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Draft – Not for Implementation

Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate

August 2024

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Active Ingredients:	Fluticasone propionate; Salmeterol xinafoate
Dosage Form:	Powder
Route:	Inhalation
Strengths:	0.1 mg/inh; EQ 0.05 mg Base/inh, 0.25 mg/inh; EQ 0.05 mg Base/inh, 0.5 mg/inh; EQ 0.05 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 all 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 flow rates of 30 L/min, 60 L/min and 90 L/min. The United States 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 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 cascade impactor data for the T and RS products, provide a table 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 cascade impactor profiles representing drug deposition on the individual stages of the cascade impactor 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:

FDA recommends that prospective applicants conduct the following pharmacokinetic bioequivalence study for all strengths of the T and RS 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.
[2] ISM is defined as a sum of the drug mass on all stages of the cascade impactor plus the terminal filter, but excluding the top cascade impactor 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 non-pregnant, non-lactating females.
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 without swallowing after each inhalation." (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 propionate and salmeterol in plasma.

Bioequivalence based on: AUC and C_{max} for fluticasone propionate and salmeterol. The 90% confidence intervals (CI) 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 consisting of a 2-week run-in period followed by a 4-week treatment period of the placebo, T or RS
Strength: 0.1 mg/inh; EQ 0.05 mg Base/inh
Dose: 0.1 mg/inh; EQ 0.05 mg Base/inh, one inhalation twice daily
Subjects: Males and non-pregnant females with asthma

Inclusion criteria should, at minimum, include:

a. Male or female subjects (≥ 12 years of age) of non-child bearing potential or of child bearing potential committing to consistent and correct use of an acceptable method of birth control.
b. Diagnosed with 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 the predicted value during the screening visit and on the first day of treatment.
d. Currently non-smoking; had not used tobacco products (i.e., cigarettes, cigars, pipe tobacco) within the past year, and had ≤ 10 pack-years of historical use.
e. ≥15% reversibility of FEV1 within 30 minutes following 360 mcg of albuterol inhalation (MDI).
f. Able to discontinue their asthma medications (inhaled corticosteroids and long-acting β agonists) during the run-in period and for remainder of the study.

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

g. Able 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 study visits).
h. Able to continue the following medications without a significant adjustment of dosage, formulation, dosing interval for the duration of the study, and judged able by the investigator to withhold them for the specified minimum time intervals prior to each clinic visit:
    - short-acting forms of theophylline 12 hours
    - twice-a-day controlled-release forms of theophylline 24 hours
    - once-a-day controlled-release forms of theophylline 36 hours
i. Able to discontinue the following medications for the specified minimum time intervals prior to the run-in period and for the remainder of the study, if the study is conducted in the US:
    - oral corticosteroids 1 month
    - parenteral corticosteroids 1 month
    - oral short-acting β-agonists 12 hours
j. Willingness to give their (and in the case of a minor their parent/guardian was able to give) 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 or during the run-in period.
b. 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.
c. Hypersensitivity to any sympathomimetic drug (e.g., salmeterol or albuterol) or any inhaled, intranasal, or systemic corticosteroid therapy.
d. Medication(s) with the potential to affect the course of asthma or to interact with sympathomimetic amines, e.g.:
    - β-blockers
    - oral decongestants
    - benzodiazepines
    - digitalis
    - phenothiazines
    - polycyclic antidepressants
    - Monoamine oxidase inhibitors
e. Viral or bacterial, upper or lower respiratory tract infection or sinus or middle ear infection within 4 weeks prior to the screening visit or during the run-in period.

f. Factors (e.g., infirmity, disability or geographic location) that the investigator felt would likely limit the patient's compliance with the study protocol or scheduled clinic visits.

Additional recommendations:

a. The study is recommended to begin with a placebo run-in period (at least 2 weeks in duration) to wash out any pre-study corticosteroids/long acting bronchodilators and to establish FEV1 baseline values.
b. 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).
c. To ensure adequate 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.
d. 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.
e. 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.
f. 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. This information is needed to determine if the incidence and severity of adverse reactions is different between the T and reference listed drug (RLD).

Bioequivalence study endpoints: (i) Area under the serial FEV1-time curve calculated from time zero to 12 hours (AUC0-12h) 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 4-week treatment.

The above two primary endpoints should be baseline adjusted (change from baseline). A 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 4-week treatment period. Sampling is recommended to correspond to the same time of day as used on the last day of a 4-week treatment.

On the first day of the treatment, FEV1 should be determined at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hour post-dose.

Bioequivalence based on: T/R ratio for the primary endpoints. The 90% CI for the T/R ratios 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 RLD is presented as a presented as a blister-based dry powder inhaler (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]

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[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.

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

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												