Contains Nonbinding Recommendations

Draft Guidance on Formoterol Fumarate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Powder; inhalation

Recommended Studies: In vitro and in vivo studies

The Agency recommends the following in vitro and in vivo studies to establish bioequivalence of the test (T) and reference (R) dry powder inhalers (DPIs) containing formoterol fumarate.

In Vitro Studies

The Agency 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) lifestages[1] of the product using flow rates of 30 L/min, 60 L/min, and 90 L/min. The U.S. Pharmacopeia (USP) <601> Apparatus B or another appropriate apparatus may be used to determine the SAC using a validated assay. The number of capsules used 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. The draft budesonide inhalation suspension BE guidance contains 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 capsules 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 bioequivalence (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 (PK) BE Study

The Agency recommends that applicants conduct the following 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. If the dose exceeds the maximum labeled number of single doses, a Bio-IND should be submitted to the Agency.
   Subjects: Normal healthy males and nonpregnant females, general populatio

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

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

Clinical Pharmacodynamic Study

The Agency recommends that applicants conduct the following clinical pharmacodynamic study for the T and R products.

[3] ISM is defined as the 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: BE study
   Design: Parallel group or crossover 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: 0.012 mg/inh (formoterol fumarate inhalation powder)
   Dose: 0.012 mg, single dose
   Subjects: Males and nonpregnant females with asthma
   Additional comments:
   - Inclusion criteria should, at minimum, include:
     a. Adult male or female subjects of non-child-bearing potential or of child-bearing potential committing 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 the screening
     c. Pre-bronchodilator FEV_1 of $\geq$ 40% and $\leq$ 85% of the predicted value during the screening visit and on the day of treatment
     d. $\geq$ 15% reversibility of FEV_1 within 30 minutes following 360 mcg of albuterol inhalation (pMDI)
     e. Ability to discontinue long-acting β agonists, if currently used, during the run-in period and on the day of treatment
     f. 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
     g. 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
     h. 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 episodes(s) requiring intubation, and/or associated with hypercapnia, respiratory arrest or hypoxic seizures, asthma-related syncopal episodes(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.)
     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

[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.

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, upper or lower respiratory tract infection, or sinus, or middle ear infection within 4 weeks prior to the screening, during the run-in period, or on the day of treatment
e. Hypersensitivity to any sympathomimetic drug (e.g., albuterol, formoterol)
f. Patients receiving β_2-blockers, antiarrhythmics, anti-depressants, and monoamine oxidase inhibitors within 4 weeks prior to the screening
g. Patients under treatment with a fixed combination of β_2-agonists and inhaled corticosteroids, if unable to transition to an ICS-only product during the run-in period of the study

- All spirometry should be conducted in accordance with ATS standards.
- The study protocol should list appropriate withholding times prior to spirometry for permitted concomitant medications (e.g., 6 hours for SABAs).
- FDA recommends the study begin with a placebo run-in period (at least 2 weeks in duration) to wash out any pre-study, long-acting bronchodilators and to establish FEV_1 baseline values.
- 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.
- 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 endpoint.
- It is the sponsor's responsibility to enroll a sufficient number of subjects for the study to demonstrate bioequivalence of the T to the R product.
- All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of an AE should include date of onset, description of AE, severity, relation to study medication, action taken, outcome, and date of resolution.

BE study primary endpoint: Area under the serial FEV_1-time curve calculated from time zero to 12 hours ($AUC_{0\text{-}12h}$) on the first say of 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 (T_{max}) and FEV_1 values at all measurement time points 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 ratio for the BE study endpoint should fall within 80.00-125.00%.

Additional Information

Formulation:

The T product is recommended to 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:

The Agency encourages sponsors to submit a working model and engineering drawings of the T product to the Office of Generic Drugs (OGD) prior to ANDA submission.

The T product should have the following characteristics :

- Passive (breath-actuated) device
- Pre-metered single-unit dose capsule-based format
- Delivery of the same number of doses as the R product; similarity in size and shape; and similar external operating principles
- Device resistance comparable to the R product's

In addition, the robustness of the T product should be demonstrated.

[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.

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												