

*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**Draft Guidance on Diclofenac Sodium**

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 the 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:** 2 studies

1. Type of study: Fasting  
Design: Single-dose, two-way crossover in vivo  
Strength: 1%  
Subjects: Healthy males and non-pregnant females, general population.  
Additional comments: None
  
2. Type of study: Bioequivalence (BE) Study with Clinical Endpoint  
Design: Randomized, double blind, parallel, placebo-controlled in vivo  
Strength: 1%  
Subjects: Healthy males and females with osteoarthritis of the knee.  
Additional comments: Specific recommendations are provided below.

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**Analytes to measure (in appropriate biological fluid):** Diclofenac in plasma (Study 1)

**Bioequivalence based on (90% CI):** Diclofenac (Study 1); Clinical endpoint (Study 2)

**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. The Office of Generic Drugs (OGD) recommends a bioequivalence study with clinical endpoint in the treatment of osteoarthritis (OA) of the knee. Subjects are to be randomized to receive an approximately 4 gram dose of the generic Diclofenac Sodium topical gel, 1%, the reference listed drug (RLD), or placebo applied to the arthritic knee four times daily for 4 weeks. The primary endpoint is to be evaluated at the end of treatment (study Week 4).
  
2. Inclusion Criteria (the sponsor may add additional criteria):
  - a. Healthy male or nonpregnant female aged  $\geq 35$  years with a clinical diagnosis of OA of the knee according to the American College of Rheumatology (ACR) criteria, including:
    - i. Symptoms for at least 6 months prior to screening, AND
    - ii. Knee (not referred) pain for 15 days of the preceding month (periarticular knee pain due to OA and not due to other conditions such as bursitis, tendonitis, etc.), AND
    - iii. The pain in the target knee required the use of NSAIDs or acetaminophen (topical or oral treatments).

- b. Had an X-ray of the target knee, taken no more than 1 year before baseline, showing evidence of OA with Kellgren-Lawrence grade 1-3 disease.
  - c. After discontinuing all pain medications for at least 7 days, had at least moderate pain on movement (POM) for target knee, defined as a baseline score of  $\geq 50$  mm on a 0-100 mm Visual Analog Scale (VAS) immediately prior to randomization, AND a baseline Western Ontario McMaster Osteoarthritis (WOMAC) pain subscale of at least 9 immediately prior to randomization.
  - d. Able to tolerate rescue medication with acetaminophen.
3. Exclusion Criteria (the sponsor may add additional criteria):
- a. Pregnant or lactating or planning to become pregnant during the study period.
  - b. X-ray showing evidence of OA with Kellgren-Lawrence grade 4 disease.
  - c. History of OA pain in the contralateral knee requiring medication within 1 year prior to screening.
  - d. After discontinuing all pain medications for at least 7 days, had a baseline score of  $\geq 20$  mm on a 0-100 mm Visual Analog Scale (VAS) for the contralateral knee immediately prior to randomization.
  - e. History of secondary OA, rheumatoid arthritis, chronic inflammatory disease (e.g., colitis) or fibromyalgia.
  - f. History of asthma, hypertension, myocardial infarction, thrombotic events, stroke, congestive heart failure, impaired renal function or liver disease.
  - g. History of gastrointestinal bleeding or peptic ulcer disease.
  - h. Known allergy to aspirin or nonsteroidal anti-inflammatory drug (NSAID).
  - i. Elevated transaminases at screening.
  - j. Use of anticoagulants, ACE-inhibitors, cyclosporine, diuretics, lithium, or methotrexate within the past month prior to entry into the study.
4. The protocol should include a list of the prescription and over-the-counter drug products that are prohibited during the study, such as:
- a. Any other topical products applied to the target site.
  - b. ACE-inhibitors, anticoagulants, aspirin, cyclosporine, diuretics, lithium, methotrexate or oral NSAIDs.
  - c. Systemic corticosteroid or immunosuppressive drugs.
  - d. Pain medication other than acetaminophen.
5. Showering/bathing should be avoided for at least 1 hour after the application. 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 be instructed to wash their hands after use, avoid exposure to sunlight, avoid the use of sunlamps, not use any type of bandage or occlusive dressing or heating pad on the treatment area, not allow the gel to come in contact with the eyes or mucous membranes, and not apply the gel to open skin wounds, infections, inflammations, or exfoliative dermatitis.
6. The recommended primary endpoint of the study is the mean change from baseline to week 4 in the WOMAC pain score (pain score = 0 to 20), which is determined by the subject's responses to five questions (S1–S5) using a 5-point Likert scale (i.e., 'none'=0; 'mild'=1; 'moderate'=2; 'severe'=3; 'extreme'=4). The questions pertain to the amount of pain the subject is currently experiencing in the target knee [i.e., 'How much pain do you have' when 'Walking on a flat surface' (S1), 'Going up or down stairs' (S2), 'At night while in bed' (S3), 'Sitting or lying' (S4), 'Standing upright' (S5)] when

7. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations.
8. The PP population includes all randomized subjects who met all inclusion/exclusion criteria, were compliant with the assigned study treatment, returned to the study site for the primary endpoint visit within the specified window (+/- 4 days) OR discontinued from the study as a treatment failure, and did not have any protocol violations. The PP population should be used for the bioequivalence evaluation of test vs. reference. The protocol should provide a definition of compliant subjects (e.g., used at least 75% and no more than 125% of study treatment doses) and specify how compliance will be verified (e.g., by the use of subject diaries).
9. 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, as a test of study sensitivity.
10. The safety population includes all randomized subjects who received study treatment.
11. Subjects discontinued early from the study due to lack of treatment effect should be included in the PP population, using Last Observation Carried Forward (LOCF). Subjects discontinued early for other reasons should also be excluded from the PP population, but included in the mITT population, using Last Observation Carried Forward (LOCF).
12. 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.
13. If the inactive ingredients are different than those contained in the RLD or in significantly different amounts, then the sponsor is to 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.
14. 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.
15. 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.
16. 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.

17. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.
18. To establish bioequivalence for the primary endpoint, the 90% confidence interval for the test/reference ratio of mean change from baseline to week 4 must be contained within [0.80, 1.25] for a continuous variable, using the PP population.
19. 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) for the primary endpoint (mean change from baseline), using the mITT study population and LOCF.
20. The following Statistical Analysis Method is recommended for equivalence testing for a continuous variable:

#### Equivalence Analysis for a Continuous Variable

The compound hypothesis to be tested is:

$$H_0: \mu_T / \mu_R \leq \theta_1 \text{ or } \mu_T / \mu_R \geq \theta_2 \text{ versus } H_A: \theta_1 < \mu_T / \mu_R < \theta_2$$

Where  $\mu_T$  = mean of test treatment, and  $\mu_R$  = mean of reference treatment

Typically, we reject  $H_0$  with a type I error  $\alpha = 0.05$  (two 1-sided tests), if the 90% confidence interval for the ratio of means between test and reference products ( $\mu_T / \mu_R$ ) is contained within the interval  $[\theta_1, \theta_2]$ , where  $\theta_1 = 0.80$  and  $\theta_2 = 1.25$ .

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

21. 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, baseline vital signs, adverse events, reasons for discontinuation of treatment, concomitant medications, medical history, compliance and comments, etc.
22. 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. Per Protocol (PP) population inclusion (yes/no)
- n. Reason for exclusion from PP population
- o. Modified Intent to Treat (mITT) population inclusion (yes/no)
- p. Reason for exclusion from mITT population
- q. Safety population inclusion (yes/no)
- r. Reason for exclusion from safety population
- s. Baseline Kellgren-Lawrence grade of OA on X-ray of the target knee
- t. Immediately prior to randomization, pain on movement on a 0-100 mm Visual Analog Scale (VAS) for target knee
- u. Immediately prior to randomization (baseline), WOMAC pain score for target knee
- v. Week 4 WOMAC pain score for target knee
- w. Treatment compliance: number of missed doses per subject
- x. Concomitant medication (yes/no)
- y. 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	pp	pp_rs	mitt	mitt_rs	safety	safe_rs	kell_b	ponvas_b	wompa_b	wompa_4	complan	CM	AE
101	1	01	22	YEARS	F	1	A	R	84	Y		Y		Y		Y						0	Y	Y
101	2	01	30	YEARS	F	1	B	L	84	Y		Y		Y		Y						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. R=right knee, L=left knee
- EXDUR: Duration of Treatment (total exposure in days)
- completd: Subject completed the study, e.g., Y, N (Yes or 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
- 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, B=negative baseline culture, 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.
- kell\_b: Baseline Kellgren-Lawrence grade of OA on X-ray of the target knee, e.g., 1, 2, 3, or 4
- pomvas\_b: Immediately prior to randomization, pain on movement for target knee on a 0-100 mm Visual Analog Scale (VAS), e.g., 0-100
- wompa\_b: Immediately prior to randomization (baseline), WOMAC pain score for target knee, e.g., 0-20
- wompa\_4: Week 4 WOMAC pain score for target knee, e.g., 0-20
- 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

23. 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
  - Kellgren-Lawrence grade of OA on X-ray of the target knee
  - Pain on movement for target knee on a 0-100 mm Visual Analog Scale (VAS)
  - WOMAC pain score for target knee
  - 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**

STUDYID	SUBJID	EXTRT	VISITNUM	SVSTDTC	ELTMBS	kell	pomvas	wompa	CMrpt	AErpt	LBtest
101	1	A	1	2004-07-01	0				Y	N	Y

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)  
ELTMBL: Elapsed Time since Baseline (days)  
kell: Baseline Kellgren-Lawrence grade of OA on X-ray of the target knee, e.g., 1, 2, 3, or 4  
pomvas: Pain on movement for target knee on a 0-100 mm Visual Analog Scale (VAS), e.g., 0-100  
wompa: WOMAC pain score for target knee, e.g., 0-20  
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

24. These recommendations are specific to this product and may not be appropriate for bioequivalence studies of any other product, including any other dosage form or strength of Diclofenac Sodium.