

*Contains Nonbinding Recommendations*  
**Draft Guidance on Diclofenac Sodium**

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

**Form/Route:** Gel/Topical

**Recommended studies:** 1 study

Type of study: Bioequivalence (BE) Study with Clinical Endpoint

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

Strength: 3%

Subjects: Immunocompetent males and nonpregnant females with clinically typical, visible, non-hyperkeratotic, and nonhypertrophic 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

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

1. These recommendations are specific to this product and should not be considered adequate or appropriate for bioequivalence studies of any other product, including any other dosage form or strength of Diclofenac Sodium.
2. The Office of Generic Drugs (OGD) recommends conducting a bioequivalence study with a clinical endpoint in the treatment of actinic keratoses (AK) of the face or bald scalp. Patients are to be randomized to receive the diclofenac sodium 3% gel test product, the RLD, or placebo control. The study drug is to be applied twice daily for 60 days using enough gel to adequately cover each lesion. Generally, 0.5 gram of gel is used to cover one contiguous 25-cm<sup>2</sup> 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).
3. A placebo control arm is recommended to demonstrate that the test product and RLD are active and the study is sufficiently sensitive to detect differences between products. This is especially important when studying a disease such as AK, in which spontaneous resolution may occur.
4. Inclusion Criteria (the sponsor may add additional criteria)  
Immunocompetent male or nonpregnant 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<sup>2</sup> treatment area located on the face or bald scalp.

5. 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 six months prior to randomization of oral isotretinoin.
  - e. Use within six 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 one 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 actinic keratosis.
  - g. Use within one 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 359, hyaluronate sodium or other excipients in the test product or RLD.
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. Topical product other than the assigned treatment (including moisturizers, sun screen, creams, ointments, lotions, powders and new brands of make-up) applied on or near the treatment area.
  - b. Any therapy for actinic keratosis, such as prescription topical retinoids, topical 5-fluorouracil, topical imiquimod, topical salicylic acid, bichloroacetic acid, trichloroacetic acid, cryodestruction, chemodestruction, surgical excision, CO<sub>2</sub> 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.
7. The recommended 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 day 90 (30 days after completion of 60 days 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.
8. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations.
  - a. The PP population 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 more than 10 consecutive scheduled applications, and completed the primary endpoint 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, and the protocol violations that would affect the treatment evaluation.
- b. The mITT population includes all randomized subjects who met all inclusion/exclusion criteria, received study treatment, and returned for at least one post-baseline visit. The mITT population should be used to compare both test and reference products to placebo.
  - c. The safety population includes all randomized subjects who received study treatment.
9. 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 who are discontinued early from the study due to lack of treatment effect after completing at least four weeks of treatment should be included in the mITT and PP population as treatment failures. Subjects discontinued early for other reasons should be excluded from the PP population, but included in the mITT population, using Last Observation Carried Forward (LOCF).
  10. 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.
  11. 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 the expected and unexpected application site reactions.
  12. 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 of each subject.
  13. 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.
  14. Please 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.

15. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.
16. To establish bioequivalence, the 90% confidence interval of the test - reference difference in the proportion of subjects with treatment success at study day 90 (30 days after completion of 60 days of treatment) must be within [-0.20, +0.20] for a dichotomous variable, using the PP population.
17. As a parameter for determining adequate study sensitivity at the lower end of the dose/response curve, 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 study day 90 (30 days after completion of 60 days of treatment) using the mITT study population and LOCF.
18. 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 test and reference treatment 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 and  $p_R$  = success/cure rate of reference treatment.

Let

$n_T$  = sample size of test treatment group

$c n_T$  = number of success/cured patients in test treatment group

$n_R$  = sample size of reference treatment group

$c n_R$  = number of success/cured patients in reference treatment group

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

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

The 90% confidence interval for the difference in proportions between test and reference was calculated 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  $H_0$  if  $L \geq -0.20$  and  $U \leq 0.20$

Rejection of the null hypothesis  $H_0$  supports the conclusion of equivalence of the two products.

19. Study data should be submitted 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.
  - 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. All SAS transport files 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, baseline admission criteria, adverse events, reasons for discontinuation of treatment, concomitant medications, medical history, compliance and comments, etc.
  
20. 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
  - 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 (cm<sup>2</sup>)
  - u. Size of at least 5 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 day 60
- x. Total number of AK lesions in the treatment area at day 90
- y. Total number of new AK lesions in the treatment area at day 60
- z. Total number of new AK lesions in the treatment area at day 90
- 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 (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	completd	disc_rs	add_trt	pp	pp_rs	mitt	mitt_rs
101	1	01	54	YEARS	F	1	A	RC	60	Y		N	Y		Y	
101	2	01	58	YEARS	F	1	B	RF	60	Y		N	Y		Y	

safety	safe_rs	sizeotra	aksizeb	aknum_b	aknum60	aknum90	naknum60	naknum90	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
- EXLOC: Location of Treatment Area, e.g. RC=right cheek, RF=right forehead, F=right and left forehead, S=bald scalp, etc.
- EXDUR: Duration of Treatment (total exposure in days)
- completd: 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 <sup>2</sup> )
aksizeb:	Size of at least 5 AK lesions within treatment area at baseline are at least 4 mm in diameter, e.g., Y=Yes, N=No
aknum_b:	Total number of AK lesions in the treatment area at baseline
aknum60:	Total number of AK lesions in the treatment area at day 60
aknum90:	Total number of AK lesions in the treatment area at day 90
naknum60:	Total number of new AK lesions in the treatment area at day 60
naknum90:	Total number of new AK lesions in the treatment area at day 90
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, e.g., Y=Yes, N=No
AE:	Adverse event(s) reported, e.g., Y=Yes, N=No

21. Please provide a dataset containing a separate line listing for each visit per subject (if data exist) using the following headers, if applicable:
- Study identifier
  - Subject identifier
  - Name of Actual Treatment (exposure): test product, RLD, placebo control
  - Visit number
  - Visit date
  - Number of days since baseline visit
  - Evaluator: identity of evaluator
  - Total number of AK lesions
  - Total number of new AK lesions within treatment area
  - Skin reaction scores for each sign and symptom evaluated (e.g., erythema, dryness, burning/stinging, erosion, edema, pain, itching, etc.)
  - Concomitant medication reported during this visit (yes/no)
  - Adverse event reported during this visit (yes/no)
  - 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 dataset containing one line listing for each visit per subject**

<b>STUDYID</b>	<b>SUBJID</b>	<b>EXTRT</b>	<b>VISITNUM</b>	<b>SVSTDTC</b>	<b>ELTMBS</b>	<b>EVAL</b>	<b>aknum</b>	<b>naknum</b>	<b>erythema</b>	<b>dryness</b>	<b>burning</b>	<b>erosion</b>	<b>edema</b>	<b>pain</b>	<b>itching</b>	<b>CMrpt</b>	<b>AErpt</b>	<b>LBtest</b>
101	1	A	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  
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