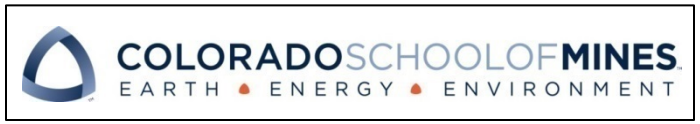


FDA Public Workshop on:

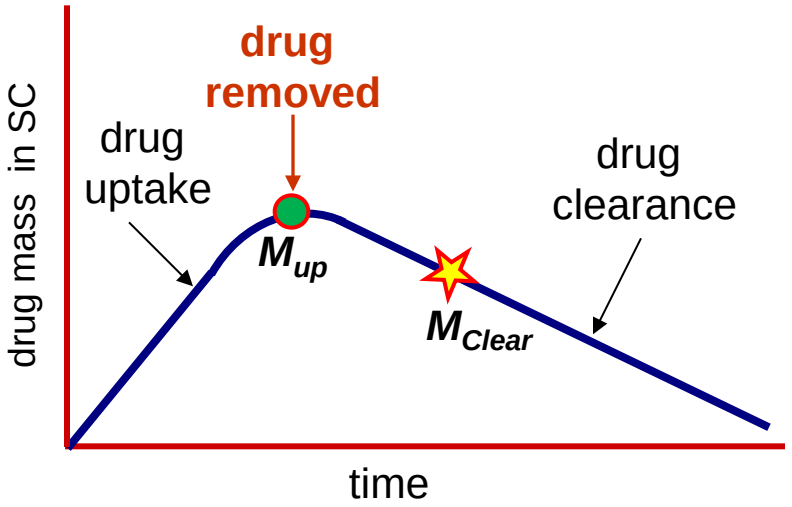
Topical Dermatological Generic Drug Products: Overcoming Barriers to Development and Improving Patient Access

Silver Spring, MD; October 20, 2017

SC sampling: *Added value for BE assessment*

- Translational methodology for *in vitro* (IVPT) observations
  - Drug/formulation specific *in vitro-in vivo correlation* (IVIVC)
  - Simpler than PK; available when plasma levels are too low for PK
  - Simpler than open flow microperfusion/microdialysis
- Measures drug delivery rate from SC
  - Measure mass of drug in SC after period of clearance (✸)
  - Compare to mass of drug in SC at end of uptake (●)
- Calculate the average flux from the SC to deeper tissues

$$\text{Average Flux} = \frac{\left(M_{Up} - M_{Clear}\right)/A}{t_{Clear} - t_{Up}}$$



