

## Draft Guidance on Tretinoin

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

**Active ingredient:** Tretinoin

**Form/Route:** Cream/Topical

**Recommended studies:** 1 study

Type of study: Bioequivalence (BE) with Clinical Endpoint Study  
Design: Randomized, double blind, parallel, placebo controlled, in vivo  
Strength: 0.0375%  
Subjects: Healthy males and nonpregnant females with acne vulgaris.  
Additional comments: Specific recommendations are provided below.

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**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

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

1. An ANDA for an intermediate strength(s) of Tretinoin Cream containing sufficient data may be approved per 21 CFR 320.24(b)(6) without conducting an in vivo BE with clinical endpoint study. This would be based on a prior determination of two acceptable BE with clinical endpoint studies conducted on a lower strength and a higher strength of the same product, the proposed active and inactive ingredients of the proposed product being qualitatively and quantitatively the same as the RLD, the formulations of the lower, intermediate, and higher strengths of the test product and RLDs are exactly the same except for the amount of tretinoin, and additional comparative data (e.g., in vitro release testing, physicochemical properties comparison including viscosity and pH) for each strength of the proposed product and RLD being provided and determined to be acceptable. If you want to pursue a strength of tretinoin not already listed in the Orange Book, you must first submit a suitability petition to request a change in dosage form according to 21 CFR § 314.93, 10.20 and 10.30.
2. The Office of Generic Drugs (OGD) recommends conducting a BE study with clinical endpoint in the treatment of acne vulgaris. Subjects are to be randomized to receive the generic Tretinoin Cream USP 0.0375%, the reference listed drug (RLD) or placebo. The study drug is to be administered once daily in the evening for 12 weeks. The primary endpoint is to be evaluated at the end of treatment (study Week 12).

3. A placebo control arm is recommended to demonstrate that the test product and RLD are active and as a parameter to establish that the study is sufficiently sensitive to detect differences between products.
4. Inclusion Criteria (the sponsor may add additional criteria)
  - a. Healthy male or nonpregnant female aged  $\geq 12$  and  $\leq 40$  years with a clinical diagnosis of acne vulgaris.
  - b. On the face,  $\geq 25$  non-inflammatory lesions (i.e., open and closed comedones) AND  $\geq 20$  inflammatory lesions (i.e., papules and pustules) AND  $\leq 2$  nodulocystic lesions (i.e., nodules and cysts).
  - c. Investigator's Global Assessment (IGA) of acne severity grade 2, 3, or 4 (per Table I).

**Table 1. Sample IGA Scale for Acne Vulgaris<sup>1</sup>**

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.
5. 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 tretinoin, retinoids, or any of the study medication ingredients.
  - 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).

<sup>1</sup> 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>

- 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 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.
6. Subjects should cleanse the face with a mild or soapless, non-medicated cleanser, dry skin gently, wait 20 to 30 minutes before applying the study product, and then apply enough product to lightly cover the entire affected areas of the face once daily at bedtime. The subject should be instructed to avoid contact of the study product with the corners of the nose, mouth, eyes and open wounds, and to wash their hands after application.
  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 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. 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.
  9. The recommended two primary endpoints of the study are 1) percent change from baseline to week 12 in the inflammatory (papules and pustules) lesion counts and 2) percent change from baseline to week 12 in the non-inflammatory (open and closed comedones) 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 non-inflammatory lesion counts.
  10. 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 apply a prespecified proportion of the scheduled applications (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 3 consecutive days, and complete the evaluation within

- the designated visit window (+/- 4 days) with no protocol violations that would affect the treatment evaluation. The protocol should specify how compliance will be verified, e.g., by the use of subject diaries.
- b. The mITT population includes all randomized subjects who met the inclusion/exclusion criteria, apply at least one dose of assigned product, and return for at least one post-baseline evaluation visit.
  - c. The safety population includes all randomized subjects who received study product.
11. Subjects who are discontinued early from the study due to lack of treatment effect after completing 4 weeks of treatment should be included in the PP population as treatment failures. 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 early for other reasons should be excluded from the PP population, but included in the mITT population, using LOCF.
  12. 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.
  13. 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.
  14. 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.
  15. If the inactive ingredients are different than those contained in the RLD or in significantly different amounts, then the sponsor is to clearly describe the differences and provide information to show that the differences will not affect the safety, efficacy and/or systemic or local availability of the drug.
  16. 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. 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.
  17. 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.
  18. 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 prior to dispensing to subjects. Retention samples should not be returned to the sponsor at any time.

19. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.
20. 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.
21. As a parameter for determining adequate study sensitivity, the test product and RLD should both be statistically superior to placebo ( $p < 0.05$ ) with regard to 1) mean percent change from baseline to week 12 in the inflammatory lesion counts and 2) mean percent change from baseline to week 12 in the non-inflammatory lesion counts, both using the intent-to-treat (ITT) study population and Last Observation Carried Forward (LOCF).
22. The following Statistical Analysis Method is recommended for equivalence testing for a continuous variable:

#### Equivalence Analysis

The compound hypothesis to be tested is:

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

Where  $\mu_T$  = mean of test treatment, and  $\mu_R$  = mean of reference treatment

Typically, we reject  $H_0$  with a type I error  $\alpha = 0.05$  (two 1-sided tests), if the 90% confidence interval for the ratio of means between test and reference products ( $\mu_T / \mu_R$ ) is contained within the interval  $[\theta_1, \theta_2]$ , where  $\theta_1 = 0.80$  and  $\theta_2 = 1.25$ .

Rejection of the null hypothesis  $H_0$  supports the conclusion of equivalence of the two products.

23. Study data should be submitted to the OGD in electronic format.
  - a. A list of file names, with a simple description of the content of each file, should be included. Such a list should include an explanation of the variables included in each of the data sets.
  - b. Please provide a “pdf” document with a detailed description of the codes that are used for each variable in each of the SAS datasets (for example, Y=yes, N=no for analysis population).
  - c. All SAS transport files, covering all variables collected in the Case Report Forms (CRFs) per subject, should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS files should be included.
  - d. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NO-LOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set).
  - e. Please provide a separate dataset for variables such as demographics, lesion counts, vital signs, adverse events, disposition (including reason for discontinuation of treatment), concomitant medications, medical history, compliance and comments, etc.

24. 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. Total number of inflammatory lesions on the face at week 12
  - x. Total number of non-inflammatory lesions on the face at week 12
  - y. Total number of nodules/cysts on the face at week 12
  - z. Treatment compliance : number of missed doses per subject
  - aa. Concomitant medication (yes/no)
  - bb. Adverse event(s) reported (yes/no)

Please refer to Table 1 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 1: 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	84	Y		N	Y		Y	
101	2	01	30	YEARS	F	1	B	Face	84	Y		N	Y		Y	

safety	safe_rs	numinfb	numnonb	numnodb	numinf12	numnon12	numnod12	complan	CM	AE
Y		32	45	0	16	30	0	0	Y	Y
Y		25	36	1	10	18	1	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 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
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
complan:	Treatment compliance, e.g., number of missed doses per subject
CM:	Concomitant medication, e.g., Y=Yes, N=No
AE:	Adverse event(s) reported, e.g., Y=Yes, N=No

25. 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. Skin reaction scores for each sign and symptom evaluated (e.g., erythema, dryness, burning/stinging, erosion, edema, pain, itching, etc.)
- m. Concomitant medication reported during this visit (yes/no)
- n. Adverse event reported during this visit (yes/no)
- o. Laboratory testing during this visit (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 dataset containing one line listing for each visit per subject**

STUDYID	SUBJID	EXTRT	EXLOC	VISITNUM	SVSTDTC	ELTMBS	EVAL	numinf	numnon	numnod	erythema	dryness	burning	erosion	edema	pain	itching	CMrpt	AErpt	LBtest
101	1	A	F	1	2004-07-01	1		35	28	1	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 Final dated 11/12/08.

- 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
- 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/stinging 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

26. 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 tretinoin.