Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Roflumilast

May 2025

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Active Ingredient:	Roflumilast
Dosage Form:	Cream
Route:	Topical
Strengths:	0.15%, 0.3%
Recommended Studies:	**0.15% Strength:** Two options: (1) two in vitro bioequivalence studies and other characterization tests or (2) one in vivo bioequivalence study with pharmacokinetic endpoints and one in vivo comparative clinical endpoint bioequivalence study (atopic dermatitis). See below for possible waiver requests if evaluating bioequivalence concurrently for both strengths. **0.3% Strength**: Two options: (1) two in vitro bioequivalence studies and other characterization tests or (2) one in vivo bioequivalence study with pharmacokinetic endpoints and one in vivo comparative clinical endpoint bioequivalence study (plaque psoriasis)

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

To demonstrate bioequivalence for roflumilast topical cream, 0.3% using in vitro studies, the following criteria should be met:

1. The test product should contain no difference in inactive ingredients 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 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 particle size distribution, crystal habit, and polymorphic form of roflumilast 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 water activity
    e. Characterization of pH
    f. Characterization of specific gravity

3. The test product and RS should have an equivalent rate of roflumilast 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: 0.3%
   Test system: A synthetic membrane in a diffusion cell system
   Analyte to measure: Roflumilast in receptor solution
   Equivalence based on: Roflumilast (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 roflumilast 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: 0.3%
   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: Roflumilast in receptor solution
   Equivalence based on: Roflumilast (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 0.15% strength: The 0.15% strength of the cream product containing sufficient data may be approved based on (i) acceptable demonstration of bioequivalence of the 0.3% 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 roflumilast 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; the data should be generated using an IVRT method that is validated for both the lower and the higher strengths. The ratio of the roflumilast release rates for the two strengths of the test product should be compared to the ratio of the roflumilast release rates for the two strengths of the RS.

To only develop a roflumilast topical cream, 0.15% test product using the bioequivalence approach outlined in Option 1, all studies outlined within the characterization-based bioequivalence approach (including the IVPT study) should be performed using the 0.15% strength of the test product and the RS.

II. Option 2: One in vivo bioequivalence study with pharmacokinetic endpoints and one in vivo comparative clinical endpoint bioequivalence study

To demonstrate bioequivalence for roflumilast topical cream, **0.3%** using in vivo studies, the following criteria should be met:

1. Type of study: Comparative clinical endpoint bioequivalence study
   Design: Randomized, double-blind, parallel-group, placebo-controlled, in vivo
   Strength: 0.3%
   Subjects: Males and non-pregnant, non-lactating females (age ≥18 years) with a clinical diagnosis of plaque psoriasis
   Additional comments: Specific recommendations are provided below.

2. Type of study: In vivo bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 0.3%
   Subjects: Healthy males and non-pregnant, non-lactating females
   Analytes to measure: Roflumilast and roflumilast N-oxide in plasma
   Equivalence based on: Roflumilast in plasma
   Additional comments: Females of reproductive potential should use non-hormonal contraception during the study. The applied dose for the study should be selected to be within the currently approved dosage regimen. Specify the application dose and site in the protocol and ensure that the dose can be consistently applied in all subjects across the study. The bioanalytical method should be sufficiently sensitive to be able to adequately characterize the pharmacokinetic profiles of the test product and RS. If roflumilast (parent drug) concentrations are too low to allow reliable analytical measurement in plasma for an adequate length of time, roflumilast N-oxide (metabolite) data obtained from these studies should be subject to the confidence interval approach for bioequivalence demonstration. Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of roflumilast. Alternatively, a parallel study design may be considered.

Additional comments regarding the comparative clinical endpoint bioequivalence study for the 0.3% strength:

1. FDA recommends conducting a comparative clinical endpoint bioequivalence study in the treatment of stable plaque psoriasis comparing the 0.3% test product versus the 0.3% RS and vehicle control, each applied to the affected areas once daily. The primary endpoint is the proportion of subjects with treatment success (defined as an Investigator Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) with a minimum 2-grade improvement from baseline at the end of treatment (Week 8; Study Day 56)).

