How to Structure Efficient Development Programs for Generic Topical Drug Products

Lessons Learned from Experience

Innovations in Dermatological Sciences

FDA: Development of Complex Generic Topical Products

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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.

Outline

- Product label for the reference product
  - Identify the ingredients, dosage and administration, indication, mechanism/site of action and other key information to consider for the product development and bioequivalence (BE) strategy
- Reference listed drug (RLD) product's formulation table
- Considerations related to formulation of the test product
  - Examine and compare potential product formulations
- Considerations related to BE strategy
- Considerations related to physical and structural (Q3) characterization and the packaging configurations

Hypothetical RLD: 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 RLD: 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.

Deformulation of the RLD

- Reverse-engineering of the RLD
- Understanding limitations of information in the RLD's label and FDA's inactive ingredient database (IID)

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

Characterization of the RLD

- 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

RHEOMACREAM :

- 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 RLD is available in tubes and non-metered pumps

Is RHEOMACREAM a complex drug-device combination product?

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 RLD.
  - 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?
  - 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

RLD 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

- 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 RLD indicates that the concentration of the cetostearyl alcohol in the RLD 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 RLD 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

Acceptability of a Test Formulation

- How would 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

- Potential BE approaches for the hypothetical RLD:
  - Comparative clinical endpoint study and vasoconstrictor (VC) studies
  - In vitro characterization-based BE approach (and systemic pharmacokinetic (PK) study)
  - Combination of the In vitro characterization-based BE and in silico approach

Considerations for BE Approach

Scenario 1: The PSG for this product recommends two types of studies: 1) VC studies and 2) a comparative clinical endpoint BE study. The primary endpoint for the clinical endpoint study is after 24 weeks of treatment.

- You want to conduct the comparative clinical endpoint BE study with the primary endpoint evaluated after 6 (not 24) weeks. How do you solicit the FDA's feedback on the acceptability of your proposed BE study?
  - As part of a pre-ANDA meeting, for example, an applicant might demonstrate that a 6-week study is appropriately sensitive, that it can differentiate formulation differences, and that the proposed study duration is clinically relevant.

    You can use modeling and simulation methods to support the earlier endpoint; simulate different scenarios (specify the conditions for these scenarios), and describe the acceptance criteria to conclude that 6 weeks timepoint may be acceptable.

Considerations for BE Approach

Scenario 2: 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 RLD related to
  - Solubility of the active ingredient in the formulation
  - Formulation/dosage form
  - Site/mechanism of action

Considerations for BE Approach

Scenario 2: There is no PSG for the RLD. If you propose a characterization-based BE approach, what studies should you include for this approach?

- Formulation sameness as the RLD (The test product contains no difference in inactive ingredients or in other aspects of the formulation relative to the RLD 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 3: The PSG recommends an in vitro characterization-based BE approach (formulation sameness, Q3, IVRT and IVPT) + 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. Are you eligible for pre-ANDA product development meeting with the Agency for an alternative BE approach?

- You may be eligible 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 Physiologically based-PK (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 RLD/RS. 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.

While the full modeling report is not required for the product development meeting, 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 study with PK endpoints, it is expected that the model performance will need to be assessed against observed data of local (IVPT, biopsy, dermal microanalysis etc.) and systemic exposure (plasma) for the same or similar drug products.

Physical and Structural Characterization

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

Note:

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

RLD 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, pH, particle size distribution of tanasone, polymorphic form and crystal habit of tanasone, and rheological behavior of the cream product.

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 RLD?

   - 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

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