

Draft Guidance on Albuterol Sulfate; Budesonide

May 2026

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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 Ingredients:	Albuterol sulfate; Budesonide
Dosage Form:	Aerosol, metered
Route:	Inhalation
Strength:	EQ 0.09 mg Base/inh; 0.08 mg/inh
Reference Listed Drug:	NDA 214070
Recommended Studies:	Four in vitro bioequivalence studies, one comparative characterization study, and two in vivo bioequivalence studies with pharmacokinetic endpoints

Eligibility: To demonstrate bioequivalence using the recommendations in this guidance, the test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference standard (RS) that may significantly affect the local or systemic availability of the active ingredient. For example, the test product can be qualitatively (Q1)¹ and quantitatively (Q2)² the same as the RS to satisfy no difference in inactive ingredients.

¹ Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RS.

² Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within $\pm 5\%$ of those used in the RS.

1. Class of study: Bioequivalence
Type of study: Single actuation content (SAC)
Design: The SAC study should be performed at the beginning (B), middle (M), and end (E) lifestages³ of the product using a flow rate of 28.3 L/min or 30 L/min.⁴ U.S. Pharmacopeia (USP) <601> Apparatus A or another appropriate apparatus may be used to determine the SAC using a validated assay. The number of actuations per determination should be one.
Strength: EQ 0.09 mg Base/inh; 0.08 mg/inh

Bioequivalence based on: Population bioequivalence (PBE) analysis of SAC. Refer to the product-specific guidance on *Budesonide Inhalation Suspension* (NDA 020929)^a for additional information regarding PBE analysis procedures.

2. Class of study: Bioequivalence
Type of study: Aerodynamic particle size distribution (APSD)
Design: The APSD study should be performed at the B and E lifestages of the product using a flow rate of 28.3 L/min or 30 L/min. A cascade impactor apparatus for inhalation aerosols as per USP <601> Table 2 or another appropriate method may be used to determine APSD using a validated assay. The APSD determination of each unit should be performed with a minimum number of inhalations justified by the sensitivity of the validated assay.
Strength: EQ 0.09 mg Base/inh; 0.08 mg/inh
Study design recommendations:
 - Drug and co-suspending agent deposition on individual sites, including the mouthpiece adapter, the induction port, each stage of the cascade impactor and the filter, is requested.
 - Mass balance accountability should be reported based on the sum of all deposition sites.
 - For electronic submission of the individual cascade impactor data for the test product and RS, provide a table using the format in the appendix and send them as part of the abbreviated new drug application (ANDA) submission.

Bioequivalence based on: PBE analysis of impactor-sized mass (ISM) of the drugs.⁵

The cascade impactor profiles representing drug and co-suspending agent deposition on the individual stages of the cascade impactor along with the mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle mass (FPM) should be submitted as supportive evidence for equivalent APSD.

³ Based on the labeled number of actuations, the terms, B lifestage, M lifestage, and E lifestage represent the first actuation(s) following the labeled number of priming actuations, the actuation(s) corresponding to 50 percent of the labeled number of actuations, and the actuation(s) corresponding to the labeled number of actuations, respectively.

⁴ The selection of flow rate should match that of the flow rate chosen for APSD testing.

⁵ ISM is defined as a sum of the drug mass on all stages of the cascade impactor plus the terminal filter but excluding the top cascade impactor stage because of its lack of a specified upper cutoff size limit.

3. Class of study: Bioequivalence
Type of study: Realistic APSD
Design: The realistic APSD study should be performed at the B lifestage of the product using mouth-throat models of different sizes (e.g., small and large) and breathing profiles (e.g., weak and strong) that are representative of the patient population. A cascade impactor apparatus for inhalation aerosols as per USP <601> Table 2 or another appropriate method may be used to determine realistic APSD using a validated assay. The realistic APSD determination of each unit should be performed with a minimum number of actuations justified by the sensitivity of the validated assay.
Strength: EQ 0.09 mg Base/inh; 0.08 mg/inh
Study design recommendations:
- Drug and co-suspending agent deposition on individual sites, including the mouthpiece adapter, the mouth-throat model, the mixing inlet, and each stage of the cascade impactor and the filter, is requested.
 - Mass balance accountability should be reported based on the sum of all deposition sites.
 - For electronic submission of the individual cascade impactor data for the test product and RS, provide a table using the format in the appendix, and send them as part of the ANDA submission.

