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

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* Stratum corneum sampling *in vivo* to replace clinical trials (primarily for bioequivalence).

- determination of drug in stratum corneum versus time curves for topical actives
- analogous to plasma drug concentration vs. time profiles after systemic administration

**Assumption:** Drug amount versus time profile in SC is a valid reflection of that in the epidermis and/or dermis.
Pivotal study, ca. 2000 (0.025% tretinoin gels)

Ortho = Spears
Ortho > Bertek
Spears > Bertek

Tretinoin mean, n = 49

Ortho ≠ Bertek
Bertek > Ortho

Pershing et al., J Am Acad Dermatol, 2003
Franz, FDA-ACPS, 11/29/2001
Stratum corneum sampling *in vivo* – improvement needed!

- Despite inconsistency, methodology discriminated between products.
- Obvious advantages:
  - *in vivo, in humans*
  - permits comparisons within subjects
  - minimally invasive
- Stripped area < drug product application area (control both).
- Simpler method: 1 uptake time, 1 clearance time, duplicate at each time.
- Improve skin surface cleaning procedure (alcohol swab).
- Reduce variability by improving drug collection.
  - collect most of stratum corneum – TEWL
  - at least 12, but no more than 30 tape-strips
  - assess drug on all tapes (none discarded)
Pivotal study: re-analysis (0.025% tretinoin gels)

Comparing Bertek (B) and Spears (C) to Ortho (A) (RLD)

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“Improved” protocol developed for FDA

- Econazole nitrate cream (1%): 2 generics to reference-listed drug (RLD)
- 4 treatment sites per product (12 sites total)
  - Duplicate determinations at 2 times
  - 1 uptake time (6 hr) & 1 clearance time (17 hr); convenient for subjects
- Unabsorbed drug removed using isopropyl alcohol wipes
- Determined all drug in SC by removing most of SC
  - Removed SC until TEWL was 8-fold greater than pre-stripping value
  - At least 12 tape strips, but not more than 30
  - Tape stripping area < drug application area (control both areas)
- BE of uptake and clearance were assessed separately
- Analyzed tape strips in groups to optimize analytical sensitivity
- Compare within each subject and then across subjects

Drug uptake from 3 clinically BE formulations measured in duplicate \((n = 14)\).

- **A** = Clay Park. **B** = Ortho (RLD). **C** = Taro.
- Duplication of measurements improved results.

Econazole clearance from SC

- Drug uptake from 3 clinically BE formulations measured in duplicate (n = 14).

Econazole: average drug amounts in SC

A = Clay Park.
B = Ortho (RLD).
C = Taro.

Econazole: assessment of bioequivalence (BE)

Both A and C were conclusively BE with B after uptake and clearance, evaluated separately.

Only 168 sites (3 products in 14 subjects with replicates for uptake & clearance = 3 x 14 x 2 x 2)

Compare with 1176 sites in tretinoin gel study (3 products in 49 subjects with 8 sites/product = 3 x 49 x 8)

Facile method, “obvious” for drugs acting on or in stratum corneum

Improved approach is much more robust than original

Direct application of approach on diseased skin is unlikely, but…
- this is true of the vasoconstriction assay for corticosteroids

Correlation with clinical outcome requires further validation
- potential complementarity with IVPT, microdialysis, etc.
- relevance for targets deeper in the skin???
- selection of optimal metrics???
Acknowledgements

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Dermatopharmacokinetics (DPK) as a test for topical bioequivalence

- **US Food & Drug Administration (FDA)**
  - Draft Guidance issued June, 1998
  - Withdrawn May, 2002

- **Japanese Division of Drugs**
  - Issued July, 2003
  - Extended November, 2006
Topical bioequivalence
Japanese Division of Drugs

- Guideline for bioequivalence studies of generic products for topical use
- July 7, 2003
- Dermatopharmacokinetic (DPK) study is acceptable if:
  - Site of action is either in or below stratum corneum (SC)
  - Drug product does not damage SC
  - Same concentration of active ingredient (even if in different formulations)
- Measure at 1 time: steady state after 1 application
- Given that amount of SC stripped by each tape is variable:
  - Determine amount of SC collected and use average drug concentration (mg/g) instead of drug amount (mg/cm^2)
  - Or, calculate average concentration from C versus x/L approach
DPK of maxacalcitol from ointment and lotion

- Maxacalcitol is 1,25-dihydroxy-22-oxavitamin D₃
- Treatment of psoriasis
- Compare lotion (generic) to Oxarol ointment (RLD)
- Amount of drug is 25 µg/g in both ointment and lotion
- Remove SC until TEWL > 50 g/m²-h or 20 tape strips

1. Pilot to assess time to reach steady state for lotion and ointment

<table>
<thead>
<tr>
<th></th>
<th>Lotion (n = 12)</th>
<th>Ointment (n = 12)</th>
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<tbody>
<tr>
<td>Concentration (µg/g)</td>
<td>11.2 ± 3.1</td>
<td>11.1 ± 3.4</td>
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<tr>
<td>90% Confidence Interval</td>
<td>88.9 – 114.6%</td>
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</tbody>
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2. Pivotal assessing bioequivalence at steady state

N'Dri-Stempfer et al., Pharm Res, 2009