“No Difference” Standard vs. Q1/Q2 Sameness for Topical Drug Products

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Learning Objectives

- Explain differences between Q1/Q2 sameness and a “no difference” standard for generic topical products
- Identify examples of differences between a test and reference topical product that may be acceptable under a “no difference” standard

Q1 sameness: Same components as the reference product
Q2 sameness: Same components and composition as the reference product

Inactive Ingredients in Topical Products

- Title 21 of the Code of Federal Regulations, Sections 314.94(a)(9)(v) and 320.22
  - An ANDA for a drug product intended for topical use may include different inactive ingredients compared to the RLD 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.
  - In vivo BE may be self-evident for a topical solution or solution-based foam aerosol if, among other things:
    - The test product contains ***"no inactive ingredient or other change in formulation…that may significantly affect systemic or local availability"***
    - **Includes but does not require Q1 and Q2 sameness**

BE: Bioequivalence; RLD: Reference Listed Drug

Q1/Q2 Sameness

- Q1/Q2 sameness of a test and reference topical product mitigates the risk of known failure modes related to:
  - Irritation and sensitization
  - Formulation interaction with diseased skin
  - Vehicle contribution to efficacy
  - Stability and solubility of the drug

Q1/Q2 Sameness

- Implementing Q1/Q2 sameness can be challenging for generic topical products.
  - Changes to the reference product formulation over time
  - Use of quantity sufficient (q.s.) for inactive ingredients
  - Discontinuation of the reference product
- A sophisticated assessment of the formulation can ensure that the test product is well-matched to the reference product.

“No Difference” Standard

- A test topical 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.

Q1/Q2 Sameness vs. “No Difference”

Q1/Q2 Sameness

- Same components in the same concentration as the reference product
- Potential tolerance of ±5% difference between the test and reference product

“No Difference”

- Based upon principles for assessing Q1/Q2 sameness, but also considers differences that have previously been determined to be acceptable based on available scientific evidence
- May be Q1/Q2 same, but not necessarily
- Does not mean that any formulation would be acceptable

“No Difference” Assessment

- Evaluates whether certain components and compositions may be acceptable for a proposed generic topical product
- Based upon:
  - Information available to the Agency, and/or
  - Evidence submitted in an ANDA (e.g., evidence to demonstrate no difference between the test and reference product in the local or systemic availability of the active ingredient)

ANDA: Abbreviated new drug application

Assessment Using the RS Product

- Q1/Q2 sameness when the RLD product is discontinued can be complicated.
- The RS product may not be Q1/Q2 the same as the RLD product.
- A test product may be assessed with respect to the RS formulation.

RLD: Reference listed drug; RS: Reference standard

Assessment of Ingredient Grade

Q1/Q2 Sameness

- Q1 sameness of 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.

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 ingredient.
- The acceptability of such difference would be determined during ANDA assessment.

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 variable quantitative amounts of sub-components.

"No Difference"

- A test product may be suitable if it contains quantitative amounts of each sub-component within the ranges that were found acceptable for the reference product.
- The acceptability of such difference would be determined during ANDA assessment.

Assessment of Ingredient Form

Q1/Q2 Sameness

- Q1 sameness of an ingredient that exists in different forms can be complicated.
- The reference product may use Edetate Disodium, USP, which may exist in a dihydrate form or an anhydrous form.

"No Difference"

- A test product may be suitable if it contains a different form of the ingredient, with adjustments to the quantitative amount of the pure ingredient and water.
- The acceptability of such difference would be determined during ANDA assessment.

Assessment of Ingredient Purity

Q1/Q2 Sameness

- Q1 sameness of an ingredient that exists in different purities can be complicated.
- The reference product may use Alcohol, USP, which is comprised of alcohol equivalent to 73.5% (w/w) alcohol as 95% alcohol (v/v).

"No Difference"

- A test product may be suitable 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 difference would be determined during ANDA assessment.

Assessment of Color or Fragrance

Q1/Q2 Sameness

- Q1 sameness of an ingredient that is added for coloring or fragrance purposes can be complicated.
- A test product may propose to use a different color or fragrance than that used for the reference product.

"No Difference"

- A test product may be suitable if it contains a different color or fragrance than the reference product if it does not affect the bioavailability of the active ingredient and/or affect the safety of the drug product.
- The acceptability of such difference would be determined during ANDA assessment.

Assessment of pH Modifier

Q1/Q2 Sameness

- Q2 sameness of a nominal amount of an ingredient can be complicated.
- The single point nominal amount of a pH modifier in the reference product composition table may not reflect the quantitative range or may be specified as a q.s. to achieve a target pH for the reference product.

"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 of the test and reference product match.
- The acceptability of such difference would be determined during ANDA assessment.

Summary

- Certain differences in components and composition may be acceptable for a generic topical product.
- Generic topical products should contain “no difference” in inactive ingredients or other aspects of the formulation that may significantly affect local or systemic bioavailability.
- A “no difference” standard expands the eligibility for a characterization-based BE approach, while preserving the scientific principles of Q1/Q2 sameness that are critical to mitigate the risks of failure modes for BE.

Challenge Question #1

Which is not true about the "no difference" standard for a proposed test product formulation (relative to the reference product)?

A. The "no difference" standard is based upon the same principles for assessing Q1/Q2 sameness.

B. A "no difference" standard considers differences in components and composition that may be acceptable based upon information available to the Agency and/or based upon evidence submitted in an ANDA.

C. A test product that is Q1/Q2 the same as the reference product is an example of a test product that meets the "no difference" standard.

D. Any proposed test formulation is acceptable for a characterization-based approach, regardless of differences relative to the reference product.

Challenge Question #2

Which of the following may not be acceptable under the "no difference" standard:

A. A test product that proposes to use White Petrolatum, USP while the reference product uses Petrolatum, USP.

B. A test product that uses a different fragrance than the reference product.

C. A test product that proposes to use 12% more than the nominal amount of pH modifier than the reference product in order to match the pH of the reference product.

D. A test product that proposes to use 12% more than the nominal amount of an emulsifying agent than the reference product.

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Questions?

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