

## Draft Guidance on Ivermectin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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*.<sup>1</sup>
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.

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<sup>1</sup> 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.

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## **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:** Males and non-pregnant, non-lactating females with rosacea

**Additional comments:** Specific recommendations are provided below.

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**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

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**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. Male or nonpregnant female aged  $\geq 18$  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. Refer to the product-specific guidance on Adapalene; Benzoyl Peroxide Topical Gel 0.3%; 2.5% for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.<sup>2</sup>
9. Study data should be submitted in a standardized format. Please refer to the study data standards published at [www.fda.gov](http://www.fda.gov)<sup>3</sup>
10. Applicants intending to propose an alternative approach by which to demonstrate bioequivalence should refer to the guidance for industry Controlled Correspondence Related to Generic Drug Development and the guidance for industry Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA for additional information describing the procedures on how to clarify regulatory expectations regarding your individual drug development program.

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<sup>2</sup> Product-Specific Guidances for Generic Drug Development available at:  
<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>

<sup>3</sup> Study Data Standards for Submission to CDER and CBER available at:  
<https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm587508.htm>