

# **Topical Drug Products Regulatory Requirements (USA)**

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**Conference on  
To and Thru the Skin**

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# **Topical Dermatological Drug Products**

- **Designed to deliver drugs to the skin to prevent or to treat skin disease and/or alleviate symptomatology.**

# Topical Dermatological Drug Products

## New Drug Applications (NDA)

- **Safety:** Toxicity Studies  
Skin Irritation  
Cutaneous Toxicity  
Contact Sensitization  
Contact Photodermatitis  
Percutaneous Absorption? Teratogen?
- **Efficacy:** Two Well Controlled Clinical Studies
- **Manufacturing Controls**
- **Bioavailability Studies**
- ***In-Vitro* Release Studies**

# Topical Dermatological Drug Products

## Abbreviated New Drug Applications (ANDA)

- (Safety Studies: Skin Irritation,  
Cutaneous Toxicity)
- Manufacturing Controls
- *In-Vivo* Bioequivalence or Clinical Study
- *In-Vitro* Release Studies
- Inactive Ingredients: Qualitively and  
Quantitively "Same"

# Topical Drug Products

## Key steps for drug absorption

- Release of the drug from the formulation
- Drug penetration – stratum corneum permeability – rate limiting
- Thermodynamic activity is the driving force for absorption
- Formulation can alter barrier properties of the skin (permeability)

# Therapeutic Equivalence

Two drug products are considered to be therapeutic equivalent (TE) if they are pharmaceutically equivalent (PE) and bioequivalent (BE); and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

$$\mathbf{TE = PE + BE}$$

# Pharmaceutical Equivalence

- Same active ingredient
- Same dosage form
- Same route of administration
- Identical strength
- Comparable labeling
- May differ in excipients, shape, packaging, ...

