Towards building a dermal model for BE assessment: The role of drug product characterization & performance data

Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches
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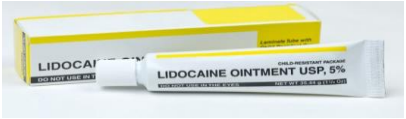
This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Learning Objectives

- *Understand the complexity of topical dermatological products*
- *Discuss bioequivalence (BE) recommendations for topical dermatological products*
- *Discuss how drug product characterization data and drug product performance data can be utilized to develop and validate models for evaluation of BE*

What are Topical Products?



PSGs for Topical Dermatological Products

Potential ways for establishing BE for complex topicals:

- Comparative clinical endpoint BE studies
  - Clinical endpoint (CE)
  - Pharmacodynamic endpoint (e.g., vasoconstrictor (VC) studies)
- *Efficient* characterization-based BE studies (e.g., in vitro)
  - in vitro
  - in vivo pharmacokinetic (PK) studies

PSG: Product-Specific Guidance

PSGs for Topical Dermatological Products

A Modular and Scalable Approach to BE Evaluation

- Sameness of inactive ingredient components and quantitative composition, e.g., qualitative **(Q1)** and quantitative **(Q2)** sameness
- **Q3** (Physical & Structural Characterization) as relevant to the nature of the product
- **IVRT** (In Vitro Release Test)
- **IVPT** (In Vitro Permeation Test) or another bio-relevant assay may be appropriate for some products
- In vivo systemic **PK** studies may be appropriate for some products

Identification of Relevant Q3

*Is the Drug Substance **Dissolved** in the Formulation?*

- Isomers of the drug
- pKa(s) of the drug
- pH of the formulation

*Is the Drug Substance **Suspended** in the Formulation?*

In addition to the potential failure modes identified on the left….

- Polymorphic forms of the drug
- Particle size distribution of the drug (and crystalline habit)

Identification of Relevant Q3

*Is the Formulation a **Single Phase** System? e.g., solution, gel*

- Viscosity/Rheology
- pH

*Is the Formulation a **Multi Phase** System? e.g., lotion, cream*

In addition to the potential failure modes identified on the left….

- Phases and arrangement of matter
- Distribution/localization of drug

PSGs for Topical Dermatological Products

Example of Q3 recommended for single phase systems

- Visual Appearance
- Microscopy
- Particle size
- Polymorphic form
- Drying rate (weight loss)
- Specific gravity
- Rheology
- pH
- Etc.

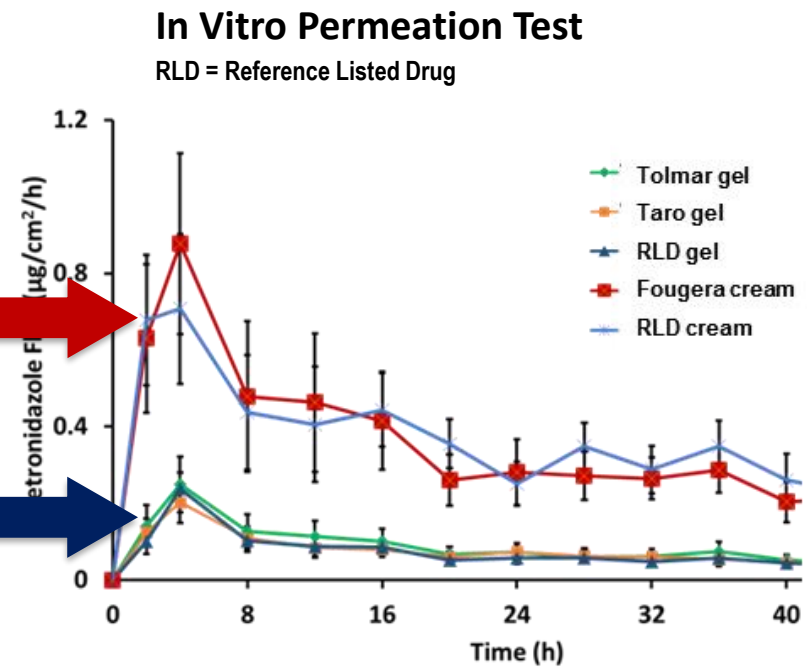
PSGs for Topical Dermatological Products

Example of Q3 recommended for multi phase systems

- Appearance
- Microscopy
- Particle size
- Polymorphic form
- Drying rate
- Specific gravity
- Rheology
- pH
- Globule size
- Etc.

