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Bioavailability (BA) and Bioequivalence (BE)

Assessment of Topical Skin Products by Measuring Drug in Tape Stripped Skin

An Update

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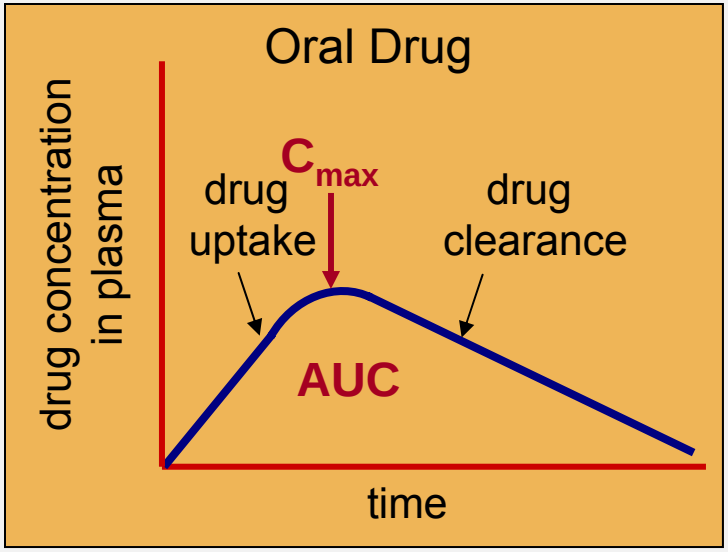
Skin Forum 6-July-2010

BA & BE Assessment of Topicals: *Why?*

- To evaluate new formulations (are they better?)
- To demonstrate that topical drug products are equivalent and can be prescribed/used interchangeably
  - Generic versus innovator products of same formulation type
  - Manufacturing or formulation changes (if SUPAC-SS not available)
  - Addition of dosage forms (e.g., add a lotion formulation when the ointment formulation is approved)
- In the US and Europe BE assessment of topical drugs requires a clinical trial
  - Corticosteroids are the exception
  - Skin vasoconstriction (blanching) test can be used
- **THE CHALLENGE:** Convenient (non-clinical) method to evaluate BA/BE of topical dosage forms

Non-clinical BA & BE Assessment of Topicals

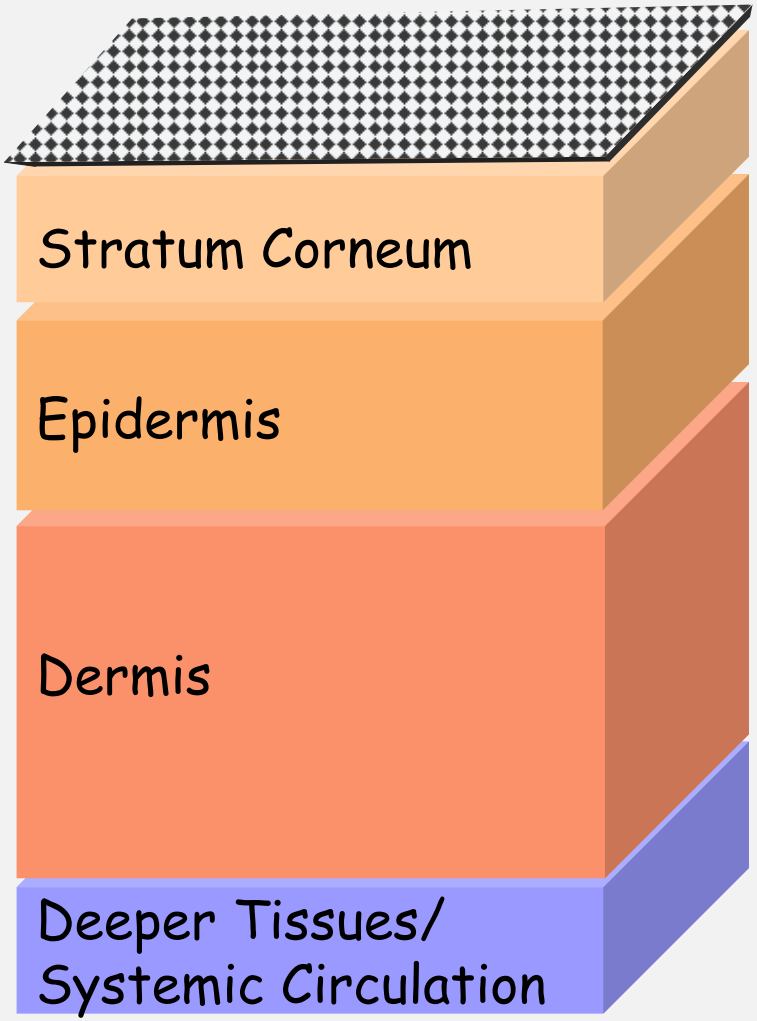
- US Food & Drug Administration (FDA) began working on developing dermatopharmacokinetic (DPK) in the 1990's
- FDA's ideas about BA & BE assessment of topicals were based on BA & BE assessment of oral drugs (i.e., C vs. t)
- Two products delivered orally are considered to be BE if C_{max} and AUC are ***the same***



- Criteria for ***the same*** is that the 90% confidence interval of the log transformed ratio (generic to innovator) is between 80 and 125%

Assessing Bioavailability of Topical Products

Where do we measure the amount of drug?

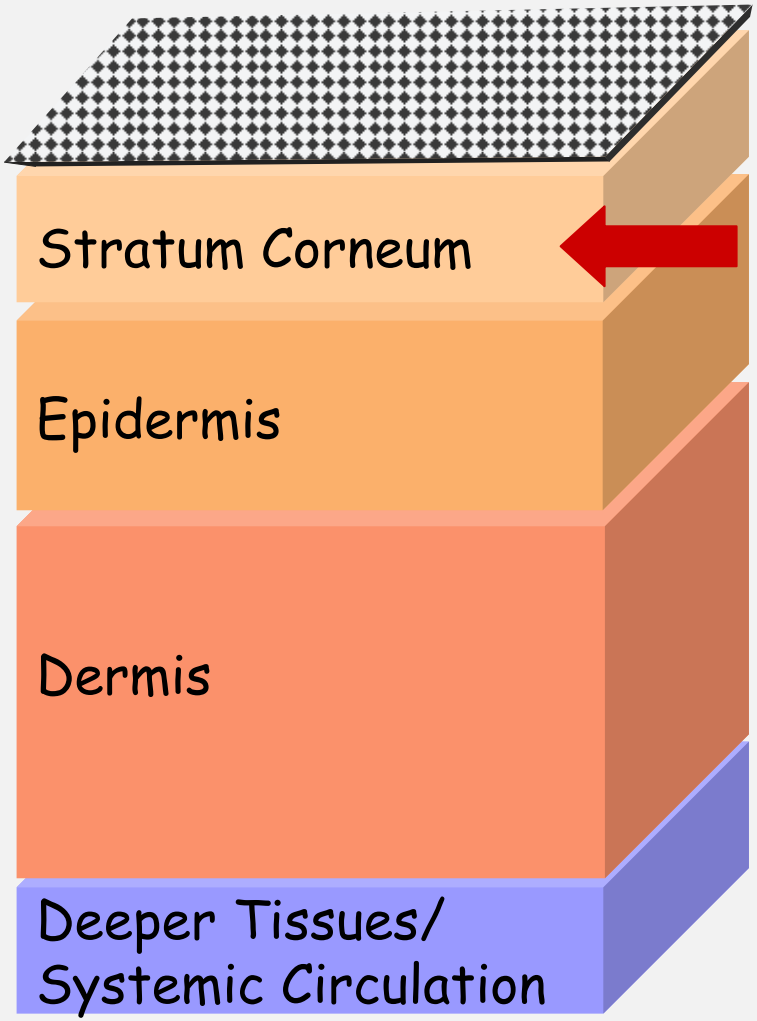


Blood levels

Urine levels

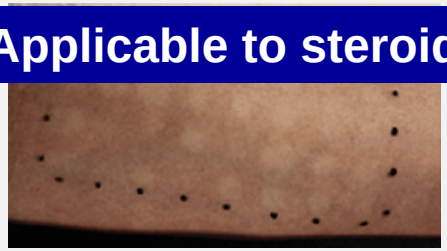
- Usually too small
- Not site of action
- Might be useful for showing low systemic effect (safety)

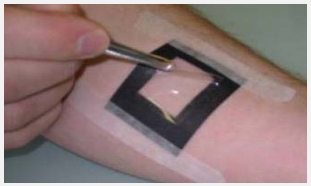
Assessing Bioavailability of Topical Products

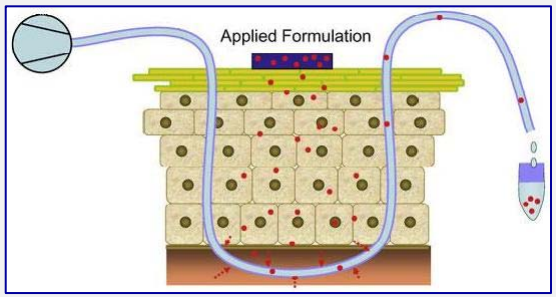


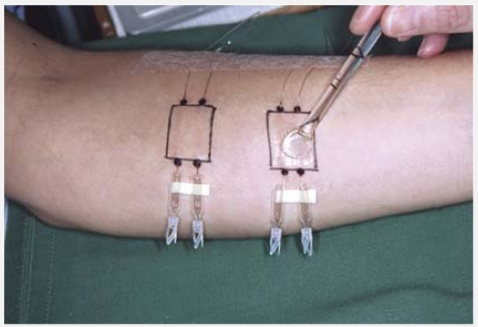
- *Pharmacodynamic (blanching) assay*
- *Tape-stripping*
- *Suction blister*
- *Microdialysis*
- *Biopsy*

Applicable to steroids





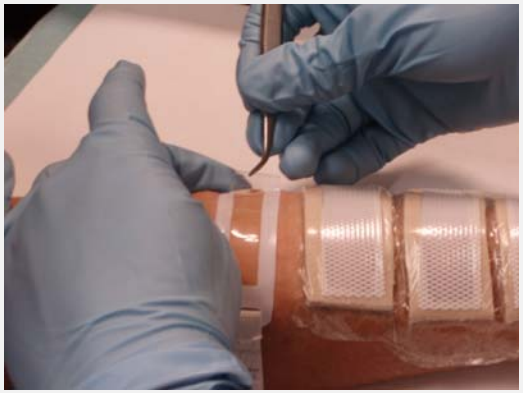


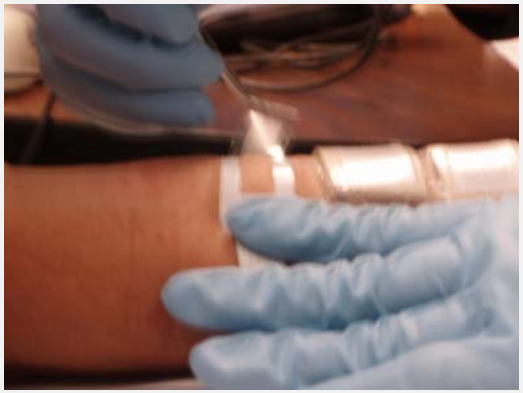


http://www.scf-online.com/english/37_e/images37_e/Skinpenetration37_13_large.jpg

Tape Stripping the Stratum Corneum

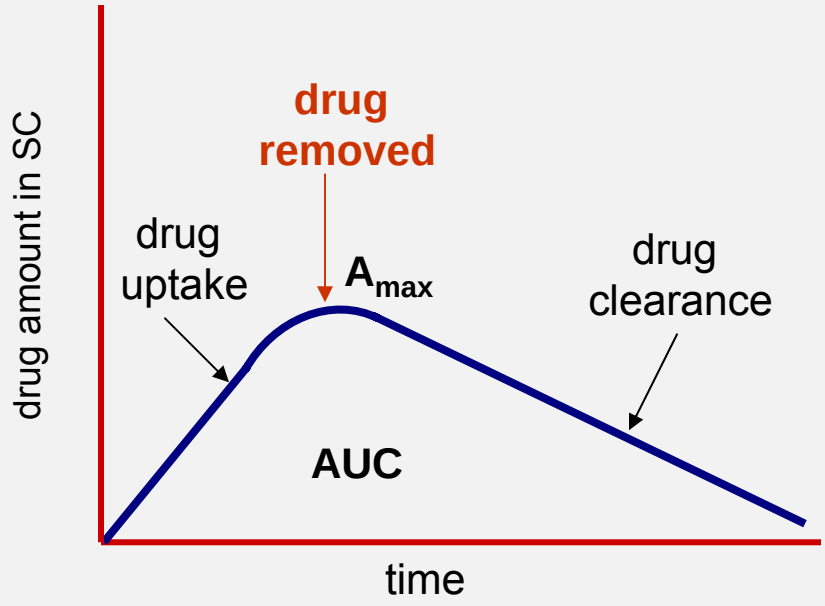
- Minimally invasive method for determining drug levels in the stratum corneum (SC) in humans *in vivo*
- Repeated application of adhesives tapes on a site that has been treated with a topical formulation
- Drug levels determined in SC collected on the tape strips
- Basis of the “Dermatopharmacokinetic” (DPK) approach
  - US Food & Drug Administration (FDA): 2 June 1998
  - Japanese Division of Drugs: 7 July 2003





Dermatopharmacokinetics (DPK)

- FDA 1998 guidance for BE assessment using DPK
- Drug amounts in SC are determined using tape stripping as a function of time
  - Post drug application (*uptake*)
  - Post drug removal (*clearance*)
- Drug level vs time characterized by *pharmacokinetic* metrics:
  - Area under drug level-time curve (AUC)
  - Maximum amount (A_{max})
- BE if AUC and A_{max} are the same

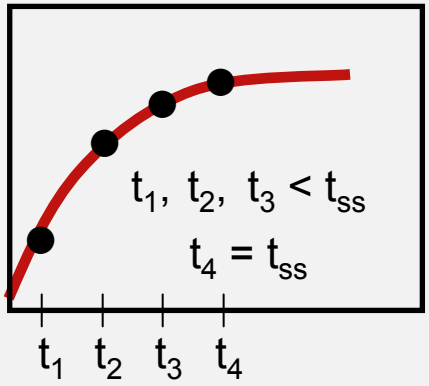


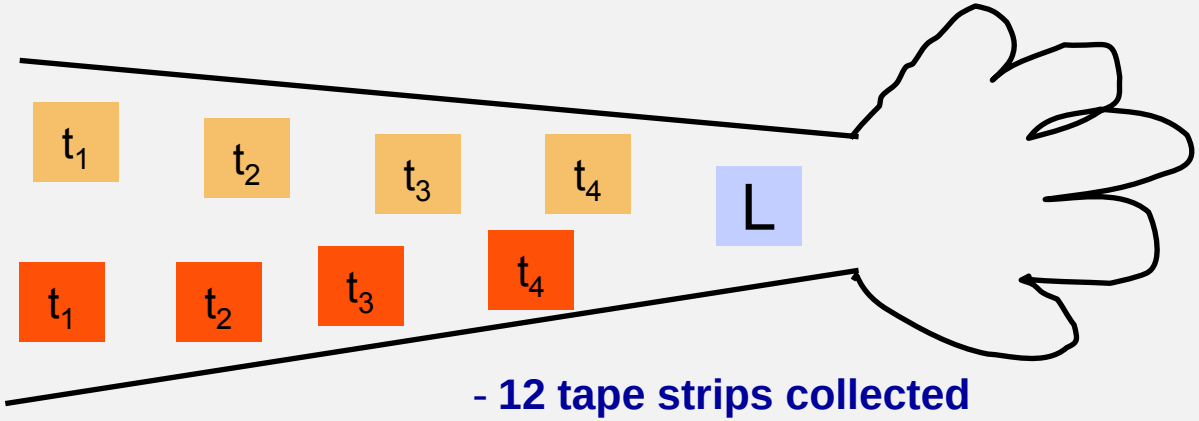
topical drug assessment

DPK for BE Assessment

test versus reference

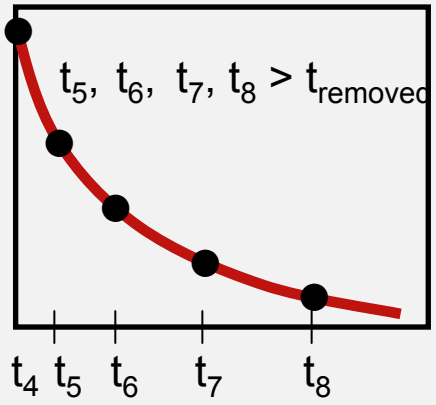
Uptake of active

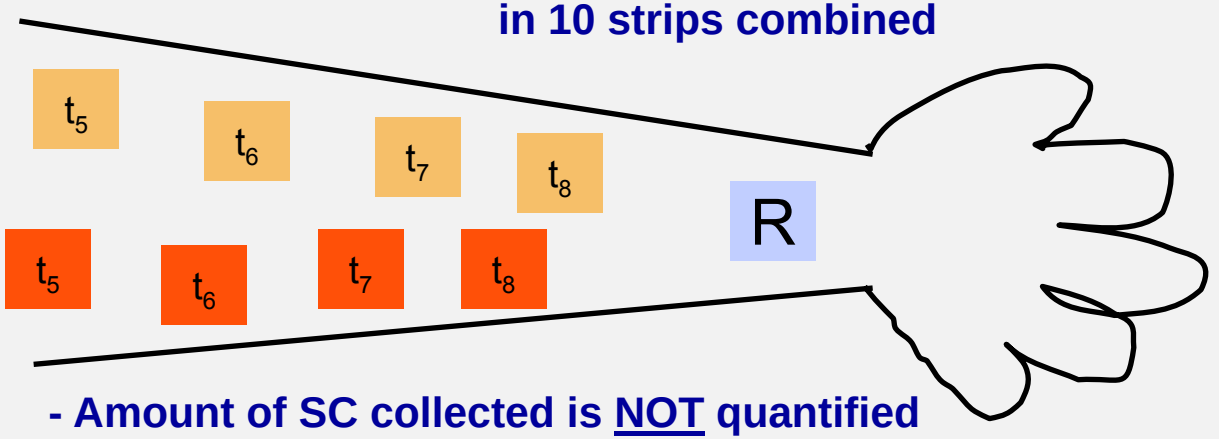




- 12 tape strips collected
- First 2 strips “discarded”
- Mass of drug/area determined in 10 strips combined

