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Draft Guidance on Methylphenidate

November 2021

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

This guidance, which interprets the Agency's regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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In July 2018, FDA issued a draft product-specific guidance for industry on generic methylphenidate. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredient: Methylphenidate

Dosage Form; Route: Tablet, orally disintegrating, extended release; oral

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: A single dose, two-treatment, two-sequence, four-period, replicate design may be considered. The orally disintegrating tablet should be placed on the tongue, allowed to disintegrate, and swallowed without water. The 90% confidence intervals (CIs) of the geometric mean test to reference 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%.

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: A single dose, two-treatment, two-sequence, four-period, replicate design may be considered. The orally disintegrating tablet should be placed on the tongue, allowed to disintegrate, and swallowed without water. The 90% CIs of the geometric mean test to reference 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%.

Analyte to measure: Methylphenidate in plasma

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

Additional strengths: Bioequivalence of the 8.6 mg and 17.3 mg strengths to the corresponding reference product strengths may be demonstrated based on principles described 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. Alternatively, 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, 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, submit the dissolution method development and validation report with the complete information/data supporting the proposed method. 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, submit 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). 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.

Alcohol dose dumping studies: Due to concerns of dose dumping of drug from this 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, 0.1N HCl, USP Apparatus 2 (paddle) at 50 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

Conduct testing on both test and reference products accordingly, and provide data on individual unit, means, range and %CV.

Revision History: Recommended July 2018; Revised November 2021

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