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Draft – Not for Implementation

Draft Guidance on Tacrolimus

May 2026

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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.

Active Ingredient:	Tacrolimus
Dosage Form:	Tablet, extended release
Route:	Oral
Strengths:	EQ 0.75 Base | EQ 1 mg Base | EQ 4 mg Base
Reference Listed Drug:	NDA 206406
Recommended Studies:	Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Class of study: Bioequivalence
   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
   Safety recommendations:
   - Subjects should be informed not to use live attenuated or live vaccines prior to and during the study.
   - Subjects should avoid consuming dietary supplements, fruits (e.g., grapefruit), and products containing these fruits that may affect the exposure of tacrolimus for a sufficient time prior to and during the study.
   - Exclude subjects with risk factors for prolonged QTc interval and Torsades de Pointes.

Study design recommendations:

- This drug product is classified as a narrow therapeutic index (NTI) drug. Refer to the Explanation section for further information.
- 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)[1] and test products should be administered at the same time of the day due to the observed diurnal pharmacokinetic variation.

2. Class of study: Bioequivalence
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
Safety recommendations: See recommendations under Study #1.
Study design recommendations: See recommendations under Study #1.

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 strengths may be demonstrated based on principles laid out in the guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application*.[a]

Dissolution: 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 product and RLD. Specifications will be determined upon review of the abbreviated new drug application.

[1] If the RLD is not available, refer to the most recent version of the guidance for industry *Referencing Approved Drug Products in ANDA Submissions.*

In addition to the method above, submit dissolution profiles on 12 dosage units for each strength of the test product 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 product and RLD accordingly, and provide data on individual unit, means, range and %CV.

Enhanced content uniformity considerations for tacrolimus: Content uniformity of tacrolimus solid oral dosage forms should meet enhanced acceptance criteria - USP <905> Level 1: The Acceptance Value for the initial 10 units should be no more than 15.0. In addition, the average content of the 10 units should be between 95 and 105 percent. Level 2 testing is not conducted.

Explanation: FDA has concluded that tacrolimus is an NTI 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 product and RLD within-subject variability.

For details about the method for statistical analysis using the reference-scaled average bioequivalence approach for NTI drugs, refer to the guidance for industry *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.[a]

Document History: Recommended June 2016; Revised August 2024, May 2026

[a] We update guidances periodically. For the most recent version of a guidance, refer to the FDA guidance webpage at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.