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*Draft – Not for Implementation*

## **Draft Guidance on Pimecrolimus**

**October 2022**

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**Active Ingredient:** Pimecrolimus

**Dosage Form; Route:** Cream; topical

**Recommended Studies:** Two options: (1) two in vitro bioequivalence studies and other characterization tests or (2) one in vivo bioequivalence study with clinical endpoint

### **I. Option 1: Two in vitro bioequivalence studies and other characterization tests**

To demonstrate bioequivalence for pimecrolimus topical cream, 1% using in vitro studies, the following criteria should be met:

1. The test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference standard that may significantly affect the local or systemic availability of the active ingredient. For example, if the test product and reference standard are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the most recent version of the FDA guidance for industry on *ANDA Submissions – Refuse-to-Receive Standards*<sup>a</sup>, and the criteria below are also satisfied, the bioequivalence of the test product may be established using a characterization-based bioequivalence approach.
2. The test product and reference standard should have the same physicochemical and structural (Q3) attributes, based upon acceptable comparative Q3 characterization tests with a minimum of three batches of the test product and three batches (as available) of the reference standard. The test product and reference standard batches should ideally represent the product at different ages throughout its shelf life. Refer to the most recent version of the FDA guidance for industry on *Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs*<sup>a</sup> for additional

information regarding comparative Q3 characterization tests. The comparison of the test product and reference standard should include characterizations of the following Q3 attributes:

- a. Characterization of visual appearance and texture
  - b. Characterization of phase states and structural organization of matter
    - Microscopic examination with representative high-resolution microscopic images at multiple magnifications
    - Analysis of particle size distribution, crystal habit, and polymorphic form of pimecrolimus in the drug product, as applicable
    - Analysis of globule size distribution
  - c. Characterization of 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 characterization of shear stress vs. shear rate and viscosity vs. shear rate. At minimum, this should consist of numerical viscosity data at three shear rates (low, medium, and high).
    - A complete flow curve across the range of attainable shear rates, until low or high shear plateaus are identified.
    - 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. Any non-linear viscosity behavior over a range of shear rates should also be investigated, measured and reported.
  - d. Characterization of pH
  - e. Characterization of specific gravity
  - f. Characterization of any other potentially relevant Q3 attributes
3. The test product and reference standard should have an equivalent rate of pimecrolimus release based upon an acceptable in vitro release test (IVRT) bioequivalence study comparing a minimum of one batch each of the test product and reference standard using an appropriately validated IVRT method.

Type of study: Bioequivalence study with IVRT endpoint

Design: Single-dose, two-treatment, parallel, multiple-replicate per treatment group study design using an occluded pseudo-infinite dose, in vitro

Strength: 1%

Test system: A synthetic membrane in a diffusion cell system

Analyte to measure: Pimecrolimus in receptor solution

Equivalence based on: Pimecrolimus (IVRT endpoint: drug release rate)

Additional comments: Refer to the most recent version of the FDA guidance for industry on *In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs<sup>a</sup>* for additional information regarding the development, validation, conduct and analysis of acceptable IVRT methods/studies. The batches of test product and reference standard evaluated in the IVRT bioequivalence study should be included among those for which the Q3 attributes are characterized.

4. The test product and reference standard should have an equivalent rate and extent of pimecrolimus permeation through excised human skin based upon an acceptable in vitro permeation test (IVPT) bioequivalence study comparing a minimum of one batch each of the test product and reference standard using an appropriately validated IVPT method.

Type of study: Bioequivalence study with IVPT endpoints

Design: Single-dose, two-treatment, parallel, multiple-replicate per treatment group study design using an unoccluded finite dose, in vitro

Strength: 1%

Test system: Barrier-competent human skin from male and/or female donors of at least 18 years of age in a diffusion cell system

Analyte to measure: Pimecrolimus in receptor solution

Equivalence based on: Pimecrolimus (IVPT endpoints: total cumulative amount (AMT) and maximum flux ( $J_{max}$ ))

Additional comments: Refer to the most recent version of the FDA guidance for industry on *In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs<sup>a</sup>* for additional information regarding the development, validation, conduct and analysis of acceptable IVPT methods/studies. The batches of test product and reference standard evaluated in the IVPT bioequivalence study should be the same as those evaluated in the IVRT bioequivalence study.

