Contains Nonbinding Recommendations

Draft Guidance on Tretinoin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Recommended studies: One study

Type of study:	Bioequivalence (BE) with Clinical Endpoint Study
Design:	Randomized, double blind, parallel, placebo controlled, in vivo
Strength:	0.05%
Subjects:	Males and nonpregnant, nonlactating females with acne vulgaris.
Additional comments:	Specific recommendations are provided below.

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

Additional comments regarding the BE with clinical endpoint study:

1. An ANDA for an intermediate strength(s) of Tretinoin Cream containing sufficient data may be approved per 21 CFR 320.24(b)(6) without conducting an in vivo BE with clinical endpoint study. This would be based on a prior determination of two acceptable BE with clinical endpoint studies conducted on a lower strength and a higher strength of the same product, the proposed active and inactive ingredients of the proposed product being qualitatively and quantitatively the same as the RLD, the formulations of the lower, intermediate, and higher strengths of the test product and RLDs are exactly the same except for the amount of tretinoin, and additional comparative data (e.g., in vitro release testing, physicochemical properties comparison including viscosity and pH) for each strength of the proposed product and RLD being provided and determined to be acceptable. If you want to pursue a strength of tretinoin not already listed in the Orange Book, you must first submit a suitability petition to request a change in dosage form according to 21 CFR § 314.93, 10.20 and 10.30.

2. The Office of Generic Drugs (OGD) recommends conducting a BE study with clinical endpoint in the treatment of acne vulgaris. Subjects are to be randomized to receive the

generic Tretinoin Cream USP 0.05%, the reference listed drug (RLD) 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).

3. A placebo (vehicle) control arm is recommended to demonstrate that the test product and RLD are active and as a parameter to establish that the study is sufficiently sensitive to detect differences between products.

4. Inclusion Criteria (the sponsor may add additional criteria)
   a. Male or nonpregnant, nonlactating female 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 I).

Table 1. Sample IGA Scale for Acne Vulgaris [1]

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.

[1] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Draft Guidance for Industry: Acne Vulgaris: Developing Drugs for Treatment. Clinical/Medical. September 2005. Accessed at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071292.pdf

5. 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 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.

6. Subjects should cleanse the face with a mild or soapless, non-medicated cleanser, dry skin gently, wait 20 to 30 minutes before applying the study product, and then apply enough product to lightly cover the entire affected areas of the face once daily at bedtime. 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.

7. 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.

8. 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.

9. The recommended two primary endpoints of the study are 1) mean percent change from baseline to Week 12 in the inflammatory (papules and pustules) lesion counts and 2) mean 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.

10. 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.

11. Please refer to the product-specific guidance on Adapalene; Benzoyl peroxide topical gel 0.3%; 2.5% ("Draft Guidance on Adapalene; Benzoyl Peroxide") for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.

12. Study data should be submitted in a standardized format. Please refer to the study data standards published at www.fda.gov[2]

[2] Study Data Standards for Submission to CDER and CBER available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm