

## Draft Guidance on Budesonide

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

**Active Ingredient:** Budesonide

**Dosage Form; Route:** Extended release tablet; oral

**Recommended Studies:** Three studies

1. Type of study: Fasting  
Design: Single-dose, partially or fully replicated crossover design, in vivo  
Strength: 9 mg  
Subjects: Normal healthy males and females, general population. Females should not be pregnant, and, if applicable, should practice abstention or contraception during the study.

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2. Type of study: Fed  
Design: Single-dose, partially or fully replicated crossover design, in vivo  
Strength: 9 mg  
Subjects: Normal healthy males and females, general population. Females should not be pregnant, and, if applicable, should practice abstention or contraception during the study.

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

**Bioequivalence based on (90% CI):** Budesonide

**Additional comments regarding the bioequivalence (BE) study with PK endpoints:**

- (1) Applicants may consider using a reference-scaled average bioequivalence approach for budesonide. If using this approach, the applicant should provide evidence of high variability in the BE parameters (i.e., within-subject variability  $\geq 30\%$ ) for the reference product. For general information on this approach, refer to the Progesterone capsule guidance for additional information regarding highly variable drug products.
- (2) For both fasting and fed studies, the following PK parameters are recommended: Log-transformed  $AUC_{8-48}$ ,  $AUC_{0-t}$ , and  $C_{max}$ , where  $AUC_{8-48}$  is the area under the plasma concentration vs. time curve from 8 to 48 hours,  $AUC_{0-t}$  is the area under the curve from 0 hours to the last measurable time point, and  $C_{max}$  is the maximum plasma concentration. There should be at least four non-zero measurements of concentrations for the partial  $AUC_{8-48}$ .

- (3) As  $AUC_{0-t}$  is recommended in place of  $AUC_{0-\infty}$ , the last sampling time point should be at least at 72 hours.
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3. Type of study: In vitro comparative dissolution study  
Strength: 9 mg  
Apparatus: USP Apparatus 2 (paddle)  
Acid stage: 2 hours in 0.1 N HCl at 100 rpm (500 mL)  
Buffer stage: Each of
- (1) pH 4.5 acetate buffer at 100 rpm
  - (2) pH 6.0 phosphate buffer at 100 rpm
  - (3) pH 6.5 phosphate buffer at 100 rpm
  - (4) pH 6.8 phosphate buffer at 100 rpm
  - (5) pH 7.2 phosphate buffer at 100 rpm
  - (6) pH 7.5 phosphate buffer at 100 rpm
- Volume: 1000 mL  
Temperature: 37°C  
Sample times: As needed for profile comparison when applicable  
Additional comments: Submit dissolution data with 0.5% of and without Macrogol Cetostearyl Ether in the buffer stage at different pH values. In addition, the applicant may also use other appropriate type(s) of surfactant in the multi-pH media at various concentrations and use other appropriate apparatus and rotational speed. Submit a detailed dissolution method development report to justify the suitability of the selected surfactant and its concentration and the selected apparatus and rotational speed to demonstrate bioequivalence between the generic product and the reference listed drug (RLD). The applicant should use at least 12 tablets per test.

**Waiver request of in vivo testing:** Not applicable

**Dissolution test method and sampling times:** The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website available to the public at the following location: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing conditions: 900 mL, 0.1 N HCl, USP apparatus 2 (paddle) @ 100 rpm, with or without alcohol

Test 1: 12 units tested according to the proposed method (with 0.1N HCl), with data collected every 15 minutes for a total of two hours

Test 2: 12 units tested by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of two hours

Test 3: 12 units tested by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of two hours

Test 4: 12 units tested by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of two hours

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range, and %CV.