

Draft Guidance on Fluorouracil

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

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 listed drug (RLD), then perform a drug stability test in the presence of benzoyl peroxide (BPO) and UV light exposure¹ and a comparative in vitro release test to support pharmaceutical equivalence. We recommend that you conduct the in vitro release 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 RLD and the generic product, we recommend that you include a third product known or designed to be different from the RLD, 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: 1 study

1. Type of study: Clinical Endpoint Bioequivalence (BE) Study
Design: Randomized, double blind, parallel, placebo controlled, in vivo
Strength: 0.5%
Subjects: Healthy males and nonpregnant 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): 27-31 (2011)

Additional comments regarding the clinical endpoint BE 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 listed drug (RLD), or placebo vehicle. Apply the study drug once daily for 2 weeks with an amount of cream sufficient to cover the lesions. Apply the study drug to the entire designated treatment area, avoiding the eyes, eyelids, nose and mouth. If applied with the fingers, wash the hands immediately afterward. For safety reasons, discontinue application 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. A placebo control arm is recommended to demonstrate that the test product and RLD are active and as a parameter to establish that the study is sufficiently sensitive to detect differences between products.
4. Inclusion Criteria (the sponsor may add additional criteria)
 - Healthy males and nonpregnant 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.
5. 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 six 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 one month prior to baseline on the face or scalp of 1) cryodestruction or chemodestruction, 2) curettage, 3) photodynamic therapy, 4) surgical excision, 5) topical 5fluorouracil, 6) topical corticosteroids 7) topical diclofenac, 8) topical imiquimod, 9) topical retinoids, or 10) other treatments for actinic keratosis.
 - d. Use within one 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 RLD.
 - f. Known dihydropyrimidine dehydrogenase (DPD) enzyme deficiency.
6. 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 actinic keratosis, 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 nonprescription UV light sources.
7. 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.
 8. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations in the protocol.
 9. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who met all inclusion/exclusion criteria, applied a prespecified proportion of the scheduled applications (e.g. 75% to 125%) of the assigned product for the specified duration of the study, did not miss the scheduled applications for more than 3 consecutive days, and completed the evaluation within the designated visit window (+/- 4 days) with no protocol violations that would affect the treatment evaluation. The protocol should specify how compliance will be verified, e.g., by the use of subject diaries.
 10. The mITT population includes all randomized subjects who met all inclusion/exclusion criteria, applied at least one dose of assigned product, and returned for at least one post-baseline evaluation visit.
 11. The safety population includes all randomized subjects who received study product.
 12. Subjects whose condition worsens and require alternate or supplemental therapy for the treatment of AK during the study should be discontinued, included in the PP population analysis as treatment failures, and provided with effective treatment. Subjects discontinued prematurely for other reasons should be excluded from the PP population, but included in the mITT population, using Last Observation Carried Forward (LOCF).
 13. The start and stop date of concomitant medication use during the study should be provided in the dataset in addition to the reason for the medication use. The sponsor should clearly explain whether the medication was used prior to baseline visit, during the study, or both.
 14. All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution.

This information is needed to determine if the incidence and severity of adverse reactions is different between the test product and RLD.

15. Application site reactions such as erythema, dryness, burning/stinging, erosion, edema, pain and itching are to be recorded at each visit to allow a comparison between treatment groups. A descriptive analysis comparing the application site reactions for each treatment group is recommended. It is important to ensure that the test product is not worse than the reference product with regard to these expected application site reactions.
16. If the inactive ingredients are different than those contained in the RLD or in significantly different amounts, then the sponsor should clearly describe the differences and provide information to show that the differences will not affect the safety, efficacy and/or systemic or local availability of the drug.
17. The method of randomization should be described in the protocol. It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. The sponsor may generate the randomization code if not involved in the packaging and labeling of the study medication. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity for each subject.
18. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test, reference and placebo products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate blinding of evaluators. When possible, neither the subject nor the investigator should be able to identify the treatment. The containers should not be opened by the subject at the study center.
19. Refer to 21 CFR 320.38, 320.63 and the Guidance for Industry, “Handling and Retention of BA and BE Testing Samples”, regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of bioequivalence testing. In addition, the investigators should follow the procedures of 21 CFR 58 and ICH E6, “Good Clinical Practice: Consolidated Guideline”, for retention of study records and data in order to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP). Retention samples should be randomly selected from the drug supplies received prior to dispensing to subjects. Retention samples should not be returned to the sponsor at any time.
20. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.
21. 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 actinic

keratoses (i.e., baseline actinic keratoses and any new actinic keratoses) within the treatment area are to be treated and included in the efficacy lesion count for each visit.

