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Draft – Not for Implementation

Draft Guidance on Amphetamine; Amphetamine Aspartate/Dextroamphetamine Sulfate
August 2022

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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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This is a new draft product-specific guidance for industry on generic amphetamine; amphetamine aspartate/dextroamphetamine sulfate.

Active Ingredients: Amphetamine; Amphetamine aspartate/Dextroamphetamine sulfate

Dosage Form; Route: Tablet, extended release; oral

Recommended Studies: Three in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 16 mg; EQ 4 mg Base
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: The tablet should be chewed, then swallowed with water.

2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 16 mg; EQ 4 mg Base
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: See comments above.
3. Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 16 mg; EQ 4 mg Base
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: The tablet should be swallowed whole with water.

Analytes to measure: d-amphetamine and l-amphetamine measured separately in plasma

Bioequivalence based on (90% CI): d-amphetamine and l-amphetamine

The 90% confidence intervals of the geometric mean test/reference ratios for the metrics (C_{max} , AUC_{0-4h} , AUC_{4h-t} , $AUC_{0-\infty}$) should fall within the limits of 80.00-125.00%.

Additional strengths: Bioequivalence of the 4 mg; EQ 1 mg Base, 8 mg; EQ 2 mg Base, and 12 mg; EQ 3 mg Base strengths to the corresponding reference product strengths may be demonstrated based on principles laid out in the most recent version of the FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application*.^a

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 ANDA.

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 (e.g., 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.

Certain strengths of amphetamine; amphetamine aspartate/dextroamphetamine sulfate extended release tablets are scored. To ensure the performance of the split tablet, perform manual as well as mechanical splitting and conduct dissolution testing of split tablet portions versus the whole tablet for both test and reference products.

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.

Unique Agency Identifier: PSG_210526

^a For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.