Dermatopharmacokinetics:

Improvement of Methodology for Assessing Bioequivalence of Topical Products

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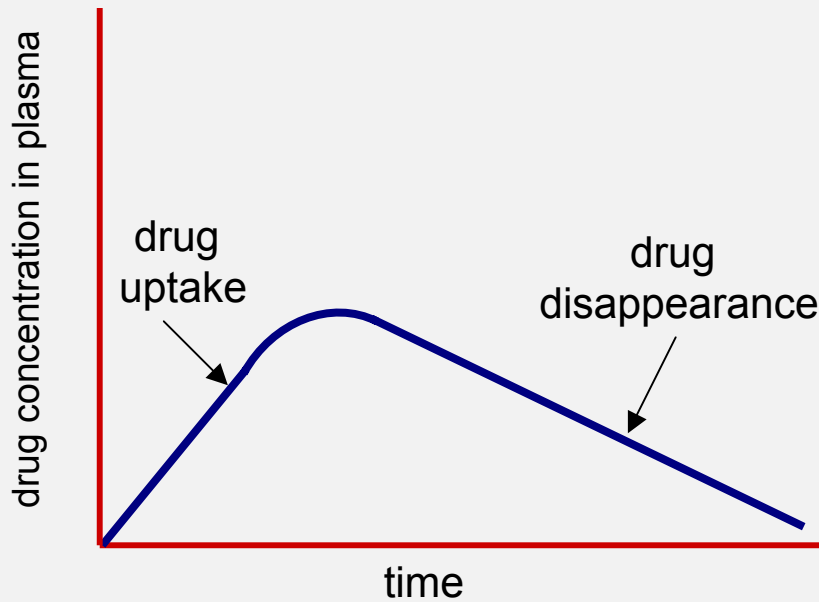
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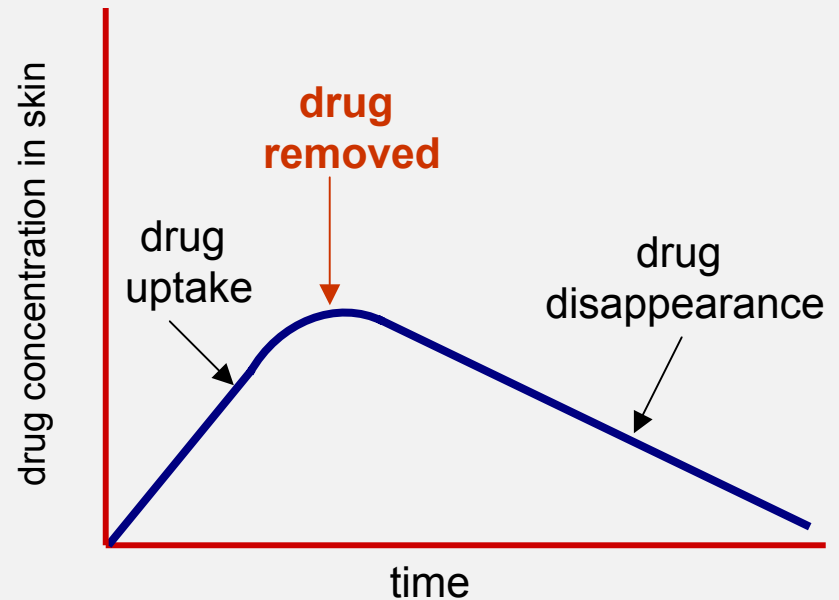
Universites de Geneve et Lyon, France

UNIVERSITÉ DE GENÈVE

DPK for topical drug assessment

Similar to pharmacokinetic methods for oral drug assessment

oral drug assessment — drug concentration in plasma vs time (drug uptake, drug disappearance)

topical drug assessment — drug concentration in skin vs time (drug uptake, drug removed, drug disappearance)

***oral drug assessment***   ***topical drug assessment***

The motivation for a DPK method

- Clinical trials are...
  - Expensive, time-consuming, "relatively insensitive"
- Need to facilitate formulation development and regulatory approval while assuring safety/efficacy
  - BA/BE assessment of generic topical dermatological drugs
  - New topical formulations
- For topicals, there are few recognized 'surrogate' measures available to replace clinical studies
  - For certain compounds, a 'pharmacodynamic response' may be used to assess BE
  - e.g., the vasoconstriction (skin blanching) assay for corticosteroids

Sampling the Skin: *Tape stripping*

Determination of drug concentration in the stratum corneum (SC) by sequential removal of thin layers of SC at the same site with adhesive tape.
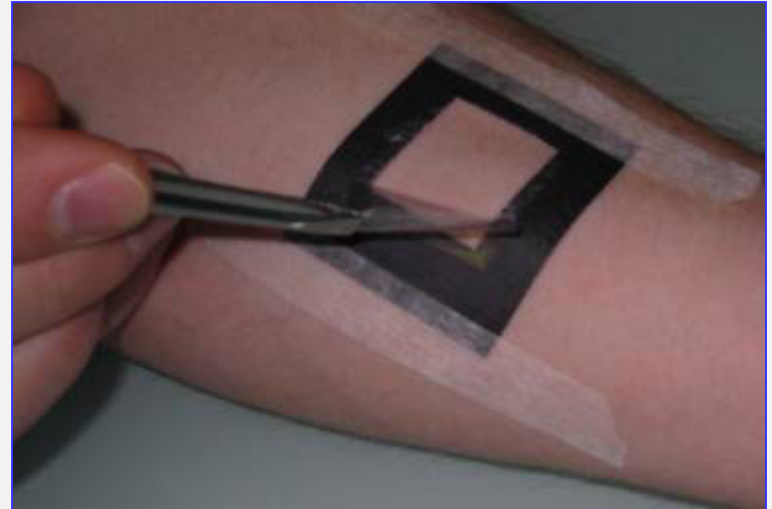
Sampling the Skin: *Tape stripping*

- Relatively non-invasive means of determining distribution of active within the SC

  - Removal of successive SC layers and assaying active concentrations therein

- Basis of the FDA "Dermatopharmacokinetic" (DPK) approach

  - Evaluation of topically applied levels in the *SC*, *in vivo*, as a function of time post-application and post-removal of the formulation
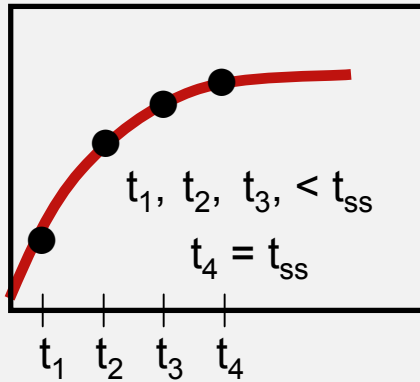
Assumptions for DPK: *Tape stripping*

- For normal, intact skin, the SC is (usually) the rate-determining barrier to percutaneous absorption.

- Concentration of active in *SC* is related to that which diffuses into underlying viable epidermis.