SC sampling *in vivo*: *Example 1*

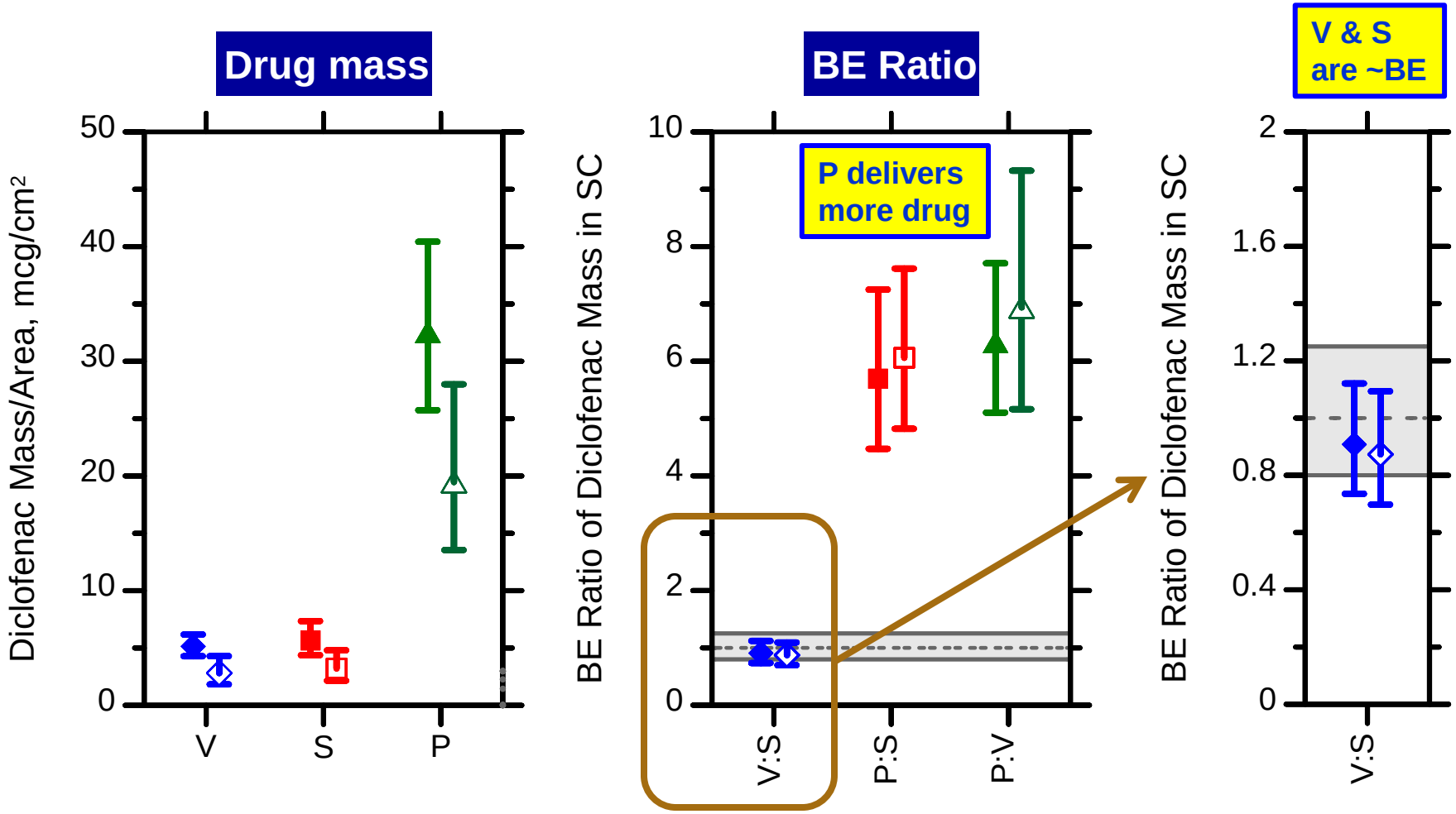
DICLOFENAC SODIUM

- Compare 3 products (all Q1 different)
  - 2% solution (Pennsaid) – 10 mg/cm^2 (contains DMSO)
  - 3% gel (Solaraze) – 20 mg/cm^2
  - 1% gel (Voltaren) – 10 mg/cm^2
- 17 h clearance after 6 h uptake
- 14 subjects

Cordery SF et al. Int J Pharm.529:55-64 (2017)

SC sampling: *Mass and BE assessment*

DICLOFENAC SODIUM



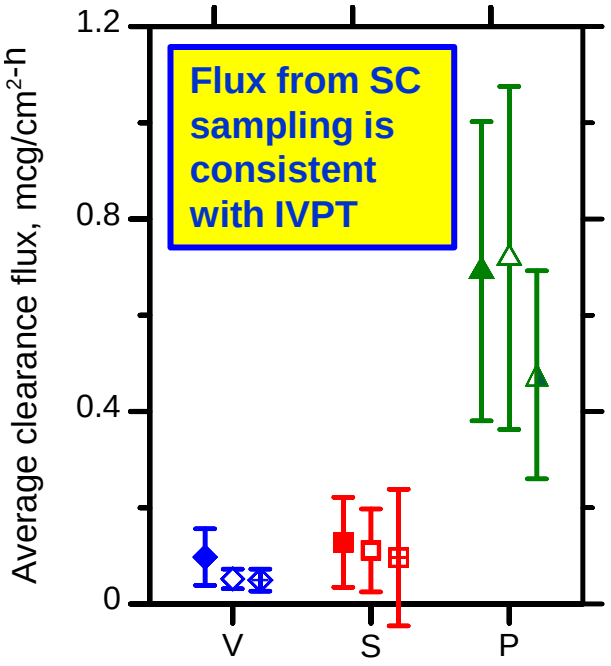
Uptake: Closed symbols
Clearance: Open symbols

Error bars, 90% CI of the log mean

SC sampling: *Average clearance flux*

DICLOFENAC SODIUM

SC sampling *in vivo*



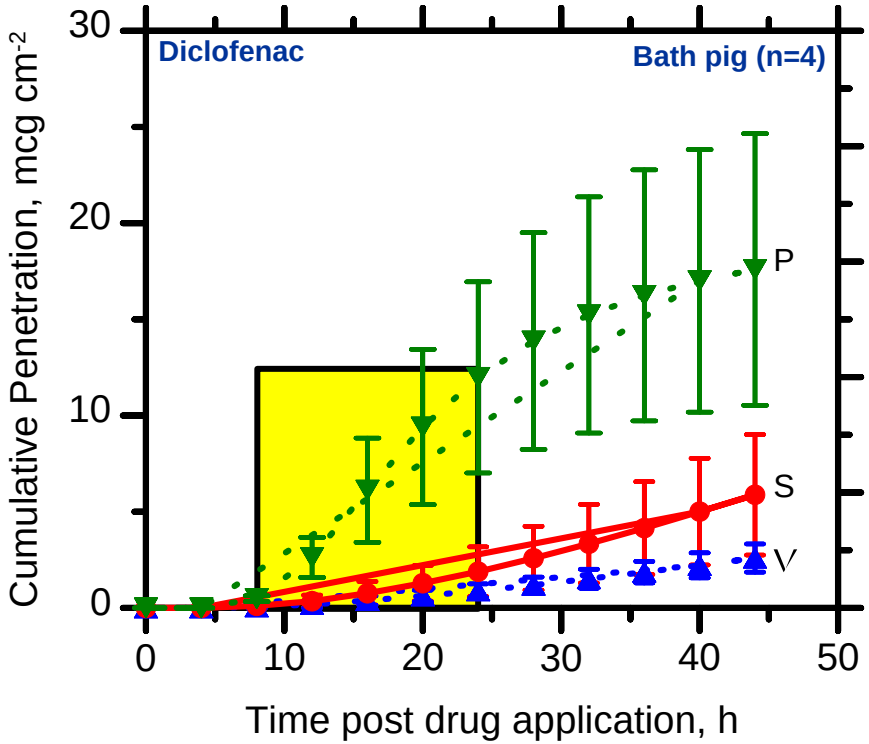
IVPT data

◇ □ △ Bath pig (n=4)