Clearance of active





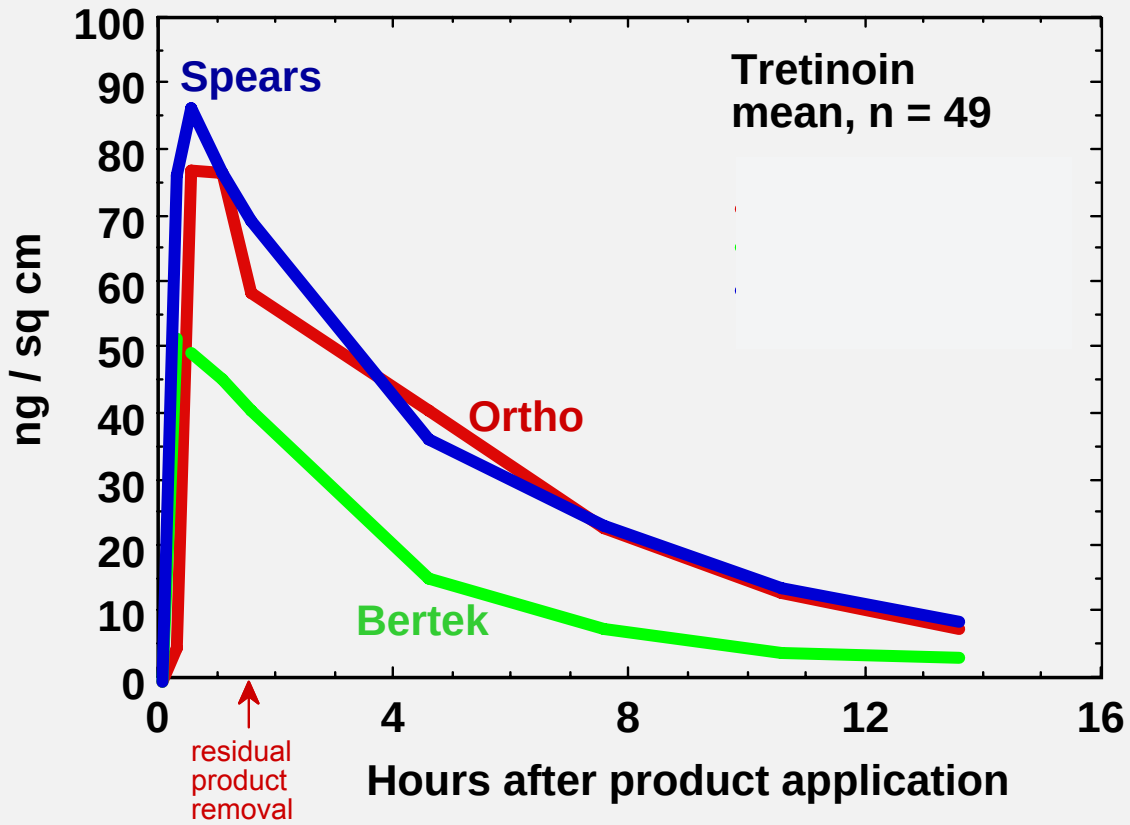
- Amount of SC collected is NOT quantified

1998 FDA guidance

DPK Bioequivalence Study: *Tretinoin #1*

0.025% Tretinoin gel products

Ortho = RLD Spears = Generic (Equivalent) Bertek = Inequivalent (less effective)



Drug Removed

0.25, 0.5, 1, 1.5 h

Tape Stripped

0.25, 0.5, 1, 1.5 h
3, 6, 9, 12 h after drug is removed at 1.5 h

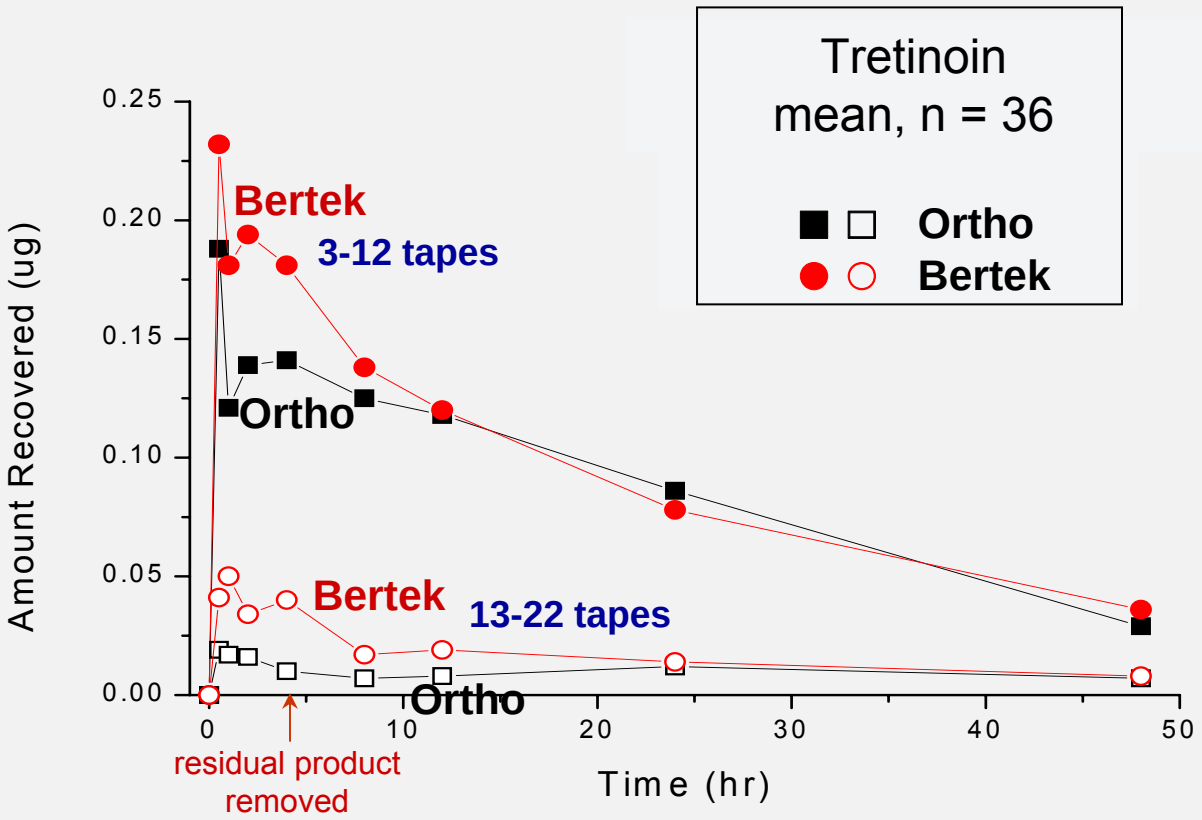
Ortho = Spears
Ortho ≠ Bertek
Ortho > Bertek

Pershing et al., 2003

DPK Bioequivalence Study: *Tretinoin #2*

DPK bioequivalence assessment Tretinoin gel, 0.025%

Ortho = Innovator Bertek = Inequivalent (less effective)



Drug Removed

0.5, 1, 2, 4 h

Tape Stripped

0.5, 1, 2, 4 h
8, 12, 24, 48 h

Ortho ≠ Bertek
Bertek > Ortho

Franz, FDA-ACPS, 11/29/2001

DPK for BE Withdrawn by FDA May 2002: *Concerns*

- Reproducibility of the method between laboratories
  - Contradictory results in studies by experts in two laboratories
- Complexity of the method
  - Number of analyses are large minimizing advantages of the method
  - Tretinoin: (49 subjects)*(8 sites/product)*(2 products) = **784 analyses**
    (36 subjects)*(8 sites/product)*(2 products)*(2 tape groups) = **1,152 analyses**
- Adequacy of DPK method to assess BE when the SC
  - Is not the target organ, or
  - Is not the sole limiting barrier (other pathways exist)
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- Effects of excipients on therapeutic effect

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Restrict DPK to:

- **Products targeting the SC ⇒ antifungal**
- **Diseases that minimally disrupt the SC barrier**
- **Products with the same formulation or containing no excipients with no effect**

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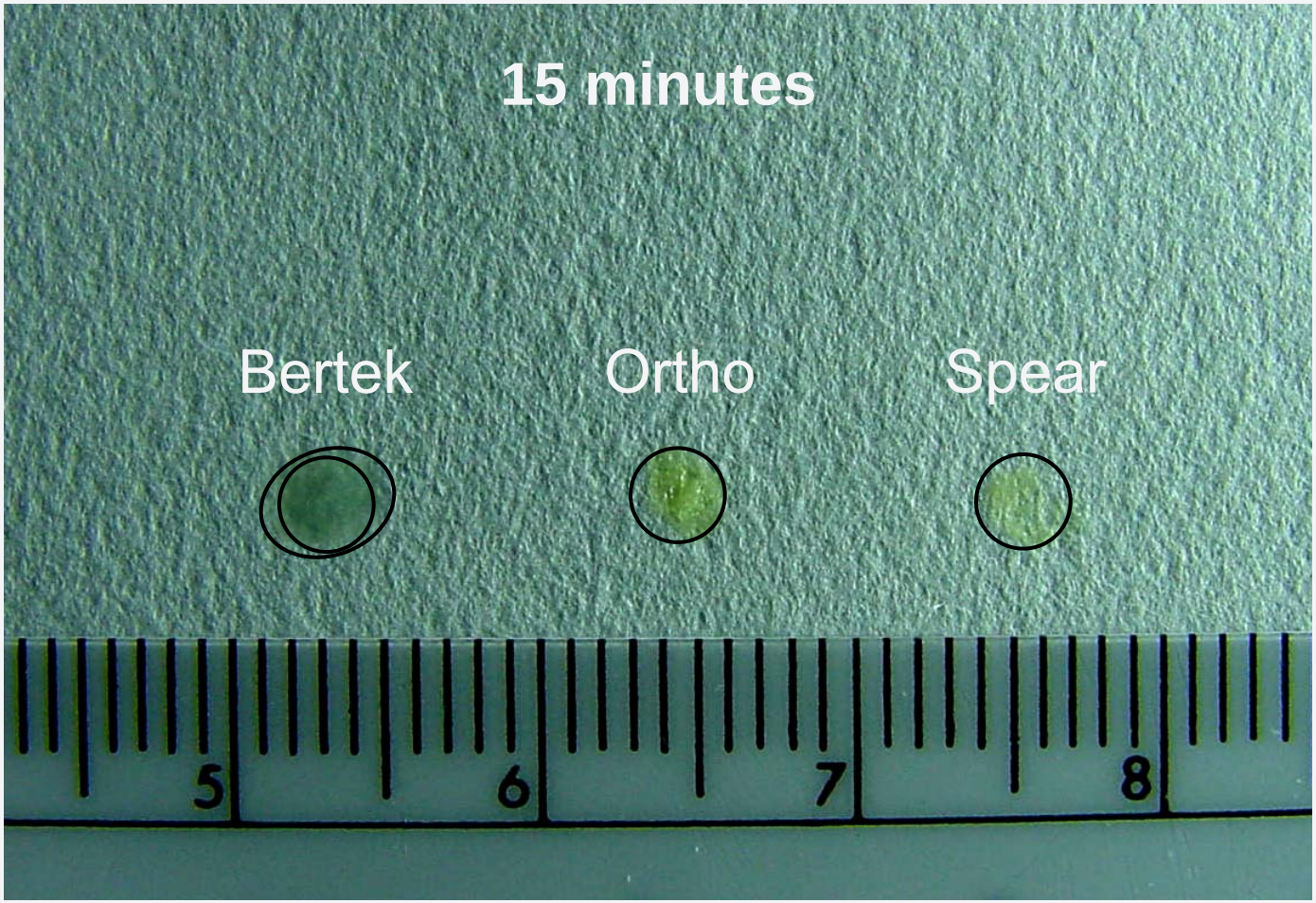

Conner, FDA-ACPS, 11/29/2001

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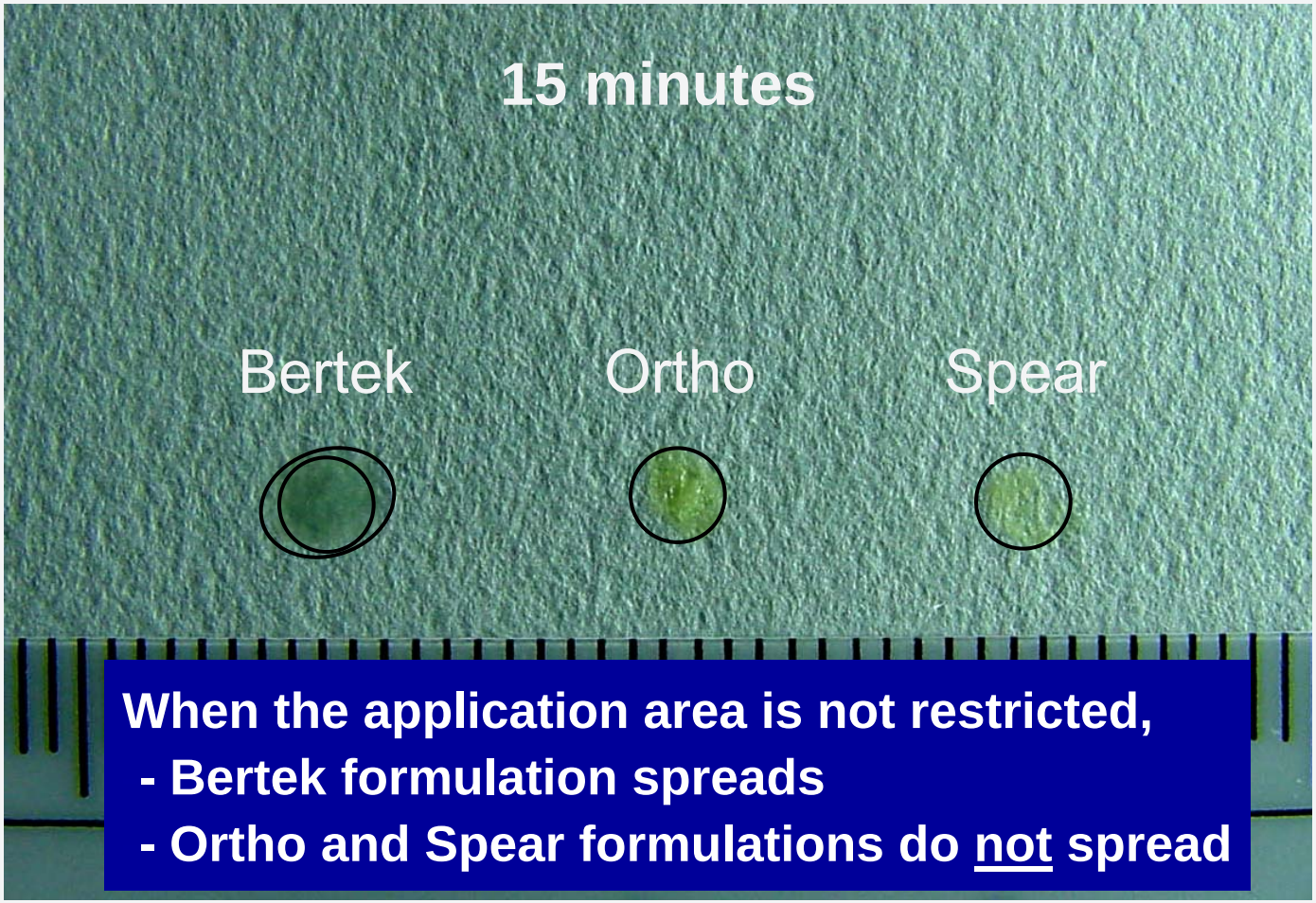
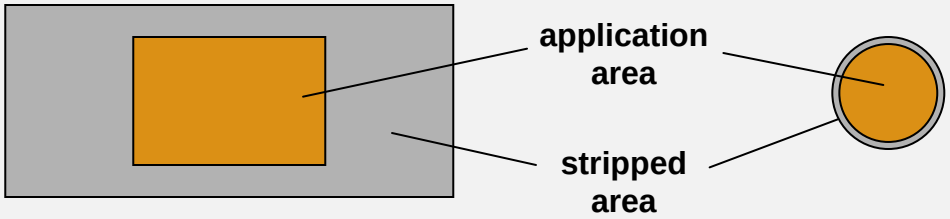


Conner, FDA-ACPS, 11/29/2001

Why the lab-to-lab differences?