2. Inclusion criteria (the sponsor may add additional criteria):
    a. Male or non-pregnant, non-lactating female adults (age ≥18 years) with a clinical diagnosis of stable (at least 6 months) plaque psoriasis involving 2% to 20% body surface area (BSA), not including the face, scalp, palms, and soles in the BSA calculation.
    b. An IGA score of 2 (mild), 3 (moderate), or 4 (severe) as shown in Table 1.

Table 1. IGA of Disease Severity

Score	Grade	Definition
0	Clear	No evidence of scaling; no evidence of erythema; no evidence of plaque elevation above normal skin level
1	Almost clear	Some plaques with fine scales; faint pink/light red erythema on most plaques slight or barely perceptible elevation of plaques above normal skin level
2	Mild	Most to all plaques have some fine scales but are not fully covered, some plaques are completely covered with fine scale; most to all plaques are pink/light red to bright red in color; some plaques have definite elevation above normal skin level, typically with edges that are indistinct and sloped on some of the plaques
3	Moderate	Some plaques are at least partially covered with a coarse scale, most to all plaques are nearly covered with fine or course scale; most to all plaques are bright red, some plaques may be dark red in color; definite elevation of most to all plaques; rounded or sloped edges on most of the plaques
4	Severe	Most or all plaques are covered with coarse, thick scales; most or all plaques are bright, dark or dusky red; almost all plaques are raised and well-demarcated; sharp edges on virtually all plaques

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. Females of reproductive potential who do not agree to utilize an effective method of contraception throughout the study.
    b. Current diagnosis of unstable forms of psoriasis in the treatment area, including guttate, erythrodermic, exfoliative or pustular psoriasis.
    c. Other inflammatory skin disease in the treatment area that may confound the evaluation of the plaque psoriasis (e.g., atopic dermatitis, contact dermatitis, tinea corporis).

d. Presence of pigmentation, extensive scarring, or pigmented lesions in the treatment areas, which could interfere with the rating of efficacy parameters.
e. History of psoriasis unresponsive to topical treatments.
f. History of hypersensitivity to any component of the test product or RS.
g. Moderate to severe liver impairment (Child-Pugh B or C).
h. Current immunosuppression.
i. Use within one month or within 5 half-lives (whichever is longer) prior to baseline of: (1) systemic steroids, (2) systemic antibiotics, (3) systemic antipsoriatic treatment, (4) psoralen plus ultraviolet A (PUVA) therapy, (5) ultraviolet B (UVB) therapy, (6) systemic anti-inflammatory agents or immunosuppressive drugs or (7) oral roflumilast or other oral or topical phosphodiesterase-4 inhibitors.
j. Use within 2 weeks prior to baseline of: (1) topical antipsoriatic drugs (e.g., salicylic acid, anthralin, coal tar, calcipotriene, tazarotene), (2) topical corticosteroids, or (3) topical retinoids.

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. Topical product other than the assigned treatment (including moisturizers, new brands of make-up, creams, ointments, lotions, powders, or bland emollients) applied on or near the treatment area.
    b. Topical or systemic antipsoriatic treatment (e.g., anthralin, coal tar, tazarotene, retinoids, tacalcitol, infliximab, adalimumab, alefacept, PUVA therapy, UVB therapy).
    c. Topical or systemic corticosteroids.
    d. Immunosuppressive drugs.
    e. Initiation of or changes to non-antipsoriatic concomitant medication that could affect psoriasis (e.g., beta blockers, lithium) during the study.
    f. Tanning booths, sun lamps, or nonprescription UV light sources.
    g. Phototherapy.
    h. The treated areas should not be bandaged, covered, or wrapped as to be occlusive.
    i. Subjects should be instructed to minimize exposure to natural sunlight, to not allow the cream to come in contact with the eyes, mouth, or vagina, and to always wash hands thoroughly after use.