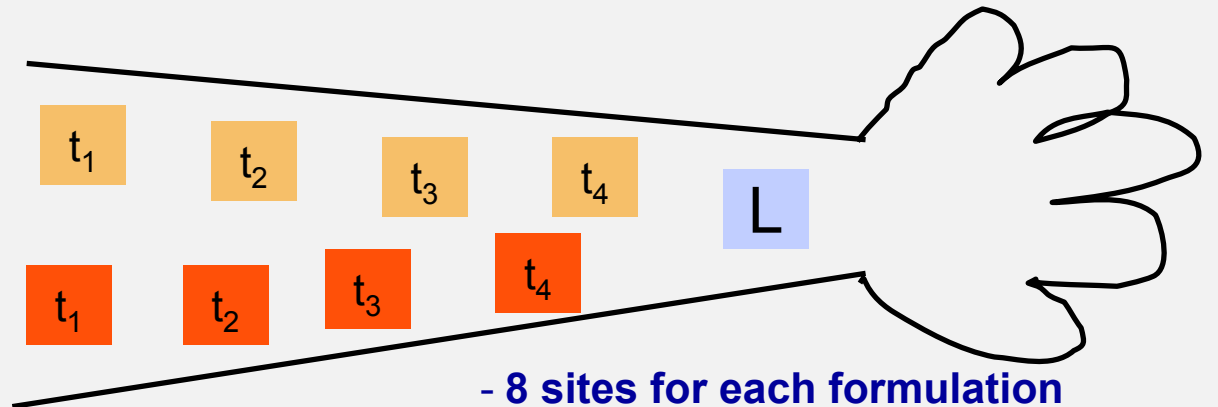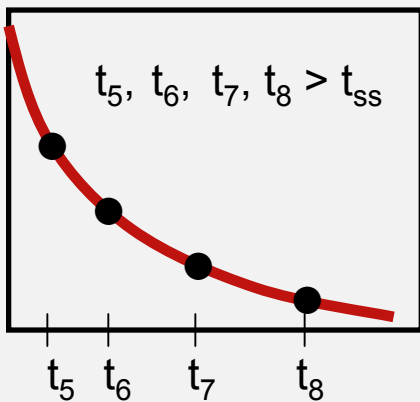- Assessment of local efficacy using *SC* levels is useful and relevant.
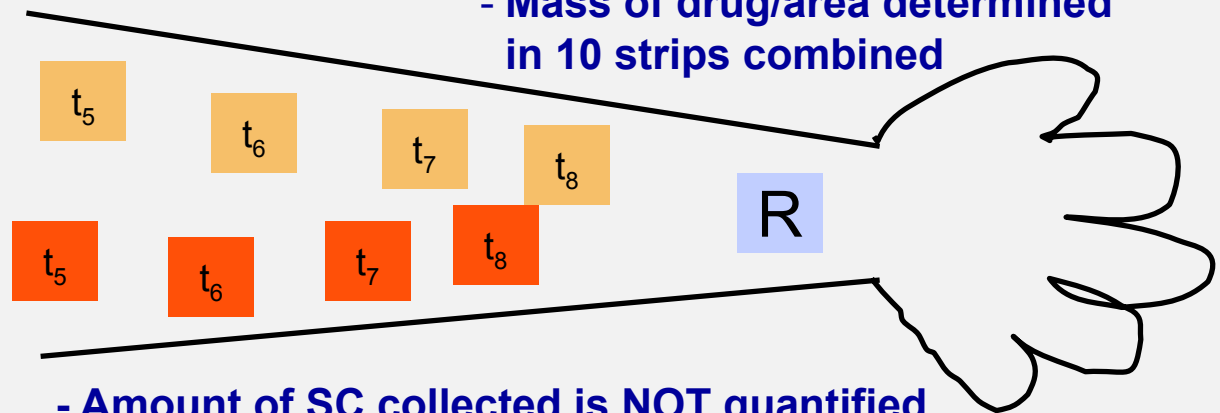
DPK bioequivalence study

test versus reference

Uptake of active

$t_1, t_2, t_3, < t_{ss}$
$t_4 = t_{ss}$

$t_1 \quad t_2 \quad t_3 \quad t_4$

$t_1 \quad t_2 \quad t_3 \quad t_4$

L

$t_1 \quad t_2 \quad t_3 \quad t_4$

- **8 sites for each formulation**
- **12 tape strips collected**
- **First 2 strips "discarded"**
- **Mass of drug/area determined in 10 strips combined**

Elimination of active

$t_5, t_6, t_7, t_8 > t_{ss}$

$t_5 \quad t_6 \quad t_7 \quad t_8$

$t_5 \quad t_6 \quad t_7 \quad t_8$

R

$t_5 \quad t_6 \quad t_7 \quad t_8$

- **Amount of SC collected is <u>NOT</u> quantified**
- **This is like measuring blood level without controlling volume**

DPK bioequivalence study: *Example 1*

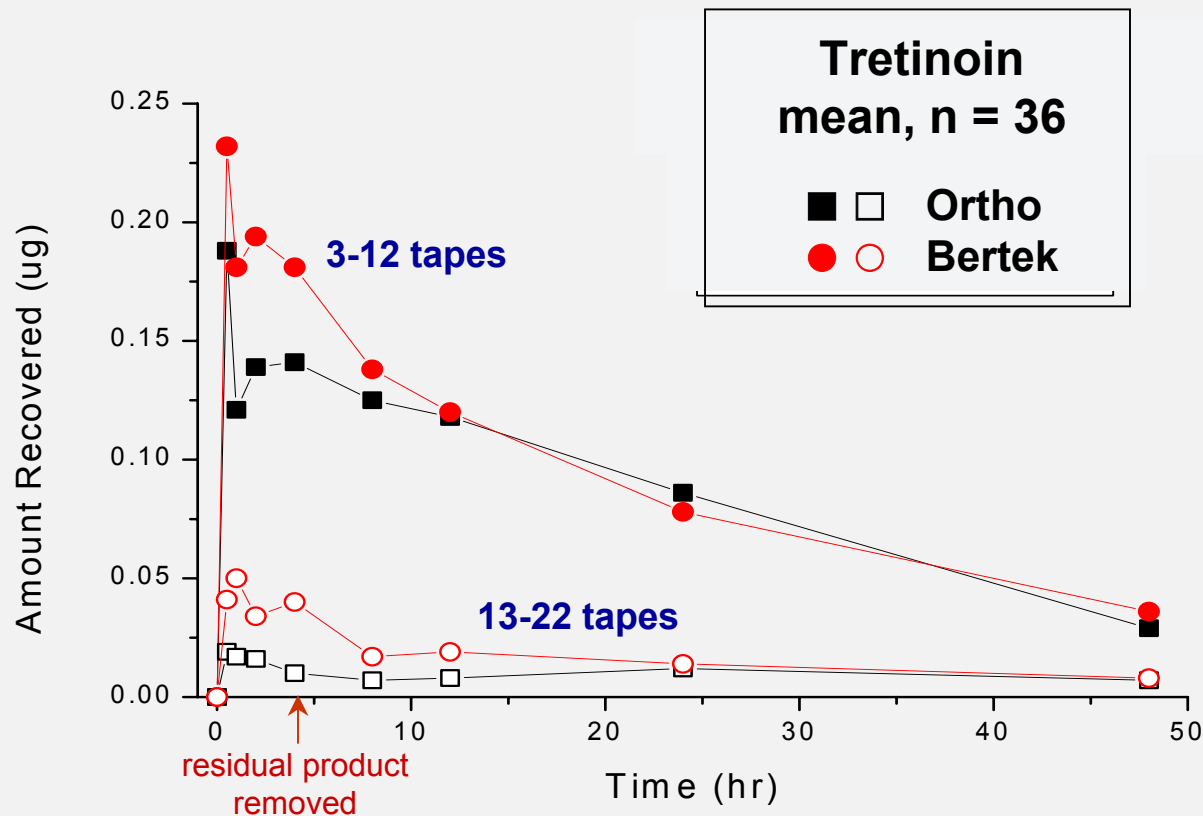## DPK bioequivalence assessment
Tretinoin gel, 0.025%
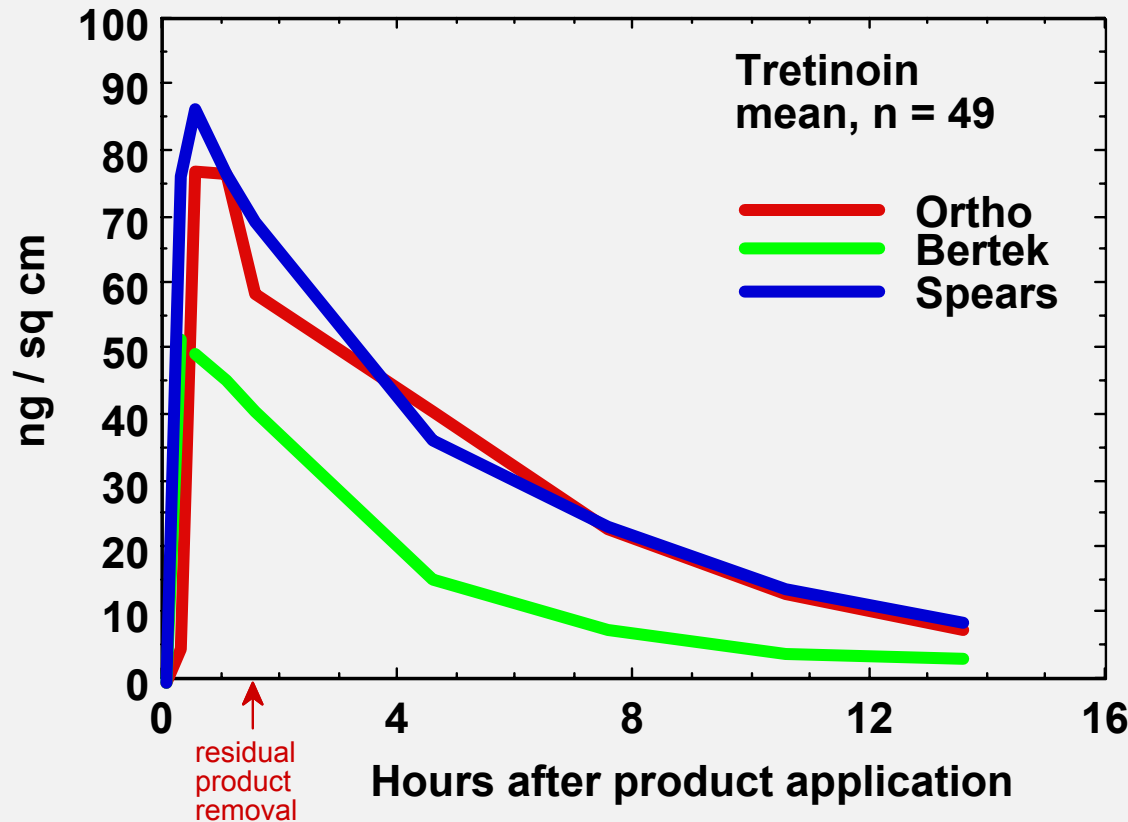
Drug Removed

0.25, 0.5, 1, 1.5 h

Tape Stripped

0.25, 0.5, 1, 1.5 h
3, 6, 9, 12 h

Ortho = Spears
Ortho ≠ Bertek
Ortho > Bertek

Pershing et al., 2003

DPK bioequivalence study: *Example 2*

DPK bioequivalence assessment
Tretinoin gel, 0.025%

Tretinoin mean, n = 36

■ □ Ortho
● ○ Bertek

3-12 tapes

13-22 tapes

Amount Recovered (ug)

Time (hr)

residual product removed

Drug Removed

0.5, 1, 2, 4 h

Tape Stripped

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

Ortho ≠ Bertek
Ortho < Bertek

Franz, FDA-ACPS, 11/29/2001

Why the lab-to-lab differences?

Control of application area
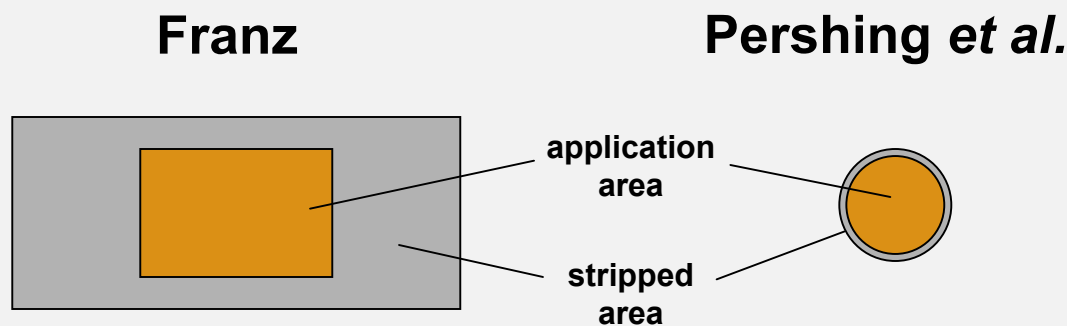
	Franz	Pershing *et al.*
Area of Application	4 cm² (uncontrolled)	1.13 cm² (controlled)
Amount Applied	20 μL	5 μL
Area Stripped	10 cm²	1.33 cm²
Tape Used	Transpore (3M)	D-Squame (Cuderm)

application area

stripped area

Why the lab-to-lab differences?

Control of application area

2 minutes

Bertek   Ortho   Spear

Conner, FDA-ACPS, 11/29/2001

Why the lab-to-lab differences?

