

Draft Guidance on Docosanol

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Cream; topical

Recommended Studies: Two options: in vitro or in vivo study

I. In vitro option:

To qualify for the in vitro option to demonstrate bioequivalence for docosanol cream, 10%, the following criteria should be met:

- A. The test and Reference Listed Drug (RLD) products in the same packaging configuration (tube or pump) should be qualitatively (Q1) and quantitatively (Q2) the same as defined in the Guidance for Industry *ANDA Submissions – Refuse-to-Receive Standards*.¹
- B. The test and RLD products in the same packaging configuration (tube or pump) should be physically and structurally similar based upon an acceptable comparative physicochemical/microstructural characterization of a minimum of three lots of the test and three lots (as available) of the RLD product. The test and RLD products should include the following comparisons of physical and structural attributes between the test and RLD products:
 1. Assessment of appearance
 2. Analysis of the polymorphic form undissolved docosanol² (if any) in the drug product
 3. Analysis of globule size distribution with representative high resolution microscopic images at multiple magnifications.
 4. Analysis of the 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 (or viscosity) vs. shear rate. At minimum this should consist of numerical viscosity data at three shear rates (low, medium and high), and may include a complete flow curve across the range of attainable shear rates, until low or high shear plateaus are identified.

¹ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs Guidances web page at

<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

² Polymorphic behavior of docosanol is discussed in Valoppi et al. (2016) Phase Transition and Polymorphic Behavior of Binary Systems Containing Fatty Alcohols. *Cryst. Growth Des.* 2016, 16, 4209-4215.

- Yield stress values should be reported if the material tested exhibits plastic flow behavior.
 - The linear viscoelastic response (storage and loss modulus vs. frequency) should be measured and reported.
5. Analysis of pH, as well as any other potentially relevant physical and structural attributes.
- C. The test and RLD products in the same packaging configuration (tube or pump) should have an equivalent rate of docosanol release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one lot each of the test and RLD products using an appropriately validated IVRT method.

Applicants should refer to FDA's current thinking in the product-specific guidance for acyclovir topical cream 5%³ products referencing NDA 021478 for detailed recommendations relating to the development, validation, design, conduct and/or analysis of the qualitative and quantitative composition, physical and structural similarity, and IVRT comparative studies.

II. In vivo option:

Type of study: Bioequivalence (BE) with Clinical Endpoint Study

Design: Randomized, double-blind, parallel, three-arm, placebo-controlled, in vivo

Strength: 10%

Subjects: Males and females (nonpregnant) with recurrent herpes labialis (cold sores)

Additional comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): N/A

Bioequivalence based on (90% CI): See additional comments for in vivo option

Dissolution test method and sampling times: N/A

Additional comments regarding the BE with clinical endpoint study:

1. The Office of Generic Drugs (OGD) recommends conducting a BE study with a clinical endpoint in adult males and females (nonpregnant) with recurrent herpes labialis (RHL) comparing the test product versus the RLD and placebo (vehicle) control with treatment initiated as early as possible following the onset of signs or symptoms of herpes labialis, i.e., during the prodrome or when lesions appear, and applied five times per day for 10 days (50 applications).

³ This guidance is available on the FDA Product-Specific Guidances for Generic Drug Development web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>

2. A placebo (vehicle) 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.
3. Inclusion criteria (the Applicant may add additional criteria):
 - a. Male or female (nonpregnant) at least 18 years of age with recurrent herpes labialis
 - b. At least 4 recurrences of a typical herpes labialis lesions within the past year
 - At least half of recurrences should be preceded by recognizable prodromal symptoms, e.g., itching, redness, burning, tingling, or a sense of irritation.
 - At least half of the episodes should develop classical lesions, e.g., ulcer, vesicle, and/or hard crust
4. Exclusion criteria (the Applicant may add additional criteria):
 - a. Females who are pregnant, breast feeding, or planning a pregnancy.
 - b. Females of childbearing potential who do not agree to utilize an adequate form of contraception.
 - c. Subject who is unable or is not expected to reliably comprehend or satisfactorily assess a herpetic lesion.
 - d. Subjects with lesions above the nares, below the chin, or inside the mouth
 - e. Subject with any abnormal skin conditions, e.g., acne, eczema, rosacea, psoriasis, albinism, or chronic vesiculo-bullous disorders, known to occur or current present in the area ordinarily affected by RHL.
 - f. Current or active immunodeficiency syndrome or disease
 - g. Current active malignancy
 - h. Current episode of herpes labialis that is not completely healed
 - i. Recent organ transplant
 - j. Chronic use of immunosuppressive drugs (e.g., systemic steroid) or topical steroids.
 - k. Chronic use of antiviral medication with activity against herpes simplex virus (HSV).
 - l. History of vaccination for HSV type 1 (typically oral herpes) or HSV type 2 (typically general genital herpes).
 - m. History of herpes keratitis
 - n. Candidate for parenteral antiviral treatment or for prophylactic antiviral therapy of their recurrent herpes labialis
 - o. Use within four weeks prior to baseline of any over-the-counter or prescription antiviral treatment.
 - p. Contraindication to antiviral therapy or known hypersensitivity to docosanol or any component of docosanol therapy.
5. A positive viral culture is not required for enrollment.
6. The protocol should include a list of the prescriptions and over-the-counter drug products, procedures, and activities that are prohibited during the study, such as:
 - a. Antiviral therapies, other than study product
 - b. Corticosteroids
 - c. Treatments for cold sores, other than study product
 - d. Topical lip balms

