Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Tacrolimus

November 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient:	Tacrolimus
Dosage Form:	Ointment
Route:	Topical
Strengths:	0.03%, 0.1%
Recommended Studies:	Two options: (1) two in vitro bioequivalence studies and other characterization tests or (2) one comparative clinical endpoint bioequivalence study

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

To demonstrate bioequivalence for tacrolimus topical ointment, 0.1% 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 (RS) that may significantly affect the local or systemic availability of the active ingredient. For example, if the test product and RS 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*[a], 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 RS 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 RS. The test

product and RS 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*[a] for additional information regarding comparative Q3 characterization tests. The comparison of the test product and RS 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 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 oleaginous components
e. Characterization of specific gravity

3. The test product and RS should have an equivalent rate of tacrolimus release based upon an acceptable in vitro release test (IVRT) bioequivalence study comparing a minimum of one batch each of the test product and RS 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: 0.1%
    Test system: A synthetic membrane in a diffusion cell system
    Analyte to measure: Tacrolimus in receptor solution
    Bioequivalence based on: Tacrolimus (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*[a] for additional information regarding the development, validation, conduct and analysis of acceptable IVRT methods/studies. The batches of test product and RS evaluated in the IVRT bioequivalence study should be included among those for which the Q3 attributes are characterized.

4. The test product and RS should have an equivalent rate and extent of tacrolimus 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 RS 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: 0.1%
    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: Tacrolimus in receptor solution
    Bioequivalence based on: Tacrolimus (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*[a] for additional information regarding the development, validation, conduct and analysis of acceptable IVPT methods/studies. The batches of test product and RS evaluated in the IVPT bioequivalence study should be the same as those evaluated in the IVRT bioequivalence study.

Waiver request for 0.03% strength: The 0.03% strength of the ointment product containing sufficient data may be approved based on (i) acceptable demonstration of bioequivalence of the 0.1% strength using the bioequivalence approach outlined within Option 1, (ii) the formulations of the lower and higher strengths of the test product are exactly the same, except for the amount of tacrolimus and the corresponding change in the amount of the diluent, and have the same manufacturing process, (iii) acceptable comparative Q3 characterization tests using a minimum of three batches of the lower strength of the test product and three batches of the higher strength of the test product; the relationship of the Q3 attributes of the two strengths of the test product should be compared to the relationship of the Q3 attributes of the two strengths of the RS, and (iv) an acceptable IVRT study with a minimum of one batch of each strength of the test product and one batch of each strength of the RS using an appropriately validated IVRT method. The release rates of tacrolimus should be proportional across all strengths.

To develop a single strength of tacrolimus topical ointment using the bioequivalence approach outlined in Option 1, all studies outlined within the characterization-based bioequivalence studies (including the IVPT study) should be performed using the single strength of the test product and RS. Refer to the most recent version of the FDA guidance for industry on *Controlled Correspondence Related to Generic Drug Development*[a] and the most recent version of the FDA guidance for industry on *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*[a] for additional information describing the procedures on how to clarify regulatory expectations regarding your individual drug development program.

II. Option 2: One comparative clinical endpoint bioequivalence study

1. Type of study: Comparative clinical endpoint bioequivalence study
   Design: Randomized, double blind, parallel, placebo-controlled, in vivo
   Strength: 0.03%
   Subjects: Non-immunocompromised male and non-pregnant, non-lactating female adults with clinical diagnosis of moderate to severe atopic dermatitis
   Additional comments: Specific recommendations are provided below.

Waiver request for 0.1% strength: The 0.1% strength of the ointment product containing sufficient data may be approved based on (i) acceptable demonstration of bioequivalence of the 0.03% strength using the bioequivalence approach outlined within Option 2, (ii) the formulations of the lower and higher strengths of the test product are exactly the same, except for the amount of tacrolimus and the corresponding change in the amount of the diluent, and have the same manufacturing process, (iii) acceptable comparative Q3 characterization tests using a minimum of three batches of the lower strength of the test product and three batches of the higher strength of the test product; the relationship of the Q3 attributes of the two strengths of the test product should be compared to the relationship of the Q3 attributes of the two strengths of the RS and (iv) an acceptable IVRT study or studies with a minimum of one batch of each strength of the test product and one batch of each strength of the RS using an appropriately validated IVRT method. The release rates of tacrolimus should be proportional across all strengths.

To develop a single strength of tacrolimus topical ointment using the bioequivalence approach outlined in Option 2, an in vivo comparative clinical endpoint bioequivalence study should be performed using the single strength of the test product and RS. Refer to the most recent version of the FDA guidance for industry on *Controlled Correspondence Related to Generic Drug Development*[a] and the most recent version of the FDA guidance for industry on *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*[a] for additional information describing the procedures on how to clarify regulatory expectations regarding your individual drug development program.

Additional comments regarding the comparative clinical endpoint bioequivalence study:

1. FDA recommends conducting a comparative clinical endpoint bioequivalence study in the treatment of moderate to severe atopic dermatitis (AD) comparing the 0.03% test product versus the 0.03% RS and vehicle control, each applied as a thin layer twice daily to the affected area(s) for 28 days (4 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 of Disease Severity (see Table 1) at the end of treatment (Study Day 29).

