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Draft Guidance on Halobetasol Propionate

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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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This is a new draft product-specific guidance for industry on generic halobetasol propionate.

Active Ingredient: Halobetasol propionate

Dosage Form; Route: Aerosol, foam; topical

Recommended Studies: Two options: (1) waiver of in vivo bioequivalence study requirement or (2) one in vivo (vasoconstrictor) bioequivalence study with pharmacodynamic endpoint

I. Option 1: Waiver of in vivo bioequivalence study requirement

1. To qualify for a waiver of the in vivo bioequivalence study requirement under 21 CFR 320.22(b)(3), generic versions of halobetasol propionate topical aerosol foam, 0.05% should contain the same active ingredient in the same concentration and dosage form as the reference product and contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference product that may significantly affect the local or systemic availability of the active ingredient.

2. For a topical solution drug product that differs from the reference product 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.

3. To support the waiver request, data from the following comparative in vitro assays of the test and reference products is requested:
    a. Microscopic birefringence analysis on the dispensed foam after complete collapse to determine whether any crystals of undissolved halobetasol propionate form during dispensing.
    b. Time to break analysis, conducted at 30°C, 33°C, 35°C, and 40°C under controlled relative humidity conditions. Time to break is the time from dispensing to complete foam collapse (break). The testing should be done on a minimum of three batches of the test product and three batches (as available) of the reference product.
    c. Weight per volume of uncollapsed foam.

II. Option 2: One in vivo (vasoconstrictor) bioequivalence study with pharmacodynamic endpoint

1a. Type of study: Pilot vasoconstrictor study
Design: A pilot dose duration-response study using the reference product under un-occluded conditions
Strength: 0.05%
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: Refer to the most recent version of the FDA guidance for industry on *Topical Dermatologic Corticosteroids: In Vivo Bioequivalence*.[a]

1b. Type of study: Pivotal vasoconstrictor bioequivalence study
Design: A pivotal bioequivalence study under un-occluded conditions
Strength: 0.05%
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: See comments above.

Additional information:

Device:
The Reference Listed Drug (RLD) product includes an actuator that is a device constituent, because it changes the drug from a solution to a foam as it delivers the drug to the user.

FDA recommends that prospective applicants examine the size and shape, external critical design attributes, and external operating principles of the RLD device when designing the test device.

User Interface Assessment:
An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a]

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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.