Formulation Considerations for In Vitro Characterization Based Approaches of Locally Acting Complex Generic Drug Products

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In Vitro Characterization Based Approaches for Demonstrating Equivalence of Locally Acting Complex Generic Drug Products

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Overview

- Generic formulation CFR requirements vs bioequivalence (BE) approaches
  - Q1 (Qualitative) /Q2 (Quantitative) sameness and “no difference”
- Case study examples of in vitro BE approaches for locally acting complex products:
  - Complex Topical Ophthalmics (e.g., suspension, emulsion, ointments, and gels)
  - Complex Topical Dermatologics (e.g., creams, lotions, ointments, and gels)
- Best practice of asking FDA formulation assessment questions and considerations when proposing a formulation

Importance of Formulation

- Formulation is the foundation of a generic drug development approach and critical to supporting approval
- Establishing generic formulation sameness to the reference listed drug (RLD) reduces potential BE failure modes and thereby may support a BE approach
  - Eligibility of certain waivers of in vivo BE studies rely upon Q1/Q2 sameness to the reference listed drug (RLD): e.g., 21 CFR 320.22(b)
  - Product-Specific Guidances (PSGs) may recommend different BE approaches depending on generic formulation comparison to the RLD
- Some routes of administration have formulation constraints with specified permissible differences generally acceptable for an ANDA submission

CFR Requirements on Generic Formulations

Section 314.94 Content and format of an ANDA

- (a)(9) Chemistry, manufacturing, and controls

➢ (ii) Inactive ingredients. Unless otherwise stated in paragraphs (a)(9)(iii) through (a)(9)(v) of this section, **an applicant must identify and characterize the inactive ingredients in the proposed drug product** and provide information **demonstrating that such inactive ingredients do not affect the safety or efficacy** of the proposed drug product (emphasis added)

➢ (iii)–(v) Specific inactive ingredient requirements for parenteral, ophthalmic, otic, inhalation, and topical drug products, and changes permitted for such products

Formulation Considerations for Different Routes of Administration

Ophthalmic 21 CFR 314.94(a)(9)(iv)

- Generally, a drug product intended for ophthalmic or otic use must contain the same inactive ingredients and in the same concentration as the RLD... However, an applicant may seek approval of a drug product that differs from the [RLD] in ***preservative, buffer, substance to adjust tonicity, or thickening agent*** …., an applicant may not change a buffer or substance to adjust tonicity for the purpose of claiming a therapeutic advantage over or difference from the listed drug (emphasis added)
- **FDA Guidance:**[1] FDA has determined that, as a scientific matter, any qualitative or quantitative deviations from the RLD in exception excipients may necessitate the need to conduct an additional in vivo bioequivalence study.

Topical 21 CFR 314.94(a)(9)(v)

- Generally, a drug product intended for topical use,… shall contain the same inactive ingredients as the reference [product] …. However, an ANDA may include different inactive ingredients provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.
- A product-specific guidance recommend a BE approach with a "no difference" in formulation that may significantly affect the local or systemic availability of the active ingredient

1. FDA Guidance for Industry, *Determining Whether to Submit an ANDA or a 505(b)(2) Application* (May 2019)

Current In Vitro BE Recommendation for Complex Locally Acting Topical Ophthalmics

- **Formulation Q1/Q2 Sameness:** The test and RLD products are qualitatively and quantitatively same
- **Comparative Physicochemical Characterization** : The physicochemical properties (e.g., appearance, pH, specific gravity, osmolality) conducted on at least three batches of test and RLD products are similar
- **Comparative Particle Size Distribution Study**
- **Comparative In Vitro Drug Release Study (IVRT)**

Formulation Sameness Assessment (Q1/Q2)

- Q1: Qualitatively the same inactive ingredients
  - An applicant should provide the ingredient name and, if needed, information on the chemistry and comparative characterization data, to support inactive ingredient sameness
- Q2: Quantitively the same amount of inactive ingredients
  - An applicant should list the amount of all ingredients, except those used on an as needed (i.e., quantity sufficient (q.s.)) basis, to a minimum of two decimal places[1] and should be reported in % w/w and/or mg/mL
    - Recommended that applicants include any calculations/equivalent amount for ingredients that may be added on a volume basis (e.g., mL/mL)
  - Generally, FDA has interpreted Q2 sameness to mean a concentration that is within 95-105% of the RLD concentration

1. It is recommended that consistent number of decimal places be used for all ingredients if an ingredient is reported out to more than two decimal places