Bioequivalence based on: PBE analysis or other appropriate statistical analysis of ISM of the drugs for each mouth-throat model-breathing profile combination. The cascade impactor profiles representing drug and co-suspending agent deposition on the individual stages of the cascade impactor along with the MMAD, GSD and FPM should be submitted as supportive evidence for equivalent realistic APSD.

Meeting recommendations: If another statistical analysis is used, it should be adequately and scientifically justified considering the purpose of the study. Prospective applicants are encouraged to discuss other statistical analysis designs with FDA via a pre-ANDA meeting request. For additional information, refer to the guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*.^b

4. Class of study: Bioequivalence
Type of study: Dissolution
Design: Dissolution studies are recommended to be performed at the B lifestage of the product. An appropriate apparatus (e.g., USP <711> Apparatus 2, USP <724> Apparatus 5, or Transwell system) may be used to determine dissolution measurements using a sufficiently developed and validated method to support its sensitivity in detecting differences in performance between the test product and RS. Dissolution tests should be performed on samples with sufficiently similar drug mass for test product and RS.
Strength: EQ 0.09 mg Base/inh; 0.08 mg/inh
Study design recommendation:
- Dissolution measurements should be reported in mass units and as percent drug dissolved.

- A comprehensive method development report should be submitted in the ANDA to show how the dissolution method parameters (e.g., equipment, sample collection, product dose amount, media, media volume, stirring/agitation rate, sampling times, etc.) were selected and optimized, and to support that the selected method parameters are appropriate.
- The submitted study method information should detail each parameter value and its sensitivity and reproducibility.
- The dissolution method should be able to demonstrate discriminatory ability (e.g., ability to detect meaningful differences in formulation or manufacturing process, such as a difference in deposited drug particle size) in measuring the dissolution kinetics of the product.

Bioequivalence based on: Comparative analysis of dissolution profiles for budesonide should be established using an appropriate statistical method (e.g., model independent approach using similarity factor (f_2)). For more information on calculation of f_2 factor, refer to the guidance for industry *M9 Biopharmaceutics Classification System-Based Biowaivers*.^b

Study design recommendations for all in vitro bioequivalence studies:

- FDA recommends that prospective applicants conduct in vitro bioequivalence studies for the test product and RS using at least three batches each of the test product and RS, with no fewer than 10 units from each batch.
 - FDA recommends that three primary stability batches be also used to demonstrate in vitro bioequivalence.
 - The three batches of test product should be manufactured from, at a minimum, three different batches of drug substances, excipients, and device constituent part components.
 - The test product should consist of the final device constituent part and final drug constituent formulation intended to be marketed.
5. Class of study: Comparative Characterization
 Type of study: Particle morphology of the emitted dose
 Study design: Imaging comparisons of the deposited particles from the emitted dose at the B lifestage should be determined to assess particle morphology and agglomeration behavior. Description for the sample collection method should be provided.
 Strength: EQ 0.09 mg Base/inh; 0.08 mg/inh
 Study design recommendation:
- The comparative characterization study should be performed on a minimum of three exhibit batches of the T product and three batches of the RS product.
6. Class of study: Bioequivalence
 Type of study: Bioequivalence study with pharmacokinetic endpoints
 Design: Fasting, single-dose, two-way crossover, in vivo
 Strength: EQ 0.09 mg Base/inh; 0.08 mg/inh
 Dose: Minimum number of inhalations that is sufficient to characterize the pharmacokinetic profiles by using a sensitive analytical method
 Subjects: Healthy males and non-pregnant, non-lactating females

Safety recommendation:

- A Bio-IND is required prior to conduct of the pharmacokinetic study if the dose exceeds the maximum labeled single dose.

Study design recommendations:

- The subjects enrolled for in vivo studies should be trained in the use of the inhalation aerosols in a standard fashion prior to each treatment session to assure a relatively consistent inspiratory flow rate and inspiratory duration.
- The subjects should adhere to the reference listed drug (RLD) labeling for administration, including rinsing the mouth with water, if available (do not swallow the water).
- Refer to the guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*^b for additional information regarding the analysis of the bioequivalence study with pharmacokinetic endpoints.