Tape stripped area > Application area



Area of Application	**4 cm^2**	**1.13 cm^2**
Application area delimited	**NO**	**YES**
Amount Applied	**20 μL**	**5 μL**
Amount Applied/Area	**5 μL/cm^2**	**4.42 μL/cm^2**
Area Stripped	**10 cm^2**	**1.33 cm^2**
Tape Used	**Transpore (3M)**	**D-Squame (Cuderm)**

Conner, FDA-ACPS, 11/29/2001

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DPK for BE assessment: *Concerns*

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DPK for BE assessment: *Concerns*

Addressing the Concerns

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- **Improve protocol**
- **Better control of application and sampling areas**
- **Protocol that is less insensitive to the operator**

DPK for BE assessment: *Concerns*

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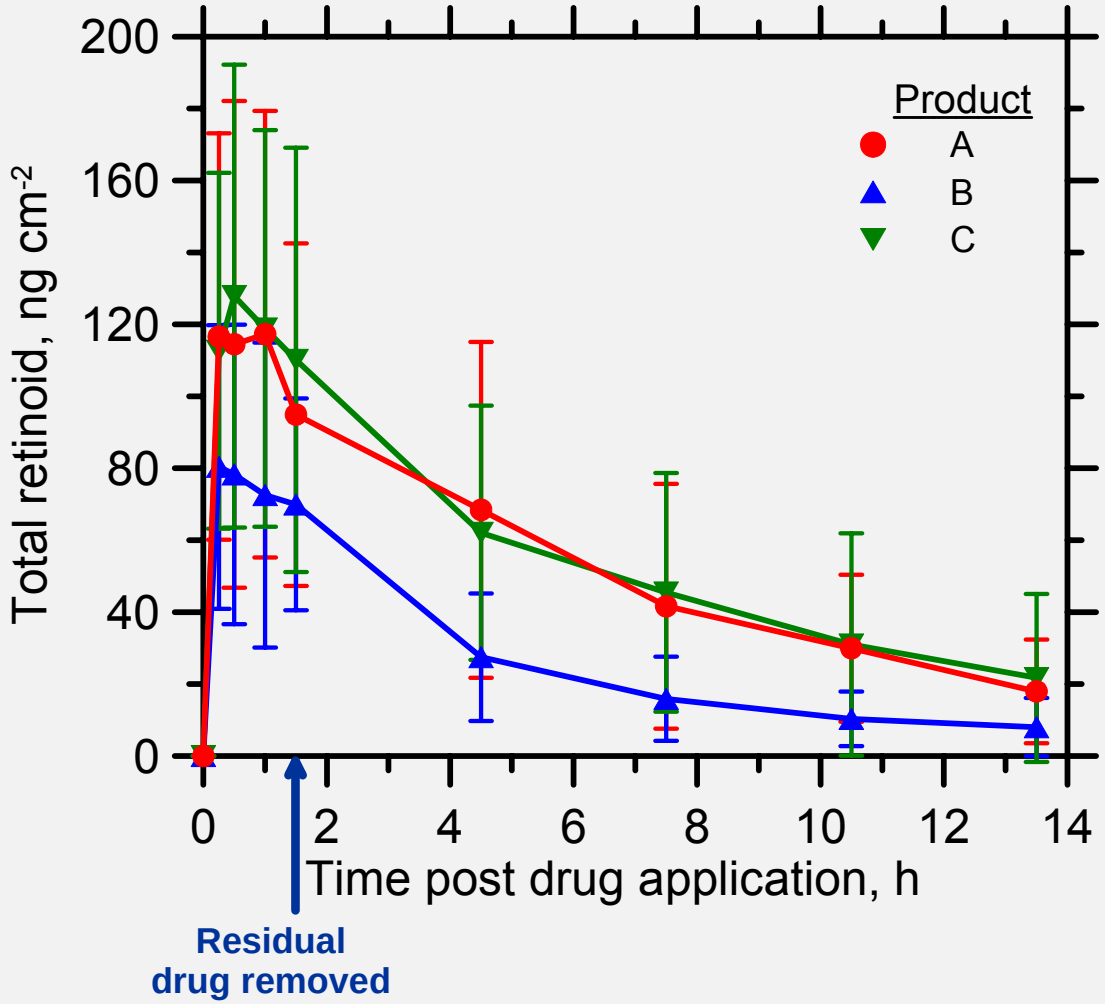
- **Reduce variability ⇒ fewer subjects required**
- **Are 8 times required?**

Are 8 time points needed? *Tretinoin data*

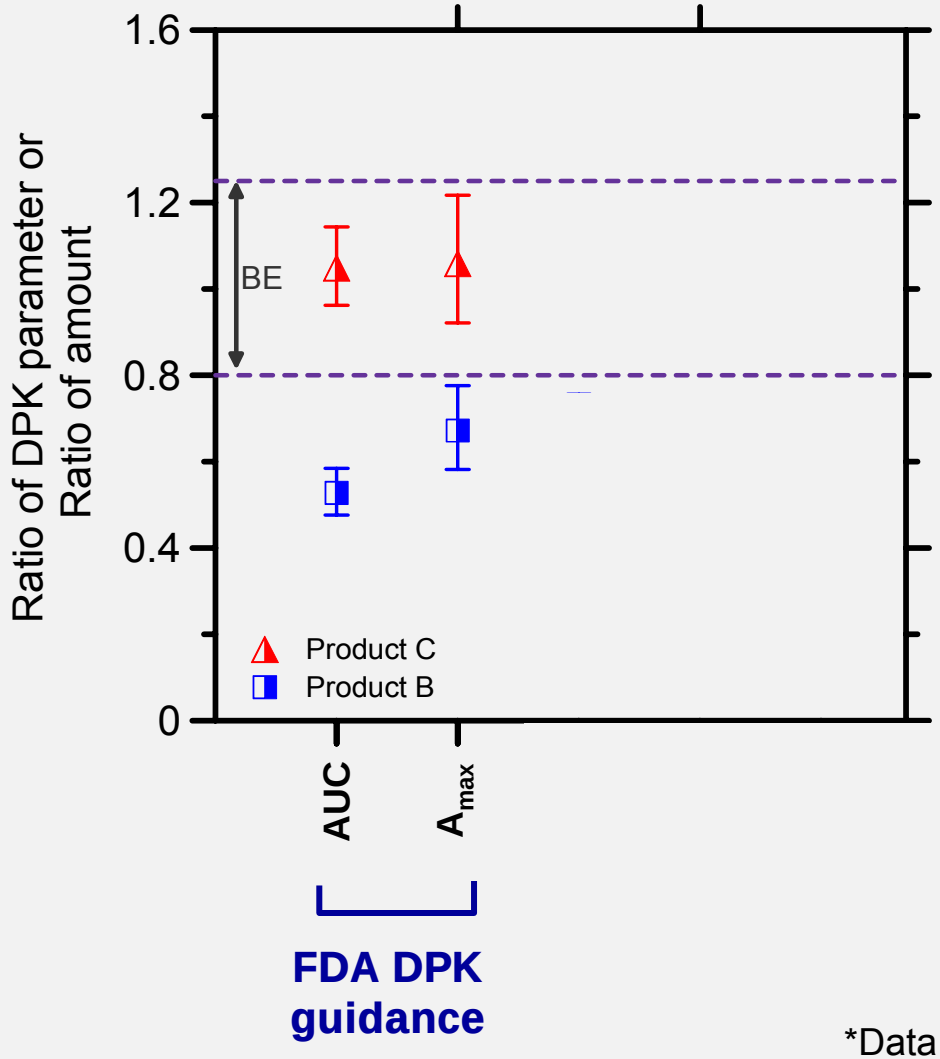
Comparing Products B and C to Product A



- **8-time points required for the AUC analysis**
- **Is AUC the best metric?**
- **Can reliable BE assess-ment be accomplished with fewer time points?**

Tretinoin gel 0.025% study: *BE metric**

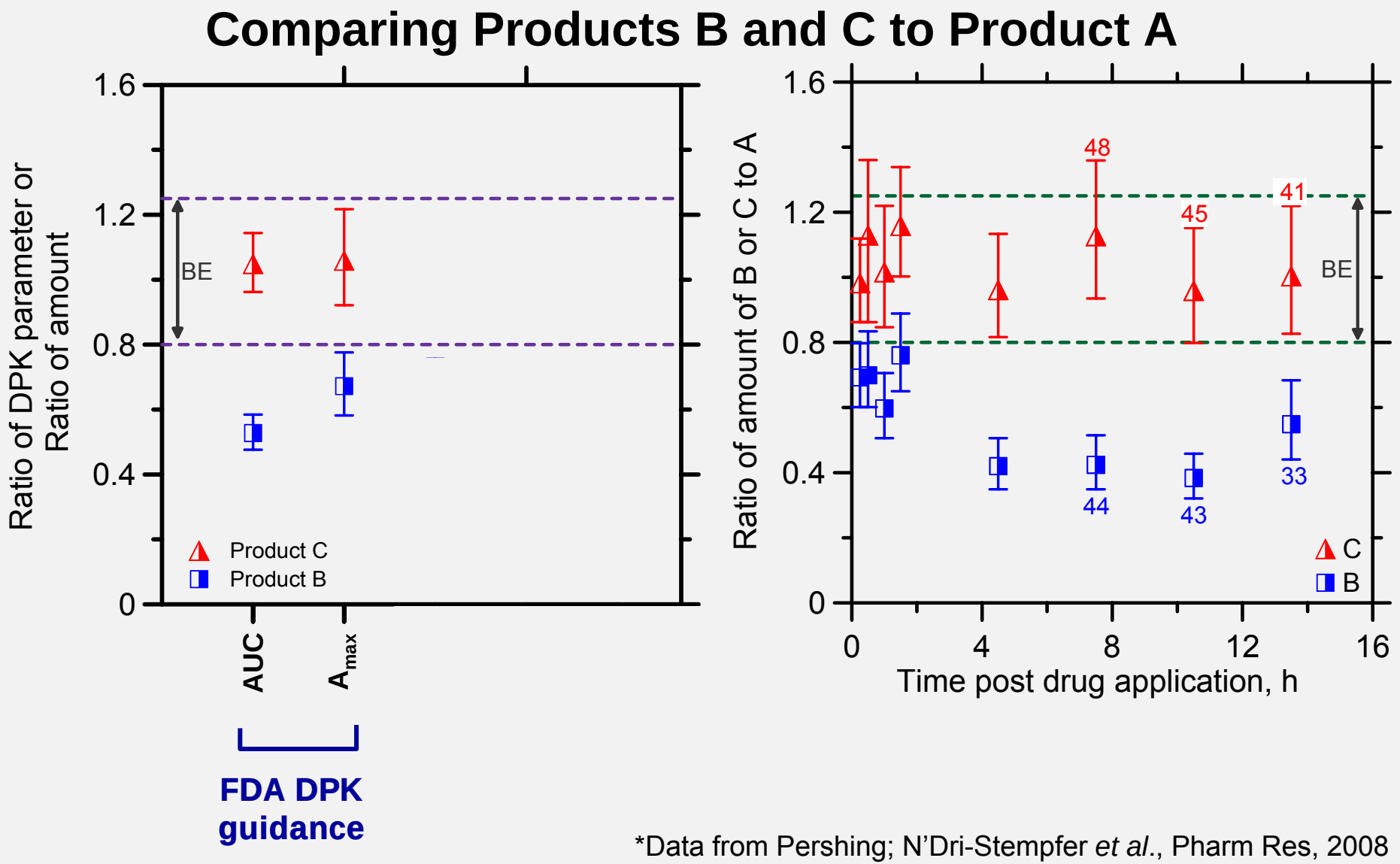
Comparing Products B and C to Product A



- **How do the drug amounts at each time compare?**

*Data from Pershing; N'Dri-Stempfer *et al*., Pharm Res, 2008

Tretinoin gel 0.025% study: *BE metric*



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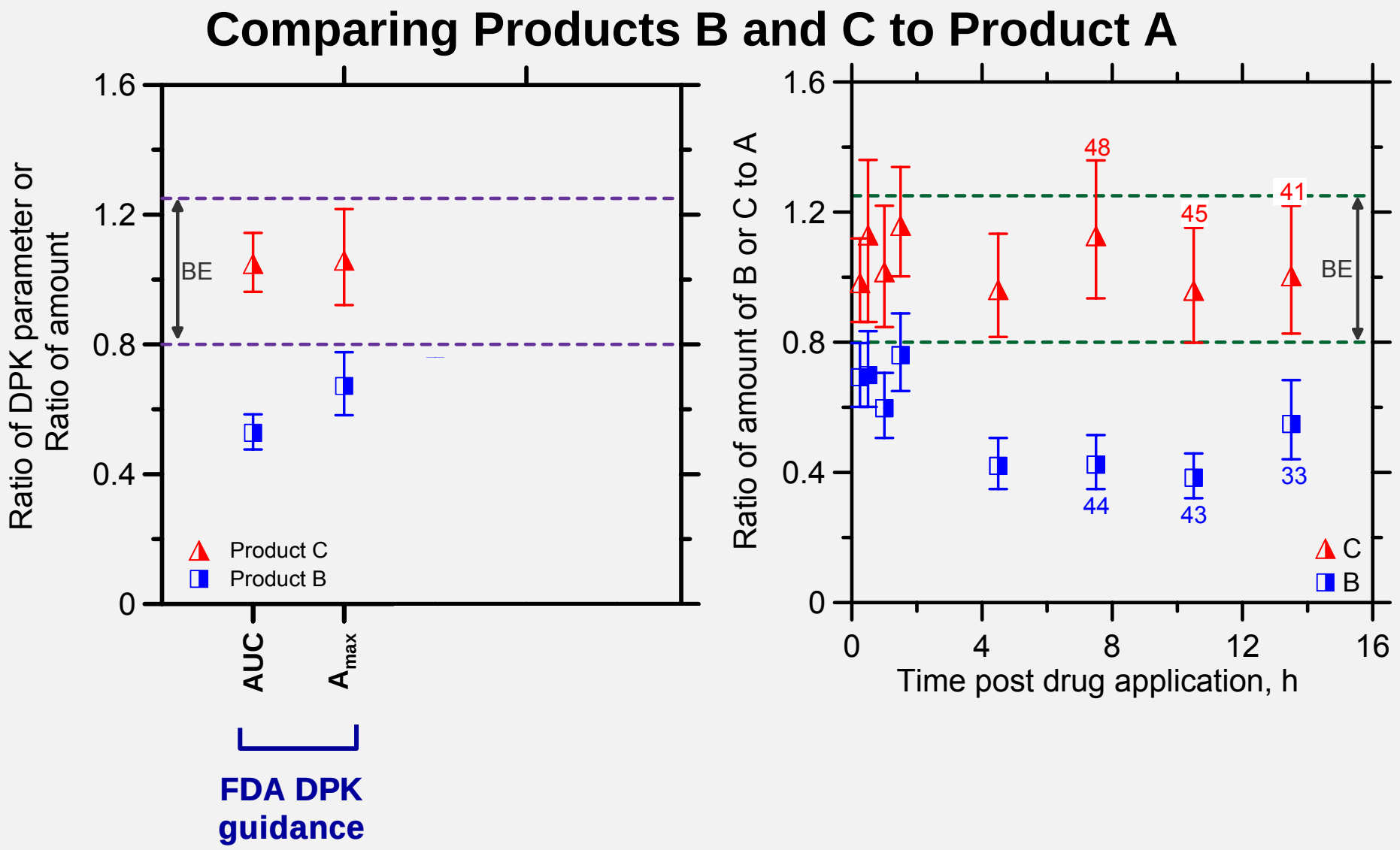
Tretinoin gel 0.025% study: *BE metric*