◆ ⊞ ◭ Yucatan mini-pig (n=4)

Error bars, 90% CI

In vitro permeation test (IVPT)



Calculate from mass permeated over comparable interval (8 - 24 h)

Error bars, 1 SD

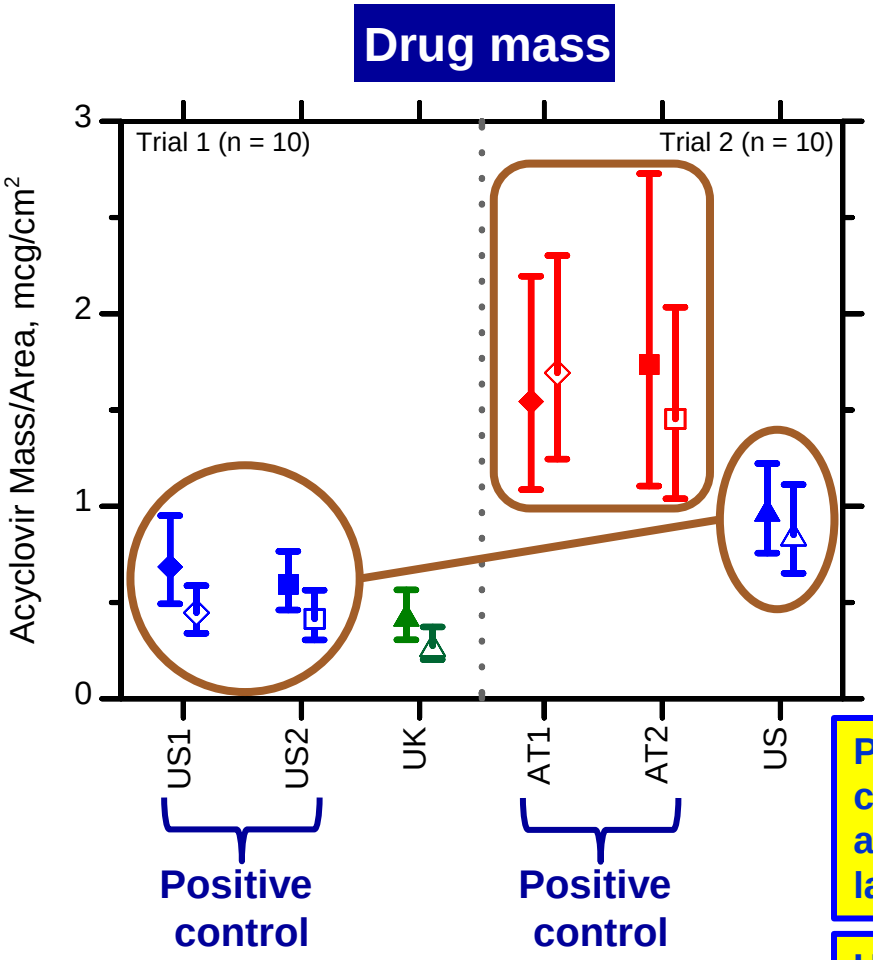
SC sampling *in vivo*: *Example 2*

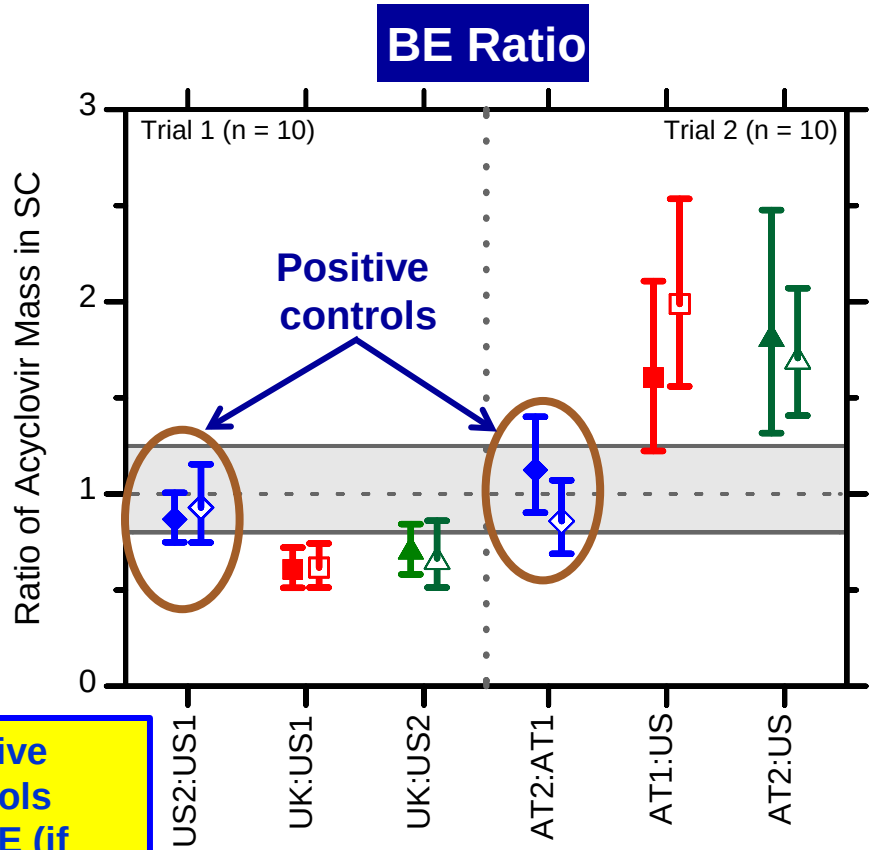
ACYCLOVIR

- Compare 3 creams (5%) in 2 trials
- Trial 1
  - US Zovirax (US)
  - UK Zovirax (UK)
- Trial 2
  - Aciclovir 1A Pharma (AT)
  - US Zovirax (US)
- 15 mg/cm^2
- 17 h clearance after 6 h uptake
- 10 subjects/trial

SC sampling: *Mass and BE assessment*

ACYCLOVIR





Positive controls are BE (if larger n)

US similar in both trials

Uptake: Closed symbols
Clearance: Open symbols

Error bars, 90% CI of the log mean

SC sampling: *BE assessment compared to dOFM*

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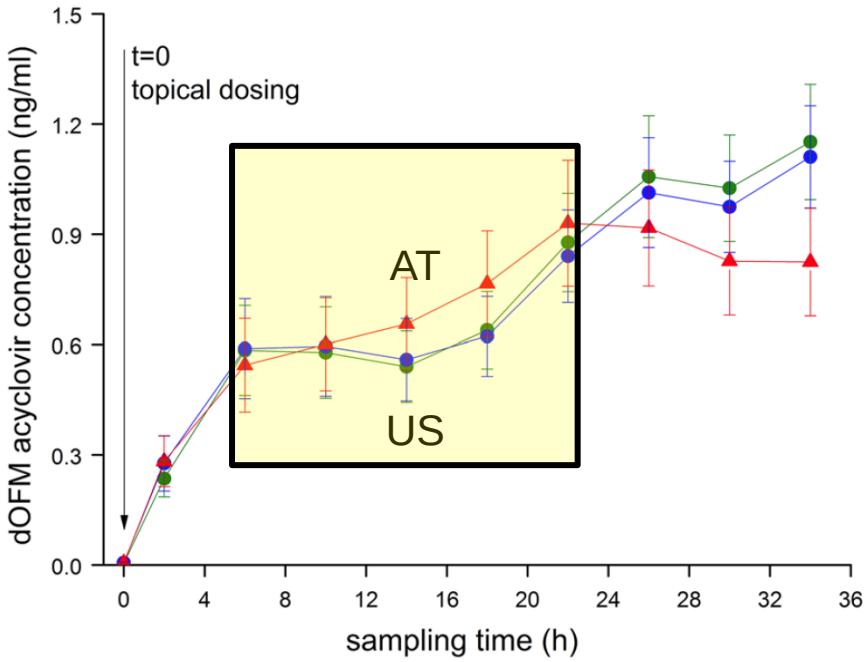
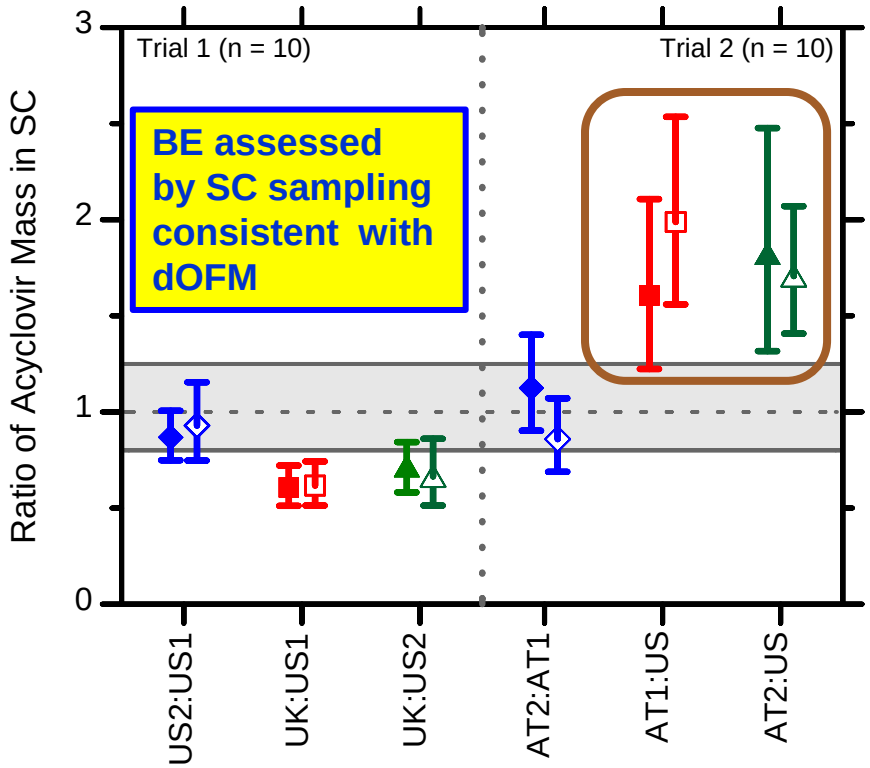
Open Flow Microperfusion (dOFM)*



Compare over comparable interval (6 - 22 h)

BE Ratio



Uptake: Closed symbols
Clearance: Open symbols

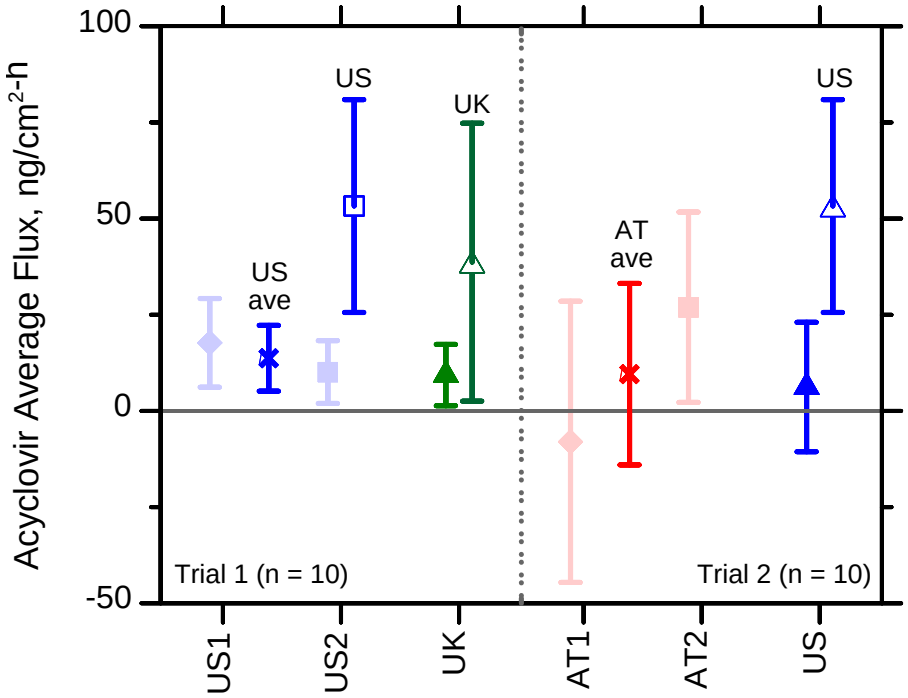
*Bodenlenz M et al. *Clin Pharmacokinet*, 56:91-98 (2017)

Error bars, 90% CI of the log mean

SC sampling: *Average clearance flux*

ACYCLOVIR

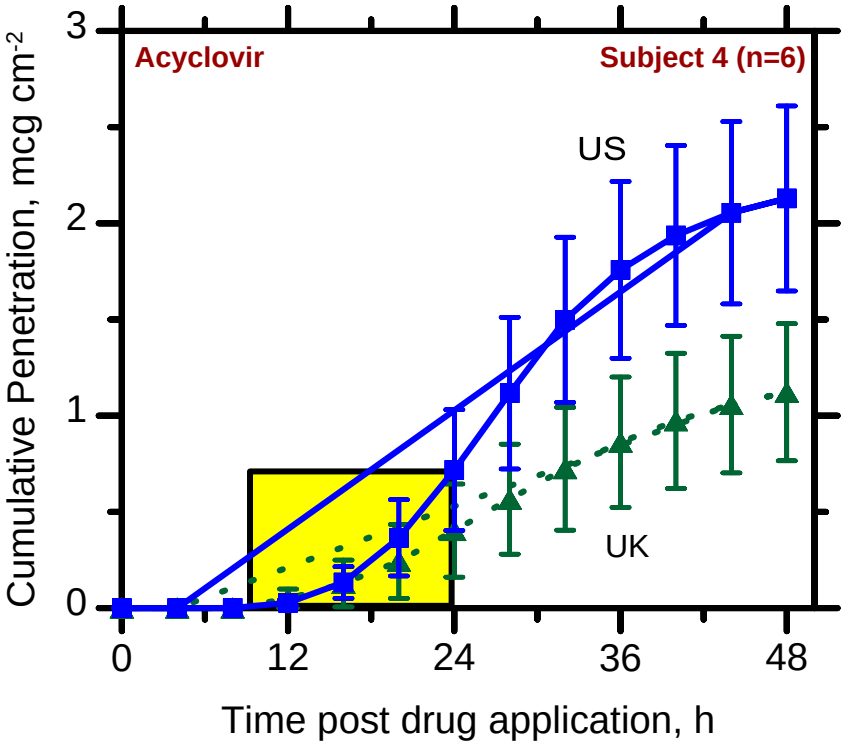
SC sampling *in vivo*



IVPT data (open symbols)