22. To establish bioequivalence, the 90% confidence interval of the test - reference difference in the proportion of subjects with treatment success at week 6 (4 weeks after completion of 2 weeks of treatment) must be within [-0.20, +0.20], using the PP population.
23. As a parameter for determining adequate study sensitivity, the test product and RLD should both be statistically superior to placebo ($p < 0.05$; two-sided) with regard to the proportion of subjects with treatment success (100% clearance of all AK lesions within the treatment area) at week 6 (4 weeks after completion of 2 weeks of treatment) using the mITT population and LOCF.
24. The following Statistical Analysis Method is recommended for equivalence testing for a dichotomous variable (success/failure):

Equivalence Analysis

Based on the usual method used in OGD for binary outcomes, the 90% confidence interval for the difference in success proportions between the test and reference treatments must be contained within [-0.20, +0.20] in order to establish equivalence.

The compound hypothesis to be tested is:

$$H_0: p_T - p_R < -0.20 \text{ or } p_T - p_R > 0.20$$

versus

$$H_A : -0.20 \leq p_T - p_R \leq 0.20$$

where p_T = success/cure rate of test treatment p_R = success/cure rate of reference treatment.

Let

n_T = sample size of test treatment group

$c n_T$ = number of subjects with treatment success in test treatment group

n_R = sample size of reference treatment group

$c n_R$ = number of subjects with treatment success in reference treatment group

$$\hat{p}_T = c n_T / n_T, \quad \hat{p}_R = c n_R / n_R,$$

$$\text{and se} = \left(\hat{p}_T (1 - \hat{p}_T) / n_T + \hat{p}_R (1 - \hat{p}_R) / n_R \right)^{1/2}$$

Calculate the 90% confidence interval for the difference in proportions between test and reference as follows, using Yates' correction:

$$L = (\hat{p}_T - \hat{p}_R) - 1.645 \text{ se} - (1/n_T + 1/n_R)/2$$

$$U = (\hat{p}_T - \hat{p}_R) + 1.645 \text{ se} + (1/n_T + 1/n_R)/2$$

We reject H0 if $L \geq -0.20$ and $U \leq 0.20$

Rejection of the null hypothesis H0 supports the conclusion of equivalence of the two products.

25. Submit the study data to the OGD in electronic format.
 - a. A list of file names with a simple description of the content of each file, should be included. Such a list should include an explanation of the variables included in each of the data sets.
 - b. Please provide a "pdf" document with a detailed description of the codes that are used for each variable in each of the SAS datasets (for example, Y=yes, N=no for analysis population).
 - c. SAS transport files, covering all variables collected in the Case Report Forms (CRFs) per subject, should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS files should be included.
 - d. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NO-LOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set).
 - e. Please provide a separate dataset for variables such as demographics, lesion counts, vital signs, adverse events, disposition (including reason for discontinuation of treatment), concomitant medications, medical history, compliance and comments, etc.

26. Please provide a summary dataset containing a separate line listing for each subject (if data exist) using the following headings, if applicable:
 - a. Study identifier
 - b. Subject identifier
 - c. Site identifier: study center
 - d. Age
 - e. Age units (years)
 - f. Sex
 - g. Race
 - h. Name of Actual Treatment (exposure): test product, RLD, placebo control
 - i. Location of Treatment Area
 - j. Duration of Treatment (total exposure in days)

- k. Completed the study (yes/no)
- l. Reason for premature discontinuation of subject
- m. Subject required additional treatment for AK due to unsatisfactory treatment response (yes/no)
- n. Per Protocol (PP) population inclusion (yes/no)
- o. Reason for exclusion from PP population
- p. Modified Intent to Treat (mITT) population inclusion (yes/no)
- q. Reason for exclusion from mITT population
- r. Safety population inclusion (yes/no)
- s. Reason for exclusion from Safety population
- t. Size of treatment area at baseline (cm²)
- u. Size of all AK lesions within treatment area at baseline are at least 4 mm in diameter (yes/no)
- v. Total number of AK lesions in the treatment area at baseline
- w. Total number of AK lesions in the treatment area at week 2
- x. Total number of AK lesions in the treatment area at week 6
- y. Total number of new AK lesions in the treatment area at week 2
- z. Total number of new AK lesions in the treatment area at week 6
- aa. Final designation as treatment success (100% clearance of all AK lesions within the treatment area) or failure
- bb. Treatment compliance: number of missed doses per subject
- cc. Concomitant medication used after receiving the study drug (yes/no)
- dd. Adverse event(s) reported (yes/no)

Please refer to Table 1 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 1: Example of a Summary Dataset Containing One Line Listing for each Subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	EXLOC	EXDUR	completed	disc_rs	add_trt	PP	PP_rs	mitt	mitt_rs
101	1	01	54	YEARS	F	1	A	RC	14	Y		N	Y		Y	
101	2	01	58	YEARS	F	1	B	RF	14	Y		N	Y		Y	

safety	safe_rs	sizeotra	aksize_b	aknum_b	aknum_2	aknum_6	naknum_2	naknum_6	success	complan	CM	AE
Y		25	Y	4	2	0	0	0	A	0	Y	Y
Y		25	Y	8	4	2	1	0	B	0	N	N

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final dated 11/12/08.

