

Draft Guidance on Amphetamine

November 2025

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In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Amphetamine

Dosage Form: Tablet, orally disintegrating, extended release

Route: Oral

Strengths: EQ 3.1 mg Base, EQ 6.3 mg Base, EQ 9.4 mg Base, EQ 12.5 mg Base, EQ 15.7 mg Base, EQ 18.8 mg Base

Recommended Studies: Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: EQ 18.8 mg Base
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments:
 - Exclude subjects with a history of recreational drug abuse or substance abuse. Exclude subjects with cardiovascular risk factors (e.g., tachycardia). Monitor vital signs during the study.
 - The orally disintegrating tablet should be placed on the tongue and allowed to disintegrate without water.
2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: EQ 18.8 mg Base
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: See comments above.

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

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

The 90% confidence intervals of the geometric mean test/reference (T/R) ratios for the metrics (C_{max}, AUC₀₋₅, AUC_{5-t}, AUC_{0-∞}) should fall within the limits of 80-125%.

Additional strengths: Bioequivalence of the EQ 3.1 mg Base, EQ 6.3 mg Base, EQ 9.4 mg Base, EQ 12.5 mg Base and EQ 15.7 mg Base 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 ANDA*.^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 the reference listed drug (RLD).¹ 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 (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.

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, 0.1 N HCl, Apparatus 2 (paddle) 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

¹ If the RLD is not available, refer to the most recent version of the FDA guidance for industry on Referencing Approved Drug Products in ANDA Submissions.

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.

Document History: Recommended May 2017; Revised November 2025

Unique Agency Identifier: PSG_204326

^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>.