

Draft Guidance on Tramadol

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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: Tramadol

Form/Route: Extended Release Tablets/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover *in-vivo*
Strength: 100 mg
Subjects: Normal healthy males and females, general population.
Additional Comments:

2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover *in-vivo*
Strength: 100 mg
Subjects: Normal healthy males and females, general population.
Additional comments:

Analytes to measure (in appropriate biological fluid): Tramadol in plasma by achiral assay (non-stereospecific method).

Bioequivalence based on (90% CI): Tramadol

Waiver request of in-vivo testing: 200 mg and 300 mg based on (i) acceptable bioequivalence studies on the 100 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:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at <http://www.fda.gov/cder/ogd/index.htm>. 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. Specifications will be determined upon review of the data submitted in the application.

Due to concerns of dose dumping from this drug product when taken with alcohol, please conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, apparatus 1 (basket) @ 75 rpm, with and without the alcohol (see below):

- 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.

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