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Draft – Not for Implementation

Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate

November 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 options: (1) four in vitro bioequivalence studies, one comparative characterization study, and two in vivo bioequivalence studies with pharmacokinetic endpoints, or (2) two in vitro bioequivalence studies, one in vivo bioequivalence study with pharmacokinetic endpoints, and one comparative clinical endpoint bioequivalence study

I. Option 1: Four in vitro bioequivalence studies, one comparative characterization study, and two in vivo bioequivalence studies with pharmacokinetic endpoints

To demonstrate bioequivalence by this option, the test (T) product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference standard (RS) product that may significantly affect the local or systemic availability of the active ingredient. For example, the T product can be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the RS product to satisfy no difference in inactive ingredients.

[1] Q1 (qualitative sameness) means that the T product uses the same inactive ingredient(s) as the RS product.
[2] 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 product.

Four in vitro bioequivalence studies:

FDA recommends that prospective applicants conduct the following in vitro bioequivalence studies for all strengths of the T and RS products. 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 a minimum, three different batches of drug substances, excipients, 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[3] 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.

   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. A cascade impactor apparatus 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.

[3] 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.

Bioequivalence based on: PBE analysis of impactor-sized mass (ISM) of the drugs.[4] 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.

3. Type of study: Realistic APSD
Design: The realistic APSD test should be performed at the B lifestage of the product using mouth-throat models of different sizes (e.g., small and large) and breathing profiles (e.g., weak and strong) that are representative of the entire patient population. A cascade impactor apparatus 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 actuations justified by the sensitivity of the validated assay.
Additional comments: Drug deposition on individual sites, including the mouthpiece adapter, the mouth-throat model, the mixing inlet, 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 ANDA submission.

Bioequivalence based on: PBE analysis or other appropriate statistical analysis of ISM of the drugs for each mouth-throat model-breathing profile combination. The cascade impactor profiles representing drug deposition on the individual stages of the cascade impactor along with the MMAD, GSD, and FPM should be submitted as supportive evidence for equivalent APSD. If another statistical analysis is used, it should be adequately and scientifically justified considering the purpose of the study. Prospective applicants are encouraged to discuss other statistical analysis designs with FDA via a pre-ANDA meeting request. For additional information, refer to the most recent version of the FDA guidance for industry on *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*.[b]

4. Type of study: Dissolution
Design: Dissolution tests are recommended to be performed at the B lifestage of the product. An appropriate apparatus (e.g., USP <711> Apparatus 2, USP <724> Apparatus 5, or Transwell system) may be used to determine dissolution measurements using a sufficiently developed and validated method to support its sensitivity in detecting differences in performance between the T and RS products. Dissolution tests should be performed on samples with sufficiently similar drug mass for T and RS products.
Additional comments: Dissolution measurements should be reported in mass units and as percent drug dissolved. A comprehensive method development report should be submitted in the ANDA to show how the dissolution method parameters (e.g., equipment, sample collection, product dose amount, media, media volume, stirring/agitation rate, sampling times, etc.) were selected and optimized, and to support that the selected

[4] 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.

method parameters are appropriate. The submitted study method information should detail each parameter value and its sensitivity and reproducibility. The dissolution method should be able to demonstrate discriminatory ability (e.g., ability to detect meaningful differences in formulation or manufacturing process, such as a difference in deposited drug particle size) in measuring the dissolution kinetics of the product.

Bioequivalence based on: Comparative analysis of dissolution profiles for fluticasone propionate should be established using an appropriate statistical method (e.g., model independent approach using similarity factor (f2)). For more information on calculation of f2 factor, refer to the most recent version of the FDA guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*.[b]

One comparative characterization study:

The comparative physicochemical characterization study of the T product and the RS product should be performed on a minimum of three exhibit batches of the T product and three batches of the RS product. The comparative characterization study should include:

1. Particle morphology of the emitted dose
    a. Imaging comparisons of the deposited particles from the emitted dose at the B lifestage should be determined to assess particle morphology and agglomeration. Description for the sample collection method should be provided. Where applicable, chemical classification of the individual components in agglomerate particles and individual drug and/or excipients can be provided using an optimized and validated analytical method (e.g., morphologically-directed Raman spectroscopy) to further describe and/or support morphology characterization.

