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Draft Guidance on Azelaic Acid

November 2024

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Active Ingredient:	Azelaic acid
Dosage Form:	Gel
Route:	Topical
Strength:	15%
Recommended Studies:	Two options: (1) two in vitro bioequivalence studies and other characterization tests or (2) one comparative clinical endpoint bioequivalence study

I. Option 1: Two in vitro bioequivalence studies and other characterization tests

To demonstrate bioequivalence for azelaic acid topical gel, 15% using in vitro studies, the following criteria should be met:

1. The test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference standard (RS) in the same packing configuration (tube or pump) that may significantly affect the local or systemic availability of the active ingredient. For example, if the test product and 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*[a], and the criteria below are also satisfied, the bioequivalence of the test product may be established using a characterization-based bioequivalence approach.

2. The test product and RS in the same packing configuration (tube or pump) should have the same physicochemical and structural (Q3) attributes, based upon acceptable comparative Q3 characterization tests with a minimum of three batches of the test product and three batches (as available) of the RS. The test product and RS batches should ideally represent the product at different ages throughout its shelf life. Refer to the most recent version of the FDA guidance for industry on *Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs*[a] for additional information regarding comparative Q3 characterization tests. The comparison of the test product and RS should include characterizations of the following Q3 attributes:
    a. Characterization of visual appearance and texture
    b. Characterization of phase states and structural organization of matter
        - Microscopic examination with representative high-resolution microscopic images at multiple magnifications
        - Analysis of particle size distribution, crystal habit, and polymorphic form of azelaic acid in the drug product
        - Analysis of globule size distribution, if feasible
    c. Characterization of rheological behavior which may be characterized using a rheometer that is appropriate for monitoring the non-Newtonian flow behavior of semi-solid dosage forms. The following evaluations are recommended:
        - A characterization of shear stress vs. shear rate and viscosity vs. shear rate. At minimum, this should consist of numerical viscosity data at three shear rates (low, medium, and high).
        - A complete flow curve across the range of attainable shear rates, until low or high shear plateaus are identified.
        - Yield stress values should be reported if the material tested exhibits plastic flow behavior.
        - The linear viscoelastic response (storage and loss modulus vs. frequency) should be measured and reported. Any non-linear viscosity behavior over a range of shear rates should also be investigated, measured and reported.
    d. Characterization of pH
    e. Characterization of specific gravity
    f. Characterization of any other potentially relevant Q3 attributes

3. The test product and RS in the same packing configuration (tube or pump) should have an equivalent rate of azelaic acid release based upon an acceptable in vitro release test (IVRT) bioequivalence study comparing a minimum of one batch each of the test product and RS using an appropriately validated IVRT method.

    Type of study: Bioequivalence study with IVRT endpoint
    Design: Single-dose, two-treatment, parallel, multiple-replicate per treatment group study design using an occluded pseudo-infinite dose, in vitro
    Strength: 15%
    Test system: A synthetic membrane in a diffusion cell system
    Analyte to measure: Azelaic acid in receptor solution
    Bioequivalence based on: Azelaic acid (IVRT endpoint: drug release rate)

Additional comments: Refer to the most recent version of the FDA guidance for industry on *In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs*[a] for additional information regarding the development, validation, conduct, and analysis of acceptable IVRT methods/studies. The batches of test product and RS evaluated in the IVRT bioequivalence study should be included among those for which the Q3 attributes are characterized.

4. The test product and RS in the same packing configuration (tube or pump) should have an equivalent rate and extent of azelaic acid permeation through excised human skin based upon an acceptable in vitro permeation test (IVPT) bioequivalence study comparing a minimum of one batch each of the test product and RS using an appropriately validated IVPT method.

Type of study: Bioequivalence study with IVPT endpoints
Design: Single-dose, two-treatment, parallel, multiple-replicate per treatment group study design using an unoccluded finite dose, in vitro
Strength: 15%
Test system: Barrier-competent human skin from male and/or female donors of at least 18 years of age in a diffusion cell system
Analyte to measure: Azelaic acid in receptor solution
Bioequivalence based on: Azelaic acid (IVPT endpoints: total cumulative amount (AMT) and maximum flux (J_{max}))
Additional comments: Refer to the most recent version of the FDA guidance for industry on *In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs*[a] for additional information regarding the development, validation, conduct and analysis of acceptable IVPT methods/studies. The batches of test product and RS evaluated in the IVPT bioequivalence study should be the same as those evaluated in the IVRT bioequivalence study.

