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**Draft Guidance on Diclofenac Sodium**

**October 2022**

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**Active Ingredient:** Diclofenac sodium

**Dosage Form; Route:** Gel; topical

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

## I. Option 1: One in vitro bioequivalence study and other characterization tests

To demonstrate bioequivalence for diclofenac sodium topical gel, 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 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
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 pH
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 diclofenac sodium 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: 3%
    Test system: A synthetic membrane in a diffusion cell system
    Analyte to measure: Diclofenac in receptor solution
    Equivalence based on**:** Diclofenac (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.

## II. Option 2: 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: 3%
   Subjects: Immunocompetent males and non-pregnant, non-lactating females with clinically typical, visible, nonhyperkeratotic, and nonhypertrophic actinic keratoses (AK) on the face or bald scalp
   Additional comments: Specific recommendations are provided below.

**Additional comments regarding the bioequivalence study with clinical endpoint:**

1. FDA recommends conducting a bioequivalence study with clinical endpoint in the treatment of AK of the face or bald scalp. Subjects are to be randomized to receive the test product, reference standard, or placebo (vehicle) twice daily for 60 days. Enough gel should be used to adequately cover each lesion. Generally, 0.5 gram of gel is used to cover one contiguous 25-$cm^2$ treatment area. Hand washing before and after gel application is recommended. The primary endpoint is to be evaluated at Study Day 90 (30 days after completion of 60 days of treatment).

2. Inclusion Criteria (the sponsor may add additional criteria):
   a. Immunocompetent male or non-pregnant, non-lactating female at least 18 years of age with at least five (5) and no more than ten (10) clinically typical, visible, discrete, nonhyperkeratotic, nonhypertrophic AK lesions, each at least 4 mm in diameter, contained within a 25-$cm^2$ treatment area located on the face or bald scalp.

3. Exclusion Criteria (the sponsor may add additional criteria):
   a. Active gastrointestinal ulceration or bleeding
   b. Severe renal or hepatic impairment
   c. Presence of atopic dermatitis, basal cell carcinoma, eczema, psoriasis, rosacea, squamous cell carcinoma, sunburn or other possible confounding skin conditions on face or bald scalp
   d. Use within 6 months prior to randomization of oral isotretinoin
   e. Use within 6 months prior to randomization on the face or bald scalp of 1) chemical peel, 2) dermabrasion, 3) laser abrasion, 4) PUVA (psoralen plus ultraviolet A) therapy, or 5) UVB therapy
   f. Use within 1 month prior to randomization on the face or bald scalp of 1) cryodestruction or chemodestruction, 2) curettage, 3) photodynamic therapy, 4) surgical excision, 5) topical 5-fluorouracil, 6) topical corticosteroids 7) topical diclofenac, 8) topical imiquimod, 9) topical retinoids, or 10) other treatments for AK
   g. Use within 1 month prior to randomization of 1) immunomodulators or immunosuppressive therapies, 2) interferon, 3) oral corticosteroids or 4) cytotoxic drugs

h. Known allergy or hypersensitivity to diclofenac, benzyl alcohol, polyethylene glycol monomethyl ether 350, sodium hyaluronate or other excipients in the test product or reference standard

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, sunscreen, creams, ointments, lotions, powders and new brands of make-up) applied on or near the treatment area.
    b. Any therapy for AK, such as prescription topical retinoids, topical 5-fluorouracil, topical imiquimod, topical salicylic acid, bichloroacetic acid, trichloroacetic acid, cryodestruction, chemodestruction, surgical excision, $CO_2$ laser vaporization, electrocautery, photodynamic therapy, or curettage.
    c. Immunomodulators or immunosuppressive therapies, interferon, oral corticosteroids, cytotoxic drugs, systemic corticosteroids, or topical steroids anywhere on the head.
    d. Tanning booths, sun lamps, or nonprescription UV light sources.
    e. The treated areas should not be bandaged, covered or wrapped as to be occlusive.
    f. Subjects should be instructed to avoid exposure to sunlight, to not allow the gel to come in contact with the eyes, and to not apply the gel to open skin wounds, infections or exfoliative dermatitis.

5. The recommended primary endpoint of the study is the proportion of subjects in the per protocol population with treatment success (100% clearance of all AK lesions within the treatment area) at Study Day 90 (30 days after completion of 60 days of treatment). All AK (i.e., baseline AK and any new AK) within the treatment area are to be treated and included in the efficacy lesion count for each visit.

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 bioequivalence studies with clinical endpoint.

7. 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.