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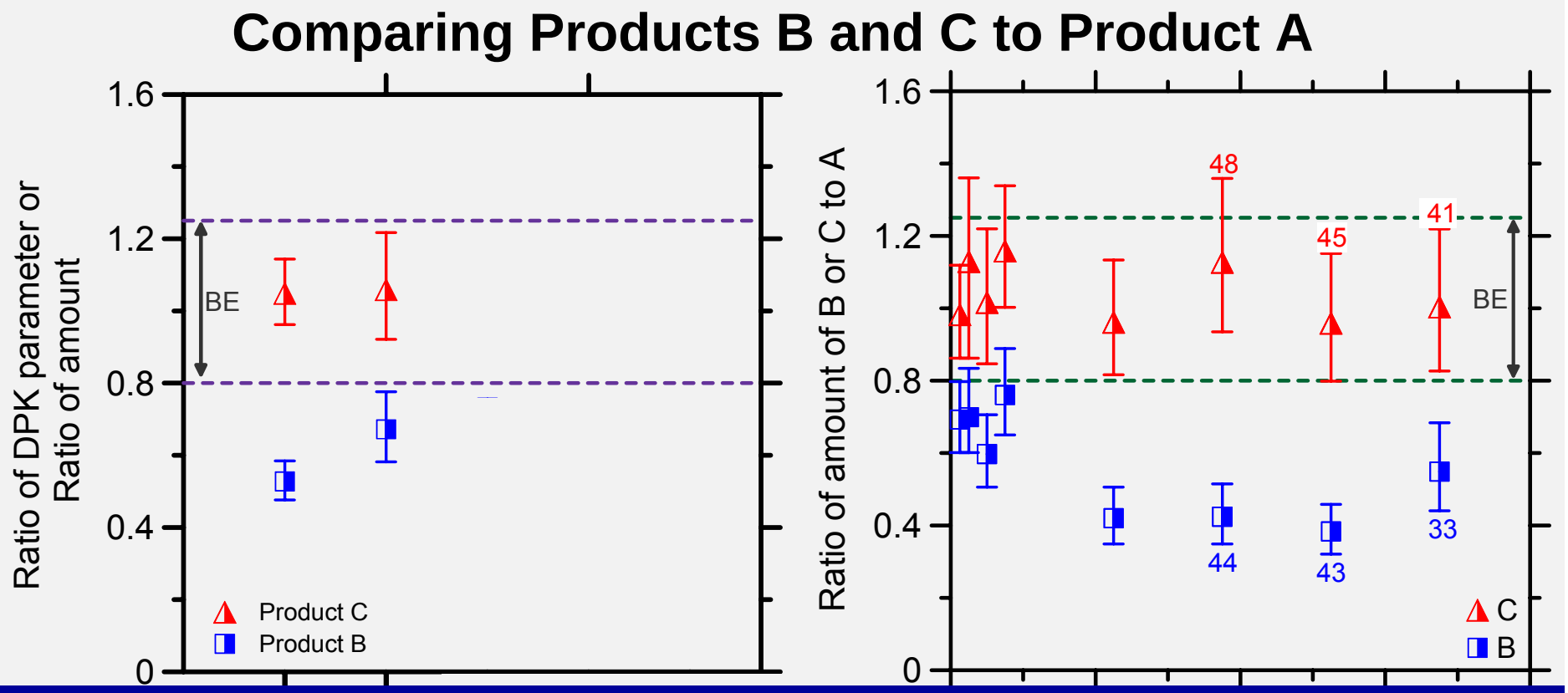
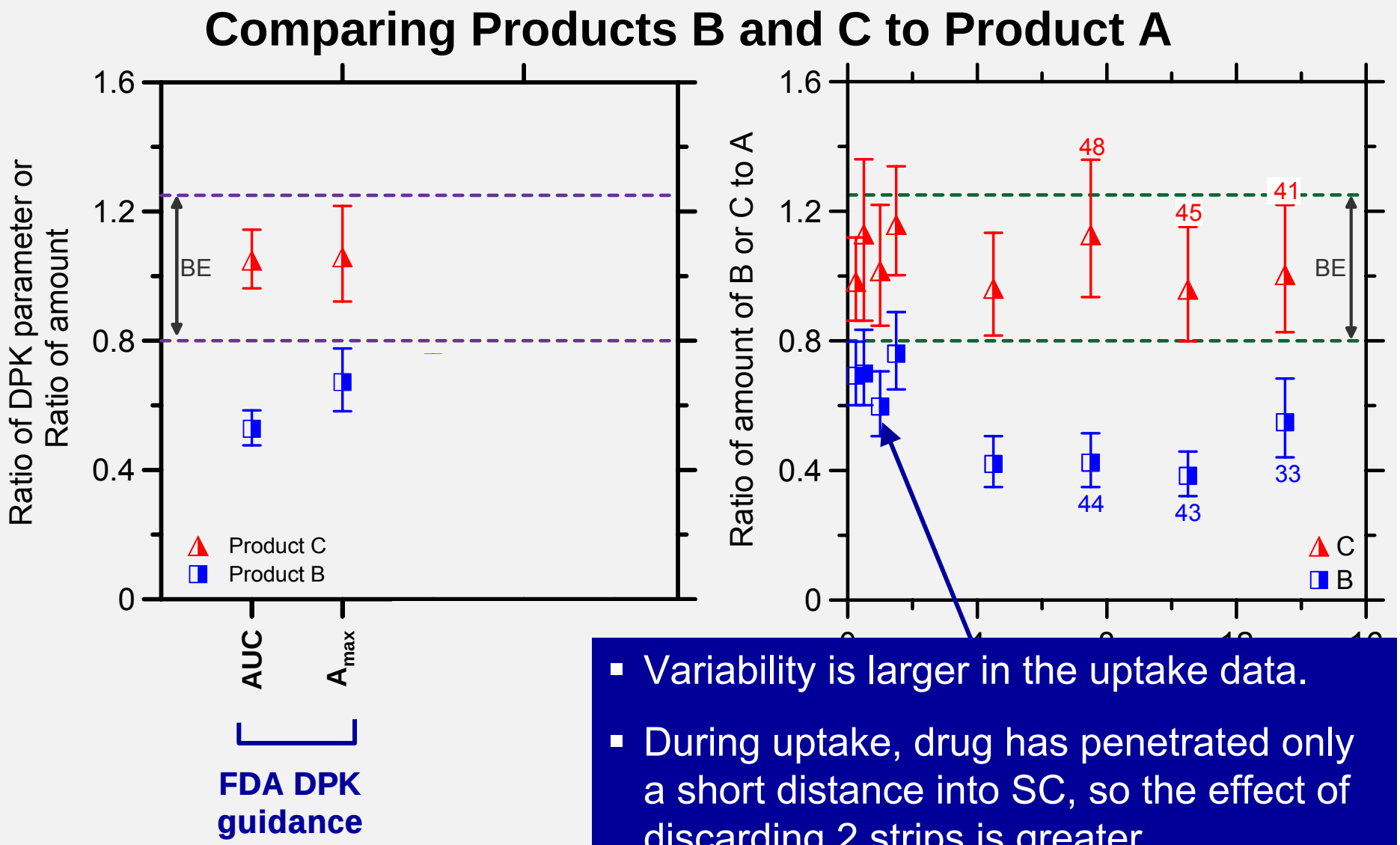


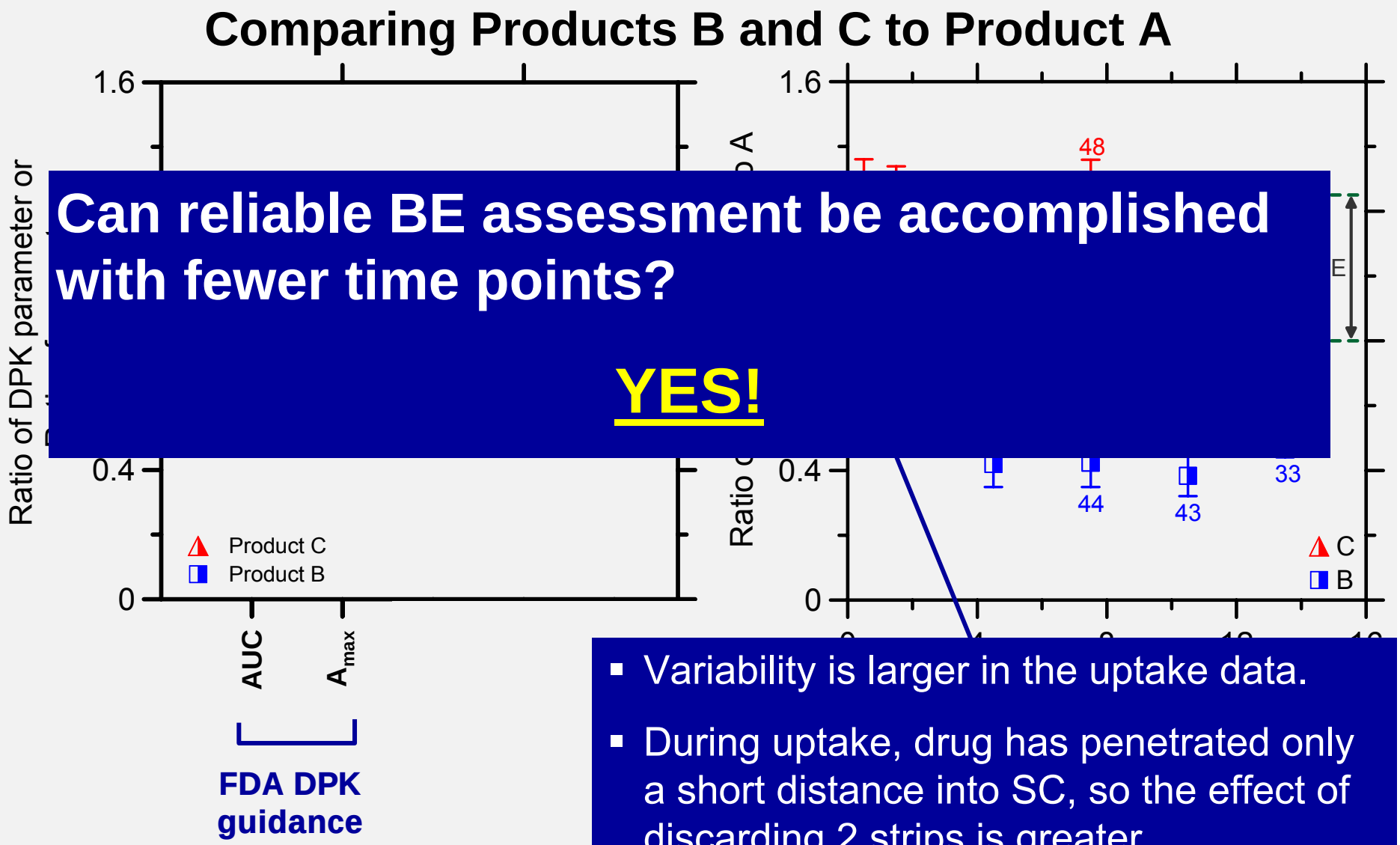
- Determinations at individual time points are the same as from AUC or A_{max}
- In some cases, conclusive assessment would require more subjects
- Larger variability at individual time points could be reduced by decreasing experimental variability and by duplicating determinations

Tretinoin gel 0.025% study: *BE metric*



- Variability is larger in the uptake data.
- During uptake, drug has penetrated only a short distance into SC, so the effect of discarding 2 strips is greater.

Tretinoin gel 0.025% study: *BE metric*



Can reliable BE assessment be accomplished with fewer time points?

YES!

- Variability is larger in the uptake data.
- During uptake, drug has penetrated only a short distance into SC, so the effect of discarding 2 strips is greater.

Assessing BA & BE at only 1 or 2 times

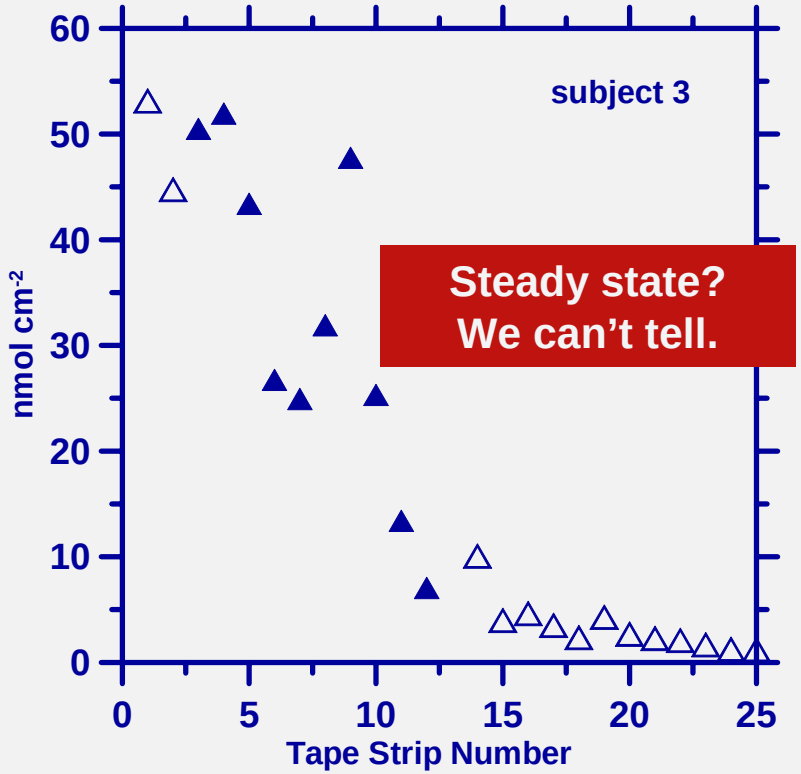
- Measure concentration (C) versus position (x) in the SC
- Collect and measure the amount of nearly all drug in the SC (12 tape strips is not enough)

Assessing BA & BE at only 1 or 2 times

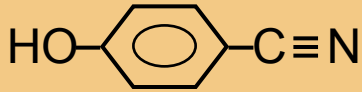
- Measure concentration (C) versus position (x) in the SC
  - Measure the mass of SC on each tape strip
  - Concentration of drug on each tape is amount of drug divided by amount of SC
  - Position (x) is determined from the mass of SC on each tape

DPK data: *Concentration versus position*

Amount of drug per area versus tape strip #



4-cyanophenol



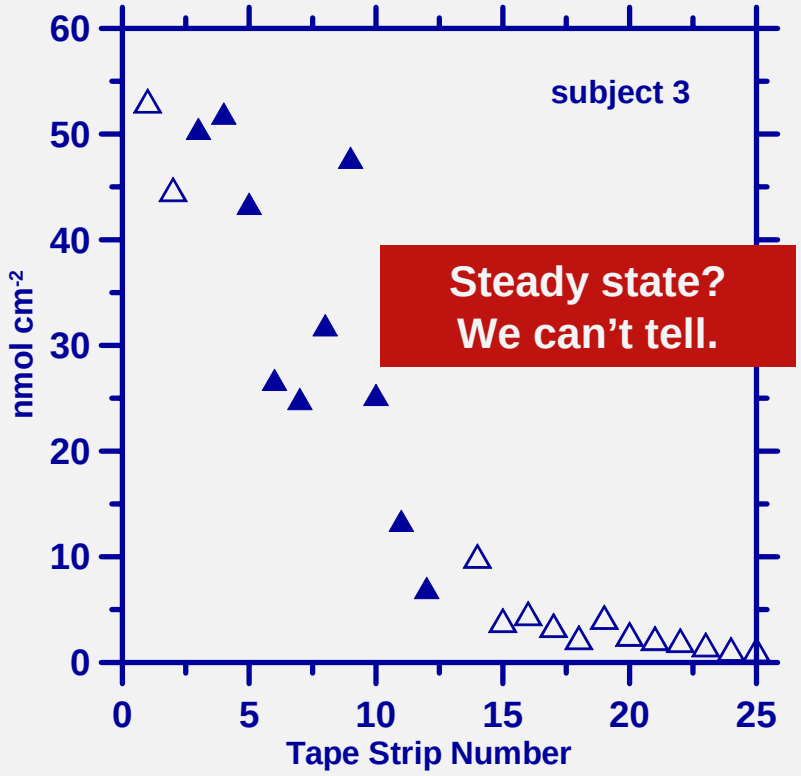
Skin tape stripped after 1 hour of uptake

DPK data: *Concentration versus position*

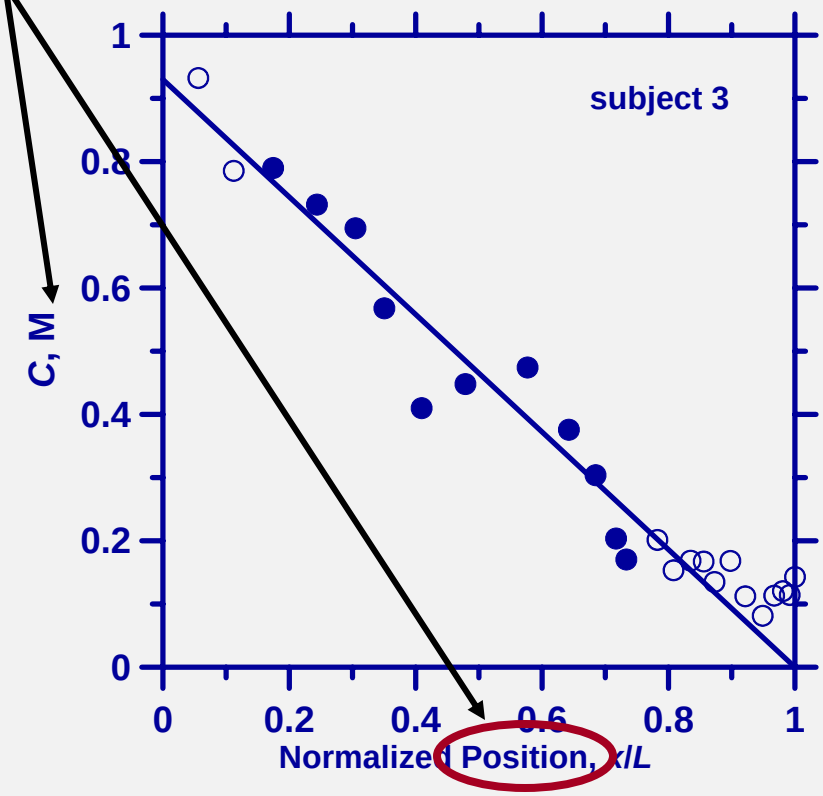
Amount of drug per area versus tape strip #

Concentration of drug in SC versus position

SC amount quantified

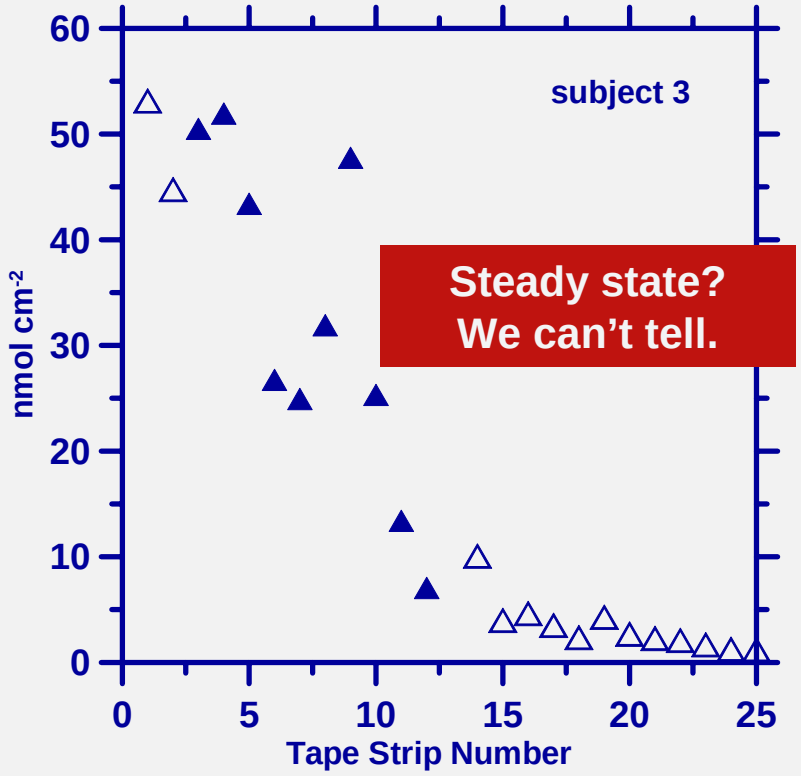


Steady state? We can't tell.

