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*Draft – Not for Implementation*

**Draft Guidance on Betamethasone Dipropionate; Calcipotriene**

**October 2022**

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**Active Ingredient:** Betamethasone dipropionate; Calcipotriene

**Dosage Form; Route:** Ointment; topical

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

## I. Option 1: Two in vitro bioequivalence studies, one in vivo (vasoconstrictor) bioequivalence study with pharmacodynamic endpoint, and other characterization tests

To demonstrate bioequivalence for betamethasone dipropionate and calcipotriene topical ointment, 0.064%; 0.005% using a combination of in vitro studies and in vivo vasoconstrictor 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 respective particle size distribution, crystal habit, and polymorphic form of drug substance(s) in the drug product
    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.
    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: 0.064%; 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: 0.064%; 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 ($J_{max}$))
   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 reference standard evaluated in the IVPT bioequivalence study should be the same as those evaluated in the IVRT bioequivalence study.

5. The test product and reference standard should demonstrate bioequivalence of betamethasone dipropionate based upon an acceptable in vivo vasoconstrictor study with one batch each of the test product and reference standard. The batches of test product and reference standard evaluated in the vasoconstrictor study should be the same as those evaluated in the IVRT and IVPT studies.

   A. Type of study: Pilot vasoconstrictor study
      Design: A pilot dose duration-response study using the reference standard
      Strength: 0.064%; 0.005%
      Subjects: Males and non-pregnant, non-lactating females, general population
      Additional comments: Refer to the most recent version of the FDA guidance for industry on *Topical Dermatological Corticosteroids: In Vivo Bioequivalence*.[a]

   B. Type of study: Pivotal vasoconstrictor bioequivalence study
      Design: A pivotal bioequivalence study
      Strength: 0.064%; 0.005%
      Subjects: Males and non-pregnant, non-lactating females, general population
      Additional comments: See comments above.

Applicants intending to propose an alternative approach (e.g., only in vitro studies by which to demonstrate the bioequivalence of betamethasone dipropionate) 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 your individual drug development program.

## II. Option 2: One in vivo (vasoconstrictor) bioequivalence study with pharmacodynamic endpoint and one in vivo bioequivalence study with clinical endpoint

1. A. Type of study: Pilot vasoconstrictor study
   Design: A pilot dose duration-response study using the reference standard
   Strength: 0.064%; 0.005%
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: Refer to the most recent version of the FDA guidance for industry on *Topical Dermatological Corticosteroids: In Vivo Bioequivalence*.[a]

   B. Type of study: Pivotal vasoconstrictor bioequivalence study
   Design: A pivotal bioequivalence study
   Strength: 0.064%; 0.005%
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: See comments above.

2. Type of study: Bioequivalence study with clinical endpoint
   Design: Randomized, double blind, parallel, placebo-controlled, in vivo
   Strength: 0.064%; 0.005%
   Subjects: Males and non-pregnant, non-lactating females with clinical diagnosis of psoriasis vulgaris (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 psoriasis vulgaris comparing the test product versus the reference standard and vehicle control, each applied once daily as an adequate layer to the affected area(s) for 28 days (4 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 target lesion site at the Week 4 visit (Study Day 29).

2. Inclusion Criteria (the sponsor may add additional criteria):
   a. Males or non-pregnant, non-lactating females aged at least 18 years with a clinical diagnosis of stable (at least 6 months) psoriasis vulgaris involving 5% to 30% body surface area (BSA).

b. A PGA of disease severity of at least moderate disease severity (grade ≥ 3, per Table 1).
c. A 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.

**Table 1. Physician's Global Assessment (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; no erythema |
| 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 Psoriasis Area Severity Index (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 | Discernable elevation above normal skin level upon examination, but |

| | | | | |
|---|---|---|---|---|
| | | | cracking | 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 Severe | Very dark red coloration with induration present | Very thick scales covering extensive area severe cracking/fissures may be evident | Very marked elevation, very hard and sharp edges to plaque |

3. Exclusion Criteria (the sponsor may add additional criteria):
    a. Females who are pregnant, breast feeding, or planning a pregnancy
    b. Females of childbearing potential who do not agree to utilize an adequate form of contraception
    c. Current diagnosis of unstable forms of psoriasis in the treatment area, including guttate, erythrodermic, exfoliative or pustular psoriasis
    d. Other inflammatory skin disease in the treatment area that may confound the evaluation of the psoriasis vulgaris (e.g., atopic dermatitis, contact dermatitis, tinea corporis)
    e. Presence of pigmentation, extensive scarring, pigmented lesions or sunburn in the treatment areas, which could interfere with the rating of efficacy parameters
    f. History of psoriasis unresponsive to topical treatments
    g. History of hypersensitivity to any component of the test product or reference standard
    h. Current or past history of hypercalcemia, vitamin D toxicity, severe renal insufficiency, or severe hepatic disorders
    i. Current immunosuppression
    j. Use within six months prior to baseline of biologic treatment for psoriasis (e.g., infliximab, adalimumab, alefacept)
    k. Use within three months prior to baseline of: 1) chemotherapy, or 2) radiation therapy
    l. Use within two months prior to baseline of: 1) immunosuppressive drugs (e.g., tacrolimus, pimecrolimus), or 2) oral retinoids
    m. Use within one month prior to baseline of: 1) systemic steroids, 2) systemic antibiotics, 3) other systemic antipsoriatic treatment, 4) PUVA therapy, 5) UVB therapy, or 6) systemic anti-inflammatory agents
    n. 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, or 3) topical retinoids

4. 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.

5. 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])

6. Calcium levels of subjects should be compared between study treatment groups to ensure that 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 4 should also be compared in all study treatment groups.

7. 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(s)) on the PGA of disease severity at the Week 4 visit (Study Day 29).
   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 4 visit (Study Day 29). Each psoriatic sign of scaling, erythema, and plaque elevation should have a score of 0 or 1 at Week 4 (Study Day 29) for the subject to be considered a success. The target lesion is to be identified at baseline as the most severe lesion.

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

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 bioequivalence studies with clinical endpoint.

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