Public comment

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

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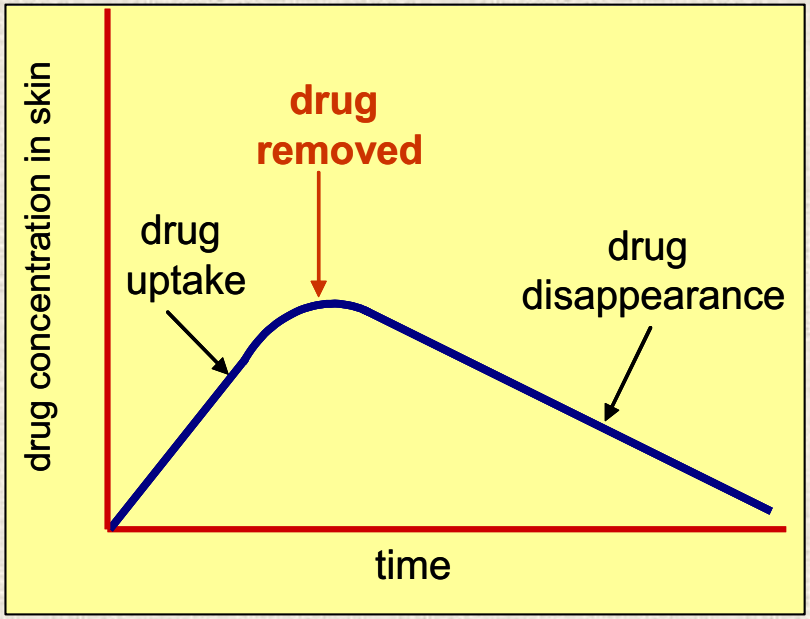
FDA Public Workshop on Topical Dermatological Generics