- e. Cosmetics or other skin products applied to the treatment area
 - f. Prolonged sun exposure (i.e., sunbathing or sunburn)
 - g. Mechanical disruption (i.e., scrubbing, lancing, shaving) of the prodromal area or lesion
 - h. Subjects should be instructed to wash their hands with soap and water before and after applying treatment, to avoid rubbing the cold sore, and to avoid contact of the study product with the eye or inside of the mouth or nose
7. The recommended primary endpoint is the duration of episode (DOE) assessed by the investigator, based on both clinical observation and review of the subject diary, and defined as:
- a. For subjects who experience a vesicular lesion, DOE is the time from the treatment initiation to the healing of primary lesions (loss of crust; residual erythema may be present after loss of hard crust).
 - b. For subjects whose primary lesions were not vesicular in nature, DOE is the time from the treatment initiation to the return to normal skin or to the cessation of symptoms, whichever occurs last.

The primary endpoint is calculated by subtracting the recorded time of the first application of study medication in the case report form from the recorded time of the investigator-assessed healing.

8. Within 24 hours (study Day 1) or soon after initiating treatment with study drug, recommend that subjects return to study site for investigator assessments and return to study site for investigator assessments at minimum daily thereafter until:
- a. Healing of the primary vesicular lesion, for those subjects who experience a vesicular lesion, OR
Return to normal skin or the cessation of symptoms, whichever occurs last, for those subjects whose primary lesions are not vesicular in nature

Subjects should return to clinic for assessment by investigator as soon as healing is noted.

9. Provide subjects with a diary and instruct them to record all study drug application times. Subjects should also record their symptoms, such as pain, tenderness, tingling, itching, discomfort, and the stage of their herpes lesions (normal lip, erythema, papule, vesicle, ulcer, crust), at a minimum of twice daily. Subjects should be educated on recognizing the symptoms and the different stages of recurrent herpes labialis.
10. A rescue clause is recommended to allow subjects who significantly worsen (e.g., significant increase in size or number of lesions beyond the patient's unusual pattern, progression of lesions after the first few days of therapy, development of severe pain, or evidence of tissue necrosis) during therapy to be discontinued from the study and provided with standard therapy.
11. 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 meet all inclusion/exclusion criteria, applied a pre-specified proportion of the scheduled doses (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 1 consecutive day, and complete the evaluation within the designated visit window (+/- 2 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 and safety populations include all randomized subjects who applied at least one dose of assigned product and return for at least one post-baseline evaluation visit.
12. Subjects who are discontinued early from the study due to insufficient or lack of treatment effect should be included in the PP population as treatment failures and assigned the longest time to healing observed in the study. Subjects discontinued early for other reasons should be excluded from the PP population, but included in the mITT population. If complete healing was noted at their last visit and assigning the longest time to healing if healing was not complete at their last visit.
13. The start and stop date of concomitant medication use should be provided in the data set in addition to the reason for the medication use. The Applicant should clearly explain whether the medication was used prior to baseline visit, during the study, or both.
14. 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.
15. If the inactive ingredients of the test product are different from those contained in the RLD or in significantly different amounts, then the Applicant must 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 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.
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 Applicant at any time.
19. It is the Applicant's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.
20. To establish bioequivalence for a continuous endpoint, it is recommended the following compound hypotheses be tested using the PP 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.

