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Draft Guidance on Ketoconazole

February 2026

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Active Ingredient: Ketoconazole

Dosage Form: Shampoo

Route: Topical

Strength: 2%

Recommended Studies: Two options: (1) one in vitro bioequivalence study and other characterization tests or (2) one comparative clinical endpoint bioequivalence study

I. Option 1: One in vitro bioequivalence study and other characterization tests

To demonstrate bioequivalence for ketoconazole topical shampoo, 2% using in vitro studies, the following criteria should be met:

1. The test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference standard (RS) that may significantly affect the local or systemic availability of the active ingredient. For example, if the test product and RS are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the most recent version of the guidance for industry *ANDA Submissions – Refuse-to-Receive Standards*[a] and the criteria below are also satisfied, the bioequivalence of the test product may be established using a characterization-based bioequivalence approach.

2. The test product and RS should have the same physicochemical and structural (Q3) attributes, based upon acceptable comparative Q3 characterization tests with a minimum of three batches of the test product and three batches (as available) of the RS. The test product and RS batches should ideally represent the product at different ages throughout

its shelf life. Refer to the most recent version of the guidance for industry *Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs*[a] for additional information regarding comparative Q3 characterization tests. The comparative Q3 characterization should be conducted with (1) the test and RS shampoo dispensed from the container closure system (CCS), (2) the foamed shampoo that is formed after lathering the test and RS shampoo (which includes diluting the shampoo with water at multiple dilution ratios, taking into consideration the in-use conditions per the product labeling), and (3) the residual formulation after the decay of the foamed shampoo.

The comparison of the test and RS shampoo dispensed from the CCS should include characterizations of the following Q3 attributes:

a. Characterization of visual appearance and texture
b. Characterization of phase states and structural organization of matter
    i. Microscopic examination with representative high-resolution microscopic images at multiple magnifications
    ii. Analysis of particle size distribution, crystal habit, and polymorphic form of the active ingredient in the drug product, as applicable
c. Characterization of 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:
    i. A characterization of shear stress vs. shear rate and viscosity vs. shear rate. At minimum, this should consist of numerical viscosity data at three shear rates (low, medium, and high).
    ii. A complete flow curve across the range of attainable shear rates, until low or high shear plateaus are identified.
    iii. Yield stress values should be reported if the material tested exhibits plastic flow behavior.
d. Characterization of specific gravity
e. Characterization of pH
f. Characterization of surface tension

The comparison of foamed shampoo that is formed after lathering the test and RS shampoo should include characterizations of the following Q3 attributes:

a. Characterization of phase states and structural organization of matter
    i. Microscopic examination with representative high-resolution microscopic images at multiple magnifications
b. Characterization of foamed shampoo
    i. Analysis of time to break (until complete foam collapse)
    ii. Analysis of foam volume over time
    iii. Analysis of bubble size distribution (at a minimum of two time points)

The dilution factor used for lathering the shampoo and the environmental conditions (i.e., temperature and relative humidity) used for conducting the Q3 characterization tests of the foamed shampoo should be consistent between the test product and RS and maintained throughout testing. Applicants should conduct the time to break analysis at a

minimum of three temperatures. Other Q3 characterization tests on the foamed shampoo may be conducted at one of the selected temperatures (e.g., 25ºC). Rationale for the selected dilution factors, temperature(s) and relative humidity should be provided.

The comparison of the residual formulation of the test product and RS after the decay of the foamed shampoo should include characterization of the following Q3 attributes:

a. Characterization of visual appearance and texture
b. Characterization of phase states and structural organization of matter
    i. Microscopic examination with representative high-resolution microscopic images at multiple magnifications
c. Characterization of surface tension

3. The test product and RS should have an equivalent rate of ketoconazole release based upon an acceptable in vitro release test (IVRT) bioequivalence study comparing a minimum of one batch each of the test product and RS using an appropriately validated IVRT method.

    Type of study: Bioequivalence study with IVRT endpoint
    Design: Single-dose, two-treatment, parallel, multiple-replicate per treatment group study design using an occluded pseudo-infinite dose, in vitro
    Strength: 2%
    Test system: A synthetic membrane in a diffusion cell system
    Analyte to measure: Ketoconazole in receptor solution
    Equivalence based on: Ketoconazole (IVRT endpoint: drug release rate)
    Additional comments: Refer to the most recent version of the guidance for industry *In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs*[a] for additional information regarding the development, validation, conduct and analysis of acceptable IVRT methods/studies. The batches of test product and RS evaluated in the IVRT bioequivalence study should be included among those for which the Q3 attributes are characterized.

