Best Practices & Efficient Strategies for Generic Topical Product Development

Complex Generic Drug Product Development Workshop

Session 2: Scientific and Regulatory Advances for Generic Topical and Transdermal Product Development

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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

- Considerations related to the formulation of the test product
- Considerations related to the bioequivalence (BE) approaches
- Considerations related to physical and structural (Q3) characterizations and the packaging configurations

Formulation of the Test Product

- Steps to identifying the proper formulation
  - Understanding limitations of information in the reference listed drug (RLD) label and FDA's inactive ingredient database (IID)
  - Deformulation (reverse engineering) of the reference product
  - 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 RLD:

- 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

Reverse engineering of the RLD

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 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?
  - No

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

- 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

Hypothetical RLD:

- The RLD 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

In vitro BE Studies

Identifying the complexities of the RLD:

- Formulation: solution, semisolid single-phase, semisolid multi-phase
- Solubility of the drug in the formulation: dissolved …. undissolved
- Site/mechanism of action: local ….. local + systemic

Considerations for BE Approach

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

- You want to conduct the comparative clinical endpoint BE study and assess the therapeutic equivalence of your test product after 6 weeks of application instead of the 24 weeks recommended in the PSG. 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.

Considerations for BE Approach

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

- Formulation sameness as the reference product (The test product 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).
- 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 pharmacokinetic (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.

Physical and Structural Characterization

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

- Topical cream with two drug molecules
- In the finished product ardamethacin is completely dissolved and tanasone is partially dissolved.
- The pH of the finished product is 5.5.
- The maximum potency of CetoStearyl Alcohol in the inactive ingredient database (IID) is 12% for a topical cream product.
- Ceteareth-30 does not have a compendial grade.

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	13.0
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	57.29

Physical and Structural Characterization

1) What 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, pH, particle size distribution of tanasone, globule size distribution, 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 is needed to support your test product is BE to both packaging configurations of the RLD?

   - You should 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.

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 modeling is involved, should contain a clear presentation of how the model will be used and how the model will be verified

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