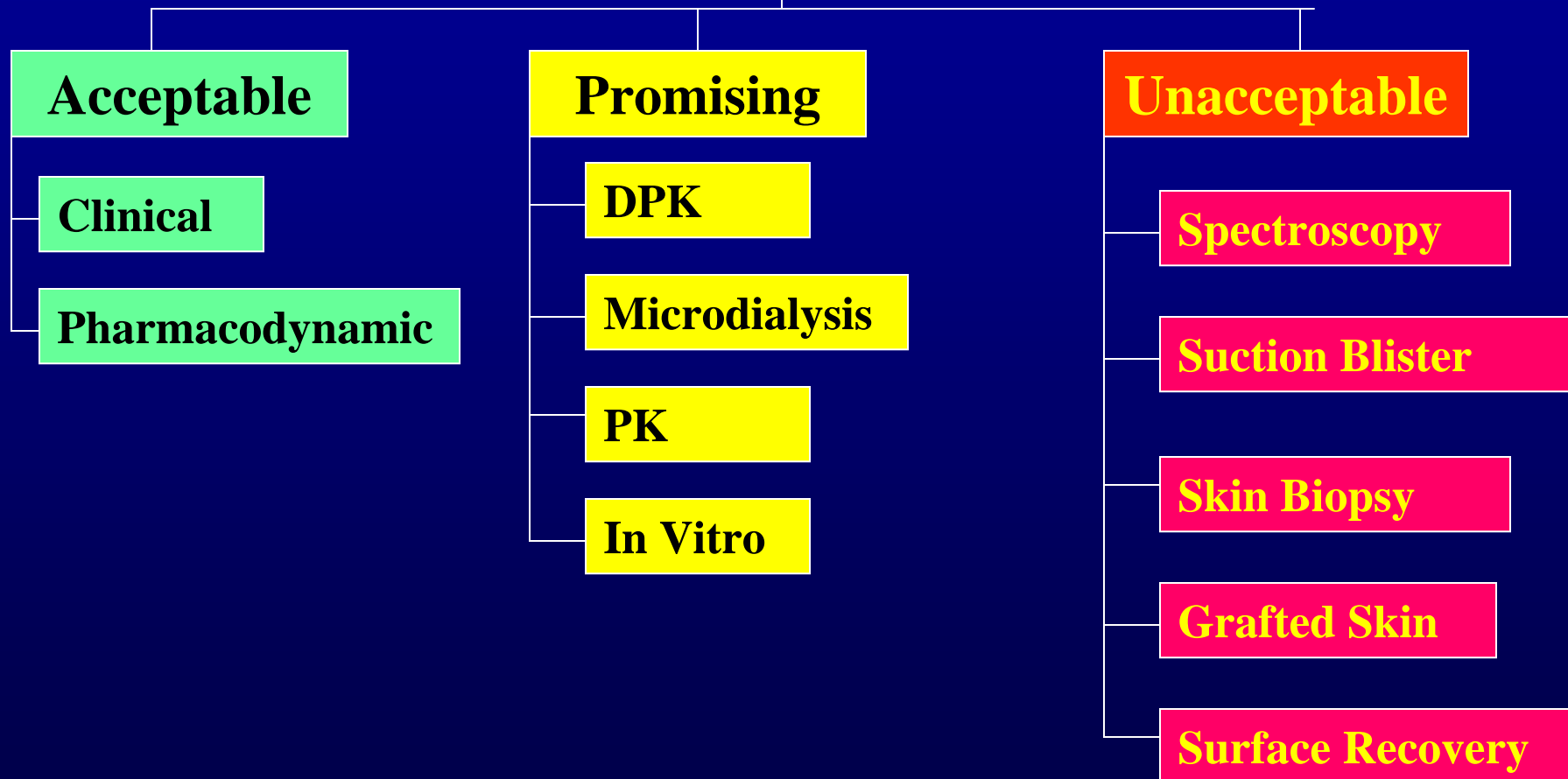
# Locally Acting Drug Products

## Methods for determining BE

- Methods for BE (identified in 21 CFR 320.24)
  - Pharmacokinetic study
  - Pharmacodynamic study
  - Clinical study (comparative clinical trials) and
  - In vitro
- A 2003 addition to the Federal FD & C Act at Section 505 (j)(8)(A)(ii) indicates that “For a drug that is not intended to be absorbed into the bloodstream, the Secretary may assess bioavailability by scientifically valid measurements to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at the site of drug action”.

# *Methods of BE of Topical Dermatological Drug Products*

## Experimental Procedures



# Acceptable Methodology

## *Comparative Clinical Trials*

- Expensive
- Large patient population
- Time consuming
- Difficult to conduct – End points have high variability
- Less sensitive

***Need alternative method to assure  
Bioequivalence and product quality***

# Acceptable Methodology

## *Pharmacodynamic Studies*

- Limited to few classes of drug products
  - Vasoconstriction (blanching) – glucocorticoids

**FDA Guidance: Topical dermatological corticosteroids: In vivo BE. 1995.**

*<http://www.fda.gov/cder/guidance>*

- Trans Epidermal Water Loss ?

