Draft Guidance on Ivermectin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Recommended Studies: Two Options: (1) a combination of in vitro studies and in vivo pharmacokinetic (PK) study, or (2) in vivo clinical endpoint study

Option I: In vitro studies and in vivo PK study

To qualify for the in vitro studies and in vivo PK study option for ivermectin cream product, all of the following criteria should be met:

1. The test and Reference Listed Drug (RLD) products are qualitatively (Q1) and quantitatively (Q2) the same as defined in the Guidance for Industry *ANDA Submissions – Refuse-to-Receive Standards*.[1]

2. The test and RLD products are physically and structurally similar based upon an acceptable comparative physicochemical characterization of a minimum of three lots of the test and three lots (as available) of the RLD product. Physicochemical characterizations should include:

    a. Assessment of appearance

    b. Analysis of physical stability and globule size

    c. Analysis of the 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 complete flow curve of shear stress (or viscosity) vs. shear rate should consist of multiple data points across the range of attainable shear rates, until low or high shear plateaus are identified. The comparative viscosity data at low, medium and high shear rates should be provided.
    - 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.

[1] Guidance for Industry ANDA Submissions – Refuse-to-Receive Standards, Revision 2 (December 2016)

d. Analysis of pH and any other potentially relevant physical and structural similarity characterizations.

3. The test and RLD products have an equivalent rate of ivermectin release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one lot each of the test and reference products using an appropriately validated IVRT method. Refer to the Guidance on Acyclovir Topical Cream for additional information regarding the development, validation, conduct, and analysis of acceptable IVRT studies.

4. The test and RLD products have an equivalent rate and extent of ivermectin permeation through excised human skin based upon an acceptable in vitro permeation test (IVPT) comparing a minimum of one lot each of the test and reference products using an appropriately validated IVPT method. Refer to the Guidance on Acyclovir Topical Cream for additional information regarding the development, validation, conduct, and analysis of acceptable IVPT studies.

5. The test and RLD products are bioequivalent based upon an acceptable in vivo bioequivalence (BE) study with PK endpoints:

Type of study: BE study with PK endpoints

Design: Single-application, two-way crossover design, in vivo

Strength: 1%

Subjects: Males and non-pregnant, non-lactating females, general population

Additional comments: A) The lots of test and RLD products evaluated in the in vivo PK study should be the same as those evaluated in the IVRT and IVPT studies, and these lots should be included among those for which the physical and structural similarity is characterized and compared. B) If the crossover study is problematic, applicants should use a BE study with a parallel design. For either a crossover or parallel study, the OGD recommends application of 1 g study cream products on the face except the eyes and lips. Sample collection time should be adequate to delineate the PK profile of ivermectin.

Option II: In vivo clinical endpoint study

Type of study: BE study with clinical endpoint

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

Strength: 1%

Subjects: Healthy males and non-pregnant, non-lactating females with rosacea

Additional comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): Ivermectin (in vitro studies), Ivermectin in plasma (in vivo PK study)

Bioequivalence based on (90% CI): See additional comments for the in vitro studies and in vivo PK study or in vivo clinical endpoint study

Waiver request of in-vivo testing: Not applicable

Dissolution test method and sampling time: Not applicable

Additional comments relating to the BE study with clinical endpoint:

1. The OGD recommends a clinical endpoint BE study in the treatment of moderate to severe rosacea. Subjects are to be randomized to receive the generic ivermectin topical cream, 1%, RLD, or placebo once daily for 12 weeks. The primary endpoint is to be evaluated at the end of treatment (study Week 12).

2. Inclusion Criteria (the Applicant may add additional criteria):
   a. Healthy male or nonpregnant female aged ≥ 18 years
   b. Clinical diagnosis of papulopustular rosacea, with an Investigator Global Assessment (IGA) score rated 3 (moderate) or 4 (severe) defined as:
      i. At least fifteen and not more than fifty inflammatory facial lesions (i.e., papules/pustules), AND
      ii. Not more than two nodules on the face at Screening or Baseline visits
   c. Subject willing to minimize external factors that might trigger rosacea flare-ups (e.g., spicy foods, thermally hot foods and drinks, hot environments, prolonged sun exposure, strong winds and alcoholic beverages).