Quality and Performance (Metronidazole)

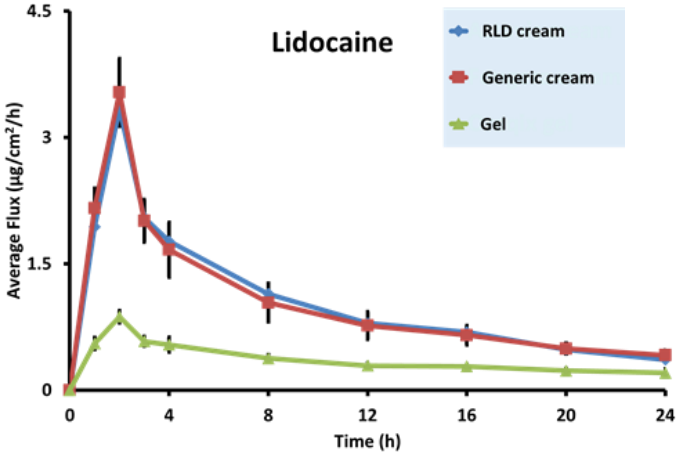
Quality Attribute	MetroCream® (RLD Cream)	Generic Crear (Fougera)	Metrogel® (RLD Gel)	Generic Gel (Tolmar)	Generic Ge (Taro)
pH	4.8	5.1	5.2	5.0	5.4
Density (g/cc)	1.02	1.02	1.01	1.02	1.02
WOA (g.sec)	57.6	63.9	39.4	43.9	42.0
Particle size (µm)	Active ingre				
Drug in Aq (mg/g)	4.20	2.92	---	---	---
Drug in Oil (mg/g)	2.58	3.94	---	---	---
Solvent Activity	0.977	0.974	0.992	0.994	1.002
Globule size, d_{50} (µm)	2.8	2.2	---	---	---
Drying, T_{30} (min)	17	11.4	5.5	4.7	6.5



Data courtesy Dr. Narasimha Murthy, U01FD005233

Quality and Performance (Lidocaine)

Q3 Attribute	Lidocaine2.5%, Prilocaine2.5% RLD Cream		Lidocaine-2.5%, Prilocaine-2.5% Generic Cream		Lidocaine-2.5%, Prilocaine-2.5% Gel
pH	9.22 ± 0.08		8.92 ± 0.03		7.76 ± 0.05
Density (g/cc)	1.0142 ± 0.0002		1.0148 ± 0.0002		1.0374 ± 0.0001
WOA (g.sec)	59.427 ± 0.338		65.893 ± 0.614		3.186 ± 0.207
Particle Size of API (µm)	Lidocaine and Prilocaine completely dissolved in the formulation				
Globule Size, d50 (µm)	3.30		3.00		---
Drug in Aqueous Phase (µg/g)	Lidocaine	1.64 ± 0.06	Lidocaine	1.74 ± 0.12	---
	Prilocaine	1.99 ± 0.06	Prilocaine	2.11 ± 0.15	
Drug in Oil Phase (µg/g)	Lidocaine	23.45 ± 0.36	Lidocaine	23.21 ± 0.18	---
	Prilocaine	23.47 ± 0.18	Prilocaine	23.12 ± 0.2	
Water Activity	1.003 ± 0.002		1.004 ± 0.007		1.002 ± 0.005
Drying,T50 (min)	3.37 ± 0.15		3.82 ± 0.73		7.9 ± 0.46
Rheology Yield Stress(Pa)	36.7 ± 1.2		35.7 ± 0.6		15.7 ± 2.3