## II. Option 2: One in vivo bioequivalence study with clinical endpoint

1. Type of study: Bioequivalence study with clinical endpoint  
Design: Randomized, double blind, parallel, placebo controlled, in vivo  
Strength: 1%  
Subjects: Non-immunocompromised males and females with clinical diagnosis of mild to moderate atopic dermatitis (AD)  
Additional comments: Specific recommendations are provided below.

### Additional comments regarding the bioequivalence study with clinical endpoint:

1. FDA recommends conducting a bioequivalence study with a clinical endpoint in the treatment of mild to moderate AD comparing the test product versus the reference standard and vehicle control, each applied as a thin layer twice daily to the affected area(s) for 14 days (2 weeks). The primary endpoint is the proportion of subjects with treatment success (a grade of clear or almost clear; a score of 0 or 1, within the treatment area) based on the Investigator's Global Assessment (IGA) of Disease Severity (see Table 1) at the end of treatment (study Day 15).
2. Inclusion Criteria (sponsor may add additional criteria):
  - a. Non-immunocompromised males or females aged 12 years and older with a clinical diagnosis of mild to moderate AD that has failed to respond adequately to other topical prescription treatments for AD, or for whom those treatments are not advisable. If the enrollment of subjects younger than aged 12 years is necessary due to the difficulty of recruiting sufficient subjects into the study, the OGD

- recommends limiting the subject’s age to 8 years and older. If pediatric subjects are included, ensure that the age distribution is similar in all treatment groups.
- b. Had a diagnosis of AD for at least 3 months.
  - c. An IGA of disease severity of mild or moderate at baseline (per Table 1, a score of 2 or 3).
  - d. Affected area of AD involvement at least 5% body surface area (BSA) at baseline as defined by the criteria of Hanifin and Rajka.<sup>1</sup>

**Table 1. IGA of Disease Severity**

Score	Category	Definition
0	Clear	Minor residual discoloration, no erythema or induration/papulation, no oozing/crusting
1	Almost clear	Trace faint pink erythema with almost no induration/papulation and no oozing/crusting
2	Mild disease	Faint pink erythema with mild induration/papulation and no oozing/crusting
3	Moderate disease	Pink-red erythema with moderate induration/papulation and there may be some oozing/crusting
4	Severe disease	Deep/bright red erythema with severe induration/papulation with oozing/crusting

3. Exclusion Criteria (sponsor may add additional criteria):
  - a. Females who are pregnant, breast feeding, or who wish to become pregnant during the study period
  - b. Active cutaneous bacterial or viral infection in any treatment area at baseline (e.g., clinically infected AD)
  - c. Sunburn, extensive scarring, or pigmented lesion(s) in any treatment area at baseline, which would interfere with evaluations
  - d. History of confounding skin conditions (e.g., psoriasis, rosacea, erythroderma, or ichthyosis)
  - e. History or presence of Netherton’s Syndrome, immunological deficiencies or diseases, HIV, diabetes, malignancy, serious active or recurrent infection, clinically significant severe renal insufficiency or severe hepatic disorders
  - f. Use within one month prior to baseline of 1) oral or intravenous corticosteroids, 2) ultraviolet A (UVA)/ultraviolet B (UVB) therapy, 3) psoralen plus ultraviolet A (PUVA) therapy, 4) tanning booths, 5) nonprescription ultraviolet (UV) light sources, 6) immunomodulators or immunosuppressive therapies, 7) interferon, 8) cytotoxic drugs, 9) tacrolimus, or 10) pimecrolimus
  - g. Use within 14 days of baseline of: 1) systemic antibiotics, 2) calcipotriene or other vitamin D preparations, or 3) retinoids
  - h. Use within 7 days prior to baseline of: 1) antihistamines, 2) topical antibiotics, 3) topical corticosteroids or 4) other topical drug products
  - i. Use within 24 hours prior to baseline of any topical product (e.g., sunscreens, lotions, creams bland emollient/moisturizer) in the areas to be treated

<sup>1</sup> Hanifin JM and Rajka G. Diagnostic Features of Atopic Dermatitis. *Acta Derm Venereol.* 1980; Suppl. 92: 44-7.