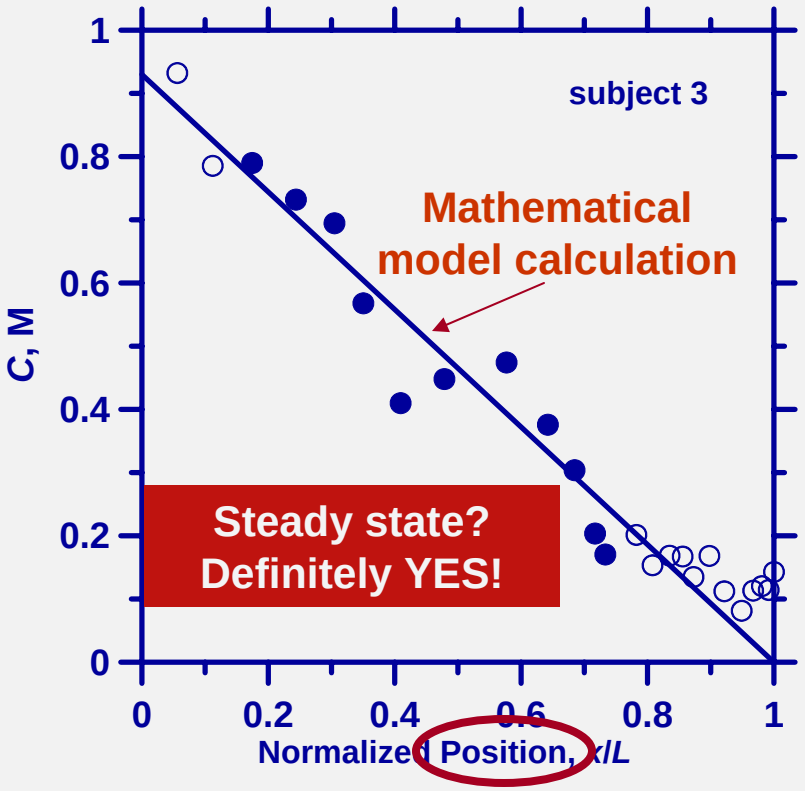


DPK data: *Concentration versus position*

Amount of drug per area versus tape strip #



Concentration of drug in SC versus position



Assessing BA & BE at only 1 or 2 times

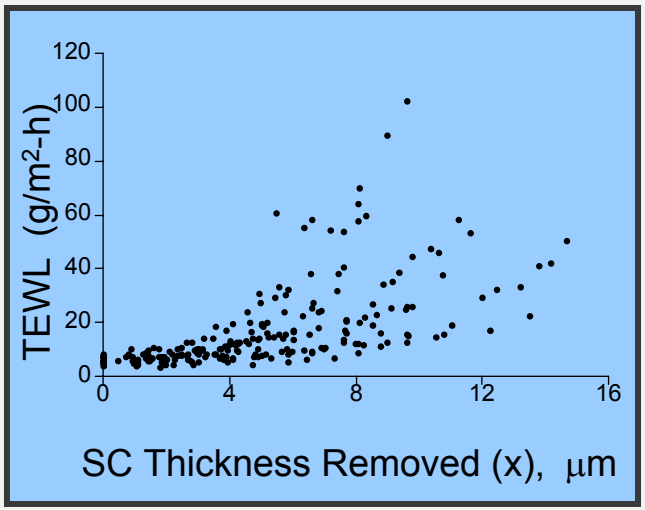
- Measure concentration (C) versus position (x) in SC
  - Measure the mass of SC on each tape strip
  - Concentration of drug on each tape is amount of drug divided by amount of SC
  - Position (x) is determined from the mass of SC on each tape
  - **Measure SC thickness (L) using weight of SC on each tape and water flux measurements (TEWL) as described by Kalia *et al.*, 1996***
  - **Normalize position (x/L)**

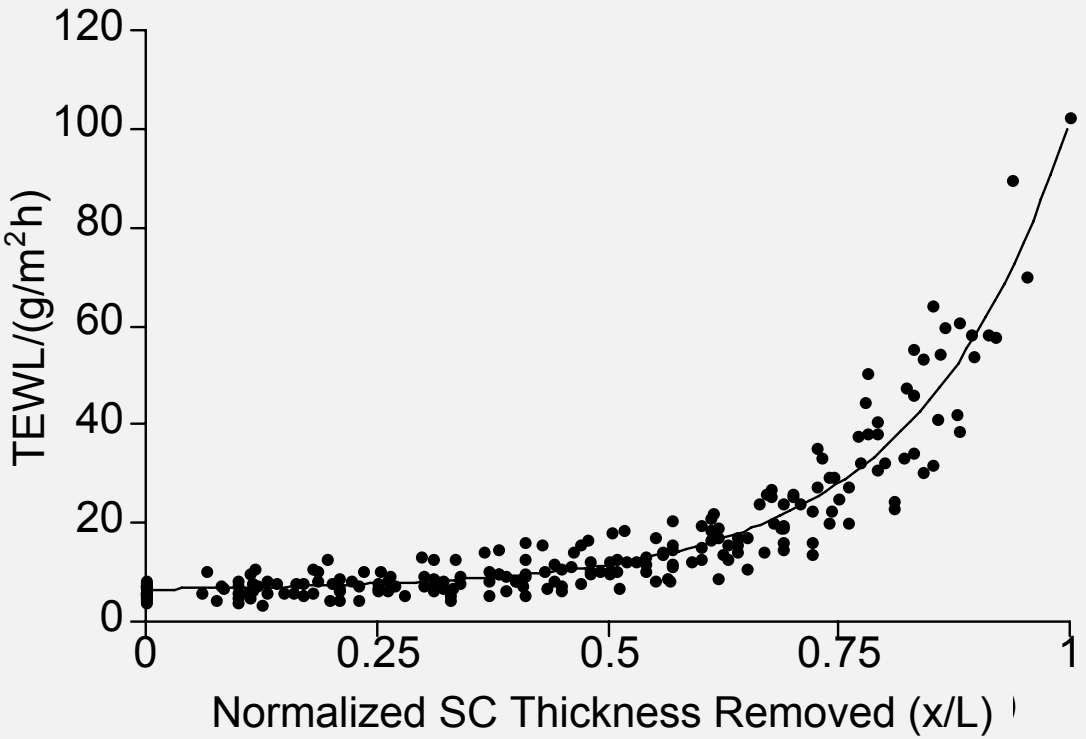
Extracting even more information…

*Kalia *et al*., Biophys J, 1996

TEWL versus normalized position (x/L)

From RH Guy

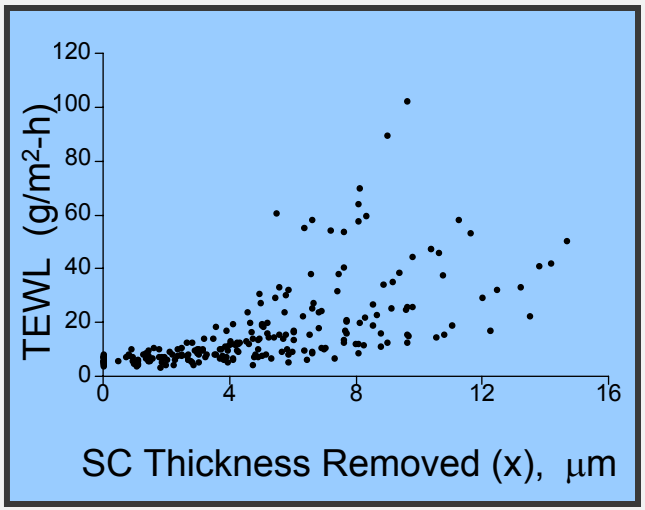


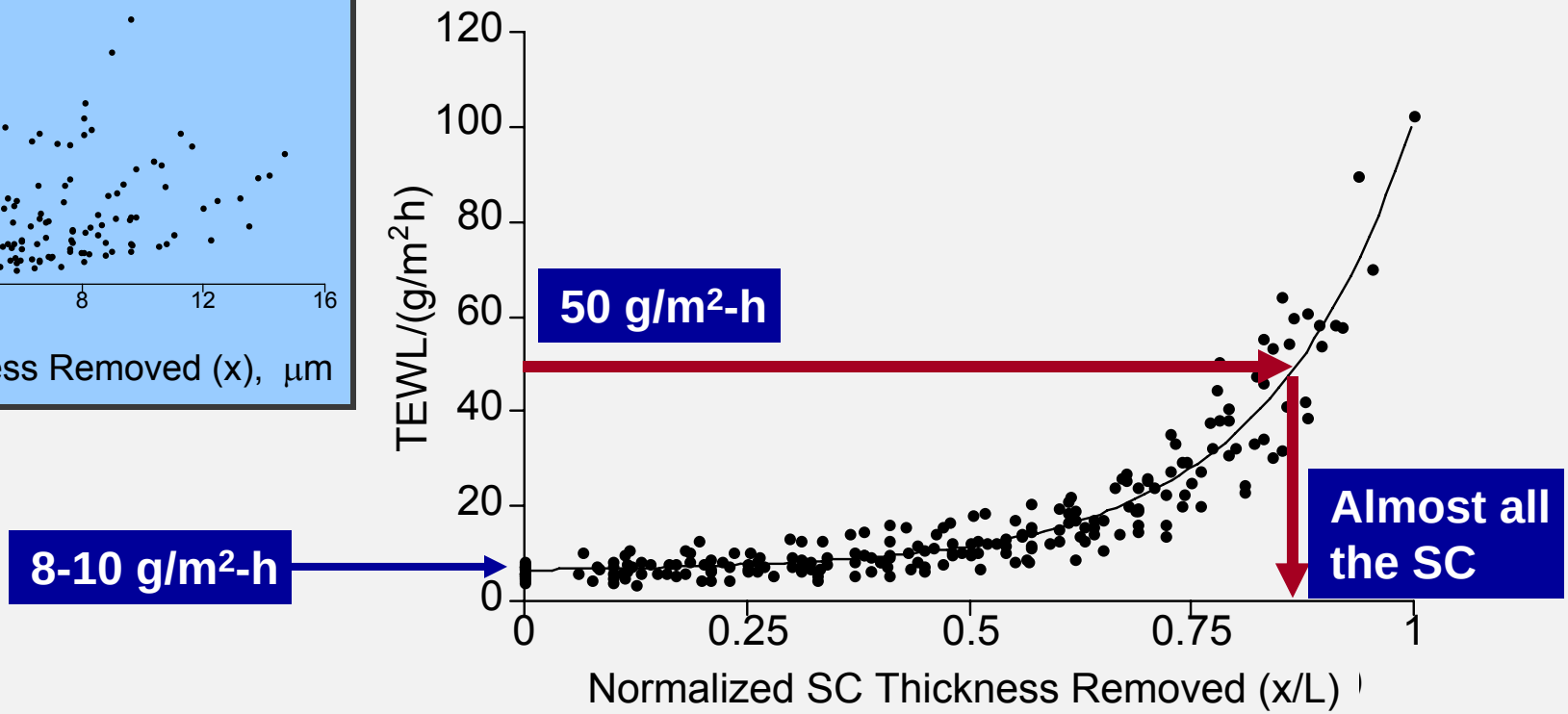


Normalization of SC amount removed (x) to total thickness of barrier (L) results in a TEWL profile which is remarkably similar between different individuals

TEWL versus normalized position (x/L)

From RH Guy

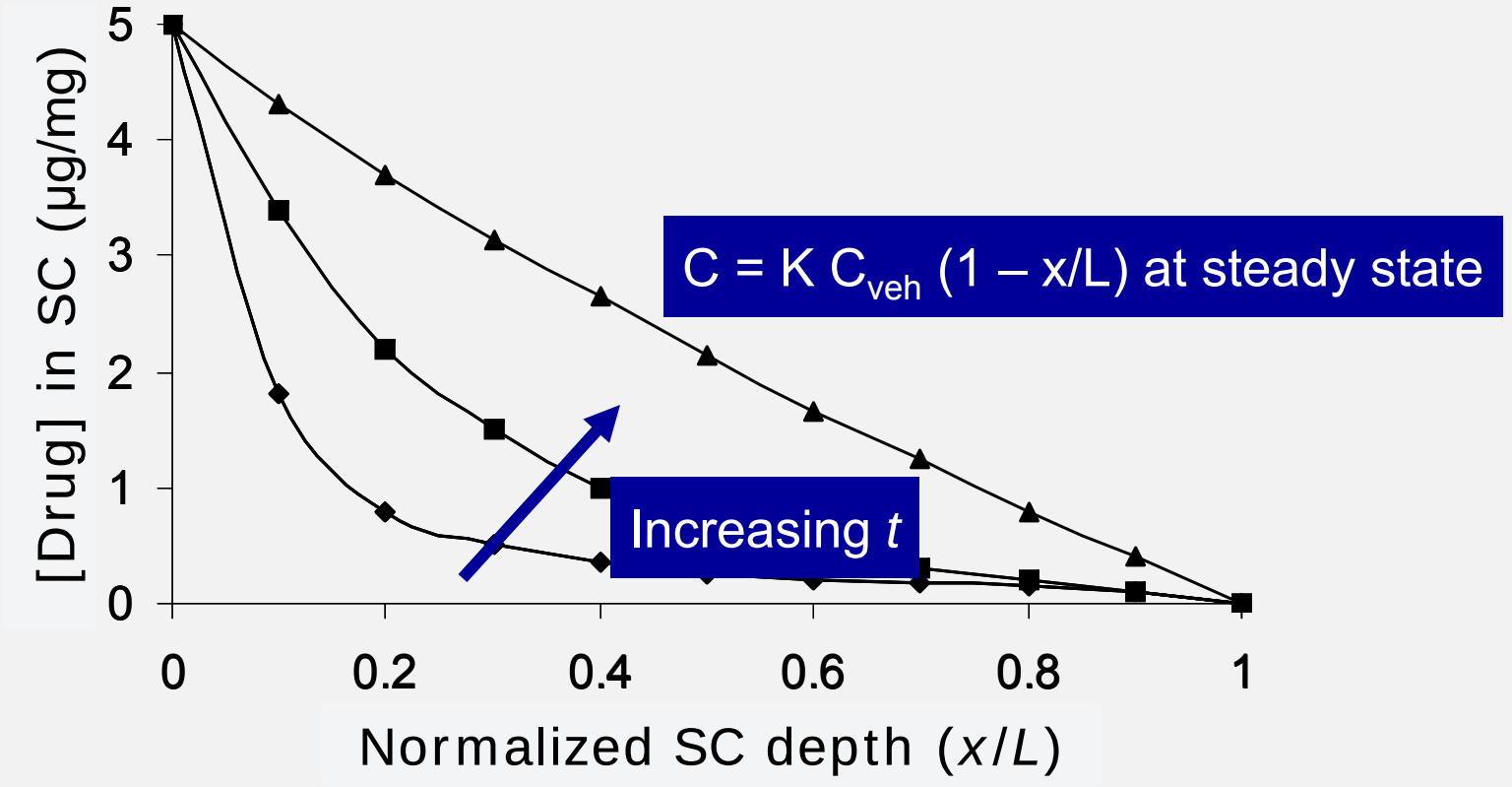




Normalization of SC amount removed (x) to total thickness of barrier (L) results in a TEWL profile which is remarkably similar between different individuals

Drug concentration profile in the SC

$$C = K C_{veh} \left\{ \left(1 - \frac{x}{L} \right) - \frac{2}{\pi} \sum_{n=1}^{\infty} \left[\frac{1}{n} \sin\left(n \pi x / L \right) \exp\left(-\left(D / L^2 \right) n^2 \pi^2 t \right) \right] \right\}$$



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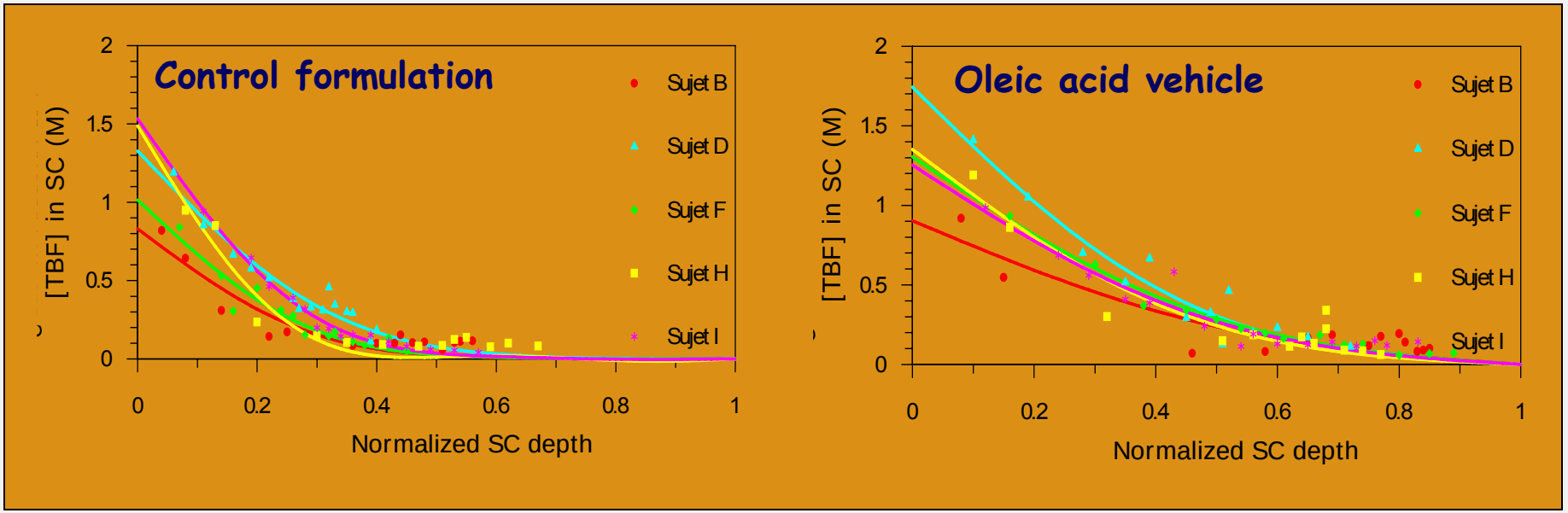
Regress *C* versus *x*/*L* data to equation to determine:

- Partition coefficient, ***K*** $\propto$ **extent** of absorption
- Diffusion coefficient, D/L^2 $\propto$ **rate** of absorption
- Permeability coefficient, $K_p = K \cdot (D/L^2) \cdot L$ $\propto$ **steady-state flux**
- Amount in the SC from integral of *C* versus *x*/*L* (**AUC**) = Average Concentration

Drug concentration profile in the SC: *Example*

From RH Guy

Terbinafine: *Effect of oleic acid*



Formulation	K	$D/L^2 * 10^6$ (s^{-1})
Control	0.70 ± 0.18	3.5 ± 0.9
Oleic acid	0.75 ± 0.17	12 ± 2.1*

*significantly different from control ($p < 0.05$)

At steady state:

C_{ave} ~ the same

Flux is different

I Alberti, YN Kalia, A Naik, J.-D. Bonny & RH Guy. *J Control Release*, 71:319 (2001).