FDA White Oak campus, Silver Spring, MD, October-2017

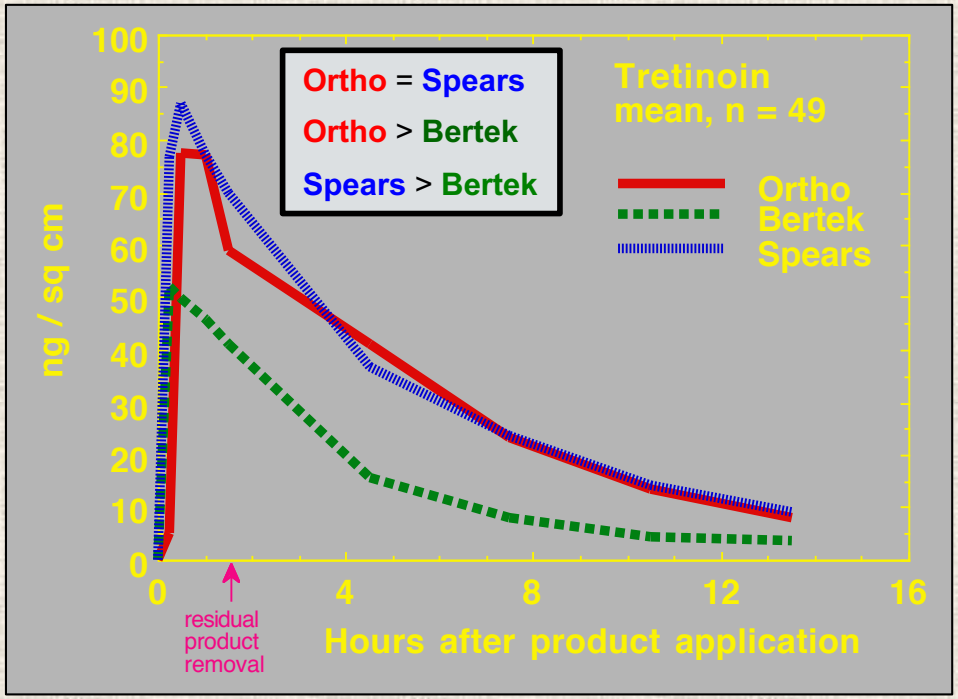
FDA draft guideline, 1998

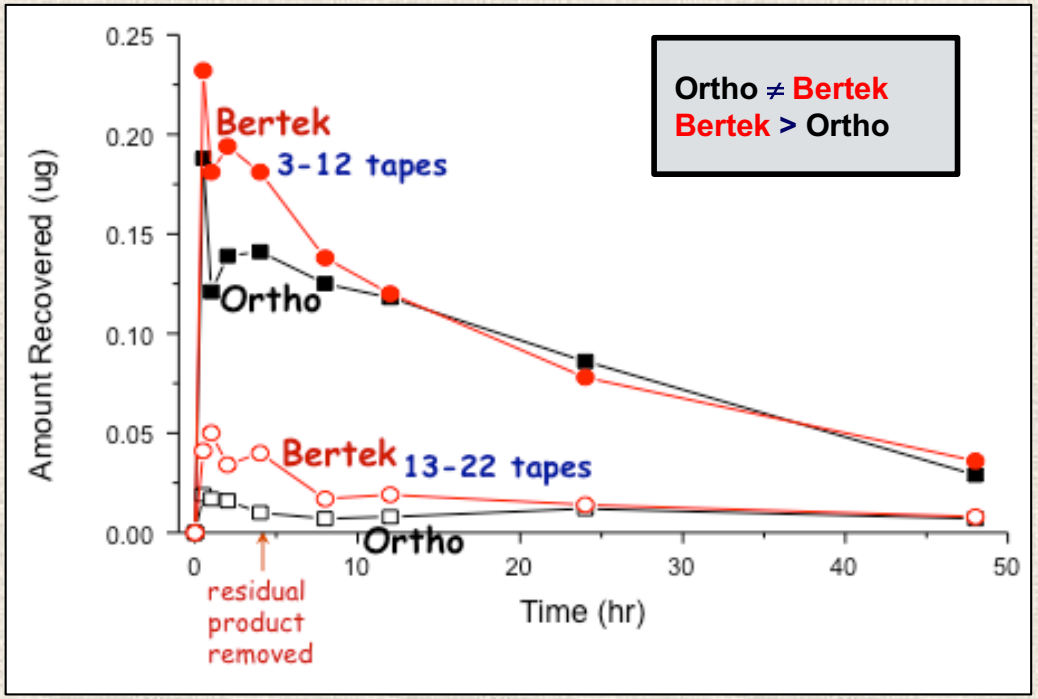
* **Stratum corneum sampling *in* vivo to replace clinical trials (primarily for bioequivalence).**
  - **determination of drug in stratum corneum versus time curves for topical actives**
  - ***analogous to plasma drug concentration vs. time profiles after systemic administration***

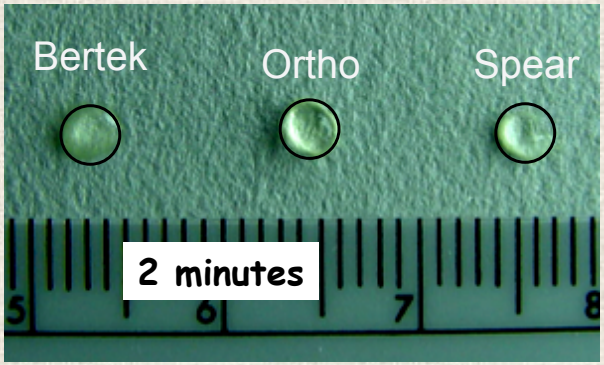
Assumption: Drug amount versus time profile in SC is a valid reflection of that in the epidermis and/or dermis.

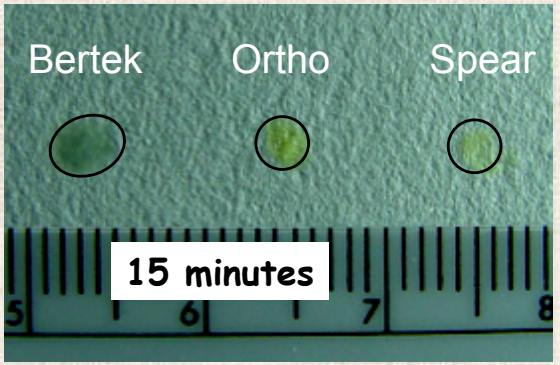


Pivotal study, *ca.* 2000 (0.025% tretinoin gels)







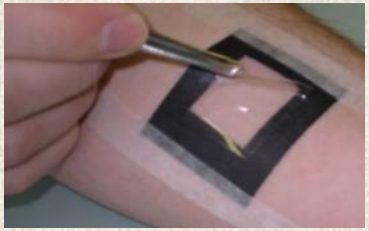


Pershing et al., J Am Acad Dermatol, 2003

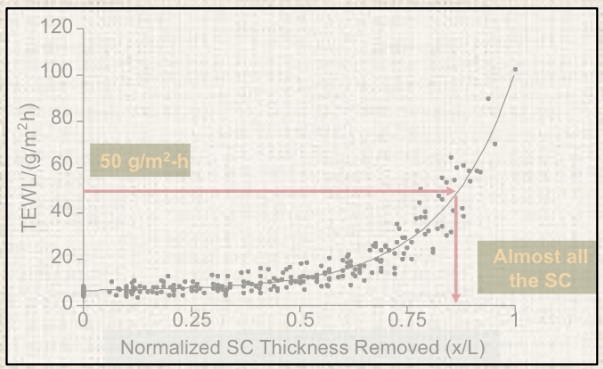
Franz, FDA-ACPS, 11/29/2001

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)

