

## Draft Guidance on Diclofenac Sodium; Misoprostol

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

**Form/Route:** Delayed Release Tablets/Oral

**Recommended studies:** 2 studies

1. Type of study: Fasting  
Design: Single-dose, two-way crossover *in-vivo*\*  
Strength: 75 mg/0.2 mg  
Subjects: Healthy males and nonpregnant females, general population.  
Additional Comments: Applicant may consider using a reference scaled average bioequivalence approach for diclofenac and misoprostol. If using this approach, please provide evidence of high variability in the bioequivalence parameters AUC and/or C<sub>max</sub> (i.e., within-subject variability > 30%). For general information on this approach, please refer to Haidar et al., Bioequivalence Approaches for Highly Variable Drugs and Drug Products, Pharm. Res. 25:237-241(2008).

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2. Type of study: Fed  
Design: Single-dose, two-way crossover *in-vivo*\*  
Strength: 75 mg/0.2 mg  
Subjects: Healthy males and nonpregnant females, general population.  
Additional Comments: Please see comment above.

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**Analytes to measure (in appropriate biological fluid):** Diclofenac and misoprostol's metabolite, misoprostol acid in plasma.

**Bioequivalence based on (90% CI):** Diclofenac and misoprostol's metabolite, misoprostol acid.

**Waiver request of *in-vivo* testing:** 50 mg/ 0.2 mg based on (i) acceptable bioequivalence studies on the 75 mg/0.2 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable *in vitro* dissolution testing of all strengths.

### Dissolution test method and sampling times:

Please note that a Dissolution Methods Database is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.