21. To establish sensitivity within the study for a continuous primary endpoint, the test and reference product should both be statistically superior to the placebo. Conduct an appropriate inferential test for a continuous endpoint (duration of episode) with a type I error rate (α) of 0.05, using the mITT population.
22. It is recommended that an analysis of covariance (ANCOVA) with two covariates be used for the estimation of the ratio of the means. The two covariates are the type of primary lesion (vesicular or not vesicular in nature) and baseline absolute lesion count.
23. In addition to the test described above, a supportive time-to-event (survival) statistical analysis using the Kaplan-Meier methodology and the Cox proportional hazards model can be performed for the DOE primary endpoint. If a subject discontinued early, this subject is censored at the date of discontinuation, if a subject uses a rescue clause, this subject is censored at the date of rescue treatment, and if a subject is not completely healed at her/his last visit, this subject is censored at their last visit date.

24. The study data should be submitted in standardized format. Please refer study data standards published at www.FDA.gov.⁴
25. Please provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
- a. Study identifier
 - b. Unique subject identifier
 - c. Subject identifier for the study
 - d. Study site identifier
 - e. Age
 - f. Age unit (years)
 - g. Sex
 - h. Race
 - i. Description of planned arm
 - j. Description of actual arm
 - k. Planned treatment (character)
 - l. Planned treatment (number)
 - m. Actual treatment (character)
 - n. Actual treatment (number)
 - o. Safety population flag (yes/no)
 - p. Reason for exclusion from safety population
 - q. Modified intent-to-treat (ITT) population flag (yes/no)
 - r. Reason for exclusion from mITT population
 - s. Per protocol (PP) population flag (yes/no)
 - t. Reason for exclusion from PP population
 - u. Completers population flag (yes/no)
 - v. Randomized population flag (yes/no)
 - w. Date of randomization
 - x. Date of enrollment
 - y. Date/time of first exposure to treatment
 - z. Date/time of last exposure to treatment
 - aa. Time to complete healing of lesions (days, not for Kaplan-Meier analysis)
 - bb. End of study date
 - cc. End of study status
 - dd. Subject required additional treatment for herpes labialis due to unsatisfactory treatment response (yes/no)
 - ee. Date of rescue treatment
 - ff. Compliance rate (%)
 - gg. Treatment compliance: number of missed doses per subject
 - hh. Concomitant medication (yes/no)
 - ii. Adverse event(s) reported (yes/no)
 - jj. Censoring status (1/0)

⁴ Study Data Standards for Submission to CDER available at:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

- kk. Time to healing for Kaplan-Meier analysis (End of study date-Date of first exposure treatment+1) (days) if a subject had rescue medications due to unsatisfactory treatment response, the time to healing should be (date of the rescue treatment –date of first exposure treatment+1)
 - ll. Type of primary lesion
 - mm. Baseline absolute lesion count
 - nn. Reason for discontinuation from study (character)
 - oo. Reason spec for discontinuation from study (character, additional details regarding subject's discontinuation from study)
 - pp. Reason for discontinuation of treatment (character)
 - qq. Reason spec for discontinuation of treatment (character, additional details regarding subject's discontinuation from treatment)
 - rr. Evaluator initial (character)
26. Please provide the basic data structure (BDS) dataset with records per subject, per analysis timepoint, using the following headings, if applicable:
- a. Study identifier
 - b. Unique subject identifier
 - c. Subject identifier for the study
 - d. Study site identifier (if applicable)
 - e. Age
 - f. Age unit (years)
 - g. Sex
 - h. Race
 - i. Safety population flag (yes/no)
 - j. Modified intent-to-treat (mITT) population flag (yes/no)
 - k. Per-protocol (PP) population flag (yes/no)
 - l. Description of planned treatment
 - m. Description of actual treatment
 - n. Planned treatment (character)
 - o. Planned treatment (number)
 - p. Actual treatment (character)
 - q. Actual treatment (number)
 - r. Completers population flag (yes/no)
 - s. Analysis date
 - t. Analysis visit
 - u. Study visit within the designated window (yes/no)
 - v. Analysis timepoint (e.g., hour 12, hour 24)
 - w. Date/time of first exposure to treatment
 - x. Date/time of last exposure to treatment
 - y. Stage of recurrent herpes labialis infection
 - z. Signs/symptoms of herpes labialis infection
 - aa. Additional treatment required during the visit (yes/no)
 - bb. Rescue treatment required (yes/no)
 - cc. Date/time of rescue treatment
 - dd. Concomitant medication during the visit (yes/no)

ee. Adverse event reported during the visit (yes/no)

27. The protocol should include a complete and full detailed statistical analysis plan and describe how missing data will be prevented and handled if exist.