Contains Nonbinding Recommendations

Draft Guidance on Efinaconazole

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Active Ingredient: Efinaconazole

Dosage Form; Route: Solution; topical

Recommended Studies: Two options: waiver or in vivo study

1. Waiver option:

A. To qualify for a waiver of the in vivo bioequivalence (BE) study requirement under 21 CFR 320.22(b)(3), generic versions of efinaconazole topical solution, 10% should contain the same active drug ingredient in the same concentration and dosage form as the Reference Listed Drug (RLD) product and contain no inactive ingredient or other change in formulation from the RLD that may significantly affect systemic or local availability.

B. For a topical solution drug product that differs from the RLD in inactive ingredients [as permitted by the chemistry, manufacturing and controls regulations for Abbreviated New Drug Applications (ANDAs), 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

Additional Comments:
In general, evidence to demonstrate that the formulation of the test product should not alter the systemic or local availability of efinaconazole, compared to that from the RLD product, may be based upon a comparison of the formulation composition as well as relevant quality and performance attributes of the test and RLD formulations.

For example, if the test and RLD products are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the Guidance for Industry *ANDA Submissions – Refuse-to-Receive Standards,* Revision 2 (December 2016)[1], relevant quality and performance attributes should include appearance, specific gravity, viscosity, evaporation (drying) rate, surface tension, and any other potentially relevant physical and chemical properties, characterized for a minimum of three batches of the test and three batches (as available) of the RLD product.

If the test product contains different inactive ingredients or other changes in the formulation compared to the RLD product, additional quality and performance characterizations should mitigate the risk that any differences between the test and RLD products could affect the

[1] Guidance for Industry: ANDA Submissions – Refuse-to-Receive Standards, Revision 2 (December 2016)

systemic or local availability of efinaconazole, local irritation, or other aspects of the formulation interaction with the disease state that may be relevant to the safety or efficacy of the drug product.

The influence of any differences in the container closure system (CCS) between the test and RLD products should be considered in the design of the characterization studies comparing the test and RLD products. The Guidance for Industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* may provide useful information about considerations relevant to a patient's use of the product.

Prospective applicants of an ANDA may request a Pre-ANDA meeting with OGD to discuss issues relevant to product characterization or pharmaceutical development for a specific test product formulation and CCS.

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2. In vivo study option:

Type of study: BE study with clinical endpoint
Design: Randomized, double-blind, parallel, placebo-controlled, in vivo
Strength: 10%
Subjects: Adult males and non-pregnant, non-lactating females with onychomycosis of the toenail
Additional comments: If an applicant chooses to conduct a BE study with clinical endpoint, the study should include subjects with onychomycosis of the toenails due to *Trichophyton rubrum* and *Trichophyton mentagrophytes*, and compare test product, reference product, and vehicle control. The primary endpoint should be a combination of evidence of both clinical cure and mycological cure [negative potassium hydroxide (KOH) microscopy and negative culture] at Week 52 (4 weeks post-treatment) of the target toenail. OGD recommends that prospective ANDA applicants request a Pre-ANDA meeting with OGD prior to conducting a clinical endpoint study.

Analytes to measure (in appropriate biological fluid): Not applicable

Bioequivalence based on (90% CI): Not applicable

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: Not applicable