Contains Nonbinding Recommendations

Draft Guidance on Benzyl Alcohol

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Benzyl alcohol

Dosage Form; Route: Lotion; topical

I. In Vitro option:

To qualify for the in vitro option for this drug product pursuant to 21 CFR 320.24(b)(6), under which "[a]ny other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence" may be acceptable for determining the bioavailability or bioequivalence (BE) of a drug product, all of the following criteria must be met:

i. Equivalent comparative qualitative and quantitative (Q1/Q2) characterization.
ii. Equivalent comparative physicochemical and microstructural (Q3) characterization of comparable pH, specific gravity, emulsion globule size distribution (e.g., evaluated microscopically, if possible) and viscosity profiles with measurements made not only to determine the linear viscoelastic response but also to investigate any nonlinear viscosity behavior over a range of shear rates. We recommend to perform these comparative studies on at least three lots of the test product, and (as available) three lots of the RLD product.
iii. Equivalent comparative dosage form performance characterization in vitro, using the USP <1724> compendial In Vitro Release Test (IVRT) method. We recommend that the IVRT method be validated to demonstrate its reproducibility and discrimination sensitivity. Discrimination sensitivity may be validated by testing of the 5% benzyl alcohol lotion, compared with altered (e.g. 2.5% and 7.5%) benzyl alcohol lotions of otherwise comparable composition, to demonstrate the sensitivity of the IVRT method to monitoring the proportionality of the release rates as a function of benzyl alcohol concentration, and to demonstrate the ability of the IVRT method to detect inequivalence of the altered formulations' drug release rates to that measured for the 5% benzyl alcohol lotion, using the statistical methodology described in <1724>.
iv. Equivalent comparative dosage form performance characterization 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., Journal of Medical Entomology 45(1):75-81. 2008).

If the generic drug product has different inactive ingredients compared to the RLD, then the Office of Generic Drugs requests a clinical endpoint study to determine bioequivalence between the products.

II. In Vivo option:

Recommended studies: One study

Type of study: Bioequivalence (BE) study with clinical endpoint
Design: Randomized, double blind, parallel, placebo-controlled, in vivo
Strength: 5%
Subjects: Healthy males and nonpregnant 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.

Analytes to measure (in appropriate biological fluid): Not Applicable (N/A)

Bioequivalence based on (90% CI): Clinical endpoint

Waiver request of in vivo testing: N/A

Dissolution test method and sampling times: N/A

Additional comments regarding the BE study with clinical endpoint:

1. The Office of Generic Drugs (OGD) 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 listed drug (RLD) 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. A placebo control arm (vehicle of test product) is recommended to demonstrate that the test product and RLD are active and as a parameter to establish that the study is sufficiently sensitive to detect differences between products.

3. Inclusion Criteria (the sponsor may add additional criteria):
   a. Healthy males or nonpregnant 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.

4. 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 RLD.
   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.

5. The primary endpoint is the proportion of subjects in the Per Protocol (PP) population 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).

6. 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.)

7. 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

Hair Length		Amount of ULESFIA® Lotion per Application	
		Ounces	8 oz bottle
	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.

8. 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.

9. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations.
   a. The PP population includes all randomized subjects who met all inclusion/exclusion criteria, applied the assigned product as instructed and completed the evaluation within the designated visit window (+/- 2 days) with no protocol violations that would affect the treatment evaluation. The protocol should specify how compliance will be verified, e.g., by the use of subject diaries, and the protocol violations that would affect the treatment evaluation.
   b. The mITT population includes all randomized subjects who met all inclusion/exclusion criteria, received the assigned study product and returned for at least one post-baseline evaluation visit.
   c. The safety population includes all randomized subjects who received study product.

10. 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.

11. 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, 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 mITT population, using Last Observation Carried Forward (LOCF).

12. The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use. The sponsor should clearly explain whether the medication was used prior to baseline visit, during the study, or both.

13. All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution.

14. 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 product with regard to the expected and unexpected application site reactions.

15. If the inactive ingredients are different than those contained in the RLD or present in significantly different amounts, then the sponsor is to clearly describe the differences and provide information to show that the differences will not affect the safety, efficacy and/or systemic or local availability of the drug.

16. The quantitative information of inactive ingredients of the vehicle/placebo control should be provided.

17. 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.

