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Draft Guidance on Ketoconazole

February 2026

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Active Ingredient: Ketoconazole

Dosage Form: Shampoo

Route: Topical

Strength: 1%

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, 1% 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 source of potential particles observed in microscopy images of the test product and RS shampoo should be confirmed.

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 (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 properties
    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 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
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: 1%
    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-during the design of the aforementioned studies, 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: 1%
    Subjects: Males and non-pregnant, non-lactating females with a clinical diagnosis of dandruff.

Additional comments regarding the comparative clinical endpoint bioequivalence study:

1. FDA recommends conducting a comparative clinical endpoint bioequivalence study in the treatment of dandruff comparing test product versus the RS and vehicle control, each applied every 3 to 4 days for 4 weeks (i.e., on study days 1, 5, 8, 12, 15, 19, 22, 26). At each application, subjects are to wet hair thoroughly, apply enough shampoo to raise a lather [approximately 15 cc (0.5 ounce)], generously lather, rinse thoroughly and repeat process. The primary endpoint "success" is to be evaluated at the end of the treatment period (study day 28; week 4).

2. Inclusion criteria (the sponsor may add additional criteria):
    a. Male or non-pregnant, non-lactating female aged ≥ 18 with a clinical diagnosis of at least moderate dandruff at baseline, defined as a scaling score of at least 3 (per Scale 1) AND/OR an erythema score of at least 2 (per Scale 2).
    b. Willing to refrain from use of any other antidandruff shampoo or antidandruff treatment during the 4-week treatment period.

Scale 1: Scaling

Score	Severity	Description
0	None	
1	Slight	Barely perceptible scale - small flakes resembling a coarse grayish powder
2	Mild	Minimal to intermediate scale
3	Moderate	Definite scale - large flakes very loosely attached to the scalp and forming an irregular whitish surface
4	Pronounced	Prominent scale - flakes apparently congealed together into yellowish plates adhering to the scalp
5	Severe	Excessive thick yellowish and crusted adherent scale

Scale 2: Erythema

Score	Severity	Description
0	None	
1	Slight	Barely perceptible
2	Mild	Slightly pink
3	Moderate	Moderately pink
4	Pronounced	Deep pink to red
5	Severe	Deep red to severely red

3. Exclusion Criteria (the sponsor may add additional criteria):
    a. Presence of any scalp condition that would interfere with the diagnosis or assessment of dandruff (e.g., scalp psoriasis, active skin infection of the scalp, eczema, ichthyosis).
    b. Atopic dermatitis.
    c. Insulin-dependent diabetes mellitus.
    d. History of hypersensitivity or allergy to ketoconazole and/or any component of the test product or RS.

e. Use within 1 month prior to baseline of (1) systemic antifungals, (2) systemic steroids, (3) systemic antibiotics, (4) systemic anti-inflammatory agents or (5) cytostatic or immunomodulating drugs (e.g., cyclosporine, tacrolimus, pimecrolimus).
Use within 2 weeks prior to baseline of (1) topical steroids, (2) topical antifungal treatments including over-the-counter preparations, (3) topical anti-inflammatory agents, (4) topical antibiotics, or (5) antidandruff or antiseborrheic topical treatment (e.g., antidandruff shampoos, antiseborrheic shampoos, coal tar preparations).

4. 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 shampoo other than study product.
    b. Topical product, other than study product, applied to scalp.
    c. Systemic steroids, systemic anti-inflammatory agents or immunosuppressive drugs.
    d. Ketoconazole tablets and any other systemic antifungal agents.
    e. Antipruritics, including antihistamines, within 24 hours of study visits.
    Subjects should be instructed to not use the study product if the scalp is broken or inflamed and to not allow the shampoo to come in contact with the eyes.

5. The recommended primary endpoint of the study is the proportion of subjects with treatment success/cure, defined as score of 0 or 1 (per Scale 3) at the end of the treatment period (study day 28; week 4).

Scale 3: Investigator's Global Evaluation Scale

Score	Severity	Description
0	None	
1	Slight	Barely perceptible scale and erythema
2	Mild	Slight scale and minimal erythema
3	Moderate	Moderate scale and moderate erythema
4	Pronounced	Pronounced scale and pronounced erythema

6. 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 apply a pre-specified 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 4 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 meet 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 receive study product.

7. Subjects who are discontinued early from the study due to lack of treatment effect after completing 2 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 dandruff 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.

8. 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. Scaling Score at baseline
    u. Erythema at baseline
    v. Scaling Score at Day 28 (Week 4)
    w. Erythema Score at Day 28 (Week 4)
    x. Investigator's Global Evaluation Score at Day 28 (Week 4)
    y. Treatment Success at Day 28 (Week 4) (yes/no)
    z. Concomitant medication (yes/no)
    aa. Adverse event(s) reported (yes/no)

9. 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. Visit number
    e. Visit date
    f. Number of days since baseline visit
    g. Evaluator: identity of evaluator
    h. Scaling Score
    i. Erythema Score
    j. Investigator's Global Evaluation Score
    k. Scalp reaction scores for each sign and symptom evaluated (e.g., dryness, burning/stinging, erosion, edema, pain, itching, etc.)
    l. Concomitant medication reported during this visit (yes/no)
    m. Adverse event reported during this visit (yes/no)

10. 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.

11. 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.