

## Draft Guidance on Tramadol Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

**Dosage Form; Route:** Extended-release capsule/oral

**Recommended Studies:** Three studies

1. Type of study: Fasting  
Design: Single-dose, two-treatment, two-period crossover in vivo  
Strength: 200 mg  
Subjects: Normal healthy males and females, general population  
Additional comments: The study design (e.g., inclusion/ exclusion criteria), procedures (e.g., safety monitoring), and concomitant medications (drug interactions) should address all of the elements related to patient safety specified in the RLD label

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2. Type of study: Fed  
Design: Single-dose, two-treatment, two-period crossover in vivo  
Strength: 200 mg  
Subjects: Normal healthy males and females, general population  
Additional comments: Same as comments above

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3. Type of study: Fasting  
Design: Single-dose, two-treatment, two-period crossover in vivo  
Strength: 300 mg  
Subjects: Normal healthy males and females, general population  
Additional comments: Same as comments above

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

**Bioequivalence based on (90% CI):** Tramadol

**Bioequivalence of other strengths:** 100 mg and 150 mg strengths based on (i) acceptable bioequivalence studies on the 200 mg strength, (ii) proportional similarity of the formulations across 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 all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

For modified-release products, dissolution profiles on 12 dosage units each of the test and reference products using U.S. Pharmacopeia (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. 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, 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 all strengths.