Control of application area

Conner, FDA-ACPS, 11/29/2001
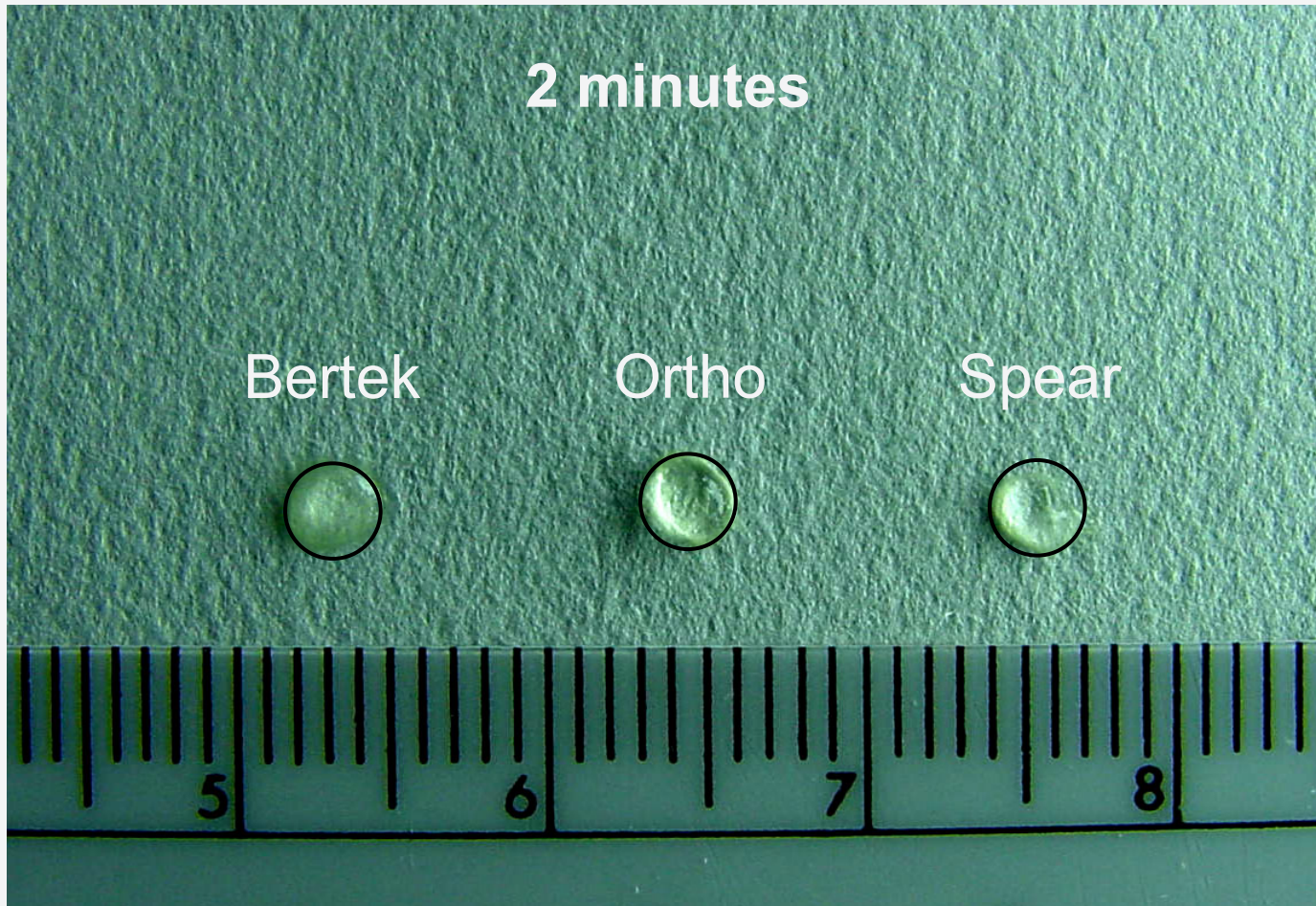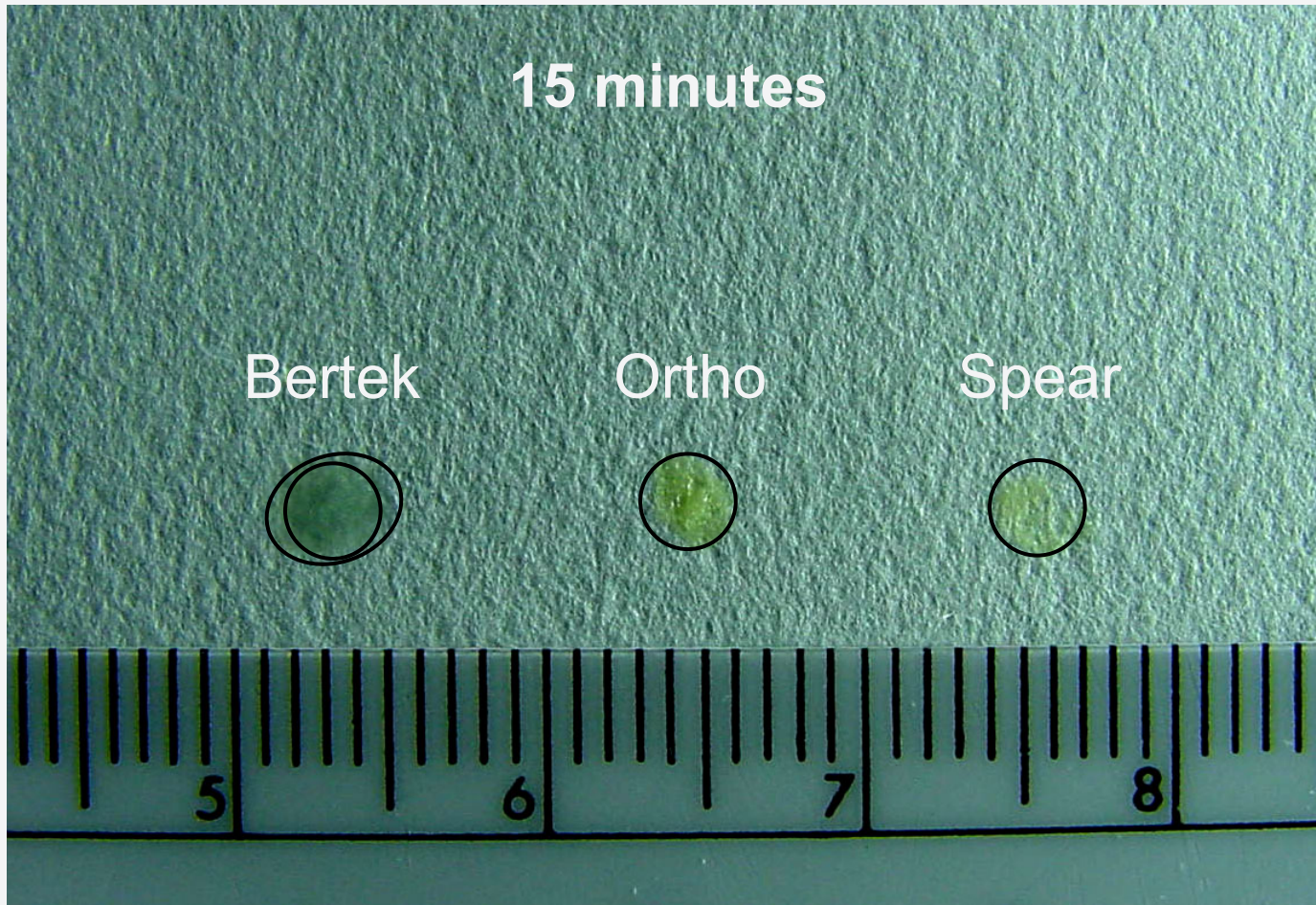
Concerns about the DPK method

