Product Development Considerations and Bioequivalence Strategies for Generic Topical Products

Research and Innovation to Enhance Patient Access to Topical Dermatological Products in the US

DIA Annual Meeting

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CDER | U.S. FDA

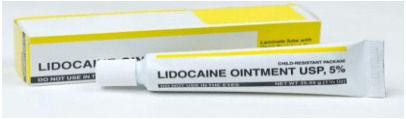
Disclaimer

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

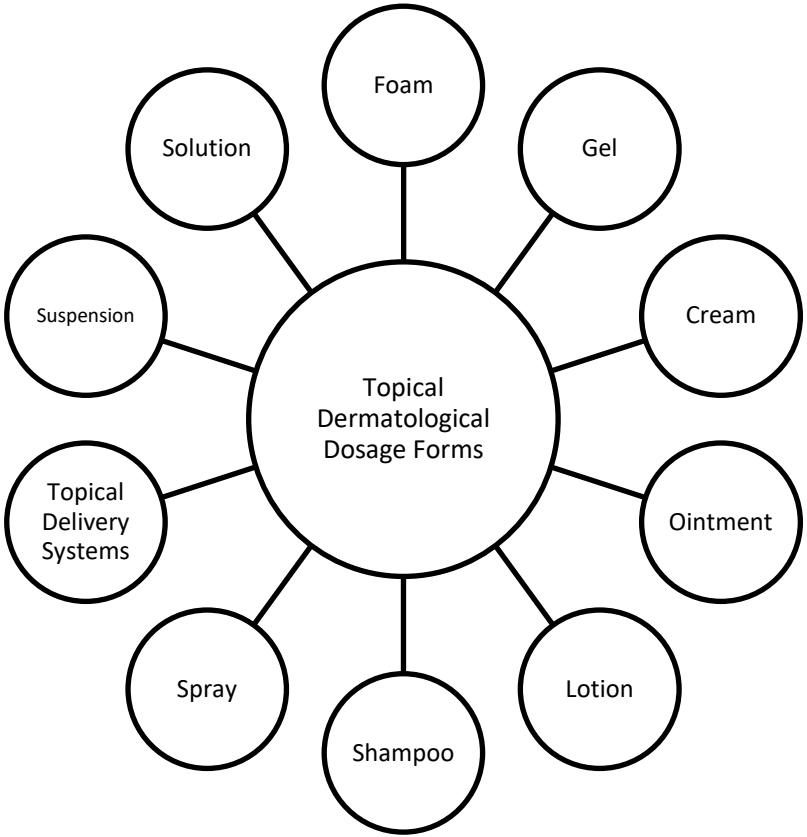
Learning Objectives

- *Describe the diversity and complexity of topical dosage forms*
- *Explain bioequivalence (BE) recommendations for topical dermatological products as reflected within product specific guidance (PSG)*
- *Potential strategy for product development (example)*

Topical Products



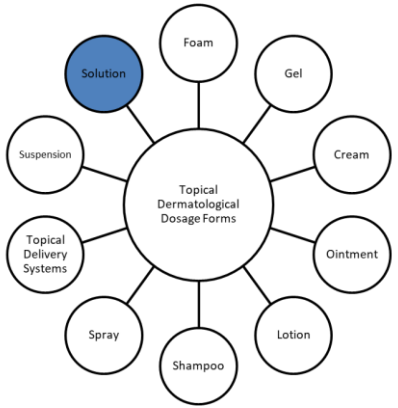
Commonly Used Dosage Forms



https://www.derm.theclinics.com/article/S0733-8635(22)00005-5/fulltext
https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book

Guidance for Topical Products

Solution-based topical products



- Waiver for generic topical solutions
- *Contains no inactive ingredient or other change in formulation…. that may significantly affect systemic or local availability for products intended to act locally.21 CFR 320.22(b)(3)*
- Product characterization is recommended to mitigate unique concerns
- **Example: Draft Guidance on Clindamycin** *(Topical Swab)*

