Contains Nonbinding Recommendations

Draft Guidance on Benzoyl Peroxide; Erythromycin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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: 5%; 3%
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

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 conducting a bioequivalence study with clinical endpoint in the treatment of acne vulgaris. Subjects are to be randomized to receive the generic benzoyl peroxide; erythromycin topical gel, 5%; 3%, the reference product or placebo. The study drug is to be administered twice daily, in the morning and evening, to affected areas of the face for 8 weeks. The primary endpoint is to be evaluated at the end of treatment (Study Week 8).

2. 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 noninflammatory 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 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 8-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 benzoyl peroxide or erythromycin and/or any of the study medication ingredients

[1] 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

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 or during the study 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 cleanse the face with a mild or soapless, non-medicated cleanser, pat dry and then apply the product onto the affected areas of the face twice daily, in the morning and evening, avoiding contact with the mouth, eyes, and other mucous membranes.

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 tanning booths, sunbathing, or excessive exposure to the sun

7. The recommended primary endpoint of the study is mean percent change from baseline to Week 8 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 noninflammatory lesion counts.

8. Noninflammatory lesions should not get any worse with treatment. Mean percent change from baseline to Week 8 in the noninflammatory lesion counts should be treated as a secondary endpoint for supportive evidence.

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. 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.

11. 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/industry/study-data-standards-resources/study-data-submission-cder-and-cber