

*Contains Nonbinding Recommendations*

**Draft Guidance on Tacrolimus**

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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:** 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: 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:** 0.5 mg and 1 mg, based on (i) acceptable bioequivalence studies on the 5 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:**

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/index.cfm>. 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.

**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.