

Contains Nonbinding Recommendations
Draft Guidance on Albuterol Sulfate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Aerosol, metered; inhalation

Strength: EQ 0.09 mg BASE/INH

Recommended Studies: In vitro and in vivo studies

The following in vitro and in vivo studies are recommended to establish bioequivalence (BE) of the test (T) and reference (R) metered dose inhalers (MDIs) containing albuterol sulfate.

In Vitro Studies

FDA recommends that applicants conduct the following in vitro studies using at least three batches each of T and R products, with no fewer than 10 units from each batch. The three batches of T product should be manufactured from, at minimum, three different batches of drug substance(s), excipient(s), and container/closure system.

1. **Type of study:** Single actuation content (SAC)
Design: The SAC test should be performed at the beginning (B), middle (M), and end (E) lifestages¹ of the product using a flow rate of 28.3 L/min. The 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.

Equivalence based on: Population bioequivalence (PBE) analysis of SAC. Please refer to the product-specific recommendation for Budesonide Inhalation Suspension for additional information regarding PBE.²

2. **Type of study:** Aerodynamic particle size distribution (APSD)
Design: The APSD test 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. The USP <601> Apparatus 1, Apparatus 6, or another appropriate method may be used to determine APSD using a validated assay.

¹ 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.

² <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM319977.pdf>

The APSD determination of each unit should be performed with a minimum number of inhalations justified by the sensitivity of the validated assay.

Additional comments: Drug deposition on individual sites, including the mouthpiece adapter, the induction port, each stage of the cascade impactor (CI) 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 CI data for the T and R products, please provide a table using the format in the Appendix, and send them as part of the abbreviated new drug application (ANDA) submission for BE evaluation.

Equivalence based on: PBE analysis of impactor-sized mass (ISM).³ The CI profiles representing drug deposition on the individual stages of the CI 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. Type of study: Spray pattern

Design: The spray pattern test should be performed at the B lifestage of the product and at two different distances from the actuator orifice. The selected distances should be at least 3 cm apart and based on the range of 3 to 7 cm from the R actuator mouthpiece.⁴ Impaction (thin-layer chromatography plate impaction), non-impaction (laser light sheet technology), or other suitable method may be used to determine the spray pattern.

Additional comments: Spray pattern should be measured quantitatively in terms of ovality ratio and area within the perimeter of the true shape (to include a high proportion, e.g., 95 % of the total pattern) for the automated analysis or ovality ratio and D_{max} for the manual analysis. Ovality ratio is defined as the ratio of D_{max} to D_{min} . D_{max} and D_{min} are the longest and shortest diameters, respectively, that pass through the center of mass or the center of gravity, as appropriate. The number of sprays per spray pattern would preferably be one.

Equivalence based on: At two selected distances, (i) qualitative comparison of spray shape, and (ii) PBE analysis of ovality ratio and area within the perimeter of the true shape or ovality ratio and D_{max} .

4. Type of study: Plume geometry

Design: The plume geometry test should be performed at B lifestage of the product. The time sequence sound-triggered flash photography method, laser light sheet technology, or other suitable method may be used to determine the plume geometry at the appropriate post-actuation delay time.

Additional comments: Plume geometry measurements should be reported at a single delay time while the fully developed plume is still in contact with the actuator mouthpiece. Plume geometry should be measured quantitatively in terms of plume angle and width. The plume angle is based on the conical region of the plume extending from a vertex that occurs at or near the actuator mouthpiece. The plume width is measured at a

³ ISM is defined as a sum of the drug mass on all stages of the CI plus the terminal filter, but excluding the top CI stage because of its lack of a specified upper cutoff size limit.

⁴ The distance between the actuator orifice and point of spray pattern measurement should be same for T and R.

distance equal to the greater of the two distances selected for characterization of the spray pattern.

Equivalence based on: Ratio of the geometric mean of the three batches of T to that of the three batches of R (based on log transformed data) for both plume angle and width, which should fall within 90-111%.

5. Type of study: Priming and repriming

Design: Priming and repriming tests should be based on the emitted dose (ex-actuator) of a single actuation immediately following the specified number of priming or repriming actuations specified in the R product labeling. The repriming test should be performed following storage for the specified period of non-use after initial use and/or other conditions (e.g., dropping), if the R product labeling provides such repriming information.

Additional comments: For BE evaluation, the priming and repriming tests should be based on products stored in the valve upright position, with the exception of MDIs for which the R labeling recommends storage in the valve down position. The priming data can be based on the SAC data at the B lifestage.

Equivalence based on: PBE analysis of the emitted dose of a single actuation immediately following the specified number of priming or repriming actuations specified in the R product labeling.

Pharmacokinetic (PK) BE Study

FDA recommends that applicants conduct the following PK BE study for the T and R products.

6. Type of Study: Fasting

Design: Single-dose, two-way crossover

Dose: 0.18 mg (two inhalations)

Subjects: Normal healthy males and non-pregnant females, general population.

Additional comments: 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.

Analyte(s) to measure (in appropriate biological fluid): Albuterol in plasma

Equivalence based on: AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} for albuterol. The 90% confidence intervals for the geometric mean T/R ratios of AUC and C_{max} should fall within the limits of 80.00-125.00%.

