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Draft Guidance on Benzoyl Peroxide; Erythromycin

May 2024

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Active Ingredients:	Benzoyl peroxide; Erythromycin
Dosage Form:	Gel
Route:	Topical
Strength:	5%; 3%
Recommended Studies:	Two options: (1) one in vitro bioequivalence study and other characterization tests or (2) one comparative clinical endpoint bioequivalence study

I. Option 1: One in vitro bioequivalence study and other characterization tests

To demonstrate bioequivalence for benzoyl peroxide; erythromycin topical gel, 5%; 3% 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 that may significantly affect the local or systemic availability of the active ingredient. For example, if the test product and reference standard 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 reference standard 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

reference standard. The test product and reference standard 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 comparative Q3 characterization should be conducted with (1) the erythromycin gel of the test product and reference standard and (2) the benzoyl peroxide gel of the test product and reference standard, unless otherwise specified. The comparison of the test product and reference standard 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 benzoyl peroxide (in the benzoyl peroxide gel).
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.
d. Characterization of pH (of the benzoyl peroxide gel)
e. Characterization of specific gravity
f. Characterization of drying rate (of the erythromycin gel)
g. Characterization of any other potentially relevant Q3 attributes

3. The test product and reference standard should have an equivalent rate of benzoyl peroxide and erythromycin release based upon an acceptable in vitro release test (IVRT) bioequivalence study comparing a minimum of one batch each of the test product and reference standard 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: 5%; 3%
    Test system: A synthetic membrane in a diffusion cell system
    Analytes to measure: Benzoyl peroxide and erythromycin in receptor solution
    Bioequivalence based on: Benzoyl peroxide and erythromycin (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 reference standard evaluated in the IVRT bioequivalence study should be included among those for which the Q3 attributes are characterized. Sample preparation for the IVRT bioequivalence study should be consistent between the test product and reference standard.

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: 5%; 3%
   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 generic benzoyl peroxide; erythromycin topical gel, 5%; 3%, the reference standard, 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 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 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
    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 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

[1] Guidance for industry *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.

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. Prior to applying the product, subjects should cleanse the face with a mild or soapless, non-medicated cleanser and pat dry. Subjects should then thoroughly mix the contents of the pouch (in the palm of the hand) immediately prior to application. Subjects should 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. Subjects should then wash their hands.

5. Subjects should not mix or apply product near an open flame. 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. Subjects should be informed that product may bleach hair or colored fabric.

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 cleansers 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, sun lamps, sunbathing, or excessive exposure to the sun

7. The recommended primary endpoint of the study is the 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 standard with regard to the expected and unexpected application site reactions.

10. Refer to the most recent version of 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 comparative clinical endpoint bioequivalence study.

11. Refer to the Study Data Standards Resources website https://www.fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources.

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[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.