Contains Nonbinding Recommendations

Draft Guidance on Fluorouracil

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Fluorouracil

Dosage Form; Route: Cream; topical

Pharmaceutical Equivalence:
If a proposed generic drug product does not use microsphere technology, or if the formulation contains microspheres that are substantially different from that of the reference product, then perform a drug stability test in the presence of benzoyl peroxide (BPO) and UV light exposure[1] and a comparative in vitro permeation test. We recommend that you conduct the in vitro permeation test using a diffusion cell system with excised human skin, a non-occlusive system in the donor cell, a finite dosing technique, and aqueous media at physiological pH in the receptor cell. Adequately validate the model. We recommend that you utilize dermatomed skin or epidermal sections of the skin and assure the barrier integrity of the skin samples. In addition to the reference product and the generic product, we recommend that you include a third product known or designed to be different from the reference product, to serve as a positive control demonstrating the sensitivity of the assay. The skin samples used in comparative groups should be from the same piece of the skin or at least the same body site.

Recommended studies: One study

1. Type of study: Clinical Endpoint Bioequivalence Study
   Design: Randomized, double blind, parallel, placebo controlled, in vivo
   Strength: 0.5%
   Subjects: Males and nonpregnant, nonlactating females with clinically typical, visible, actinic keratosis (AK) on the face or bald scalp.
   Additional comments: Specific recommendations are provided below.

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

[1] L.H. Kircik. Microsphere Technology: Hype or Help? The Journal of Clinical and Aesthetic Dermatology 4(5): 2731 (2011)

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 clinical endpoint bioequivalence study:

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 clinical endpoint bioequivalence study in the treatment of actinic keratoses (AK). Subjects are to be randomized to receive the generic fluorouracil 0.5% cream (test) product, the reference product, or placebo vehicle. The study drug is to be applied once 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 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_2 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.[2]

9. Study data should be submitted in a standardized format. Please refer to the study data standards published at www.fda.gov[3]

[2] Product-Specific Guidances for Generic Drug Development available at: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

[3] Study Data Standards for Submission to CDER and CBER available at: https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm587508.htm