

Draft Guidance on Methylphenidate Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Extended release tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: 20 mg
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments: The fasting BE 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}, AUC₀₋₃, AUC₃₋₇, AUC_{7-t}, AUC_{0-∞}) should fall within the limits of 80-125%.

2. Type of study: Fed
Design: Single-dose, two-way crossover in vivo
Strength: 20 mg
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments: The fed BE 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}, AUC₀₋₄, AUC₄₋₈, AUC_{8-t}, AUC_{0-∞}) should fall within the limits of 80-125%.

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

Bioequivalence based on (90% CI): Methylphenidate

Please refer to Additional Comments above for more guidance regarding bioequivalence.

Waiver request of in vivo testing: 10 mg based on (i) acceptable bioequivalence studies on the 20 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 Please refer to the Mirtazapine Tablet Draft Guidance for additional information regarding waivers of in vivo testing.¹

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 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.

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 2 (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.

¹ CFR § 320.24(b)(6)