# Promising Methodology

*Dermatopharmacokinetics (DPK)*

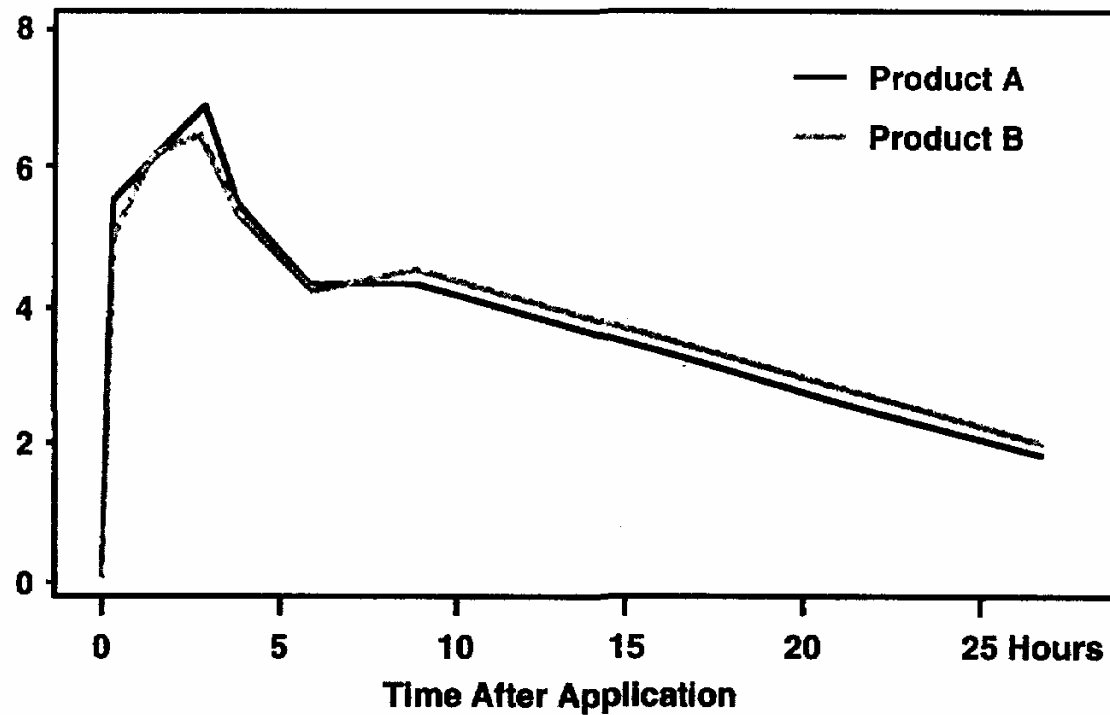
# Dermatopharmacokinetics

- Measurement of drug uptake and elimination from stratum corneum (SC) may provide a dermatokinetic means of assessing BE of two topical drug products.
- Two formulations that produce a comparable drug concentration in SC/time curves may be bioequivalent, just as two oral formulations are judged bioequivalent if they provide comparable plasma concentration/time curves.

# Dermatopharmacokinetics

## Mean Concentrations in Stripped Skin

Concentration (amount/sq cm) area



# Topical Drug Products

## Dermatopharmacokinetics (DPK)

1. BE of topical dermatological dosage forms –  
Methods of evaluation of BE.  
Workshop Report - Pharm Res 15:167-171, 1998.
2. Draft Guidance (withdrawn) Topical  
dermatological drug product NDAs and ANDAs  
– In vivo BA, BE, In vitro release and associated  
studies (1998).

**Assessment of  
dermatopharmacokinetic approach in  
the bioequivalence determination of  
topical tretinoin gel products**

**LK Pershing, JL Nelson, JL Corlett,  
SP Shrivastava, DB Hare and VP Shah**

***J Am Acad Dermatology: 48: 740-751, 2003***

# Tretinoin Research

## Products:

- A. Retin-A gel, 0.025%, Ortho
- B. Tretinoin gel, 0.025%, Spear
- C. Avita tretinoin gel, 0.025%, Bertek

## Clinical Findings:

- Retin-A gel = Tretinoin gel (A=B)
- Retin-A gel  $\neq$  Avita gel (A  $\neq$  C), but Avita gel is effective

