Draft Guidance on Hydrocortisone Acetate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form: Route: Metered aerosol; rectal

Recommended Studies: In vivo and in vitro studies

FDA recommends the following in vivo and in vitro studies to establish bioequivalence (BE) of the test (T) and reference (R) hydrocortisone acetate rectal aerosol foam, provided that the T drug product is qualitatively (Q1) \(^1\) and quantitatively (Q2) \(^2\) the same as the R drug product.

1. **Type of Study:** Bioequivalence study with pharmacokinetic endpoints  
   **Design:** Single-dose, two-way crossover study under fasted conditions  
   **Strength:** 10%  
   **Subjects:** Health males and nonpregnant females, general population  
   **Additional comments:**  
   a. A 4 mg dose of dexamethasone should be administered 10 hours prior to drug administration as a pre-treatment to lower endogenous hydrocortisone levels.  
   b. ANDA applicants are obligated to consider the data evaluation process (e.g., baseline correction) and ensure its appropriateness.

   **Analytes to measure (in appropriate biological fluid):** Hydrocortisone in plasma

   **Bioequivalence based on (90% CI):** Baseline-corrected \(C_{\text{max}}\) and AUC for hydrocortisone. The 90% confidence interval for the geometric mean T/R ratios of baseline-corrected \(C_{\text{max}}\) and AUC should fall within the limits of 80.00 – 125.00%.

2. **Type of Study:** In vitro comparative physicochemical characterization of the T and R formulations  
   **Design:** The following in vitro tests should be performed on 3 separate lots of R drug product and 3 separate lots of T drug product (with each lot manufactured separately):

   a. **Test:** pH  
      **Design:** pH should be evaluated on the dispensed and collapsed foam.

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\(^1\) Q1 (qualitative sameness) means that the T product uses the same inactive ingredient(s) as the R product.  
\(^2\) Q2 (quantitative sameness) means that concentrations of the inactive ingredient(s) used in the T product are within ±5% of those used in the R product.
b. Test: Weight per Volume and Delivery Amount per Dose
   Design: Weight per volume should be conducted on the uncollapsed foam. Delivery
   amount per dose should be conducted over the entire contents of the canister using the
   proposed canister and applicator following the approved labeling.

c. Test: Comparative Pressure Test
   Design: Canister pressure should be compared between the T and R drug product.

d. Test: Microscopic Birefringence Analysis
   Design: Microscopic birefringence analysis should be conducted on the dispensed
   foam after complete collapse to determine whether any crystals of undissolved drug
   form during dispensing.

e. Test: Time to Break Analysis
   Design: Time to break analysis should be conducted at 30 °C, 33 °C, 35 °C, and 40
   °C. Time to break is the time from dispensing to complete foam collapse (i.e., break).

   Additional comments: If microscopic birefringence analysis demonstrates the presence of
   suspended API particles in the dispensed foam, both particle size analysis and in vitro
   release testing (IVRT) should be conducted on the dispensed foam.

Additional Information

Device:

FDA recommends sponsors consider the following characteristics of the R drug product in
designing the T drug product:

- A multi-dose device capable of delivering the same number of doses as the R drug
  product
- Similar external design (size, shape, and components) as the R drug product
- Similar external operating principles as the R drug product

Sponsors should refer to FDA’s guidance entitled, Comparative Analyses and Related
Comparative Use Human Factors Studies (January 2017), which provides the Agency’s current
thinking on the identification and assessment of any differences in the design of the user
interface for a proposed generic drug-device combination product when compared to its RLD.³

Early in product development and/or prior to the submission of an ANDA, FDA recommends
applicants submit to OGD via controlled correspondence and/or pre-ANDA meeting request, the
results of the comparative analyses (e.g., comparative labeling analysis, comparative task
analyses, comparison in the design of the delivery device constituent), including overall

assessment, of any identified differences between the user interface of the T product when compared to the R product, as described in the guidance referenced above.