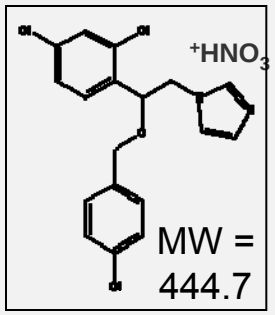
Assessing BA & BE at only 1 or 2 times

- Measure concentration (C) versus position (x/*L*) in the SC
  - Requires determination of SC thickness (*L*)
  - Requires measurements at many different positions
  - Lots of chemical analyses are required (a disadvantage)
  - Differentiates contributions of rate and extent on flux of drug (an advantage)
  - Perhaps more useful for formulation development than regulatory BE assessment
  - It is insensitive to differences in SC stripping efficiency of the operator
- Collect and measure the amount of nearly all drug in the SC at a specified time

Assessing BA & BE at only 1 or 2 times

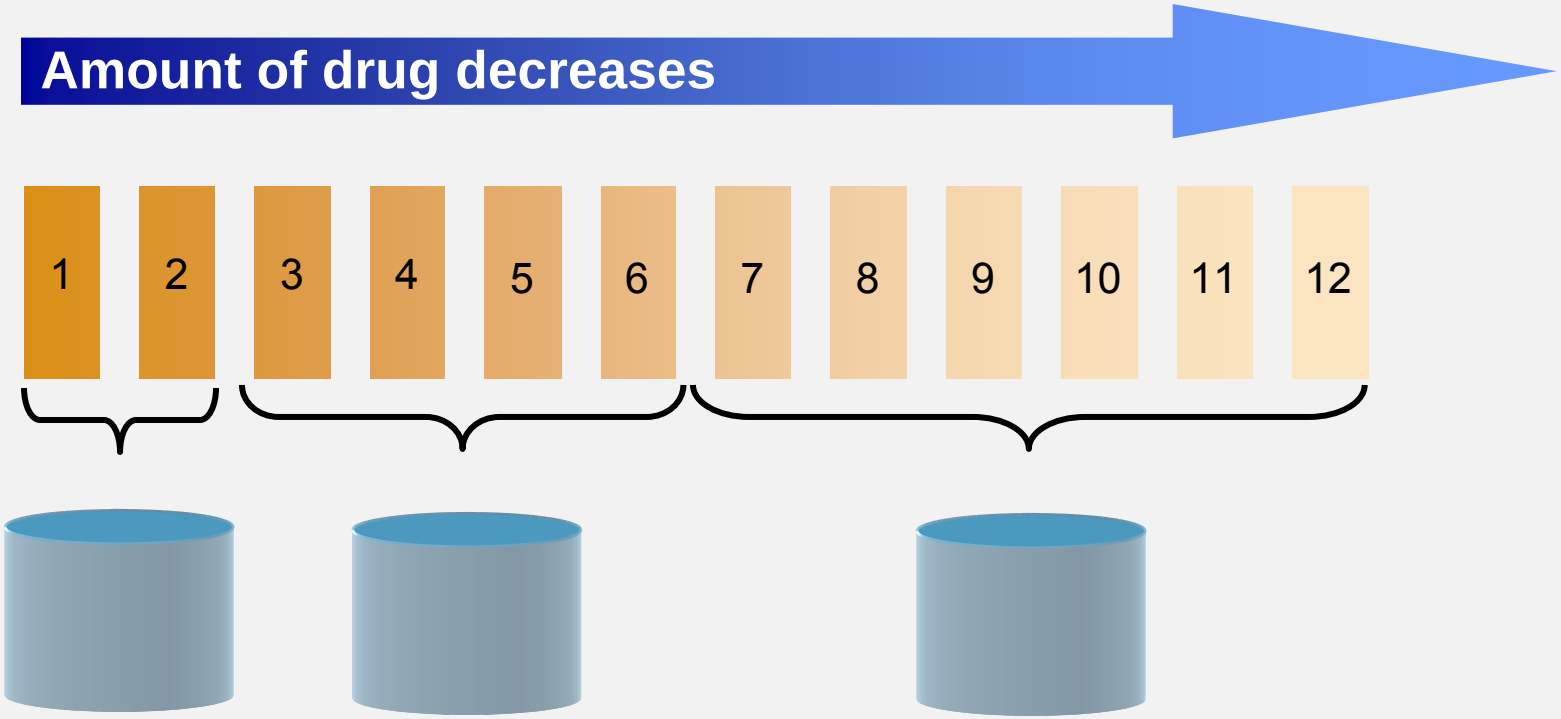
- Measure concentration (C) versus position (x/*L*) in the SC
- Collect and measure the amount of nearly all drug in the SC at a specified time
  - "Improved protocol" developed for FDA (but not adopted)
  - Protocol approved by the Japanese Division of Drugs

“Improved protocol” developed for FDA



- Econazole nitrate creams: 2 (BE) generics to RLD
- 4 treatment sites / product (12 sites total)
  - Duplicate determinations at each time of 2 times
  - 1 uptake time (6 h)
  - 1 clearance time (17 h)
- Unabsorbed drug removed using isopropyl alcohol wipes and all tapes included in drug quantification
- Determine *all* drug in SC by removing nearly all of the SC
  - Remove SC until TEWL > 8 x (TEWL before stripping)
  - At least 12 tape strips, but not more than 30 tape strips
- Analyze tape strips in groups to optimize analytical sensitivity

Analysis of drug on tape strips



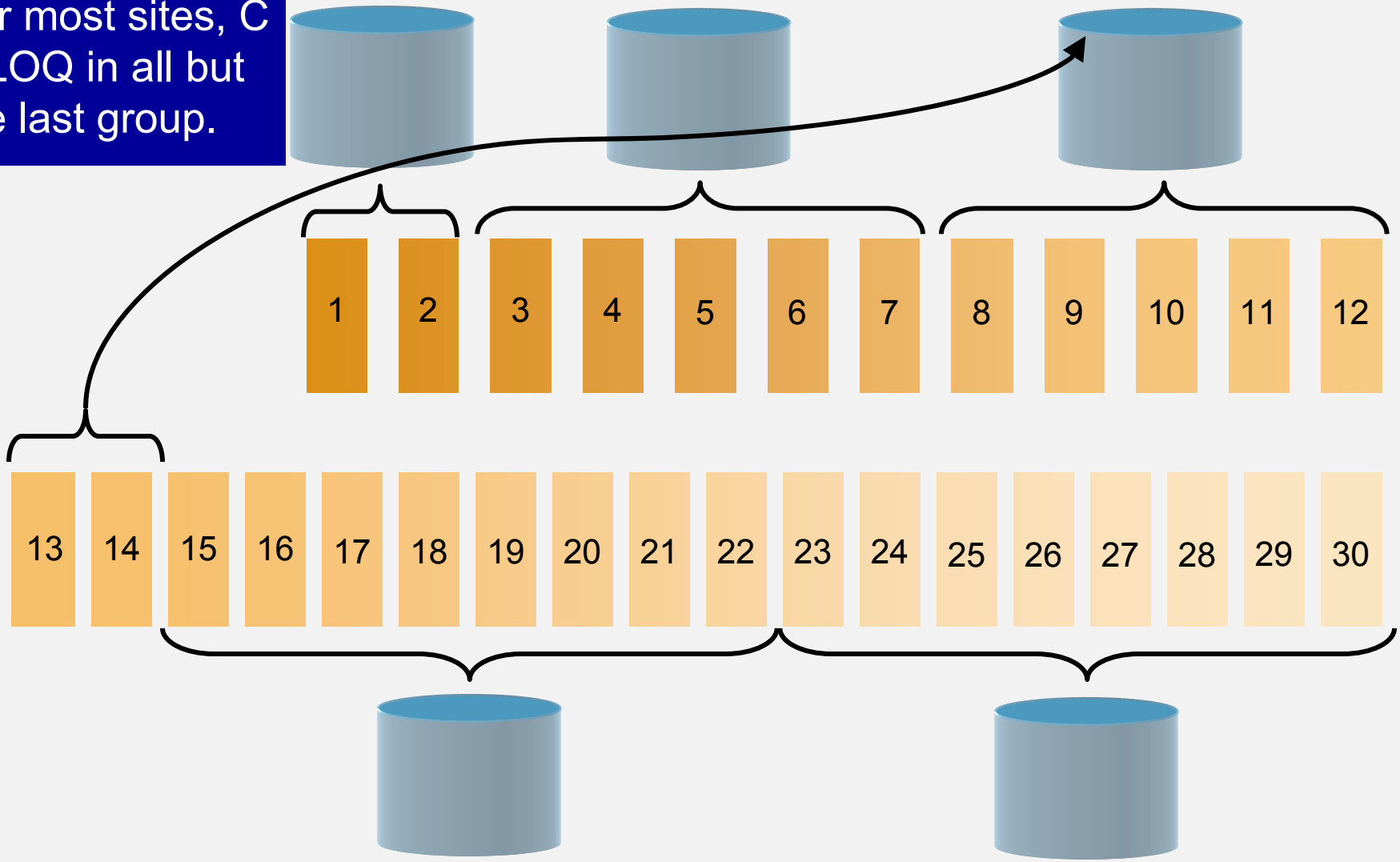
Extract first 2 tape strips separately

Extract a few groups of tape strips in the smallest possible volume of solvent

Goal: Concentration > LOQ in at least 2 groups of tapes

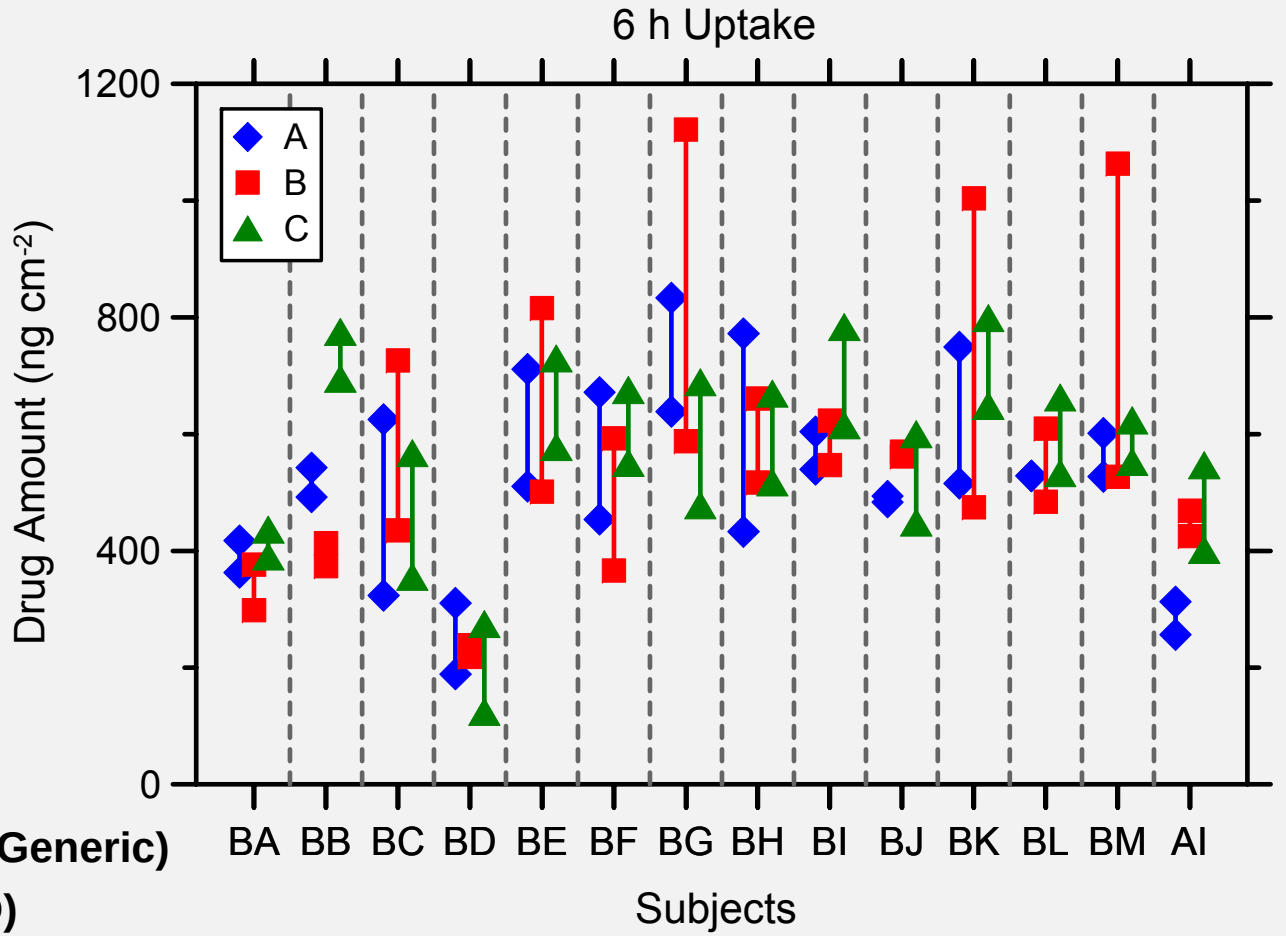
Analysis of drug on tape strips: More than 12

For most sites, C > LOQ in all but the last group.