STUDYID:	Study Identifier
SUBJID:	Subject Identifier for the Study
SITEID:	Study Site Identifier
AGE:	Age
AGEU:	Age units (years)
SEX:	Sex, e.g., M=Male, F=Female, U=Unknown
RACE:	Race, e.g., 1=White, 2=Black or African American, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or Other Pacific Islanders
EXTRT:	Name of Actual Treatment (exposure), e.g., A=test product, B= RLD, C=placebo control
EXLOC:	Location of Treatment Area, e.g. RC=right cheek, RF=right forehead, etc.
EXDUR:	Duration of Treatment (total exposure in days)
completed:	Subject completed the study, e.g., Y=Yes, N=No
disc_rs:	Reason for premature discontinuation from the study, e.g., A=adverse event, B=death, C=lost to follow-up, D=non-compliance with treatment, E=treatment unblinded, F=subject moved out of area, G=unsatisfactory treatment response, H=withdrew consent, I=protocol violation, K=other event
add_trt:	Subject required additional treatment for AK due to unsatisfactory treatment response, e.g., Y=Yes, N=No
pp:	Per Protocol (PP) population inclusion, e.g., Y=Yes, N=No
pp_rs:	Reason for exclusion from PP population, e.g., A=prematurely discontinued, B=lost to follow-up, C=subject moved out of the area, D=noncompliant, etc.
mitt:	Modified Intent to Treat (mITT) population inclusion, e.g., Y=Yes, N=No
mitt_rs:	Reason for exclusion from mITT population, e.g., A=never treated, etc.
safety:	Safety population inclusion, e.g., Y=Yes, N=No
safe_rs:	Reason for exclusion from Safety population, e.g., A=never treated, etc.
sizetrta:	Size of treatment area at baseline (cm ²)
aksize_b:	Size of all AK lesions within treatment area at baseline are at least 4 mm in diameter, e.g., Y, N (Yes or No)
aknum_b:	Total number of AK lesions in the treatment area at baseline
aknum_2:	Total number of AK lesions in the treatment area at week 2
aknum_6:	Total number of AK lesions in the treatment area at week 6
naknum2:	Total number of new AK lesions in the treatment area at week 2
naknum6:	Total number of new AK lesions in the treatment area at week 6
success:	Final designation as treatment success (100% clearance of all AK lesions within the treatment area) or failure (A=success, B=failure)
complan:	Treatment compliance, e.g., number of missed doses per subject
CM:	Concomitant medication used after receiving the study drug, e.g., Y=Yes, N=No
AE:	Adverse event(s) reported, e.g., Y=Yes, N=No

27. Please provide a dataset containing a separate line listing for each visit per subject (if data exist) using the following headers, if applicable:

- a. Study identifier
- b. Subject identifier
- c. Name of Actual Treatment (exposure): test product, RLD, placebo control
- d. Location of Dose Administration: application site
- e. Visit number
- f. Visit date
- g. Number of days since baseline visit
- h. Evaluator: identity of evaluator
- i. Total number of AK lesions
- j. Total number of new AK lesions within treatment area
- k. Skin reaction scores for each sign and symptom evaluated (e.g., erythema, dryness, burning/stinging, erosion, edema, pain, itching, etc.)
- l. Concomitant medication reported during this visit (yes/no)
- m. Adverse event reported during this visit (yes/no)
- n. Laboratory testing during this visit (yes/no)

Please refer to Table 2 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 2: Example of a Dataset Containing One Line Listing for each Visit per Subject

STUDYID	SUBJID	EXTRT	EXLOC	VISITNUM	SVSTDTC	ELTMBS	EVAL	aknum	naknum	erythema	dryness	burning	erosion	edema	pain	itching	CMrpt	AErpt	LBtest
101	1	A	RC	1	2004-07-01	1		7	1	1	0	0	1	0	0	0	Y	Y	N

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final dated 11/12/08.

- STUDYID: Study Identifier
SUBJID: Subject Identifier for the Study
EXTRT: Name of Actual Treatment (exposure), e.g. A=test product, B=RLD, C= placebo control
EXLOC: Location of Treatment Area: specific anatomical site of application, e.g., RC=right cheek, RF=right forehead, etc.
VISITNUM: Visit Sequence Number
SVSTDTC: Visit date: (SVSTDTC=Subject Visit Start Date Time-Character)
ELTMBS: Elapsed Time since Baseline (days)
EVAL: Evaluator: identity of the evaluator
aknum: Total number of AK lesions within treatment area
naknum: Total number of new AK lesions within treatment area

erythema: Skin reaction erythema score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)

dryness: Skin reaction dryness score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)

burning: Skin reaction burning score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)

erosion: Skin reaction erosion score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)

edema: Skin reaction edema score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)

pain: Skin reaction pain score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)

itching: Skin reaction itching score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)

CMrpt: Concomitant Medication reported during this visit, e.g., Y=Yes, N=No

AErpt: Adverse Event reported during this visit, e.g., Y=Yes, N=No

LBtest: Laboratory Testing performed during this visit, e.g., Y=Yes, N=No