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Draft – Not for Implementation

Draft Guidance on Miconazole Nitrate

October 2025

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In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient:	Miconazole nitrate
Dosage Form:	Cream
Route:	Vaginal
Strengths:	2%, 4%
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 studies and other characterization tests

To demonstrate bioequivalence for miconazole nitrate vaginal cream, 2% or 4% using in vitro studies, the following criteria should be met:

1. The test product should contain no difference in inactive ingredient 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 FDA guidance for industry on *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 in the same packaging configuration 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 FDA guidance for industry on *Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs*[a] for additional information regarding comparative Q3 characterization tests. The comparison of the test product and RS 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
    - Microscopic examination with representative high-resolution microscopic images at multiple magnifications
    - Analysis of particle size distribution, crystal habit, and polymorphic form of miconazole nitrate in the drug product, as applicable
    - Analysis of globule size distribution
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:
    - 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).
    - A complete flow curve across the range of attainable shear rates, until low or high shear plateaus are identified.
    - 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. Any non-linear viscosity behavior over a range of shear rates should also be investigated, measured and reported.
d. Characterization of pH
e. Characterization of specific gravity

3. The test product and RS in the same packaging configuration should have an equivalent rate of miconazole 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% or 4%
    Test system: A synthetic membrane in a diffusion cell system
    Analyte to measure: Miconazole in receptor solution
    Bioequivalence based on: Miconazole (IVRT endpoint: drug release rate)
    Additional comments: The IVRT study should be conducted at 37°C based on the route of administration of this drug product. Refer to the most recent version of the FDA guidance for industry on *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.

Note: The specific study recommendations above apply to either strength. Under Option 1 independent IVRT bioequivalence study and Q3 characterization tests are recommended for each of the two strengths, 2% and 4%.

II. Option 2: One comparative clinical endpoint bioequivalence study

1. Type of study: Comparative clinical endpoint bioequivalence study
   Design: Randomized, double blind, parallel, placebo-controlled, in vivo
   Strength: 2% (dose: one full applicator of miconazole nitrate vaginal cream, 2% once daily at bedtime for 7 consecutive days) [**NOTE**: If approval is sought only for 4% strength, the dose would be one full applicator of miconazole nitrate vaginal cream, 4% once daily at bedtime for 3 consecutive days.]
   Subjects: Healthy females with vulvovaginal candidiasis
   Additional comments: Specific recommendations are provided below.

Waiver request for 4% strength: The 4% strength of the cream product containing sufficient data may be approved based on (i) acceptable demonstration of bioequivalence of the 2% strength using the bioequivalence approach outlined within Option 2, (ii) the formulations of the lower and higher strengths of the test product are exactly the same, except for the amount of miconazole nitrate and the corresponding change in the amount of the diluent, and have the same manufacturing process, (iii) acceptable comparative Q3 characterization tests using a minimum of three batches of the lower strength of the test product and three batches of the higher strength of the test product; the relationship of the Q3 attributes of the two strengths of the test product should be compared to the relationship of the Q3 attributes of the two strengths of the RS, and (iv) an acceptable IVRT study or studies with a minimum of one batch of each strength of the test product and one batch of each strength of the RS using an appropriately validated IVRT method. The ratio of the miconazole release rates for the two strengths of the test product should be compared to the ratio of the miconazole nitrate release rates for the two strengths of the RS.

To develop a single strength of miconazole nitrate vaginal cream using the bioequivalence approach outlined in Option 2, a comparative clinical endpoint bioequivalence study should be performed using the single strength of the test product and RS.

Additional comments regarding the comparative clinical endpoint bioequivalence study:

1. FDA recommends conducting a comparative clinical endpoint bioequivalence study for the treatment of vaginal yeast infection comparing miconazole nitrate vaginal cream, 2% test product, versus the 2% RS, and placebo control. Each product is administered by inserting one full applicator of cream into the vagina once daily at bedtime for 7 consecutive days (study Day 1-7), with the primary endpoint evaluation at the test-of-cure visit conducted on study Day 21-30 (i.e., at the visit occurring between 14-23 days after administration of the last vaginal cream). [**NOTE**: If approval is sought only for miconazole nitrate vaginal cream, 4% under Option 2, a comparative clinical endpoint

bioequivalence study should be conducted to compare 4% test product, 4% RS, and placebo control. Each product is administered by inserting one full applicator of cream into the vagina once daily at bedtime for 3 consecutive days (study Day 1-3), with the primary endpoint evaluation at the test-of-cure visit conducted on study Day 21-30 (i.e., at the visit occurring between 18-27 days after administration of the last dose of vaginal cream)].

