

## Draft Guidance on Levetiracetam

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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:** Levetiracetam
- Dosage Form; Route:** Tablet for oral suspension; oral
- Recommended Studies:** Two options: Biopharmaceutics Classification System (BCS) or in vivo studies

See “Important Administration Instruction” in the currently approved drug label. Proposed generic drugs are expected to meet both methods of administration as described in the drug label.

### I. BCS waiver option:

In vivo testing for this product may be requested to be waived with submission of appropriate documentation of high solubility, high permeability and rapid dissolution as detailed in the guidance for industry *Waiver of In Vivo Bioavailability and Bioequivalence for Immediate – Release Solid Oral Dosage Forms Based on the Biopharmaceutics Classification System* in the application. You may use information contained in the approved labeling of the reference product. Peer-reviewed articles alone may not contain the necessary details of the testing for the Agency to make a judgment regarding the quality of the studies. A decision regarding the acceptability of the waiver request can only be made upon review of complete data as submitted in the application.

### II. In vivo option: Two studies

1. Type of study: Fasting  
Design: Single-dose, two-way crossover in-vivo  
Strength: 1000 mg  
Subjects: Males and non-pregnant, non-lactating females, general population.  
Additional Comments: We recommend the primary method of administration (allow to disintegrate in the mouth with a sip of water before swallowing) as described in the approved drug label for the recommended BE studies.

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  2. Type of study: Fed  
Design: Single-dose, two-way crossover in-vivo  
Strength: 1000 mg  
Subjects: Males and non-pregnant, non-lactating females, general population.  
Additional Comments: See comment above
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**Analytes to measure (in appropriate biological fluid):** Levetiracetam in plasma.

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

**Waiver request of in-vivo testing:** 250 mg, 500 mg, and 750 mg based on (i) acceptable bioequivalence studies on the 1000 mg strength, (ii) acceptable in vitro multimedia dissolution testing (pH 1.2, 4.5, 6.8) of all strengths, and (iii) proportional similarity of the formulations across all strengths.

**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/>. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. For bio-waiver of the lower strengths, dissolution profiles on 12 dosage units each of test and reference products generated using USP 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.

In addition to the method above, disintegration testing should be used for quality control instead of dissolution testing for Levetiracetam Tablets for Oral Suspension. The disintegration specification will be determined upon review of the abbreviated new drug application (ANDA).