Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Benzoyl Peroxide; Tretinoin

August 2026

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form: Cream

Route: Topical

Strengths: 3%; 0.1%

Reference Listed Drug: NDA 214902

Recommended Studies: Comparative clinical endpoint bioequivalence study

Meeting recommendations: The reference listed drug (RLD) uses silica (silicon dioxide) core shell structures to separately micro-encapsulate tretinoin crystals and benzoyl peroxide crystals enabling inclusion of the two active ingredients in the cream. For proposed generic products that have differences in formulation design compared to the RLD, it would be imperative to ascertain the stability of the proposed formulation prior to conducting the recommended comparative clinical endpoint bioequivalence study. Applicants intending to submit an abbreviated new drug application (ANDA) for this drug product are encouraged to seek feedback about their drug product development program by submitting a pre-ANDA product development meeting request that includes information related to the proposed formulation design and available stability data prior to initiating the comparative clinical endpoint bioequivalence study. Additionally, applicants intending to propose an alternative approach by which to demonstrate bioequivalence should also consider a pre-ANDA product development meeting. Refer to the guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*[a] for additional information describing the procedures on how to clarify regulatory expectations regarding your individual drug development program.

1. Class of study: Bioequivalence
   Type of study: Comparative clinical endpoint bioequivalence study
   Design: Randomized, double blind, parallel, placebo-controlled, in vivo
   Strength: 3%; 0.1%
   Subjects: Males and non-pregnant, non-lactating females with acne vulgaris

Additional study design recommendations for comparative clinical endpoint bioequivalence study:

1. FDA recommends conducting a comparative clinical endpoint bioequivalence study in the treatment of moderate to severe acne vulgaris. Subjects are to be randomized to receive the test product, the reference standard (RS), or placebo (vehicle). The study treatment is to be administered once daily in the evening for 12 weeks. The two primary endpoints are to be evaluated at the end of treatment (Study Week 12).

2. Inclusion criteria (the sponsor may add additional criteria):
   a. Male or non-pregnant, non-lactating 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 3 and 4 (per Table 1)

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

Score	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 described in the safety evaluation.

   d. Willing to refrain from use of all other topical acne medications, all other benzoyl peroxide medications, or antibiotics during the 12-week treatment period

[1] Guidance for Industry: *Acne Vulgaris: Developing Drugs for Treatment.* Clinical/Medical. Accessed at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/acne-vulgaris-establishing-effectiveness-drugs-intended-treatment

e. If female of childbearing potential, willing to use an acceptable contraceptive method 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 tretinoin, retinoids, benzoyl peroxide 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
    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 be instructed to 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 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.

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. 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 hormonal contraceptives should not be initiated or changed during the study
    j. Use of tanning booths, sunbathing, or excessive exposure to the sun

7. The recommended 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.

8. 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 RS with regard to the expected and unexpected application site reactions.

9. The study site(s) should maintain photographic evidence to document all subjects enrolled in the study and their clinical severity. Ideally, the photographic evidence should be able to document the impact of the treatment, at a minimum, at baseline, and at end of treatment.

10. Refer to 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 the comparative clinical endpoint bioequivalence study.

11. Refer to the study data standards resources, https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

Document History: Recommended August 2026

[a] We update guidances periodically. For the most recent version of a guidance, refer to the FDA guidance webpage at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[b] We update guidances periodically. For the most recent version of a product-specific guidance, refer to the FDA guidance webpage at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.