- Reproducibility of the method between laboratories
- Effect of excipients on skin permeability or therapeutic effect
- Healthy versus diseased skin
- Adequacy of DPK method to assess BE of topical products for which the SC
  - Is not the target organ, or
  - Is not the sole limiting barrier (other pathways exist)

DPK: *Where are we now?*

- Draft guidance was withdrawn May 2002
- DPK is a new and "immature" method
- With further development and limited application, DPK has important potential
- Reducing variability in DPK data is essential
  - Reduce lab-to-lab variability
  - Need to reduce the number of subjects
    - 36 and 49 in the retin-A studies
    - 8 sites/drug & 2 drugs & 50 subjects = 800 experiments
- Sources of variability must be identified

DPK: *Identifying sources of variability*

- New 1-year contract with CSM and U Geneva to begin this process

- New DPK data will be collected

- Thorough examination of previous DPK measurements from our laboratories

- Combine experiments with mathematical modelling of dermal absorption mechanisms to identify the key issues

Sources of Variability: *SC Collection*

	Subject 1	Subject 2	Subject 3	All Subjects
*Mass of SC Collected (μg)	313.4	254.1	225.7	**264.4**
SD	85.5	45.4	60.6	**73.2**
CV%	**27.3%**	**17.9%**	**21.8%**	**27.7%**

*Average of 8 sites, 4 sites on each arm. The same operator for all subjects.
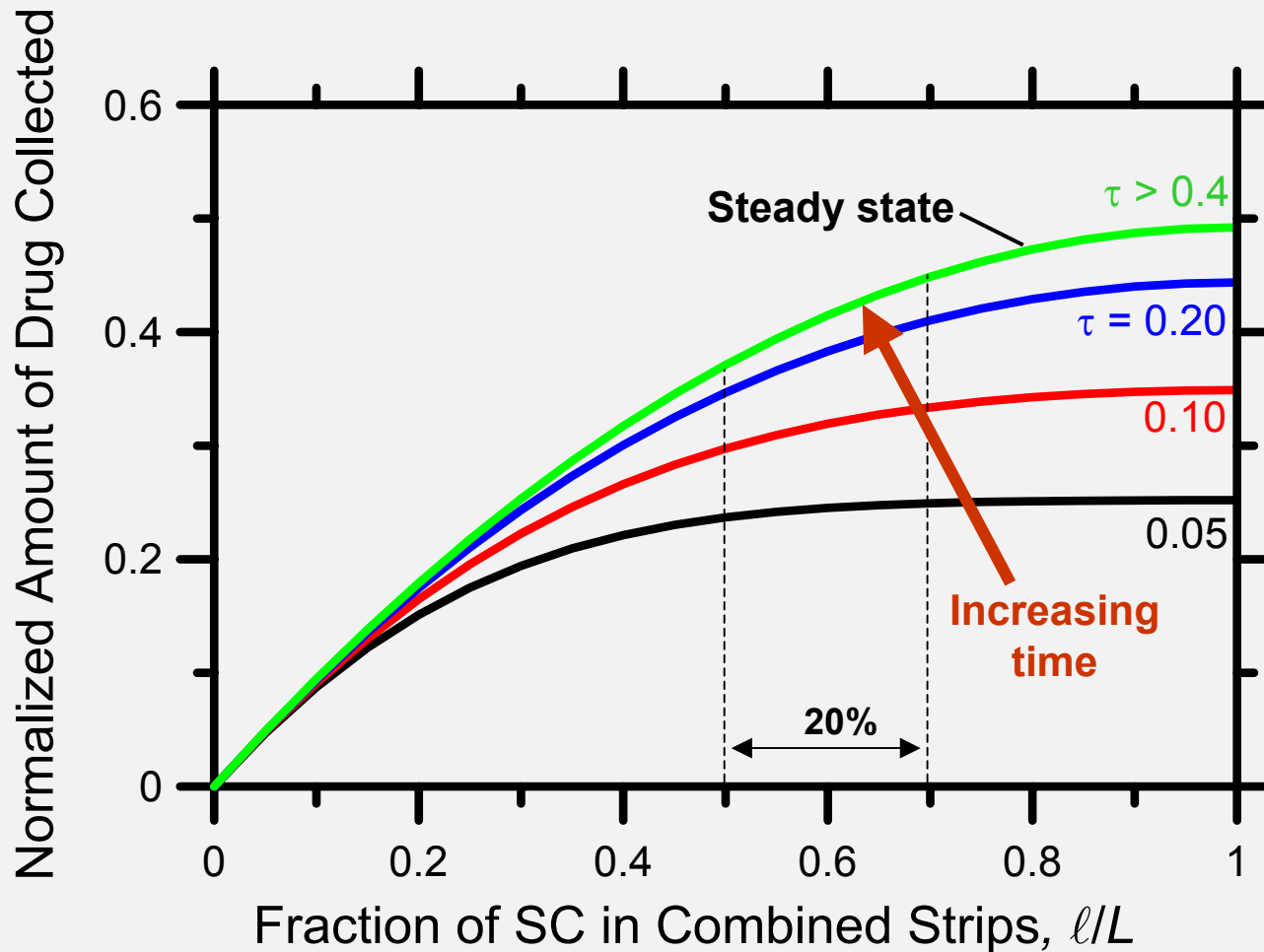
Even for the same operator:

- **The amount of SC collected is highly variable**
- **Variability is the same <u>between</u> subjects and <u>within</u> subjects**
- **The amount of SC collected changes with depth (data not shown)**
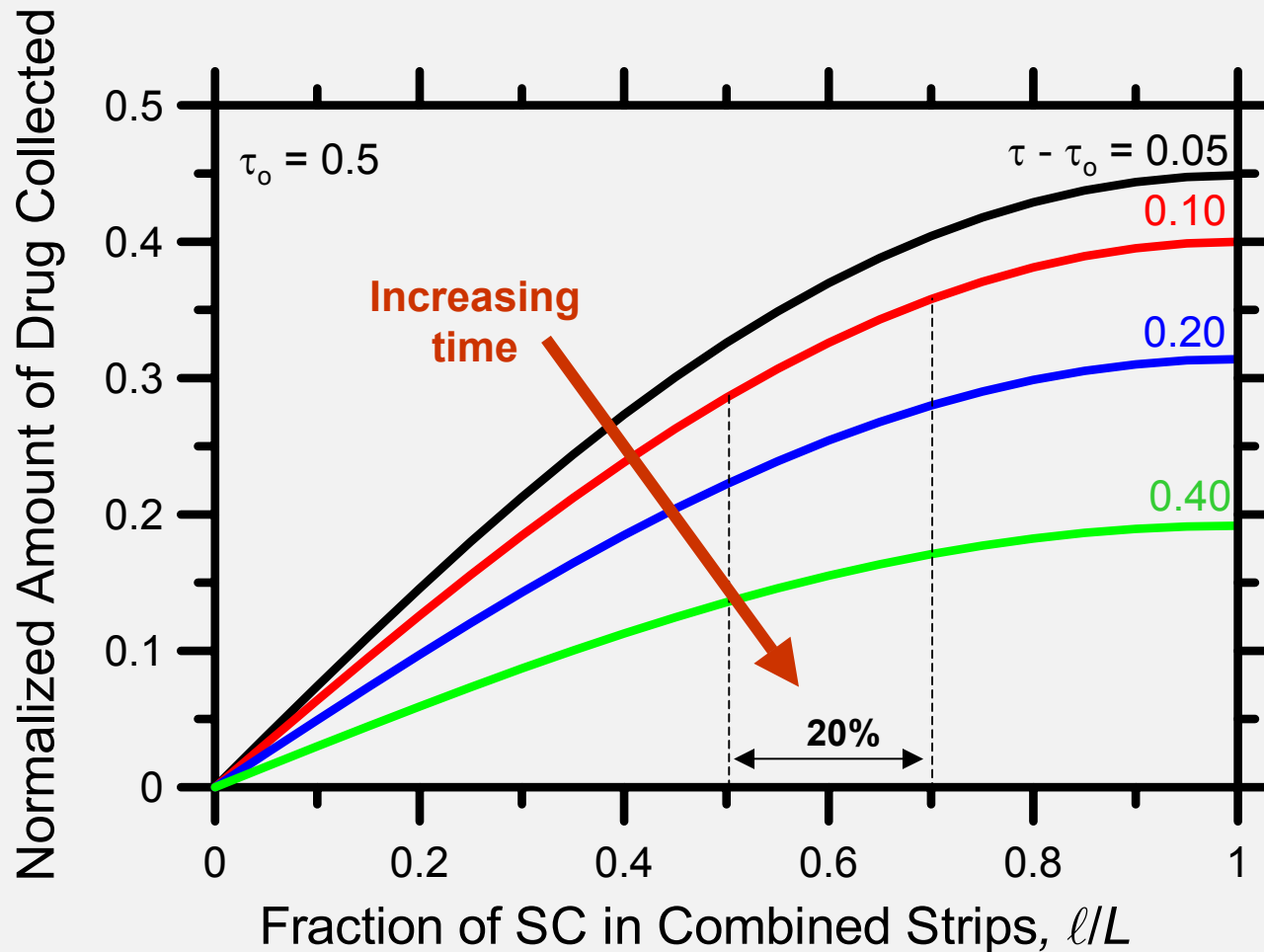- **How does variable SC collection affect the DPK result?**

Uptake
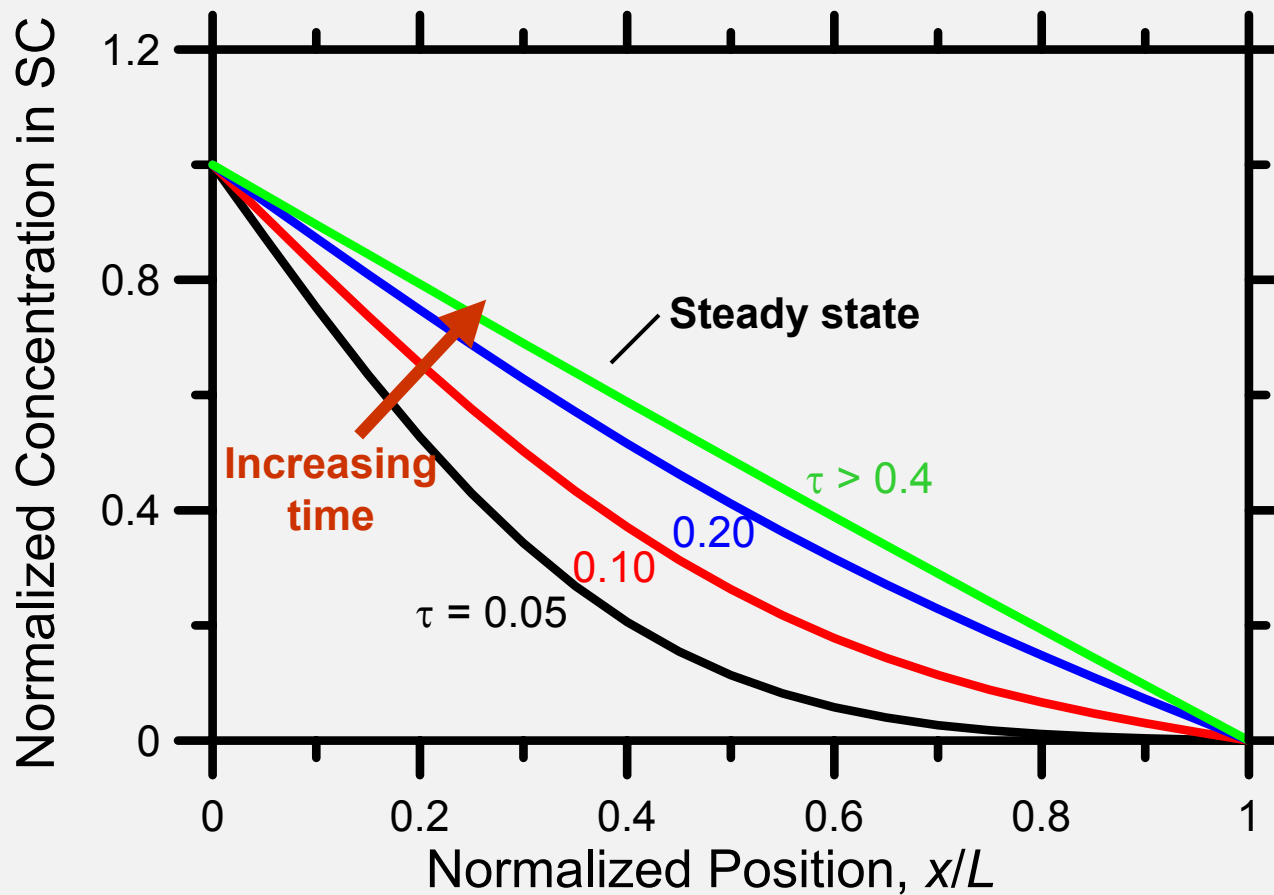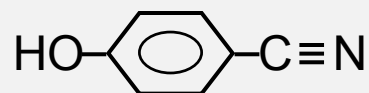
Uptake: *Effect of Variable SC Collection*