3. Exclusion Criteria (the Applicant may add additional criteria):
   a. Pregnant or lactating or planning to become pregnant during the study period.
   b. Presence of other forms of rosacea (rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin) or other dermatoses that may be confounded with papulopustular rosacea, such as peri-oral dermatitis, facial keratosis pilaris, seborrheic dermatitis and acne.
   c. Clinically significant abnormal laboratory values according to the investigator at screening.
   d. Excessive facial hair (e.g. beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of rosacea.
   e. History of hypersensitivity or allergy to propylene glycol or any other component of the formulation.
   f. Use within 6 months prior to baseline of oral retinoids (e.g. Accutane®) or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed).
   g. Use for less than 3 months prior to baseline of estrogens or oral contraceptives; use of such therapy must remain constant throughout the study.

h. Use within 1 month prior to baseline of
    i. Topical facial treatment with retinoids benzoyl peroxide, antibiotics (metronidazole & macrolides), corticosteroids, immunomodulators, other topical rosacea treatment (e.g. azelaic acid & metronidazole),
    ii. Systemic treatment with antibiotics known to have an impact on the severity of facial rosacea (e.g., containing tetracycline and its derivatives, erythromycin and derivatives, sulfamethoxazole, or trimethoprim), corticosteroids.
i. Use within 6 weeks prior to baseline of 1) topical corticosteroids, 2) topical antibiotics or 3) topical medications for rosacea (e.g., metronidazole, azelaic acid).
j. Exposure to excessive UV radiation within two weeks prior baseline, or the subject is planning exposure during the study (e.g. occupational exposure to the sun, planned holidays in the sun during the study, phototherapy, tanning salon).
k. Subjects with moderate or severe rhinophyma, dense telangiectases, or plaque-like facial edema.
l. Ocular rosacea (e.g., conjunctivitis, blepharitis, or keratitis) of sufficient severity to require topical or systemic antibiotics.

4. The protocol should include a list of the prescription and over-the-counter drug products that are prohibited during the study, such as:
    a. Any other topical products applied to the target site (e.g., metronidazole, topical antibiotics, topical steroids).
    b. Oral retinoids.
    c. Systemic (e.g., oral or injectable) antibiotics known to have an impact on the severity of facial rosacea (e.g., containing tetracycline, erythromycin, sulfamethoxazole, or trimethoprim or their derivatives).
    d. Systemic corticosteroid or immunosuppressive drugs.
    e. Antipruritics, including antihistamines, within 24 hours of study visits.

5. Subjects should not apply moisturizers, new brands of make-up, creams, lotions, powders or any topical product other than the assigned treatment to the treatment area. Occlusive dressings or wrappings should be avoided in treatment areas. Subjects should minimize exposure to sunlight, including sunlamps, while using the product. Use of sunscreen products and protective clothing over treated areas is recommended when sun exposure cannot be avoided.

6. Areas to be treated should be washed with a mild cleanser before application and patted dry with a soft towel. A thin layer of study treatment should be gently massaged into the affected areas on the face once daily for 12 weeks. Contact with the mouth, eyes and other mucous membranes should be avoided. The hands should be washed following application.

7. The recommended primary endpoint of the study is the mean percent change from baseline to week 12 in the inflammatory (papules and pustules) lesion counts. The protocol should clearly define papules, pustules, and nodules. When counting facial lesions, it is important that all lesions be counted, including those present on the nose. Counts of nodules should be reported separately and not included in the inflammatory lesion counts.

8. An Investigator Global Assessment (IGA) score should be recorded as a secondary endpoint for the statistical analysis. The IGA should be a static scale, describing the extent of disease associated with each score. This scale should not be a reflection of treatment response, but should describe the condition at each visit. Therefore, no reference should be made to baseline in the evaluation.
   The scale should be dichotomized into "success" and "failure." "Success" should be defined either as a score consistent with clear or almost clear at the final visit.

Score	Grade	Definition
0	Clear	No inflammatory lesions present; at most, mild erythema
1	Almost Clear	Very mild erythema present. Very few small papules/pustules
2	Mild	Mild erythema. Several small papules/pustules
3	Moderate	Moderate erythema. Several small or large papules/pustules, and up to 2 nodules
4	Severe	Severe erythema. Numerous small and/or large papules/pustules, up to several nodules

9. Inflammatory (papules and pustules) lesion counts and IGA scores at interim visits (e.g., week 4 and week 8) should be recorded.

10. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations.
    a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who meet all inclusion/exclusion criteria, dosed a pre-specified proportion of the scheduled doses (e.g., 75% to 125%) of the assigned product for the specified duration of the study, do not miss a pre-specified number of scheduled doses for more than pre-specified number of days (e.g. 3 consecutive day), and complete the evaluation within the designated visit window 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)
    b. The mITT and safety populations include all randomized subjects who apply at least one apply at least one dose of assigned product.