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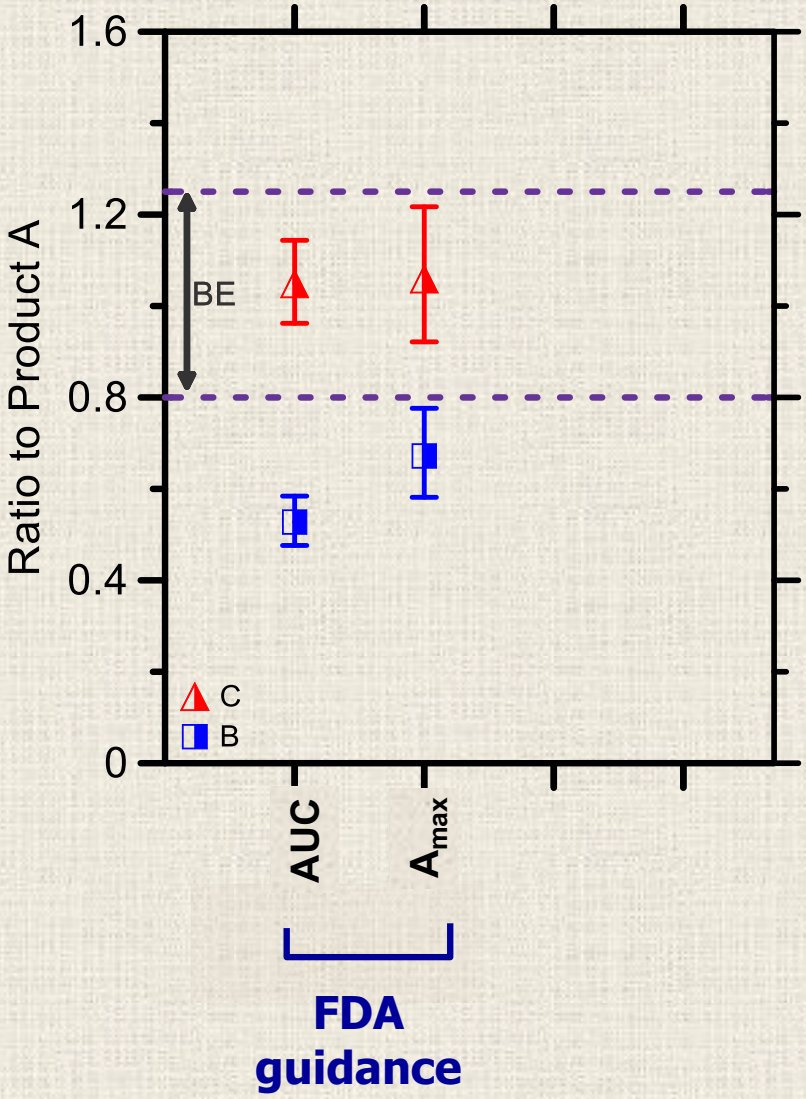

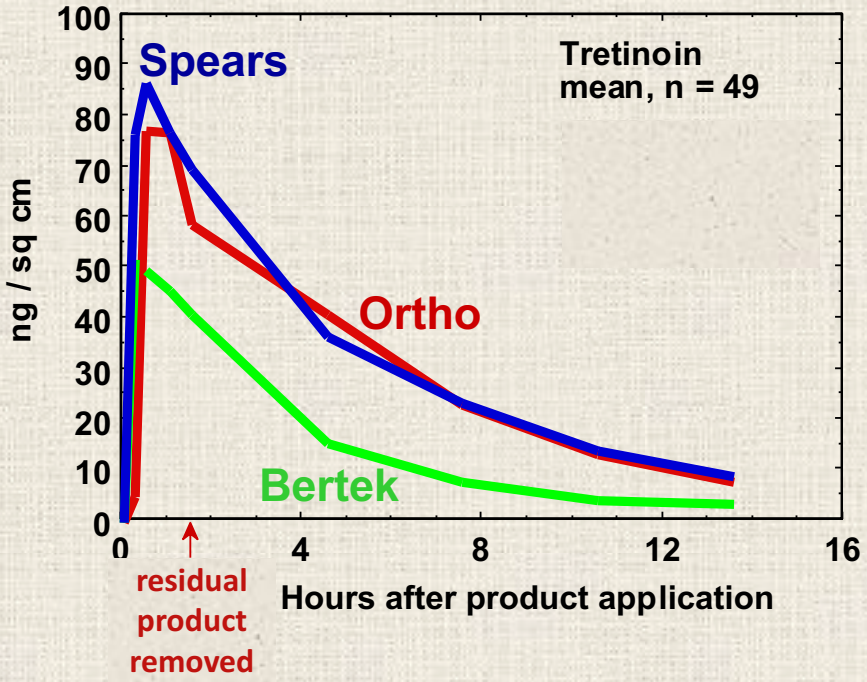

N'Dri-Stempfer *et al.*, Pharm. Res. 25, 1621-1630 (2008)

