Identification of Research Needs During Product Development Prior to ANDA Submission

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Learning Objectives

- Understanding the role of GDUFA research in development of bioequivalence (BE) recommendations
  - Using Topical Dermatological Dosage Forms
- Identification of research challenges/needs prior to submission of an ANDA
  - Topical Gels
  - Topical Creams/Lotions (Emulsions)
  - Topical Foams

PSGs for Topical Dermatological Products

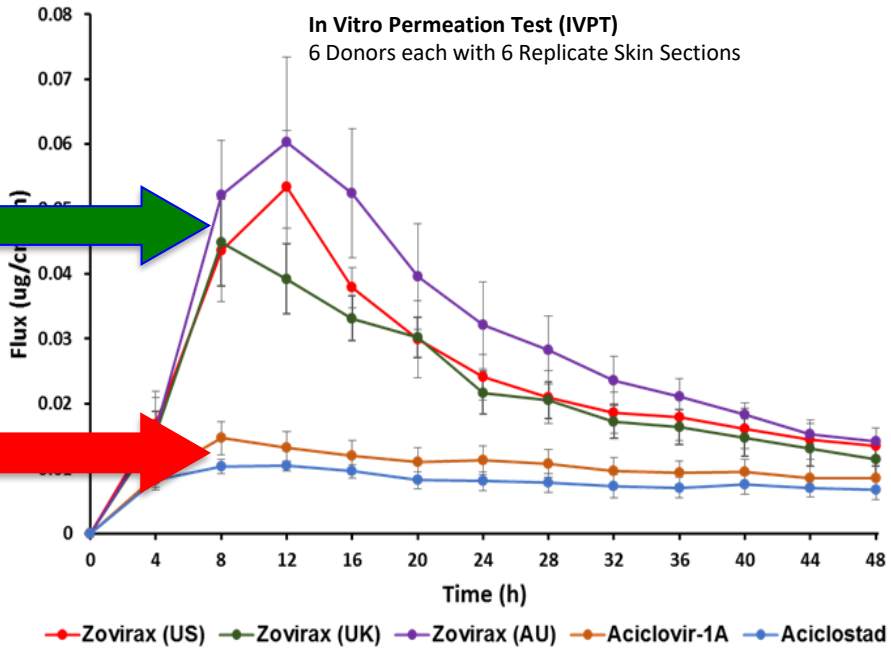
Potential ways for establishing BE for complex topicals:

- 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

In Vitro Characterization (Acyclovir)

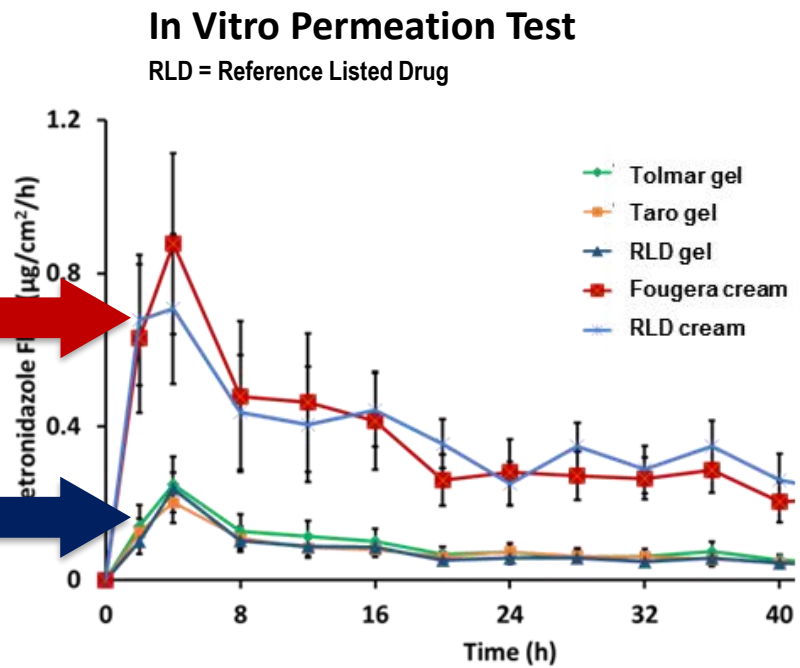
	Zovirax (USA)	Zovirax (UK)	Zovirax (Austria)	Aciclostad (Austria)	Aciclovir-1A (Austria)
	Water	Water	Purified water	Water	Water
	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol
	Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
	White petrolatum	White soft paraffin	White Vaseline	White Vaseline	White Vaseline
	Cetostearyl alcohol	Cetostearyl alcohol	Cetostearyl alcoh	Cetyl alcohol	Cetyl alcohol
	SLS	SLS	SLS		
	Poloxamer 407	Poloxamer 407	Poloxamer 407		
		Dimethicone 20	Dimethicone 20	Dimethicone	Dimethicone
		Arlacel 165	Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate
		Arlacel 165	Polyoxyethylene stearate	Macrogol Stearate	Polyoxyethylene stearate
Density (g/cc)	1.02	1.02	1.02	1.02	1.01
Content Uniformity (%)	97.9 ± 0.7	99.6 ± 1.4	100 ± 2.2	99.7 ± 1.7	98.3 ± 2.6
Polymorphic Form	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate
Crystilline Habit	Rectangular	Rectangular	Rectangular	Ovoid	Ovoid
Particle size (d50) (µm)	3.8	2.5	3.4	6.8	6
pH	7.74	7.96	7.54	4.58	6.05
Work of Adhesion	59	81	60	17	18
Drug in Aq (mg/g)	0.49	0.64	0.49	0.37	0.26
Drying Rate (T-30%)	>12h	~8h	~7h	<1h	<1h
Water Activity	0.75	0.73	0.74	0.95	0.95



Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) **FDA Award U01-FD005223**

In Vitro Characterization (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



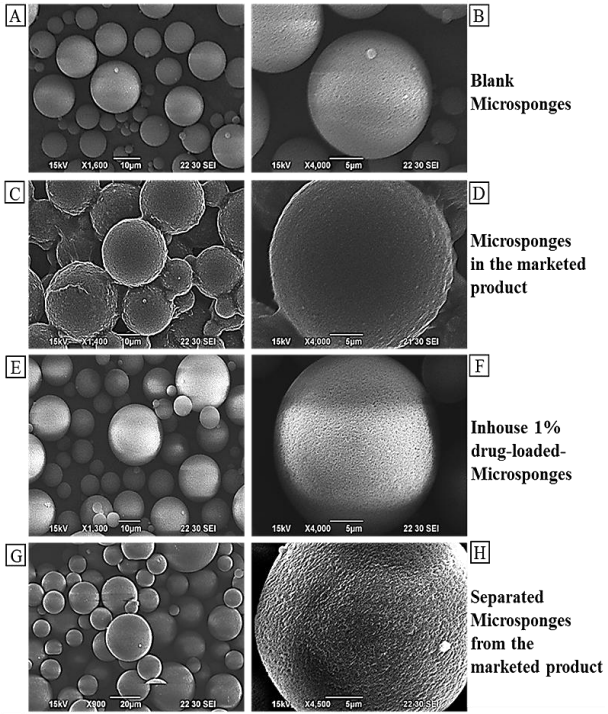
Data provided courtesy of Dr. Narasimha Murthy associated with FDA funding for award U01FD0005233

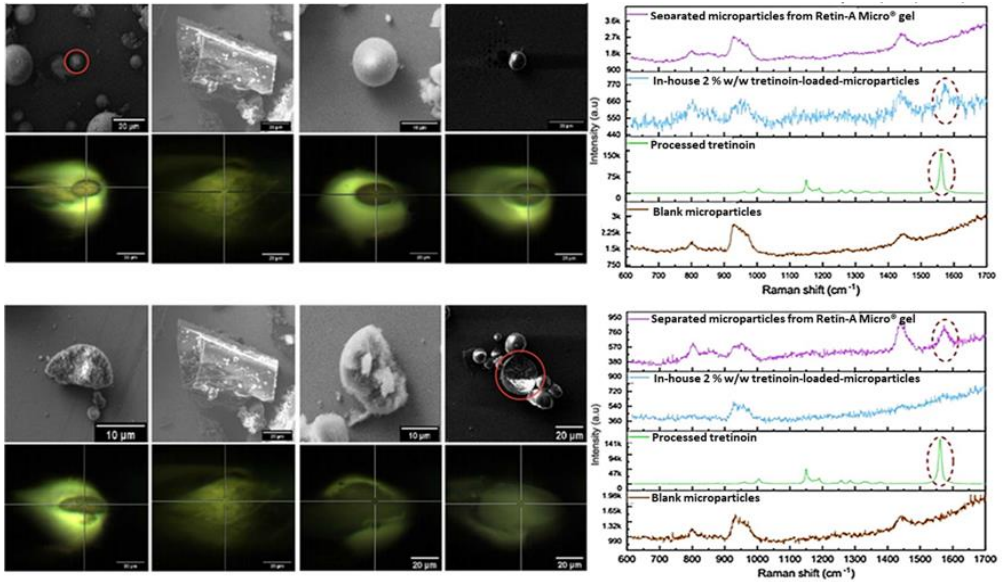
PSGs for Topical Dermatological Products

