BIOEQUIVALENCE OF GENERIC TOPICAL DERMATOLOGICAL DRUG PRODUCTS

Generic + Biosimilar Medicines Conference/ Complex Product Workshop
Session 3: Topical Dermatologic Cream
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Topical Dermatological Drug Products

PSGs for Topical Dermatological Products

Potential ways to establish bioequivalence (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

Generic Topical Product Development

- Other Methodologies of Interest
  - **In Vivo** Cutaneous PK Studies
    - ✓ Dermal Open Flow Microperfusion (dOFM)
    - ✓ Dermal Microdialysis (dMD)
    - ✓ Epidermal and/or Dermal Pharmacokinetic Tomography

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

PSGs for Topical Dermatological Products

- Formulation
  - What do we mean by no difference in inactive ingredients

1. In vitro option:

To qualify for the in vitro option to demonstrate bioequivalence for metronidazole topical gel, 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], 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.

Failure Modes (BE) – Drug Substance

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)

Failure Modes (BE) – Dosage Form

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

Mechanism and/or Site of Action

Is the Mechanism/Site of Action **Well Understood?**

- Acyclovir Topical Cream
- Benzyl Alcohol Topical Solution

An in vitro characterization-based approach may be recommended

Is the Mechanism/Site of Action **Not Well Understood?**

- Dapsone Topical Gel
- Ivermectin Topical Cream

If the mechanism and/or site of action may be (partially) systemic, an in vivo PK study may also be recommended

Regulatory Utility of Dermal PBPK Models

Generic drug approval

- Support alternative BE approaches
  - Comparative clinical endpoint BE studies may not be sensitive to formulation differences
  - BE assessment for Q1/Q2 formulations leveraging in vitro testing
- Define a “safe space” for formulation attributes
  - Risk assessments on the impact of product attributes on in vivo drug product performance
- Extrapolate BE assessments from healthy to diseased subpopulations

Source: 2018 SBIA OGD Complex Generic Drug Product Workshop

Regulatory Utility of Pharmacometric Approaches

How can pharmacometric approaches be leveraged?

- For designing an adequately powered comparative CE BE study

- To justify:
  - A shorter duration comparative CE BE study
  - Appropriate timepoints for comparative CE BE study
  - A pharmacodynamic endpoint in lieu of a CE

- Propose different endpoint, e.g., area under effect curve (AUEC), maximum effect (E_{max}) in place of fixed time point comparison

Outline for Breakout Session

- Product label for the (hypothetical) reference product
  - Components and composition
  - Dosage and administration
  - Indication
  - Mechanism/site of action
  - Other key information to consider for the product development and BE strategy
- Considerations related to formulation of the test product
  - Examine and compare potential product formulations
- Considerations related to BE strategy
  - Including PBPK-based approaches
- Considerations related to Q3 characterization and the packaging configurations

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ADMINISTRATION

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

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- To justify:
  - A shorter duration comparative CE BE study
  - Appropriate timepoints for comparative CE BE study
  - A pharmacodynamic endpoint in lieu of a CE

- Propose different endpoint, e.g., area under effect curve (AUEC), maximum effect (E_{max}) in place of fixed time point comparison

Generic Topical Product Development

- If a PSG is available
  - Follow the recommendation in the PSG to establish BE
  - Submit a pre-ANDA meeting request when you propose an alternative BE approach
  - Submit controlled correspondence (CC) for questions related to appropriateness of a formulation for a specific BE approach, etc.

- If PSG is Unavailable

  Steps toward the development of a generic topical product
  - Identify the reference product
  - Identify the studies proposed to support a demonstration of BE appropriate to the complexity of the dosage form
  - Submit a pre-ANDA meeting request with specific questions to obtain the Agency's feedback

Hypothetical Reference Product: RHEOMACREAM

Relevant sections of the product label:

This is a fictional drug label for a fictitious drug, designed for EDUCATIONAL PURPOSES ONLY. This fictitious label is not representative of a complete and accurate FDA approved drug label.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RHEOMACREAM™ Cream safely and effectively. See full prescribing information.

RHEOMACREAM™ Cream (Tanasone; Ardamethacin) topical cream, For topical use only

---------- **INDICATIONS AND USAGE** ----------

RHEOMACREAM™ Cream is a combination of Tanasone, and Ardamethacin, and is indicated for relief of signs and symptoms of rheumatoid arthritis in adults.