Two in vivo bioequivalence studies with pharmacokinetic endpoints:

FDA recommends that prospective applicants conduct the following pharmacokinetic bioequivalence study #1 for all strengths of the T and RS products and pharmacokinetic bioequivalence study #2 for the lowest (0.1 mg/inh; EQ 0.05 mg Base/inh) and highest (0.5 mg/inh; EQ 0.05 mg Base/inh) strengths of the T and RS products.

1. Type of Study: Fasting
   Design: Single-dose, two-way crossover
   Dose: Minimum number of inhalations that is sufficient to characterize the pharmacokinetic profiles 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 powder 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 breathing in the medicine. Spit out the water. Do not swallow it." (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 (CIs) for the geometric mean T/R ratios of AUC and C_{max} should fall within the limits of 80.00% - 125.00%.

2. Type of study: Fasting
Design: Single-dose, two-way crossover with charcoal block
Dose: Minimum number of inhalations that is sufficient to characterize the pharmacokinetic profiles by using a sensitive analytical method.
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: (1) The 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 breathing in the medicine. Spit out the water. Do not swallow it." (3) A Bio-IND is required prior to conduct of the pharmacokinetic study if the dose exceeds the maximum labeled single dose. (4) Justification for the charcoal dose should be provided in the ANDA submission.

Analyte to measure: Salmeterol in plasma

Bioequivalence based on: AUC and C_{max} for salmeterol. The 90% CIs for the geometric mean T/R ratios of AUC and C_{max} should fall within the limits of 80.00% - 125.00%.

II. Option 2: Two in vitro bioequivalence studies, one in vivo bioequivalence study with pharmacokinetic endpoints, and one comparative clinical endpoint bioequivalence study

To demonstrate bioequivalence by this option, it is recommended to conduct the in vitro bioequivalence studies #1 through #2 and the in vivo pharmacokinetic bioequivalence study #1 as described in Option 1. In addition, it is recommended to conduct the comparative clinical endpoint bioequivalence study, described below.

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 0.05 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-childbearing potential or of childbearing 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)[5] at least 12 weeks prior to screening.
c. Pre-bronchodilator forced expiratory volume in one second (FEV_1) 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 FEV_1 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.
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 hypercapnoea; respiratory arrest or hypoxic seizures, asthma related syncopal episode(s), or hospitalizations within the past year or during the run-in period.

[5] 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.

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 comments:

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 FEV_1 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 (AE) 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) products.

g. Refer to the most recent version of the FDA product-specific guidance on *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)[a] for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.

Bioequivalence study endpoint: (i) Area under the serial FEV_1-time curve calculated from time zero to 12 hours ($AUC_{0\text{-}12h}$) 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 FEV_1 baseline is defined as the average of pre-dose FEV_1 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 endpoint. The 90% CIs for the T/R ratios for the bioequivalence study endpoint should fall within the limits of 80.00% - 125.00%.

Additional information:

An optional computational modeling study may be used to support bioequivalence of the T and RS products. Refer to the most recent version of the FDA product-specific guidance on *Formoterol Fumarate; Glycopyrrolate Inhalation Metered Aerosol* (NDA 208294)[a] for additional information regarding the development and conduct of an optional computational modeling study.

In order to clarify the FDA's expectations for prospective applicants early in product development, and to assist applicants to submit an ANDA as complete as possible, FDA strongly encourages applicants to discuss their development program and plans for conducting an optional computational modeling study with the FDA via the pre-ANDA meeting pathway. For additional information, refer to the most recent version of the FDA guidance for industry on *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*.[b]

Device:
The 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]

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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.

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	FRM

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												