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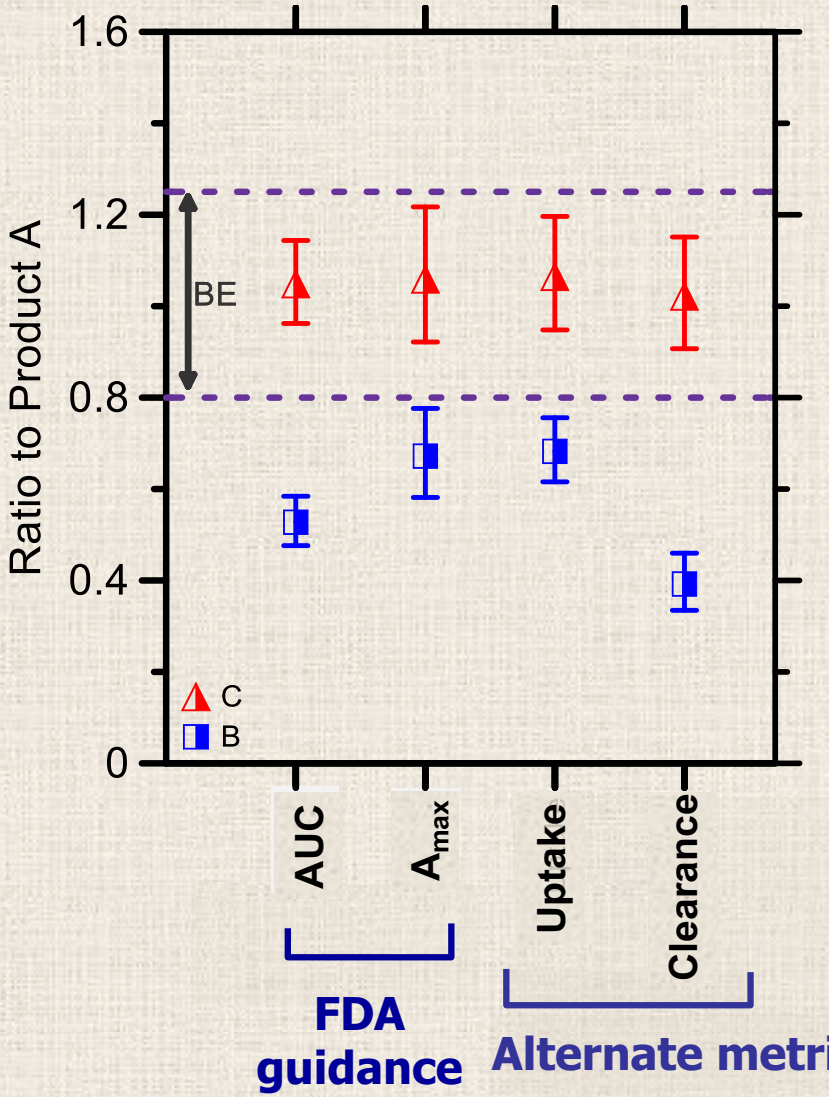

