

Draft Guidance on Propafenone Hydrochloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Extended Release Capsules/ Oral

Recommended studies: 2 studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in-vivo
Strength: 425 mg
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments:

2. Type of study: Fed
Design: Single-dose, two-way crossover in-vivo
Strength: 425 mg
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments:

Special Considerations: Applicants may consider using a reference-scaled average bioequivalence approach for propafenone. If using this approach, the applicant should provide evidence of high variability (i.e., within-subject variability $\geq 30\%$) in bioequivalence parameters. Applicants who would like to use this approach are encouraged to submit a protocol for review by the Division of Bioequivalence in the Office of Generic Drugs.

Analytes to measure (in appropriate biological fluid): Propafenone and its metabolite 5-OH propafenone in plasma.

Bioequivalence based on (90% CI): Propafenone

Please submit the metabolite data for 5-OH propafenone as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}.

Waiver request of in-vivo testing: 225 mg and 325 mg based on (i) acceptable bioequivalence studies on the 425 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

In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.