**DPK Research: To confirm and validate Clinical Findings, using A, B and C.**

# Tretinoin - DPK Study Comparison

## Pershing Study:

Retin-A = Generic

Retin-A  $\neq$  Avita

Retin A > Avita

## Franz Study:

Retin-A  $\neq$  Avita

Retin A < Avita

**Retin-A (Ortho); Avita (Bertek), Generic (Spear)**

# DPK Study

## *Lessons Learned*

**The methodology must be standardized**

- drug application area
- drug removal area

# **Dermatopharmacokinetics**

**What is needed to have a confidence in DPK?**

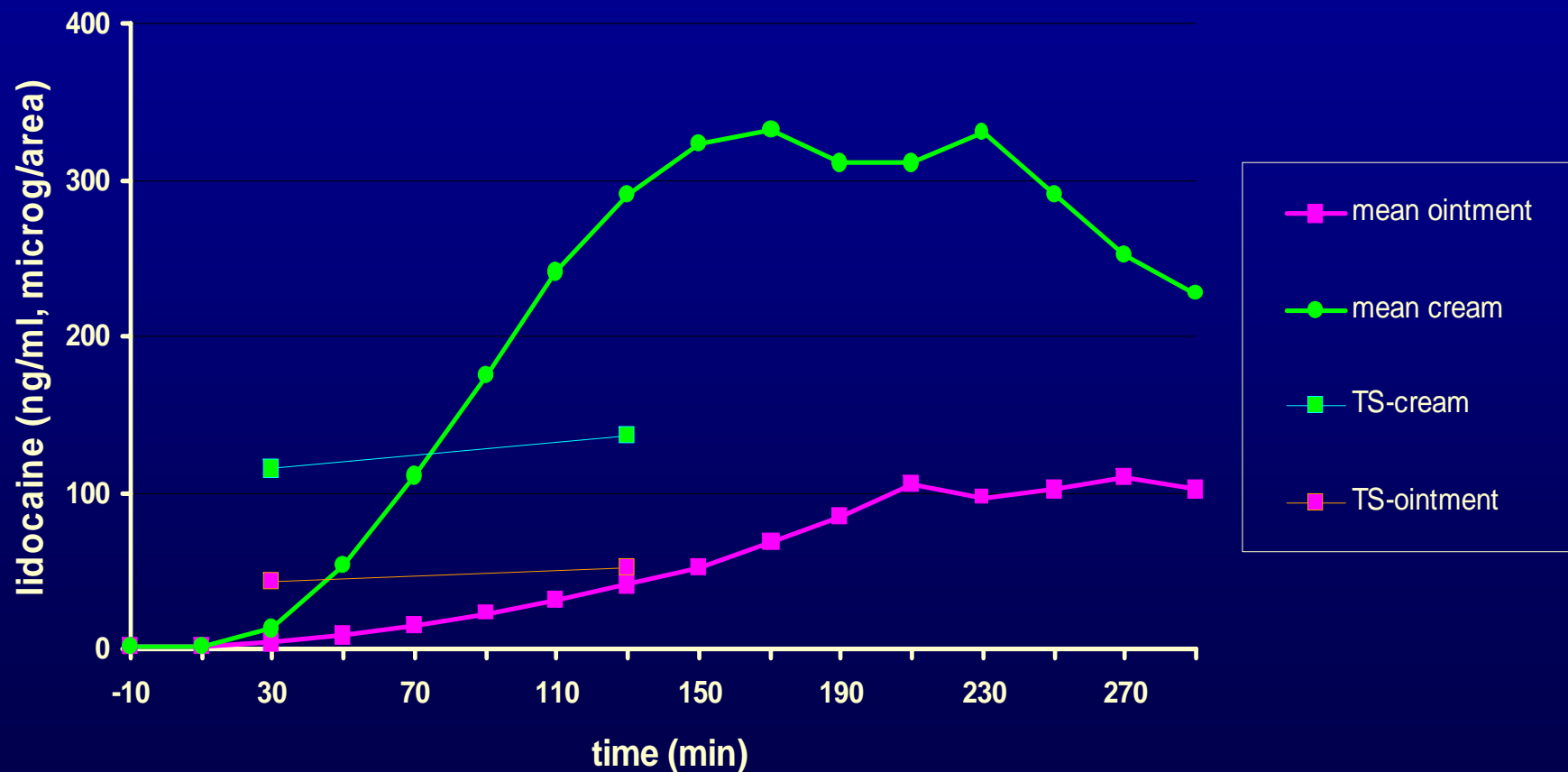
- **Relevance to clinical efficacy (data)**
- **Ability of DPK to differentiate between formulations**
- **Reliability and reproducibility of the method**

# Promising Methodology

*Microdialysis*

*Dermal Microdialysis (DMD)*

# Lidocaine in dialysates and tape-strips: cream vs. ointment



# Formulations

## Product similarity

- $Q_1$ : Same components (Qualitative)
- $Q_2$ : Same components in same amount (Quantitative)
- $Q_3$ : Same components in same amount with the same arrangement of matter (microstructure) - Rheology
  - Can be assured with similar in vitro release profile.

# Promising Methodology

## *In Vitro Drug Release*

Can provide supportive data  
with other promising methods

- Vertical Diffusion Cell - Synthetic Membrane
  - Assuring product sameness – SUPAC-SS
- Information on vehicle properties, including drug delivery –  
“Q<sub>3</sub>” structural phasic sameness

# Decision Tree (Targeting SC)

- If  $Q_1$  and  $Q_2$  equivalent
  - In vitro testing
  - In vivo testing waived based on in vitro results
- If  $Q_1$  equivalent but  $Q_2$  difference
  - In vitro testing
  - In vivo tests if  $Q_2$  difference is potentially significant
- If  $Q_1$  and  $Q_2$  differ
  - In vitro testing
  - In vivo tests required to demonstrate no formulation effect on absorption

# Causes of Inequivalence

(for equal drug content)

- Application
  - Different spreading on the skin
- In the formulation
  - Drug does not leave formulation
  - Thermodynamic activity is different (suspension v. dissolved drug)
- Across the stratum corneum
  - Formulations have different effects on stratum corneum
  - One formulation prefers follicular pathway

# Conclusion

- IVR can be used for BE determination of antifungal drug products
- “A simplified DPK approach, using one uptake and one elimination point” can be used for BE
- Can expensive clinical comparative BE studies be replaced with
  - DPK + IVR or
  - DPK + DMD or
  - DMD + IVR ?

*Thank You*