Pharmacodynamic (PD) BE Study

FDA recommends that applicants conduct a method using either bronchoprovocation (7a) or bronchodilatation (7b) study for the T and R products for this part of in vivo requirements.

7a. Type of Study: Bronchoprovocation study

Design: Single-dose, double-blind, double dummy, randomized, crossover study that is recommended at minimum to consist of:

- Zero dose: One actuation each from two different placebo R inhalation aerosols and one actuation each from two different placebo T inhalation aerosols
- 0.09 mg of R: One actuation each from the R inhalation aerosol and the placebo R inhalation aerosol and one actuation each from two different placebo T inhalation aerosols
- 0.18 mg of R: One actuation each from two different R inhalation aerosol and one actuation each from two different placebo T inhalation aerosols
- 0.09 mg of T: One actuation each from the T inhalation aerosol and the placebo T inhalation aerosol and one actuation each from two different placebo R inhalation aerosols

No less than a 24 hour washout period should be allotted between treatments.

Subjects: Males and non-pregnant females with asthma

Additional comments:

- Inclusion criteria should, at minimum, include:
 - a. Male and non-pregnant female subjects (18-65 years of age).
 - b. Stable mild asthmatics based on National Asthma Education and Prevention Program (NAEPP) guidelines.
 - c. $FEV_1 \geq 80\%$ of predicted.
 - d. Airway responsiveness to methacholine demonstrated by a pre-albuterol-dose (baseline) $PC_{20} \leq 8$ mg/mL.
 - e. Nonsmokers for at least six months prior to the study and a maximum smoking history of five pack-years (the equivalent of one pack per day for five years).
 - f. Written informed consent.
- Exclusion criteria should, at minimum, include:
 - a. Evidence of upper or lower respiratory tract infection (e.g., pneumonia, bronchitis, sinusitis) within six weeks prior to the study.
 - b. History of seasonal asthma exacerbations, in which case the subject should be studied outside of the relevant allergen season.
 - c. History of cystic fibrosis, bronchiectasis or other respiratory diseases.
 - d. History of cardiovascular, renal, neurologic, liver or endocrine dysfunction, including ECG with evidence of ischemic heart disease.
 - e. Treatment in an emergency room or hospitalization for acute asthmatic symptoms or need for daily oral corticosteroids within past three months.
 - f. Known intolerance or hypersensitivity to any component of the albuterol MDI.
- The study day evaluation should take into consideration the following:
 - a. Drug administration should begin within two weeks following screening for admission to the study.

- b. Baseline FEV₁ should not be less than 70% of predicted normal value and within 88-112% of qualifying day FEV₁ value. If either occurs, the study should be rescheduled.
 - c. FEV₁ due to the saline control should fall no more than 10% from the baseline FEV₁, or the study should be postponed. This limits the drop in FEV₁ shown by some subjects due to the saline control vehicle in which the challenge agent is dissolved.
 - d. A subject failing three consecutive visits should be dropped from the study.
- A Bio-IND is required prior to conduct of the PD study as the concentration of methacholine chloride solution may exceed the labeled 25.0 mg/mL concentration, particularly at the higher albuterol dose (e.g., 0.18 mg) where 25.0 mg/mL methacholine chloride may not lead to a 20% reduction in FEV₁.
 - Firms are encouraged to consider the conduct of a pilot study to refine the study design (e.g., inclusion and exclusion criteria) and estimate the study power based on intra- and inter-subject variability and slope of the E_{max} dose-response curve. The method for blinding should be described.

PD endpoint(s): Post-dose PC₂₀ or PD₂₀, which are the provocative concentration or dose, respectively, of the methacholine challenge agent required to reduce the forced expiratory volume in one second (FEV₁) by 20% following administration of differing doses of albuterol (or placebo) by inhalation. The 20% reduction in FEV₁ is determined relative to the saline FEV₁ measured before the placebo or albuterol administration.

Equivalence based on: Dose-scale analysis of the PD data. For details regarding the dose-scale analysis, please refer to the product-specific recommendation for Orlistat Oral Capsule.⁵ The 90% confidence intervals for the relative bioavailability (F) should fall within 67.00-150.00% to establish equivalence in the PD study.

7b. Type of Study: Bronchodilatation study

Design: Single-dose, double-blind, double-dummy, randomized, crossover study that is recommended at minimum to consist of:

- Zero dose: One actuation each from two different placebo R inhalation aerosols and one actuation each from two different placebo T inhalation aerosols
- 0.09 mg of R: One actuation each from the R inhalation aerosol and the placebo R inhalation aerosol and one actuation each from two different placebo T inhalation aerosols
- 0.18 mg of R: One actuation each from two different R inhalation aerosol and one actuation each from two different placebo T inhalation aerosols
- 0.09 mg of T: One actuation each from the T inhalation aerosol and the placebo T inhalation aerosol and one actuation each from two different placebo R inhalation aerosols

No less than a 24 hour washout period should be allotted between treatments.

