

## Draft Guidance on Tacrolimus

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

**Dosage Form; Route:** Extended release tablet; oral

**Recommended Studies:** Two studies

1. Type of study: Fasting  
Design: Single-dose, 4-way fully replicated crossover design in vivo  
Strength: 4 mg  
Subjects: Healthy males and females (nonpregnant), general population  
Additional comments: Applicants should use the reference-scaled average bioequivalence approach for tacrolimus. The reference and test products should be administered at the same time of the day due to the observed diurnal pharmacokinetic variation.

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2. Type of study: Fed  
Design: Single-dose, 4-way fully replicated crossover design in vivo  
Strength: 4 mg  
Subjects: Healthy males and females (nonpregnant), general population  
Additional comments: See additional comments above.

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

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

**Waiver request of in vivo testing:**

0.75 mg and 1 mg based on (i) acceptable bioequivalence studies on the 4 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths

**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, 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 on **all strengths** using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, USP apparatus 2 (paddle) at 50 rpm, with or without alcohol

Test 1: 12 units tested according to the proposed method (with 0.1N 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.

**Explanation:**

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

- The range between therapeutic and toxic whole blood concentrations of tacrolimus is narrow
- Some tacrolimus toxicities are serious and/or irreversible
- Sub-therapeutic 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
- 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 Guidance on Warfarin Sodium.