Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Amphetamine

August 2026

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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:	Suspension, extended release
Route:	Oral
Strength:	EQ 1.25 mg Base/mL
Reference Listed Drug:	NDA 204325
Recommended Studies:	Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Class of study: Bioequivalence
   Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 1.25 mg Base/mL
   Dose: EQ 12.5 mg Base (10 mL)
   Subjects: Healthy males and non-pregnant, non-lactating females
   Safety recommendations:
   - Exclude subjects with a history of recreational drug use or substance abuse.
   - Exclude subjects with cardiovascular risk factors (e.g., tachycardia).
   - Monitor vital signs during the study.

2. Class of study: Bioequivalence
Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: EQ 1.25 mg Base/mL
Dose: EQ 12.5 mg Base (10 mL)
Subjects: Healthy males and non-pregnant, non-lactating females
Safety recommendations: See recommendations under Study #1.

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

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

The following pharmacokinetic parameters will be evaluated for bioequivalence based on 90% CI: Log-transformed area under the concentration (AUC) time curve from hour 0 to hour 5 ($AUC_{0\text{-}5h}$), AUC from hour 5 to the last measurable time point ($AUC_{5h\text{-}t}$), AUC from hour 0 extrapolated to infinite time ($AUC_{0\text{-}\infty}$), and maximum concentration (C_{max}).

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 of the test product and 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 of the test product and RLD generated using USP Apparatus 1 at 100 rpm 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 using various concentrations of ethanol in the dissolution medium as follows:

Testing conditions: 750 mL, 0.1 N HCl, USP Apparatus 2 (paddle) at 75 rpm, with or without alcohol

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

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 product and RLD accordingly, and provide data on individual unit, means, range and %CV.

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