- j. Known allergy or hypersensitivity to pimecrolimus or any other component of the test product or reference standard
  - k. Not willing to minimize or avoid natural and artificial sunlight exposure during treatment
4. The protocol should include a list of the prescription and over-the-counter drug products, procedures, and activities that are prohibited during the study, such as:
    - a. Other treatments for AD, including the use of bland emollient
    - b. Topical or systemic corticosteroid, topical or systemic antibiotic, topical or systemic antifungal, oral or topical antihistamine, immunosuppressive drugs, immunomodulator (e.g., tacrolimus), calcipotriene or other vitamin D preparations, retinoids, interferon, cyclosporine, methotrexate, azathioprine or antihistamines (e.g., diphenhydramine, hydroxyzine)
    - c. CYP3A inhibitor (e.g., erythromycin, itraconazole, ketoconazole, fluconazole, calcium channel blockers cimetidine, grapefruit or grapefruit juice)
    - d. Topical product, other than the assigned treatment (e.g., sunscreen, new brand of cosmetic or cleanser, cream, lotion, ointment, powder, or bland emollient) applied on or near the treatment area(s).
    - e. Phototherapy, e.g., PUVA, UVA or UVB therapy
    - f. Bathing, showering or swimming right after applying study treatment
    - g. Prolonged baths (i.e., longer than 5 minutes), excessive exposure to sunlight, or use of tanning booths, sun lamps or nonprescription UV light sources
    - h. Covering any treated area with bandage(s), dressing(s) or wrap(s)
    - i. Allowing the study treatment to come in contact with the eyes, nose, mouth, vagina, or rectum (mucous membranes)
  5. When applying assigned study treatment after a bath or shower, the skin should be dry. Caregivers applying study treatment to a subject, or subject who is not treating their hands should wash their hands with soap and water after applying study treatment.
  6. It is the sponsor's responsibility to include a provision in the protocol and subject consent form to ensure appropriate referral for continued therapy and follow-up of subjects according to the standard of care after the end of the study. If there is worsening during the treatment period, no improvement in the follow-up period, or signs and symptoms persist beyond the treatment period, subjects must be evaluated by a healthcare provider for careful re-evaluation, and consideration should be given to performing a skin biopsy in such cases to rule out malignancy.
  7. The primary endpoint is the proportion of subjects in the per protocol population in each treatment group with treatment success (i.e., a grade of clear or almost clear; a score of 0 or 1, within all treatment areas) based on the IGA of Disease Severity (see Table 1) at the end of treatment (week 2 visit; study Day 15). This is the earliest time at which a significant success proportion is expected. This shorter treatment duration would be most likely to detect differences between test product and reference standard and is intended to minimize systemic exposure to the drug and the potential cancer risk.

8. The secondary endpoints are change in severity from baseline to week 2 (study Day 15) of four individual signs and symptoms of AD (i.e., erythema, induration/papulation, lichenification and pruritus; see Table 2) and are considered supportive information. It is recommended that pruritus be assessed by questioning the subject or the subject's parent/legal guardian regarding the intensity of overall itching/scratching/discomfort in the 24 hours prior to the visit.

