Scientific and Regulatory Considerations for Q3 Characterization of Topical Products

SBIA Webinar on Best Practices for Topical Generic Product Development and ANDA Submission

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The Concepts of Q1, Q2, Q3

Q1: Components in a topical product

- Q1 characterization of a topical product provides a profile of the qualitative components (ingredients) in that product

Q2: Composition of a topical product

- Q2 characterization of a topical product provides a profile of the quantitative formulation composition of that product

Q3: Arrangement of matter in a topical product

- Q3 characterization of a topical product provides a profile of physicochemical and structural attributes that is quintessentially characteristic of that product

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

Basic Q3 Characterization

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2. Characterization of phase states
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Comprehensive 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

Utility of Q3 Characterization

1. To describe a **dosage form**:
   - **Basic** Q3 characterization of a topical product can be used to describe its dosage form (e.g., an emulsion).
   - **Basic** Q3 characterizations, ***compared*** for both the test topical product and the reference standard (RS), can demonstrate that the two products are the same dosage form.

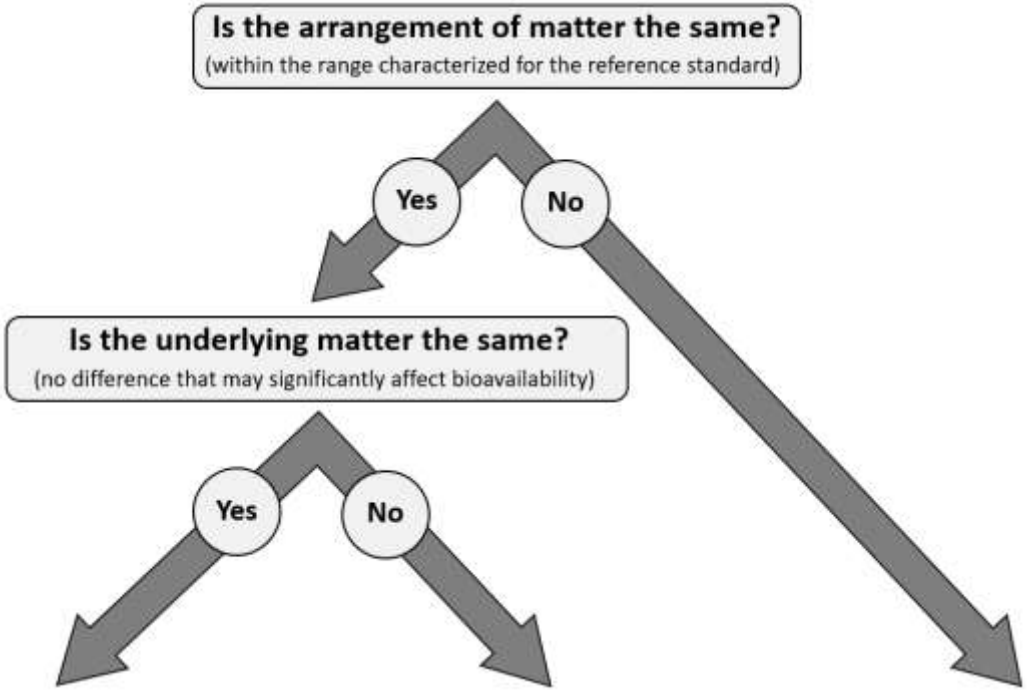
Utility of Q3 Characterization

2. To support a demonstration of **bioequivalence (BE)**:

   - **Comprehensive** Q3 characterization of a topical product can be used to compile a detailed profile of Q3 attributes that specifically describes the nature of that product and the arrangement of matter that may modulate the systemic or local availability of the active ingredient(s) from the product.

   - **Comprehensive** Q3 characterizations, ***compared*** for both the test topical product and the RS, can demonstrate that there are no significant differences in Q3 attributes between the two products (this substantially mitigates the risk of potential failure modes for BE that may otherwise arise from any differences in Q3 attributes).

Product-Specific Guidances (PSGs)



Generally eligible for characterization-based bioequivalence approaches in current PSGs

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Generally eligible for traditional in vivo bioequivalence approaches in current PSGs

Q1/Q2 Sameness vs. NSD

- **NSD** (No Significant Difference) formulation assessments are based upon principles for assessing Q1 and Q2 sameness, but also consider certain differences that have previously been determined to be acceptable based on available scientific evidence.
- Certain minor differences in components and composition may also be acceptable based upon:
  - Information available to FDA
  - Evidence submitted in an ANDA (e.g., demonstrating no significant difference in the local or systemic availability of the active ingredient relative to the RS)

Assessment in Relation to the RS

- When the reference listed drug (RLD) for a topical product is discontinued, it may not be feasible to ascertain its Q1 and Q2 attributes.
- The RS for a topical product may not be Q1 or Q2 the same as the RLD.
- A test topical product may be assessed in relation to the RS.