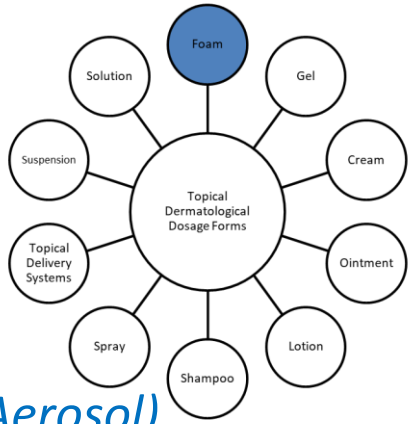
  "In addition, adequate information should be provided to ensure that the composition of the pledget will not affect the performance of the drug product…"

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_050537-Swa.pdf

Guidance for Topical Products

Solution-based foam aerosols

- In vitro evidence to support a waiver of in vivo evidence of bioavailability(BA) or BE per 21 CFR 320.22(b)(3)



- **Example: Draft Guidance on Clobetasol Propionate** *(Foam Aerosol)*

  Comparative physicochemical characterizations:

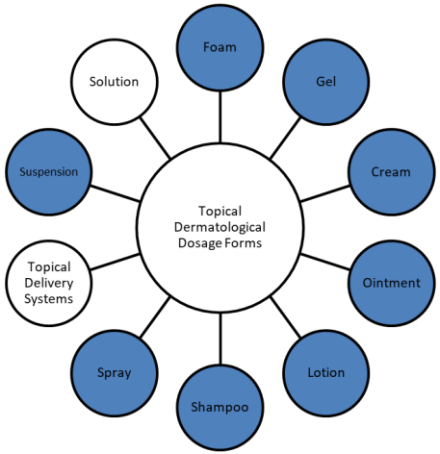
  - *Microscopic Birefringence Analysis (do crystals form upon dispensing?)*
  - *Time to Break Analysis (conducted at 30°C, 33°C, 35°C & 40°C)*
  - *Weight per Volume of un-collapsed foam aerosol*

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

Guidance for Topical Products

Potential ways for establishing BE for complex topicals:

- Comparative clinical endpoint BE studies
  - Clinical endpoint (CE)
- Pharmacodynamic endpoint
  - Vasoconstrictor (VC) studies
- *Efficient* characterization-based BE studies
  - in vitro
  - In vitro and in vivo pharmacokinetic (PK) studies



Comparative CE Studies

Example: Draft Guidance on Minocycline *(Foam Aerosol)*

Active Ingredient: Minocycline hydrochloride

Dosage Form; Route: Aerosol, foam; topical

Recommended Study: One study

1. Type of study: Bioequivalence study with clinical endpoint
   Study Design: Randomized, double blind, parallel, placebo controlled, in vivo
   Strength: EQ 4% Base
   Subjects: Males and non-pregnant, non-lactating females with acne vulgaris
   Additional comments: Specific recommendations are provided below

Analyte to measure: Not applicable

Bioequivalence based on (90% CI): Clinical endpoint

Waiver request of in vivo testing: Not applicable

Recommended Nov 2021

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_212379.pdf

Pharmacodynamic VC studies

Example: Draft Guidance on Clobetasol *(Cream)*

Active Ingredient: Clobetasol propionate

Dosage Form; Route: Cream; topical

Recommended Studies: Two studies

1. Type of study: Pilot vasoconstrictor study
   Design: Pilot dose duration-response study using the reference product under un-occluded conditions
   Strength: 0.05%
   Subjects: Healthy males and females (non-pregnant, non-lactating), general population
   Additional comments: Refer to the guidance "Topical Dermatological Corticosteroids: In Vivo Bioequivalence" available at:
   http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070234.pdf.

2. Type of study: Pivotal vasoconstrictor study
   Design: Pivotal in vivo bioequivalence study under un-occluded conditions
   Strength: 0.05%
   Subjects: Healthy males and females (non-pregnant, non-lactating), general population
   Additional comments: See comments above.

