

Draft Guidance on Ketoconazole

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Ketoconazole

Dosage Form; Route: Foam aerosol; topical 2%

I. Waiver option:

- a. To qualify for a waiver of the in vivo bioequivalence (BE) study requirements under 21 CFR 320.22(b)(3), a generic ketoconazole topical foam aerosol product must have the same active ingredient in the same concentration and dosage form as the reference listed drug product (RLD) and must not have an inactive ingredient or other change in formulation from the RLD that may significantly affect systemic or local availability.
- b. For a topical drug product with inactive ingredients that differ from the RLD or are present in significantly different amounts [as permitted by the chemistry, manufacturing and controls regulations for abbreviated new drug applications, 21 CFR 314.94(a)(9)(v)], the regulation specifies that the applicant must identify and characterize the differences and provide information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.
- c. To support the waiver request, data from the following comparative in vitro assays are requested:
 - Microscopic Birefringence Analysis on the dispensed foam after complete collapse to determine whether any crystals of undissolved ketoconazole form during dispensing.
 - Time to Break Analysis, conducted at 30°C, 33°C, 35°C, and 40°C. Time to break is the time from dispensing to complete foam collapse (break). The testing should be done on at least 3 different lots of the RLD and at least 3 lots of the test product (with each lot manufactured separately).
 - Weight per volume of uncollapsed foam.

II. In Vivo option:

Recommended Studies: One study

Type of study: Clinical Endpoint Bioequivalence (BE) Study

Design: Randomized, double blind, parallel, placebo-controlled in vivo

Strength: 2%

Subjects: Healthy males and females with seborrheic dermatitis

Additional comments: FDA recommends submitting a protocol for review and comment prior to conducting the study.

Analytes to measure (in appropriate biological fluid): Not Applicable (N/A)

Bioequivalence based on (90% CI): Clinical endpoint (in vivo option)

Dissolution test method and sampling times: N/A