*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

**Draft Guidance on Benzoyl Peroxide; Clindamycin Phosphate**

**February 2023**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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| **Active Ingredients:** | Benzoyl peroxide; Clindamycin phosphate |
| **Dosage Form; Route:** | Gel; topical |
| **Strengths:** | 2.5%; EQ 1.2% Base and 3.75%; EQ 1.2% Base |
| **Recommended Studies:** | Two options: (1) one in vitro bioequivalence study and other characterization tests or (2) one in vivo bioequivalence study with clinical endpoint |

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

To demonstrate bioequivalence for benzoyl peroxide; clindamycin phosphate topical gel, 2.5%; EQ 1.2% Base or 3.75%; EQ 1.2% Base 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 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 the drug substance(s) in the drug product
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
e. Characterization of specific gravity
f. Characterization of any other potentially relevant Q3 attributes

3. The test product and reference standard should have an equivalent rate of benzoyl peroxide and clindamycin phosphate 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: 2.5%; EQ 1.2% Base or 3.75%; EQ 1.2% Base
    Test system: A synthetic membrane in a diffusion cell system
    Analytes to measure: Benzoyl peroxide and clindamycin phosphate in receptor solution
    Equivalence based on: Benzoyl peroxide and clindamycin phosphate (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.

Note: The specific study recommendations above apply to either strength. Under Option I independent IVRT bioequivalence study and Q3 characterization tests are recommended for each of the two strengths, 2.5%; EQ 1.2% Base and 3.75%; EQ 1.2% Base.

## II. Option 2: One in vivo bioequivalence study with clinical endpoint

1. Type of study: Bioequivalence study with clinical endpoint
   Design: Randomized, double blind, parallel, placebo controlled, in vivo
   Strength: 2.5%; EQ 1.2% Base or 3.75%; EQ 1.2% Base
   Subjects: Males and non-pregnant, non-lactating females with acne vulgaris
   Additional comments: Specific recommendations are provided below.

**Additional comments regarding the bioequivalence study with clinical endpoint:**

1. The specific study recommendations below apply to either strength. Under Option II separate bioequivalence study with clinical endpoint is recommended for 2.5%; EQ 1.2% Base and 3.75%; EQ 1.2% Base strengths. If an applicant seeks approval for only one of the strengths listed above only one study, evaluating the desired strength, is recommended. If both strengths are sought, two studies are recommended.

2. FDA recommends conducting a bioequivalence study with a clinical endpoint in the treatment of acne vulgaris comparing the test product versus the reference standard and placebo control, each applied as one "pea-sized" amount once daily for 84 days (12 weeks) as a thin layer to the affected areas of the face after the skin is gently washed with a mild soap, rinsed with warm water and patted dry. The two co-primary endpoints of the study are: 1) mean percent change from baseline to Week 12 (Study Day 84) in the inflammatory (papules and pustules) lesion count, and 2) mean percent change from baseline to Week 12 in the non-inflammatory (open and closed comedones) lesion count.

3. 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 non-inflammatory lesions |
| 1 | Almost clear; rare non-inflammatory lesions with no more than one small inflammatory lesion |
| 2 | Mild severity; greater than Grade 1; some non-inflammatory 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 non-inflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion |
| 4* | Severe; greater than Grade 3; up to many non-inflammatory 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. Pregnant or breast feeding
    b. History or presence of Crohn's disease, ulcerative colitis, regional enteritis, or antibiotic-associated colitis
    c. 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)
    d. Excessive facial hair (e.g., beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of acne vulgaris
    e. History of hypersensitivity or allergy to benzoyl peroxide or clindamycin and/or any of the study medication ingredients
    f. 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)
    g. Use for less than 3 months prior to baseline of estrogens or oral contraceptives; use of such therapy must remain constant throughout the study

[1] Guidance for industry on Acne Vulgaris: Establishing Effectiveness of Drugs Intended for Treatment. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatoryinformation/search-fda-guidance-documents.

h. 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
i. 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
j. 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, 5) medicated cleansers or 6) topical antibiotics

5. 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.
    j. Use of hormonal contraceptives should not be initiated or changed during the study.
    k. Subjects should not apply the assigned drug treatment inside their nose or mouth, on their eyes, lips, or mucous membranes, or on any cuts or open wounds.

6. Subjects should minimize exposure to sunlight while using the product. Use of sunscreen products and protective clothing over treated areas is recommended when sun exposure cannot be avoided. Subjects should avoid getting the assigned treatment on their hair or on colored fabric because it may bleach hair or colored fabric.

7. The two co-primary endpoints of the study are: 1) mean percent change from baseline to Week 12 (Study Day 84) in the inflammatory (papules and pustules) lesion count, and 2) mean percent change from baseline to Week 12 in the non-inflammatory (open and closed comedones) lesion count. Total lesion count assessment is no longer considered. 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. Due to the warning contained in the label of this product, subjects should be carefully monitored for adverse events associated with severe colitis (diarrhea and bloody diarrhea). If significant diarrhea occurs, the drug should be discontinued for that subject.

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 bioequivalence studies with clinical endpoint.

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

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**Revision History**: Recommended January 2011; Revised June 2016, November 2018, November 2019, February 2023

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[a] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatoryinformation/search-fda-guidance-documents.
[b] For the most recent version of a product-specific guidance, check the FDA product-specific guidance web page at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.