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Draft Guidance on Fluorouracil

October 2022

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Active Ingredient: Fluorouracil

Dosage Form; Route: Cream; 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 fluorouracil topical cream, 4% 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 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 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 fluorouracil 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: 4%
    Test system: A synthetic membrane in a diffusion cell system
    Analyte to measure: Fluorouracil in receptor solution
    Equivalence based on: Fluorouracil (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 fluorouracil 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: 4%
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: Fluorouracil in receptor solution
Equivalence based on: Fluorouracil (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.

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: 4%
Subjects: Males and non-pregnant, non-lactating females with clinically typical, visible, actinic keratosis (AK) on the face, ears or bald scalp.
Additional comments: Specific recommendations are provided below.

Additional comments regarding the bioequivalence study with clinical endpoint:

1. Submission of an investigational new drug application is required prior to conducting a bioequivalence study for a cytotoxic drug product such as fluorouracil (see 21 CFR 320.31).

2. FDA recommends conducting a bioequivalence study with a clinical endpoint in the treatment of AK. Subjects are to be randomized to receive the test fluorouracil cream, 4% product, the reference standard, or placebo vehicle. The study drug is to be applied once daily for 4 weeks with an amount of cream sufficient to cover the lesions. Prior to application of the study drug, wash, rinse, and dry the treatment areas. The study drug is to be applied to the entire designated treatment areas, avoiding the eyes, eyelids, nose, mouth or mucous membranes. If applied with the fingers, the hands should be washed immediately afterward. For safety reasons, applications should be discontinued at the first sign of epidermal erosion.

3. Inclusion Criteria
    a. Males and non-pregnant, non-lactating females ≥18 years of age with at least five (5) to ten (10) clinically typical, visible, discrete, AK lesions, each at least 4 mm in diameter on the face, ears or bald scalp

4. Exclusion Criteria
    a. Presence of atopic dermatitis, basal cell carcinoma, eczema, psoriasis, rosacea, squamous cell carcinoma, or other possible confounding skin conditions on the face ears, or bald scalp
    b. Use within 6 months prior to baseline on the face, ears or bald scalp of 1) chemical peel, 2) dermabrasion, 3) laser abrasion, 4) psoralen plus ultraviolet A therapy, or 5) ultraviolet B therapy
    c. Use within 1 month prior to baseline on the face, ears or 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
    d. Use within 1 month prior to baseline of 1) immunomodulators or immunosuppressive therapies, 2) interferon, 3) oral corticosteroids or 4) cytotoxic drugs
    e. Known allergies to fluorouracil or any excipients in the test product or reference standard
    f. Known dihydropyrimidine dehydrogenase enzyme deficiency

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. Any therapy for AK, such as prescription topical retinoids, topical imiquimod, topical diclofenac, topical salicylic acid, bichloroacetic acid, trichloroacetic acid, cryodestruction, chemodestruction, surgical excision, CO2 laser vaporization, electrocautery, photodynamic therapy, or curettage
    b. Topical steroids anywhere on the head
    c. Immunomodulators or immunosuppressive therapies, interferon, cytotoxic drugs, or systemic corticosteroids
    d. Tanning booths or non-prescription ultraviolet light sources

6. Subjects should not apply moisturizers, make-up, creams, lotions, powders or any topical product other than the assigned treatment to the treatment area. Subjects should avoid exposure to sunlight and avoid the use of sunlamps. Sunscreens may be applied after application of the product to prevent patients from photosensitivity reactions of topical fluorouracil (e.g., severe sunburn). They should not use any type of bandage or occlusive dressing on the treatment area, not allow the cream to come in contact with the eyes, eyelids, nose, mouth or mucous membranes, and not apply the cream to open skin wounds, infections or exfoliative dermatitis.

7. The 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 Week 8 (4 weeks after completion of 4 weeks 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.

8. 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.

9. 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.