

*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

### **Draft Guidance on Azelaic Acid**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

**Active Ingredient:** Azelaic acid

**Dosage Form; Route:** Aerosol, foam; topical

**Recommended Study:** One study

Type of study: Bioequivalence study with clinical endpoint  
Design: Randomized, double blind, parallel, placebo controlled, in vivo  
Strength: 15%  
Subjects: Males and nonpregnant, nonlactating females with rosacea  
Additional comments: Specific recommendations are provided below.

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**Analyte to measure:** Not applicable

**Bioequivalence based on (90% CI):** Clinical endpoint

**Waiver request of in vivo testing:** Not applicable

**Dissolution test method and sampling times:** Not applicable

Applicants intending to propose an alternative approach by which to demonstrate bioequivalence should refer to the guidance for industry *Controlled Correspondence Related to Generic Drug Development* and the guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* for additional information describing the procedures on how to clarify regulatory expectations regarding your individual drug development program.

**Additional comments regarding the bioequivalence study with clinical endpoint:**

1. The Office of Generic Drugs recommends a clinical endpoint bioequivalence study in the treatment of moderate rosacea. Subjects are to be randomized to receive the test product, the reference product, or placebo 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. Male or nonpregnant, nonlactating female aged  $\geq 18$  years with a clinical diagnosis of moderate facial rosacea, defined as the presence of:
    - i. At least eight and not more than fifty inflammatory facial lesions (i.e., papules/pustules), AND
    - ii. Persistent erythema, AND
    - iii. 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 (e.g., Accutane<sup>®</sup>) 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 known 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 applied to the entire facial area (cheeks, chin, forehead, and nose) 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. An Investigator's Global Evaluation (IGE) should be evaluated as a secondary endpoint for the statistical analysis. The IGE should be a static scale, describing the extent of disease associated with each score. This scale should not reflect treatment response, but should describe the condition at each visit. Therefore, no reference should be made to baseline in the evaluation. The scale should be dichotomized into "success" and "failure". "Success" should be defined either as a score consistent with clear or almost clear at the final visit.

Score	Grade	Definition
0	Clear	No inflammatory lesions present; at most, mild erythema
1	Almost Clear	Very mild erythema present. Very few small papules/pustules
2	Mild	Mild erythema. Several small papules/pustules
3	Moderate	Moderate erythema. Several small or large papules/pustules, and up to 2 nodules
4	Severe	Severe erythema. Numerous small and/or large papules/pustules, up to several nodules

9. Refer to the product-specific guidance on adapalene; benzoyl peroxide topical gel, 0.3%; 2.5% entitled *Guidance on Adapalene; Benzoyl Peroxide* for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.
10. Study data should be submitted in a standardized format. Please refer to study data standards published at [www.FDA.gov](http://www.FDA.gov)<sup>1</sup>.

<sup>1</sup> Study Data Standards for Submission to CDER and CBER available at: <https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources>