

## Draft Guidance on Tretinoin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

**Dosage Form; Route:** Gel; topical

**Recommended Studies:** One study

Type of study: Bioequivalence study with clinical endpoint

Design: Randomized, double blind, parallel, placebo controlled, in vivo

Strength: 0.04%

Subjects: Males and nonpregnant, nonlactating females with acne vulgaris

Additional comments: Specific recommendations are provided below.

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**Analytes to measure (in appropriate biological fluid):** 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 with clinical endpoint study:**

1. The Office of Generic Drugs recommends conducting a bioequivalence study with clinical endpoint in the treatment of acne vulgaris. Subjects are to be randomized to receive the generic tretinoin gel, 0.04%, the reference product or placebo. The study drug is to be administered once daily in the evening for 12 weeks. The primary endpoint is to be evaluated at baseline (Day 0) and at the end of treatment (Study Week 12).
2. A placebo control arm is recommended to demonstrate that the test product and reference product are active and as a parameter to establish that the study is sufficiently sensitive to detect differences between products.

3. Inclusion Criteria (the sponsor may add additional criteria)
  - a. Male or nonpregnant, nonlactating female aged  $\geq 12$  and  $\leq 40$  years with a clinical diagnosis of acne vulgaris
  - b. On the face,  $\geq 25$  non-inflammatory lesions (i.e., open and closed comedones) AND  $\geq 20$  inflammatory lesions (i.e., papules and pustules) AND  $\leq 2$  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 Vulgaris<sup>1</sup>**

Grade	Description
0	Clear skin with no inflammatory or noninflammatory lesions
1	Almost clear; rare noninflammatory lesions with no more than one small inflammatory lesion
2	Mild severity; greater than Grade 1; some noninflammatory 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 noninflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion
4*	Severe; greater than Grade 3; up to many noninflammatory 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
4. 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

<sup>1</sup> Guidance for industry *Acne Vulgaris: Establishing Effectiveness of Drugs Intended for Treatment*. Accessed at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/acne-vulgaris-establishing-effectiveness-drugs-intended-treatment>

- c. History of hypersensitivity or allergy to tretinoin, retinoids, or any of the study medication ingredients
  - d. Use within 6 months prior to baseline of oral retinoids (e.g., Accutane®) 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
  - 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
5. Subjects should cleanse the face with a mild or soapless, non-medicated cleanser, dry skin gently, and then apply enough product to lightly cover the entire affected areas of the face once daily in the evening. The subject should be instructed to avoid contact of the study product with the corners of the nose, mouth, eyes and open wounds, and to wash their hands after application.
  6. 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.
  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 two primary endpoints of the study are 1) percent change from baseline to Week 12 in the inflammatory (papules and pustules) lesion counts and 2) percent change from baseline to Week 12 in the non-inflammatory (open and closed

comedones) 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. Application site reactions such as erythema, dryness, burning/stinging, erosion, edema, pain and itching are to be recorded at each visit to allow a comparison between treatment groups. A descriptive analysis comparing the application site reactions for each treatment group is recommended. It is important to ensure that the test product is not worse than the reference product with regard to the expected and unexpected application site reactions.
10. To establish bioequivalence, the 90% confidence interval of the test/reference ratio of the mean percent change from baseline to Week 12 in the inflammatory (papules and pustules) lesion counts and in the non-inflammatory (comedones) lesion counts should be contained within [0.80, 1.25], using the per protocol population.
11. These recommendations are specific to this product and may not be appropriate for bioequivalence studies of any other product, including any other dosage form or strength of tretinoin.
12. Please 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.
13. Study data should be submitted in a standardized format. Please refer to the study data standards published at [www.fda.gov](http://www.fda.gov)<sup>2</sup>.

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<sup>2</sup> Study Data Standards for Submission to CDER and CBER available at:  
<https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>