---------- **DOSAGE AND ADMINISTRATION** ----------

Apply a thin layer of the RHEOMACREAM™ Cream to the affected area twice daily.

---------- **DOSAGE FORMS AND STRENGTHS** ----------

RHEOMACREAM™ Cream exists in one strength: 0.1% Tanasone; 0.5% Ardamethacin

---------- **WARNING** ----------

RHEOMACREAM™ can cause serious skin adverse events such as exfoliative dermatitis and toxic epidermal necrolysis (TEN), which can be fatal. RHEOMACREAM™ Cream should be discontinued if rash or other signs of local skin reaction occur.

---------- **ADVERSE REACTIONS** ----------

Most common adverse reactions during application of RHEOMACREAM™ Cream in clinical trials were application site reaction and drowsiness.

See below for FDA-approved patient labeling

Revised: 10/2018

RHEOMACREAM™ Cream is available in tubes containing 50 g of the topical cream and pumps containing 70 g of the topical cream.

Hypothetical Reference Product : RHEOMACREAM

2 DOSAGE AND ADMINISTRATION

The proper amount of RHEOMACREAM™ Cream should be measured using the dosing card supplied in the drug product carton. The dosing card should be used for each application of drug product. The cream should be applied within the oblong area of the dosing card up to the 2 gram or 4 gram line. The dosing card can be used to apply the cream to the affected areas. The hands should then be used to gently rub the cream into the skin. Apply a thin layer of the cream to the affected area twice daily. Do not apply more than 6 g daily to any affected area. RHEOMACREAM™ Cream is not for oral, ophthalmic, or intravaginal use.

4 DESCRIPTION

RHEOMACREAM™ is an opaque, white oil in water emulsion-based cream, consisting of benzyl alcohol as a preservative, ceteareth-30, cetostearyl alcohol, mineral oil, phosphoric acid, propylene glycol, purified water, sodium phosphate monobasic monohydrate, and petrolatum.

- Ardamethacin is an odorless, white crystalline powder, insoluble in water and soluble in ethanol.
- Tanasone is a white to creamy-white, odorless crystalline powder, insoluble in water. Tanasone is the R-enantiomer and contains one chiral center.

5 CLINICAL PHARMACOLOGY

5.1 Mechanism of Action

Ardamethacin inhibits an enzyme that reduces the formation of prostaglandins. Tanasone is a corticosteroid with anti-inflammatory, and anti-pruritic properties. The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear. The exact mechanisms of action for the therapeutic efficacy of both drugs are not understood, and there is some evidence to suggest a mechanism of action for Ardamethacin in this indication via the central nervous system.

Formulation of the Test Product

- Steps to identifying an appropriate formulation
  - Deformulation (reverse engineering) of the reference product
  - Understanding limitations of information in the reference listed drug (RLD) label and FDA's inactive ingredient database (IID)
  - Developing a thorough understanding of the product by characterizing multiple (fresh and aged) batches of the reference product
  - Formulating the test product to match the reference product, determining critical quality attributes (CQAs), and failure modes for BE

Deformulation and Characterization

- Hypothetical Reference Product:
- Topical cream with two drug molecules
- Oil in water emulsion
- In the finished product ardamethacin is completely dissolved and tanasone is partially dissolved.
- The pH of the finished product is 5.5
- The reference product is available in tubes and non-metered pumps

Reverse engineering of the Reference Product

Ingredients	Function	% W/W
Tanasone,	Active ingredient	0.1
Ardamethacin,	Active ingredient	0.5
White Petrolatum	Emollient, oil phase	15.0
Mineral Oil	Emollient, oil phase	2.0
CetoStearyl Alcohol	Stiffening agent, emulsifier	12.5
Propylene Glycol	Solvent, humectant	10.0
Ceteareth-30	Emulsifier	1.8
Sodium Phosphate Monobasic Dihydrate,	Buffering agent	0.30
Sodium Hydroxide	pH adjuster	0.002
Phosphoric Acid	pH adjuster	0.006
Benzyl alcohol	Preservative	1.00
Purified water	Vehicle	57.79

Seeking Acceptability of a Formulation

Assessment of qualitative (Q1) and quantitative (Q2) sameness

✓ **Assessment of acceptability of a test formulation for the proposed BE approach**

- When the product-specific guidance (PSG) recommends that 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.
  - Via a controlled correspondence
- When there is no PSG for the reference product.
  - Via a pre-abbreviated new drug application (pre-ANDA) meeting request in parallel with proposing a specific BE approach

Acceptability of a Test Formulation

- Is the following formulation acceptable for the in vitro BE approach?

