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Draft Guidance on Ivermectin

October 2022

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Active Ingredient: Ivermectin

Dosage Form; Route: Cream; topical

Recommended Studies: Two options: (1) two in vitro bioequivalence studies, one in vivo bioequivalence study with pharmacokinetic endpoints, and other characterization tests or (2) one in vivo bioequivalence study with clinical endpoint

I. Option 1: Two in vitro bioequivalence studies, one in vivo bioequivalence study with pharmacokinetic endpoints, and other characterization tests

To demonstrate bioequivalence for ivermectin topical cream, 1% using a combination of in vitro studies and an in vivo study with pharmacokinetic endpoints, 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 that may significantly affect the local or systemic availability of the active ingredient. For example, if the test product and reference standard 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 reference standard 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 reference standard. The test product and reference standard 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 reference standard 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 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
f. Characterization of any other potentially relevant Q3 attributes

3. The test product and reference standard should have an equivalent rate of ivermectin release based upon an acceptable in vitro release test (IVRT) bioequivalence study comparing a minimum of one batch each of the test product and reference standard 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: Ivermectin in receptor solution
    Equivalence based on**:** Ivermectin (IVRT endpoint: drug release rate)
    Additional comments: 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 reference standard evaluated in the IVRT bioequivalence study should be included among those for which the Q3 attributes are characterized.

4. The test product and reference standard should have an equivalent rate and extent of ivermectin permeation through excised human skin based upon an acceptable in vitro permeation test (IVPT) comparing a minimum of one batch each of the test product and reference standard using an appropriately validated IVPT method.

   Type of study: Bioequivalence study with IVPT endpoints
   Design: Single-dose, two-treatment, parallel, multiple-replicate per treatment group study design using an unoccluded finite dose, in vitro
   Strength: 1%
   Test system: Barrier-competent human skin from male and/or female donors of at least 18 years of age in a diffusion cell system
   Analyte to measure: Ivermectin in receptor solution
   Equivalence based on: Ivermectin (IVPT endpoints: total cumulative amount (AMT) and maximum flux (J_{max}))
   Additional comments: Refer to the most recent version of the FDA guidance for industry on *In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs*[a] for additional information regarding the development, validation, conduct and analysis of acceptable IVPT methods/studies. The batches of test product and reference standard evaluated in the IVPT bioequivalence study should be the same as those evaluated in the IVRT bioequivalence study.

5. The test product and reference standard should demonstrate bioequivalence based upon an acceptable in vivo pharmacokinetic study with one batch each of the test product and reference standard.

   Type of study: In vivo pharmacokinetic study
   Design: Single-application, two-way crossover study design
   Strength: 1%
   Subjects: Males and non-pregnant, non-lactating females, general population
   Analyte to measure: Ivermectin in plasma
   Equivalence based on: Ivermectin
   Additional comments: A clinically relevant dose (e.g., 2 mg/cm^2) may be applied on the face of the subjects (except the upper and lower eyelids and lips), for a total of 1 g of the drug product. It may be acceptable to apply a total dose of less than 1 g of the drug product, as long as the total dose of the test product and reference standard is the same across all subjects, the amount of dose per unit area (per cm^2) is clinically relevant, well-controlled, and consistent among all subjects, and the bioanalytical method is sufficiently sensitive to be able to adequately characterize the pharmacokinetic profiles of the test product and reference drug products. If the crossover study is problematic, applicants should use a bioequivalence study with a parallel design. Refer to the most recent version of the FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*[a] for additional information regarding the analysis of the pharmacokinetic bioequivalence study. The batches

of test product and reference standard evaluated in the in vivo pharmacokinetic study should be the same as those evaluated in the IVRT and IVPT studies.

II. Option 2: One in vivo bioequivalence study with clinical endpoint

1. Type of study: Bioequivalence study with clinical endpoint
   Design: Randomized, double blind, parallel, placebo controlled, in vivo
   Strength: 1%
   Subjects: Males and non-pregnant, non-lactating females with rosacea
   Additional comments: Specific recommendations are provided below.

Additional comments regarding the bioequivalence study with clinical endpoint:

1. FDA recommends a bioequivalence study with clinical endpoint in the treatment of moderate to severe rosacea. Subjects are to be randomized to receive the test ivermectin topical cream, 1%, reference standard, or placebo once daily for 12 weeks. The primary endpoint is to be evaluated at the end of treatment (Study Week 12).

2. Inclusion Criteria (the applicant may add additional criteria):
   a. Males or non-pregnant, non-lactating females aged ≥ 18 years
   b. Clinical diagnosis of papulopustular rosacea, with an Investigator Global Assessment score rated 3 (moderate) or 4 (severe) defined as:
      - At least fifteen and not more than fifty inflammatory facial lesions (i.e., papules/pustules),
      - Not more than two nodules on the face at screening or baseline visits
   c. Subject willing to minimize external factors that might trigger rosacea flare-ups (e.g., spicy foods, thermally hot foods and drinks, hot environments, prolonged sun exposure, strong winds and alcoholic beverages)

3. Exclusion Criteria (the applicant may add additional criteria):
   a. Pregnant or lactating or planning to become pregnant during the study period
   b. Presence of other forms of rosacea (rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin) or other dermatoses that may be confounded with papulopustular rosacea, such as peri-oral dermatitis, facial keratosis pilaris, seborrheic dermatitis and acne
   c. Clinically significant abnormal laboratory values according to the investigator at screening
   d. Excessive facial hair (e.g., beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of rosacea
   e. History of hypersensitivity or allergy to propylene glycol or any other component of the formulation
   f. Use within 6 months prior to baseline of oral retinoids (e.g., Accutane®) or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed)
   g. Use for less than 3 months prior to baseline of estrogens or oral contraceptives; use of such therapy must remain constant throughout the study

h. Use within 1 month prior to baseline of:
    - Topical facial treatment with retinoids benzoyl peroxide, antibiotics (metronidazole and macrolides), corticosteroids, immunomodulators, other topical rosacea treatment (e.g., azelaic acid & metronidazole),
    - Systemic treatment with antibiotics known to have an impact on the severity of facial rosacea (e.g., containing tetracycline and its derivatives, erythromycin and derivatives, sulfamethoxazole, or trimethoprim), corticosteroids
i. Use within 6 weeks prior to baseline of 1) topical corticosteroids 2) topical antibiotics or 3) topical medications for rosacea (e.g., metronidazole, azelaic acid)
j. Exposure to excessive UV radiation within two weeks prior baseline, or the subject is planning exposure during the study (e.g., occupational exposure to the sun, planned holidays in the sun during the study, phototherapy, tanning salon)
k. Subjects with moderate or severe rhinophyma, dense telangiectases, or plaque-like facial edema
l. Ocular rosacea (e.g., conjunctivitis, blepharitis, or keratitis) of sufficient severity to require topical or systemic antibiotics

4. The protocol should include a list of the prescription and over-the-counter drug products that are prohibited during the study, such as:
    a. Any other topical products applied to the target site (e.g., metronidazole, topical antibiotics, topical steroids)
    b. Oral retinoids
    c. Systemic (e.g., oral or injectable) antibiotics known to have an impact on the severity of facial rosacea (e.g., containing tetracycline, erythromycin, sulfamethoxazole, or trimethoprim or their derivatives)
    d. Systemic corticosteroid or immunosuppressive drugs
    e. Antipruritic, including antihistamines, within 24 hours of study visits

5. Subjects should not apply moisturizers, new brands of make-up, creams, lotions, powders or any topical product other than the assigned treatment to the treatment area. Occlusive dressings or wrappings should be avoided in treatment areas. Subjects should minimize exposure to sunlight, including sunlamps, while using the product. Use of sunscreen products and protective clothing over treated areas is recommended when sun exposure cannot be avoided.

6. Areas to be treated should be washed with a mild cleanser before application and patted dry with a soft towel. A thin layer of study treatment should be gently massaged into the affected areas on the face once daily for 12 weeks. Contact with the mouth, eyes and other mucous membranes should be avoided. The hands should be washed following application.

7. The recommended primary endpoint of the study is the mean percent change from baseline to Week 12 in the inflammatory (papules and pustules) lesion counts. The protocol should clearly define papules, pustules, and nodules. When counting facial lesions, it is important that all lesions be counted, including those present on the nose.

Counts of nodules should be reported separately and not included in the inflammatory lesion counts.

8. 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 BE studies with clinical endpoint.

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

Revision History: Recommended October 2017; Revised May 2019, October 2022

Unique Agency Identifier: PSG_206255

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