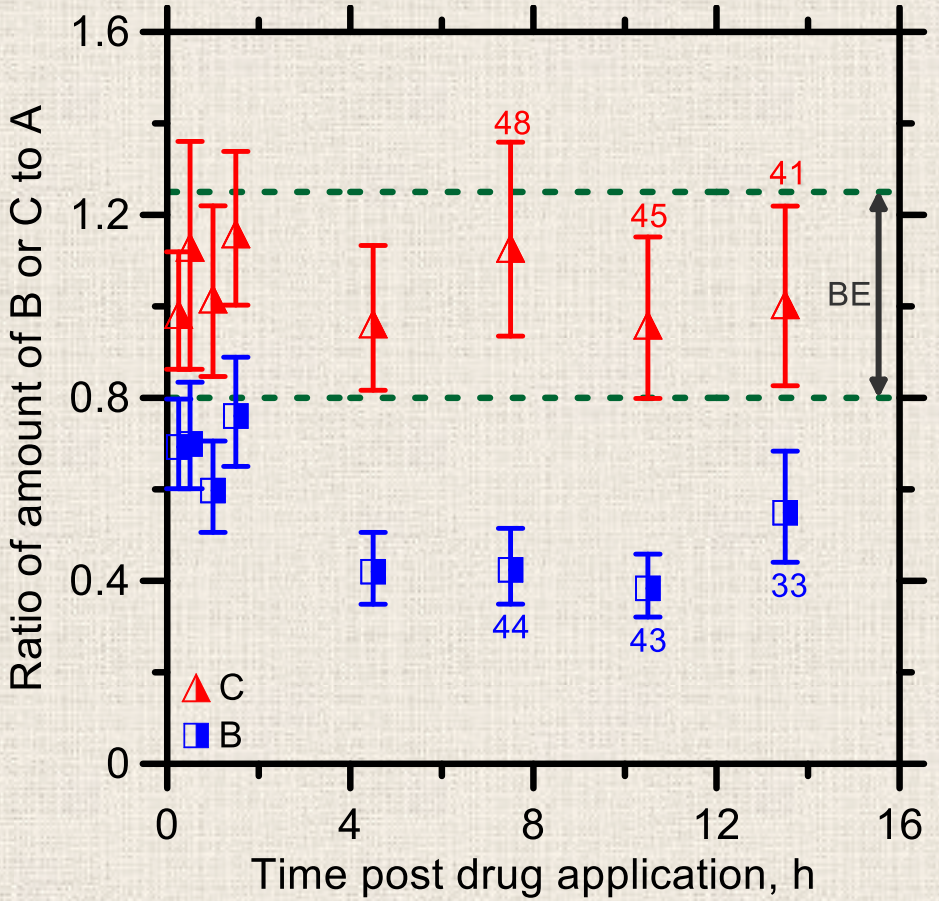

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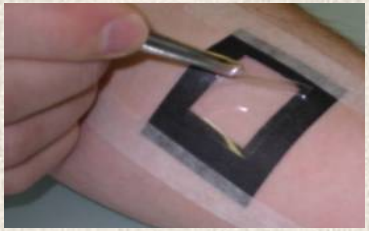

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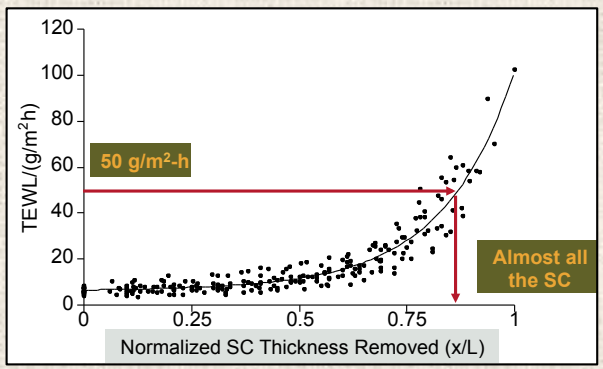


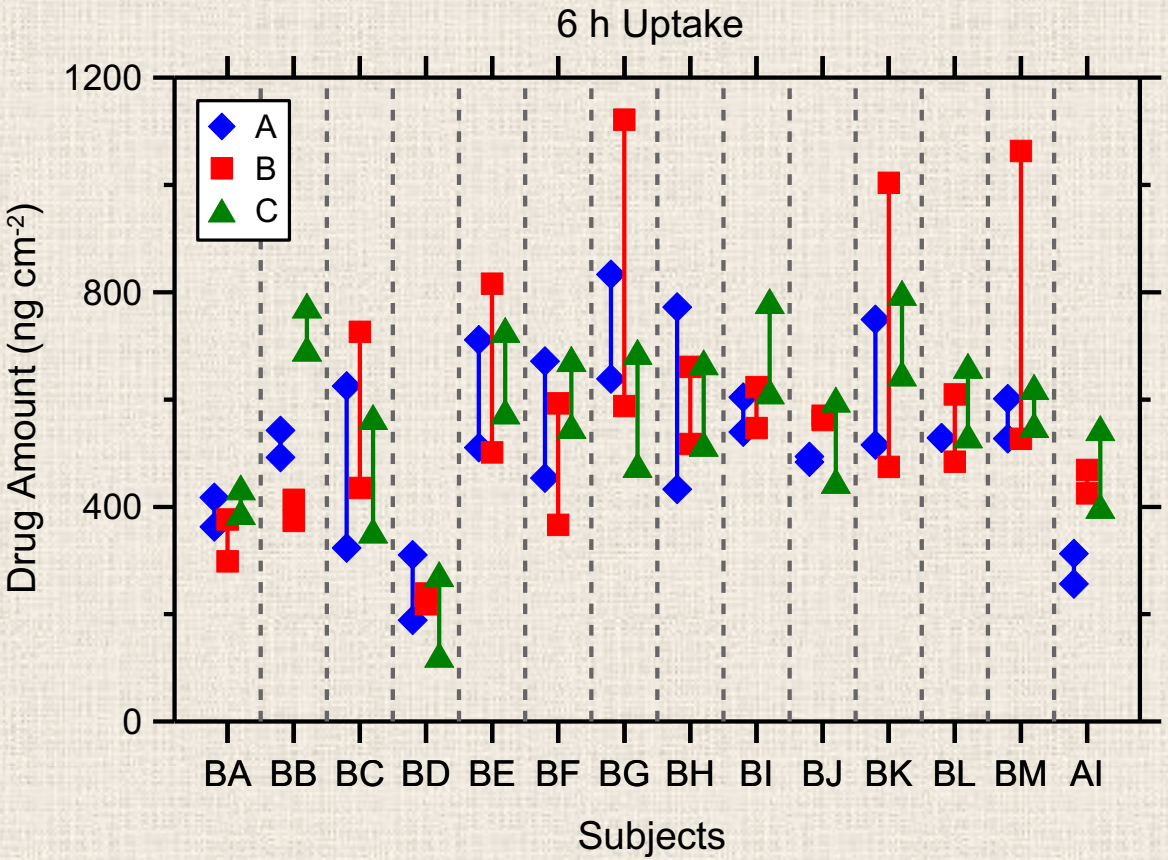
Kalia et al. *Pharm. Res.* 17: 1148-1150 (2000).