Analytes to measure (in appropriate biological fluid): Not Applicable

Bioequivalence based on (90% CI): Pivotal vasoconstrictor assay study

Waiver request of in vivo testing: Not Applicable

Dissolution test method and sampling times: Not Applicable

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Clobetasol%20propionate_topical%20cream_RLD%2074220_RC04-16.pdf

Characterization-Based BE Approach

Example: Draft Guidance on Metronidazole *(Gel)*

Active Ingredient: Metronidazole

Dosage Form; Route: Gel; topical

Recommended Studies: Two options: in vitro or in vivo study

1. In vitro option:

To qualify for the in vitro option to demonstrate bioequivalence for metronidazole topical gel, 1% the following criteria should be met:

A. The test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference product in the same packaging configuration (tube or pump) that may significantly affect the local or systemic availability of the active ingredient. For example, if the test and reference products are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the Guidance for Industry *ANDA Submissions – Refuse-to-Receive Standards*[1], the bioequivalence of the test product with respect to the reference product may be established using the in vitro option if the criteria below are also satisfied.

B. The test and reference products in the same packaging configuration (tube or pump) should be physically and structurally similar based upon an acceptable comparative physicochemical characterization of a minimum of three batches of the test and three batches (as available) of the reference product. The characterization of the test and reference products should include the following comparisons of physical and structural attributes between the test and reference products:

i. Assessment of visual appearance with representative microscopic images at multiple magnifications.

ii. Analysis of the rheological behavior which may be characterized using a rheometer that is appropriate for monitoring the non-Newtonian flow behavior of semi-solid dosage forms. The following evaluations are recommended:

- A characterization of shear stress and viscosity vs shear rate. At minimum this should consist of numerical viscosity data at three shear rates (low, medium, and high), and may include a complete flow curve across the range of attainable shear rates, until low or high shear plateaus are identified.
- Yield stress values should be reported if the material tested exhibits plastic flow behavior.
- The linear viscoelastic response (storage and loss modulus vs. frequency) should be measured and reported.

iii. Analysis of pH, specific gravity, and any other potentially relevant physical and structural attributes.

C. The test and reference products in the same packaging configuration (tube or pump) should have an equivalent rate of metronidazole release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one batch each of the test and reference products using an appropriately validated IVRT method. Refer to the *Draft Guidance on Acyclovir* (for acyclovir topical cream, 5%)[2] for additional information regarding the development, validation, conduct, and analysis of acceptable IVRT methods/studies. The batches of test and reference products evaluated in the IVRT study should be included among those for which the physical and structural similarity is characterized and compared.

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021789.pdf

Characterization-Based BE Approach

Example: Draft Guidance on Metronidazole (Cream)

Active Ingredient: Metronidazole

Dosage Form; Route: Cream; topical

Recommended Studies: Two options: in vitro or in vivo study

1. In vitro option:

To qualify for the in vitro option to demonstrate bioequivalence for metronidazole topical cream, 0.75% the following criteria should be met:

A. The test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference product that may significantly affect the local or systemic availability of the active ingredient. For example, if the test and reference products are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the Guidance for Industry *ANDA Submissions – Refuse-to-Receive Standards*[1], with allowance for the amount of a pH modifier utilized to match the pH of the reference product the bioequivalence of the test product with respect to the reference product may be established using the in vitro option if the criteria below are also satisfied.

B. The test and reference products should be physically and structurally similar based upon an acceptable comparative physicochemical characterization of a minimum of three batches of the test and three batches (as available) of the reference product. The characterization of the test and reference products should include the following comparisons of physical and structural attributes between the test and reference products:

i. Assessment of visual appearance with representative microscopic images at multiple magnifications.

ii. Characterization of the globule size distribution of the emulsion.

iii. Analysis of the rheological behavior which may be characterized using a rheometer that is appropriate for monitoring the non-Newtonian flow behavior of semi-solid dosage forms. The following evaluations are recommended:

- A characterization of shear stress and viscosity vs shear rate. At minimum this should consist of numerical viscosity data at three shear rates (low, medium, and high), and may include a complete flow curve across the range of attainable shear rates, until low or high shear plateaus are identified.
- Yield stress values should be reported if the material tested exhibits plastic flow behavior.
- The linear viscoelastic response (storage and loss modulus vs. frequency) should be measured and reported.

iv. Analysis of pH, specific gravity, and any other potentially relevant physical and structural attributes.