Econazole *UPTAKE* into SC

Econazole nitrate from 3 bioequivalent formulations measured in duplicate (n=14)



A = Clay-Park (Generic)

B = Ortho (RLD)

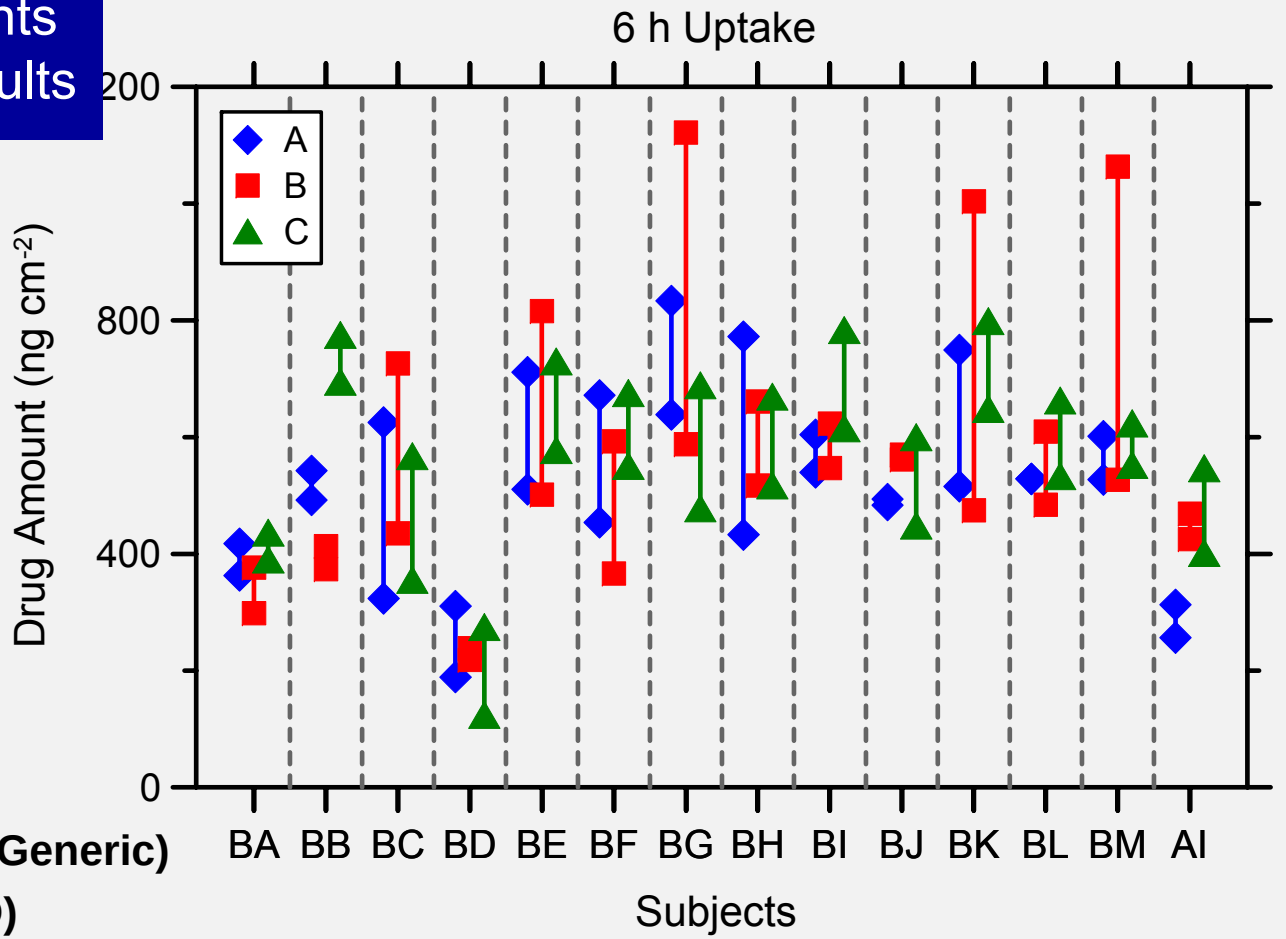
C = Taro (Generic)

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

Econazole *UPTAKE* into SC

Duplication of measurements improved results

from 3 bioequivalent formulations measured in duplicate (n=14)



A = Clay-Park (Generic)

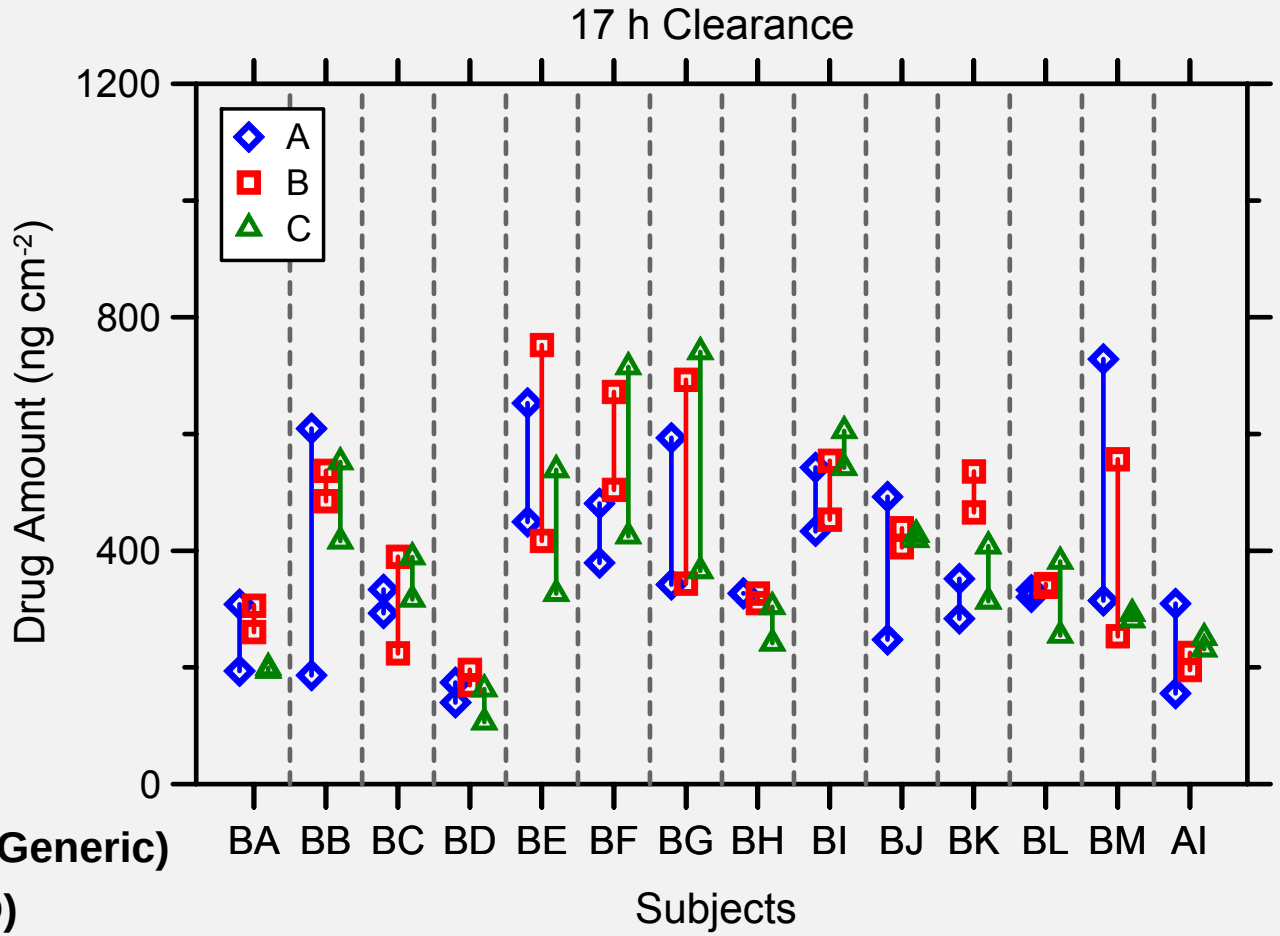
B = Ortho (RLD)

C = Taro (Generic)

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

Econazole *CLEARANCE* from SC

Econazole nitrate from 3 bioequivalent formulations measured in duplicate (n=14)



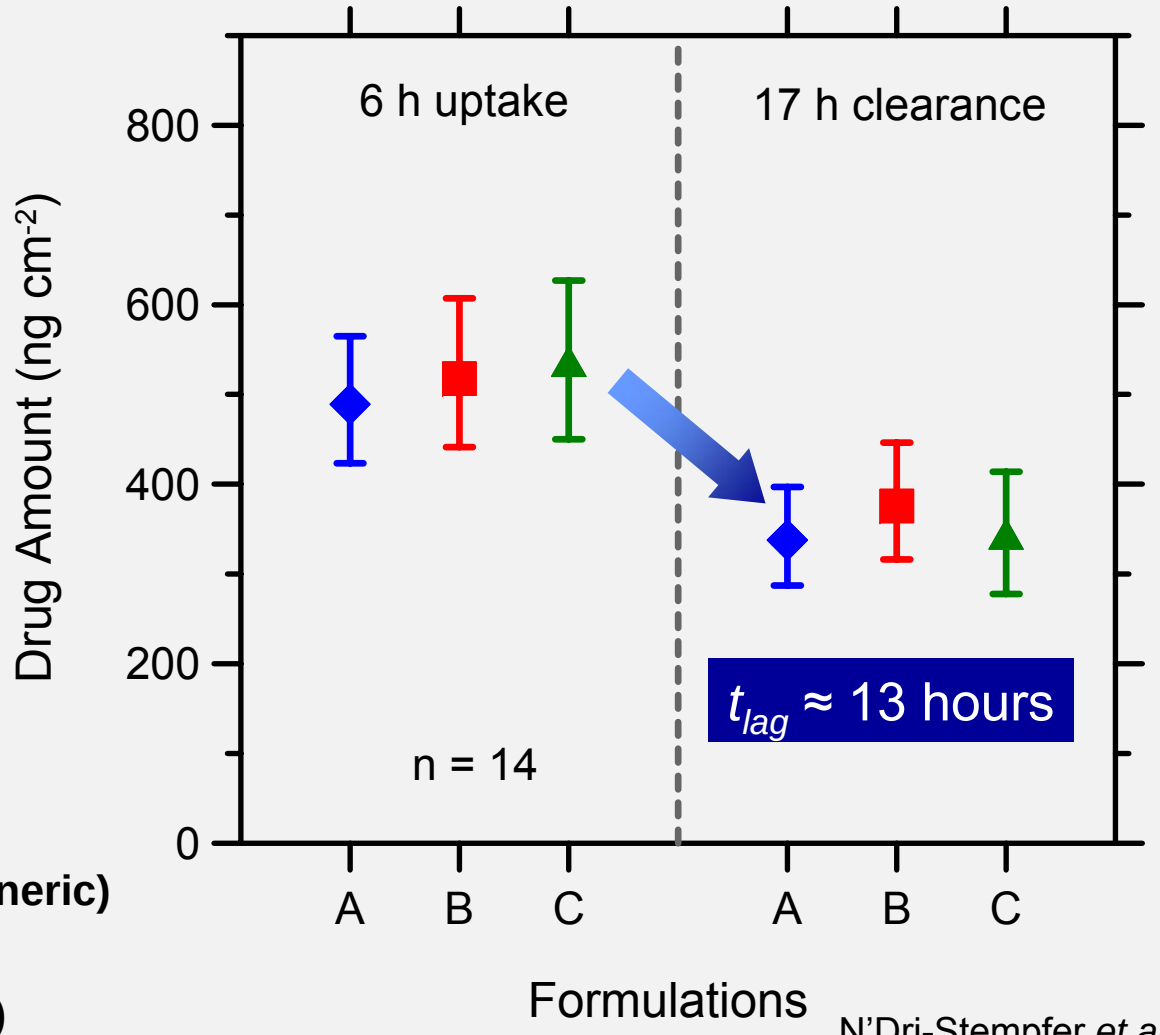
A = Clay-Park (Generic)

B = Ortho (RLD)

C = Taro (Generic)

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

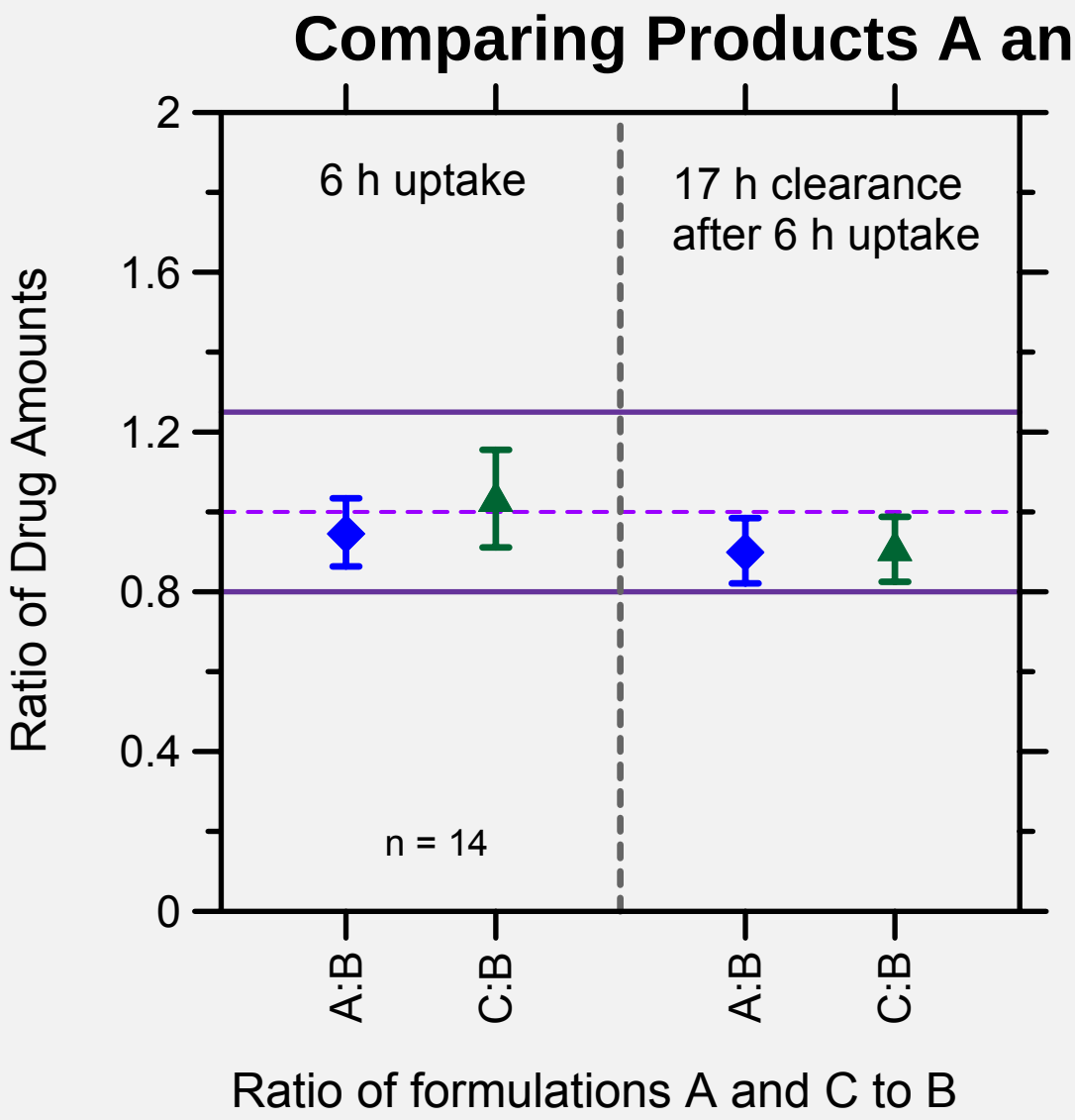
Econazole in SC: *Average drug amounts*



A = Clay-Park (Generic)
B = Ortho (RLD)
C = Taro (Generic)

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

Econazole in SC: *BE assessment*

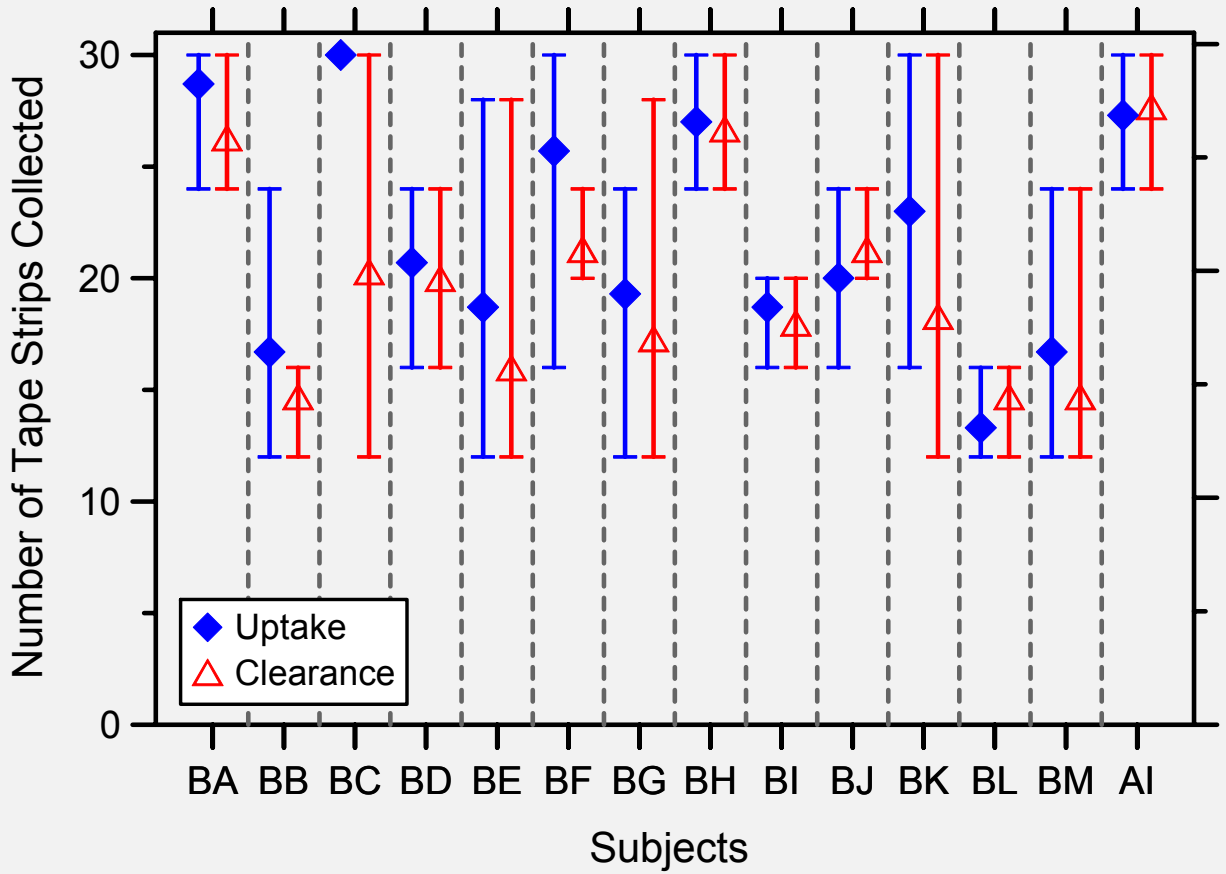


- Both A and C were conclusively BE with B after uptake and clearance, evaluated separately.
- Only 168 sites (3 products in 14 subjects with replicates for uptake & clearance = 3 x 14 x 2 x 2)
- Compare with 1176 sites in tretinoin gel study (3 products in 49 subjects with 8 sites/product = 3 x 49 x 8)