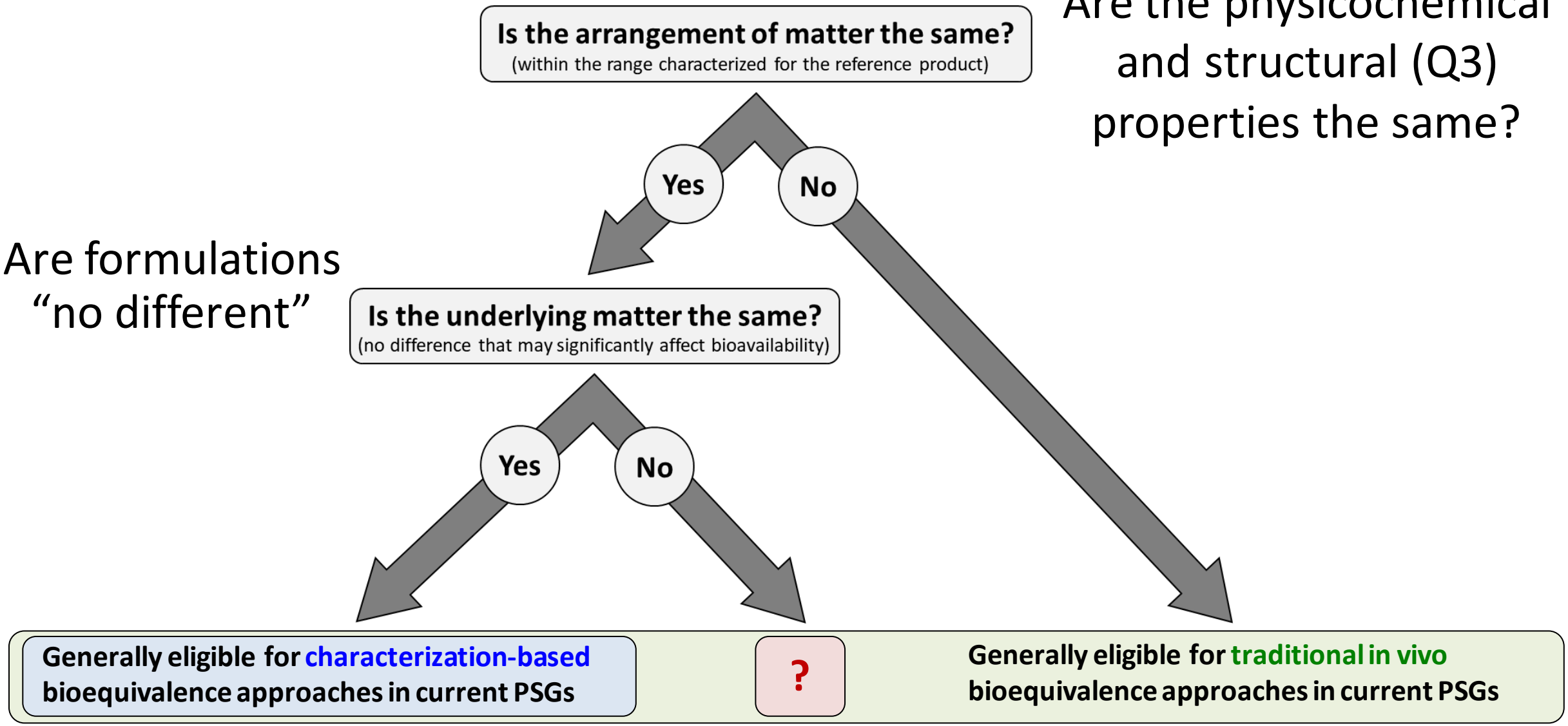
Justifying Quantitative (Q2) Differences

- In some instances, an applicant may include additional information such as reverse engineering and/or rationale for why a proposed ingredient may not be within or limited to ±5% of a nominally listed amount. For example,
  - Ingredients for which variability in the RLD may be more than ±5%
    - Provide information in a pre-ANDA correspondence or meeting request to support the observed RLD variability and that the proposed amount in the test product is within the RLD range
  - Buffers where the equilibrium ratio (concentration) of buffer components may not be within ±5% of the original amount of each component added
    - Provide information that the total buffer concentration (buffer capacity) of the test product is ±5% of the RLD and that the pH is similar

Current BE Recommendations for Complex Locally Acting Topical Dermal

- **Formulation:** The test and reference products are “no different”
- **Q3 Studies**: The physicochemical and structural (Q3) properties of test and reference products are matched
- **In Vitro Release Test (IVRT) Studies**: The test and reference products have an equivalent rate of drug release
- **In Vitro Permeation Test (IVPT) Studies**: The test and reference products have an equivalent rate and extent of drug permeation through excised human skin

Considerations for Locally Acting Topical Product BE Approaches



Clarifying Formulation Assessment for Products Not Required to be Q1/Q2

Drug products not required to be Q1/Q2 the same as the reference listed drug, such as topical dermatological products, may be eligible for a characterization-based BE approach when:

- 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:
  - The test product has similar physical and structural (Q3) characteristics to the reference product
  - The test product has an equivalent rate of drug release compared to the reference product
  - Evidence from in vitro studies support a demonstration of BE

Q1/Q2 Sameness vs. “No Difference”

Q1/Q2 Sameness

- All of the same components in the same concentrations as the RLD product.
- Ingredient concentrations should be within 95-105% of the RLD concentration

“No Difference”

- Based upon principles for assessing Q1/Q2 sameness, but also considers differences that have previously been determined to be acceptable (e.g., RLD and/or Reference Standard (RS)) based on available scientific evidence
- May be Q1/Q2 same, but not necessarily
- Does not mean that any formulation would be acceptable

Assessment of Ingredient Grade

Q1/Q2 Sameness

- In general, different grades of an ingredient are not considered to be a Q1 difference.[1]
- However, what may be considered different grades of an ingredient can be complicated.
  - Is Carbopol 974P the same as Carbopol 934P?
  - Is White Petrolatum, USP the same as Petrolatum, USP?

