Regulatory Challenges and Standards for Bioequivalence Evaluation of Topical Drug Products

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Evaluation of New and Generic Topical Drug Products – Current Challenges in Bioequivalence, Quality and Novel Assessment Technologies

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Topical Drug Products

- **Challenges**
  - Pros and cons of different methods for BE
- **Standards for topical drug products**
  - USP <3> and <1724>
- **Future steps**
  - DPk
  - DPK with DMD
  - In vitro release

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 dissolution / release

- 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”.

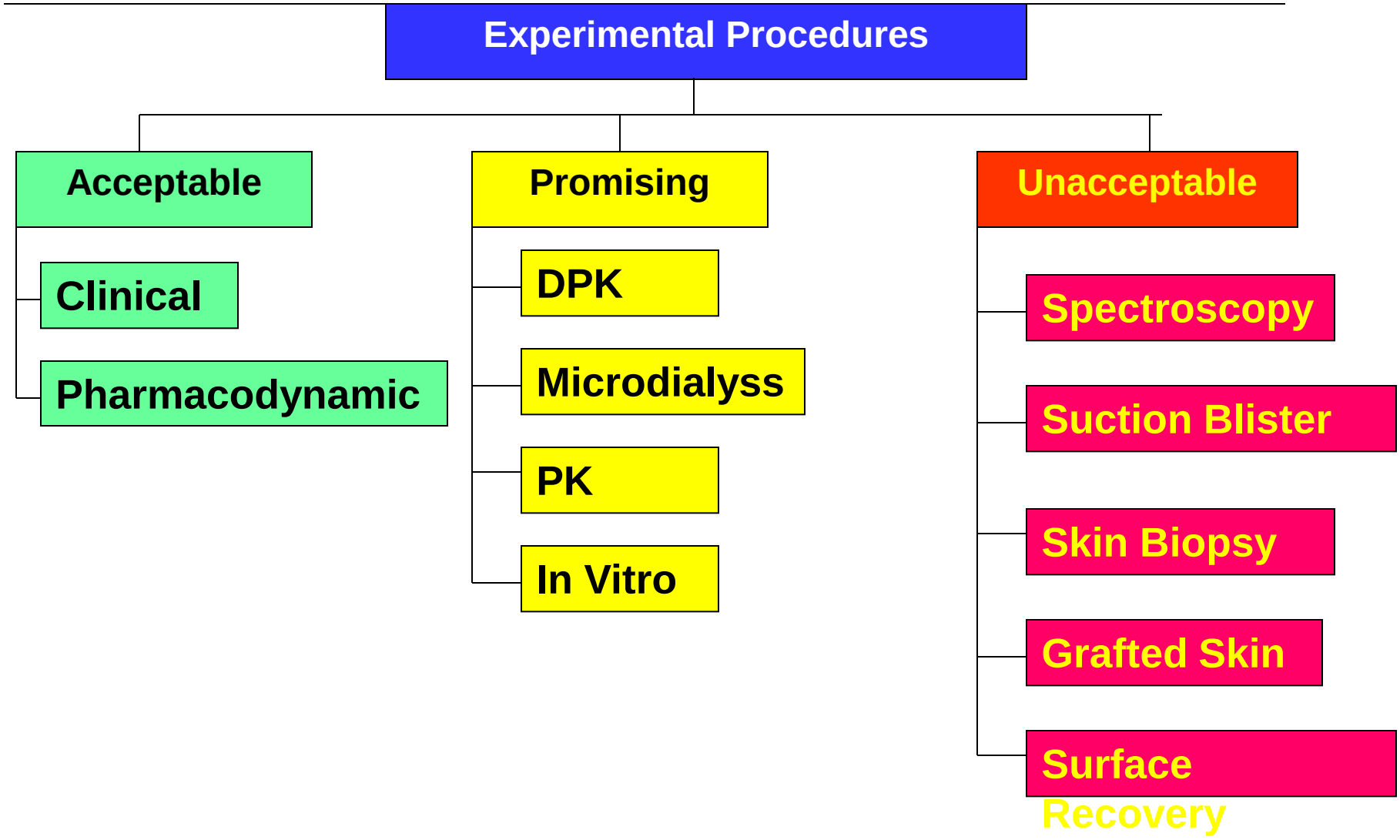
Topical Drug Products

- Critical pathway identified by the Agency with regard to BE of topical drug products
  - In vitro studies
    - Excised human/animal skin (for TDS)
    - Synthetic membrane. In vitro diffusion studies combined with rheological testing to demonstrate BE of Q1/Q2 equivalent drug products
  - Dermatopharmacokinetics
  - Dermal microdialysis
  - Near IR spectroscopy

