

Draft Guidance on Adapalene; Benzoyl peroxide

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Gel; Topical

Recommended Studies: One study

Type of study: Bioequivalence (BE) Study with clinical endpoint Design: Randomized, double blind, parallel, placebo controlled, in vivo

Strength: 0.3%; 2.5%

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 (N/A)

Bioequivalence based on (90% CI): Clinical endpoint

Waiver request of in vivo testing: N/A

Dissolution test method and sampling times: N/A

Additional comments regarding the BE study with clinical endpoint:

1. The Office of Generic Drugs (OGD) recommends conducting a BE study with a clinical endpoint in the treatment of acne vulgaris comparing adapalene and benzoyl peroxide gel, 0.3%/2.5% test product versus the reference listed drug (RLD) and placebo (vehicle) control, each administered as one application once a day in the evening for 12 weeks.
2. The recommended two primary endpoints of the study are: 1) mean percent change from baseline to Week 12 (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. 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.
4. Subjects should be instructed to cleanse the face with a mild or soapless, non-medicated

cleanser, pat dry and then apply a thin layer of the product to the entire face, avoiding contact with the eyes, lips, angles of the nose, and mucous membranes and washing hands before and after applications. Subjects should be instructed to not apply the product to cuts, abrasions, eczematous skin, or sunburned skin, not apply the product more than once daily, not use more than the recommended amount and not use “waxing” as a depilatory method on skin treated with the product.

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 be instructed to 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. Inclusion Criteria (the sponsor may add additional criteria)
- a. Male or nonpregnant 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

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>

during the 12-week treatment period.

e. If female of childbearing potential, willing to use an acceptable form of birth control during the study.

7. Exclusion Criteria (the sponsor may add additional criteria)

- a. Pregnant, breast feeding or planning a pregnancy.
- b. 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).
- c. Excessive facial hair (e.g. beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of acne vulgaris.
- d. History of hypersensitivity or allergy to adapalene, retinoids and/or any of the study medication ingredients.
- e. Use within 6 months prior to baseline or during the study of oral retinoids (e.g. Accutane®) or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed).
- f. Use for less than 3 months prior to baseline of estrogens or oral contraceptives; use of such therapy must remain constant throughout the study.
- g. 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.
- h. Use within 1 month prior to baseline or during the study of 1) systemic steroids, 2) systemic antibiotics, 3) systemic treatment for acne vulgaris (other than oral retinoids, which require a 6-month washout), or 4) systemic anti-inflammatory agents.
- i. Use within 2 weeks prior to baseline or during the study 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.

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

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. Study data should be submitted in a standardized format. Please refer to the study data standards published at www.fda.gov²

The following comments are the recommended approach to statistical analysis and study design for all bioequivalence studies with clinical endpoints.

1. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations.

- a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who:
 1. Meet all inclusion/exclusion criteria
 2. Are dosed a pre-specified proportion of the scheduled doses (Generally At least 75% and no more than 125%) of the assigned product for the specified duration of the study. The protocol should specify how compliance will be verified, (e.g., by the use of subject diaries).
 3. Do not miss a pre-specified number of scheduled doses for more than pre-specified number of consecutive days.
 4. Complete the evaluation within the designated visit window with no protocol violations that would affect the treatment evaluation.
- b. The mITT and safety populations include all randomized subjects who use at least one dose of product.

2. Subjects who are discontinued early from the study due to lack of treatment effect should be included in the PP population using Last Observation Carried Forward (LOCF). Subjects whose condition worsens and who require alternate or supplemental therapy for the treatment of their condition during the treatment phase of the study should be discontinued, included in the mITT and PP population analyses using LOCF, and provided with effective treatment. Subjects discontinued early for other reasons should be excluded from the PP population, but included in the mITT population, using LOCF. Applicants should provide a pre-specified definition of lack of treatment effect.

3. The start and stop calendar date (e.g., mm/dd/yyyy) and study day (e.g. Day X) of concomitant medication use should be provided in the data set in addition to the reason for the medication use. The Applicant should clearly note whether the medication was used prior to baseline visit, during the study, or both.

