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*Draft – Not for Implementation*

## **Draft Guidance on Tacrolimus**

**August 2024**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In general, FDA’s guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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<b>Active Ingredient:</b>	Tacrolimus
<b>Dosage Form:</b>	Tablet, extended release
<b>Route:</b>	Oral
<b>Strengths:</b>	EQ 0.75 mg Base, EQ 1 mg Base, EQ 4 mg Base
<b>Recommended Studies:</b>	Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting  
Design: Single-dose, two-treatment, two-sequence, four-period, fully replicate crossover in vivo  
Strength: EQ 4 mg Base  
Subjects: Healthy males and non-pregnant, non-lactating females  
Additional comments: This drug product is classified as a narrow therapeutic index drug. See the Explanation section for further information. Exclude subjects with risk factors for prolonged QTc interval and Torsades de Pointes. Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of tacrolimus. The reference listed drug (RLD) and test products should be administered at the same time of the day due to the observed diurnal pharmacokinetic variation.
2. Type of study: Fed  
Design: Single-dose, two-treatment, two-sequence, four-period, fully replicate crossover in vivo  
Strength: EQ 4 mg Base  
Subjects: Healthy males and non-pregnant, non-lactating females  
Additional comments: See comments above.

**Analyte to measure:** Tacrolimus in whole blood

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

**Additional strengths:** Bioequivalence of the EQ 0.75 mg Base and EQ 1 mg Base strengths to the corresponding RLD product strengths may be demonstrated based on principles laid out in the most recent version of the FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application*.<sup>a</sup>

**Dissolution test method and sampling times:** For modified release drug products, applicants should develop specific discriminating dissolution methods. Alternatively, applicants may use the dissolution method set forth in any related official United States Pharmacopeia (USP) drug product monograph, or in the FDA's database, <http://www.accessdata.fda.gov/scripts/cder/dissolution/>, provided that applicants submit adequate dissolution data supporting the discriminating ability of such a method. If a new dissolution method is developed, submit the dissolution method development and validation report with the complete information/data supporting the proposed method. Conduct comparative dissolution testing on 12 dosage units for each strength of the test and RLD. Specifications will be determined upon review of the abbreviated new drug application.

In addition to the method above, submit dissolution profiles on 12 dosage units for each strength of the test and RLD generated using USP Apparatus 1 at 100 rpm and/or Apparatus 2 at 50 rpm in at least three dissolution media (e.g., pH 1.2, 4.5 and 6.8 buffer). Agitation speeds may 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.

**Alcohol dose dumping studies:** Due to concerns of dose dumping of drug from this product when taken with alcohol, 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 with 0.005% hydroxypropyl cellulose and 0.5% sodium lauryl sulfate, USP Apparatus 2 (paddle) at 100 rpm, with or without alcohol

Test 1: 12 units tested according to the proposed method (with 0.1 N HCl with 0.005% hydroxypropyl cellulose and 0.5% sodium lauryl sulfate) 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

Conduct testing on both test and RLD products accordingly, and provide data on individual unit, means, range and %CV.

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

- The range between the effective tacrolimus concentrations and the concentrations associated with serious toxicity is narrow.
- Sub-optimal tacrolimus concentrations lead to severe therapeutic failure or toxicity.
- Tacrolimus is subject to therapeutic drug monitoring based on pharmacokinetics measures.
- Tacrolimus exhibits low-to-moderate within-subject variability.
- Dose adjustments are in small increments in clinical practice.

The in vivo bioequivalence studies should be of a fully replicate crossover design to

- Scale bioequivalence limits to the variability of the RLD.
- Compare test and RLD within-subject variability.

For details about the method for statistical analysis using the reference-scaled average bioequivalence approach for narrow therapeutic index drugs, refer to the most recent version of the FDA guidance for industry on *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.<sup>a</sup>

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**Document History:** Recommended June 2016; Revised August 2024

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<sup>a</sup> For the most recent version of a guidance, check the FDA guidance website at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.