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Draft Guidance on Budesonide

December 2025

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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Active Ingredient:	Budesonide
Dosage Form:	Capsule, delayed release
Route:	Oral
Strength:	4 mg
Recommended Studies:	Two in vivo bioequivalence studies with pharmacokinetic endpoints and one in vitro comparative dissolution study

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 4 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments:
   - Females of reproductive potential should use effective contraception during the study and for one week after the last dose.
   - Applicants may consider using a reference-scaled average bioequivalence approach for budesonide. If using this approach, provide evidence of high variability in the pharmacokinetic parameters (i.e., within-subject variability ≥30%) for the reference listed drug (RLD). [1] For detailed information on this approach, refer to the most recent version of the guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.[a]

[1] If the RLD is not available, refer to the most recent version of the guidance for industry *Referencing Approved Drug Products in ANDA Submissions.*

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 4 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Same comments above.

Analyte to measure: Budesonide in plasma

Bioequivalence based on (90% CI): Budesonide

1. For the fasting study, the following pharmacokinetic parameters will be evaluated for bioequivalence based on 90% CI: Log-transformed area under the concentration (AUC) time curve from hour 4 to the last measurable time point (AUC_{4-t}), AUC from hour 0 to the last measurable time point (AUC_{0-t}), AUC from hour 0 extrapolated to infinite time ($AUC_{0-\infty}$), and maximum concentration (C_{max}). At least four non-zero measurements of concentration are recommended for AUC4-t, with sampling points adequately distributed across the time interval to ensure accurate characterization of the concentration-time profile.

2. For the fed study, the following pharmacokinetic parameters will be evaluated for bioequivalence based on 90% CI: Log-transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}.

Additional pharmacokinetic assessments:

1. For both the fasting and fed studies, submit AUC from 0 hours to 4 hours (AUC_{0-4}) to ensure that budesonide releases in the ileum and not earlier. Budesonide delayed release capsules are intended to primarily release the drug in the ileum, a target site of inflammatory reactions related to progression of primary immunoglobulin A nephropathy. At least four measurements of concentration are recommended for AUC_{0-4}, with sampling timepoints adequately distributed across the 0-4 hour interval to accurately characterize the early concentration-time profile and detect any premature drug release.

2. For the fed study, submit AUC_{4-t} data as supportive evidence of comparable therapeutic outcome. At least four non-zero measurements of concentration are recommended for AUC_{4-t}, with sampling points adequately distributed across the time interval to ensure accurate characterization of the concentration-time profile.

One in vitro comparative dissolution study:

1. Type of study: In vitro comparative dissolution study
   Strength: 4 mg
   Apparatus: United States Pharmacopoeia (USP) Apparatus 2 (paddle)
   Acid stage: 2 hours in 900 mL 0.1N HCl at 100 rpm
   Buffer stage: Each of
   pH 4.5 acetate buffer at 100 rpm
   pH 6.0 phosphate buffer at 100 rpm
   pH 7.2 phosphate buffer at 100 rpm
   Volume: 900 mL
   Temperature: 37ºC
   Sample times: As needed for profile comparison when applicable
   Additional comments: The applicant should use at least 12 dosage units for each of the test product and RLD per test.[1]

Additional strengths: Not applicable

Dissolution test method and sampling times: For modified release drug products, applicants should develop specific discriminating dissolution methods. Alternatively, applicants may use the dissolution method set forth in any related official USP drug product monograph, or in the FDA's database, http://www.accessdata.fda.gov/scripts/cder/dissolution/, provided that applicants submit adequate dissolution data supporting the discriminating ability of such a method. If a new dissolution method is developed, submit the dissolution method development and validation report with the complete information/data supporting the proposed method. Conduct comparative dissolution testing on 12 dosage units for each of the test product and RLD.[1] Specifications will be determined upon review of the abbreviated new drug application.

Alcohol dose dumping studies: Due to concerns of dose dumping of drug from this product when taken with alcohol, conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium as follows:

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

Test 1: 12 units tested according to the proposed method (with 0.1 N HCl) with data collected every 15 minutes for a total of 2 hours

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

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Conduct testing on both test product and RLD accordingly, and provide data on individual unit, means, range and %CV.[1]

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[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.