10. Subjects who are discontinued early from the study due to lack of treatment effect after completing 4 weeks of treatment should be included in the PP population using LOCF. Subjects whose condition worsens and who require alternate or supplemental therapy for the treatment of diarrhea during the treatment phase of the study should be discontinued, included in the PP population analysis using LOCF, 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).

11. The start and stop calendar date (e.g. mm/dd/yyyy) and study date (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.

12. 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. This information is needed to determine if the incidence and severity of adverse reactions is different between the test product and RLD.

13. If the inactive ingredients are different than those contained in the RLD or in significantly different amounts, then the Applicant 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.

14. The method of randomization should be described in the protocol and the randomization schedule should be provided. 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 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.

15. 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.

16. 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 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 Applicant at any time.

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

18. To establish bioequivalence for a dichotomous endpoint, it is recommended the following compound hypotheses be tested using the per protocol population:

$$H_O: \pi_T - \pi_R \leq \Delta_1 \text{ or } \pi_T - \pi_R \geq \Delta_2 \quad \text{versus} \quad H_A: \Delta_1 < \pi_T - \pi_R < \Delta_2$$

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

The null hypothesis, H_O, is rejected with a type I error (α) 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.

To establish bioequivalence for a continuous endpoint, it is recommended the following compound hypotheses be tested using the per protocol population:

$$H_O: \mu_T/\mu_R \leq \theta_1 \quad \text{or } \mu_T/\mu_R \geq \theta_2 \quad \text{versus} \quad HA: \ \theta_1 < \mu_T/\mu_R < \theta_2$$

where μT = mean of the primary endpoint for the test group, and
μR = mean of the primary endpoint of the reference group

The null hypothesis, H_O, is rejected with a type I error (α) of 0.05 (two one-sided tests) if the estimated 90% confidence interval for the ratio of the means between test and reference products (μ_T/μ_R) is contained within the interval $[\theta_1, \theta_2]$, where $\theta_1 = 0.80$ and $\theta_2 = 1.25$. Rejection of the null hypothesis supports the conclusion of equivalence of the two products.

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

20. The study data should be submitted in standardized format. Please refer to study data standards published at www.FDA.gov.[2]

21. The protocol should include a full detailed statistical analysis plan.

22. Please provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Study site identifier (if applicable)
    d. Age
    e. Sex
    f. Race
    g. Name of planned treatment
    h. Name of actual treatment
    i. Safety population flag (yes/no)
    j. Reason for exclusion from safety population
    k. Modified Intent-to-Treat (mITT) population flag (yes/no)
    l. Reason for exclusion from mITT population
    m. Per-Protocol (PP) population flag (yes/no)
    n. Reason for exclusion from PP population

[2] Study Data Standards for Submission to CDER available at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

o. Safety population inclusion (yes/no)
p. Reason for exclusion from safety population
q. Completers population flag (yes/no)
r. Randomized population flag (yes/no)
s. Datetime of first exposure to treatment
t. Datetime of last 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. Baseline inflammatory lesion count (papules and pustules)
y. Week 12 inflammatory lesion count (papules and pustules)
z. Baseline IGA score
aa. Week 12 IGA score
bb. Compliance rate (%)
cc. Subject missed the scheduled applications for more than 3 consecutive days (yes/no)
dd. Adverse event reported (yes/no)
ee. Concomitant medication (yes/no)

23. Please provide the basic data structure (BDS) dataset with records per subject, per visit, analysis timepoint, using the following headings, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Study site identifier (if applicable)
    d. Name of planned treatment
    e. Name of actual treatment
    f. Safety population flag (yes/no)
    g. Modified Intent-to-Treat (mITT) population flag (yes/no)
    h. Per-Protocol (PP) population flag (yes/no)
    i. Completers population flag (yes/no)
    j. Analysis date
    k. Analysis visit
    l. Study visit within the designated window (yes/no)
    m. Visit date
    n. Number of days since baseline visit
    o. Evaluator: identity of evaluator
    p. Inflammatory lesions count (papule and pustule)
    q. Papule count
    r. Pustule count
    s. Nodule count
    t. IGA score
    u. Additional treatment required during visit (yes/no)
    v. Concomitant medication reported during this visit (yes/no)
    w. Adverse event reported during this visit (yes/no)
    x. Laboratory testing during this visit (yes/no)