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Draft Guidance on Albuterol Sulfate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Strength: EQ 0.090 mg Base/Inh

Recommended Studies: In vitro and in vivo studies

FDA recommends the following in vitro and in vivo studies to establish bioequivalence (BE) of the test (T) and reference (R) dry powder inhalers (DPIs) containing albuterol sulfate.

In Vitro Studies:

FDA recommends that prospective applicants conduct the following in vitro studies using at least three batches each of the T and R products, with no fewer than 10 units from each batch. FDA recommends that three primary stability batches be also used to demonstrate in vitro BE. The three batches of T product should be manufactured from, at minimum, three different batches of drug substance(s), excipient(s), and device components. The T product should consist of the final device constituent part and final drug constituent formulation intended to be marketed.

1. Type of study: Single actuation content (SAC)
   Design: The SAC test should be performed at the beginning (B), middle (M), and end (E) lifestages[1] of the product, using a flow rate of 31.5 L/min, 63 L/min and 94.5 L/min. U.S. Pharmacopoeia (USP) <601> Apparatus B or another appropriate apparatus may be used to determine the SAC using a validated assay. The number of actuations per determination should be one. The volume of air drawn through the delivery system should be 2 L.

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

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 flow rates of 31.5 L/min, 63 L/min and 94.5 L/min. The USP <601> Apparatus 3,

[1] Based on the labeled number of actuations, the terms, B lifestage, M lifestage, and E lifestage represent the first actuation(s) following the priming, 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.

Apparatus 5, 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. The volume of air drawn through the delivery system should be 4 L.
Additional comments: Drug deposition on individual sites, including the mouthpiece adapter, the induction port, the pre-separator, and 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, 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).[2] 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.

Pharmacokinetic Study

FDA recommends that prospective applicants conduct the following pharmacokinetic (PK) BE study for both strengths of the T and R products.

3. Type of study: Fasting
   Design: Single-dose, two-way crossover
   Dose: 0.18 mg (two inhalations)
   Subjects: Adult males and non-pregnant females, general population
   Additional comments: Subjects enrolled for in vivo studies should be trained in the use of the inhalation powders 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 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

A method using bronchoprovocation study is recommended for this part of the in vivo requirements.

4. Type of study: Bronchoprovocation study

[2] 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.

Design: Single-dose, double-blind, double-dummy, randomized, crossover study. FDA recommends that the study consist of, at a minimum:

- Zero dose: One actuation each from two different placebo R inhalation powders and one actuation each from two different placebo T inhalation powders
- 0.090 mg of R: One actuation each from the R inhalation powder and the placebo R inhalation powder, and one actuation each from two different placebo T inhalation powders
- 0.18 mg of R: One actuation each from two different R inhalation powders and one actuation each from two different placebo T inhalation powders
- 0.090 mg of T: One actuation each from the T inhalation powder and the placebo T inhalation powder, and one actuation each from two different placebo R inhalation powders

No less than a 24-hour washout period should be allotted between treatments.
Subjects: Adult male and nonpregnant females with asthma
Additional Comments:

- Inclusion criteria should, at minimum, include:
    a. Adult male or female subjects of non-childbearing potential, or of childbearing potential committing to consistent and correct use of an acceptable method of birth control.
    b. Stable mild asthmatics based on National Asthma Education and Prevent 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 minimum 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 6 weeks prior to the study.
    b. If a history of seasonal asthma exacerbations, the subject should be studied outside of the relevant allergen season.
    c. History of cystic fibrosis, bronchiectasis, or other respiratory disease
    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 DPI.

- The study-day evaluation should take into consideration the following:
    a. Drug administration should begin within two weeks following screening for admission.

b. Baseline FEV_1 should not be less than 70% of predicted normal value and within 88 – 112% of qualifying day FEV_1 value. If either occurs, the study should be rescheduled.
c. FEV_1 due to the saline control should fall no more than 10% from the baseline FEV_1, or the study should be postponed. This limits the drop in FEV_1 shown by some patients 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 FEV_1.
- 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 of blinding should be described.

PD endpoint: Post-dose PC_{20} or PD_{20}, which are the provocative concentration or dose, respectively, of the methacholine challenge agent required to reduce the forced expiratory volume in one second (FEV_1) by 20% following administration of different doses of albuterol (or placebo) by inhalation. The 20% reduction in FEV_1 is determined relative to the saline FEV_1 measured before the placebo or albuterol administration.

Equivalence based on: Dose-scale analysis of the PD data. For details regarding the dose-scale analysis, refer to the product-specific guidance for *Orlistat Oral Capsule*. The 90% confidence intervals for the relative bioavailability (F) 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 prospective applicant'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 prospective applicant 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 Emax model is recommended for dose-scale analysis.

Additional Information

Formulation:

FDA recommends that the T formulation be qualitatively (Q1)[3] and quantitatively (Q2)[4] the same as the R formulation.

If a prospective applicant uses a Q2-different formulation for its T product, the prospective applicant should explain the reason(s) for not using a T formulation that is Q2 the same as the R formulation. In addition, the prospective applicant should provide pharmaceutical development data, involving in vitro testing of multiple drug-to-excipient ratios that encompass combinations below and above the ratios used in the T and R products.

Device:

Prospective applicants should refer to FDA's guidance entitled, *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January 2017), which, when finalized, will provide the Agency's current thinking on the identification and assessment of any differences in the design of the user interface for a proposed generic drug-device combination product when compared to its RLD.

FDA recommends that prospective applicants consider the following characteristics of the R product when designing the T product:

- Passive (breath-actuated) device
- Device-metered multi-dose format
- Number of doses of the R product
- External operating principles and external critical design attributes of the R product
- Size and shape of the R product

[3] Q1 (qualitative sameness) means that the T product uses the same inactive ingredient(s) as the R product.
[4] Q2 (quantitative sameness) means that concentration of the inactive ingredient(s) used in the T product are within ± 5% of those used in the R product.

- Device resistance of the R product
- Dose indicator/counter

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												