Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Fluticasone Furoate; Umeclidinium Bromide; Vilanterol Trifenatate

February 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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 Ingredients:	Fluticasone furoate; Umeclidinium bromide; Vilanterol trifenatate
Dosage Form:	Powder
Route:	Inhalation
Strengths:	0.1 mg/inh; EQ 0.0625 mg Base/inh; EQ 0.025 mg Base/inh, 0.2 mg/inh; EQ 0.0625 mg Base/inh; EQ 0.025 mg Base/inh
Recommended Studies:	Two in vitro bioequivalence studies, one in vivo bioequivalence study with pharmacokinetic endpoints, and one comparative clinical endpoint bioequivalence study

Two in vitro bioequivalence studies:

FDA recommends that prospective applicants conduct the following in vitro bioequivalence studies for both strengths of the test (T) and reference standard (RS) products. For each strength, use at least three batches each of the T and RS 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 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 30 L/min, 60 L/min and 90 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.

Bioequivalence based on: Population bioequivalence (PBE) analysis of SAC. Refer to the most recent version of the FDA product-specific guidance on *Budesonide Inhalation Suspension* (NDA 020929)[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 for inhalation powders 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 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 RS products, provide a timetable using the format in the appendix, and send them as part of the abbreviated new drug application (ANDA) submission.

Bioequivalence 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.

One in vivo bioequivalence study with pharmacokinetic endpoints:

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: Adult males and non-pregnant females, general population

[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] 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.

Additional comments: (1) 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. (2) The subjects should adhere to labeling as follows: "Rinse your mouth with water after you have used the inhaler and spit the water out. Do not swallow the water." (3) A Bio-IND is required prior to conduct of the pharmacokinetic study if the dose exceeds the maximum labeled single dose.

Analytes to measure: Fluticasone furoate, umeclidinium, and vilanterol in plasma

Bioequivalence based on: AUC and C_{max} for fluticasone furoate, umeclidinium and vilanterol. 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%.

One comparative clinical endpoint bioequivalence study:

1. Type of study: Comparative clinical endpoint bioequivalence study
Design: A randomized, multiple-dose, placebo-controlled, parallel group design, at minimum consisting of a 2-week run-in period followed by a 4-week treatment period of the placebo, T or RS product
Strength: 0.1 mg/inh; EQ 0.0625 mg Base/inh; EQ 0.025 mg Base/inh
Dose: 0.1 mg/inh; EQ 0.0625 mg Base/inh; EQ 0.025 mg Base/inh, one inhalation once daily

   Inclusion and exclusion criteria:
   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. Diagnosis of asthma as defined by the National Asthma Education and Prevention Program (NAEPP)[3] at least 12 weeks prior to screening.
   c. Pre-bronchodilator FEV1 of ≥ 40% and ≤ 85% of predicted value during the screening visit and on the first day of treatment.
   d. ≥ 12% and 0.20 L reversibility of FEV1 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.

[3] 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.

g. Ability to replace current short-acting β-agonist (SABA) 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 study visits.
h. Ability to discontinue their asthma medications (inhaled corticosteroids, long-acting muscarinic antagonist 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.

The 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, cystic fibrosis, bronchiectasis, tuberculosis, chronic bronchitis, emphysema, 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 investigator, would put the patient at risk through study participation, or would affect the study analyses if the disease exacerbates 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, during the run-in period, or on the day of treatment.
e. Hypersensitivity to any sympathomimetic drug (e.g., albuterol, vilanterol), to any long-acting muscarinic antagonist (e.g., umeclidinium, tiotropium, ipratropium) or to any inhaled, intranasal, or systemic corticosteroid therapy, or to milk proteins, or to excipients in the dry powder inhaler (DPI).
f. Patients receiving systemic, oral, parenteral or depot corticosteroids, or Anti-IgE therapy within 12 weeks prior to screening and during the study.
g. Patients receiving β2-blockers, anti-arrhythmics, anti-depressants, monoamine oxidase inhibitors, cytochrome P450 3A4 inhibitors, and diuretics within 4 weeks prior to the screening.

Additional comments:

a. 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 for study).
b. 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.

c. 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.
d. All spirometry should be conducted in accordance with American Thoracic Society Standards.
e. The study should begin with a placebo run-in period at least 2 weeks in duration to wash out any pre-study corticosteroids and/or long-acting bronchodilators and to establish FEV1 baseline values.
f. 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.
g. The study protocol should provide a definition of compliant subjects (e.g., used at least 75% and no more than 125% of study drug doses) and specify how compliance will be verified (e.g., by the use of subject diaries).
h. To ensure study sensitivity, the T and RS products should both be statistically superior to placebo ($p < 0.05$) with regard to the bioequivalence study primary endpoints.
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 RS product.
j. 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.
k. 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, at minimum, the date of onset, description of AE, severity, relation to study medication, action taken, outcome, and date of resolution.

Bioequivalence study endpoint: (i) Area under the serial FEV1-time curve calculated from time zero to 24 hours (AUC0-24h) on the first day of the treatment, and (ii) FEV1 measured in the morning prior to the dosing of inhaled medications on the last day of a four-week treatment period.

The above two primary endpoints should be baseline adjusted (change from baseline). An FEV1 baseline is defined as the average of pre-dose FEV1 values of at least two time points measured in the morning of the first day of a four-week treatment period. Sampling is recommended to correspond to the same time of day as used on the last day of a four-week treatment period.

On the first day of the treatment, serial FEV1 should be determined at 0, 5 and 30 min, 1, 2, 3, 4, 6, 8, 10, 12, 23, and 24 hours post-dose.

Bioequivalence based on: T/R ratio for the primary endpoints. The 90% confidence intervals for the T/R ratio for the primary endpoints should fall within the limits of 80.00% - 125.00%.

Additional information:

Formulation:
To demonstrate bioequivalence, the T product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the RS product that may significantly affect the local or systemic availability of the active ingredient. For example, the T product can be qualitatively (Q1)[4] and quantitatively (Q2)[5] the same as the RS product to satisfy no difference in inactive ingredients.

Device:
The reference listed drug (RLD) is presented as a blister-based DPI. The DPI 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 T devices. In addition, T device design should take into consideration the following characteristics of the RLD:

- Passive (breath-actuated), pre-metered, multi-dose format
- Number of doses
- Device airflow resistance
- Dose indicator/counter

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]

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

Document History: Recommended May 2021; Revised February 2024

Unique Agency Identifier: PSG_209482

[a] For the most recent version of a product-specific guidance, check the FDA product-specific guidance website at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.
[b] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

APPENDIX

Variable Name	**Variable Name**	**Variable Name**	**Variable Name**
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												