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

3. Assignment of the test product, RS, and placebo should be randomized. 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.

4. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test product, RS, and placebo should be similar in appearance to make differences in treatment less obvious to the patients and to maintain adequate blinding of evaluators. When possible, neither the patient nor the investigator should be able to identify the treatment. The containers should not be opened by the patient at the study center.

5. Inclusion criteria (the sponsor may add additional criteria):
    a. Healthy, postmenarcheal female.
    b. Clinical diagnosis of symptomatic vulvovaginal candidiasis (VVC) confirmed at baseline by positive potassium hydroxide (KOH) wet mount (i.e., when examined microscopically, vaginal secretions obtained by swab of the vaginal mucosa, placed on a slide and diluted with 10% room temperature KOH reveal filamentous hyphae/pseudohyphae and/or budding yeast cells).
    c. Presence of at least one vulvovaginal sign (vulvovaginal erythema, edema, or excoriation) as assessed by the investigator at baseline.
    d. Presence of at least one vulvovaginal symptom (vulvovaginal itching, burning, or irritation) as reported by the patient at baseline.
    e. At baseline, ≥ 50% of the patients should have at least moderate severity of VVC, defined as having a minimum composite vulvovaginal signs and symptoms score of 7 (see Comment #11).
    f. Documented Papanicolaou (Pap) test at baseline or during the previous 12 months reported as either “negative for intraepithelial lesion or malignancy” or “ASCUS-atypical squamous cells of undetermined significance”.

6. Exclusion criteria (the sponsor may add additional criteria):
    a. Pregnant or nursing. [**NOTE**: Pregnant women can be included in the study after completing the first trimester of pregnancy. If pregnant women are enrolled, it is important that the proportion of pregnant patients be similar among all treatment groups, because cure rates might differ in pregnant versus non-pregnant women.]
    b. Diabetes mellitus. [**NOTE**: If diabetic women are enrolled, it is important that their diabetes be controlled and the proportion of diabetic patients be similar among all treatment groups, because cure rates might differ in diabetic versus nondiabetic women.]
    c. Use of systemic, topical (applied to the vulva) or vaginal antibiotics, antifungals or antitrichomonals within 7 days prior to randomization.
    d. Use of any systemic corticosteroid, immunosuppressive, or immune-stimulating drug within 3 months prior to randomization.
    e. Use of anticoagulation therapy (e.g., warfarin).
    f. Presence of concomitant vulvovaginitis caused by other infections (e.g., bacterial vaginosis, *Trichomonas vaginalis*, *Chlamydia trachomatis* or *Neisseria gonorrhoeae*).
    g. Presence of another vaginal or vulvar condition that would confound the interpretation of clinical response.
    h. History of allergy or sensitivity to miconazole nitrate, related compounds or any component of the formulation.

7. Vaginal discharge should not be an inclusion criterion or included in the evaluation of treatment as this sign cannot be consistently correlated with the presence or absence of VVC.

8. Positive vaginal fungal culture at baseline should not be an inclusion criterion due to the time lag between obtaining the culture specimen and receiving the culture results. However, a vaginal fungal culture must be obtained at baseline. Testing should be performed to identify the isolates to the species level (e.g., *Candida albicans*, *Candida tropicalis*, or *Candida glabrata*). Only patients with a pretreatment, baseline vaginal fungal culture that is positive for a *Candida* species should be included in the per protocol (PP) and modified intent to treat (mITT) populations for the primary endpoint analysis.

9. Provide a listing of the prescription and over-the-counter drug products that are contraindicated during the study, such as:
    a. Topical products applied to the vulva or vagina (e.g., antibiotic, antifungal, antitrichomonal, corticosteroid or anti-inflammatory topical products)
    b. Vaginal products other than study product (e.g., vaginal estrogen, vaginal progesterone, douches, spermicides, condoms, tampons, diaphragms, contraceptive cream, contraceptive foam, or contraceptive film).
    c. Oral antibiotics, antifungals, or antitrichomonals.
    d. Oral or injectable corticosteroid or immunosuppresive.
    e. Anticoagulation therapy (e.g., warfarin)

10. The recommended primary endpoint of the study is the proportion of patients with therapeutic cure, defined as both mycological cure and clinical cure, at the test-of-cure visit conducted on study Days 21-30. Mycological cure is defined as a negative KOH wet mount test of vaginal secretions and a negative vaginal fungal culture for *Candida* species. Clinical cure is defined as <u>all</u> of the following:
    a. Any vulvovaginal sign or symptom with a baseline score of 1 or 2 (on a 4-point scale as provided in Comment #11) has a score of 0 (absent) at the test-of-cure visit on study Day 21-30.
    b. Any vulvovaginal sign or symptom with a baseline score of 3 (on a 4-point scale as provided in Comment #11) has a score of 0 (absent) or 1 (mild) at the test-of-cure visit on study Day 21-30.
    c. Any new sign or symptom observed at the test-of-cure visit is determined by the investigator not to be related to VVC.
    d. The subject did not use any topical drug therapy (such as topical analgesics or corticosteroid products) other than the study product for the treatment of vulvovaginal irritation and/or pruritus.

