

## Draft Guidance on Fluorouracil

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

**Active Ingredient:** Fluorouracil

**Dosage Form; Route:** Cream; topical

**Recommended Studies:** One study

Type of study: Bioequivalence Study with Clinical Endpoint

Design: Randomized, double blind, parallel, placebo controlled, in vivo

Strength: 1%

Subjects: Males and nonpregnant, nonlactating females with clinically typical, visible, actinic keratoses (AK) on the face or bald scalp.

Additional comments: Specific recommendations are provided below.

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**Analytes to measure (in appropriate biological fluid):** Not Applicable

**Bioequivalence based on (90% CI):** Clinical endpoint

**Waiver request of in-vivo testing:** Not Applicable

**Dissolution test method and sampling times:** Not Applicable

Applicants intending to propose an alternative approach by which to demonstrate bioequivalence should refer to the guidance for industry *Controlled Correspondence Related to Generic Drug Development* and the guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* for additional information describing the procedures on how to clarify regulatory expectations regarding your individual drug development program.

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

1. Submission of an Investigational New Drug Application (IND) is required prior to conducting a bioequivalence study for a cytotoxic drug product such as fluorouracil (see 21 C.F.R. § 320.31).
2. The Office of Generic Drugs (OGD) recommends conducting a bioequivalence study with a clinical endpoint in the treatment of actinic keratoses (AK). Subjects are to be randomized to receive the generic fluorouracil 1% cream (test) product, the reference product, or placebo vehicle. The study drug is to be applied twice daily for 2 weeks with

an amount of cream sufficient to cover the lesions. The study drug is to be applied to the entire designated treatment area, avoiding the eyes, eyelids, nose and mouth. 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. The primary endpoint is the proportion of subjects with treatment success (100% clearance of all AK lesions within the treatment area) at Study Week 6 (4 weeks after completion of 2 weeks of treatment).

3. Inclusion Criteria (the sponsor may add additional criteria)
  - Males and nonpregnant, nonlactating females at least 18 years of age with at least five (5) and no more than ten (10) clinically typical, visible, discrete, AK lesions, each at least 4 mm in diameter on the face or bald scalp.
4. Exclusion Criteria (the sponsor may add additional criteria)
  - a. Presence of atopic dermatitis, basal cell carcinoma, eczema, psoriasis, rosacea, squamous cell carcinoma, or other possible confounding skin conditions on the face or bald scalp.
  - b. Use within 6 months prior to baseline 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.
  - c. Use within 1 month prior to baseline on the face 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 actinic 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 or reference product.
  - f. Known dihydropyrimidine dehydrogenase (DPD) 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, CO<sub>2</sub> 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 nonprescription UV light sources.
6. Subjects should not apply moisturizers, sun screen, 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. 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, or mouth, 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 (PP) population with treatment success (100% clearance of all AK lesions within the treatment area) at Study Week 6 (4 weeks after completion of 2 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 product-specific guidance on Adapalene; Benzoyl Peroxide Topical Gel 0.3%; 2.5% for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.<sup>1</sup>
9. Study data should be submitted in a standardized format. Please refer to the study data standards published at [www.fda.gov](http://www.fda.gov)<sup>2</sup>

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<sup>1</sup> Product-Specific Guidances for Generic Drug Development available at:  
<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>

<sup>2</sup> Study Data Standards for Submission to CDER and CBER available at:  
<https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm587508.htm>