4. If the study allows for the use of a rescue medication, the Applicant should submit a data set that includes the date and time of each rescue medication use for each subject who used the

² Study Data Standards for Submission to CDER and CBER available at: <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/cm248635.htm>

rescue medication at any point during the study. The Applicant should pre-specify rescue medication use (name, type, frequency, reason to use), maximum allowable amount of daily rescue medication use, and any limitations (e.g. cannot use rescue medication within pre-specified number of hours prior to primary endpoint evaluation) for rescue medication use during the study.

5. All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the test product and RLD.

6. All pregnancies should be reported, including outcome information.

7. If the inactive ingredients are different than those contained in the RLD or in significantly different amounts, then the Applicant is to clearly describe the differences and provide information to show that the differences will not affect the safety, efficacy, or systemic or local availability of the drug. Inactive ingredients used should provide adequate margins of safety for the proposed clinical exposure in the target population (e.g., 2 months and older).

8. The method of randomization should be described in the protocol and the randomization schedule should be provided. It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. The Applicant may generate the randomization code if not involved in the packaging and labeling of the study medication. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each subject.

9. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test, reference and placebo products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate blinding of evaluators. When possible, neither the subject nor the investigator should be able to identify the treatment. The containers should not be opened by the subject at the study center.

10. Please refer to 21 CFR 320.38, 320.63 and the Guidance for Industry, "Handling and Retention of BA and BE Testing Samples", regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of bioequivalence testing. In addition, the investigators should follow the procedures of 21 CFR 58 and ICH E6, "Good Clinical Practice: Consolidated Guideline", for retention of study records and data in order to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP). Retention samples should be randomly selected from the drug supplies received for each shipment prior to dispensing to subjects. Retention samples should not be returned to the Applicant at any time.

11. It is the Applicant's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.

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

13. To establish bioequivalence for a dichotomous endpoint, it is recommended the following compound hypotheses be tested using the per protocol population:

$$H_0: \pi_T - \pi_R < \Delta_1 \text{ or } \pi_T - \pi_R > \Delta_2 \text{ versus } H_A: \Delta_1 \leq \pi_T - \pi_R \leq \Delta_2$$

where π_T = the success rate of the primary endpoint for the treatment group, and
 π_R = the success rate of the primary endpoint for the reference group.

The null hypothesis, H_0 , is rejected with a type I error (α) of 0.05 (two one-sided tests) if the estimated 90% confidence interval for the difference of the success rates between test and reference products ($\pi_T - \pi_R$) is contained within the interval $[\Delta_1, \Delta_2]$, where $\Delta_1 = -0.20$ and $\Delta_2 = 0.20$. Rejection of the null hypothesis supports the conclusion of equivalence of the two products.

To establish bioequivalence for a continuous endpoint, it is recommended the following compound hypotheses be tested using the per protocol population:

$$H_0: \mu_T / \mu_R < \theta_1 \text{ or } \mu_T / \mu_R > \theta_2 \text{ versus } H_A: \theta_1 \leq \mu_T / \mu_R \leq \theta_2$$

where μ_T = mean of the primary endpoint for the test group, and
 μ_R = mean of the primary endpoint for the reference group

The null hypothesis, H_0 , is rejected with a type I error (α) of 0.05 (two one-sided tests) if the estimated 90% confidence interval for the ratio of the means between test and reference products (μ_T / μ_R) is contained within the interval $[\theta_1, \theta_2]$, where $\theta_1 = 0.80$ and $\theta_2 = 1.25$. Rejection of the null hypothesis supports the conclusion of equivalence of the two products.

14. To establish sensitivity within the study for either a dichotomous or continuous primary endpoint, the test and reference products should both be statistically superior to the placebo. Conduct an appropriate two-sided inferential test with a type I error (α) of 0.05, using the mITT population.

15. The protocol should include a section with fully detailed statistical analysis plan.