

Draft Guidance on Diazepam

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in-vivo
Strength: 10 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional Comments: Ensure that there are adequate washout periods between treatments in the crossover studies due to the long terminal elimination half-life. Also, consider using a parallel study design due to the long half-life. For long half-life drug products with low intra-subject variability in distribution and clearance, an AUC truncated to 72 hours may be used in place of AUC_{0-t} or AUC_{0-∞}. For either a crossover or parallel study, sample collection time should be adequate to ensure completion of gastrointestinal transit of the drug product and absorption of the drug substance. Collect sufficient blood samples in the bioequivalence studies to adequately characterize the peak concentration (C_{max}) and time to reach peak concentration (t_{max}).

2. Type of study: Fed
Design: Single-dose, two-way crossover in-vivo
Strength: 10 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional Comments: See comments above.

Analytes to measure (in appropriate biological fluid): Diazepam and its active metabolite, N-desmethyldiazepam, in plasma.

Submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}.

Bioequivalence based on (90% CI): Diazepam

Waiver request of in-vivo testing: 2 mg and 5 mg strengths based on (i) acceptable bioequivalence studies on the 10 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods web site, 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 the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).