Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Propranolol Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Tablet; oral

Recommended Studies: Two options: Biopharmaceutics Classification System (BCS) or in vivo studies

I. BCS Class 1-based biowaiver option:

A waiver request of in vivo testing for this product may be considered provided that the appropriate documentation regarding high solubility, high permeability and rapid dissolution as detailed in the Guidance for Industry: *Waiver of In Vivo Bioavailability and Bioequivalence for Immediate–Release Solid Oral Dosage Forms Based on the Biopharmaceutics Classification System* is submitted in the application. Applicants may use information contained in the approved labeling of the reference product. Peer-reviewed articles may not contain the necessary details of the testing for the Agency to make a judgment regarding the quality of the studies. A decision regarding the acceptability of the waiver request will be made upon assessing the data submitted in the application.

II. In vivo bioequivalence study option:

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 80 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: None

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2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 80 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: None

Analytes to measure: Propranolol and its active metabolite, 4-hydroxypropranolol, in plasma using an achiral assay

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 area under the curve and maximum concentration.

Bioequivalence based on (90% CI): Propranolol

Waiver request of in vivo testing: 10 mg, 20 mg, 40 mg, and 60 mg strengths based on (i) acceptable bioequivalence studies on the 80 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:
The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units for each of all strengths of the test and reference products. Specifications will be determined upon evaluation of the abbreviated new drug application.

If any strength of the tablet product has a functional score, additional dissolution profile testing should be conducted for each segment of the split tablet after manual and mechanical splitting as per Guidance for Industry on *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation*.