Clearance: *Effect of Variable SC Collection*

DPK Data: *Effect of Variable SC Collection*

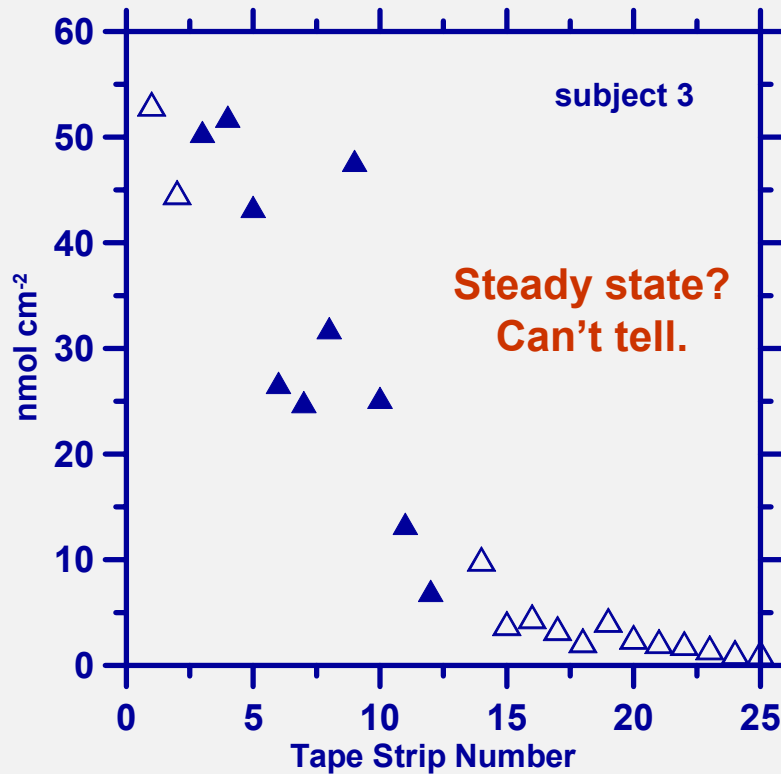## Uptake and Clearance of 4-cyanophenol (CP)

$$HO-\bigcirc-C\equiv N$$

- Applied in a saturated solution of water
- Tape stripping
  - After 1 hour uptake (steady state?)
  - After 1 hour clearance
- For each tape strip, we determined
  - Mass of SC collected
  - CP concentration
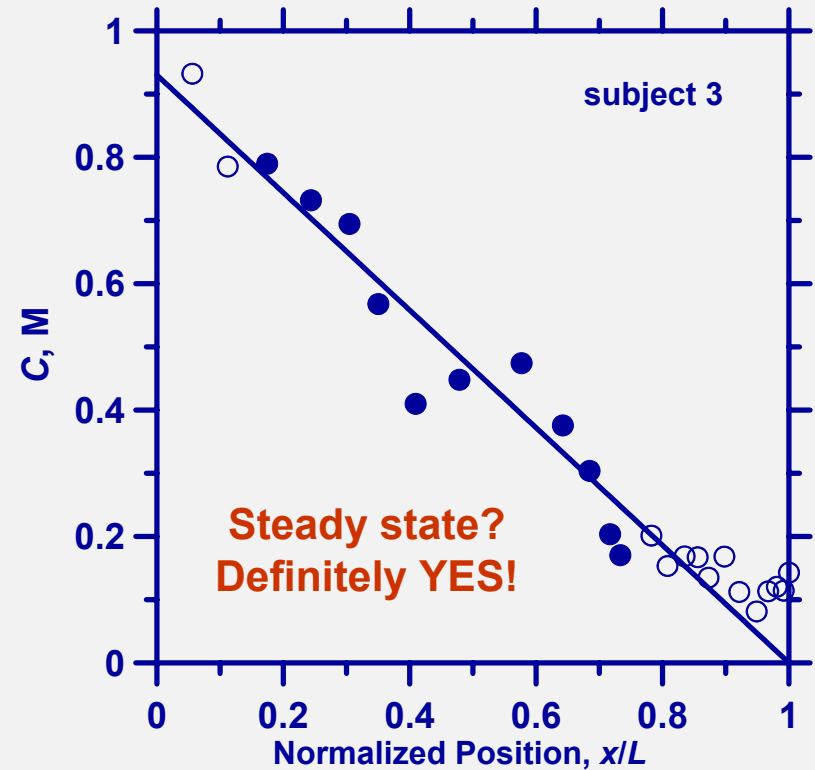
Reddy et al.,Pharm Res, 2002o

DPK Data: *Effect of Variable SC Collection*

Uptake

Amount of Drug = 320 nmol cm⁻²

Average Drug C = 0.465 M

subject 3

Steady state? Can't tell.

subject 3

Steady state? Definitely YES!

DPK Data: *Effect of Variable SC Collection*

Clearance

**Amount of Drug =
147 nmol cm^{-2}**

**Average Drug C =
0.237 M**

subject 3
clearance
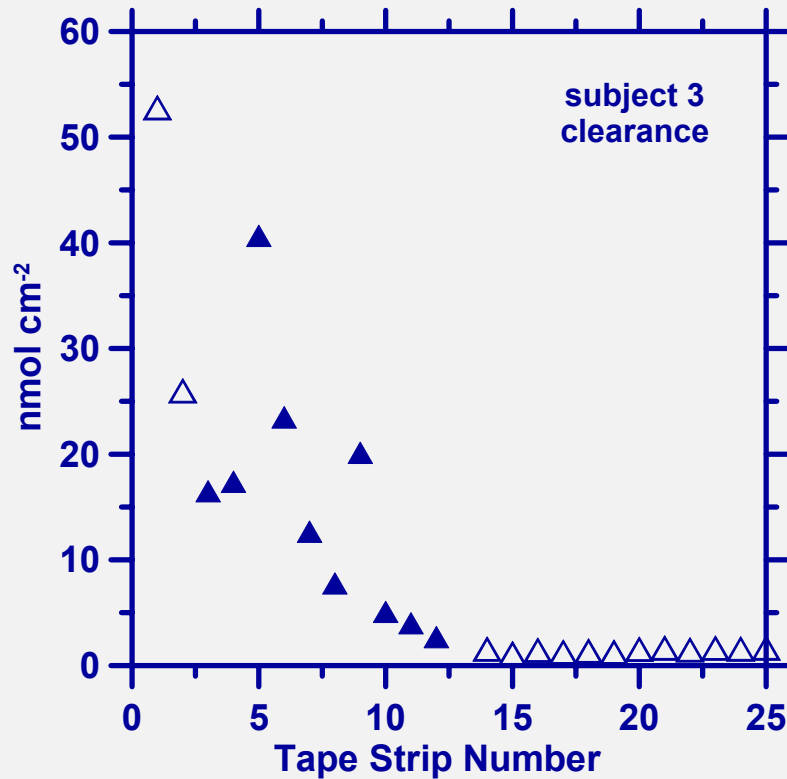
subject 3
clearance
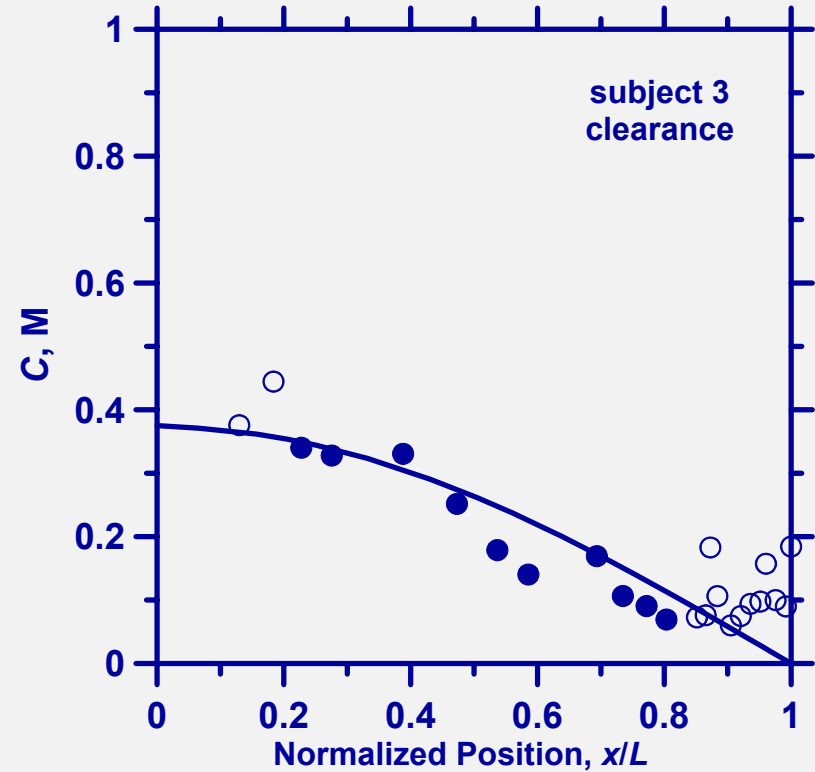
DPK Data: *Effect of Variable SC Collection*