Data courtesy Dr. Narasimha Murthy, U01FD005233

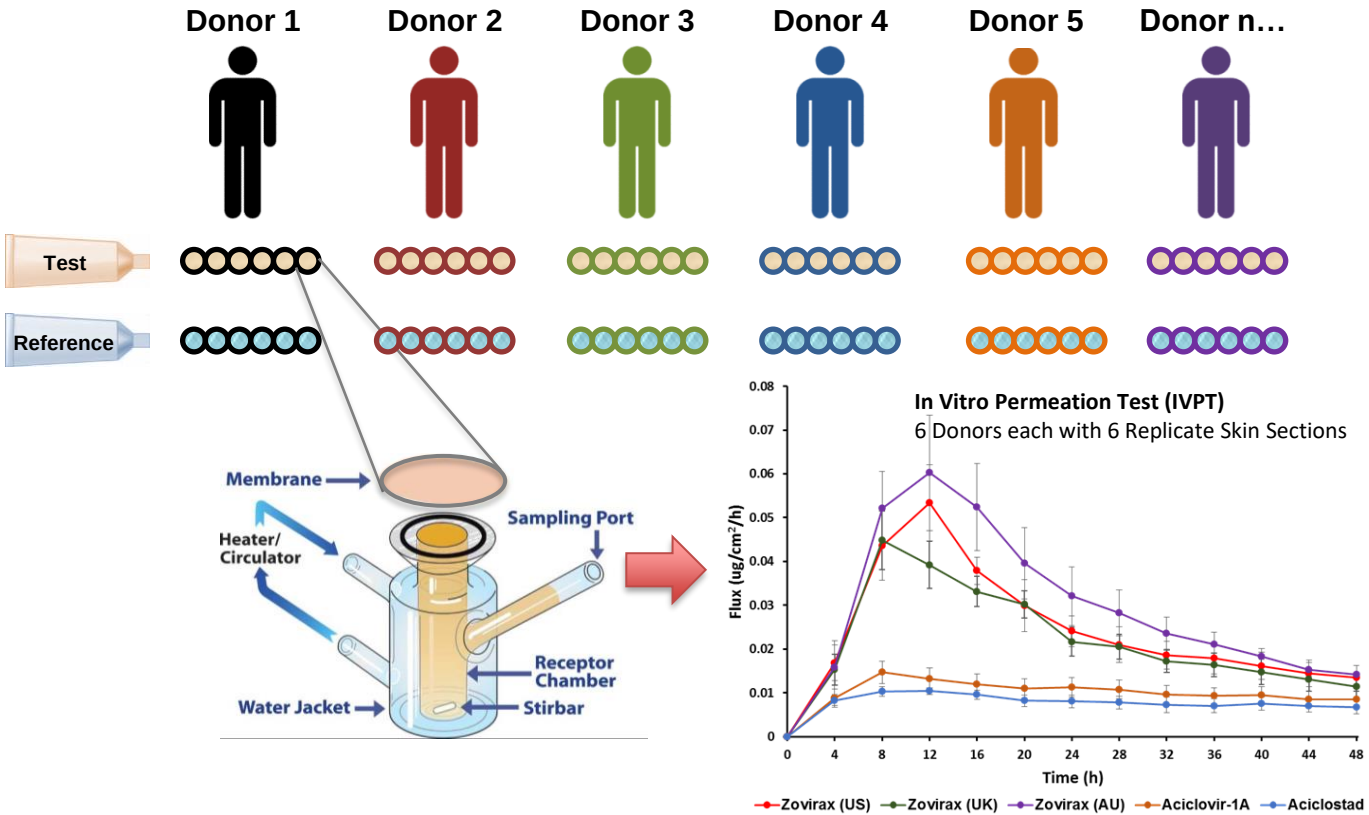
Role of IVPT

- IVPT

> The test and RLD products are bioequivalent based upon an acceptable in vitro permeation test (IVPT) comparing the rate and extent of acyclovir permeation through excised human skin from a minimum of one lot each of the test and RLD products using an appropriately validated IVPT method.

  - IVPT method development
  - IVPT method validation (includes a pilot study)
  - IVPT pivotal study

IVPT STUDY DESIGN



Data courtesy Dr. Narasimha Murthy, U01FD005233

IVPT Method Development

- *Apparatus Selection*
- *Selection of Skin Source*
- *Selection of Receptor Solution*
- *Assessment of the Barrier Integrity*
- *Selection of Dose Amount, Dosing Technique, and Dose Duration*
- *Selection of Study Duration, Sampling Schedule and Method*

IVPT Method Validation

Discrimination Sensitivity and Selectivity

- Sensitivity
  - Modulation of Dose Amount
  - Modulation of Dose Duration
- Selectivity
  - Test product, Reference Product, and Altered Product

Cutaneous Pharmacokinetic Data

Microdialysis (dMD) and Open Flow Microperfusion (dOFM) directly measure the in vivo rate and extent of drug bioavailability at/near the site of action in the skin.

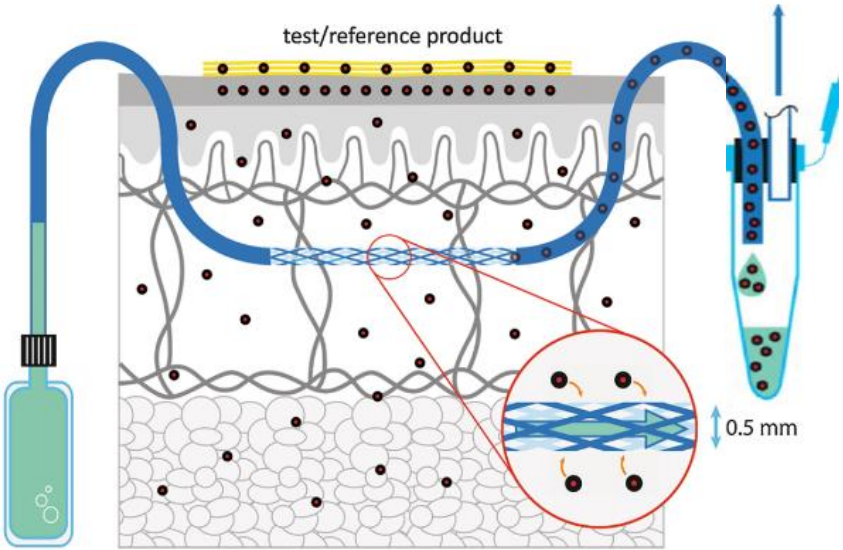


Image provided courtesy of Dr. Frank Sinner, Joanneum Research

Summary

- Topical dermatological drug products are generally complex dosage forms
- Understanding the behavior of a given formulation during metamorphosis is critical to be able to model the bioavailability of the active ingredient from the drug product
- Drug product characterization data can facilitate the development and validation of models that can be utilized for evaluation of BE
- Drug product performance data generated using in vitro (e.g., IVPT) and/or in vivo (e.g., dOFM) methodologies can also be utilized to develop and validate models. Methodologies used for drug product performance evaluation should be sensitive and discriminating
- Goal of the GDUFA regulatory science research program is to facilitate the development of modeling strategies that can be utilized as a tool to facilitate drug development and/or assess BE

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