

Draft Guidance on Hydrocortisone

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Active Ingredient: Hydrocortisone

Dosage Form; Route: Enema; rectal

Recommended Studies: One in vivo bioequivalence study with pharmacokinetic endpoints and other characterization tests

To demonstrate bioequivalence for hydrocortisone rectal enema, 100 mg/60mL using a combination of in vitro studies and an in vivo study with pharmacokinetic endpoints, 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 particle size distribution, crystal habit and polymorphic form of hydrocortisone in the drug product
 - 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.
 - d. Characterization of pH
 - e. Characterization of specific gravity
 - f. Characterization of any other potentially relevant Q3 attributes
3. The test product and reference standard should demonstrate bioequivalence based upon an acceptable in vivo pharmacokinetic study with one batch each of the test product and reference standard.

Type of study: Fasting bioequivalence study with pharmacokinetic endpoints

Design: Single-dose, two-way crossover study, in vivo

Strength: 100mg/60mL

Subjects: Males and non-pregnant, non-lactating females, general population

Analyte to measure: Hydrocortisone in plasma

Equivalence based on: Hydrocortisone, using baseline-corrected data

Additional comments: Dexamethasone should be administered prior to administration of the drug product as a pre-treatment to lower endogenous hydrocortisone levels. Applicants should ensure that the selected dose of dexamethasone is sufficient to suppress endogenous hydrocortisone levels during the entire sampling time period of the bioequivalence study with pharmacokinetic endpoints, and the selected dose of dexamethasone is safe for use in the intended study population. Pharmacokinetic and statistical analyses should be performed on both uncorrected and corrected data. Determination of bioequivalence should be based on the baseline-corrected data. The bioanalytical method should be sufficiently sensitive to be able to adequately characterize the pharmacokinetic profiles of the test product and reference standard. Refer to the most recent version of the FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*^a for additional information regarding the analysis of the bioequivalence study with

pharmacokinetic endpoints. The batches of test product and reference standard evaluated in the bioequivalence study with pharmacokinetic endpoints should be included among those for which the Q3 attributes are characterized.

Applicants intending to propose an alternative approach by which to demonstrate bioequivalence should refer to the most recent version of the FDA guidance for industry on *Controlled Correspondence Related to Generic Drug Development*^a and the most recent version of the FDA guidance for industry on *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*^a for additional information describing the procedures on how to clarify regulatory expectations regarding your individual drug development program.

Additional information:

Device:

The Reference Listed Drug (RLD) is presented in a single-dose bottle with an attached, lubricated applicator tip. The bottle with applicator tip is a 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:

- A lubricated rectal applicator tip

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

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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>.