FDA: Critical path opportunities for Generic Drugs. May 2007

Lionberger, RA. FDA Critical path initiatives: Opportunities for generic developments. AAPSJ 2008. 10: 103-9.

Methods of BE of Topical Dermatological Drug Products



Accepted Methodology

Comparative Clinical Trials

- Expensive
- Less sensitive
- High variability
- Difficult to conduct

Accepted Methodology

Pharmacodynamic Studies

- Limited to one class of drug products
  - Vasoconstriction (blanching) - glucocorticoids
  - Trans Epidermal Water Loss ?

Dermatopharmacokinetics

- A tool for BA/BE assessment of topical drug products
- Draft Guidance: 1998
- Both T and R products can be tested at the same time in the same subject, each subject serving as his/her control.
- Useful technique, particularly for drugs for which the site of action is stratum corneum
- Why is DPK 'not accepted' by FDA (as of now) in spite of it showing good initial promise?
- Draft guidance withdrawn in 2002 when contradictory results were obtained from two independent laboratories during method validation using tretinoin. (However, the protocol and procedure was not the same).
- Is the method reproducible? Reliable?
- Lessons learned
- Need to move on … Future steps

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

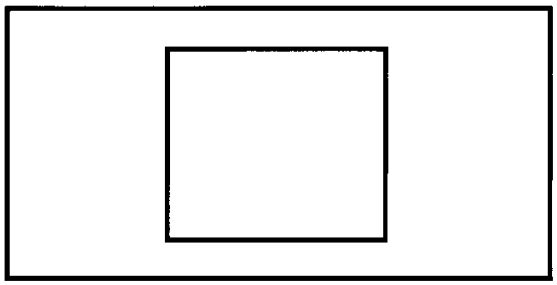
Retin-A (Ortho); Avita (Bertek), Generic (Spear)

Tretinoin - DPK Study Comparison

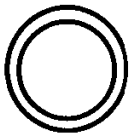
- Both the studies confirmed that Retin-A was bioinequivalent to Avita. However, the order of drug concentration profile in the skin (DPK) was reversed.
- Obviously, because of inconsistency and contradictory DPK results (due to a flawed comparison), use of DPK in BE study was questioned and was rejected by the Agency – resulting in withdrawal of the guidance.
- However, further investigation revealed … both the investigators followed different protocols which resulted in different findings.

Dermatopharmacokinetics

Comparison of two tape stripping procedures



Tom Franz/Spears

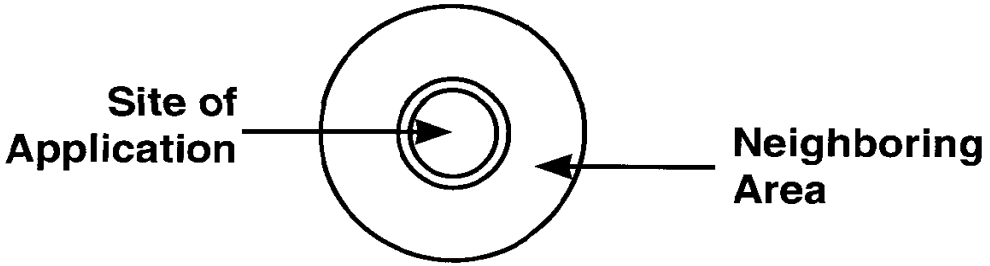


Lynn Pershing

Area of Application:	**2 x 2 cm**	**1.12 cm diameter**
Amount applied	**20 ul**	**5 ul**
Area tape stripped	**2.5 x 5 - 5.5 cm**	**1.3 cm diameter**
Tape used	**Transpore (3M)**	**D-Square (Cuderm)**