Test Formulation	
Ingredients	% W/W
Tanasone, USP	0.10
Ardamethacin, USP	0.50
Petrolatum, USP	15.00
Mineral Oil, USP	1.70
CetoStearyl Alcohol, NF	12.5 (The IID limit is 12%)
Propylene Glycol, USP	10.00
Ceteareth-30	1.80
Sodium Phosphate Monobasic Dihydrate, USP	0.30
Sodium Hydroxide, NF	0.004 (QS to target pH 5.5)
Phosphoric Acid, NF	0.006
Benzyl alcohol, NF	1.00
Purified water, USP	56.10

Reference Product Formulation	
Ingredients	% W/W
Tanasone, USP	0.10
Ardamethacin, USP	0.50
White Petrolatum, USP	15.00
Mineral Oil, USP	2.00
CetoStearyl Alcohol, NF	12.00
Propylene Glycol, USP	10.50
Ceteareth-30	1.80
Sodium Phosphate Monobasic Dihydrate, USP	0.30
Sodium Hydroxide, NF	0.002
Phosphoric Acid, NF	0.006
Benzyl alcohol, NF	1.00
Purified water, USP	57.00

Acceptability of a Test Formulation

- Is the following formulation acceptable for the in vitro BE approach?
  - May not be acceptable

Test Formulation	
Ingredients	% W/W
Tanasone, USP	0.10
Ardamethacin, USP	0.50
Petrolatum, USP	15.00
Mineral Oil, USP	1.70
CetoStearyl Alcohol, NF	12.5 (The IID limit is 12%)
Propylene Glycol, USP	10.00
Ceteareth-30	1.80
Sodium Phosphate Monobasic Dihydrate, USP	0.30
Sodium Hydroxide, NF	0.004 (QS to target pH 5.5)
Phosphoric Acid, NF	0.006
Benzyl alcohol, NF	1.00
Purified water, USP	56.10

Reference Product Formulation	
Ingredients	% W/W
Tanasone, USP	0.10
Ardamethacin, USP	0.50
White Petrolatum, USP	15.00
Mineral Oil, USP	2.00
CetoStearyl Alcohol, NF	12.00
Propylene Glycol, USP	10.50
Ceteareth-30	1.80
Sodium Phosphate Monobasic Dihydrate, USP	0.30
Sodium Hydroxide, NF	0.002
Phosphoric Acid, NF	0.006
Benzyl alcohol, NF	1.00
Purified water, USP	57.00

Acceptability of a Test Formulation

- How can you change your test formulation table below before submitting it to the Agency for an assessment?

Ingredients	Function	% W/W
Tanasone, USP	Active ingredient	0.1
Ardamethacin, USP	Active ingredient	0.5
White Petrolatum	emollient, oil phase	15
Mineral Oil, USP	emollient, oil phase	2
Cetyl alcohol plus stearyl alcohol	stiffening agent, emulsifier	12
Propylene Glycol, USP	solvent, humectant	10
Ceteareth-30	Emulsifier	1.8
Sodium Phosphate Monobasic Dihydrate, USP	buffering agent	0.35
Sodium Hydroxide, NF	pH adjuster	QS to 100
Phosphoric Acid, NF	pH adjuster	QS to 100
Benzyl alcohol, NF	preservative	1.0
Water, USP	Vehicle	QS to 100

Acceptability of a Test Formulation

- Quantitative nominal amount for each (and every) ingredient in the composition table
- Quantitative nominal amount specified to the same number of decimal places (at least two)
- The correct compendial grades and names of each excipient should be specified

Ingredients	Function	% W/W
Tanasone, USP	Active ingredient	0.10
Ardamethacin, USP	Active ingredient	0.50
White Petrolatum, USP	emollient, oil phase	15.00
Mineral Oil, USP	emollient, oil phase	2.00
Cetyl alcohol plus stearyl alcohol (Stenol® I665)	stiffening agent, emulsifier	12.00
Propylene Glycol, USP	solvent, humectant	10.00
Ceteareth-30 (EUMULGIN® B 3)	Emulsifier	1.77
Sodium Phosphate Monobasic Dihydrate, USP	buffering agent	0.35
Sodium Hydroxide, NF	pH adjuster	0.003^
Phosphoric Acid, NF	pH adjuster	0.006^
Benzyl alcohol, NF	preservative	1.00
Purified Water, USP	Vehicle	58.00