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

19. Please refer to 21 CFR 320.38, 320.63 and the Guidance for Industry, “Handling and Retention of BA and BE Testing Samples”, regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of bioequivalence testing. In addition, the investigators should follow the procedures of ICH E6, “Good

Clinical Practice: Consolidated Guideline", for retention of study records and data in order to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP). Retention samples should be randomly selected from the drug supplies received prior to dispensing to subjects. Retention samples should not be returned to the sponsor at any time.

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

21. To establish bioequivalence, the 90% confidence interval of the test - reference difference between products for the primary endpoint (success proportion) must be contained within [-0.20, +0.20] for dichotomous variables (success versus failure), using the PP population.

22. As a parameter for determining adequate study sensitivity, the test product and RLD should both be statistically superior to placebo control ($p < 0.05$, two-sided) for the primary endpoint using the mITT population and LOCF.

23. The following Statistical Analysis Method is recommended for equivalence testing for a dichotomous variable (success/failure):

    Equivalence Analysis

    Based on the usual method used in OGD for binary outcomes, the 90% confidence interval for the difference in success proportions between test and reference treatment must be contained within [-0.20, +0.20] in order to establish equivalence.

    The compound hypothesis to be tested is:

    H_0: $p_T - p_R < -0.20$ or $p_T - p_R > 0.20$

    versus

    H_A: $-0.20 \leq p_T - p_R \leq 0.20$

    where p_T = success rate of test treatment and p_R = success rate of reference treatment.

    Let
    n_T = sample size of test treatment group
    cn_T = number of successes in test treatment group
    n_R = sample size of reference treatment group
    cn_R = number of successes in reference treatment group

$\hat{p}_T = c\,n_T / n_T$, $\hat{p}_R = c\,n_R / n_R$,

and se = $(\hat{p}_T(1 - \hat{p}_T)/n_T + \hat{p}_R(1 - \hat{p}_R)/n_R)^{½}$.

The 90% confidence interval for the difference in proportions between test and reference was calculated as follows, using Yates' correction:

$L = (\hat{p}_T - \hat{p}_R) - 1.645\ se - (1/n_T + 1/n_R)/2$

$U = (\hat{p}_T - \hat{p}_R) + 1.645\ se + (1/n_T + 1/n_R)/2$

We reject H_0 if $L \geq -0.20$ and $U \leq 0.20$

Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

24. The Case Report Form (CRF) 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. Study data should be submitted to the OGD in electronic format.
    a. A list of file names, with a simple description of the content of each file, should be included. Such a list should include an explanation of the variables included in each of the data sets.
    b. Please provide a "pdf" document with a detailed description of the codes that are used for each variable in each of the SAS datasets (for example, Y=yes, N=no for analysis population).
    c. SAS transport files, covering all variables collected in the Case Report Forms (CRFs) per subject, should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS files should be included.
    d. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NO-LOCF-pure data set) and Last Observation Carried Forward (LOCF- modified data set).
    e. Please provide a separate dataset for variables such as demographics, disease severity (IGA), vital signs, adverse events, disposition (including reason for discontinuation of treatment,) concomitant medications, medical history, compliance and comments, etc.

25. Please 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, RLD, placebo
i. Date of Treatment One
j. Date of Treatment Two
k. Completed the study (yes/no)
l. Reason for premature discontinuation of subject
m. Subject required additional treatment for *Pediculus humanus capitis* due to unsatisfactory treatment response (yes/no)
n. Per Protocol (PP) population inclusion (yes/no)
o. Reason for exclusion from PP population
p. Modified Intent to Treat (mITT) population inclusion (yes/no)
q. Reason for exclusion from mITT population
r. Safety population inclusion (yes/no)
s. Reason for exclusion from safety population
t. Final designation of treatment outcome (success/failure) on study Day 15
u. Compliance (i.e., was lotion applied and removed as instructed?) (yes/no)
v. Concomitant medication (yes/no)
w. Adverse event(s) reported (yes/no)

Please refer to Table 2 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 2: Example of a summary dataset containing one line listing for each subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	trt1_date	trt2_date	completd	disc_rs	add_tx	pp	pp_rs	mitt	mitt_rs	safety	safe_rs	tx_out	complian	CM	AE
101	1	01	5	YEARS	F	1	A	11-5-14	11-12-14	Y		N	Y		Y		Y		S	0	Y	Y
101	2	01	8	YEARS	F	1	B	12-2-14	12-9-14	Y		N	Y		Y		Y		S	0	N	N

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final dated 11/12/08.

