*Contains Nonbinding Recommendations*

**Draft Guidance on Methylphenidate Hydrochloride**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

**Recommended Studies**: Three studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two period crossover in vivo
   Strength: 60 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: A single dose, two-treatment, two-sequence, four-period, replicated design may be considered. The 90% confidence intervals (CIs) of the geometric mean test/reference ratios for the metrics (Cmax, $AUC_{0-3}$, $AUC_{3-7}$, $AUC_{7-12}$, $AUC_{0-\infty}$) 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: 60 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: A single dose, two-treatment, two-sequence, four-period, replicated design may be considered. The 90% CIs of the geometric mean test/reference ratios for the metrics (Cmax, $AUC_{0-4}$, $AUC_{4-8}$, $AUC_{8-12}$, $AUC_{0-\infty}$) should fall within the limits of 80.00-125.00%.

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3. Type of study: Fasting, sprinkle-in-applesauce
   Design: Single-dose, two-treatment, two period crossover in vivo
   Strength: 60 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: A single dose, two-treatment, two-sequence, four-period, replicated design may be considered. The 90% CIs of the geometric mean test/reference ratios for the metrics (Cmax, $AUC_{0-3}$, $AUC_{3-7}$, $AUC_{7-12}$, $AUC_{0-\infty}$) should fall within the limits of 80.00-125.00%.

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*Recommended Nov 2011; Revised Mar 2015, Jun 2020*

**Analyte to measure (in appropriate biological fluid):** Methylphenidate in plasma

**Bioequivalence based on (90% CI):** Methylphenidate
Refer to the additional comments above for more guidance regarding bioequivalence.

**Additional strengths:** Bioequivalence of 10 mg, 20 mg, 30 mg and 40 mg strengths to the corresponding reference product strengths may be demonstrated based on principles laid out in the FDA guidance on *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.

**Dissolution test method and sampling times:** For modified release drug products, applicants should develop specific discriminating dissolution methods. Applicants may use the dissolution method set forth in any related official United States Pharmacopeia (USP) drug product monograph, or in the FDA's database (available at http://www.accessdata.fda.gov/scripts/cder/dissolution/), provided that applicants submit adequate dissolution data supporting the discriminating ability of such a method. If a new dissolution method is developed, the dissolution method development and validation report with the complete information/data supporting the proposed method should be submitted. Conduct comparative dissolution testing on 12 dosage units for each strength of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

In addition to the method above, dissolution profiles on 12 dosage units for each strength of the test and reference products generated using USP Apparatus 1 at 100 rpm and/or Apparatus 2 at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted. Agitation speeds may be increased 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.

Due to concerns of dose dumping from this drug product when taken with alcohol, conduct additional dissolution testing on all strengths using various concentrations of ethanol in the dissolution medium as follows:

Testing Conditions: 900 mL, 0.1 N HCl, USP Apparatus 1 (basket) at 100 rpm, with or without alcohol;

Test 1: 12 units tested according to the proposed method (with 0.1 N 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 reference products should be tested accordingly, and data should be provided on individual unit, means, range and %CV.