Subjects: Males and non-pregnant females with asthma

⁵ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201268.pdf>

Additional comments:

- Inclusion criteria should, at minimum, include:
 - a. Male and non-pregnant female subjects (18-65 years of age).
 - b. Moderate-to-severe asthmatics based on NAEPP guidelines.
 - c. FEV₁ within 40-70% of predicted.
 - d. Reversible airway obstruction as demonstrated by an improvement of 15% or more in FEV₁ 30 minutes after inhalation of two puffs (0.18 mg) of R inhalation aerosol.
 - e. Nonsmokers for at least six months prior to the study and a maximum smoking history of five pack-years (the equivalent of one pack per day for five years).
 - f. Written informed consent.
- Exclusion criteria should, at minimum, include:
 - a. History of cardiovascular, renal, neurologic, liver or endocrine dysfunction.
 - b. Evidence of upper or lower respiratory tract infection (e.g., pneumonia, bronchitis, sinusitis) within six weeks prior to the study.
 - c. Intolerance to aerosolized β_2 -adrenergic agonists.
 - d. Inability to tolerate temporary withdrawal of current asthma medication.
 - e. Other co-morbid respiratory and sinus diseases.
 - f. History of status asthmaticus, cystic fibrosis or bronchiectasis.
 - g. History of frequent exacerbations in the previous year.
 - h. Asthmatics who are taking oral corticosteroids.
 - i. Known intolerance or hypersensitivity to any component of the albuterol MDI.
- The study day evaluation should take into consideration the following:
 - a. Randomized treatment should begin within two weeks of the screening visit.
 - b. Baseline FEV₁ should not be less than 45% of predicted or vary by more than $\pm 12\%$ from screening visit FEV₁ value. If either occurs, the study should be rescheduled. If the subject fails to meet these criteria on three separate study days (consecutive or not), they should be dropped from the study.
- Firms are encouraged to consider the conduct of a pilot study to refine the study design (e.g., inclusion and exclusion criteria) and estimate the study power based on intra- and inter-subject variability and slope of the E_{max} dose-response curve. The method for blinding should be described.
- FEV₁ should be measured at 0, 10, 15, 30, 60, 90, 120, 180, 240, 300 and 360 minutes (6 hours) post-dose. FEV₁ should be defined as the highest of the three values obtained at each pulmonary function evaluation period.
- For each treatment group, time to peak bronchodilator response (T_{max}) and FEV₁ values at all measurement times within each evaluation period should be included in the final study report.

PD endpoint(s): Areas under the effect curve calculated from the zero time to four hours (AUEC_{0-4h}) and from zero time to six hours (AUEC_{0-6h}) and maximum FEV₁ (FEV_{1max}). These endpoints should be baseline-adjusted using the pre-dose FEV₁.

Equivalence based on: Dose-scale analysis of the PD data. The 90% confidence intervals for Fs should fall within 67.00-150.00% to establish equivalence in the PD study.

Additional comments:

- The PD BE study may enroll all asthma patients who meet the inclusion and exclusion criteria, or may be enriched by using a sub-population of patients predicted to respond well to the study treatment (appropriate justification should be included for the population chosen for the study).
- All spirometry should be conducted in accordance with the American Thoracic Society (ATS) standards.
- The study protocol should include pre-specified definitions of asthma exacerbation, as well as pre-specified and appropriate escape criteria with consideration to patient safety.
- It is the sponsor's responsibility to enroll a sufficient number of subjects for the study to demonstrate BE of the T product to the R product.
- The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use. The sponsor should clearly explain whether the medication was used prior to baseline visit, during the study or both.
- All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of each AE should include the date of onset, description of AE, severity, relation to study medication, action taken, outcome, and date of resolution. The information will assist FDA in determining whether the incidence and severity of adverse reactions is different between the T and R products.
- Subjects who discontinued from the study early should be identified, and the protocol should clearly, prospectively state how missing data will be handled in the statistical analysis and provide justification for the method chosen. The protocol should also include subject retention strategies and other plans to minimize missing data.
- If there are missing data, adequate justification should be provided that the missing data do not lead to biased F estimation.
- Detailed information for all subjects who are discontinued from the study should be provided.
- Log transformation of the PD data before fitting the E_{max} model is recommended for dose-scale analysis.

Additional Information

Formulation

The T formulation is recommended to be qualitatively (Q1)⁶ and quantitatively (Q2)⁷ the same as the R formulation.

Device

The T product should be similar in shape and size to the R product. The T product should have a dose counter if the R product has a dose counter. In vitro and in-use studies should be conducted to support the functionality, accuracy and robustness of the proposed T product.

Applicants are encouraged to submit a working model of the proposed T MDI device to the Office of Generic Drugs prior to the ANDA submission, in order to ensure the eligibility of the proposed T MDI device under the 505(j) pathway.

⁶ Q₁ (qualitative sameness) means that the T product uses the same inactive ingredient(s) as the R product.

⁷ Q₂ (quantitative sameness) means that concentration of the inactive ingredient(s) used in the T product are within $\pm 5\%$ of those used in the R product.

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).
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	FRM

Example

PRODUCT	LOT	Unit	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												