

Draft Guidance on Adapalene; Benzoyl Peroxide

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: Healthy males and nonpregnant 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. A placebo (vehicle) 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.
5. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.
6. 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.
7. 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.
8. Assignment of the test product, RLD, and placebo control should be randomized. The method of randomization should be described in the protocol. 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. 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. The packaging of both the tube and the outer containers of the test, reference, and placebo products should be similar in appearance. If the appearance of the test, reference, or placebo products is markedly different, maintaining adequate blinding of the study for the subjects, evaluators and investigators will be a challenge. As much as possible, subjects should be blinded to the identity of their treatment. At a minimum, the placebo control should appear identical to the test product, and all study drugs should be provided in identical packaging. A detailed description of the blinding procedure should be provided in the protocol.
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 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 by each drug site prior to dispensing to subjects. Retention samples should not be returned to the sponsor at any time.

11. Inclusion Criteria (the sponsor may add additional criteria)

- a. Healthy 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 Vulgaris¹

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 12-week treatment period.
- e. If female of childbearing potential, willing to use an acceptable form of birth control during the study.

12. 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.

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>

- 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.
13. 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.
14. To establish bioequivalence, the 90% confidence interval of the test/reference ratio of the mean percent change from baseline to week 12 in the inflammatory (papules and pustules) lesion counts and in the non-inflammatory (comedones) lesion counts should be contained within [0.80, 1.25], using the per protocol (PP) population.
15. To establish sensitivity within the study for both primary endpoints, the test and reference product should both be statistically superior to the placebo ($p < 0.05$, two-sided) using the modified intent-to-treat (mITT) study population and Last Observation Carried Forward (LOCF).
16. The dichotomized IGA severity scale should be treated as a secondary endpoint for supportive evidence. This secondary endpoint should be evaluated as the proportion of subjects with a clinical response of “success” at week 12. Success should be defined as an

IGA score that is at least 2 grades less than the baseline assessment. Failure should be defined as an IGA score that is the same, higher or one grade lower than the baseline assessment.

17. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations in the protocol.
 - a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who meet all inclusion/exclusion criteria, applied a pre-specified proportion of the scheduled doses (insert recommended pre-specified proportion, for ex. “e.g., 75% to 125%”) of the assigned product for the specified duration of the study, do not miss the scheduled applications for more than (insert number of days, for ex. “1 consecutive day”), and complete the evaluation within the designated visit window (insert the recommended visit window, for ex. “+/- 2 days”) with no protocol violations that would affect the treatment evaluation. The protocol should specify how compliance will be verified, (insert recommended method of verifying compliance, for ex. “e.g., by the use of subject diaries”).
 - b. The mITT population includes all randomized subjects who apply at least one dose of assigned product.
 - c. The safety population includes all randomized subjects who receive study product.
18. Subjects who are discontinued prematurely from the study due to lack of treatment effect should be included in the PP population as treatment failures (i.e., non-responders). Subjects whose condition worsens and require alternate or supplemental therapy for the treatment of acne vulgaris during the study should be discontinued, included in the PP population analysis, and provided with effective treatment. Subjects discontinued prematurely for other reasons should be excluded from the PP population, but included in the mITT population, using LOCF.
19. 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, 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.
20. 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.
21. The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use.
22. If the inactive ingredients are different than those contained in the RLD or in significantly different amounts, then the sponsor should clearly describe the differences and provide information to show that the differences will not affect the safety, efficacy and/or systemic or local availability.

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

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

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.

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

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

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

25. Rank transformation of the data may be needed if the data is significantly skewed such that analysis of the raw data would not be valid.

26. The method of randomization should be described in the protocol and the randomization schedule provided as a SAS data set in .xpt format (created using SAS XPORT). 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 sponsor 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.

27. Study data should be submitted to the OGD in electronic format. All data should be submitted as a SAS .xpt file, created using SAS XPORT (not CPORT).

