

## Draft Guidance on Amphetamine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

**Active Ingredient:** Amphetamine

**Dosage Form; Route:** Extended release suspension; oral

**Recommended Studies:** Two studies

1. Type of study: Fasting  
Design: Single-dose, two-way crossover in vivo  
Strength: EQ 2.5 mg Base/mL (8x EQ 2.5 mg Base/mL)  
Subjects: Healthy males and non-pregnant, non-lactating females, general population  
Additional comments: Amphetamine, a CNS stimulant, has a high potential for abuse and dependence, and can cause sudden death or other serious heart problems at recommended doses according to the drug product label, applicants should assess the risk of abuse and the presence of cardiac diseases prior to the study. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, and other serious heart problems. Monitor for signs of abuse and heart problems during the study.
  
2. Type of study: Fed  
Design: Single-dose, two-way crossover in vivo  
Strength: EQ 2.5 mg Base/mL (8x EQ 2.5 mg Base/mL)  
Subjects: Healthy males and non-pregnant, non-lactating females, general population  
Additional comments: See comments above.

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**Analytes to measure (in appropriate biological fluid):** d-amphetamine and l-amphetamine, separately, in plasma

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

**Waiver request of in vivo testing:** Not applicable.

**Dissolution test method and sampling times:** The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website available to the public at the following location: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and

reference products. Note that a dosage unit for a suspension is the labeled strength (mL). Specifications will be determined upon review of the abbreviated new drug application (ANDA).

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. Specifications will be determined upon review of the data submitted in the application.

Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: Volume: 900 mL 0.1N HCl, apparatus 2 (Paddle) at 50 rpm, with and without the alcohol;

Test 1: Twelve units tested according to the proposed method, with data collected every 15 minutes for a total of 2 hours

Test 2: Twelve 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: Twelve 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: Twelve 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

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range and %CV on all strengths.

#### **Additional Comments:**

DYANA VEL XR is an extended-release liquid formulation containing immediate and extended-release components in a 3.2 to 1 ratio of d-amphetamine to l-amphetamine, allowing to be taken once daily for its quick-onset and sustained activities. As per the FDA-approved labeling, the median (range) time to peak plasma concentrations ( $T_{max}$ ) were 4.0 (2 – 7) hours after a single, 18.8 mg oral dose of DYANA VEL XR under fasting conditions, and the clinical efficacy studies of DYANA VEL XR indicates that SKAMP-Combined change scores from pre-dose demonstrated a statistically significant improvement at the time points of 1, 2, 4, 6, 8, 10, 12, 13 hours post-dosing with DYANA VEL XR, using the change from pre-dose in the SKAMP-

Combined score at 4 hours post-dosing as the primary efficacy endpoint, and the onset and duration of clinical effect as the key secondary efficacy parameters. To ensure that a generic version of is therapeutically equivalent to the corresponding reference product, the firm should conduct the following pAUC metrics in addition to the traditional ( $AUC_{0-\infty}$  and  $C_{max}$ ) metrics:

- $AUC_{0-4}$  should compare test & reference systemic exposure responsible for early onset of response during the early part of the once-daily dosing interval; and
- $AUC_{4-t}$  should compare test & reference systemic exposure responsible for sustaining the response later during the once-daily dosing interval.

The 90% confidence intervals of the geometric mean test/reference (T/R) ratios for the above four metrics ( $C_{max}$ ,  $AUC_{0-4}$ ,  $AUC_{4-t}$ ,  $AUC_{0-\infty}$ ) should fall within the BE limits of 80-125%.

The sampling time of 4 hours for the first pAUC is based on the pharmacokinetic profiles and clinical efficacy studies from FDA-approved drug product label.