

## **Draft Guidance on Propranolol Hydrochloride**

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

**Form/Route:** Extended Release Capsule/Oral

**Recommended studies:** 2 studies

1. Type of study: Fasting  
Design: Single-dose, two-way crossover in vivo  
Strength: 160 mg  
Subjects: Healthy males and nonpregnant females, general population.

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2. Type of study: Fed  
Design: Single-dose, two-way crossover in vivo  
Strength: 160 mg  
Subjects: Healthy males and nonpregnant females, general population.  
Additional Comments: Please refer to the Amantadine Hydrochloride Tablet Draft Guidance for additional information regarding fed studies.

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**Analytes to measure (in appropriate biological fluid):** Total propranolol and its active metabolite, total 4-hydroxypropranolol, in plasma

Please submit the metabolite data 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<sub>max</sub>.

**Bioequivalence based on (90% CI):** Propranolol

**Waiver request of in vivo testing:** 60 mg, 80 mg, and 120 mg based on (i) acceptable bioequivalence studies on the 160 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths. Please refer to the Mirtazapine Tablet Draft Guidance for additional information regarding waivers of in vivo testing.

**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.