- a. Include a list of file names, a description of the content of each file, an explanation of the variables within each file, and a description of all variable codes (for example, for the treatment variable, A = TEST and B = RLD).
- b. Provide two primary data sets: one with No Last Observation Carried Forward (NO-LOCF - pure data set) and one with the Last Observation Carried Forward (LOCF - modified data set).
- c. Provide a separate dataset for demographic, vital sign, adverse event, disposition (including reason for discontinuation of treatment), concomitant medication,

medical history, compliance, and comment variables.

28. Please provide a summary dataset containing a separate line listing for each subject (if data exist) using the following headings, if applicable:
- a. Study identifier
 - b. Subject identifier
 - c. Site identifier: study center
 - d. Age
 - e. Age units (years)
 - f. Sex
 - g. Race
 - h. Name of Actual Treatment (exposure): test product, RLD, placebo control
 - i. Location of Treatment Area
 - j. Duration of Treatment (total exposure in days)
 - k. Completed the study (yes/no)
 - l. Reason for premature discontinuation of subject
 - m. Subject required additional treatment for acne vulgaris due to unsatisfactory treatment response (yes/no)
 - n. Per Protocol (PP) population inclusion (yes/no)
 - o. Reason for exclusion from PP population
 - p. Modified Intent to Treat (mITT) population inclusion (yes/no)
 - q. Reason for exclusion from mITT population
 - r. Safety population inclusion (yes/no)
 - s. Reason for exclusion from Safety population
 - t. Total number of inflammatory lesions on the face at baseline
 - u. Total number of non-inflammatory lesions on the face at baseline
 - v. Total number of nodules/cysts on the face at baseline
 - w. IGA score at baseline
 - x. Total number of inflammatory lesions on the face at week 12
 - y. Total number of non-inflammatory lesions on the face at week 12
 - z. Total number of nodules/cysts on the face at week 12
 - aa. IGA score at week 12
 - bb. Final designation for IGA (success/failure)
 - cc. Treatment compliance : number of missed doses per patient
 - dd. Concomitant medication (yes/no)
 - ee. Adverse event(s) reported (yes/no)

Please refer to Table 2 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 2: Example of a summary dataset containing one line listing for each subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	EXLOC	EXDUR	completd	disc_rs	add_trt	pp	pp_rs	mitt	mitt_rs
101	1	01	21	YEARS	F	1	A	Face	14	Y		N	Y		Y	
101	2	01	30	YEARS	F	1	B	Face	14	Y		N	Y		Y	

safety	safe_rs	numinfb	numnonb	numnodb	iga_b	numinf12	numnon12	numnod12	iga_12	iga_f	complan	CM	AE
Y		32	45	0	3	16	30	0	2	F	0	Y	Y
Y		25	36	1	3	10	18	1	1	S	0	N	N

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final dated 11/12/08.

- STUDYID: Study Identifier
- SUBJID: Subject Identifier for the Study
- SITEID: Study Site Identifier
- AGE: Age
- AGEU: Age units (years)
- SEX: Sex, e.g., M=Male, F=Female, U=Unknown
- RACE: Race, e.g., 1=White, 2=Black or African American, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or Other Pacific Islanders
- EXTRT: Name of Actual Treatment (exposure), e.g., A=test product, B=RLD, C=placebo control
- EXLOC: Location of Treatment Area, e.g. F=face, etc.
- EXDUR: Duration of Treatment (total exposure in days)
- completd: Subject completed the study, e.g., Y=Yes, N=No
- disc_rs: Reason for premature discontinuation from the study, e.g., A=adverse event, B=death, C=lost to follow-up, D=non-compliance with treatment, E=treatment unblinded, F=subject moved out of area, G=unsatisfactory treatment response, H=withdrew consent, I=protocol violation, K=other event
- add_trt: Subject required additional treatment for acne vulgaris due to unsatisfactory treatment response, e.g., Y=Yes, N=No
- pp: Per Protocol (PP) population inclusion, e.g., Y=Yes, N=No
- pp_rs: Reason for exclusion from PP population, e.g., A=prematurely discontinued, B=lost to follow-up, C=subject moved out of the area, D=noncompliant, etc.
- mitt: Modified Intent to Treat (mITT) population inclusion, e.g., Y=Yes, N=No
- mitt_rs: Reason for exclusion from mITT population, e.g., A=never treated, etc.
- safety: Safety population inclusion, e.g., Y=Yes, N=No