2. Inclusion criteria (the sponsor may add additional criteria):
   a. Non-immunocompromised male or non-pregnant, non-lactating female aged 12 years and older with a clinical diagnosis of moderate to severe 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, FDA 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 Investigator's Global Assessment (IGA) of disease severity of at least moderate at baseline (per Table 1, a score of 3 or 4).
d. Affected area of AD involvement at least 20% body surface area (BSA) at baseline as defined by the criteria of Hanifin and Rajka.[1]

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 (the 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) UVA/UVB therapy, (3) psoralen plus ultraviolet A (PUVA) therapy, (4) tanning booths, (5) non-prescription 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

[1] Hanifin JM and Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol. 1980; Suppl. 92: 44-7

i. Use within 24 hours prior to baseline of any topical product (e.g., sunscreens, lotions, creams, emollients, moisturizers) in the areas to be treated
j. Known allergy or hypersensitivity to tacrolimus or any other component of the test product or RS
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. Treatment for AD, other than assigned treatment
    b. Topical or systemic corticosteroid, topical or systemic antibiotic, topical or systemic antifungal, oral or topical antihistamine, immunosuppressive drugs, immunomodulator (e.g., pimecrolimus), 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 assigned treatment, (e.g., sunscreen, new brand of cosmetic or cleanser, cream, lotion, ointment, or powder) 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 non-prescription 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 or mouth

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 (PP) 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 Investigator's Global Assessment of Disease Severity (see Table 1) at the end of treatment (Week 4 visit; Study Day 29). 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

RS 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 4 (Study Day 29) 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

Erythema		
0	None	No erythema present
1	Mild	Slight erythema: very light-pink
2	Moderate	Dull red, clearly distinguishable
3	Severe	Deep/dark red
Induration/Papulation		
0	None	None
1	Mild	Slightly perceptible elevation
2	Moderate	Clearly perceptible elevation but not extensive
3	Severe	Marked and extensive elevation
Lichenification		
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
Pruritus		
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 4 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 29) should receive continuing treatment with the RS and appropriate follow-up according to the standard of care. Per the RS labeling, if signs and symptoms of AD do not improve within 6 weeks, subjects should be re-examined.

10. FDA recommends blood sampling for tacrolimus trough serum concentrations on Study Day 4 (prior to application of 8th dose of study treatment) as a safety measure to assure that the frequency and magnitude of measurable serum concentrations is not apparently greater with the test than with the RS. Based on previous pharmacokinetic data for tacrolimus, steady state concentrations are expected to be reached by Study Day 4, and sampling at this time would likely reflect any systemic accumulation of tacrolimus with repeated applications to the same treatment area before significant healing takes place. Available data suggest that systemic exposure decreases as the lesions heal.

    For measuring trough levels, FDA recommends the following procedures on Study Day 4:

    a. The blood should be sampled at the same time point for all patients.
    b. The blood samples should not be taken from areas treated with tacrolimus ointment.
    c. The study tube should be weighed (dose) before and after the morning dose on Study Day 4.
    d. The blood should be sampled just before the evening dose (i.e., 12 hours after the 7^{th} dose was administered in the morning) on Study Day 4.
    e. To maintain blinding, tacrolimus trough concentrations should be taken from all study patients in the test, reference and placebo groups. Blood samples from the placebo group need not be analyzed to determine tacrolimus concentrations.

    For serum concentrations obtained as a safety measure, FDA does not require the sponsor to meet the usual pharmacokinetic bioequivalence limits used to determine equivalence.

11. Application site reactions such as dryness, burning/stinging, erosion, edema, and pain are to be recorded at each visit to allow a comparison between treatment groups. 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 RS with regard to the expected and unexpected application site reactions.

12. The size of the treatment area and the site of the treatment area should be compared and tabulated for each treatment group.

13. Provide Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:

    a. Study identifier
    b. Unique subject identifier
    c. Subject identifier
    d. Study site identifier (if applicable)
    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. 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^2)
z. Previous use of AD treatment (yes/no)
aa. Reason for premature discontinuation of subject
bb. Percent (%) BSA involvement at baseline
cc. Percent (%) BSA involvement at Study Day 29
dd. IGA score at baseline
ee. IGA score at Study Day 29
ff. Date/time of tacrolimus trough blood sample
gg. Tacrolimus trough blood concentration (on Study Day 4)
hh. Weight of study drug before and after the morning dose on Study Day 4
ii. Final designation of treatment outcome (success/failure) based on IGA
jj. Compliance rate (%)
kk. Subject missed pre-specified number of scheduled doses for more than pre-specified number of consecutive days (yes/no)
ll. Adverse event reported (yes/no)
mm. Concomitant medication (yes/no)

14. 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. Name of planned treatment
    f. Name of actual treatment (exposure): test product, RS, 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)

15. Refer to the most recent version of the FDA product-specific guidance on *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)[b] for a recommended approach to statistical analysis and study design for the comparative clinical endpoint bioequivalence study.

16. 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 Nov 2013, Sep 2018, Oct 2022 (0.01% strength)
Recommended March 2012; Revised Nov 2013, Sep 2018, Oct 2022 (0.03% strength)
Merged Nov 2024

Unique Agency Identifier: PSG_050777

[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[b] For the most recent version of a product-specific guidance, check the FDA product-specific guidance website at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.