

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**Draft Guidance on Diclofenac Sodium**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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:** Diclofenac sodium

**Dosage Form; Route:** Gel; topical

**Recommended Studies:** Two 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: Males and females with osteoarthritis of the knee.  
Additional comments: Specific recommendations are provided below.

---

**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 or longer (See item 8). The primary endpoint is to be evaluated at the end of treatment.
2. Inclusion Criteria (the sponsor may add additional criteria):
  - a. 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 replace all current pain medications with acetaminophen for use as needed during the duration of the study [subjects should be able to withhold all rescue medication (e.g., acetaminophen) use for at least 24 hours prior to all WOMAC pain score assessments at study visits].
- 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. Systemic and topical pain medications other than acetaminophen.
- 5. The Applicant should pre-specify rescue medication use (name, type, amount, frequency, reason for use), maximum allowable amount of daily rescue medication use, and any limitations such as subjects cannot use rescue medication within pre-specified number of hours (e.g., at least 24 hours) prior to all WOMAC pain score assessments in the study protocol.
- 6. 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.

7. The recommended primary endpoint of the study is the mean change from baseline to week 4 (or to the end of treatment as pre-specified) 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)].
8. Due to known significant placebo effect of this product, modifications to the recommended study design such as adding a placebo run-in period and increasing the treatment duration to increase assay sensitivity may be considered. All modifications to the study design must be pre-specified in the study protocol prior to unblinding of data and justification should be provided for the modifications.
9. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations.
  - a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who:
    - i. Meet all inclusion/exclusion criteria
    - ii. Are dosed a pre-specified proportion of the scheduled doses (Generally at least 75% and no more than 125%) of the assigned product for the specified duration of the study. The protocol should specify how compliance will be verified, (e.g., by the use of subject diaries).
    - iii. Do not miss a pre-specified number of scheduled doses for more than pre-specified number of consecutive days.
    - iv. Complete the evaluation within the designated visit window with no protocol violations that would affect the treatment evaluation.
  - b. The mITT and safety populations include all randomized subjects who use at least one dose of product.
10. Subjects who are 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 whose condition worsens and who require alternate or supplemental therapy (other than rescue medication) for the treatment of their condition during the treatment phase of the study should be discontinued, included in the mITT and PP population analyses using LOCF, and provided with effective treatment. Subjects discontinued early for other reasons should be excluded from the PP population, but included in the mITT population, using LOCF. Applicants should provide a pre-specified definition of lack of treatment effect.
11. The start and stop calendar date (e.g., mm/dd/yyyy) and study day (e.g. Day X) of concomitant medication use should be provided in the data set in addition to the reason for the medication use. The Applicant should clearly note whether the medication was used prior to baseline visit, during the study, or both.
12. The Applicant should submit a data set that includes the name, type, dose, date and time of each rescue medication use for each subject who used the rescue medication at any point during the study.

13. 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.
14. All pregnancies should be reported, including outcome information.
15. If the inactive ingredients are different than those contained in the RLD or in significantly different amounts, then the Applicant is to clearly describe the differences and provide information to show that the differences will not affect the safety, efficacy, or systemic or local availability of the drug. Inactive ingredients used should provide adequate margins of safety for the proposed clinical exposure in the target population (e.g., 2 months and older).
16. The method of randomization should be described in the protocol and the randomization schedule should be provided. 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 Applicant 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.
17. 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.
18. 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 for each shipment prior to dispensing to subjects. Retention samples should not be returned to the Applicant at any time.
19. It is the Applicant's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.
20. To establish bioequivalence for a continuous endpoint, it is recommended the following compound hypotheses be tested using the per protocol population:  
 $H_0: \mu_T / \mu_R < \theta_1 \quad \text{or} \quad \mu_T / \mu_R > \theta_2 \quad \text{versus} \quad H_A: \theta_1 \leq \mu_T / \mu_R \leq \theta_2$   
 where  $\mu_T$  = mean of the primary endpoint for the test group, and  
 $\mu_R$  = mean of the primary endpoint for the reference group

The null hypothesis,  $H_0$ , is rejected with a type I error ( $\alpha$ ) of 0.05 (two one-sided tests) if the estimated 90% confidence interval for the ratio of the 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 supports the conclusion of equivalence of the two products.

21. To establish sensitivity within the study for a continuous primary endpoint, the test and reference products should both be statistically superior to the placebo. Conduct an appropriate two-sided inferential test with a type I error ( $\alpha$ ) of 0.05, using the mITT population and the primary endpoint.
22. The study data should be submitted in standardized format. Please refer to study data standards published at [www.FDA.gov](http://www.FDA.gov)<sup>1</sup>
23. The protocol should include a section with full details of the planned statistical analysis.
24. Please provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
  - a. Study identifier
  - b. Unique subject identifier
  - c. Subject identifier for the study
  - d. Study site identifier (if applicable)
  - e. Age
  - f. Age units (years)
  - g. Sex
  - h. Race
  - i. Name of planned treatment
  - j. Name of Actual Treatment (exposure): test product, RLD, placebo
  - k. Location of Treatment Area
  - l. Safety population flag (yes/no)
  - m. Reason for exclusion from safety population
  - n. Modified Intent-to-Treat (mITT) population flag (yes/no)
  - o. Reason for exclusion from mITT population
  - p. Per-Protocol (PP) population flag (yes/no)
  - q. Reason for exclusion from PP population
  - r. Randomized population flag (yes/no)
  - s. Date/time of first exposure to treatment
  - t. Date/time of last exposure to treatment
  - u. End of study date
  - v. End of study status
  - w. Subject required additional treatment due to unsatisfactory treatment response (yes/no)
  - x. Baseline Kellgren-Lawrence grade of OA on X-ray of the target knee
  - y. Immediately prior to randomization (baseline), pain on movement on a 0-100 mm Visual Analog Scale (VAS) for target knee
  - z. Immediately prior to randomization (baseline), WOMAC pain score for target knee
  - aa. At the end of treatment WOMAC pain score for target knee
  - bb. Change from baseline to the end of treatment WOMAC pain score for target knee
  - cc. Compliance rate (%)
  - dd. Subject missed the pre-specified number of scheduled doses for more than pre-specified number of consecutive days (yes/no)
  - ee. Concomitant medication (yes/no)
  - ff. Adverse event(s) reported (yes/no)

---

<sup>1</sup> Study Data Standards for Submission to CDER available at:  
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

25. Please provide the analysis dataset with records per subject, per visit, per analysis timepoint, using the following headings, if applicable:
- a. Study identifier
  - b. Unique subject identifier
  - c. Subject identifier for the study
  - d. Study site identifier (if applicable)
  - e. Name of planned treatment
  - f. Name of actual treatment
  - g. Safety population flag (yes/no)
  - h. Modified ITT population flag (yes/no)
  - i. Per-Protocol (PP) population flag (yes/no)
  - j. Analysis date
  - k. Analysis visit
  - l. Study visit within the designated window (yes/no)
  - m. Pain on movement for target knee on a 0-100 mm Visual Analog Scale (VAS)
  - n. WOMAC pain score for target knee
  - o. Additional treatment required during the visit (yes/no)
  - p. Concomitant medication reported during this visit (yes/no)
  - q. Adverse event reported during this visit (yes/no)
  - r. Laboratory testing during this visit (yes/no)