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

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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

\[
\text{Average Flux} = \frac{(M_{Up} - M_{Clear})}{A} \quad \frac{t_{Clear} - t_{Up}}{A}
\]

\[
M_{up} \quad \text{drug uptake} \\
M_{Clear} \quad \text{drug removed}
\]

\[
\text{time}
\]
SC sampling *in vivo*: **Example 1**

**DICLOFENAC SODIUM**

- Compare 3 products (all Q1 different)
  - 2% solution (Pennsaid) – 10 mg/cm² (contains DMSO)
  - 3% gel (Solaraze) – 20 mg/cm²
  - 1% gel (Voltaren) – 10 mg/cm²
- 17 h clearance after 6 h uptake
- 14 subjects

**SC sampling:** Mass and BE assessment

**DICLOFENAC SODIUM**

**Drug mass**

- Diclofenac Mass/Area, mcg/cm²

**BE Ratio**

- BE Ratio of Diclofenac Mass in SC
  - V & S are ~BE
  - P delivers more drug

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***

- Average clearance flux, mcg/cm²-h
- Error bars, 90% CI

**In vitro permeation test (IVPT)**

- Cumulative Penetration, mcg cm⁻²
- Error bars, 1 SD

**IVPT data**
- ▲ Bath pig (n=4)
- ◯ Yucatan mini-pig (n=4)

*Flux from SC sampling is consistent with IVPT*

Calculate from mass permeated over comparable interval (8 - 24 h)
SC sampling *in vivo*: Example 2

- 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/cm²
- 17 h clearance after 6 h uptake
- 10 subjects/trial
**SC sampling: Mass and BE assessment**

**ACYCLOVIR**

### Drug mass

- **Trial 1 (n = 10)**
- **Trial 2 (n = 10)**

### BE Ratio

- **UK:US1**
- **UK:US2**
- **US2:US1**
- **AT1:US**
- **AT2:US**
- **AT2:AT1**

#### Positive controls
- 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**

**ACYCLOVIR**

Open Flow Microperfusion (dOFM)*

![Graph showing concentration over time for AT and US with error bars and 95% CI.](image)

**BE Ratio**

![Bar chart showing BE ratio for different conditions.](image)

**Ratio of Acyclovir Mass in SC**

- **BE assessed by SC sampling consistent with dOFM**

Compare over comparable interval (6 - 22 h)

**Uptake: Closed symbols**

**Clearance: Open symbols**


Error bars, 90% CI of the log mean
**SC sampling:**  
**Average clearance flux**

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**SC sampling in vivo**

**In vitro permeation test (IVPT)**

### IVPT data (open symbols)

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

### Cumulative Penetration, mcg cm⁻²

**Acyclovir Average Flux, ng/cm²-h**

- **US**
- **UK**
- **AT**

**US ave**

**Trial 1 (n = 10)**

**Trial 2 (n = 10)**

**Cumulative Penetration, mcg cm⁻²**

**Acyclovir**

**Subject 4 (n=6)**

**Time post drug application, h**

0 12 24 36 48

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

**Error bars, 90% CI**

**Flux from SC sampling similar for US, UK & AT**

**Flux from IVPT for US & UK also similar**

**Drug removed in SC sampling but not in IVPT may explain quantitative differences**
SC sampling in vivo: Example 3

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

Confidential data – publication in preparation
SC sampling: Mass and BE assessment

Drug mass

Mass of Drug Z/Area, arbitrary units

Mass of Drug Z/Area, arbitrary units

BE Ratio

Ratio of Drug Z Mass in SC

Error bars, 90% CI of the log mean

Positive control is BE

Test2 with more gelling agent not BE

Uptake: Closed symbols
Clearance: Open symbols
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)
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SC sampling *in vivo*: Assess repeat dose effect

**Gel vs. lotion at same strength**

**One application**

- Drug mass in SC "plateaued" by ~2 h

**Daily application**

- Sampled 2 h after application

Dry clean; first 2 tapes discarded; 22 tapes (n = 4)

**One application**: Drug mass in SC "plateaued" by ~2 h

**Daily application**: Sampled 2 h after application

Nathalie Wagner
PQRI, Rockville, MD
March 13, 2013

GALDERMA
Committed to the future of dermatology
SC sampling *in vivo*: Assess repeat dose effect

- 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

**Gel vs. lotion at same strength**

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**One application**

- Gel
- Lotion

**Daily application**

- Gel
- Lotion