

Draft Guidance on Mirtazapine

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Dosage Form; Route: Tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: 15 mg
Subjects: Healthy males and nonpregnant females, general population
Additional comments: None

2. Type of study: Fed
Design: Single-dose, two-way crossover in vivo
Strength: 15 mg
Subjects: Healthy males and nonpregnant females, general population
Additional comments: Refer to the amantadine hydrochloride tablet draft guidance for additional information regarding fed studies

Analytes to measure (in appropriate biological fluid): Mirtazapine in plasma using an achiral assay. Refer to the amiodarone hydrochloride tablet draft guidance for additional information regarding long half-life drug studies.

Bioequivalence based on (90% CI): Mirtazapine

Waiver request of in vivo testing: 30 mg and 45 mg based on (i) acceptable bioequivalence (BE) studies on the 15 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths. See below for additional information regarding waivers of in vivo testing.

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/>. The 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).

Waivers of in vivo testing:

It is generally recommended that an in vivo study be conducted for all solid oral dosage forms approved after 1962 and for drug products approved before 1962 for which actual or potential BE problems have not been resolved by adequate evidence of BE (bioproblem drugs). Waivers of in vivo studies for different strengths of an immediate-release drug product can be granted under 21 CFR 320.22(d)(2) when (1) the drug product is in the same dosage form, but in a different strength; (2) this different strength is *proportionally similar* in its active and inactive ingredients to the strength of the product for which the same manufacturer has conducted an appropriate in vivo study; and (3) the new strength meets an appropriate in vitro dissolution test.

Proportionally similar is defined in the following ways:

- All active and inactive ingredients are in similar proportion between different strengths (e.g., a tablet of 50-mg strength has all the inactive ingredients— almost exactly half that of a tablet of 100-mg strength, and almost twice that of a tablet of 25-mg strength).
- For high-potency drug substances (where the amount of active drug substance in the dosage form is relatively low): (1) the total weight of the dosage form remains nearly the same for all strengths (within $\pm 10\%$ of the total weight of the strength on which a biostudy was performed), (2) the same inactive ingredients are used for all strengths, and (3) the change in any strength is obtained by altering the amount of the active ingredients and one or more of the inactive ingredients.
- Active and inactive ingredients that are not in similar proportion between different strengths can be considered proportionally similar with adequate justification.

For highly soluble, highly permeable, rapidly dissolving, and orally administered immediate release drug products, waivers of in-vivo testing can be requested based on the biopharmaceutics classification system. In addition, waivers of in- vivo BE testing can request for drugs approved before 1962 that are not bioproblem drugs.

Different strengths of a modified-release drug product can be deemed bioequivalent to the corresponding reference standard product strengths under 21 CFR 320.24(b)(6) if the same conditions exist as listed above.