General Guidances

Characterization-Based Bioequivalence Approaches for Topical Products
Part 1: Q3 Guidance

SBIA 2023—Advancing Generic Drug Development:
Translating Science to Approval

Day (1), Session (1): Noteworthy Guidances and Generic Approvals for Topical and Transdermal Products

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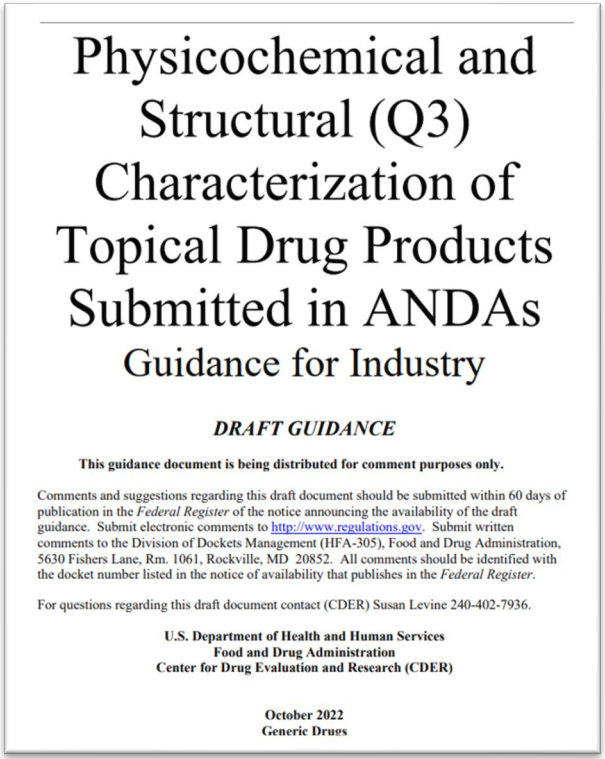
Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Learning Objectives

- Key concepts in the General Guidance
  - Concepts of Q3 sameness vs Q3 similarity
    - Concepts behind formulation sameness or “no significant difference” (NSD)
- How to interact with the FDA



Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Susan Levine 240-402-7936.

U.S. Department of Health and Human Services
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https://www.fda.gov/regulatory-information/search-fda-guidance-documents/physicochemical-and-structural-q3-characterization-topical-drug-products-submitted-andas

The Concepts of Q1, Q2, Q3

- Q1: Components in a product
- Q2: Composition of a product

RS Formulation	
Ingredients	**% w/w**
Tanasone, USP (active ingredient)	0.25
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
Paramix® *	0.12
Sodium Hydroxide, NF	0.03 (pH 5.5)
Benzyl Alcohol, NF	1.00
Purified Water, USP	57.00
*Mixture of methylparaben, USP and propylparaben, USP (1:1)	

The Concepts of Q1, Q2

The test product should contain ***no difference in inactive ingredients or in other aspects of the formulation relative to the reference standard (no significant difference, NSD)*** that may significantly affect the local or systemic availability of the active ingredient. For example, if the test product and reference standard (RS) are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the most recent version of the FDA guidance for industry on ANDA Submissions – Refuse-to-Receive Standards, and the criteria below are also satisfied, the bioequivalence of the test product may be established using a characterization-based bioequivalence approach.