"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

N'Dri-Stempfer *et al.,* Pharm. Res., 26, 316-328 (2009).

Econazole uptake into SC



- 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.

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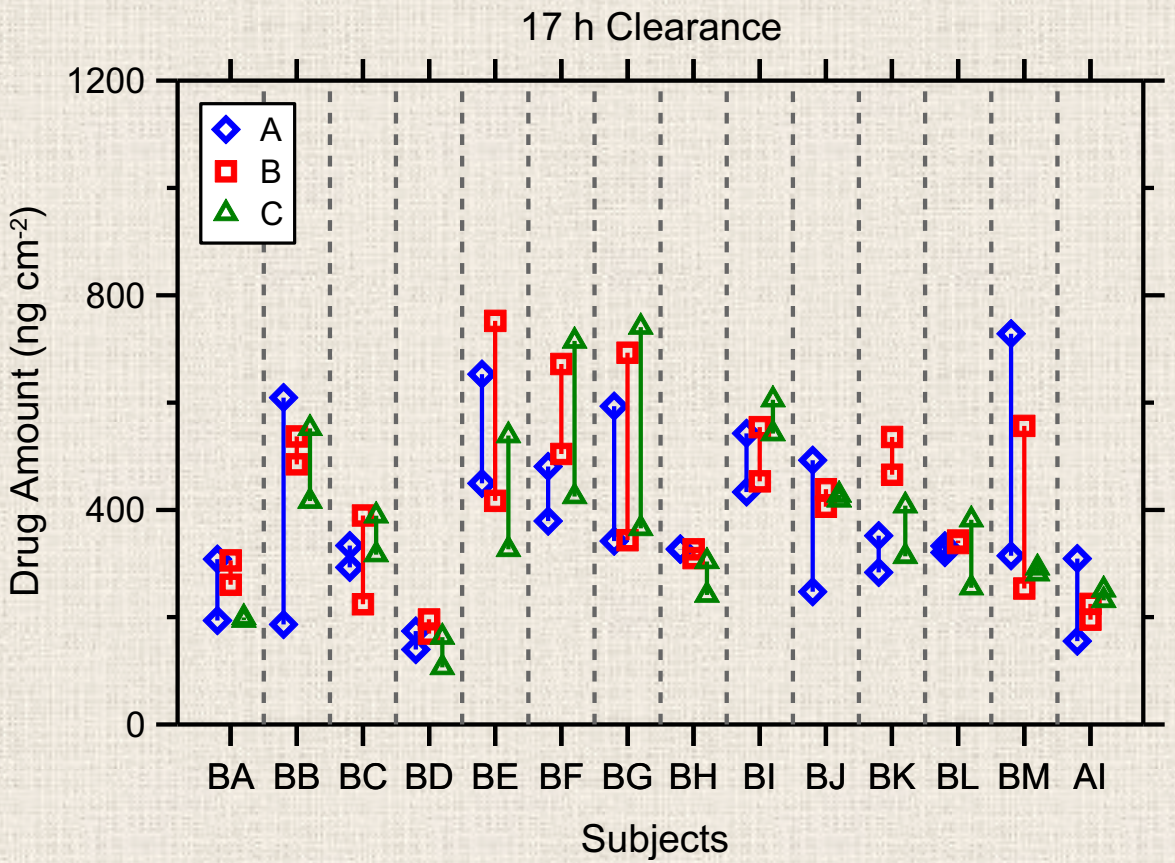
Econazole clearance from SC