**Table 2. Individual Signs and Symptoms of AD**

<b>Erythema</b>		
0	None	No erythema present
1	Mild	Slight erythema: very light-pink
2	Moderate	Dull red, clearly distinguishable
3	Severe	Deep/dark red
<b>Induration/Papulation</b>		
0	None	None
1	Mild	Slightly perceptible elevation
2	Moderate	Clearly perceptible elevation but not extensive
3	Severe	Marked and extensive elevation
<b>Lichenification</b>		
0	None	None
1	Mild	Slight thickening of the skin discernible only by touch and with skin markings minimally exaggerated
2	Moderate	Definite thickening of the skin with skin marking exaggerated so that they form a visible criss-cross pattern
3	Severe	Thickened indurated skin with skin markings visibly portraying an exaggerated criss-cross pattern
<b>Pruritus</b>		
0	None	None
1	Mild	Occasional, slight itching/scratching
2	Moderate	Constant or intermittent itching/scratching/discomfort which is not disturbing sleep
3	Severe	Bothersome itching/scratching/discomfort which is disturbing sleep

9. If the signs and symptoms of AD resolve during treatment, subjects should continue the application of the study drug for at least 2 weeks and should not stop treatment. Subjects should not be discontinued early from the study due to lack of treatment effect. Subjects who do not show complete clearing of all lesions by the end of the study (study Day 15) should receive continuing treatment with the reference standard and appropriate follow-up according to the standard of care.
10. Provide Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
- Study identifier
  - Unique subject identifier
  - Subject identifier

- d. Study site identifier
  - e. Age
  - f. Age units (years)
  - g. Sex
  - h. Race
  - i. Name of planned treatment
  - j. Name of actual treatment
  - k. Safety population flag (yes/no)
  - l. Reason for exclusion from safety population
  - m. Modified Intent-to-Treat (mITT) population flag (yes/no)
  - n. Reason for exclusion from mITT
  - o. Per-Protocol (PP) population flag (yes/no)
  - p. Reason for exclusion from PP population
  - q. Randomized population flag (yes/no)
  - r. Date/time of first exposure to treatment
  - s. Date/time of last exposure to treatment
  - t. End of study date
  - u. End of study status
  - v. Subject required additional treatment due to unsatisfactory treatment response (yes/no)
  - w. Specific reason for use of this product (e.g., A= failure to respond adequately to other topical prescription treatments for AD, B=when those treatments are not advisable)
  - x. Location of Treatment Area (i.e., neck, elbow, knee, hand, wrist, ankle)
  - y. Size of Treatment Area (e.g., cm<sup>2</sup>)
  - z. Previous use of AD treatment (yes/no)
  - aa. Reason for premature discontinuation of subject
  - bb. Percent (%) Body Surface Area (BSA) involvement at baseline
  - cc. Percent (%) BSA involvement at study Day 15
  - dd. IGA score at baseline
  - ee. IGA score at study Day 15
  - ff. Final designation of treatment outcome (success/failure) based on IGA
  - gg. Compliance rate (%)
  - hh. Subject missed pre-specified number of scheduled doses for more than pre-specified number of consecutive days (yes/no)
  - ii. Adverse event reported (yes/no)
  - jj. Concomitant medication (yes/no)
11. 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
  - e. Name of planned treatment
  - f. Name of Actual Treatment (exposure): test product, reference standard, placebo

- g. Location of Dose Administration: application site
  - h. Safety population flag (yes/no)
  - i. Modified ITT population flag (yes/no)
  - j. PP population flag (yes/no)
  - k. Analysis visit
  - l. Analysis date
  - m. Study visit within designated window (yes/no)
  - n. IGA score
  - o. Individual signs and symptoms of AD score for erythema, induration/papulation, lichenification, and pruritus
  - p. Skin reaction score for each sign and symptom evaluated (e.g., dryness, burning/stinging, erosion, edema, pain)
  - q. Additional treatment required during the visit (yes/no)
  - r. Concomitant medication during the visit (yes/no)
  - s. Adverse event reported during the visit (yes/no)
  - t. Laboratory testing during the visit (yes/no)
12. Refer to the most recent version of the FDA product-specific guidance on *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)<sup>b</sup> for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoint.
13. Refer to the study data standards resources, <https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources>.

**Revision History:** Recommended March 2012; Revised November 2019, October 2022

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<sup>a</sup> For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

<sup>b</sup> For the most recent version of a product-specific guidance, check the FDA product-specific guidance web page at <https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm>.