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

Example 1 - Topical Gels





In-SEM SCA Raman analysis of Microsponges® at the surface and inside broken Microsponges®.

FY2021 GDUFA Science and Research Report Ch6 Dermatological available at https://www.fda.gov/drugs/generic-drugs/fy-2021-gdufa-science-and-research-report
Content was adapted from Dr. Ahmed Zidan's presentation at SBIA 2021 available at https://sbiaevents.com/advancing-generics-2021/#files

Example 1 - Topical Gels

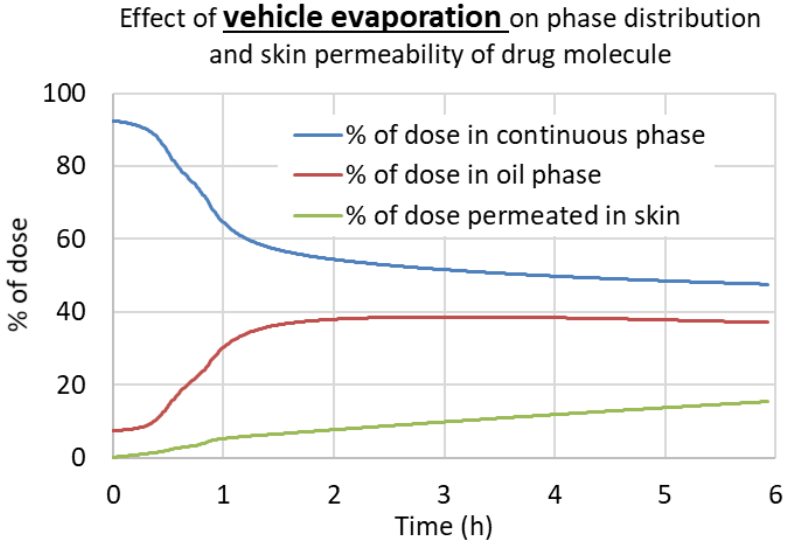
Recommendations for a single phase topical dermatological gel may include

- Sameness of inactive ingredient components and quantitative composition, e.g., **Q1** and **Q2** sameness
- **Q3** as relevant to the nature of the product
- **IVRT**

Additional considerations for products containing microparticles

- Characterization of the material constituting the particles (e.g., polymers)
- Assessment of particle size distribution of the particles
- Characterization of the morphology including the surface area and porosity
- Assessment of drug loading, drug distribution, localization and physical state, etc.
- Evaluation of drug release
- Evaluation of cutaneous pharmacokinetics

Example 2 - Topical Emulsions



The lotion contains cetostearyl alcohol (2.5%); glycerin; glyceryl stearate SE (with potassium monostearate); isostearyl alcohol (2.5%); methylparaben (0.3%); sodium lauroyl sarcosinate; stearic acid; and purified water.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/050537s040,050600s017,050615s018lbl.pdf

https://www.webmd.com/drugs/2/drug-61196/cleocin-t-topical/details

Content was adapted from Dr. Khondokar Alam's presentation at SBIA 2021 available at https://sbiaevents.com/advancing-generics-2021/#files

Example 2 - Topical Emulsions

Considerations for topical emulsions

- Challenges with conduct and data analysis of IVPT studies
  - Aberrant data
  - Outliers
- Potential additional challenges with products containing “prodrugs”
  - Selection of the receptor solution
  - Analyte to measure

https://complexgenerics.org/IVRTIVPT/

Example 3 - Topical Foams

Active ingredient: Clobetasol Propionate

Form/Route: Aerosol, Foam/Topical

I. Waiver option:

a. To qualify for a waiver of the in vivo bioequivalence (BE) study requirements under 21 CFR 320.22(b)(3), a generic Clobetasol Propionate Aerosol, Foam/Topical, 0.05% must be a solution for aerosolization, have the same active ingredient in the same concentration and dosage form as the reference listed drug product (RLD) and must not have an inactive ingredient or other change in formulation from the RLD that may significantly affect systemic or local availability.