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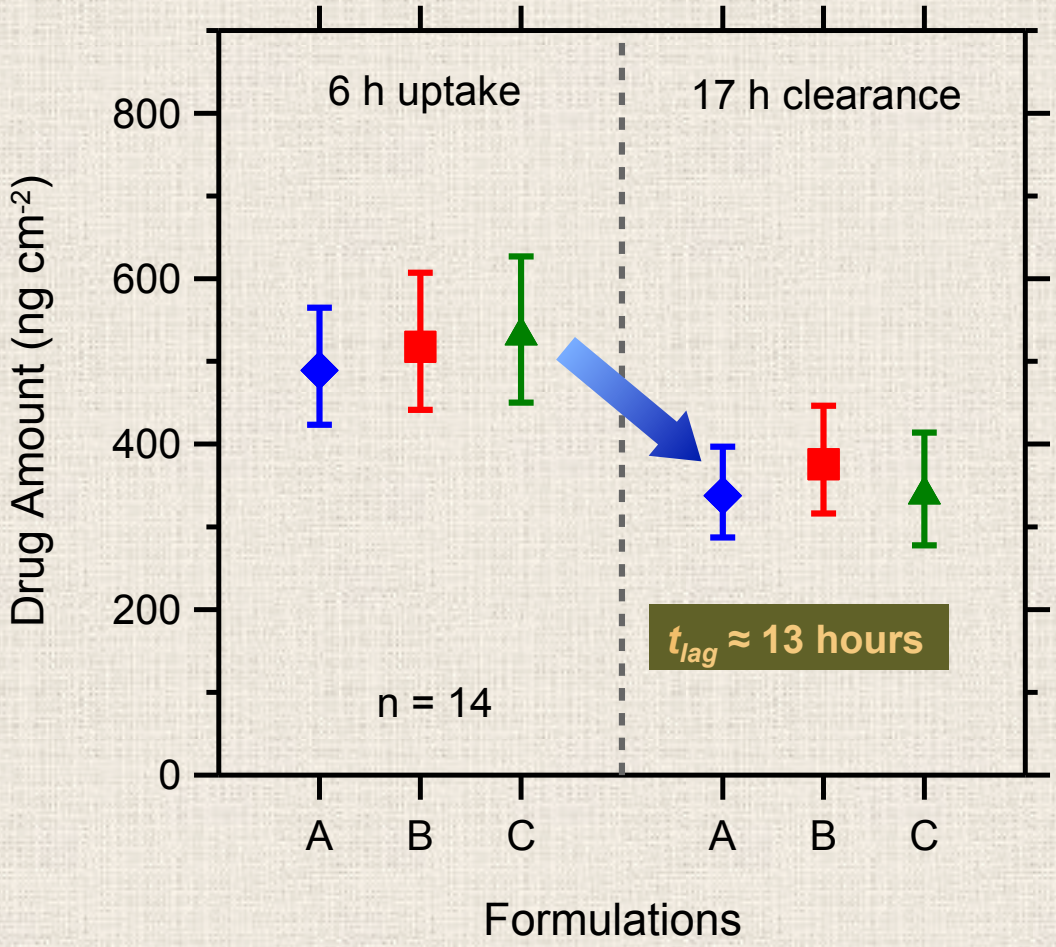
Econazole: average drug amounts in SC



A = Clay Park.

B = Ortho (RLD).

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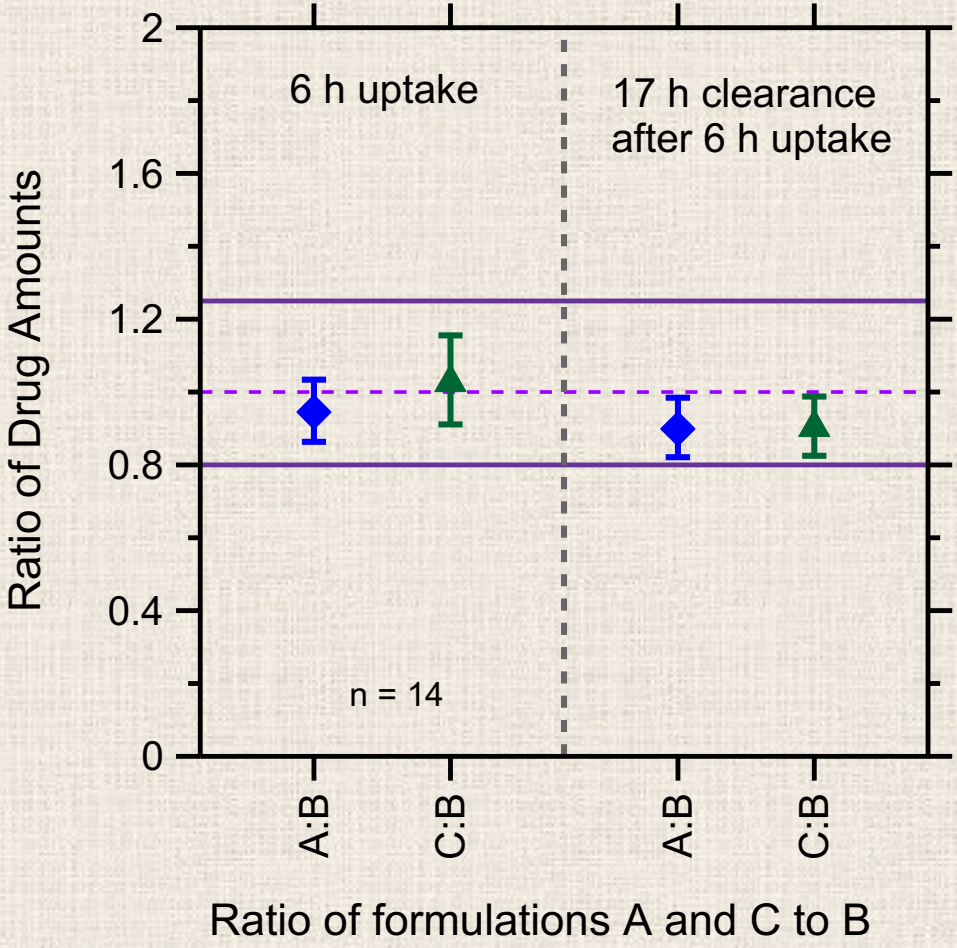
Econazole: assessment of bioequivalence (BE)