"No Difference"

- A test product may be suitable if it contains Carbopol 974P instead of Carbopol 934P and White Petrolatum, USP instead of Petrolatum, USP.
- The acceptability of such difference would be determined during ANDA assessment.

1. The grade of an ingredient should be appropriate to ensure the safety and quality of the product.

Assessment of Sub-Components

Q1/Q2 Sameness

- Q1 sameness of an ingredient that is comprised of a mixture of sub-components can be complicated.
- The reference product may use a proprietary ingredient that is a pre-blended mixture of specific quantitative amounts of sub-components.

"No Difference"

- A test product may be suitable if it contains the same quantitative amounts of each sub-component, rather than using the proprietary blended ingredient.
- The acceptability of such difference would be determined during ANDA assessment.

Assessment of pH Adjusters

Q1/Q2 Sameness

- pH adjusters are not "exception excipients", so a generic formulation should use the same pH adjuster ingredients as the RLD, even those that may be used on as needed basis (q.s.).
- If the RLD has a q.s. amount of pH adjuster the generic product may propose a fixed or q.s. amount.
- If the RLD has a fixed amount of pH adjuster the generic product should include a fixed amount that is within the Q2 limits of 95 -105% of the RLD amount.

"No Difference"

- A test product may be suitable if it does not contain the same nominal amount of a pH modifier, as long as the pH and other Q3 properties of the test and reference product match.
- The acceptability of such difference would be determined during ANDA assessment.

Where /How to Ask Formulation Questions

- For parenteral, ophthalmic, and otic dosage forms where Q1/Q2 sameness is required by regulation, an applicant may submit a controlled correspondence to request a Q1/Q2 assessment for up to three proposed formulations
  - Draft Guidance for Industry, *Controlled Correspondence Related to Generic Drug Development* (December 2020) https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm583436.pdf
  - If co-packaged as product and diluent, a Q1/Q2 assessment is made on the entire drug product and not on the individual components

Where /How to Ask Formulation Questions (continued)

- For routes of administration where regulations **do not** require Q1/Q2 sameness:
  - A non-Q1/Q2 application may be submitted to FDA, so sending controlled correspondence asking if a formulation is Q1/Q2 is **not** recommended (see Controlled Correspondence Guidance)
  - However, a test product's formulation (e.g., Q1/Q2, 'no difference', or different) may determine if a BE approach recommended in a product-specific guidance (PSG) would be suitable
    - You may submit a controlled correspondence asking if (up to 3) proposed formulations may be eligible for a specific BE option recommended in a PSG

Where /How to Ask Formulation Questions (continued)

- For routes of administration where regulations do not require Q1/Q2 sameness and there is no PSG available, or the posted PSG does not have a formulation consideration BE option, you may propose a BE approach that includes matching the test formulation to the reference product as part of demonstrating BE and ask FDA[1] if it *is acceptable to use such a BE approach with your proposed generic formulation.*

1. It is currently suggested that these requests be submitted as a pre-ANDA meeting request.

General Considerations When Submitting a Formulation Assessment Request

- Specify the quantitative amount of each inactive ingredient
- Specify the target value if the term “quantity sufficient” (q.s.) is used
- Specify the nominal amount, not including any overages
- Use matching names of compendial standards and/or trade name if such materials are used
- The amount of any inactive ingredient should generally be aligned with the relevant limit in the FDA’s Inactive Ingredient Database (IID)
- Perform comparative characterizations on complex inactive ingredients if recommended by product-specific guidance

Special Considerations: RLD Labeling

- If you believe there is an error in the RLD labeling or the FDA's response to your formulation assessment question:
  - Provide detailed information (e.g., characterization data that detect a component not listed in the labeling, literature, etc.) that supports your position
  - Submit another controlled correspondence or a pre-ANDA meeting request

Summary

- Qualitative (Q1) and Quantitative (Q2) sameness refers to the same inactive ingredients (identity) and amounts (each within ±5%) to the RLD.
- "No Difference" is based upon principles for assessing Q1/Q2 sameness, but also considers differences that have previously been determined to be acceptable (e.g., RLD and/or RS) based on available scientific evidence
- A bioequivalence approach may depend on the generic formulation comparability to the RLD the product .
  - A product-specific guidance may recommend an in vitro BE approach for a qualitatively and quantitatively comparable product, e.g., Q1/Q2 or "no difference".
- Focus your questions about formulation assessments on whether specific formulations may be considered suitable for a specified BE approach.

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    - Team of orally inhaled, nasal, and drug-device combination products
    - Team of topical dermatological and transdermal products
    - Team of immediate-release oral dosage form products
  - Office of Bioequivalence
  - Office of Generic Drug Policy
  - Office of Regulatory Operations
    - Division of Filing Review

Questions?


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