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

6. 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.

7. Refer to the Study Data Standards Resources website https://www.fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources.

To demonstrate bioequivalence for roflumilast topical cream, **0.15%** using in vivo studies, the following criteria should be met:

1. Type of study: Comparative clinical endpoint bioequivalence study
   Design: Randomized, double blind, parallel, placebo-controlled, in vivo
   Strength: 0.15%
   Subjects: Males and non-pregnant, non-lactating female adults (age ≥18 years) with clinical diagnosis of mild to moderate atopic dermatitis
   Additional comments: Specific recommendations are provided below.

2. Type of study: In vivo bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, two treatment, two-period crossover in vivo
   Strength: 0.15%
   Subjects: Healthy males and non-pregnant, non-lactating females
   Analytes to measure: Roflumilast and roflumilast N-oxide in plasma
   Equivalence based on: Roflumilast in plasma
   Additional comments: Females of reproductive potential should use non-hormonal contraception during the study. The applied dose for the study should be selected to be within the currently approved dosage regimen. Specify the application dose and site in the protocol and ensure that the dose can be consistently applied in all subjects across the study. The bioanalytical method should be sufficiently sensitive to be able to adequately characterize the pharmacokinetic profiles of the test product and RS. If roflumilast (parent drug) concentrations are too low to allow reliable analytical measurement in plasma for an adequate length of time, roflumilast N-oxide (metabolite) data obtained from these studies should be subject to the confidence interval approach for bioequivalence demonstration. Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of roflumilast. Alternatively, a parallel study design may be considered.

Waiver request for 0.15% strength: The 0.15% strength of the cream product containing sufficient data may be approved without conducting an in vivo bioequivalence study with pharmacokinetic endpoints using the 0.15% strength of the proposed test product. This would be based on: (i) the formulations of the lower and higher strengths of the test product are exactly the same, except for the amount of roflumilast and the corresponding change in the amount of the diluent, and have the same manufacturing process, (ii) acceptable in vivo bioequivalence study with pharmacokinetic endpoints on the 0.3% strength, and (iii) acceptable comparative clinical endpoint bioequivalence studies on both the 0.15% strength and the 0.3% strength.

Additional comments regarding the comparative clinical endpoint bioequivalence study for the 0.15% strength:

1. FDA recommends conducting a comparative clinical endpoint bioequivalence study in the treatment of mild to moderate atopic dermatitis (AD) comparing the 0.15% test product versus the 0.15% RS and vehicle control, each applied once 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 IGA of Disease Severity (see Table 2) at the end of treatment (Study Day 29).

2. Inclusion criteria (the sponsor may add additional criteria):
    a. Male or non-pregnant, non-lactating female aged at least 18 years with a clinical diagnosis of mild to moderate AD
    b. Had a diagnosis of AD for at least 3 months
    c. An IGA of disease severity of at least mild to moderate at baseline (per Table 2, a score of 2 or 3)
    d. Affected area of AD involvement of up to 20% BSA at baseline as defined by the criteria of Hanifin and Rajka[1]

Table 2. IGA of Disease Severity

Score	Grade	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. Females of reproductive potential who do not agree to utilize an effective method of contraception throughout the study.
    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. Moderate to severe liver impairment (Child-Pugh B or C)

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

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, (10) pimecrolimus, or (11) oral roflumilast or other oral or topical phosphodiesterase-4 inhibitors
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, emollients, moisturizers) in the areas to be treated
j. Known allergy or hypersensitivity to roflumilast 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, 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., 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, 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 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. 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.

6. 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 a lack of treatment effect. Subjects who do not show complete clearing of all lesions by the end of the study (Day 29) should receive continuing treatment with the RS and appropriate follow-up according to the standard of care.

7. 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. 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)

8. 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, vehicle control
    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)

9. 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.

10. Refer to the study data standards resources, https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

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[a] 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.
[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.