

Draft Guidance on Spinosad

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Spinosad

Dosage Form; Route: Suspension; topical

Recommended Studies: Two options: in vitro or in vivo studies

1. In vitro option:

The test product formulation should be qualitatively (Q1) and quantitatively (Q2) the same as the reference listed drug (RLD) to qualify for a waiver of the in vivo bioequivalence (BE) study requirement. In addition, the firm should also submit data to support comparable physicochemical properties, such as viscosity, pH, and specific gravity of its proposed test product to the RLD.

2. In vivo option:

If the test product formulation is not Q1/Q2 the same as the RLD, BE should be established by conducting an in vivo study with clinical endpoint.

Recommended studies: One study

Type of study: BE study with clinical endpoint

Design: Randomized, double blind, parallel, placebo-controlled, in vivo

Strength: 0.9%

Subjects: Healthy males and females (non-pregnant), 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): 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 BE 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 RLD and 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. 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 females (nonpregnant),
 - 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. 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.
 - 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.
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 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. 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.
5. 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).

6. 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).
7. Provide oral and written instructions to the subject and/or parent/guardian as follows:
 - Shake bottle well immediately prior to use
 - Cover your face and eyes with a towel and keep your eyes closed tightly.
 - Apply the product directly to dry hair. Completely cover the scalp first, and then apply outwards towards the ends of the hair.
 - Use as much product as needed to completely cover the entire scalp and all scalp hair.
 - 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.
 - Continue to keep eyes covered to prevent dripping into your eyes. If any product gets in the eye, flush with water right away.
 - After 10 minutes, completely rinse your hair and scalp with warm water.
 - You or anyone who helps you apply the product should wash hands after application.
 - It is okay to shampoo your hair any time after the treatment.
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 brushes used by the infected patient.
9. The protocol should clearly define the PP, modified intent-to-treat (mITT), and safety populations:
 - a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who met all inclusion/exclusion criteria, applied a pre-specified proportion of the scheduled doses (e.g., 75% to 125%) of the assigned product for the specified duration of the study, 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.
 - b. The mITT population includes all randomized subjects who met all inclusion/exclusion criteria and received the assigned study product.
 - 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 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 mITT population.

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 and the randomization schedule provided as a SAS data set in .xpt format (created using SAS XPORT). 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 and content 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. 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 BE testing. In addition, the investigators should follow the procedures of 21 CFR 58 and 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 BE between the products.
21. To establish BE for the primary dichotomous endpoint, it is recommended the following compound hypotheses be tested using the PP population:

$$H_0: \pi_T - \pi_R < \Delta_1 \text{ or } \pi_T - \pi_R > \Delta_2 \text{ versus } H_A: \Delta_1 \leq \pi_T - \pi_R \leq \Delta_2$$

where π_T = the success rate of the primary endpoint for the test treatment group, and π_R = the success rate of the primary endpoint for the reference treatment group.

The null hypothesis, H_0 , is rejected with a type I error (α) of 0.05 (two one-sided tests) if the estimated 90% confidence interval of the treatment difference in success rate between products ($\pi_T - \pi_R$) is contained within the interval $[\Delta_1, \Delta_2]$, where $\Delta_1 = -0.20$ and $\Delta_2 = +0.20$. Rejection of the null hypothesis supports the conclusion of BE of the two products.

22. To establish assay sensitivity of the study, the test and reference products should both be statistically superior to the placebo. Conduct an appropriate inferential test with a type I error (α) of 0.05 (two-sided) for each comparison, using the mITT population for the primary endpoint.
23. Provide a PDF file including a list of file names, a description of the content of each file, an explanation of the variables within each file, and a description of all variable codes (for example, for the treatment variable, A = TEST and B = RLD).
24. Study data should be submitted to OGD in electronic format. All data should be submitted as a SAS.xpt file, created using SAS XPORT (not CPORT). Provide a separate dataset for each of the demographic, vital sign, adverse event, disposition (including reason for discontinuation of treatment), concomitant medication, medical history, compliance, and comment variables.
25. Please provide a summary dataset containing a separate line listing for each subject (if data exist) using the following headings, if applicable:
- Study identifier
 - Subject identifier
 - Site identifier: study center
 - Age
 - Age units (years)
 - Sex
 - Race

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

Please refer to Table 1 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 1: Example of a summary dataset containing one line listing for each subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	trt1_date	completd	disc_rs	add_tx	pp	pp_rs	mitt	mitt_rs	safety	safe_rs	tx_out	complan	CM	AE
101	1	01	5	YEARS	F	1	A	11-5-14	Y		N	Y		Y		Y		S	0	Y	Y
101	2	01	8	YEARS	F	1	B	12-2-14	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, 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 (e.g., November 5, 2014 would be displayed as 11-5-14)

completd: Subject completed the study, 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, Y=yes, N=no
 pp: Per Protocol (PP) population inclusion, 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, Y=yes, N=no
 mitt_rs: Reason for exclusion from mITT population, e.g., A=never treated, etc.
 safety: Safety population inclusion, 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?), Y=yes, N=no
 CM: Concomitant medication, Y=yes, N=no
 AE: Adverse event(s) reported, 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:
- Study identifier
 - Subject identifier
 - Name of actual treatment (exposure): test product, RLD, placebo
 - Visit number
 - Visit date
 - Number of days since baseline visit
 - Evaluator: identity of evaluator
 - Number of live head lice
 - Adverse reaction score for each sign and symptom evaluated (e.g., erythema, pyoderma, excoriation, edema, pain, eye irritation)
 - Concomitant medication reported during this visit (yes/no)
 - Adverse event reported during this visit (yes/no)
 - Laboratory testing during this visit (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 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)
ELTMBS:	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, Y=yes, N=no
AErpt: Adverse Event reported during this visit, Y=yes, N=no
LBtest: Laboratory Testing performed during this visit, Y=yes, N=no

27. The study data should be submitted in a standardized format. Consider the implementation and use of data standards as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis stages of clinical studies. Please refer to more details at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>
28. The protocol should include a full detailed statistical analysis plan and describe how missing data will be prevented and handled if exist.
29. These recommendations are specific to this product and may not be appropriate for BE studies of any other product, including any other dosage form or strength of spinosad.