□△△ Human (n=6 subjects, 4-7 samples/n)

In vitro permeation test (IVPT)



Flux from SC sampling similar for US, UK & AT

Flux from IVPT for US & UK also similar

Average flux from mass permeated over comparable interval (8 - 24 h)

Drug removed in SC sampling but not in IVPT may explain quantitative differences

Error bars, 90% CI

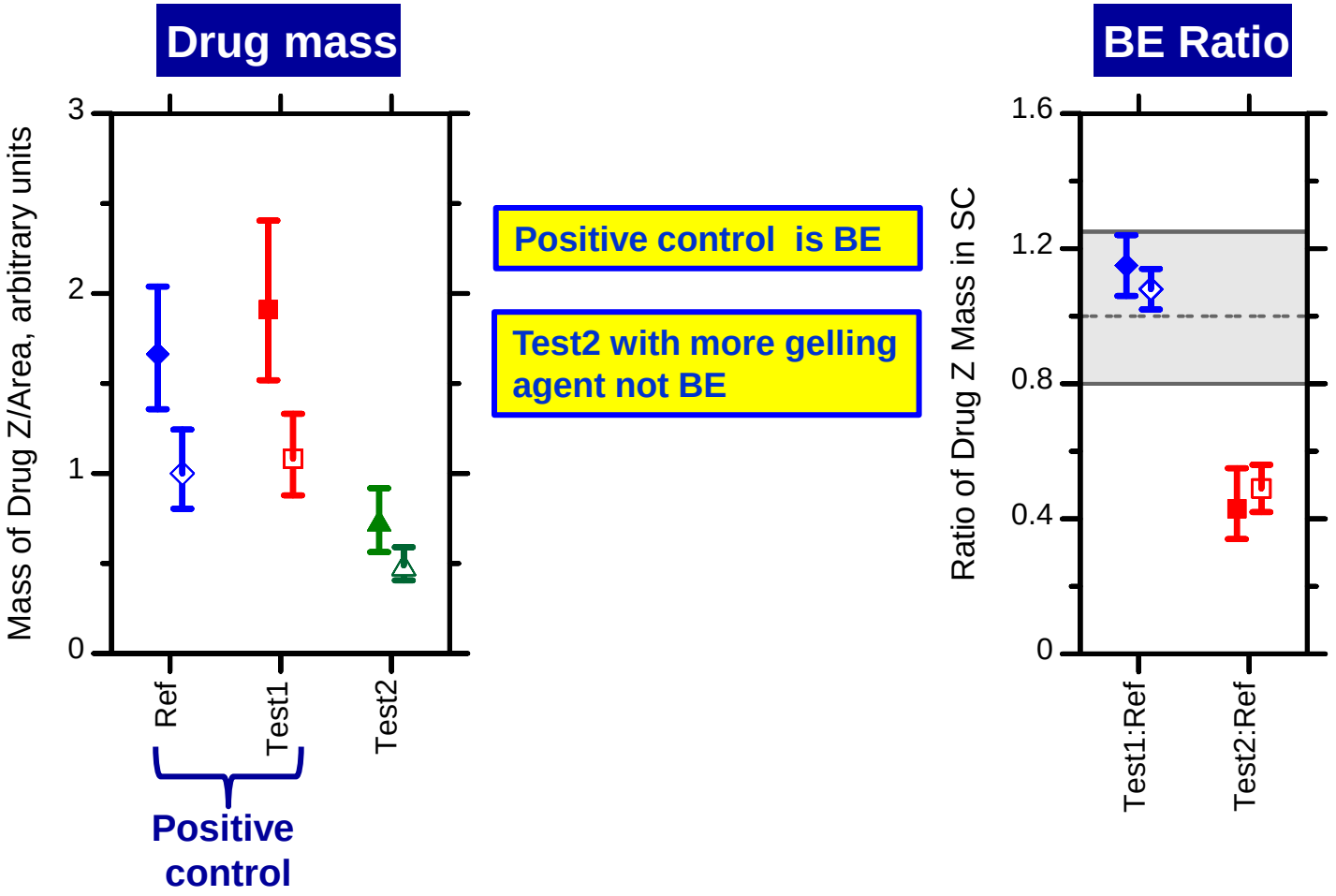
SC sampling *in vivo*: *Example 3*

DRUG Z

- 3 gel products with the same concentration of Z
  - Ref – Commercial product
  - Test1 – Q1 & Q2 equivalent to Ref
  - Test2 – more gelling agent; otherwise Q1 & Q2 equivalent
- Identical amounts of each formulation applied
- 12 h clearance after 6 h uptake
- 14 subjects