11. Each of the following six vulvovaginal signs and symptoms should be individually scored using an accepted scale and then added together to determine the composite vulvovaginal signs and symptoms score.
    a. Vulvovaginal Signs: erythema, edema, or excoriation
    b. Vulvovaginal Symptoms: itching, burning, or irritation
    c. Scoring Scale: Each score should be objectively defined. The following is an example of an acceptable scale.
        0 = none (absent)
        1 = mild (slight)
        2 = moderate (definitely present)
        3 = severe (marked, intense)

12. The accepted PP population used for bioequivalence evaluation includes all randomized patients who had a positive baseline vaginal fungal culture for *Candida* species, were compliant with the assigned study product, and completed the evaluation at the test-of-cure visit within the designated visit window (study Day 21-30) with no protocol violations that would affect the treatment evaluation. The protocol should provide a definition of compliant patients (e.g., having used at least 75% and no more than 125% of study drug doses) and specify how compliance will be verified, e.g., by the use of patient diaries.

13. The usual mITT population includes all randomized patients who had a positive baseline vaginal fungal culture for *Candida* species, used at least one dose of study product, and returned for at least one post-baseline visit.

14. The usual safety population includes all randomized patients who received study product.

15. Patients who are discontinued early from the study due to lack of treatment effect after completing 6 consecutive days of treatment should be included in the PP population as treatment failures (i.e., non-responders). Patients discontinued early for other reasons should be excluded from the PP population, but included in the mITT population, using LOCF.

16. Patients who receive or self-administer topical drug therapy for the treatment of vulvovaginal irritation/pruritus after the treatment phase of the study should be analyzed in the mITT and PP populations as a treatment failure.

17. Patients with a negative vaginal fungal culture at baseline should be discontinued from the study and excluded from the PP and mITT populations but included in the safety population for the safety analyses.

18. 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, RS, placebo
    i. Duration of Treatment (total exposure in days)
    j. PP population inclusion (yes/no)
    k. Reason for exclusion from PP population
    l. mITT population inclusion (yes/no)
    m. Reason for exclusion from mITT population
    n. Safety population inclusion (yes/no)
    o. Reason for exclusion from safety population
    p. Final designation as therapeutic cure (yes/no)
    q. Treatment compliance: number of missed doses per patient
    r. Concomitant medication (yes/no)
    s. Adverse event(s) reported (yes/no)

19. Provide a dataset containing a separate line listing for each 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, RS, placebo control
    d. Visit number
    e. Visit date
    f. Number of days since baseline visit
    g. Evaluator: identity of evaluator

h. Vulvovaginal erythema score
i. Vulvovaginal edema score
j. Vulvovaginal excoriation score
k. Vulvovaginal itching score
l. Vulvovaginal burning score
m. Vulvovaginal irritation score
n. Composite vulvovaginal signs and symptoms score
o. KOH result
p. Culture result
q. Mycological cure (yes/no)
r. Clinical cure (yes/no)
s. Therapeutic cure (yes/no)
t. Concomitant medication reported during this visit (yes/no)
u. Adverse event reported during this visit (yes/no)
v. Laboratory testing during this visit (yes/no)

20. Refer to the most recent version of the FDA product-specific guidance on *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.

21. Refer to the study data standards resources, https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

Additional information:

Device:
The reference listed drug (RLD) for the 2% cream is presented in a carton containing a tube of drug product with disposable vaginal applicators or a reusable vaginal applicator. The RLD for the 4% cream is presented in a carton containing a tube of drug product with a reusable vaginal applicator or pre-filled vaginal applicators. The vaginal applicators are the device constituent part.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the test device including:

- Number of co-packaged applicators
- Compatibility of the applicator with the container opening
- Reusable applicator can be disassembled and washed with soap and water

User interface assessment:
An abbreviated new drug application for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a]

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[a] For the most recent version of a guidance, check 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, check the FDA product-specific guidance website at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.