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Draft Guidance on Clobetasol Propionate

May 2023

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Active Ingredient: Clobetasol propionate

Dosage Form; Route: Lotion; Topical

Recommended Studies: Two options: (1) two in vitro bioequivalence studies and other characterization tests, or (2) one in vivo (vasoconstrictor) bioequivalence study with pharmacodynamic endpoint

I. Option 1: Two in vitro bioequivalence studies and other characterization tests

To demonstrate bioequivalence for clobetasol propionate topical lotion, 0.05% using in vitro studies, the following criteria should be met:

1. The test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference standard that may significantly affect the local or systemic availability of the active ingredient. For example, if the test product and reference standard are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the most recent version of the FDA guidance for industry on *ANDA Submissions – Refuse-to-Receive Standards*^a, and the criteria below are also satisfied, the bioequivalence of the test product may be established using a characterization-based bioequivalence approach.
2. The test product and reference standard should have the same physicochemical and structural (Q3) attributes, based upon acceptable comparative Q3 characterization tests with a minimum of three batches of the test product and three batches (as available) of the reference standard. The test product and reference standard batches should ideally represent the product at different ages throughout its shelf life. Refer to the most recent version of the FDA guidance for industry on *Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs*^a for additional

information regarding comparative Q3 characterization tests. The comparison of the test product and reference standard should include characterizations of the following Q3 attributes:

- a. Characterization of visual appearance and texture
 - b. Characterization of phase states and structural organization of matter
 - Microscopic examination with representative high-resolution microscopic images at multiple magnifications
 - Analysis of globule size distribution
 - c. Characterization of rheological behavior which may be characterized using a rheometer that is appropriate for monitoring the non-Newtonian flow behavior of semi-solid dosage forms. The following evaluations are recommended:
 - A characterization of shear stress vs. shear rate and viscosity vs. shear rate. At minimum, this should consist of numerical viscosity data at three shear rates (low, medium, and high).
 - A complete flow curve across the range of attainable shear rates, until low or high shear plateaus are identified.
 - Yield stress values should be reported if the material tested exhibits plastic flow behavior.
 - The linear viscoelastic response (storage and loss modulus vs. frequency) should be measured and reported. Any non-linear viscosity behavior over a range of shear rates should also be investigated, measured, and reported.
 - d. Characterization of water activity
 - e. Characterization of pH
 - f. Characterization of specific gravity
 - g. Characterization of any other potentially relevant Q3 attributes
3. The test product and reference standard should have an equivalent rate of clobetasol propionate release based upon an acceptable in vitro release test (IVRT) bioequivalence study comparing a minimum of one batch each of the test product and reference standard using an appropriately validated IVRT method.

Type of study: Bioequivalence study with IVRT endpoint

Design: Single-dose, two-treatment, parallel, multiple-replicate per treatment group study design using an occluded pseudo-infinite dose, in vitro

Strength: 0.05%

Test system: A synthetic membrane in a diffusion cell system

Analyte to measure: Clobetasol propionate in receptor solution

Equivalence based on: Clobetasol propionate (IVRT endpoint: drug release rate)

Additional comments: Refer to the most recent version of the FDA guidance for industry on *In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs*^a for additional information regarding the development, validation, conduct and analysis of acceptable IVRT methods/studies. The batches of test product and reference standard evaluated in the IVRT bioequivalence study should be included among those for which the Q3 attributes are characterized.

4. The test product and reference standard should have equivalent rate and extent of clobetasol propionate permeation through excised human skin based upon an acceptable in vitro permeation test (IVPT) bioequivalence study comparing a minimum of one batch each of the test product and reference standard using an appropriately validated IVPT method.

Type of study: Bioequivalence study with IVPT endpoints

Design: Single-dose, two-treatment, parallel, multiple-replicate per treatment group study design using an unoccluded finite dose, in vitro

Strength: 0.05%

Test system: Barrier-competent human skin from male and/or female donors of at least 18 years of age in a diffusion cell system

Analyte to measure: Clobetasol propionate in receptor solution

Equivalence based on: Clobetasol propionate (IVPT endpoints: total cumulative amount (AMT) and maximum flux (J_{max}))

Additional comments: Refer to the most recent version of the FDA guidance for industry on *In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs*^a for additional information regarding the development, validation, conduct and analysis of acceptable IVPT methods/studies. The batches of test product and reference standard evaluated in the IVPT bioequivalence study should be the same as those evaluated in the IVRT bioequivalence study.

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

- A. Type of study: Pilot vasoconstrictor study

Design: A pilot dose duration-response study using the reference standard

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 Dermatological Corticosteroids: In Vivo Bioequivalence*.^a

- B. Type of study: Pivotal vasoconstrictor bioequivalence study

Design: A pivotal bioequivalence study

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) is presented in a bottle with a metered-dose pump actuator with an integrated pump locking feature. The metered-dose pump actuator with integrated pump locking feature is the device constituent.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the Test (T) device including:

- Metered, multi-dose format of RLD device
- Same number of doses
- Pump locking feature

User interface assessment:

An abbreviated new drug application (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

Unique Agency Identifier: PSG_213691

^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>.