SC sampling: *Mass and BE assessment*

DRUG Z



Uptake: Closed symbols
Clearance: Open symbols

Error bars, 90% CI of the log mean

SC sampling *in vivo*: *Valuable tool to assess BE*

- Measured in humans *in vivo*
- Improved SC sampling protocol demonstrated to be robust and reliable across labs and operators
  - Demonstrated for 4 drugs, 3 formulations/drug, 3 labs, 5 operators (including econazole presented in presentation by Dr. Richard Guy)
  - Technically accessible and economical method
- Complementary to other surrogate assessment methods
  - IVPT, open flow microperfusion/microdialysis, plasma PK
  - Obvious value for drugs acting on or in the stratum corneum
  - Added value for drugs acting deeper in the skin
- Can assess clinically-relevant topical bioavailability (BA)
  - Formulation effects on skin barrier function after repeat dosing (see two slides at end of this presentation)

Acknowledgements

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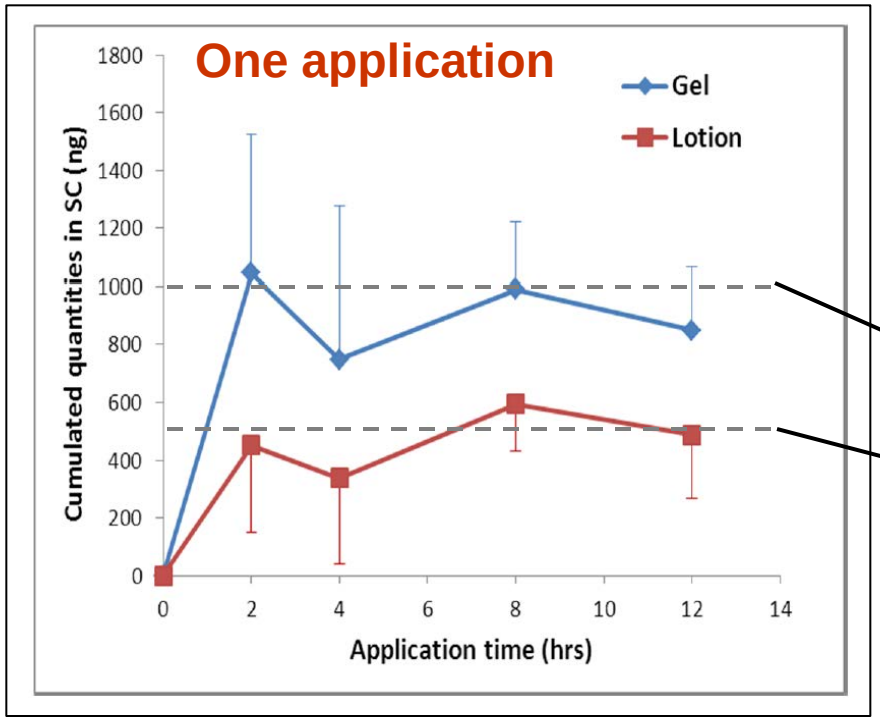
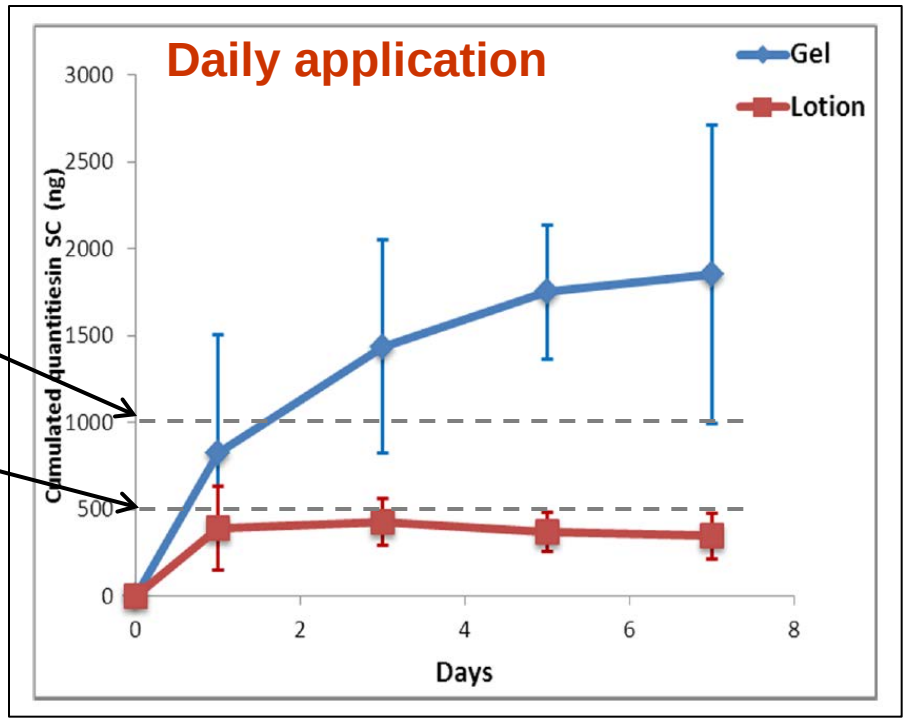
SC sampling *in vivo*: *Assess repeat dose effect*