If challenges arise, applicants should refer to the most recent version of the guidance for industry *Controlled Correspondence Related to Generic Drug Development*[a] and the most recent version of the guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*[a] for additional information describing the procedures on how to clarify regulatory expectations regarding the applicants' individual drug development program.

II. Option 2: One comparative clinical endpoint bioequivalence study

1. Type of study: Comparative clinical endpoint bioequivalence study
    Design: Randomized, double-blind, parallel-group, placebo-controlled, in vivo
    Strength: 2%
    Subjects: Males and non-pregnant, non-lactating females with a clinical diagnosis of tinea versicolor.

Additional comments regarding the comparative clinical endpoint bioequivalence study:

1. FDA recommends conducting a comparative clinical endpoint bioequivalence study in the treatment of tinea versicolor comparing the test product versus the RS and vehicle control, each applied once to the infected and surrounding areas of the body on a single occasion as directed in the product labeling. Subjects should be evaluated at baseline (Day 0), at an interim visit on Day 7, and at Day 28.

2. Inclusion criteria (the applicant may add additional criteria):

   The inclusion criteria should therefore include patients with a clinical diagnosis of tinea versicolor and both of the following:
   - A combined severity score of at least 4, with at least one of the following signs and symptoms rated at least 2, using the following scale:

Signs/symptoms	**Scale**
desquamation/scaling pruritis/itching erythema	0 = absent 1 = mild 2 = moderate 3 = severe

   - Presence of infection with *Malassezia furfur (Pityrosporum orbiculare or P. ovale)* confirmed by a positive KOH cellophane tape test showing the characteristic "spaghetti and meatballs" appearance of the round budding yeast cells and short hyphae.

3. The categories mild, moderate, and severe on the above signs and symptoms scoring scale, should be clearly defined for each of the signs and symptoms with an objective description. When evaluating signs and symptoms, the entire body should be evaluated. A Baseline Body Diagram may be helpful for location.

4. A Physician's Global Assessment (PGA) should also be incorporated into the assessment. The evaluation should be a static scale, describing the severity of lesions associated with each score. This scale should not be an assessment of treatment response but should clearly describe the condition at the time of each visit. Therefore, no reference should be made to baseline in the evaluation. The following is an example of a scale that could be used:

   0 = clear; no scaling, itching or erythema
   1 = mild scaling, limited distribution, with or without itching and with or without erythema
   2 = moderate scaling, with or without itching
   3 = severe, extensive distribution of scaling, with or without itching
   Mild, moderate, and severe should be objectively defined.
   A score of "0 = clear" would be considered a "success."

The use of shampoos and soaps during the study needs to be addressed and clearly explained to the patients. It is recommended that only shampoos and soaps that are non-medicated are used during the entire study period (through Day 28) and that the products are approved by the investigator prior to study initiation.

5. In order to aid in fungal detection, patients should be instructed not to bath or shower prior to each visit.

6. The primary endpoint for this product is the proportion of patients with treatment success/cure at the Day 28 visit. To establish bioequivalence, the 90% confidence interval of the difference between products for the primary endpoint (success proportion) must be within (-0.20, +0.20) for dichotomous variables (cure versus failure) using the per-protocol (PP) population for analysis. It is important that overall success be defined in terms of mycology, clinical signs and symptoms score, and the PGA *a priori*. For example:
   Success should be defined as:
   - A negative cellophane tape test (absence of hyphae); and
   - A PGA score of "clear"; and
   - A severity score of 0 for erythema, 0 for pruritis/itching, and 0 for scaling/desquamation

   Failure should be defined as:
   - A positive cellophane tape test (presence of hyphae); or
   - A PGA score other than "clear"; or
   - A severity score on the clinical signs and symptoms of one or greater for erythema or pruritis/itching or scaling/desquamation.

7. Refer to the most recent version of the product-specific guidance *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)[b] for a recommended approach to statistical analysis and study design for the comparative clinical endpoint bioequivalence study.

8. Refer to the Study Data Standards resources, https://www.fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources.

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[a] For the most recent version of a guidance, refer to the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[b] For the most recent version of a product-specific guidance, refer to the FDA product-specific guidance website at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.