

Contains Nonbinding Recommendations
Draft – Not for Implementation
Draft Guidance on Formoterol Fumarate
May 2023

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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 Ingredient:	Formoterol fumarate
Dosage Form; Route:	Powder; Inhalation
Strength:	0.012 mg/inh
Recommended Studies:	Two in vitro bioequivalence studies, one in vivo bioequivalence study with pharmacokinetic endpoints, and one comparative clinical endpoint bioequivalence study

FDA 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 bioequivalence studies:

FDA recommends that prospective applicants conduct the following in vitro bioequivalence 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. FDA recommends that three primary stability batches be also used to demonstrate in vitro bioequivalence. The three batches of T product should be manufactured from, at minimum, three different batches of drug substance(s), excipient(s), and device constituent part 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^{1,2} 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. Refer to the most recent version of the FDA product-specific guidance for *Budesonide Inhalation Suspension*^a 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 28.3 L/min or 30 L/min, 60 L/min, and 90 L/min. Cascade impaction devices 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 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 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.

In vivo bioequivalence study with pharmacokinetic endpoints:

FDA recommends that prospective applicants conduct the following pharmacokinetic bioequivalence study for the T and R products.

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. In vitro lifestage testing should be conducted on the to be marketed packaging configuration with the highest number of doses. For example, the B, M, and E lifestage for a 60 capsule packaging configuration may correspond to actuations 1, 30, and 60.

² When conducting in vitro studies at different lifestages, doses between those tested at each lifestage should be actuated using the device. For example, prospective applicants testing at the E lifestage should actuate all doses leading up to the dose used to test the E lifestage.

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.

1. Type of Study: Fasting
Design: Single-dose, two-way crossover
Dose: Minimum number of inhalations that is sufficient to characterize a pharmacokinetic profile by using a sensitive analytical method.
Subjects: Healthy males and nonpregnant females
Additional comments: (1) Subjects enrolled for in vivo bioequivalence 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 of the pharmacokinetic bioequivalence study if the dose exceeds the maximum labeled single dose.

Analyte to measure: 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%.

Comparative clinical endpoint bioequivalence study:

FDA recommends that prospective applicants conduct the following comparative clinical endpoint bioequivalence study for the T and R products.

1. Type of Study: Comparative clinical endpoint bioequivalence 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 non-pregnant females with asthma
Additional comments:
 - a. Inclusion criteria should, at minimum, include:
 - 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
 - Diagnosis of asthma as defined by the National Asthma Education and Prevention Program (NAEPP)⁴ at least 12 weeks prior to the screening
 - Pre-bronchodilator forced expiratory volume in one second (FEV₁) of $\geq 40\%$ and $\leq 85\%$ of the predicted value during the screening visit and on the day of treatment
 - $\geq 15\%$ reversibility of FEV₁ within 30 minutes following 360 mcg of albuterol inhalation (pMDI)

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.

- Ability to discontinue long-acting β agonists, if currently used, during the run-in period and on the day of treatment
 - 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
 - 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
 - Willingness to give their written informed consent to participate in the study
- b. Exclusion criteria should, at minimum, include:
- 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
 - Significant respiratory disease other than asthma (COPD, interstitial lung disease, etc.)
 - 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
 - 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
 - Hypersensitivity to any sympathomimetic drug (e.g., albuterol, formoterol)
 - Patients receiving β_2 -blockers, antiarrhythmics, anti-depressants, and monoamine oxidase inhibitors within 4 weeks prior to the screening
 - 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
- c. A clear list of permitted and restricted medications should be provided, including justification for use (or restriction) of certain classes of respiratory therapies, considering the current standard of care for asthma.
- d. All spirometry should be conducted in accordance with American Thoracic Society (ATS) standards.
- e. The study protocol should list appropriate withholding times prior to spirometry for permitted concomitant medications (e.g., 6 hours for SABAs).
- f. FDA recommends the study 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, long-acting bronchodilators and to establish FEV₁ baseline values.

- g. 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.
- h. To ensure adequate study sensitivity, the T and R products should both be statistically superior to placebo ($p < 0.05$) with regard to the bioequivalence study primary endpoint.
- i. It is the prospective applicant's responsibility to enroll a sufficient number of subjects for the study to demonstrate bioequivalence of the T to the R product.
- j. 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.
- k. 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 analyses 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.

Bioequivalence study primary endpoint: Area under the serial FEV₁-time curve calculated from time zero to 12 hours (AUC_{0-12h}) on the first day of treatment.

The above bioequivalence study endpoint should be baseline-adjusted (change from baseline). FEV₁ measurements should be performed and interpreted in accordance with ATS guidelines.

Serial spirometry (FEV₁) 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 FEV₁ 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 study endpoint should fall within 80.00% - 125.00%.

Additional information:

Formulation:

The T product is recommended to be qualitatively (Q₁)⁵ and quantitatively (Q₂)⁶ the same as the R product. 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:

The reference listed drug (RLD) is presented in drug capsules co-packaged with a dry powder inhaler. The inhaler is the device constituent part.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the test devices including:

- Passive (breath-actuated), pre-metered, single-unit dose, capsule-based format of the RLD device
- Number of doses of the RLD product
- Device resistance of the RLD product

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 most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.^b

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^a For the most recent version of a product-specific guidance, check the FDA product-specific guidance web page at <https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm>.

^b For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

⁵ Q1 (qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.

⁶ Q2 (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	S 1	S 2	S 3	S 4	S 5	S 6	S 7	S8 or Filter	ISM	MMAD	GSD	FPM
TEST	1234	1												
		2												
		3												
		4												
		5												
		6												
		7												
		8												
		9												
		10												