Gel vs. lotion at same strength





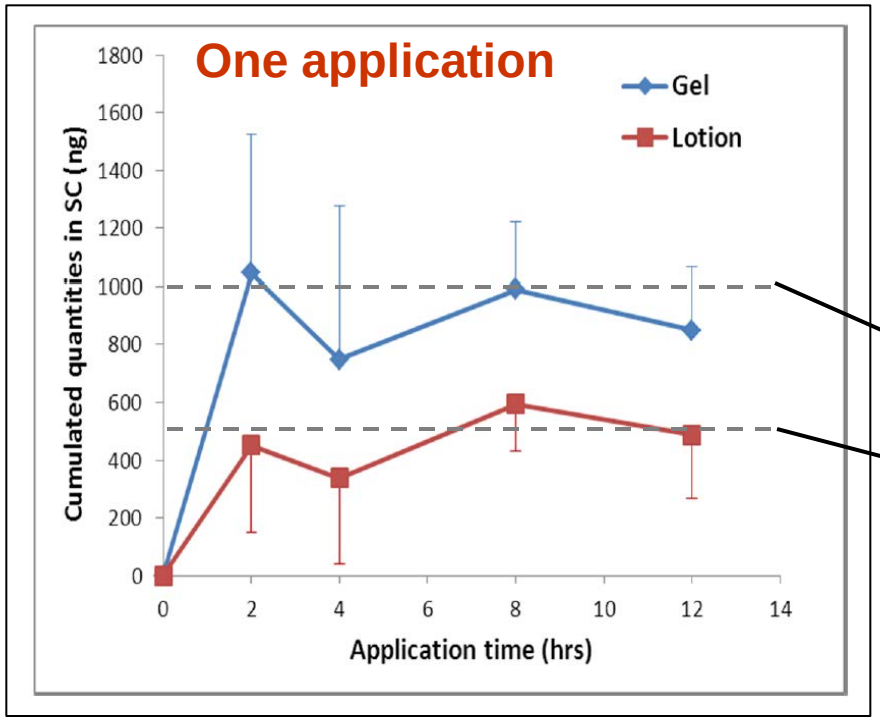
Nathalie Wagner
PQRI, Rockville, MD
March 13, 2013

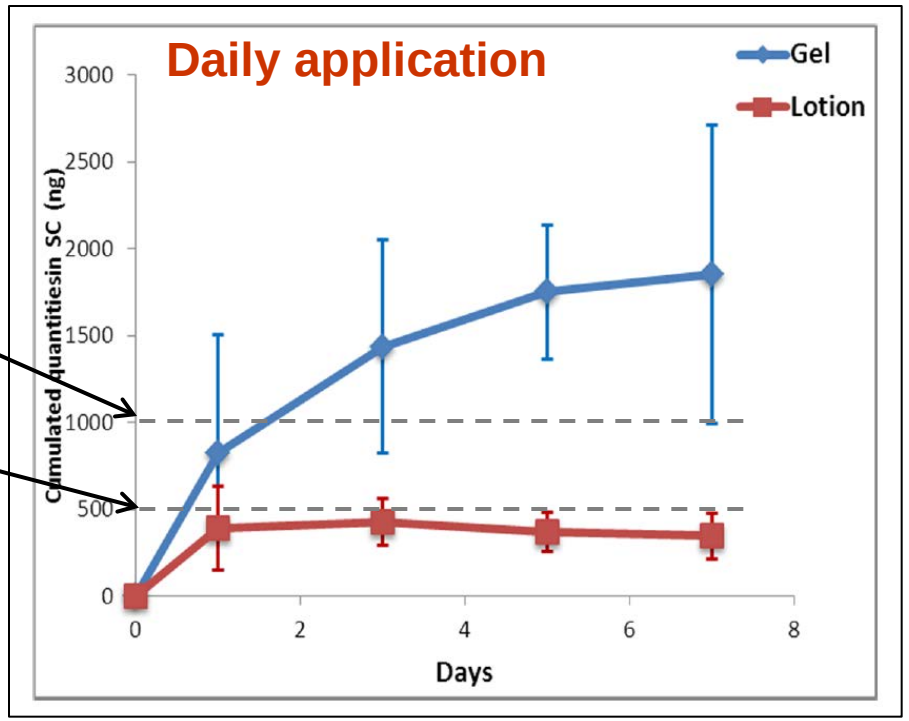
Dry clean; first 2 tapes discarded; 22 tapes (n = 4)
<u>One application:</u> Drug mass in SC “plateaued” by ~2 h
<u>Daily application</u>: Sampled 2 h after application

GALDERMA
Committed to the future of dermatology

SC sampling *in vivo*: *Assess repeat dose effect*

Gel vs. lotion at same strength





- Different “steady state” after 1 and multiple applications
- Measurements after a few applications on the recommended clinical schedule might be appropriate for formulations containing ingredients that affect the SC
- Multiple applications more representative of the clinical intended use