STUDYID: Study Identifier
SUBJID: Subject Identifier for the Study
SITEID: Study Site Identifier
AGE: Age
AGEU: Age units (years)

SEX:	Sex, e.g., M=Male, F=Female, U=Unknown
RACE:	Race, e.g., 1=White, 2=Black or African American, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or Other Pacific Islanders
EXTRT:	Name of Actual Treatment (exposure), e.g., A=test product, B= RLD, C=placebo
trt1_date:	Date of Treatment #1 (ex. November 5, 2014 would be displayed as 11-5-14)
trt2_date:	Date of Treatment #2 (ex. November 12, 2014 would be displayed as 11-12-14)
completd:	Subject completed the study, e.g., Y=Yes, N=No
disc_rs:	Reason for premature discontinuation from the study, e.g., A=adverse event, B=death, C=lost to follow-up, D=non-compliance with treatment, E=treatment unblinded, F=subject moved out of area, G=unsatisfactory treatment response, H=withdrew consent, I=protocol violation, K=other event, L=live lice noted at Visits 2, 3, or 4
add_trt:	Subject required additional treatment for *Pediculus humanus capitis* due to unsatisfactory treatment response, e.g., Y=Yes, N=No
pp:	Per Protocol (PP) population inclusion, e.g., Y=Yes, N=No
pp_rs:	Reason for exclusion from PP population, e.g., A=prematurely discontinued, B=lost to follow-up, C=subject moved out of the area, D=noncompliant, etc.
mitt:	Modified Intent to Treat (mITT) population inclusion, e.g., Y=Yes, N=No
mitt_rs:	Reason for exclusion from mITT population, e.g., A=never treated, etc.
safety:	Safety population inclusion, e.g., Y=Yes, N=No
safe_rs:	Reason for exclusion from Safety population, e.g., A=never treated, etc.
tx_out:	Final designation of treatment outcome based of live head lice on study Day 15, e.g., A=success, B=failure
complian:	Treatment compliance (was lotion applied and removed as instructed?), e.g., Y=Yes, N=No
CM:	Concomitant medication, e.g., Y=Yes, N=No
AE:	Adverse event(s) reported, e.g., Y=Yes, N=No

26. Please 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, RLD, placebo
    d. Visit number
    e. Visit date
    f. Number of days since baseline visit
    g. Evaluator: identity of evaluator
    h. Number of live head lice
    i. Skin reaction score\s for each sign and symptom evaluated (e.g., erythema, pyoderma, excoriation, edema, and pain)

j. Concomitant medication reported during this visit (yes/no)
k. Adverse event reported during this visit (yes/no)
l. Laboratory testing during this visit (yes/no)

Please refer to Table 3 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 3: Example of dataset containing one line listing for each visit per subject

STUDYID	SUBJID	EXTRT	VISITNUM	SVSTDTC	ELTMBS	EVAL	live_lic	sr_eryth	sr_pyod	sr_excor	sr_edema	sr_pain	CMrpt	AErpt	LBtest
101	1	A	1	2004-07-01	0		4	0	0	1	0	0	Y	N	Y

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final dated 11/12/08.

STUDYID: Study Identifier
SUBJID: Subject Identifier for the Study
EXTRT: Name of Actual Treatment (exposure), e.g., A=test product, B=RLD, C=placebo
VISITNUM: Visit Sequence Number
SVSTDTC: Visit date: (SVSTDTC=Subject Visit Start Date Time-Character)
ELTMBL: Elapsed Time since Baseline (days)
EVAL: Evaluator: identity of the evaluator
live_lic: Number of live head lice
sr_eryth: Skin reaction erythema score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
sr_pyod: Skin reaction pyoderma score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3-severe (marked, intense)
sr_excor: Skin reaction excoriation score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
sr_edema: Skin reaction edema score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
sr_pain: Skin reaction pain score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
CMrpt: Concomitant Medication reported during this visit, e.g., Y=Yes, N=No

AErpt: Adverse Event reported during this visit, e.g., Y=Yes, N=No
LBtest: Laboratory Testing performed during this visit, e.g., Y=Yes, N=No

27. These recommendations are specific to this product and may not be appropriate for bioequivalence studies of any other product, including any other dosage form or strength of benzyl alcohol.