II. Option 2: One comparative clinical endpoint bioequivalence study

1. Type of study: Comparative clinical endpoint bioequivalence study
Design: Randomized, double blind, parallel, placebo-controlled, in vivo
Strength: 15%
Subjects: Males and non-pregnant, non-lactating females with rosacea
Additional comments: Specific recommendations are provided below.

Additional comments regarding the comparative clinical endpoint bioequivalence study:

1. FDA recommends conducting a comparative clinical endpoint bioequivalence study in the treatment of moderate rosacea. Subjects are to be randomized to receive the test product, the RS, or placebo (vehicle) twice daily for 12 weeks. The primary endpoint is to be evaluated at the end of treatment (Study Week 12).

2. Inclusion criteria (the sponsor may add additional criteria):
    a. Males or non-pregnant, non-lactating females aged ≥18 years with a clinical diagnosis of moderate facial rosacea, defined as the presence of:
        - At least eight and not more than fifty inflammatory facial lesions (i.e., papules/pustules), and
        - Persistent erythema, and
        - Telangiectasia
    b. Subject willing to minimize external factors that might trigger rosacea flare-ups (e.g., spicy foods, thermally hot foods and drinks, hot environments, prolonged sun exposure, strong winds and alcoholic beverages).

3. Exclusion criteria (the sponsor may add additional criteria):
    a. Pregnant or lactating or planning to become pregnant during the study period
    b. Presence of any skin condition on the face that would interfere with the diagnosis or assessment of rosacea
    c. Excessive facial hair (e.g., beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of rosacea
    d. History of hypersensitivity or allergy to propylene glycol or any other component of the formulation
    e. Use within 6 months prior to baseline of oral retinoids or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed)
    f. Use for less than 3 months prior to baseline of estrogens or oral contraceptives; use of such therapy must remain constant throughout the study
    g. Use within 1 month prior to baseline of (1) topical retinoids to the face, (2) systemic antibiotics known to have an impact on the severity of facial rosacea (e.g., containing tetracycline and its derivatives, erythromycin and its derivatives, sulfamethoxazole, or trimethoprim), or (3) systemic corticosteroids
    h. Use within 2 weeks prior to baseline of (1) topical corticosteroids, (2) topical antibiotics, or (3) topical medications for rosacea (e.g., metronidazole, azelaic acid)
    i. Subjects with moderate or severe rhinophyma, dense telangiectases, or plaque-like facial edema
    j. Ocular rosacea (e.g., conjunctivitis, blepharitis, or keratitis) of sufficient severity to require topical or systemic antibiotics

4. The protocol should include a list of the prescription and over-the-counter drug products that are prohibited during the study, such as:
    a. Any other topical products applied to the target site (e.g., metronidazole, topical antibiotics, topical steroids)
    b. Oral retinoids
    c. Systemic (e.g., oral or injectable) antibiotics know to have an impact on the severity of facial rosacea (e.g., containing tetracycline, erythromycin, sulfamethoxazole, or trimethoprim or their derivatives)
    d. Systemic corticosteroid or immunosuppressive drugs
    e. Antipruritics, including antihistamines, within 24 hours of study visits

5. Subjects should not apply moisturizers, new brands of make-up, creams, lotions, powders or any topical product other than the assigned treatment to the treatment area. Occlusive dressings or wrappings should be avoided in treatment areas. Subjects should minimize exposure to sunlight, including sunlamps, while using the product. Use of sunscreen products and protective clothing over treated areas is recommended when sun exposure cannot be avoided.

6. Areas to be treated should be washed with a mild cleanser before application and patted dry with a soft towel. A thin layer of study treatment should be gently massaged into the affected areas on the face twice daily, in the morning and evening, for 12 weeks. Contact with the mouth, eyes and other mucous membranes should be avoided. The hands should be washed following application.

7. The recommended primary endpoint of the study is the mean percent change from baseline to Week 12 in the inflammatory (papules and pustules) lesion counts. The protocol should clearly define papules, pustules, and nodules. When counting facial lesions, it is important that all lesions be counted, including those present on the nose. Counts of nodules should be reported separately and not included in the inflammatory lesion counts.

8. Refer to the most recent version of the FDA product-specific guidance on *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)[b] for a recommended approach to statistical analysis and study design for comparative clinical endpoint bioequivalence studies.

9. Refer to the Study Data Standards Resources website https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

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[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[b] For the most recent version of a product-specific guidance, check the FDA product-specific guidance website at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.