**Draft Guidance on Ivermectin**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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:** Ivermectin

**Dosage Form; Route:** Lotion; topical

**Recommended Studies:** Two options: in vitro or in vivo study

1. **In vitro option:**

   To qualify for the in vitro option for this drug product the following criteria should be met:

   **A.** The test and Reference Listed Drug (RLD) products should be qualitatively (Q1) and quantitatively (Q2) the same as defined in the Guidance for Industry ANDA Submissions – Refuse-to-Receive Standards, Revision 2 (December 2016).

   **B.** The test and RLD products should be physically and structurally similar based upon an acceptable comparative characterization of a minimum of three batches of the test and three batches (as available) of the RLD product. The influence of any differences in the container closure systems between the test and RLD products, which may influence the physicochemical properties of the lotion when dispensed, should be considered in the design of the physical and structural characterization studies. Physicochemical characterizations should include:

   i. Assessment of appearance.

   ii. Analysis of globule size distribution with representative high resolution microscopic images at multiple magnifications.

   iii. Evaluation of the 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.

   iv. Analysis of pH and specific gravity as well as any other potentially relevant physical and structural attributes.

   **C.** The test and RLD products should have an equivalent rate of ivermectin release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one batch each of the test and RLD products using an appropriately validated IVRT method. Refer to the Guidance on

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1 Guidance for Industry: ANDA Submissions – Refuse-to-Receive Standards, Revision 2 (December 2016)
Acyclovir (for acyclovir topical cream, 5%)\(^2\) for additional information regarding the development, validation, conduct and analysis of acceptable IVRT methods/studies.

D. The test and RLD products should have an equivalent comparative dosage form performance characterization ex vivo in *Pediculus humanus capitis* (head lice), based on 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). The batches of test and RLD products evaluated in the pediculicide hair tuft assay should be the same as those evaluated in the IVRT study, and these batches should be included among those for which the physical and structural similarity is characterized and compared.

2. **In vivo option:**

   Number of Studies: One Study  
   Type of study: Bioequivalence study with clinical endpoint  
   Design: Randomized, double blind, parallel, placebo-controlled, in vivo  
   Strength: 0.5%  
   Subjects: Males and females (non-pregnant, non-lactating) ages 6 months to 64 years, inclusive, with active infestation with *Pediculus humanus capitis* (head lice and their ova)

Analytes to measure (in appropriate biological fluid): Not applicable

Bioequivalence based on (90% CI): See additional comments below for the bioequivalence study with clinical endpoint

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: Not applicable

Additional comments regarding the bioequivalence study with clinical endpoint:

1. The Office of Generic Drugs (OGD) 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 RLD 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)].

\(^2\) Draft Guidance on Acyclovir for acyclovir topical cream, 5% (recommended Dec 2014; revised Dec 2016).
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. 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. Males or females (non-pregnant, non-lactating).
   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.

4. 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 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 each treatment group with treatment success (i.e., absence of live head lice) when examined on study Day 15 (14 days post-treatment).

6. Subjects with live lice noted at visits 2, 3, or 4 should be discontinued from study treatment, included in the PP and 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.

7. Provide oral and written instructions to the subject and/or parent/guardian as follows:
   - 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.
   - Use as much as the entire tube to completely cover scalp and hair to the tip. Then rub the drug product throughout the hair.
• 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.
• After 10 minutes, completely rinse hair and scalp using only water.
• You or anyone who helps you apply the drug product should wash their hands after application.
• It is recommended to wait 24 hours before applying shampoo to hair or scalp.
• Avoid contact with eyes.
• Lactating women should avoid accidental transfer of the drug product to the breast where an infant might accidentally ingest the drug product.

8. Provide details in the protocol regarding the procedures to be taken to decrease re-infestation, such as:
   • the examination of household members of enrolled subjects for head lice (and treatment of such household members found to be infested);
   • avoidance of direct head-to-head contact with anyone who has an active head lice infestation;
   • 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 subjects.

9. 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.

10. 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, 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 product with regard to expected and unexpected application site reactions.

11. The protocol should clearly define per-protocol (PP), modified intent-to-treat (mITT), and safety populations.
   a. The acceptable PP population used for bioequivalence evaluation includes all randomized subjects who:
      i. Meet all inclusion/exclusion criteria
      ii. Are dosed a pre-specified proportion of the scheduled doses (e.g., at least 75% and no more than 125%) of the assigned product for the specified duration of the study. The protocol should specify how compliance will be verified, (e.g., using subject diaries).
      iii. Do not miss a pre-specified number of scheduled doses for more than pre-specified number of consecutive days.
      iv. Complete the evaluation within the designated visit window with no protocol violations that would affect the treatment evaluation.
   b. The mITT and safety populations include all randomized subjects who use at least one dose of product.
12. The start and stop calendar date (e.g., mm/dd/yyyy) and study day (e.g., Day X) of concomitant medication use should be provided in the data set in addition to the reason for the medication use. The Applicant should clearly explain whether the medication was used prior to baseline visit, during the study, or both.

