Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Sirolimus

May 2023

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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:	Sirolimus
Dosage Form; Route:	Powder; Intravenous
Strength:	100 mg/vial
Recommended Studies:	One in vivo bioequivalence study with pharmacokinetic endpoints and one in vitro bioequivalence study with supportive characterization studies

To be eligible for the bioequivalence studies recommended in this guidance, the test product should meet the following criteria:

1. The test and reference listed drug (RLD) formulations are qualitatively (Q1)[1, 2] and quantitatively (Q2)[3] the same.[4]

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.
[2] It is recommended that human serum albumin be sourced from a CBER licensed facility and comply with USP standards and other applicable requirements.
[3] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ± 5% of those used in the reference product.
[4] Per 21 CFR § 314.94 (a)(9)(iii), as a parenteral drug product, a generic sirolimus intravenous powder must be Q1 and Q2 the same as the RLD, except differences in buffers, preservatives, and antioxidants provided that the applicant identifies and characterizes these differences and demonstrates that the differences do not impact the safety/efficacy profile of the drug product.

2. Acceptable comparative physicochemical characterization of the test and the reference standard (RS) products. The comparative study should be performed on a minimum of three exhibit batches of the test product[5] and three batches of the RS product and should include:
    a. Particle morphology
    b. Particle surface potential
    c. Crystallinity of sirolimus
    d. Fraction of free, albumin-bound, and particle-bound sirolimus in reconstituted suspension
    e. Fraction of free and particle-bound albumin in reconstituted suspension
    f. Nature of bond of sirolimus and albumin
    g. Oligomeric status of albumin in excipient and final drug product

One in vitro bioequivalence study:

1. Type of study: Particle size and size distribution
   Design: In vitro bioequivalence study on at least three batches of both the Test and the RS products

Parameters to measure: D10, D50, D90; or z-average diameter and polydispersity index (PDI)

Bioequivalence based on (95% upper confidence bound): Population Bioequivalence (PBE) approach on D50 and SPAN [i.e. (D90-D10)/D50], or alternatively on the harmonic intensity-weighted average particle diameter (z-average) and PDI derived from cumulant analysis of the size intensity distribution. Refer to the most recent version of the FDA product-specific guidance on *Budesonide Inhalation Suspension* (NDA 020929)[a] for additional information regarding PBE.

One in vivo bioequivalence study with pharmacokinetic endpoints:

1. Type of study: Bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, two-way crossover, in vivo
   Strength: 100 mg/vial
   Subjects: Males and non-pregnant, non-lactating females, with locally advanced unresectable or metastatic malignant perivascular epithelioid cell tumor
   Additional comments: See specific recommendations below.

Additional comments regarding the in vivo bioequivalence study with pharmacokinetic endpoints:

Due to safety concerns, the recommended study population are males and non-pregnant, non-lactating females, with locally advanced unresectable or metastatic malignant perivascular epithelioid cell tumor who had not been previously treated with an mTOR inhibitor.

[5] The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches.

If the patient's health status prevents fasting, the sponsor may provide a non-high-fat diet during the proposed study provided that all periods are conducted under same conditions.

If the patient's health status necessitates a dose reduction or any change in the recommended 100 mg/m^2 dose administered via intravenous infusion in 30 minutes, they are to be withdrawn from the study.

The pivotal bioequivalence study should be conducted using test product manufactured on the proposed commercial scale.

Analytes to measure: Unbound and total sirolimus in whole blood.

Bioequivalence based on (90% CI): AUC and C_{max} for total sirolimus. Submit AUC and C_{max} of unbound sirolimus as supportive data.

Waiver request of in vivo testing: Not applicable

Unique Agency Identifier: PSG_213312

[a] For the most recent version of a product-specific guidance, check the FDA product-specific guidance web page at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.