Analytes to measure: Albuterol and budesonide in plasma

Bioequivalence based on (90% confidence interval [CI]): AUC_{0-t}, AUC_{0-inf}, and C_{max} for albuterol and budesonide.

7. Class of study: Bioequivalence

Type of study: Bioequivalence study with pharmacokinetic endpoints

Design: Fasting, single-dose, two-way crossover, in vivo with charcoal block

Dose: Minimum number of inhalations that is sufficient to characterize the pharmacokinetic profiles by using a sensitive analytical method

Subjects: Healthy males and non-pregnant, non-lactating females

Safety recommendation:

- A Bio-IND is required prior to conduct of the pharmacokinetic study if the dose exceeds the maximum labeled single dose.

Study design recommendations:

- The subjects enrolled for in vivo studies should be trained in the use of the inhalation aerosols in a standard fashion prior to each treatment session to assure a relatively consistent inspiratory flow rate and inspiratory duration.
- The subjects should adhere to the RLD labeling for administration, including rinsing the mouth with water, if available (do not swallow the water).
- Refer to the guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*^b for additional information regarding the analysis of the bioequivalence study with pharmacokinetic endpoints.
- Justification for the charcoal dose should be provided in the ANDA submission.

Analytes to measure: Albuterol and budesonide in plasma

Bioequivalence based on (90% CI): AUC_{0-t}, AUC_{0-inf}, and C_{max} for albuterol and budesonide.

Meeting recommendations: Before conducting a charcoal block pharmacokinetic study, prospective applicants are encouraged to discuss their study design and bioequivalence strategy with FDA via a pre-ANDA meeting request. For additional information, refer to the guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*.^b

Computational model(s) for regional drug delivery: An optional computational modeling study may be used to support bioequivalence of the test product and RS. Refer to the product-specific guidance on *Formoterol Fumarate; Glycopyrrolate Inhalation Aerosol, Metered* (NDA 208294)^a for additional information regarding the development and conduct of an optional computational modeling study. In order to clarify the FDA's expectations for prospective applicants early in product development, and to assist applicants to submit an ANDA as complete as possible, FDA strongly encourages applicants to discuss their development program and plans for conducting an optional computational modeling study with the FDA via the pre-ANDA meeting pathway. For additional information, refer to the guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*.^b

Device: The RLD is presented as a metered dose inhaler. The device constituent parts are the actuator and the canister with metering valve. FDA recommends that prospective applicants examine the size and shape, external critical design attributes, and external operating principles of the RLD device when designing the test device including:

- Active, metered, multi-dose format
- Number of doses
- Dose indicator/counter

User interface assessment: An 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 guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.^b

Document History: Recommended May 2025; Revised May 2026

^a We update guidances periodically. For the most recent version of a product-specific guidance, refer to the FDA guidance webpage at <https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm>.

^b We update guidances periodically. For the most recent version of a guidance, refer to the FDA guidance webpage at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

APPENDIX

Variable Name	Variable Type	Content	Notes
Product Name	Character	TEST or REF	Identifier for product
LOT Number	Alphanumeric/Numeric	Alphanumeric/Numeric	Identifier for product lot
UNIT Number	Numeric	Numeric values	Identifier for unit must be unique for each product (e.g. #1-30 for TEST and #31-60 for REF).
Mouthpiece Adapter	Numeric	Numeric Values	MA
Induction Port/Mouth-Throat	Numeric	Numeric Values	IP/MT
Stage 1	Numeric	Numeric Values	S1
Stage 2	Numeric	Numeric Values	S2
Stage 3	Numeric	Numeric Values	S3
Stage 4	Numeric	Numeric Values	S4
Stage 5	Numeric	Numeric Values	S5
Stage 6	Numeric	Numeric Values	S6
Stage 7	Numeric	Numeric Values	S7
Stage 8 or Filter	Numeric	Numeric Values	S8
ISM	Numeric	Numeric Values	ISM
MMAD	Numeric	Numeric Values	MMAD
GSD	Numeric	Numeric Values	GSD
FPM	Numeric	Numeric Values	FPM

Example:

PRODUCT	LOT	Unit	MA	IP/MT	S1	S2	S3	S4	S5	S6	S7	S8 or Filter	ISM	MMAD	GSD	FPM
TEST	1234	1														
		2														
		3														
		4														
		5														
		6														
		7														
		8														
		9														
		10														