Draft Guidance on Ivermectin

October 2022

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Active Ingredient: Ivermectin

Dosage Form; Route: Lotion; topical

Recommended Studies: Two options: (1) one in vitro bioequivalence study, one pediculicide hair tuft assay, and other characterization tests or (2) one in vivo bioequivalence study with clinical endpoint

I. Option 1: One in vitro bioequivalence study, one pediculicide hair tuft assay, and other characterization tests

To demonstrate bioequivalence for ivermectin topical lotion, 0.5% 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 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: 0.5%
    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 equivalent performance ex vivo in *Pediculus humanus capitis* (head lice), using an appropriate pediculicide hair tuft assay with relevant controls (e.g., similar to Strycharz et al.).[1] The batches of test product and reference standard evaluated in the pediculicide hair tuft assay study should be the same as those evaluated in the IVRT study.

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: 0.5%
   Subjects: Males and non-pregnant, non-lactating females ages 6 months to 64 years, inclusive, with active infestation with *Pediculus humanus* capitis (head lice and their ova)
   Additional comments: Specific recommendations are provided below.

Additional comments regarding the bioequivalence study with clinical endpoint:

1. FDA recommends the following:
   a. Conducting a bioequivalence study with a clinical endpoint in the treatment of active infestation with *Pediculus humanus capitis* (head lice and their ova) comparing the test product versus the reference standard and vehicle control.
   b. A single at-home application of study drug on Study Day 1 by the subject or his/her caregiver.
   c. Four site visits -- Visit 1 [Study Day 1 (before at-home treatment)], Visit 2 [Study Day 2 (1 day post-treatment)], Visit 3 [Study Day 8 (7 days post-treatment)], and Visit 4 [Study Day 15 (14 days post-treatment)].
   d. At each site visit, subjects should undergo visual examination for the presence of live lice by the evaluator with the aid of a 5X lighted magnifier and a wide tooth comb to part and separate the subject's hair.

2. Inclusion Criteria (the sponsor may add additional criteria):
   a. Males or non-pregnant, non-lactating females.
   b. Ages 6 months to 64 years, inclusive.
   c. Active infestation of *Pediculus humanus capitis* (human head lice).
   d. The youngest subject with head lice infestation from each household is considered the index subject of the household for evaluation of the primary endpoint. Index subjects must have at least three "live lice" (defined as live adults and/or nymphs) at baseline.
   e. Other members in the household with at least one "live louse" may be enrolled into the study for evaluation of safety parameters.

[1] Strycharz JP, Yoon KS, Clark JM. A New Ivermectin Formulation Topically Kills Permethrin-Resistant Human Head Lice (Anoplura: Pediculidae). J Med Entomol. 2008; 45(1): 75-81.

3. Exclusion Criteria (the sponsor may add additional criteria):
    a. Females (including caregivers) who are pregnant, breast feeding, or who wish to become pregnant during the study period
    b. Known allergy or hypersensitivity to any component of the test product or reference standard
    c. Scalp condition that could make it difficult to evaluate the extent and severity of an infestation or that would present a problem in the evaluation of response to therapy (e.g., psoriatic scalp lesions, extensive seborrheic dermatitis)
    d. Known history of irritation or sensitivity to pediculicides or hair care products
    e. Previous treatment with a pediculicide within four weeks of randomization
    f. Subject with very short (shaved) hair, subject who plans to shave head during the study, and/or subject who used any hair dye, bleaches, hair straightening, or permanent wave solution on the hair within 14 days of randomization

4. The primary endpoint is the proportion of primary subjects in each treatment group with treatment success (i.e., absence of live head lice) when examined on Study Day 15 (14 days post-treatment).

5. Subjects with live lice noted at Visits 2, 3, or 4 should be discontinued from study treatment, included in the per-protocol (PP) and modified intent-to-treat (mITT) population analysis as treatment failures, and provided with standard therapy for treatment of their *Pediculus humanus capitis* (i.e., early escape clause). Subjects discontinued early for other reasons should be excluded from the PP population but included in the mITT population.

6. Provide oral and written instructions to the subject and/or parent/guardian as follows:
    a. Apply the drug product directly to dry scalp and dry hair. Completely cover scalp and hair closest to scalp first, then apply outwards towards ends of the hair.
    b. Use as much as the entire tube to completely cover scalp and hair to the tip. Then rub the drug product throughout the hair.
    c. Allow the drug product to stay on hair and scalp for 10 minutes. Use a timer or clock and start timing after hair and scalp are completely covered with the drug product.
    d. After 10 minutes, completely rinse hair and scalp using only water.
    e. You or anyone who helps you apply the drug product should wash their hands after application.
    f. It is recommended to wait 24 hours before applying shampoo to hair or scalp.
    g. Avoid contact with eyes.
    h. Lactating women should avoid accidental transfer of the drug product to the breast where an infant might accidently ingest the drug product.

7. Provide details in the protocol regarding the procedures to be taken to decrease re-infestation, such as:
    a. The examination of household members of enrolled subjects for head lice (and treatment of such household members found to be infested);
    b. Avoidance of direct head-to-head contact with anyone who has an active head lice infestation;
    c. Decontamination of clothing and bed linen that may have been contaminated by the infested individual prior to treatment
    d. Disinfection of combs and brushes used by the infected subjects.

8. It is important to ensure that evaluators (experienced professionals) conduct a thorough and consistent evaluation for the presence of lice. This information could be captured as the time spent by the evaluator to assess for the presence of lice.

9. Application site reactions such as irritation, erythema, pyoderma, excoriation, edema, pain, and ocular irritation are to be recorded at each visit to allow a comparison between treatment groups. Local safety evaluation should be performed on a four-point scale [0 (absent), 1 (mild), 2 (moderate), and 3 (severe)] for five categories: pruritus, pain, erythema, pyoderma, and excoriation. A descriptive analysis comparing the application site reactions for each treatment group is recommended. It is important to ensure that the test product is similar to the reference standard with regard to expected and unexpected application site reactions.

10. Provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
    a. Study identifier
    b. Unique subject identifier
    c. Subject identifier for the study
    d. Study site identifier (if applicable)
    e. Age
    f. Age units (years)
    g. Sex
    h. Race
    i. Index subject (yes/no)
    j. Household member (yes/no)
    k. Name of planned treatment
    l. Name of actual treatment
    m. Safety population flag (yes/no)
    n. Reason for exclusion from safety population
    o. mITT population flag (yes/no)
    p. Reason for exclusion from mITT population
    q. PP population flag (yes/no)
    r. Reason for exclusion from PP population
    s. Randomized population flag (yes/no)
    t. Date/time of exposure to treatment
    u. End of study date

v. End of study status
w. Subject required additional treatment due to unsatisfactory treatment response (yes/no)
x. Description of rescue treatment
y. Date of rescue treatment
z. Study day of rescue treatment
aa. Completed the study (yes/no)
bb. Reason for premature discontinuation of subject (character)
cc. Final designation as treatment success (yes/no)
dd. Reason for discontinuation from study (character, additional details regarding subject's discontinuation from study)
ee. Reason for discontinuation from treatment (character)
ff. Reason for discontinuation from treatment (character, additional details regarding subject's discontinuation from treatment)
gg. Compliance (i.e., was lotion applied and removed as instructed?) (yes/no)
hh. Concomitant medication (yes/no)
ii. Adverse event(s) reported (yes/no)
jj. Evaluator initial (character)

11. Provide the basic data structure (BDS) dataset with records per subject, per visit, per analysis timepoint, using the following headings, if applicable:
    a. Study identifier
    b. Unique subject identifier
    c. Subject identifier for the study
    d. Study site identifier (if applicable)
    e. Index subject flag (yes//no)
    f. Household subject flag (yes/no)
    g. Name of planned treatment
    h. Name of actual treatment
    i. Safety population flag (yes/no)
    j. mITT population flag (yes/no)
    k. PP population flag (yes/no)
    l. Visit number
    m. Visit date
    n. Number of days since baseline visit
    o. Evaluator: identity of evaluator
    p. Study visit within designated window (yes/no)
    q. Number of live head lice
    r. Rescue treatment required (yes/no)
    s. Date/time rescue treatment
    t. Pruritus score
    u. Erythema score
    v. Pyoderma score
    w. Excoriation score
    x. Edema score
    y. Pain score

z. Ocular irritation score
aa. Concomitant medication reported during this visit (yes/no)
bb. Adverse event reported during this visit (yes/no)
cc. Laboratory testing during this visit (yes/no)

12. 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.

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

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[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.