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)

N'Dri-Stempfer *et al.*, Pharm. Res., 26, 316-328 (2009).

Stratum corneum sampling *in vivo*

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

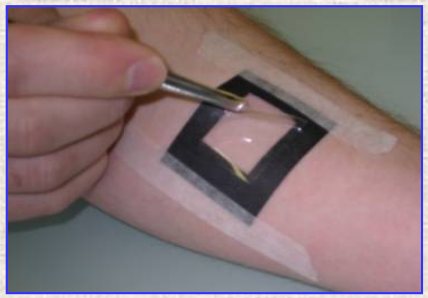
- Drs. Annette Bunge, Audra Stinchcomb, Leila Leal, Begoña Delgado-Charro, Tom Franz, Sam Raney, Priyanka Ghosh, Wing Chiu, Sarah Cordery and Andrea Pensado, Berthe N'Dri-Stempfer, William Navidi

- U.S. Department of Health & Human Services, Food & Drug Administration (award numbers: D3921303 and 1-U01-FD-004947). *The views expressed in this presentation do not reflect the official policies of the U.S. Food & Drug Administration or the U.S. Department of Health & Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.*

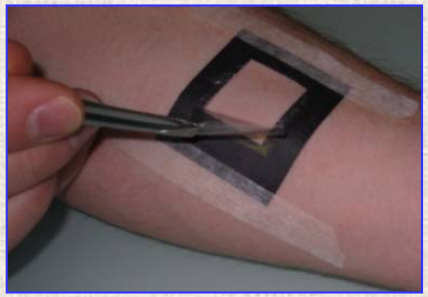
- CAPES Foundation, Ministry of Education, Brazil (Chamada de Projetos MEC/MCTI/CAPES/CNPq/FAPs, Nº 09/2014).

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
- http://www.nihs.go.jp/drug/be-guide%28e%29/Topical_BE-E.pdf
- 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

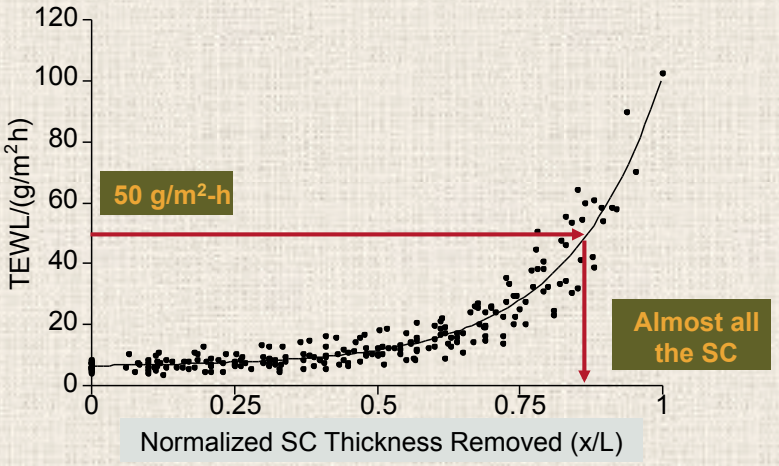
- Maxacalcitol is 1,25-dihydroxy-22-oxavitamin D_3
- Treatment of psoriasis
- Compare lotion (generic) to Oxarol ointment (RLD)
- Amount of drug is 25 µg/g in both ointment and lotion
- Remove SC until TEWL > 50 g/m^2-h or 20 tape strips

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

	Lotion (n = 12)	Ointment (n = 12)
Concentration (µg/g)	11.2 ± 3.1	11.1 ± 3.4
90% Confidence Interval	88.9 – 114.6%	

Umemura K, et al., Int J Clin Pharmacol Ther, 46, 289-294 (2008)

2. Pivotal assessing bioequivalence at steady state



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