Assessment of Ingredient Grade

- The RS may contain a specific grade of an inactive ingredient (e.g., Carbopol 934P or Petrolatum, USP)
- A test topical product may be considered to have **NSD** if it contains minor differences in ingredient grade. For example:
  - Carbopol 974P instead of Carbopol 934P
  - White Petrolatum, USP instead of Petrolatum, USP
- The acceptability of such ingredients would be determined during ANDA assessment.

Assessment of Sub-Components

- The RS may contain a proprietary ingredient that is a pre-blended mixture of **specific** quantitative amounts of sub-components.
- A test topical product may be considered to have **NSD** if it contains the same quantitative amounts of each sub-component, rather than using the proprietary ingredient.
- The acceptability of such ingredients would be determined during ANDA assessment.

Assessment of Sub-Components

- The RS may use a proprietary ingredient that is a pre-blended mixture of **variable** quantitative amounts of sub-components.
- A test topical product may be considered to have **NSD** if it contains quantitative amounts of each sub-component within the ranges that were found acceptable for the RS product.
- The acceptability of such ingredients would be determined during ANDA assessment.

Assessment of Ingredient Form

- The RS may contain an ingredient (e.g., Edetate disodium, USP) which may exist in a dihydrate form or an anhydrous form.
- A test topical product may be considered to have **NSD** if it contains a different (hydrate) form of the ingredient, with adjustments to the quantitative amount of the pure ingredient (and water).
- The acceptability of such ingredients would be determined during ANDA assessment.

Assessment of Ingredient Purity

- The RS may contain an ingredient of specific purity; e.g., Alcohol, USP, which is comprised of an amount of alcohol equivalent to 73.5% (w/w) alcohol as 95% alcohol (v/v), or 72.57% (w/w) of alcohol as 96% alcohol (v/v).
- A test topical product may be considered to have **NSD** if it contains a different purity of the ingredient, with adjustments to the quantitative amount of the pure ingredient (and water).
- The acceptability of such ingredients would be determined during ANDA assessment.

Assessment of Color or Fragrance

- The RS may contain a specific color or fragrance ingredient.
- A test topical product may be considered to have **NSD** if it contains a different color or fragrance than the RS, if it does not affect the bioavailability of the active ingredient and does not affect the safety of the drug product.
- The acceptability of such ingredients would be determined during ANDA assessment.

Assessment of pH Modifier

- The single point nominal amount of a pH modifier in the RS composition table may not reflect the quantitative range determined to be acceptable for the RS or may be specified as a quantity sufficient (q.s.) to achieve a target pH for the RS.
- A test topical product may be considered to have **NSD** if it does not contain the same nominal amount of a pH modifier, as long as the pH of the test topical product and RS match.
- The acceptability of such ingredients would be determined during ANDA assessment.

Conclusions

- Q3 characterization of an RS provides a profile of physicochemical and structural attributes that is quintessentially characteristic of that RS; these attributes may potentially be critical to product performance
- Basic Q3 characterization can demonstrate that a test topical product and its RS are the same dosage form
- Comprehensive Q3 characterization establishes a detailed profile of measurements for Q3 attributes that may be critical to product performance; when these are the same for a test topical product and its RS, it can support a demonstration of bioequivalence

Conclusions

- Generic topical products are generally eligible for in vitro characterization-based bioequivalence approaches described in current PSGs when:
  - there is NSD in inactive ingredients or other aspects of the formulation that may significantly affect local or systemic bioavailability, and
  - each relevant Q3 attribute of the test topical product, characterized in multiple batches, is demonstrated by the applicant to be within the range characterized for that Q3 attribute of the RS (e.g., in multiple batches), or determined by FDA to be within the acceptable variability for the RS

Communication with FDA

- Applicants intending to submit an ANDA for a topical product that relies upon a Q3-characterization-based bioequivalence approach, for which relevant recommendations have not been published in a PSG, are encouraged to request a pre-ANDA meeting with the FDA to discuss their proposed BE approach
- A pre-ANDA product development meeting package should include data and information on Basic Q3 characterization of the test topical product and its RS, and product characterizations relevant to the nature and complexity of the product that may help identify potential (therapeutic) failure modes for the product

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