

Draft Guidance on Gabapentin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Tablet (once daily); oral

Recommended Studies: Two studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: 600 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: 600 mg
Subjects: Healthy males and nonpregnant females, general population
Additional comments: None

Analytes to measure (in appropriate biological fluid): Gabapentin in plasma

Bioequivalence based on (90% CI): Gabapentin

Waiver request of in vivo testing: 300 mg strength based on (i) acceptable bioequivalence studies on the 600 mg strength, (ii) proportional similarity of the formulations between both strengths, (iii) acceptable in vitro swelling testing for both strengths, and (iv) acceptable in vitro dissolution testing for both strengths.

Conduct a single-dose two-way crossover fed study on the 300 mg strength if any of the criteria listed above are not met.

In vitro swelling test method and sampling times: Conduct the swelling tests with both modified fasted state simulated gastric fluid (SGF) (USP SGF preparation pH 1.2 without enzyme with 0.1% w/v TritonTM X 100) and fed state SGF (FeSSGF; a 1:1 by volume mixture of pH 5.0 acetate buffer and milk; for additional details regarding the composition of FeSSGF, refer to: Jantratid, Ekarat, et al. "Dissolution media simulating conditions in the proximal human gastrointestinal tract: an update." *Pharmaceutical Research* 25.7 (2008): 1663-1676) and submit

multiple tablet dimensions (i.e., width, length, height, and % weight gain/loss) of the swelling study data on both 300 mg and 600 mg strengths of the test and reference products on at least 6 units each. Submit multiple tablet dimensions at sampling times 0, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours. The swelling study data on the test products should be comparable to the reference products.

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).

In addition to the method above, dissolution profiles on 12 dosage units each of test and reference products generated 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, the Agency currently requests that additional in vitro dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing conditions: 900 mL, 0.1 N HCl, apparatus I (basket) @ 100 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 Alcohol USP for 5% of test medium (v/v), with data collected every 15 minutes for a total of 2 hours

Test 3: 12 units analyzed by substituting Alcohol USP for 20% of test medium (v/v), with data collected every 15 minutes for a total of 2 hours

Test 4: 12 units analyzed by substituting Alcohol USP for 40% of test medium (v/v), with data collected every 15 minutes for a total of 2 hours

Both strengths of the test and the corresponding reference products should be tested accordingly, and data should be provided on individual unit, means, range, and %CV, including f2 similarity values and dissolution plots.