13. If the study allows for the use rescue therapy in subjects who have failed study treatment, the Applicant should submit a data set that includes data for everyone who used the alternate therapy at any point during the study. The Applicant should pre-specify alternate therapy use (e.g., type, amount, frequency, reason to use) and any limitations for alternate therapy use during the study.

14. All adverse events (AEs) should be reported, regardless of their relation 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. This information is needed to determine if the incidence and severity of adverse reactions is different between the test product and RLD.

15. All pregnancies should be reported, including outcome information.

16. If inactive ingredients in test product are qualitatively and quantitatively different than those contained in the RLD, then the sponsor should clearly describe the differences. In addition, the sponsor should provide information to show that the differences will not affect safety, efficacy, and/or systemic or local availability of the drug.

17. The method of randomization should be described in the protocol and randomization schedule provided. It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study to minimize bias. The Applicant 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 should be provided in the protocol. The packaging of test, reference, and placebo products should be similar in appearance to make differences in treatment less obvious to subjects and to maintain adequate blinding of evaluators. When possible, neither subject nor investigator should be able to identify the treatment. 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, investigators should follow the procedures of 21 CFR 58 and ICH E6, “Good Clinical Practice: Consolidated Guideline”, for retention of study records and data to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP). Retention samples should be randomly selected from drug supplies.
received prior to dispensing to subjects. Retention samples should not be returned to the Applicant at any time.

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

21. To establish bioequivalence for a dichotomous endpoint, it is recommended the following compound hypotheses be tested using the per protocol 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 \( \pi_T \) = the success rate of the primary endpoint for the treatment group, and \( \pi_R \) = the success rate of the primary endpoint for the reference group.

The null hypothesis, \( H_0 \), is rejected with a type I error (\( \alpha \)) of 0.05 (two one-sided tests) if the estimated 90% confidence interval for the difference of the success rates between test and reference 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 equivalence of the two products.

22. To establish sensitivity within the study for either a dichotomous or continuous primary endpoint, the test and reference products should both be statistically superior to the placebo. Conduct an appropriate two-sided inferential test with a type I error (\( \alpha \)) of 0.05, using the mITT population and the primary endpoint.

23. The study data should be submitted in standardized format. Please refer to study data standards published at www.FDA.gov.³

24. The protocol should include a fully detailed statistical analysis plan.

25. Please 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 Site identifier for the study
   d. Study site identifier: study center
   e. Age
   f. Age units (years)
   g. Sex
   h. Race
   i. Index subject (yes/no)
   j. Household member (yes/no)
   k. Description of planned arm
   l. Description of actual arm

m. Planned treatment (character)

n. Planned treatment (number)

o. Actual treatment (character)

p. Actual treatment (number)

q. Safety population flag (yes/no)

r. Reason for exclusion from safety population

s. Modified intent to treat (mITT) population flag (yes/no)

t. Reason for exclusion from mITT population

u. PP population flag (yes/no)

v. Reason for exclusion from PP population

w. Randomized population flag (yes/no)

x. Date of randomization

y. Date of enrollment

z. Date/time of exposure to treatment

aa. End of study date

bb. End of study status

c. End of treatment status

d. Subject required additional treatment for *Pediculus humanus capitis* due to unsatisfactory treatment response (yes/no)

e. Description of rescue treatment

f. Date of rescue treatment

g. Study day of rescue treatment

h. Completed the study (yes/no)

i. Reason for premature discontinuation of subject (character)

j. Final designation as treatment success (yes/no)

k. Reason for discontinuation from study (character, additional details regarding subject’s discontinuation from study)

l. Reason for discontinuation from treatment (character)

mm. Reason for discontinuation from treatment (character, additional details regarding subject’s discontinuation from treatment)

nn. Compliance (i.e. was lotion applied and removed as instructed?) (yes/no)

oo. Concomitant medication (yes/no)

pp. Adverse event(s) reported (yes/no)

qq. Evaluator initial (character)

26. Please 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. Modified ITT population flag (yes/no)
k. Per-Protocol (PP) population flag (yes/no)
l. Planned treatment (character)
m. Planned treatment (number)
n. Name of Actual Treatment (exposure): test product, RLD, placebo control
o. Actual treatment (number)
p. Date/time treatment exposure
q. Visit number
r. Visit date
s. Number of days since baseline visit
t. Evaluator: identity of evaluator
u. Visit number
v. Visit date
w. Number of days since baseline visit
x. Study visit within designated window (yes/no)
y. Evaluator: identity of evaluator
z. Number of live head lice
aa. Rescue treatment required (yes/no)
bb. Date/time rescue treatment
cc. Erythema score
dd. Pyoderma score
ee. Excoriation score
ff. Edema score
gg. Pain score
hh. Ocular irritation score
ii. Concomitant medication reported during this visit (yes/no)
jj. Adverse event reported during this visit (yes/no)
kk. Laboratory testing during this visit (yes/no)