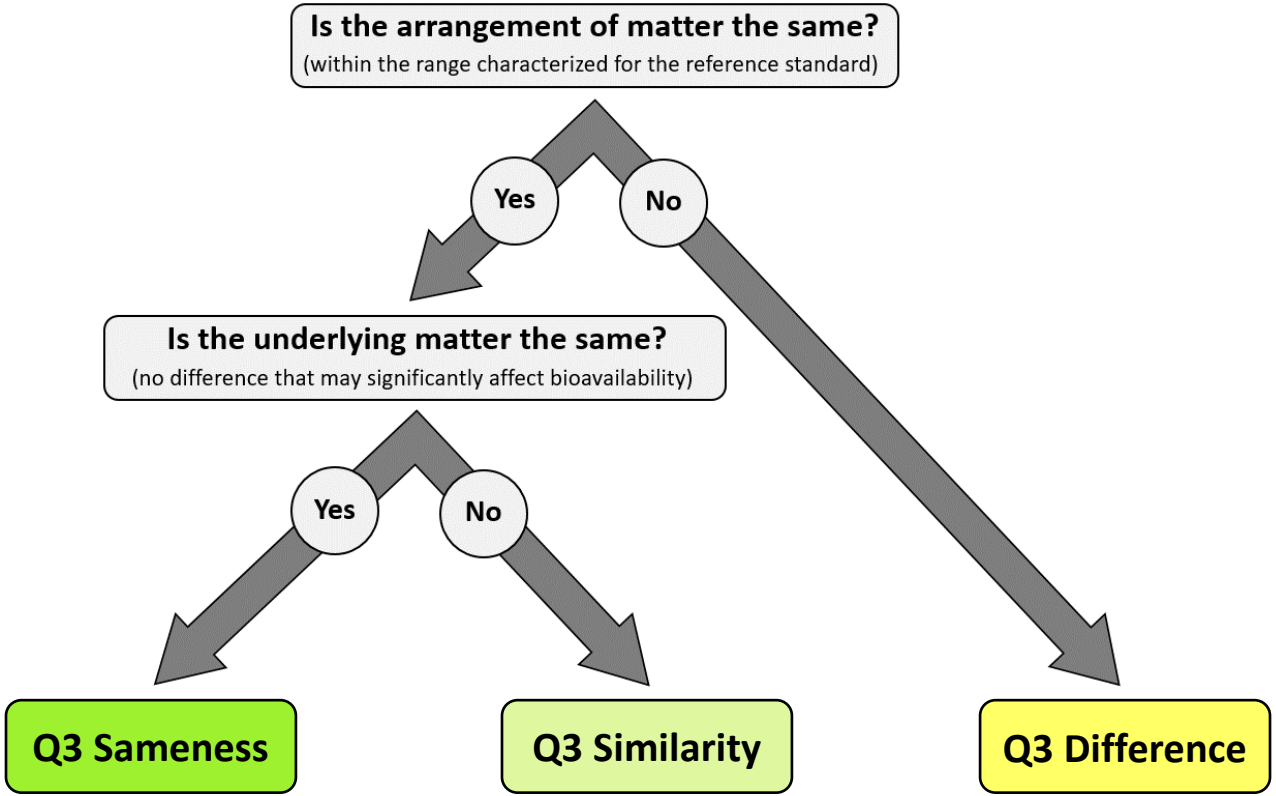
The Concepts of Q1, Q2, Q3

- Q1: Components in a product
- Q2: Composition of a product
- Q3: Arrangement of matter in a product

Q3 Attribute	Lidocaine2.5%, Prilocaine2.5% RLD Cream		Lidocaine-2.5%, Prilocaine-2.5% Generic Cream	
pH	9.22 ± 0.08		8.92 ± 0.03	
Density (g/cc)	1.0142 ± 0.0002		1.0148 ± 0.0002	
WOA (g.sec)	59.427 ± 0.338		65.893 ± 0.614	
Particle Size of API (µm)	Lidocaine and Prilocaine completely dissolved			
Globule Size, d50 (µm)	3.30		3.00	
Drug in Aqueous Phase (µg/g)	Lidocaine	1.64 ± 0.06	Lidocaine	1.74 ± 0.12
	Prilocaine	1.99 ± 0.06	Prilocaine	2.11 ± 0.15
Drug in Oil Phase (µg/g)	Lidocaine	23.45 ± 0.36	Lidocaine	23.21 ± 0.18
	Prilocaine	23.47 ± 0.18	Prilocaine	23.12 ± 0.22
Water Activity	1.003 ± 0.002		1.004 ± 0.007	
Drying,T50 (min)	3.37 ± 0.15		3.82 ± 0.73	
Rheology Yield Stress(Pa)	36.7 ± 1.2		35.7 ± 0.6	

Data courtesy Dr. Narasimha Murthy, U01FD005233

Q3 Draft Guidance for Industry



Basic 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

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

Communication with FDA

Prospective Generic that **meets** the "NSD" criteria

- If a product-specific guidance (PSG) is available
  - Submit controlled correspondence if you have questions about the recommendations in the PSG
  - Follow the recommendations in the PSG or submit preANDA if you would like to propose an alternative approach
- If PSG is not available
  - Review relevant guidances
  - Submit preANDA (include formulation information and empirical data to support the proposed bioequivalence approach)

Prospective Generic that **DOES NOT** meet the "NSD" criteria

- Review relevant general guidances
- Submit preANDA
  - Summarize your assessment of the differences in formulation between the proposed product and RS
  - Include Q3 characterization data that illustrates why you think the product meets the "Q3 similar" criteria
  - Include your proposal for studies you would like to conduct (supported by preliminary data) to mitigate the risk associated with potential differences in bioavailability that may arise due to the differences in the formulation

Challenge Question

Which of the Following Statements is True:

A. Basic Q3 characterizations can demonstrate that a test topical product and its RS are the same dosage form, supporting a demonstration of bioequivalence.

B. Comprehensive Q3 characterizations matching the detailed profile of Q3 attributes for the test product to the detailed profile of Q3 attributes for the RS substantially mitigates the risk of potential failure modes for bioequivalence, supporting a demonstration of bioequivalence.

C. All of the above.

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Questions?

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