This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

**Recommended Studies:** Two studies

1. **Type of study:** Fasting  
   **Design:** Single-dose, four-way fully replicated crossover design in vivo  
   **Strength:** EQ 1 mg Base/Package  
   **Subjects:** Males and non-pregnant, non-lactating females, general population  
   **Additional comments:** Use a reference-scaled average bioequivalence approach for tacrolimus. Ensure adequate washout periods between treatment periods due to tacrolimus’ long terminal elimination half-life.

2. **Type of study:** Fed  
   **Design:** Single-dose, two-treatment, two-period crossover in vivo  
   **Strength:** EQ 1 mg Base/Package  
   **Subjects:** Males and non-pregnant, non-lactating females, general population  
   **Additional comments:** See comments above

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

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

**Waiver request of in vivo testing:** EQ 0.2 mg Base/packet based on (i) acceptable bioequivalence studies on the EQ 1 mg Base/Package strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across both 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/](http://www.accessdata.fda.gov/scripts/cder/dissolution/). Conduct comparative dissolution testing on 12 dosage units for each strength of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

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

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*Recommended Mar 2020*
• 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, refer to Guidance on Warfarin Sodium.