^ QS to pH 5.5

BE Strategy

Hypothetical Reference Product:

- The reference product is indicated for relief of signs and symptoms of rheumatoid arthritis in adults.
- Ardamethacin inhibits an enzyme that reduces the formation of prostaglandins. Tanasone is a corticosteroid with anti-inflammatory, and anti-pruritic properties.
- Potential BE approaches for the hypothetical product:
  - Comparative clinical endpoint study and vasoconstrictor (VC) studies
  - In vitro characterization-based BE approach (and systemic pharmacokinetic study)
  - Combination of the In vitro characterization-based BE and in silico approach

Considerations for BE Approach

Scenario 1: The PSG is not published. If you propose a characterization-based BE approach, what studies would you include for this approach?

- First step: To identify the complexities associated with the reference product related to
  - Solubility of the active ingredient in the formulation
  - Formulation/dosage form
  - Site/mechanism of action

Considerations for BE Approach

Scenario 1: There is no PSG for the reference product. If you propose a characterization-based BE approach, what studies should you include for this approach?

- Formulation sameness (The test product contains 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).
- Similar physical/structural properties (Q3)
- Equivalent drug release rate through in vitro release test (IVRT) for both of the active ingredients
- Equivalent rate and extent of permeation through human skin using a validated in vitro permeation test (IVPT) for both of the active ingredients

Considerations for BE Approach

Scenario 2: The PSG recommends an in vitro characterization-based BE approach (formulation sameness, Q3, IVRT and IVPT) and an in vivo PK study with a single-dose, two-way, crossover design.

1) You are proposing to establish BE using a Q1/Q2 formulation by showing Q3 similarity, IVRT, and in vivo PK. Will your pre-ANDA product development meeting with the Agency for an alternative BE approach be granted?

- Your meeting may be granted if you submit sufficient justifications and propose alternative studies to provide relevant information about the cutaneous PK of the drug product in order to support the proposed BE approach for your test product.

Considerations for BE Approach

2) You are trying to establish BE using a Q1/Q2 formulation by showing Q3 similarity, IVRT and using PBPK modeling. How can you solicit feedback from the FDA regarding acceptability of your proposed BE approach? What information should you submit to the agency at this stage?

– A PBPK model could serve multiple purposes in an ANDA. From a BE perspective, a PBPK model could be used to justify an alternative BE approach such as not conducting IVPT or in vivo studies depending on the product of interest. It could be used to justify any difference in in vitro BE results between the test product and reference product. Given the novelty of utilizing a PBPK model in an ANDA, the pre-ANDA product development meeting in GDUFA II would be the suitable choice for soliciting feedback from the FDA.

Considerations for BE Approach (cont'ed)

2) You are trying to establish BE using a Q1/Q2 formulation by showing Q3 similarity, IVRT and using PBPK modeling. How can you solicit feedback from the FDA regarding acceptability of your proposed BE approach? What information should you submit to the agency at this stage?

– While the full modeling report is not required at this stage, information that is provided can lead to a better discussion of the model application. Since the model intends to replace IVPT and an in vivo PK study, the model needs to be verified (assumptions/limitations/refinement) and validated for its intended purpose. It is expected that the model performance will be assessed against observed data of local (IVPT, biopsy, dermal microanalysis) and systemic exposure (plasma) for the same or similar drug products. It is expected that the virtual BE studies performed using the proposed model are adequately designed and documented in the modeling report.

Physical and Structural Characterization

1) What Q3 tests are recommended as part of in vitro characterization-based approach for this product?

Note:

- The reference product is an O/W emulsion cream.
- In the finished product ardamethacin is completely dissolved and tanasone is partially dissolved.

Reference Product Formulation	
Ingredients	% W/W
Tanasone, USP	0.10
Ardamethacin, USP	0.50
White Petrolatum, USP	15.00
Mineral Oil, USP	2.00
CetoStearyl Alcohol, NF	12.00
Propylene Glycol, USP	10.50
Ceteareth-30	1.80
Sodium Phosphate Monobasic Dihydrate, USP	0.30
Sodium Hydroxide, NF	0.002
Phosphoric Acid, NF	0.006
Benzyl alcohol, NF	1.00
Purified water, USP	57.00

Physical and Structural Characterization

1) What Comparative Q3 tests are recommended as part of in vitro characterization-based approach for this product?

