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Draft – Not for Implementation

Draft Guidance on Spinosad

October 2022

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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: Spinosad

Dosage Form; Route: Suspension; topical

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

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

To demonstrate bioequivalence for spinosad topical suspension, 0.9% 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
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.
d. Characterization of water activity
e. Characterization of specific gravity
f. Characterization of pH
g. Characterization of any other potentially relevant Q3 attributes

3. The test product and reference standard should have an equivalent rate of spinosyn A and spinosyn D 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: 0.9%
    Test system: A synthetic membrane in a diffusion cell system
    Analytes to measure: Spinosyn A and spinosyn D in receptor solution
    Equivalence based on: Spinosyn A and spinosyn D (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.

    Note that the reference standard label states that spinosad is a mixture of spinosyn A and spinosyn D. Therefore, both spinosyn A and spinosyn D should be monitored and considered for equivalence evaluation for the IVRT bioequivalence study.

Applicants intending to propose an alternative approach (e.g., alternative method for evaluation of the IVRT data) should refer to the most recent version of the FDA guidance for industry *Controlled Correspondence Related to Generic Drug Development*[a] and the most recent version of the FDA guidance for industry on *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 your individual drug development program.

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: 0.9%
   Subjects: Males and non-pregnant, non-lactating females, aged 6 months to 60 years, 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 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 placebo (vehicle) control, applied at one time at home on Study Day 1 by the subject or their caregiver. Four site visits, each including a 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, are recommended as follows: Visit 1 (Study Day 1; before home treatment), Visit 2 (Study Day 2; one day after home treatment), Visit 3 (Study Day 8; seven days after home treatment) and Visit 4 (Study Day 15; 14 days after home treatment).

2. Inclusion Criteria (the sponsor may add additional criteria):
   a. Males or non-pregnant, non-lactating females.
   b. Aged 6 months to 60 years.
   c. Both inclusive with an active infestation of *Pediculus humanus capitis* (human head lice) with at least three "live lice" (defined as live adults and/or nymphs) at baseline.
   d. Subject and/or parent/guardian agree(s) that the subject will not use any other form of lice treatment during the duration of the study.
   e. The youngest subject (with head lice infestation as defined above) from each household is considered to be the primary subject of the household for evaluation of the primary endpoint. Other members in the household are enrolled in the study as secondary subjects and evaluated for all safety parameters.

3. Exclusion Criteria (the sponsor may add additional criteria):
   a. Females 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 the per protocol (PP) population in each treatment group with treatment success (i.e., absence of live head lice) when examined on Study Day 15 (14 days after first application of study treatment).

5. Subjects who do not respond to the initial treatment (i.e., subjects found to have live head lice during Visit 3 on Study Day 8, seven days after treatment) will be treated as failures of therapy in the final analysis and should be provided with standard (effective) therapy for the second treatment (i.e., seven days after the first treatment).

6. Provide oral and written instructions to the subject and/or parent/guardian as follows:
    a. Shake bottle well immediately prior to use.
    b. Cover your face and eyes with a towel and keep your eyes closed tightly.
    c. Apply the product directly to dry hair. Completely cover the scalp first, and then apply outwards towards the ends of the hair.
    d. Use as much product as needed to completely cover the entire scalp and all scalp hair.
    e. Allow the product to stay on your hair for 10 minutes. Use a timer or clock and start timing after you have completely covered your hair and scalp with the product.
    f. Continue to keep eyes covered to prevent dripping into your eyes. If any product gets in the eye, flush with water right away.
    g. After 10 minutes, completely rinse your hair and scalp with warm water.
    h. You or anyone who helps you apply the product should wash hands after application.
    i. It is okay to shampoo your hair any time after the treatment.

7. Provide details in the protocol regarding the procedures to be taken to decrease reinfestation, such as:
    a. Examination of household members of the enrolled subjects for head lice (and treatment of such household members found to be infested)
    b. Decontamination of clothing and bed linen that may have been contaminated by the infested individual prior to treatment, and
    c. Disinfection of combs and brushed used by the infected patient

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. Subjects with live lice noted at Visits 2, 3, or 4 and any subjects whose condition worsens and require alternate or supplemental therapy for the treatment of their *Pediculus humanus capitis* during the study should be discontinued from the study treatment, included in the PP population analysis as treatment failures, and provided with effective treatment. Subjects discontinued early for other reasons should be excluded from the PP population but included in the modified intent-to-treat (mITT) population.

10. Application site reactions such as irritation, erythema, pyoderma, excoriation, edema, anesthesia, 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 not worse than the reference standard with regard to the expected and unexpected application site reactions.

11. Provide the subject-level analysis dataset, 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. Primary subject (yes/no)
    j. Secondary subject (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 on Study Day 15 (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)

12. Provide the basic data structure 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)

13. 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 bioequivalence studies with clinical endpoint.

14. 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.