Draft Guidance on Acyclovir

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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: Acyclovir

Form/Route: Ointment; Topical

Recommended study: 2 Options: *In Vitro or In Vivo Study*

I. In Vitro option:

To qualify for the in vitro option for this drug product pursuant to 21 CFR 320.24 (b)(6), under which “any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence” may be acceptable for determining the bioavailability or bioequivalence (BE) of a drug product, all of the following criteria must be met:

i. The test and Reference Listed Drug (RLD) formulations are qualitatively and quantitatively the same (Q1/Q2).

ii. Acceptable comparative physicochemical characterization of the test and RLD formulations.

iii. Acceptable comparative in vitro drug release rate tests of acyclovir from the test and RLD formulations.

II. In Vivo option:

Type of study: BE Study with Clinical Endpoint

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

Strength: 5%

Subjects: Immunocompromised males and nonpregnant females with recurrent herpes simplex labialis

Additional comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): Not Applicable

Bioequivalence based on (90% CI): Clinical endpoint (in vivo option)

Dissolution test method and sampling times: Not Applicable

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 immunocompromised males and nonpregnant females with recurrent herpes simplex labialis comparing the test product versus the RLD and placebo control with treatment initiated at the onset of signs or symptoms and applied every three hours six times daily for 7 days.

*Recommended Mar 2012*
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 at the lower end of the dose/response curve.

3. Inclusion Criteria (the sponsor may add additional criteria)
   a. Immunocompromised (defined according to underlying disease and/or the administration of immunosuppressant medication) male or nonpregnant females aged at least 18 years with limited, non-life-threatening, recurrent herpes simplex labialis.
   b. At least 3 recurrences of herpes simplex labialis per year for the past two years.
      • At least half of recurrences preceded by recognizable prodromal symptoms.
      • At least half of prodromes followed by classical lesions.

4. Exclusion Criteria (the sponsor 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. Candidate for parental antiviral treatment or for prophylactic antiviral therapy of their recurrent herpes simplex labialis.
   d. Recent transplant.
   e. CD4 counts below 200 cells/μl (HIV subjects are generally considered to be immunocompromised without regard to an upper limit for CD4 counts).
   f. Recent major change in immune status that could seriously affect the clinical manifestations of herpes simplex labialis and need for treatment.
   g. Current episode of herpes simplex labialis that is not completely healed.
   h. History of herpes keratitis.
   i. Contraindication to antiviral therapy or known hypersensitivity to any component of acyclovir therapy.
   j. Use within one week prior to baseline of antiviral therapy

5. A positive viral culture is not required for enrollment.

6. Subjects should be instructed to use a finger cot or rubber glove when applying the study product to prevent autoinoculation of other body sites and transmission of infection to other persons.

7. 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. Antiviral therapies, other than study product.
   b. Topical lip-balms.
   c. Treatments for cold sores.
   d. Cosmetics applied to the treatment area.
   e. Prolonged sun exposure (i.e., sunbathing or sunburn).
   f. Subjects should be instructed to avoid contact of the study product with the eye.

8. The recommended primary endpoint is time to complete healing of lesions (defined as loss of crust and re-epithelialization with or without erythema, as assessed by the investigator, based on both clinical observation and review of the subject diary), measured in days from the time of first dosing. Subjects who experience a prodrome and start treatment at that time, but who do not subsequently develop any lesion should be assigned a value of zero (0) for time to complete healing of lesions.
9. Cessation of viral shedding has not been shown to correlate well with clinical outcome. It may be included as a secondary endpoint.

10. Within 24 hours (study Day 1) of initiating treatment with study drug, recommend that subjects return to study site for investigator assessments. Site visits are recommended on study Days 2, 3, and 4, and then every other day until the investigator deemed that lesion healing had occurred or up to study Day 14. In any cases where healing did not occur by study Day 14, another site visit is recommended at study Day 21.

11. 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 usual 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.

12. 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 population includes all randomized subjects who meet all 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 receive study product.

13. Subjects who are discontinued early from the study due to insufficient or lack of treatment effect after completing 5 days of treatment 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, using Last Observation Carried Forward (LOCF) 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.

14. 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. The sponsor should clearly explain whether the medication was used prior to baseline visit, during the study, or both.

15. 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.

16. If the inactive ingredients of the test product are different than those contained in the RLD or in significantly different amounts, then the sponsor 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.
17. 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.

18. 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.

19. 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.

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

21. To establish bioequivalence, the 90% confidence interval of the test/reference ratio for the primary endpoint must be contained within [0.80, 1.25] for a continuous variable, using the PP population.

22. 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 the primary endpoint, using the mITT study population and LOCF.

23. The following Statistical Analysis Method is recommended for equivalence testing for a continuous variable:

   **Equivalence Analysis**

   The compound hypothesis to be tested is:

   \[
   H_0: \frac{\mu_T}{\mu_R} \leq \theta_1 \text{ or } \frac{\mu_T}{\mu_R} \geq \theta_2 \text{ versus } H_A: \theta_1 < \frac{\mu_T}{\mu_R} < \theta_2
   \]

   Where \( \mu_T = \text{mean of test treatment, and } \mu_R = \text{mean of reference treatment} \)

   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 \( \theta_2 = 1.25 \).

24. 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. 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, vital signs, adverse events, disposition (including reason for discontinuation of treatment), concomitant medications, medical history, compliance and comments, etc.

25. 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, vehicle control
- i. Completed the study (yes/no)
- j. Reason for premature discontinuation of subject
- k. Subject required additional treatment for herpex simplex labialis due to unsatisfactory treatment response (yes/no)
- l. Per Protocol (PP) population inclusion (yes/no)
- m. Reason for exclusion from PP population
- n. Modified Intent to Treat (mITT) population inclusion (yes/no)
- o. Reason for exclusion from mITT population
- p. Safety population inclusion (yes/no)
- q. Reason for exclusion from Safety population
- r. Time to complete healing of lesions (days)
- s. Treatment compliance: number of missed doses per subject
- t. Concomitant medication (yes/no)
- u. 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

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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=vehicle control
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 psoriasis 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.
tim_heal: Time to complete healing of lesions (days)
complian: 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

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 acyclovir.