Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Hydrocortisone

August 2026

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Hydrocortisone

Dosage Form: Granule

Route: Oral

Strengths: 0.5 mg | 1 mg | 2 mg | 5 mg

Reference Listed Drug: NDA 213876

Recommended Studies: Three in vivo bioequivalence studies with pharmacokinetic endpoints

1. Class of study: Bioequivalence
   Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 5 mg
   Dose: 5 mg administered as granules
   Subjects: Healthy males and non-pregnant, non-lactating females
   Study design recommendations:
   - Administer the 5 mg dose by opening the capsule and pouring the dry granules directly onto the subject's tongue; the subject should swallow the granules dry within 5 minutes of opening, immediately followed by the ingestion of 240 mL of water to ensure that all granules are swallowed.
   - A pre- and post-dose dexamethasone regimen should be utilized to adequately suppress endogenous cortisol production during the study. Provide scientific justification for the selected dexamethasone regimen, including the selected dose, timing intervals relative to Hour 0, and total duration of administration.

2. Class of study: Bioequivalence
Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 5 mg
Dose: 5 mg administered as granules
Subjects: Healthy males and non-pregnant, non-lactating females
Study design recommendations: See recommendations under Study #1.

3. Class of study: Bioequivalence
Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 0.5 mg
Dose: 0.5 mg administered as granules
Subjects: Healthy males and non-pregnant, non-lactating females
Study design recommendations:
    - See recommendations under Study #1.
    - In vivo testing of the 0.5 mg strength under the fasting condition may be waived when the test product has the same product design as the RLD including the critical excipient(s) (e.g., hypromellose) and manufacturing techniques. The critical excipient(s) should not differ from the RLD by more than 10% (w/w) based on the total weight of the critical excipient(s).

Analyte to measure: Hydrocortisone in serum

The pre-dose serum cortisol concentrations should be used for baseline correction. Pharmacokinetics and statistical analyses should be performed on both baseline uncorrected and baseline corrected data.

Bioequivalence based on (90% CI): Baseline-corrected hydrocortisone

Bioequivalence of additional strengths: Waiver request of in vivo testing of additional strength based on (i) acceptable bioequivalence studies on the bio-strength(s), (ii) acceptable comparative in vitro dissolution studies between the additional strengths and the bio-strength(s) using 12 units per strength, and (iii) proportional similarity of the formulations across all strengths, and the same weight ratio of critical excipient(s) to active pharmaceutical ingredient (e.g., hypromellose to hydrocortisone) between the additional strengths and the bio-strength(s)

Dissolution: Dissolution test(s) should be included for quality control and to support a waiver request of in vivo testing of additional strengths. For the quality control dissolution method, provide a dissolution method development report for the test product containing information and data that demonstrate appropriateness of the selected dissolution method[1] and sampling times, such as the discriminating ability to detect changes in critical quality attributes that could potentially impact drug product performance.

Document History: Recommended August 2026

[1] Applicant-developed, United States Pharmacopeia drug product monograph or Dissolution Methods database, https://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm