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Draft Guidance on Benzyl Alcohol

October 2022

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Active Ingredient: Benzyl alcohol

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 benzyl alcohol topical lotion, 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 benzyl alcohol 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: 5%
    Test system: A synthetic membrane in a diffusion cell system
    Analyte to measure: Benzyl alcohol in receptor solution
    Equivalence based on: Benzyl alcohol (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 bioequivalence 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: 5%
Subjects: Healthy 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 vehicle control, applied at one time at home on study Day 1 by the subject or their caregiver and one time at home again on Day 8. The primary endpoint is the proportion of subjects with treatment success, defined as absence of live head lice when examined 14 days after the last application of study treatment (Study Day 22). 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 #1), Visit 2 (Study Day 2; one day after home treatment #1), Visit 3 (Study Day 9; one day after home treatment #2) and Visit 4 (Study Day 22; 14 days after home treatment #2).

2. Inclusion Criteria (the sponsor may add additional criteria):
    a. Healthy males or non-pregnant, non-lactating females aged 6 months to 60 years, 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.
    b. Subject and/or parent/guardian agree that the subject will not use any other form of lice treatment during the duration of the study.

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 benzyl alcohol or any component of the test product or reference standard.

[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.

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. Within 4 weeks of randomization treatment with a pediculicide.
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 subjects in each treatment group with treatment success (i.e., absence of live head lice) when examined 14 days after the last application of study treatment (Study Day 22; 14 days after home treatment #2).

5. Subjects who do not respond to therapy (i.e., if any live head lice are noted during Visit 2, 3, or 4) will receive standard therapy (i.e., early escape clause). Such subjects will be treated as failures of therapy in the final analysis. Subjects with no live lice should be provided with sufficient study drug for the second treatment (e.g., 7 days after the first treatment).

6. Provide oral and written instructions to the subject and/or parent/guardian as follows:
   a. Cover face and eyes with a towel and keep eyes closed tightly. Apply the lotion directly to the dry scalp and rub into hair to completely cover the entire scalp and all scalp hair. When applying the lotion, pay particular attention to the back of the neck and behind the ears. Follow the Usage Guideline in Table 1 for the amount of lotion needed per application:

Table 1: Benzyl Alcohol Lotion, 5% Usage Guideline

Hair Length		**Amount of ULESFIA® Lotion per Application**	
		Ounces	**8 oz bottle**
Short	0-2 inches	4-6 oz	½-¾ bottle
	2-4 inches	6-8 oz	¾-1 bottle
Medium	4-8 inches	8-12 oz	1-1½ bottles
	8-16 inches	12-24 oz	1½-3 bottles
Long	16-22 inches	24-32 oz	3-4 bottles
	Over 22 inches	32-48 oz	4-6 bottles

   b. Massage the lotion into hair and scalp. Leave the lotion on for 10 minutes; then thoroughly rinse off with water.
   c. Repeat application after 7 days after the first application.
   d. Avoid eye exposure. If lotion comes in contact with the eyes, flush them immediately with water. If irritation persists, consult a physician.

e. Anyone applying the lotion should wash their hands immediately after the application process is complete.
f. Keep out of reach of children.

7. Provide details in the protocol regarding the procedures to be taken to decrease reinfestation, such as the examination of household members of the enrolled subjects for head lice (and treatment of such household members found to be infested), decontamination of clothing and bed linen that may have been contaminated by the infested individual prior to treatment and 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. 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, 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.

10. The Case Report Form should clearly document the specific reason for use of this product (e.g., new infestation of lice or failure to respond adequately to other topical prescription or over-the counter treatments).

11. 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. Name of planned treatment
    j. Name of actual treatment
    k. Safety population flag (yes/no)
    l. Reason for exclusion from safety population
    m. Modified Intent-to-Treat (mITT) population flag (yes/no)
    n. Reason for exclusion from mITT population
    o. PP population flag (yes/no)
    p. Reason for exclusion from PP population

q. Randomized population flag (yes/no)
r. Number of live head lice at baseline
s. Date/time of first exposure to treatment
t. Date/time of second 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. Final designation of treatment outcome (success/failure) on Study Day 22
y. Compliance rate (%)
z. Subject missed the pre-specified number of scheduled doses for more than pre-specified number of consecutive days (yes/no)
aa. Adverse event reported (yes/no)
bb. Concomitant medication (yes/no)

12. 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. Name of planned treatment
    f. Name of actual treatment
    g. Safety population flag (yes/no)
    h. mITT population flag (yes/no)
    i. PP population flag (yes/no)
    j. Analysis date
    k. Number of days since baseline visit
    l. Analysis visit
    m. Evaluator: identity of evaluator
    n. Number of live head lice
    o. Skin reaction score(s) for each sign and symptom evaluated (e.g., erythema, pyoderma, excoriation, edema, and pain)
    p. Study visit within the designated window (yes/no)
    q. Analysis timepoint (e.g., hour 0, hour 2) (if applicable)
    r. Additional treatment required during the visit (yes/no)
    s. Adverse event reported during the visit (yes/no)
    t. Concomitant medication during the 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.