

Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Azelaic Acid

August 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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.

In general, FDA’s guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Azelaic acid

Dosage Form: Cream

Route: Topical

Strength: 20%

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 cream, 20% 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) 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 should have the same physicochemical and structural (Q3) attributes, based upon acceptable comparative Q3 characterization of 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
 - 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 water activity
 - e. Characterization of pH
 - f. Characterization of specific gravity
 - g. Characterization of any other potentially relevant Q3 attributes
3. The test product and RS 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: 20%

Test system: A synthetic membrane in a diffusion cell system

Analytes 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 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: 20%

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: 20%
Subjects: Males and non-pregnant, non-lactating females with acne vulgaris
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 acne vulgaris. Subjects are to be randomized to receive the test product, the RS, or placebo (vehicle). The study drug is to be administered twice daily, in the morning and evening, to the face 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 ≥ 12 and ≤ 40 years with a clinical diagnosis of acne vulgaris
 - b. On the face, ≥ 25 non-inflammatory lesions (i.e., open and closed comedones) and ≥ 20 inflammatory lesions (i.e., papules and pustules) and ≤ 2 nodulocystic lesions (i.e., nodules and cysts)

- c. Investigator’s Global Assessment (IGA) of acne severity Grade 2, 3, or 4 (per Table 1)

Table 1. Sample IGA Scale for Acne Vulgaris¹

Grade	Description
0	Clear skin with no inflammatory or noninflammatory lesions
1	Almost clear; rare non-inflammatory lesions with no more than one small inflammatory lesion
2	Mild severity; greater than Grade 1; some non-inflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions)
3	Moderate severity; greater than Grade 2; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion
4*	Severe; greater than Grade 3; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than a few nodular lesions

* The Case Report Forms for acne studies can allow for reporting by investigators of lesion worsening beyond Grade 4 with treatment. It is recommended that enrollment of acne vulgaris subjects not include subjects with nodulocystic acne. Subjects who worsen beyond Grade 4 are to be described in the safety evaluation.

- d. Willing to refrain from use of all other topical acne medications or antibiotics during the 12-week treatment period
 - e. If female of childbearing potential, willing to use an acceptable form of birth control during the study
3. Exclusion criteria (the sponsor may add additional criteria):
- a. Presence of any skin condition that would interfere with the diagnosis or assessment of acne vulgaris (e.g., on the face: rosacea, dermatitis, psoriasis, squamous cell carcinoma, eczema, acneform eruptions caused by medications, steroid acne, steroid folliculitis, or bacterial folliculitis)
 - b. Excessive facial hair (e.g., beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of acne vulgaris
 - c. History of hypersensitivity or allergy to azelaic acid and/or any of the study medication ingredients
 - d. 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).
 - e. Use for less than 3 months prior to baseline of estrogens or oral contraceptives; use of such therapy must remain constant throughout the study
 - f. Use on the face within 1 month prior to baseline of (1) cryodestruction or chemodestruction, (2) dermabrasion, (3) photodynamic therapy, (4) acne surgery, (5) intralesional steroids, or (6) x-ray therapy

¹ Guidance for industry on *Acne Vulgaris: Establishing Effectiveness of Drugs Intended for Treatment*. For the most recent version of a guidance, check the FDA guidance website at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

- g. Use within 1 month prior to baseline of (1) spironolactone, (2) systemic steroids, (3) systemic antibiotics, (4) systemic treatment for acne vulgaris (other than oral retinoids, which require a 6-month washout), or (5) systemic anti-inflammatory agents
 - h. Use within 2 weeks prior to baseline of (1) topical steroids, (2) topical retinoids, (3) topical acne treatments including over-the-counter preparations, (4) topical anti-inflammatory agents, or (5) topical antibiotics
4. Subjects should cleanse the face with a mild or soapless, non-medicated cleanser, pat dry and then gently but thoroughly massage a thin film of product into the affected areas of the face twice daily, in the morning and evening, avoiding contact with the mouth, eyes, and other mucous membranes and washing hands after applications.
 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. 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. Subjects should avoid the use of occlusive wrappings or dressings on the face.
 7. The protocol should include a list of the prescription and over-the-counter drug products, procedures, and activities that are prohibited during the study, such as:
 - a. Any other topical products applied to face
 - b. Medicated soaps used on face
 - c. Spironolactone
 - d. Oral retinoids, therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed) or other systemic treatment for acne vulgaris
 - e. Systemic (e.g., oral or injectable) antibiotics
 - f. Systemic steroids, systemic anti-inflammatory agents or immunosuppressive drugs.
 - g. Antipruritics, including antihistamines, within 24 hours of study visits
 - h. Use on the face of (1) cryodestruction or chemodestruction, (2) dermabrasion, (3) photodynamic therapy, (4) acne surgery, (5) intralesional steroids, or (6) x-ray therapy
 - i. Use of tanning booths, sunbathing, or excessive exposure to the sun
 8. The recommended primary endpoint of the study is percent change from baseline to Week 12 in the inflammatory (papules and pustules) lesion counts. The protocol should clearly define papules, pustules, open comedones, closed comedones, nodules and cysts. When counting facial acne lesions, it is important that all lesions be counted, including those present on the nose. Counts of nodules and cysts should be reported separately and not included in the inflammatory or non-inflammatory lesion counts.

9. Refer to most recent version of the FDA product-specific guidance on *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207017)^b for a recommended approach to statistical analysis and study design for comparative clinical endpoint bioequivalence studies.
 10. Refer to the Study Data Standards Resources website <https://www.fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources>.
-

Document History: Recommended May 2010; Revised November 2018, May 2019, August 2024

Unique Agency Identifier: PSG_020428

^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>.