

**Draft Guidance on Amphetamine Aspartate; Amphetamine Sulfate;  
Dextroamphetamine Saccharate; Dextroamphetamine Sulfate**

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

**Active ingredient:** Amphetamine Aspartate; Amphetamine Sulfate;  
Dextroamphetamine Saccharate; Dextroamphetamine Sulfate

**Form/Route:** Capsule, Extended Release/Oral

**Recommended studies:** 3 studies

1. Type of study: Fasting  
Design: Single-dose, two-way crossover in-vivo  
Strength: 7.5 mg; 7.5 mg; 7.5 mg; 7.5 mg  
Subjects: Healthy males and nonpregnant females, general population.  
Additional Comments:  

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2. Type of study: Fed  
Design: Single-dose, two-way crossover in-vivo  
Strength: 7.5 mg; 7.5 mg; 7.5 mg; 7.5 mg  
Subjects: Healthy males and nonpregnant females, general population.  
Additional Comments: Please refer to the Amantadine Hydrochloride Tablet Draft Guidance for additional information regarding fed studies.  

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3. Type of study: Fasting sprinkle (capsule compared to RLD, capsule contents sprinkled on a spoonful of applesauce)  
Design: Single-dose, two-way crossover in-vivo  
Strength: 7.5 mg; 7.5 mg; 7.5 mg; 7.5 mg  
Subjects: Healthy males and nonpregnant females, general population.  
Additional Comments: Fasting study, with contents sprinkled over a spoonful of applesauce in accordance with the approved labeling of the RLD.  

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

**Bioequivalence based on (90% CI):** *d*-amphetamine and *l*-amphetamine.  
Please refer to Additional Comments below for more guidance regarding bioequivalence.

**Waiver request of in-vivo testing:** (1.25 mg; 1.25 mg; 1.25mg; 1.25 mg), (2.5 mg, 2.5 mg, 2.5 mg, 2.5 mg), (3.75 mg, 3.75 mg, 3.75 mg, 3.75 mg), (5 mg, 5 mg, 5 mg, 5 mg), and (6.25 mg, 6.25 mg, 6.25 mg, 6.25 mg) based on (i) acceptable bioequivalence studies on the (7.5 mg, 7.5 mg, 7.5 mg, 7.5 mg) strength, (ii) acceptable dissolution testing across all strengths, and (iii) proportional similarity in the formulations across all strengths. Please refer to the Mirtazapine Tablet Draft Guidance for additional information regarding waivers of in-vivo testing.

**Dissolution test method and sampling times:**

Please note that a Dissolution Methods Database is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm>. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

In addition to the method above, for modified-release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please 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.

**Additional Comments:**

The Adderall XR<sup>®</sup> Capsule labeling states that “Adderall XR<sup>®</sup> capsule contains two types of drug-containing beads designed to give a double-pulsed delivery of amphetamines, which prolongs the release of amphetamine from Adderall XR<sup>®</sup> compared to the conventional Adderall (immediate-release) tablet formulation.” Further, the label states that “patients taking divided doses of immediate-release Adderall<sup>®</sup>, (for example, twice daily), may be switched to Adderall XR<sup>®</sup> at the same total daily dose taken once daily.”

Thus, Adderall XR<sup>®</sup> is a multiphasic, modified-release formulation designed to mimic the drug release of two Adderall [immediate release (IR) mixed amphetamine] tablet formulations taken four hours apart. According to the FDA-approved labeling for this product, clinical studies showed statistically significant improvement in behavioral assessment scores, following once daily dosing of Adderall XR<sup>®</sup>. As this multiphasic, modified-release dosage form is designed to achieve quick onset of activity, mimicking that of IR mixed amphetamine tablet formulation followed by sustained activity for the remainder of the day, the FDA suggests that additional BE metrics may be appropriate to ensure that a generic (test) version is therapeutically equivalent to the corresponding reference product. Thus, for Adderall XR<sup>®</sup> the following two pAUC metrics are proposed in addition to the traditional metrics [AUC<sub>∞</sub> (area under the curve from 0 to infinity), and C<sub>max</sub> (maximum plasma concentration)]:

- $AUC_{0-5}$  should compare test & reference systemic exposure responsible for early onset of response during the early part of the once-daily dosing interval, where  $AUC_{0-5}$  is the area under the plasma-concentration vs. time curve from 0 to 5 hours; and
- $AUC_{5-t}$  should compare test & reference systemic exposure responsible for sustaining the response later during the once-daily dosing interval, where  $AUC_{5-t}$  is area under the curve from 5 hours to the last measurable time point.

The 90% confidence intervals of the geometric mean test/reference (T/R) ratios for the above four metrics ( $C_{max}$ ,  $AUC_{0-5}$ ,  $AUC_{5-t}$ ,  $AUC_{\infty}$ ) should fall within the BE limits of 80-125% for *d*-amphetamine and *l*-amphetamine.

Fasting, Fed, and Fasting sprinkle-in-applesauce Studies: Log-transformed  $AUC_{0-5}$ ,  $AUC_{5-t}$ ,  $AUC_{\infty}$ , and  $C_{max}$ . The partial AUCs (pAUCs),  $AUC_{0-5}$  and  $AUC_{5-t}$ , have been determined to be the most appropriate parameters for evaluation of the drug bioavailability responsible for the rapid onset and sustained maintenance of the clinical response throughout the 24 hr dosing period<sup>1</sup>. These two pAUCs replace the usual  $AUC_{0-t}$ , and together with the other bioequivalence (BE) parameters,  $AUC_{0-\infty}$  and  $C_{max}$ , will ensure that the pharmacokinetic profiles and clinical effects of test and reference products are sufficiently similar.

The sampling time of 5 hours for the first pAUC is based on time at which 90-95% of subjects are likely to achieve optimal early onset of response, for the following reasons:

- The  $T_{max}$  of IR mixed amphetamine formulation is about 3 hours in fasting subjects. Available evidence indicates that food does not affect the  $T_{max}$  of this IR formulation;
- The standard deviation of  $T_{max}$  for IR mixed amphetamine formulation is 1 hour;
- Since, approximately 95% of observations fall within two standard deviations of the mean, the first pAUC sampling time will be  $T_{max}$  mean  $\pm$  2 x standard deviation of the IR formulation, i.e. 3 hr  $\pm$  2 hr.

This should provide additional assurance that a test and reference product will be therapeutically equivalent over the early part of the daily dosing interval, corresponding to onset of response. Likewise,  $AUC_{5-t}$  should ensure that two products are therapeutically equivalent over the later part of the daily dosing interval.

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<sup>1</sup> CFR § 320.24(b)(6)