	Uptake Phase		Clearance Phase	
	Average C (M)	**Amount/Area (nmol cm^{-2})**	**Average C (M)**	**Amount/Area (nmol cm^{-2})**
Subject 1	0.548	372	0.260	209
Subject 2	0.534	258	0.236	117
Subject 3	0.465	320	0.237	147
Mean	0.516	317	0.244	158
SD	0.045	57	0.0136	47
CV%	**8.6%**	**18.0%**	**5.6%**	**29.8%**

Variability is reduced significantly by ~

- **Quantifying the amount of SC**
- **Reporting concentration instead of drug amount**

DPK Bioequivalence Protocol: *Japan*

Issued: July 7, 2003

Ch 2.II.1. DPK test (p. 5)

- "The amount of layers of the SC stripped off with one adehsive tape will change depending on the stripping technique of each operator and *will vary between and within subjects*."

- "The recoveries of the SC layers … *will be variable* even if the *number* of adhesive tapes used for the stripping *is specified* in SOP, which lowers the power of the test. "

- "… to increase the power, it may be advantageous to use the *average drug concentration* …"

DPK bioequivalence: *Which metric?*

- Several different DPK metrics can be used to assess bioequivalence

  - ◆ AUC of concentration vs. time curve

  - ◆ Maximum concentration

  - ◆ Clearance rate

- Which should be used?

- Bioavailability is the rate (kinetic) and extent (thermodynamics) of absorption
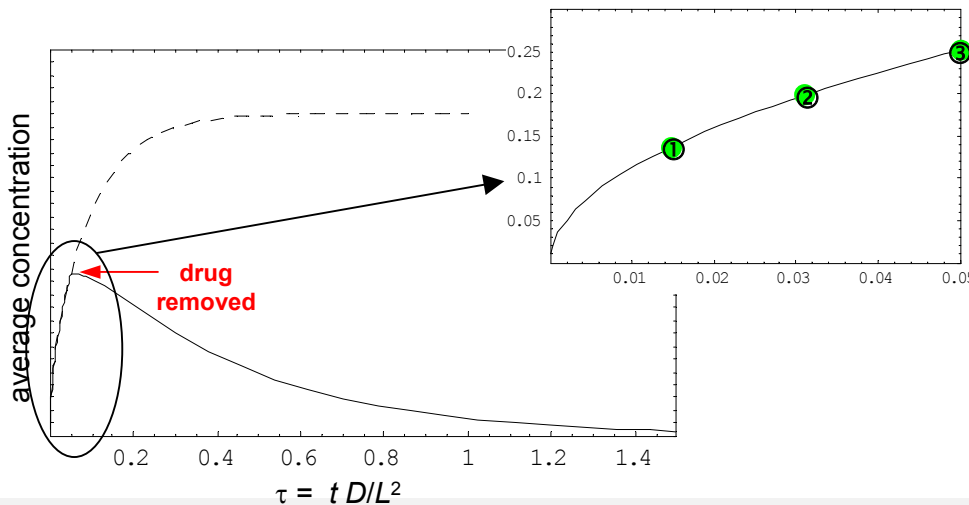
DPK bioequivalence: *Which metric?*

Uptake depends on K & D/L²
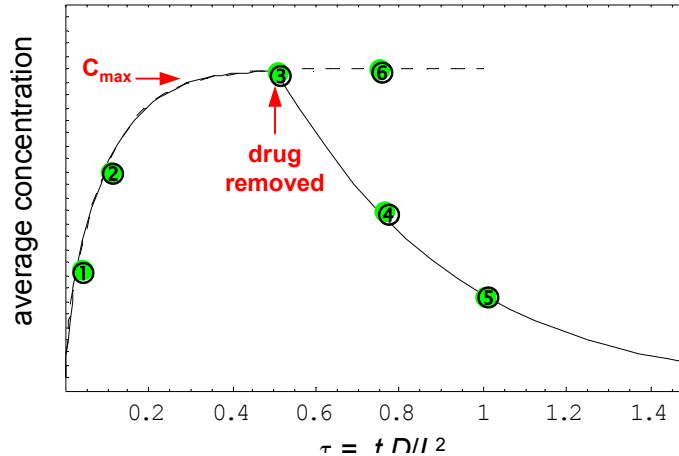
Elimination depends on D/L²

C_{max} depends on duration

Depending on the duration, AUC may weight uptake or elimination more

Improving the DPK method: *Goals*

- Reproducible within and between laboratories
- Minimize the number and the extensiveness of required tests
- Optimize the test design to produce maximum information at minimum cost
- Can be set up in any testing laboratory with reasonable scientific skill
- Has a sound basis in the mechanisms of drug delivery to the SC
- Provide the simplest possible information structure required for a regulatory decision

Improving the DPK method: *Issues*

- Quantification of SC collected

- Quantification of SC thickness

- Control of drug application area

- Method for reproducible drug application

- Protocol needs to be as explicit as needed and no more

Improved DPK method: *Experiments*

- Drug: Clotrimazole (Lotrimin 1% cream by Schering Plough)
  - Antifungal
  - Safe and effective for treatment of athlete's foot, jock itch & ring worm
  - SC is the site of action
- Measure
  - L (thickness of SC)
  - x (location of each tape strip within the SC)
  - ℓ (total amount of SC collected)
  - Amount of drug on each tape strip (HPLC method available)
- Goals
  - Quantify variability
  - Relate variability to mechanisms of dermal absorption
  - Develop methods for reducing variability

Improving the DPK method: *Team*

- Professor Annette Bunge, CSM
    - ¤ Professor of Chemical Engineer
    - ¤ Dermal absorption experiments
    - ¤ Mechanistic modeling of dermal absorption
- Richard Guy, U Geneva
    - ¤ Professor of Pharmacuetical Chemistry
    - ¤ Dermal absorption measurements of pharmaceutical products

Summary

- DPK is a potentially powerful technique
  - May permit facile determination of topical bioavailability/ bioequivalence
  - Allows comparison of formulations
- DPK is a new technique and needs further development
- Variability needs to be reduced
- Validation is required!