

## Draft Guidance on Tacrolimus

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

**Form/Route:** Extended Release Capsule/Oral

**Recommended studies:** 2 studies

1. Type of study: Fasting  
Design: Single-dose, 4-way, fully replicated crossover design in vivo  
Strength: 5 mg  
Subjects: Healthy males and nonpregnant females, general population.  
Additional Comments: Applicants may consider using the reference-scaled average bioequivalence approach for tacrolimus.

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2. Type of study: Fed  
Design: Single-dose, 4-way, fully replicated crossover design in vivo  
Strength: 5 mg  
Subjects: Healthy males and nonpregnant females, general population.  
Additional Comments: Please see comment above.

**Analytes to measure (in appropriate biological fluid):** Tacrolimus in whole blood

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

**Waiver request of in-vivo testing:** 0.5 mg and 1 mg based on (i) acceptable bioequivalence studies on the 5 mg strength, (ii) acceptable in-vitro dissolution testing of all strengths, and (iii) proportional similarity of 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, USP apparatus 1 (basket) @75 rpm, with or without alcohol:

- Test 1: 12 units tested according to the proposed method (with 0.1N HCl), and data collected every 15 minutes for a total of 2 hours
- Test 2: 12 units tested 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 tested 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 tested 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.

**Explanation:** FDA has concluded that tacrolimus is a narrow therapeutic index (NTI) drug based on the following evidence:

- The range between tacrolimus therapeutic and toxic tacrolimus whole blood concentrations is narrow;
- Some tacrolimus toxicities are serious and/or irreversible;
- Subtherapeutic tacrolimus concentrations may lead to morbidity/mortality associated with graft rejection;
- Tacrolimus requires individual dose titration to achieve a satisfactory balance between maximizing efficacy and minimizing serious dose-related toxicity; Therapeutic drug monitoring is routinely employed to facilitate tacrolimus dose titration; and
- Tacrolimus has small to medium within subject variability.

The study should be a fully replicated crossover design in order to

- Scale bioequivalence limits to the variability of the reference product; and
- Compare test and reference product within-subject variability

For details about Method for Statistical Analysis Using the Reference-Scaled Average Bioequivalence Approach for narrow therapeutic index drugs, please refer to draft Guidance on Warfarin Sodium.