*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

**Draft Guidance on Roflumilast**

**December 2025**

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| **Active Ingredient:** | Roflumilast |
| **Dosage Form:** | Foam |
| **Route:** | Topical |
| **Strength:** | 0.3% |
| **Recommended Studies:** | Two options: (1) two in vitro bioequivalence studies and other characterization tests or (2) one in vivo bioequivalence study with pharmacokinetic endpoints and one comparative clinical endpoint bioequivalence study |

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

To demonstrate bioequivalence for roflumilast topical foam, 0.3% 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 comparative Q3 characterization should be conducted with the uncollapsed foam of the test product and RS and the collapsed foam of the test product and RS.

The comparison of the uncollapsed foam 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
    i. Microscopic examination with representative high-resolution microscopic images at multiple magnifications
c. Characterization of spreadability, if feasible
d. Characterization of foam decay
    i. Analysis of time to break (until complete foam collapse)
    ii. Analysis of foam volume over time
    iii. Analysis of bubble size distribution (at a minimum of two time points)
e. Characterization of drying rate
f. Characterization of foam relative density

The environmental conditions (i.e., temperature and relative humidity) used for conducting the Q3 characterization tests of the uncollapsed foam should be consistent between the test product and RS and maintained throughout testing. Applicants should conduct the time to break analysis at a minimum of three temperatures selected within or near the storage (e.g., 25 ºC) and use (e.g., 32 ºC) temperature range of the drug product. Other Q3 characterization tests on the uncollapsed foam may be conducted at one of the selected temperatures. Rationale for the selected temperature(s) and relative humidity should be provided.

The comparison of the collapsed foam 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
    i. Microscopic examination with representative high-resolution microscopic images at multiple magnifications
    ii. Analysis of particle size distribution, crystal habit, and polymorphic form of roflumilast in the drug product, as applicable
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:

i. 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).
ii. A complete flow curve across the range of attainable shear rates, until low or high shear plateaus are identified.
iii. Yield stress values should be reported if the material tested exhibits plastic flow behavior.
iv. 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 specific gravity
e. Characterization of pH

The methodology and environmental conditions for preparation of the collapsed foam should be consistent between the test product and RS across the Q3 characterization tests, the IVRT bioequivalence study, and the IVPT bioequivalence study. Rationale for the selected temperature and relative humidity should be provided.

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. The collapsed foam should be used for dosing in the IVRT bioequivalence study. The methodology and environmental conditions for preparation of the collapsed foam should be consistent between the test product and RS across the Q3 characterization tests, the IVRT bioequivalence study, and the IVPT bioequivalence study.

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. The collapsed foam should be used for dosing in the IVPT bioequivalence study. The methodology and environmental conditions for preparation of the collapsed foam should be consistent between the test product and RS across the Q3 characterization tests, the IVRT bioequivalence study, and the IVPT bioequivalence study.

If challenges arise (for example, with preparation of the collapsed foam samples due to the presence of aggregates and/or agglomerates under Option 1 or with the conduct of the IVRT and IVPT study), applicants should 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 the applicants' individual drug development program.

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

To demonstrate bioequivalence for roflumilast topical foam, 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 of the scalp
   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:**

1. FDA recommends conducting a comparative clinical endpoint bioequivalence study in the treatment of stable plaque psoriasis of the scalp comparing the test product versus the RS and vehicle control, each applied to the affected areas of the scalp 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 4; Study Day 28)).

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 of the scalp involving at least 10% of the scalp and clinical signs of plaque psoriasis on the body, not including the palms and soles. The percent body surface area (%BSA) affected by psoriasis across the scalp and body should be no greater than 25%. Non-scalp BSA should not exceed 20%.
    b. An IGA score of 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 |
| 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 on the scalp, including guttate, erythrodermic, exfoliative or pustular psoriasis.
    c. Other inflammatory skin disease on the scalp that may confound the evaluation of the plaque psoriasis of the scalp (e.g., atopic dermatitis, contact dermatitis, tinea capitis).
    d. Presence of pigmentation, extensive scarring, or pigmented lesions or sunburn on the scalp, 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 foam to come in contact with the eyes, mouth, or vagina, and to always wash hands thoroughly after use.

5. BSA percentage and distribution, as well as the scalp surface area affected with psoriasis, should be recorded at baseline.

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

7. 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.

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

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[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.