EUFEPS BABP Network
The Global Bioequivalence Harmonisation Initiative

U.S. FOOD & DRUG ADMINISTRATION

U.S. FDA Recommendation on Bioequivalence Demonstration of Topical Drug Products

Wenlei Jiang, Ph.D.

Senior Advisor for Innovation and Strategic Outreach

Co-contributors: Priyanka Ghosh, Sam G Raney and Markham Luke

Office of Research and Standards
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration (FDA)

September 29th, 2022

The 5th Global Bioequivalence Harmonization Initiative Conference
Amsterdam, Netherland

Disclaimer

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

Diverse Topical Dermatological Products

Foam

Spray

Shampoo

Drug Device Combination Product

Topical delivery systems (patches)

Solution

Suspension

Gel

Lotion

Cream

Ointment

Topical Dermatological Product Dosage Forms

Increased complexity

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

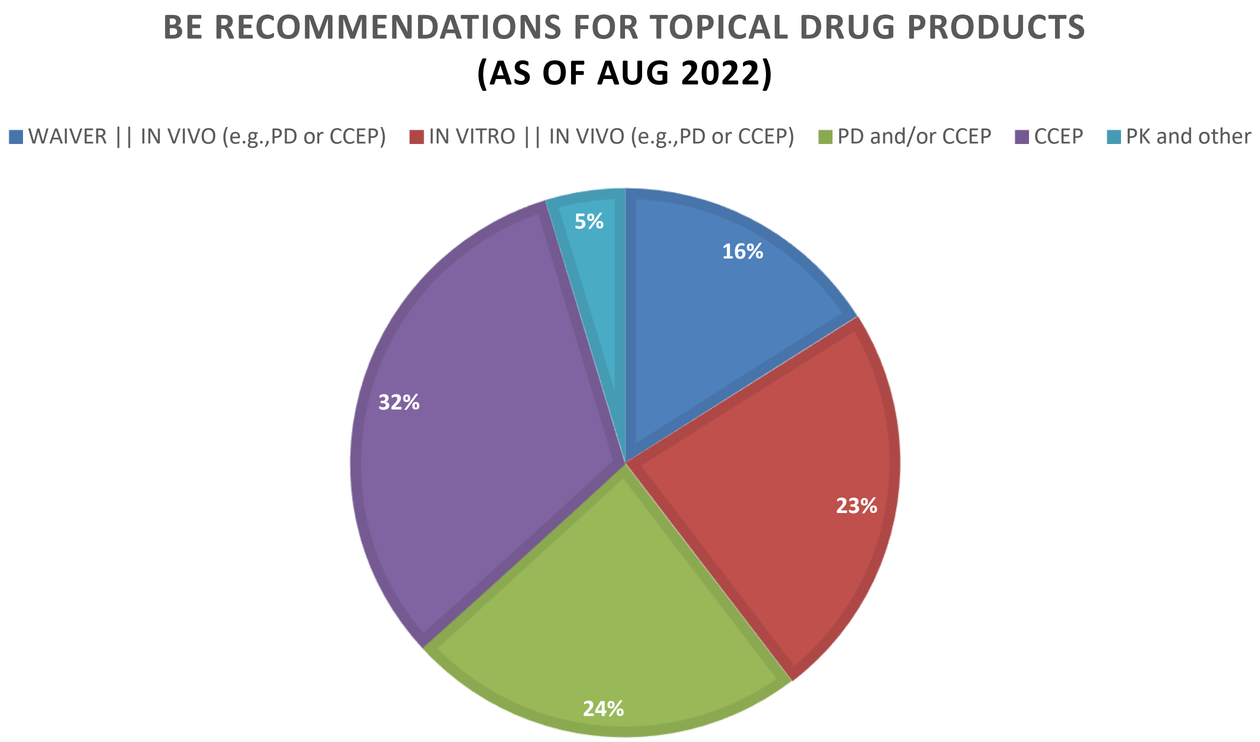
U.S. FDA Recommendation for Bioequivalence (BE) Demonstration for Topical Products

- Waiver of in vivo BE study
- In Vitro Methods to Support of BE Demonstration
  - Qualitative (Q1) and Quantitative (Q2) Sameness or '*No Difference*'
  - Physicochemical and Structural (Q3) Sameness/Similarity
  - IVRT (In Vitro Release Test)
  - IVPT (In Vitro Permeation Test)
- In Vivo/In Silico Methods to Support BE Demonstration
  - In Vivo Pharmacokinetic (PK) Studies
  - In Vivo Pharmacodynamic (PD, e.g., vasoconstrictor) Studies
  - In Vivo Comparative Clinical Endpoint (CCEP) BE Studies
  - In Silico Quantitative Methods, Modeling and Simulation (Research ongoing)

Concepts of Q1, Q2, Q3

- Q1: Components in a product
  - Q1 characterization of a reference product provides a profile of the qualitative components (ingredients) in that reference product
- Q2: Composition of a product
  - Q2 characterization of a reference product provides a profile of the quantitative formulation composition of that reference product
- Q3: Arrangement of matter in a product
  - Q3 characterization of a reference product provides a profile of physicochemical and structural attributes that is quintessentially characteristic of that reference product

BE Recommendations in Product-Specific Guidances



BE Demonstration for Solution-based Topical Products

Solution-based topical products

- Waiver of in vivo BE study
- *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…"

BE Demonstration for Solution-based 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

BE Demonstration for Complex Topical Products

- 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

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

Identify relevant Q3 properties for characterization depending on the state of the drug, formulation phase, and others.

Characterization-Based BE Approach for Topical Gel

Example: Draft Guidance on Metronidazole

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 for Topical Cream

Example: Draft Guidance on Metronidazole

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.

---

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

BE Demonstration for Topical Delivery Systems

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

For drug-device combination topical drug products, some specific considerations about device are provided.

Relevant Resources

- **General guidances**
  - Topical Dermatologic Corticosteroids: in Vivo Bioequivalence (June 1995) https://www.fda.gov/media/70931/download
  - "Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA" (Aug 2021) 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 (Oct 2018) https://www.fda.gov/media/98634/download
  - Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs (Oct 2018) https://www.fda.gov/media/117569/download
  - Transdermal and Topical Delivery Systems – Product Development and Quality Considerations (Nov 2019) https://www.fda.gov/media/132674/download

- **Product-Specific Guidances (PSGs) for Generic Drug Development**
  https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances- generic-drug-development

Summary

- Topical drug products range from simple solutions to complex emulsions and delivery systems.
- Depending on topical drug product complexity, in vitro and/or in vivo methods are recommended for BE demonstration.
- More characterization-based BE approaches are developed as an alternative to comparative clinical endpoint BE studies for demonstrating BE for complex topical drug products.
- Recommendations for topical drug product development
  - Follow the recommendations in the PSG to establish BE if one is available, in conjunction with relevant general guidances
  - Request product development meetings to engage with the Agency when utilizing alternative approaches if PSGs are not available or proposing different approaches

Acknowledgements

U.S. Food & Drug Administration

- Joseph Kotsybar, PharmD
- Megan Kelchen, PhD
- Tannaz Ramezanli, PharmD, PhD
- Mengmeng Niu, PhD
- Ying Jiang, PhD
- Ahmed Zidan, PhD
- Pahala Simamora, PhD
- Bing Cai, PhD
- Lei Zhang, PhD
- Robert Lionberger, PhD

U.S. FOOD & DRUG
ADMINISTRATION