- The recommended Q3 tests may include, but are not limited to,
  - assessment of appearance,
  - microscopic images at multiple magnification,
  - globule size distribution,
  - particle size distribution of tanasone,
  - polymorphic form and crystal habit of tanasone,
  - rheological behavior of the cream product and
  - pH.

Physical and Structural Characterization

2) You are developing a generic version of the hypothetical product with only one packaging configuration (pump). What data could support your test product is BE to both packaging configurations of the reference product?

   - You could perform the comparative Q3 tests of the formulation inside the tube and pump and compare the formulation dispensed from the pump for both the reference and your test product.

Physical and Structural Characterization

3) The RLD is discontinued. What would you use as reference product to conduct the comparative in vitro studies?

- In this situation you may use the reference standard (RS). You may submit a CC to the Agency to get clarification about this issue.

Conclusions

- Developers of complex topical dermatological drug products can ensure that the products are of high quality and can bring greater predictability and timeliness to the review of generic drug applications by
  - Demonstrating a comprehensive understanding of the product complexities and manufacturing issues.
  - Providing information that mitigates risks of potential failure modes for therapeutic equivalence.
  - Initiating pre-ANDA communication with the FDA during product and program development, if
    - Proposing a BE approach when the PSG is not available,
    - Proposing an alternative BE approach,
    - Proposing to use novel techniques such as modeling and simulation approaches.

Conclusions

- A good Pre-ANDA product development meeting package
  - Should clearly characterize the complexity of the drug product.
  - Should contain the formulation composition of the test product.
  - Should provide clear and concise information about how the proposed approach can systematically mitigate concerns related to potential failure modes for BE.
  - Should contain sufficient data and rationale to support the questions.
  - Should include the information to support the feasibility of any proposed novel techniques.
  - If a modeling and simulation approach is proposed, should contain a clear presentation of how the model will be used and how the model will be verified.

Mock Pre ANDA Question 1

- If the maximum concentration of cetostearyl alcohol in the IID is 12% for a topical emulsion-based cream product but the results of your reverse engineering of the reference product indicates that the concentration of the cetostearyl alcohol in the reference product is 12.5%. What could you do to facilitate assessment of your test formulation?

Ingredients	Function	% W/W
Tanasone,	Active ingredient	0.1
Ardamethacin,	Active ingredient	0.5
White Petrolatum	emollient, oil phase	15.0
Mineral Oil	emollient, oil phase	2.0
CetoStearyl Alcohol	stiffening agent, emulsifier	12.5
Propylene Glycol	solvent, humectant	10.0
Ceteareth-30	Emulsifier	1.8
Sodium Phosphate Monobasic Dihydrate,	buffering agent	0.30
Sodium Hydroxide	pH adjuster	0.002
Phosphoric Acid	pH adjuster	0.006
Benzyl alcohol	preservative	1.00
Purified water	Vehicle	57.79

Acceptability of a Test Formulation

- If the maximum concentration of cetostearyl alcohol in the IID is 12% for a topical emulsion-based cream product but the results of your reverse engineering of the reference product indicates that the concentration of the cetostearyl alcohol in the reference product is 12.5%. What could you do to facilitate assessment of your test formulation?
  - One option may be to submit at least two test formulations, one with 12% and the other with 12.5% cetostearyl alcohol concentration and ask the Agency about the acceptability of the proposed formulations for a proposed BE approach, as well as whether additional safety studies are needed to support a 12.5% concentration of cetostearyl alcohol in your test formulation. Also submit results for the reverse engineering of the reference product and explain the apparent discrepancy with the IID limit.

Ingredients	Function	% W/W
Tanasone,	Active ingredient	0.1
Ardamethacin,	Active ingredient	0.5
White Petrolatum	emollient, oil phase	15.0
Mineral Oil	emollient, oil phase	2.0
CetoStearyl Alcohol	stiffening agent, emulsifier	12.5
Propylene Glycol	solvent, humectant	10.0
Ceteareth-30	Emulsifier	1.8
Sodium Phosphate Monobasic Dihydrate,	buffering agent	0.30
Sodium Hydroxide	pH adjuster	0.002
Phosphoric Acid	pH adjuster	0.006
Benzyl alcohol	preservative	1.00
Purified water	Vehicle	57.79