C. The test and reference products should have an equivalent rate of metronidazole release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one batch each of the test and reference products using an appropriately validated IVRT method. Refer to the *Draft Guidance on Acyclovir* (for acyclovir topical cream, 5%)[2] for additional information regarding the development, validation, conduct, and analysis of acceptable IVRT methods/studies. The batches of test and reference products evaluated in the IVRT study should be included among those for which the physical and structural similarity is characterized and compared.

D. The test and reference products should have an equivalent rate and extent of metronidazole permeation through excised human skin based upon an acceptable in vitro permeation test (IVPT) comparing a minimum of one batch each of the test and reference products using an appropriately validated IVPT method. Refer to the *Draft Guidance on Acyclovir* (for acyclovir topical cream, 5%)[2] for additional information regarding the development, validation, conduct, and analysis of acceptable IVPT methods/studies. The batches of test and reference products evaluated in the IVPT study should be the same as those evaluated in the IVRT study.

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2. In vivo option:

Type of study: Clinical Endpoint Bioequivalence Study
Design: Randomized, double blind, parallel, placebo controlled in vivo
Strength: 0.75%
Subjects: Males and nonpregnant, nonlactating females with rosacea
Additional comments: Specific recommendations are provided below

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_020531.pdf

Characterization-based BE Approach

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

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_020126.pdf

Q3 Characterization

1. Characterization of appearance and texture
2. Characterization of phase states
3. Characterization of structural organization of matter
4. Characterization of polymorphic form of the active ingredient
5. Characterization of rheological behavior
6. Characterization of water activity and/or drying rate
7. Characterization of pH and buffering
8. Characterization of oleaginous components
9. Characterization of specific gravity
10. Characterization of metamorphosis-related changes

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*

- Excipient differences
- 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
- Additional performance tests (e.g., IVPT) may be required

Note: The packaging configuration itself may impact bioavailability

Characterization-based BE Approach

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
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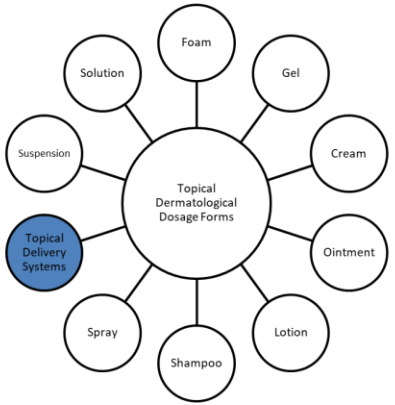
- In vivo systemic **PK** studies may be appropriate for some products

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_020126.pdf

Guidance for Topical Products

- **Topical Delivery Systems (TDS)**
  - An in vivo BE study with PK endpoints
  - An in vivo comparative adhesion study
  - An in vivo comparative irritation/sensitization study
  - Potentially a comparative CE study



Relevant Resources

- **General guidances**
  - Topical Dermatologic Corticosteroids: in Vivo Bioequivalence https://www.fda.gov/media/70931/download
  - Bioequivalence studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA" for the design and conduct of the PK BE study https://www.fda.gov/media/87219/download
  - Assessing Adhesion with Transdermal Delivery Systems and Topical Patches for ANDAs https://www.fda.gov/media/98634/download
  - Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs https://www.fda.gov/media/117569/download
  - Transdermal and Topical Delivery Systems – Product Development and Quality Considerations https://www.fda.gov/media/132674/download
- **Product-Specific Guidances for Generic Drug Development** https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances- generic-drug-development

Summary

- Topical products range from simple solutions to complex emulsions and delivery systems
- Within the scope of the GDUFA Research Program, the Agency has made significant advances in development of BE approaches for such products
- The Agency's current thinking is reflected in general and product-specific guidances (PSGs)
- Resources for product development
  - Follow the recommendation in the PSG to establish BE, if one is available, in conjunction with relevant general guidances
  - Product development meetings may be an efficient mechanism to engage with the Agency when utilizing alternative approaches

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