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**Draft Guidance on Calcipotriene**

**October 2022**

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**Active Ingredient:** Calcipotriene

**Dosage Form; Route:** Ointment; 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 calcipotriene topical ointment, 0.005% 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*[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 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*[a] 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 calcipotriene 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 oleaginous components
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 calcipotriene 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: 0.005%
    Test system: A synthetic membrane in a diffusion cell system
    Analyte to measure: Calcipotriene in receptor solution
    Equivalence based on: Calcipotriene (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 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 calcipotriene 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: 0.005%
   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: Calcipotriene in receptor solution
   Equivalence based on: Calcipotriene (IVPT endpoints: total cumulative amount (AMT) and maximum flux (Jmax))
   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 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: 0.005%
   Subjects: Males and non-pregnant, non-lactating females with clinical diagnosis of plaque psoriasis
   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 stable plaque psoriasis comparing the test product versus the reference standard and placebo control, each administered once daily to the affected area for 56 days (8 weeks). The two co-primary endpoints are the proportions of subjects with treatment success on the Physician's Global Assessment (PGA) and clinical success on the Psoriasis Area Severity Index (PASI) scale at the end of treatment (Study Day 56).

2. Inclusion Criteria (the sponsor may add additional criteria):
   a. Male or non-pregnant, non-lactating females with a clinical diagnosis of stable (at least 3 months) plaque-type psoriasis involving 5 to 20% body surface area (BSA), not including the face, scalp, groin, hands, and feet.
   b. A PGA of disease severity of at least moderate disease severity (grade ≥ 3, per Table 1).

c. A minimum plaque elevation of at least moderate severity (grade ≥ 3, per Table 2) at the target lesion site. The most severe lesion at baseline should be identified as the target lesion.

3. BSA percentage is no longer requested as an individual component sign in the PASI scale but the BSA percentage and distribution should be recorded at baseline.

**Table 1. PGA of Disease Severity**

| Score | Grade | Definition |
|---|---|---|
| 0 | None | No plaque elevation above normal skin level; may have residual non-erythematous discoloration; no psoriatic scale |
| 1 | Minimal | Essentially flat with possible trace elevation; faint erythema; no psoriatic scale |
| 2 | Mild | Slight but definite elevation of plaque above normal skin level; may have up to moderate erythema (red coloration); fine scales with some lesions partially covered |
| 3 | Moderate | Moderate elevation with rounded or sloped edges to plaque; moderate erythema (red coloration); somewhat coarse scales with most lesions partially covered |
| 4 | Severe | Marked elevation with hard, sharp edges to plaque; severe erythema (very red coloration); coarse, thick scales with virtually all lesions covered and a rough surface |
| 5 | Very Severe | Very marked elevation with very hard, sharp edges to plaque; very severe erythema (extreme red coloration); very coarse, thick scales with all lesions covered and a very rough surface |

**Table 2. Severity of PASI at the Target Lesion Site**

| Score | Grade | Erythema | Scaling | Plaque Elevation |
|---|---|---|---|---|
| 0 | Clear | No evidence of erythema | No evidence of scaling | No evidence of plaques above normal skin level |
| 1 | Almost Clear | Pink discoloration, minimal erythema | Occasional fine scales hardly noticeable | Slight, just discernable elevation above normal skin level |
| 2 | Mild | Light red coloration | Slight but definite roughness, fine scale present, no cracking | Discernable elevation above normal skin level upon examination, but not pronounced |
| 3 | Moderate | Moderate redness, but not dark | Moderate roughness, somewhat coarse scaling | Definite plaque formation with rounded/sloped edges to plaque |
| 4 | Severe | Dark red coloration | Marked roughness, coarse/thick scaling, cracking may be evident | Marked elevation with hard, distinct edges to plaque |
| 5 | Very | Very dark red | Very thick scales | Very marked elevation, |

| | | | | |
|---|---|---|---|---|
| | Severe | coloration with induration present | covering extensive area severe cracking/fissures may be evident | very hard and sharp edges to plaque |

4. Exclusion Criteria (the sponsor may add additional criteria):
    a. Females who are pregnant, breast feeding, or planning a pregnancy.
    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 reference standard.
    g. Current or past history of hypercalcemia, vitamin D toxicity, severe renal insufficiency, or severe hepatic disorders.
    h. Current immunosuppression.
    i. Use within one month 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, or 6) systemic anti-inflammatory agents.
    j. Use within 2 weeks prior to baseline of: 1) topical anti-psoriatic drugs (e.g., salicylic acid, anthralin, coal tar, calcipotriene, tazarotene), 2) topical corticosteroids, 3) immunosuppressive drugs (e.g., tacrolimus, pimecrolimus), or 4) topical retinoids.

5. 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, and powders) 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. Calcium supplements.
    f. More than 400 IU/day of vitamin D or vitamin D analogs.
    g. Initiation of or changes to non antipsoriatic concomitant medication that could affect psoriasis (e.g., beta blockers, lithium) during the study.
    h. Tanning booths, sun lamps, or nonprescription UV light sources.
    i. Phototherapy.
    j. The treated areas should not be bandaged, covered or wrapped as to be occlusive.

k. Subjects should be instructed to minimize exposure to natural sunlight, to not allow the ointment to come in contact with the face or eyes and to always wash hands thoroughly after use.

6. The recommended co-primary endpoints are both:
    a. The proportion of subjects in each treatment group with treatment success (defined as absent or very mild disease, a score of 0 or 1, within the treatment area) on the PGA of disease severity at the Week 8 visit. (Study Day 56)
    b. The proportion of subjects in each treatment group with clinical success (defined as absent or mild, a score of 0 or 1, at the target lesion site) on the PASI at the Week 8 visit (Study Day 56). Each psoriatic sign of scaling, erythema, and plaque elevation should have a score of 0 or 1 at Week 8 (Study Day 56) for the subject to be considered a success. The target lesion is to be identified at baseline as the most severe lesion.

7. Due to the possibility of elevated serum calcium levels with calcipotriene absorption, serum calcium, serum albumin and albumin-corrected serum calcium levels should be included in serum chemistry analysis. Subjects with elevation in serum calcium outside the normal range should be discontinued from the study. The serum calcium level should be corrected for serum albumin level as follows:

    "corrected" serum calcium=serum calcium mg/dL + (0.8 x[4.0-albumin g/dL])

8. Calcium levels of subjects in study treatment groups should be evaluated to ensure similar effects are seen with both active treatments. The number of subjects with elevated serum calcium levels and the mean albumin corrected calcium levels at baseline and at Week 8 should also be compared in all study treatment groups.

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

10. 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 bioequivalence studies with clinical endpoint.

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

**Revision History:** Recommended August 2010; Revised September 2010, February 2019, October 2022

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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 web page at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.