

Contains Nonbinding Recommendations
Draft Guidance on Quetiapine Fumarate

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Extended Release Tablets/Oral

Recommended study: 2 studies

1. Type of study: Fasting
Design: Single-dose, two way crossover *in-vivo*
Strength: 200 mg
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments: Since there is the evidence of high rate of syncope and syncope like events in healthy volunteers taking quetiapine , the following safety precautions are recommended:

Subjects should be kept in supine or semi-recumbent positions within 15-30 minutes of dosing and for at least 10 hours after dosing. They should rise only with assistance during this period of time and at the first rising when this period is over. Orthostatics should be assessed at the end of the 10 hour period before allowing subjects to rise without further assistance. Elderly subjects should be excluded from bioequivalence studies.

-
2. Type of study: Fed
Design: Single-dose, two way crossover *in-vivo*
Strength: 200 mg
Subjects: Healthy males and nonpregnant females, general population.
Additional comments: Please see comments above.

Analytes to measure (in appropriate biological fluid): Quetiapine in plasma.

Bioequivalence based on (90% CI): Quetiapine.

Waiver request of *in-vivo* testing: 50 mg, 150 mg, 300 mg and 400 mg based on (i) acceptable bioequivalence studies on the 200 mg strength, (ii) acceptable dissolution testing of all strengths and (iii) proportionally similar in the formulations across 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.accessdata.fda.gov/scripts/cder/dissolution/>. 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 I (basket) @ 200 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.