Contains Nonbinding Recommendations

Draft Guidance on Methylphenidate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Extended release tablet; orally disintegrating

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 25.9 mg
   Subjects: Males and non-pregnant, non-lactating females, general population

   Additional comments:
   The fasting bioequivalence study may be conducted in a single dose, two-treatment, two-sequence, four-period, replicated design. The 90% confidence intervals of the geometric mean test/reference (T/R) ratios for the metrics (C_{max}, AUC_{0-3}, AUC_{3-7}, AUC_{7-12}, $AUC_{0-\infty}$) should fall within the limits of 80.00-125.00%.

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2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 25.9 mg
   Subjects: Males and non-pregnant, non-lactating females, general population

   Additional comments:
   The fed bioequivalence study may be conducted in a single dose, two-treatment, two-sequence, four-period, replicated design. The 90% confidence intervals of the geometric mean T/R ratios for the metrics (C_{max}, AUC_{0-4}, AUC_{4-8}, AUC_{8-12}, $AUC_{0-\infty}$) should fall within the limits of 80.00-125.00%.

Analytes to measure (in appropriate biological fluid): Methylphenidate in plasma

Bioequivalence based on (90% CI): Methylphenidate

Refer to Additional Comments above for more guidance regarding bioequivalence.

Waiver request of in vivo testing: 8.6 mg and 17.3 mg based on (i) acceptable bioequivalence studies on the 25.9 mg strength, (ii) acceptable in-vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths.

Dissolution test method and sampling times:

The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods web site, available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. 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 abbreviated new drug application (ANDA).

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 changed if appropriate. It is acceptable to add a small amount of surfactant, if necessary. 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.

Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, USP Apparatus II (paddle) @50 rpm, with or without alcohol;

Test 1: 12 units tested according to the proposed method (with 0.1N HCl), with data collected every 15 minutes for a total of 2 hours

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range, and %CV on all strengths.