Contains Nonbinding Recommendations

Draft Guidance on Salmeterol Xinafoate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Powder; inhalation

Strength: EQ 0.05 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 salmeterol xinafoate.

In Vitro Studies

FDA recommends that applicants conduct the following in vitro studies for the T and R products. Use 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) lifestages[1] of the product using flow rates of 30 L/min, 60 L/min, and 90 L/min. The 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. Please refer to the product-specific guidance 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 flow rates of 28.3 L/min or 30 L/min, 60 L/min, and 90 L/min. The USP <601> Apparatus 3, Apparatus 5, or another appropriate method may be used to determine

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

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).[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.

Pharmacokinetic Study

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

3. Type of study: Fasting
   Design: Single-dose, two-way crossover
   Dose: Minimum number of inhalations that is sufficient to characterize a PK profile by using a sensitive analytical method
   Subjects: Normal males and non-pregnant females, general population
   Additional comments: (1) Subjects enrolled for in vivo studies should be trained in the use of the inhalation powder in a standard fashion, prior to each treatment session, to assure a relatively consistent inspiratory flow rate and inspiratory duration. (2) A Bio-IND is required prior to conduct the PK study if the dose exceeds the maximum labeled single dose.

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

   Equivalence based on: AUC and C_{max} for salmeterol. 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 %.

Comparative Clinical Pharmacodynamic Study

FDA recommends that applicants conduct the following comparative clinical pharmacodynamic (PD) BE study for the T and R products.

[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. Type of Study: Comparative clinical PD BE study

Design: This study could be either of crossover or parallel-group design, taking into consideration the patient population and the current standard-of-care treatment for asthma, and should include appropriate justification for the design chosen. The study should be randomized, single-dose and placebo-controlled, at minimum consisting of a 2-week run-in period followed by a one-day treatment period of the placebo, T, or R product.

Strength: EQ 0.05 mg base/inh (salmeterol xinafoate inhalation powder)

Dose: 0.05 mg salmeterol, single-dose of one inhalation

Subjects: Males and non-pregnant females with asthma. The study may enroll all asthma patients who meet the inclusion and exclusion criteria, or may be enriched by using a subpopulation of patients predicted to respond well to the study treatment (appropriate justification should be included for the population chosen).

Inclusion and exclusion criteria:

Inclusion criteria should, at minimum, include:

a. Adult male or female subjects of non-child-bearing potential or of child-bearing potential committed to consistent and correct use of an acceptable method of birth control
b. Diagnosis of asthma, as defined by the National Asthma Education and Prevention Program (NAEPP),[4] at least 12 weeks prior to screening
c. Pre-bronchodilator FEV_1 of $\geq 40\%$ and $\leq 85\%$ of the predicted value during the screening visit and on the first day of treatment
d. $\geq 15\%$ reversibility of FEV_1 within 30 minutes following 360 mcg of salbutamol/albuterol inhalation (pMDI)
e. Patients should be stable on their chronic asthma treatment regimen for at least 4 weeks prior to screening
f. Currently non-smoking; having not used tobacco products (i.e., cigarettes, cigars, pipe tobacco) within the past year, and having had ≤ 10 pack-years of historical use
g. Ability to replace current short-acting β-agonists (SABAs) with salbutamol/albuterol inhaler for use as needed for the duration of the study. Subjects should be able to withhold all inhaled SABAs for at least 6 hours prior to lung function assessments on the study visit
h. Ability to discontinue their asthma medications (inhaled corticosteroids and long-acting β-agonists) during the run-in period and for remainder of the study
i. Willingness to give their written informed consent to participate in the study

Exclusion criteria should, at minimum, include:

a. Life-threatening asthma, defined as a history of asthma episode(s) requiring intubation, and/or associated with hypercapnia, respiratory arrest or hypoxic seizures, asthma-related syncopal episode(s), or hospitalizations within the past year prior to the screening or during the run-in period
b. Significant respiratory disease other than asthma (COPD, interstitial lung disease, etc.)

[4] Guidelines for the Diagnosis and Management of Asthma: Expert Panel Report 3. National Education and Prevention Program; National Institute of Health; National Heart, Lung and Blood Institute. 2007, Publication No. 07-4051.

c. Evidence or history of clinically significant disease or abnormality, including congestive heart failure, uncontrolled hypertension, uncontrolled coronary artery disease, myocardial infarction, or cardiac dysrhythmia. In addition, historical or current evidence of significant hematologic, hepatic, neurologic, psychiatric, renal, or other diseases that, in the opinion of the investigator, would put the patient at risk through study participation, or would affect the study analyses if the disease exacerbated during the study
d. Viral or bacterial, fungal or parasitic, upper or lower respiratory tract infection, or sinus, or middle ear infection within 4 weeks prior to the screening visit, during the run-in period, or on the day of treatment
e. Hypersensitivity to any sympathomimetic drug (e.g., salmeterol/albuterol), or to any inhaled, intranasal, or systemic corticosteroid therapy, or to milk proteins, or to excipients in the DPI
f. Patients receiving systemic, oral, parenteral or depot corticosteroid therapy, or who have ceased use of maintenance oral steroids within 4 weeks of Visit 1
g. Patients receiving β2-blockers, antiarrhythmic agents, antidepressants, monoamine oxidase inhibitors, cytochrome P450 3A4 inhibitors, and diuretics, within 4 weeks prior to the screening.

Additional comments:

a. A clear list of permitted and restricted medications should be provided, including justification for use (or restriction) of certain classes of respiratory therapies, that considers the current standard of care for asthma.
b. All spirometry should be conducted in accordance with ATS standards.
c. The study protocol should list appropriate withholding times prior to spirometry for permitted concomitant medications (e.g., 4 hours for short-acting beta-agonists, 12 or 24 hours for long-acting beta-agonists).
d. The study should begin with a placebo run-in period (at least 2 weeks in duration; appropriate justification should be included for the duration chosen) to wash out any pre-study corticosteroids/long-acting bronchodilators and to establish FEV_1 baseline values.
e. To ensure adequate study sensitivity, the T and R products should both be statistically superior to placebo ($p < 0.05$) with regard to the BE study primary endpoints.
f. It is the sponsor's responsibility to enroll a sufficient number of subjects for the study to demonstrate BE of the T to the R product.
g. All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome, and date of resolution.
h. 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.
i. Appropriate pre-defined withdrawal criteria should be described for patients who may require withdrawal during washout period due to asthma exacerbation or inability to tolerate withdrawal of baseline therapy.
j. Subjects who discontinue 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 appropriate 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 equivalence determination. Detailed information for all subjects who are discontinued from the study should be provided.

BE study endpoints: Area under the serial FEV_1-time curve calculated from time zero to 12 hours ($AUC_{0\text{-}12h}$) following the treatment.

The above BE study endpoint should be baseline adjusted (change from baseline). FEV_1 measurements should be performed and interpreted in accordance with ATS guidelines.

Serial spirometry (FEV_1) should be measured at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours post-dose.

For each treatment group, time to peak bronchodilator response (Tmax) and FEV1 values at all measurement times within each evaluation period should be included in the final study report.

Equivalence based on: T/R ratio for the primary endpoint. The 90% confidence intervals for the T/R ratios for the BE study endpoint should fall within the limits of 80.00 - 125.00%.

Additional Information

Formulation:

FDA recommends that the T product be qualitatively (Q_1)[5] and quantitatively (Q_2)[6] the same as the R product.

If a sponsor uses a Q_2-different formulation for its T product, the sponsor should explain the reason(s) for not using a T formulation that is Q_2 the same as the R formulation. In addition, the sponsor 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:

Applicants should refer to the FDA Guidance for Industry 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

[5] Q_1 (qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.
[6] Q_2 (quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the reference product.

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 applicants consider the following characteristics of the R product when designing the T product:

- Passive (breath-actuated) device
- Pre-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
- Device resistance of the R product
- Dose indicator/counter

In addition, in vitro and in use studies should be conducted to support the functionality, accuracy and robustness of the proposed T 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	FPM

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												