Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Tacrolimus

May 2026

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Active Ingredient:	Tacrolimus
Dosage Form:	Capsule
Route:	Oral
Strengths:	EQ 0.25 mg Base | EQ 0.5 mg Base | EQ 0.75 mg Base | EQ 1 mg Base | EQ 2 mg Base | EQ 3 mg Base | EQ 5 mg Base
Reference Listed Drug:	NDA 050708; FDA-2021-P-0083 (EQ 0.25 mg Base, EQ 0.75 mg Base, EQ 2 mg Base, EQ 3 mg Base)
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 5 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.
- $AUC_{(0\text{-}72h)}$ may be used in place of $AUC_{(0\text{-}t)}$ for comparing the extent of absorption, due to tacrolimus's long half-life. Ensure adequate washout periods between treatments in the crossover study.

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 5 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

Waiver request of in vivo testing of additional strengths: Justification based on (i) acceptable bioequivalence studies on the EQ 5 mg Base strength, (ii) acceptable comparative in vitro dissolution studies between the additional strengths and the EQ 5 mg Base strength using 12 units per strength, and (iii) acceptable proportional similarity of the formulations and the same weight ratio of critical excipient(s) to active pharmaceutical ingredient (e.g., dispersing excipient in solid dispersion to tacrolimus) between the additional strengths and the EQ 5 mg strength

Dissolution: Dissolution test(s) should be included for quality control and to support a waiver request of in vivo testing of additional strengths. For the quality control dissolution method, provide a dissolution method development report for the test product containing information and data that demonstrate appropriateness of the selected dissolution method[1] and sampling times, such as the discriminating ability to detect changes in critical quality attributes that could potentially impact drug product performance.

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.

[1] Applicant-developed, United States Pharmacopeia drug product monograph or Dissolution Methods database, https://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm

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: Finalized September 2009; Revised December 2012, 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.