Dermatopharmacokinetics

Spreadability and tape stripping



Drug Concentration in Neighboring Area

Time	Retin - A	Avita
0.5 hours	2.33	5.33
2.0 hours	1.64	22.01

Ref: VP Shah, European J of Pharm. and Biopharm. 60: 309-314, 2005

DPK Study

Lessons Learned

The methodology must be standardized

- **drug application area**
- **drug / stratum corneum removal area**

Dermatopharmacokinetics

	Therapeutic Class	Comments
High Risk	Vaginal	Different physiological environment, mucous membrane
	Antiacne (Retinoid)	Follicular penetration
	Antiviral	Site of action not well defined
	Antibiotics	
	Glucocorticoid	
Low Risk	Antifungal	Close to site of action

Promising Methodology

Microdialysis (Dermal Microdialysis - DMD)

- **Direct method for measuring drug levels in skin, with the measurement in the dermis, providing relevant information on BA (and BE) of drugs in target organ, the skin**
- **Measurement of barrier perturbation on cutaneous drug penetration**
- **Technique applicable to the study of normal, diseased and/or perturbed human skin**

Promising Methodology

Pharmacokinetic Measurements

- **Blood level measurements (may be feasible in some cases with improved analytical methodology).**

Promising Methodology

In Vitro Methods

- **Cadaver skin**
  - Important during drug development
  - Surrogate to clinical BE studies ?
- **Synthetic Membrane**

  - QC measure
  - Can provide supportive data with other promising methods
  - with Q1 and Q2, can provide information on Q3, and can be used for drug approval*

*** Draft Guidance on Acyclovir – March 2012**

In vitro Release Test (IVR)

- Reasonable test
- Batch-to-batch uniformity
- QbD emphasizes development of a meaningful drug development specification based on clinical performance. IVR is the first step towards this goal.
- **To be implemented as a required drug product release and stability test.**

Ref: R-K Chang, A Raw, R Lionberger and L Yu. Generic development of topical dermatologic products: Formulation development, process development, and testing of topical dermatologic products. AAPS Journal, 15 (1), 41-52, 2013.

Q1, Q2 and Q3. In vitro Release

- Q1 – Same ingredients/components as RLD
- Q2 – Same ingredients/components in the same concentration as RLD
- Q3 – Same ingredients/components/in the same concentration with same arrangement of matter (microstructure) as RLD
- Acceptable comparative physicochemical characterization and equivalent in vitro release (Q3) to RLD
- Biowaiver may be granted with supportive data to demonstrate Q1 and Q2 same and similar physicochemical characteristics (Q3 – IVR)

Ref: R-K Chang, A Raw, R Lionberger and L Yu. AAPS Journal, 15 (1), 41-52, 2013.

Unacceptable Methodology

Due to -

- Invasive nature of the protocol
  - Suction blister
  - Skin biopsy
- Insensitivity of methodology
  - Near infrared spectroscopy (interference in quantitation) – more work needs to be done
  - Raman spectroscopy – not drug specific
  - Surface Recovery
- Premature and difficult
  - Human grafted skin

Conclusions

- Alternative to clinical methods should be explored for BE determination of topical drug products
- Procedure for DPK should be standardized
- Potential use of IVR should be explored.
- This workshop offers an opportunity to discuss ways to enhance the development and evaluation of topical products with the input from the expert panels and audience, there may be new directions for the regulatory consideration with simpler, less variable and more reliable BE methods for generic products.

Thank You for Your Attention

Drug Product Quality Tests

- Strength, efficacy, purity and safety characterization
- Qualitative description organoleptic qualities and product consistency
- Visual test of homogenity
- Identification
- pH potential effects
- Variation is specific gravity
- Monitoring water content and alcohol content (where applicable)
- Container closure system
- Preservative
- Antioxidants
- impurity

Product Quality and Product Performance Test

Chapters in USP:

- <3> Topical and transdermal drug products – product quality tests. Official in USP

- <724> Drug release (for TDS)

- <1724> Semisolid drug products – Performance test. Official in USP36/NF 31, Supplement 1; Official in August 1, 2013.