b. For a topical drug product with inactive ingredients that differ from the RLD or are present in significantly different amounts [as permitted by the chemistry, manufacturing and controls regulations for abbreviated new drug applications (ANDAs), 21 CFR 314.94(a)(9)(v)], the regulation specifies that the applicant must identify and characterize the differences and provide information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product. If the generic Clobetasol Propionate Aerosol, Foam/Topical, 0.05% has different inactive ingredients compared to the RLD or differences in the amounts of the same inactive ingredients that are proportionally more than +/- 5% compared to the RLD, then the Office of Generic Drugs (OGD) may request a bioequivalence study with clinical endpoints to determine bioequivalence between the products

c. For products applied to the scalp, differences in surfactants or potential penetration enhancers may change the distribution of the product over the scalp or penetration of the drug into the diseased tissues. Therefore, clinical endpoint bioequivalence studies are requested for generic shampoo products with differences in these ingredients that are proportionally more than +/- 5% compared to the RLD.

d. To support the waiver request, data from the following comparative in vitro assays of test vs. reference are requested:
- Microscopic Birefringence Analysis on the dispensed foam after complete collapse to determine whether any crystals of undissolved clobetasol propionate form during dispensing.
- Time to Break Analysis, conducted at 30ºC, 33ºC, 35ºC, and 40ºC. Time to break is the time from dispensing to complete foam collapse (break). The testing should be done on at least 3 different lots of the RLD and at least 3 lots of the test product (with each lot manufactured separately).
- Weight per volume of uncollapsed foam.

Active Ingredient: Clobetasol propionate

Dosage Form; Route: Aerosol, foam; topical

Recommended Studies: Two studies

1. Type of study: Pilot vasoconstrictor study
Design: A pilot dose duration-response study using the reference product
Strength: 0.05%
Subjects: Males and nonpregnant, nonlactating females, general population
Additional comments: Refer to the guidance for industry *Topical Dermatologic Corticosteroids: In Vivo Bioequivalence*.

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2. Type of study: Pivotal vasoconstrictor study
Design: A pivotal bioequivalence study
Strength: 0.05%
Subjects: Males and nonpregnant, nonlactating females, general population
Additional comments: See comments above.

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https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_022013.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/psg/Clobetasol_Propionate_fmaerosol_21142_RC2-11.pdf

Example 3 - Topical Foams

Active Ingredient: Azelaic acid

Dosage Form; Route: Aerosol, foam; topical

Recommended Study: One study

Type of study: Bioequivalence study with clinical endpoint
Design: Randomized, double blind, parallel, placebo controlled, in vivo
Strength: 15%
Subjects: Males and nonpregnant, nonlactating females with rosacea
Additional comments: Specific recommendations are provided below.

Finacea (azelaic acid) topical foam	Finacea Foam also contains benzoic acid, cetostearyl alcohol, dimethyl isosorbide, medium-chain triglycerides, methylcellulose, mono- and di-glycerides, polyoxyl 40 stearate, polysorbate 80, propylene glycol, purified water, sodium hydroxide, and xanthan gum https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207071s000lbl.pdf
Amzeeq (minocycline) topical foam	4% Amzeeq topical foam contains the following inactive ingredients: soybean oil, coconut oil, light mineral oil, cyclomethicone, cetostearyl alcohol, stearic acid, myristyl alcohol, hydrogenated castor oil, white wax (beeswax), stearyl alcohol, docosanol…. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212379s000lbl.pdf

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_207071.pdf

Example 3 - Topical Foams

Considerations for topical aerosol foams

- Understanding the microstructure of the foams and how inactive ingredients may influence the microstructure
- Relevant Q3 studies based on the complexity of the product
- Potential methodologies for conducting performance studies (e.g., IVRT and IVPT)

Summary

- Topical dermatological drug products are generally complex dosage forms
- Efficient characterization-based approaches have been developed for topical gels, creams, lotions, etc., supported by data generated within the GDUFA regulatory science and research program
- However, there are complex formulations for which there are outstanding questions related to development of efficient characterization-based approaches
- The goal of the GDUFA regulatory science and research program as well as the pre-ANDA program is to facilitate early awareness and engagement with industry to be able to identify/develop strategies that can be utilized to facilitate generic drug development

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