

Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Tacrolimus

August 2022

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This guidance, which interprets the Agency’s regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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In March 2020, FDA issued a draft product-specific guidance for industry on generic tacrolimus. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredient:	Tacrolimus
Dosage Form; Route:	For suspension; oral
Recommended Studies:	Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
Design: Single-does, four-way fully replicated crossover design in vivo
Strength: EQ 1 mg Base/packet
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-does, four-way fully replicated crossover design in vivo
Strength: EQ 1 mg Base/packet
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: See comments above.

Analyte to measure: Tacrolimus in whole blood

Bioequivalence based on (90% CI): Tacrolimus

Waiver request of in vivo testing: EQ 0.2 mg Base/packet strength based on (i) acceptable bioequivalence studies on the EQ 1 mg Base/packet strength, (ii) acceptable in vitro dissolution testing of both strengths, and (iii) proportional similarity of the formulations between both strengths

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units each of both strengths of the test and reference products. Specifications will be determined upon review of the ANDA.

Explanation: FDA has concluded that tacrolimus is a narrow therapeutic index 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 methods 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 Abbreviated New Drug Application*.^a

Revision History: Recommended March 2020; Revised August 2022

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