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

Number of tape strips collected

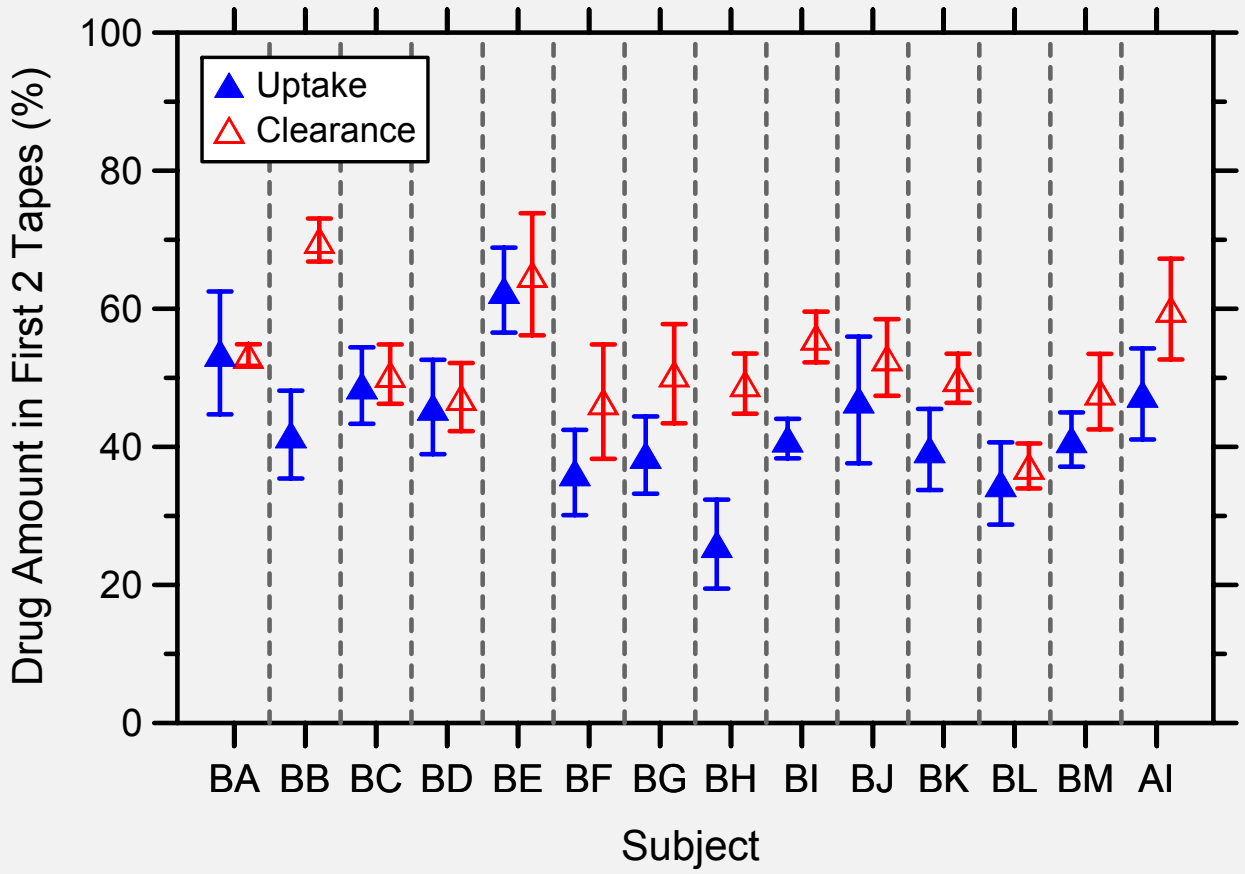
6 uptake sites and 6 clearance sites



- Symbol = mean number
- Error bars = maximum and minimum number
- Number of tape strips collected varied within and between subjects

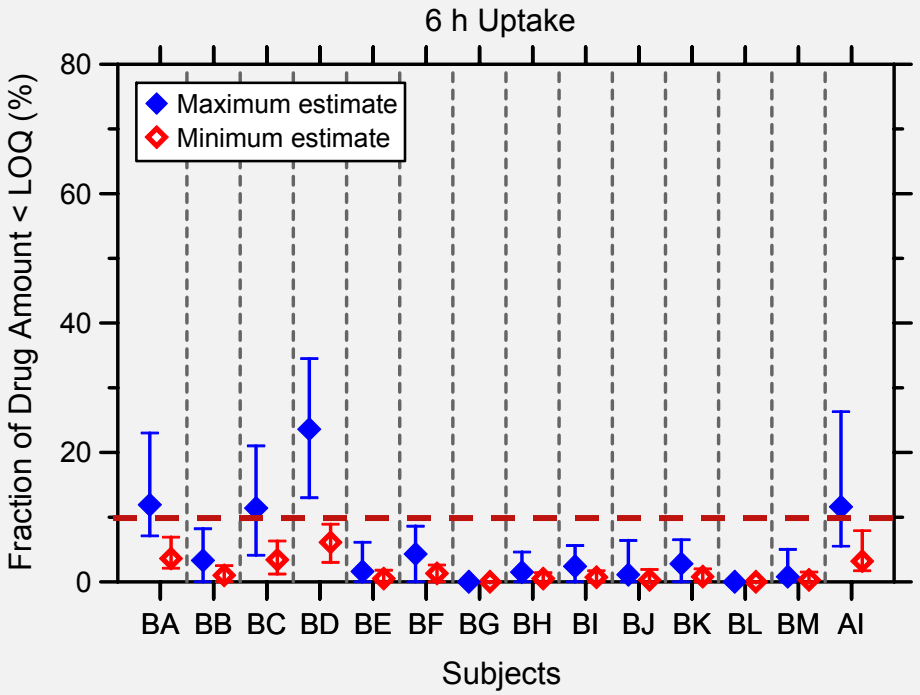
N'Dri-Stempfer *et al*., Pharm Res, 2009

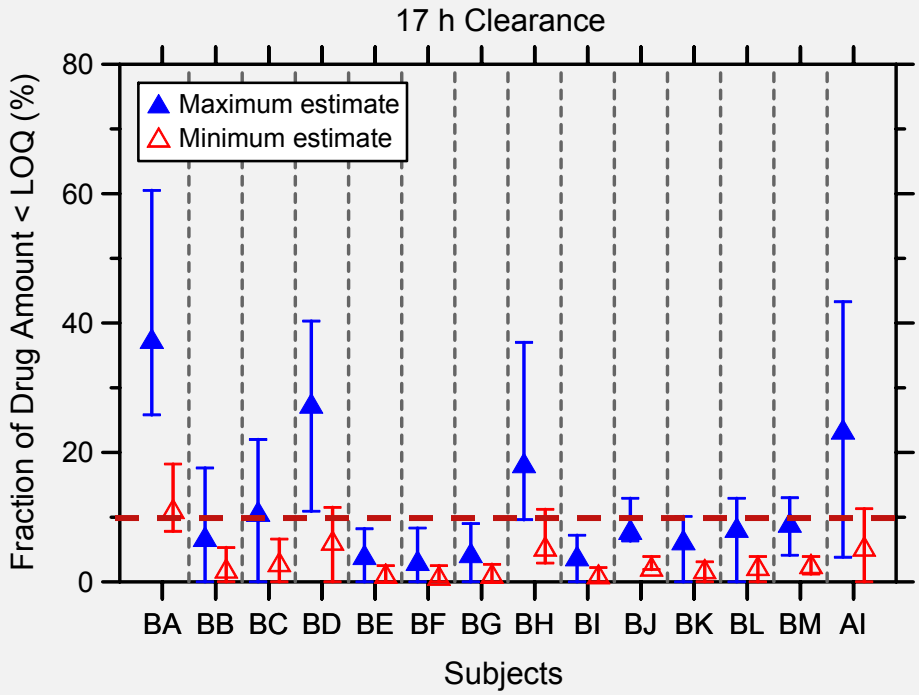
Drug amount in first 2 tape strips



- Mean ± 1 standard deviation
- Significant & variable fraction (30-70%) of drug is in first 2 tape strips
- Not including drug from first 2 strips would greatly increase variability in the amount of drug

Estimated drug amount < LOQ





$$(\text{Maximum amount} < \text{LOQ}) = (N_{\text{tapes}<\text{LOQ}})*\text{LOQ} + (N_{\text{tapes}<\text{LOD}})*\text{LOD}$$

$$(\text{Minimum amount} < \text{LOQ}) = (N_{\text{tapes}<\text{LOQ}})*\text{LOD} + (N_{\text{tapes}<\text{LOD}})*0$$

- Typically, less than 10% of the measured amount of drug < LOQ
- Fraction < LOQ is slightly larger for clearance than uptake

“Improved protocol” developed for FDA

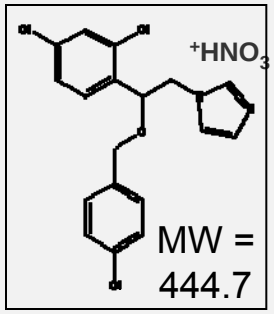
- Econazo
- 4 treatm
  - 1 uptake time (0 h), enough drug
  - 1 clearance time (17 h); enough drug & convenient for subjects
  - Duplicate d
- Unabsorbed hol wipes
- Determine a of the SC
  - Remove SC until TEWL > 8 x (TEWL before stripping)
  - At least 12 tape strips, but not more than 30 tape strips
  - Tape stripping area < drug application area (control both areas)
- BE of uptake and clearance were assessed separately
- Analyze tape strips in groups to optimize analytical sensitivity

Report delivered to FDA January 2007

WHAT HAPPENED?

NOTHING

No change has occurred at FDA with respect to the use of DPK



BE of Topical Drugs: *Japanese Division of Drugs*

Guideline for Bioequivalence Studies of Generic Products for Topical Use

July 7, 2003

局所皮膚適用製剤の後発医薬品のための
生物学的同等性試験ガイドライン

http://www.nihs.go.jp/drug/DrugDiv-E.html

BE of Topical Drugs: *Japanese Division of Drugs*

Bioequivalence Study Options for Topicals

- Clinical study (therapeutic response)
- Pharmacological study (vasoconstriction) **Applicable to steroids**
- Dermatopharmacokinetic (DPK) study
  - Site of action is either in or below the stratum corneum (SC)
  - Drug product does not damage the SC

BE of Topical Drugs: *Japanese Division of Drugs*

DPK Bioequivalence Study Guidelines

- Compare same amount of same active in same dosage form
- Extended in 2006 for addition of dosage forms (if new form has the same amount of the same active)
- Measured at 1 time: steady state after only one application
- Replication recommended to reduce study variability
- “Normal” healthy skin in healthy volunteers without occlusion (unless prescribed in application method)
- Control skin condition (environment)
- Detailed standard operating procedures for application, cleaning, tape stripping, and chemical analysis

BE of Topical Drugs: *Japanese Division of Drugs*

DPK Bioequivalence Study Guidelines (more)

Because the 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

BE of Topical Drugs: *Japanese Division of Drugs*

DPK Bioequivalence Study Guidelines

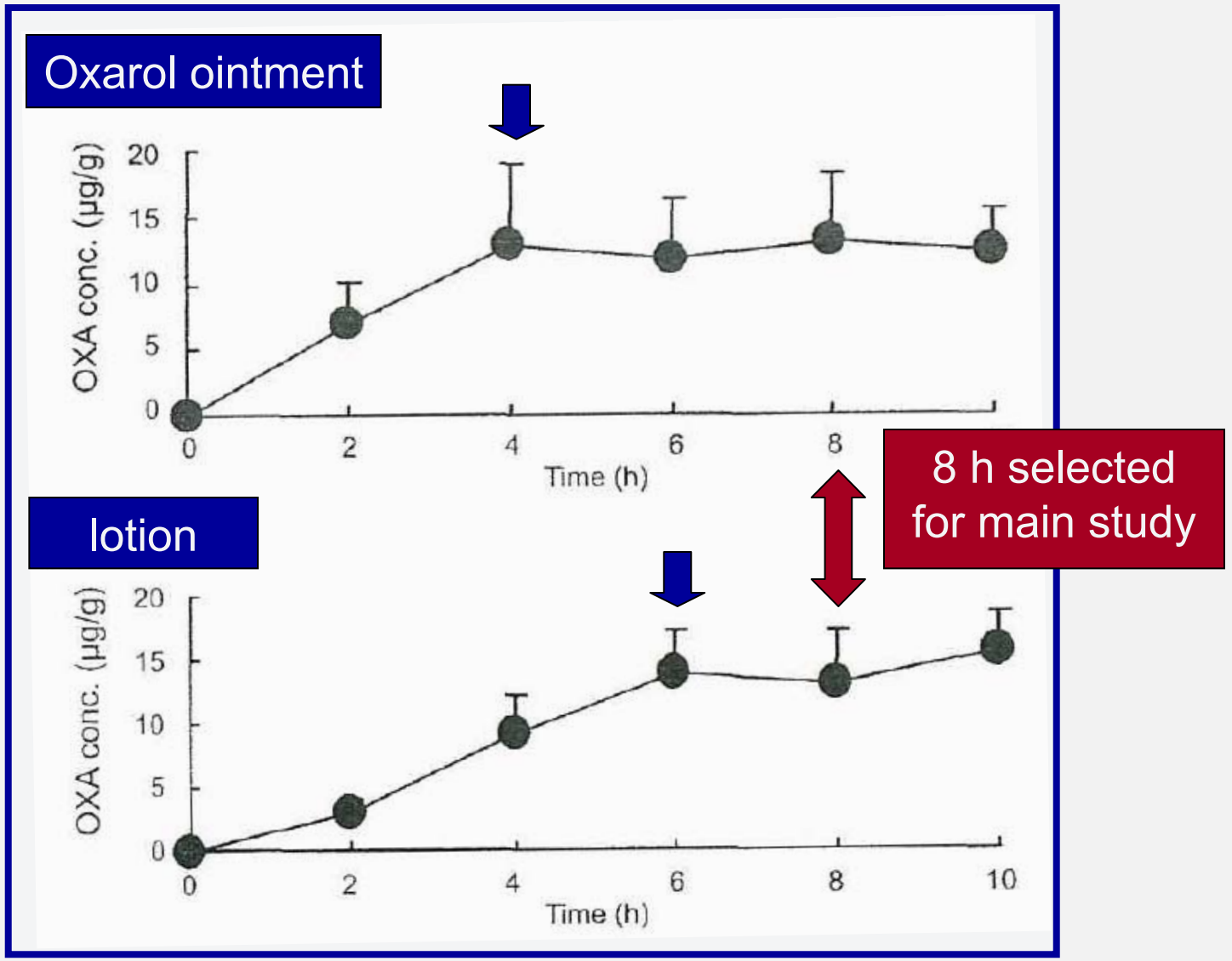
EXAMPLE DPK STUDY

Umemura K, Ikeda Y, Kondo K, Hirata K, Amagishi H, Ishihama Y and Tokura Y, Cutaneous pharmacokinetics of topically applied maxacalcitol ointment and lotion, Int J Clin Pharmacol Ther, 46, 289-294 (2008)

DPK of Maxacalcitol from ointment & lotion

- Maxacalcitol is 1α,25-dihydroxy-22 oxavitamin D_3
- Treatment of psoriasis
- Compare lotion (new dosage form) to *Oxarol* ointment (approved dosage form)
- 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
- Two studies
  - Study 1: Pilot study to assess time to reach steady state for lotion and ointment
  - Study 2: Main study assessing bioequivalence at steady state

Study 1 Results



Study 2 Results

Each product was replicated in each subject
(2 treatment sites x 2 products = 4 treatment sites total)

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

To establish bioequivalence: 90% confidence interval must be between 80 and 125%

Lotion and ointment are BE (confirmed by clinical study)

Assessing BA & BE by Tape stripping: *Summary*

- Dermatopharmacokinetic (DPK) as specified by FDA in 1998
  - Measure concentration versus time
  - Determine AUC and A_{max}
  - Requires measurements at many different times (lots of data)
- Measure concentration (C) versus position (x/L) in SC
  - Measure SC thickness (L)
  - Regress mathematical model of C versus x/L to data
  - Determine diffusion and partition coefficient
  - Calculate steady-state permeability (flux) or average concentration
- Collect and measure the amount of nearly all drug in the SC at a specified time
  - Collect nearly all of the drug by collecting nearly all of the SC
  - If nearly all of the SC is collected, L does not need to be determined

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Many chemical analyses are required, but can distinguish between the effects of rate and extent on flux.

- Collect and measure the amount of nearly all drug in the SC at a specified time
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Simplest approach requiring fewest analyses, but provides less information than C vs. x/L

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Many chemical analyses are required, but can distinguish between the effects of rate and extent on flux.

- **Insensitive to differences in efficiency of SC collection on tapes**
- **Lab-to-lab differences should be minimized**

- C unt of nearly all drug in the SC at
  - Collect nearly all of the drug by collectin
  - If nearly all of the SC is collected, L does

Simplest approach requiring fewest analyses, but provides less information than C vs. x/L

Acknowledgements

- Econazole tape strip study
  - United States Food and Drug Administration
  - Berthe N'Dri Stempfer and Amanda Bowers
  - William Navidi (statistics) and Richard Guy (consultant)
  - Volunteers
- Concentration versus position studies
  - Richard Guy
  - Students and post-docs in the "Guy" lab

No endorsement from the FDA or US government should be inferred.