safe_rs:	Reason for exclusion from Safety population, e.g., A=never treated, etc.
numinfb:	Total number of inflammatory lesions on face at baseline
numnonb:	Total number of noninflammatory lesions on face at baseline
numnodb:	Total number of nodular/cystic lesions on face at baseline
iga_b:	IGA score at baseline, e.g., 0=Clear; 1=Almost clear, 2=Mild, 3=Moderate, 4=Severe
numinf12:	Total number of inflammatory lesions on face at week 12
numnon12:	Total number of noninflammatory lesions on face at week 12
numnod12:	Total number of nodular/cystic lesions on face at week 12
iga_12:	IGA score at week 12, e.g., 0=Clear; 1=Almost clear, 2=Mild, 3=Moderate, 4=Severe
iga_f:	Final designation for IGA, e.g., S=Success; F=Failure
complian:	Treatment compliance, e.g., number of missed doses per patient
CM:	Concomitant medication, e.g., Y=Yes, N=No
AE:	Adverse event(s) reported, e.g., Y=Yes, N=No

28. Please provide a dataset containing a separate line listing for visit per subject (if data exist) using the following headers, if applicable:

- a. Study identifier
- b. Subject identifier
- c. Name of Actual Treatment (exposure): test product, RLD, placebo control
- d. Location of Dose Administration: application site
- e. Visit number
- f. Visit date
- g. Number of days since baseline visit
- h. Evaluator: identity of evaluator
- i. Total number of inflammatory lesions
- j. Total number of noninflammatory lesions
- k. Total number of nodular/cystic lesions
- l. IGA score
- m. Skin reaction scores for each sign and symptom evaluated (e.g., erythema, dryness, burning/stinging, erosion, edema, pain, itching, etc.)
- n. Concomitant medication reported during this visit (yes/no)
- o. Adverse event reported during this visit (yes/no)
- p. Laboratory testing during this visit (yes/no)

Please refer to Table 3 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 3: Example of dataset containing one line listing for each visit per subject

STUDYID	SUBJID	EXTRT	EXLOC	VISITNUM	SVSTDTC	ELTMBS	EVAL	numinf	numnon	numnod	iga
101	1	A	F	1	2004-07-01	1		35	28	1	3

erythema	dryness	burning	erosion	edema	pain	itching	CMrpt	AErpt	LBtest
1	0	0	1	0	0	0	Y	Y	N

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Draft dated 7/25/07.

- STUDYID: Study Identifier
SUBJID: Subject Identifier for the Study
EXTRT: Name of Actual Treatment (exposure), e.g. A=test product, B=RLD, C=placebo control
EXLOC: Location of Treatment Area: specific anatomical site of application, e.g., F=face etc.
VISITNUM: Visit Sequence Number
SVSTDTC: Visit date: (SVSTDTC=Subject Visit Start Date Time-Character)
ELTMBS: Elapsed Time since Baseline (days)
EVAL: Evaluator: identity of the evaluator
numinf: Total number of inflammatory lesions on face
numnon: Total number of noninflammatory lesions on face
numnod: Total number of nodular/cystic lesions on face
iga: IGA score, e.g., 0=Clear; 1=Almost clear, 2=Mild, 3=Moderate, 4=Severe
erythema: Skin reaction erythema score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
dryness: Skin reaction dryness score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
burning: Skin reaction burning score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
erosion: Skin reaction erosion score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
edema: Skin reaction edema score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
pain: Skin reaction pain score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
itching: Skin reaction itching score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)

CMrpt: Concomitant Medication reported during this visit, e.g., Y=Yes, N=No
AErpt: Adverse Event reported during this visit, e.g., Y=Yes, N=No
LBtest: Laboratory Testing performed during this visit, e.g., Y=Yes, N=No

29. The study data should be submitted in standardized format. Refer to more details at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>
30. These recommendations are specific to this product and may not be appropriate for bioequivalence studies of any other product, including any other dosage form or strength of adapalene or benzoyl peroxide, as a single active ingredient or as a combination drug product.