Contains Nonbinding Recommendations

Draft Guidance on Fluticasone Propionate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Aerosol, metered; inhalation

Strengths: 0.044 mg/INH
0.11 mg/INH
0.22 mg/INH

Recommended Studies: In vitro and in vivo studies

FDA recommends the following in vitro and in vivo studies to establish bioequivalence (BE) of the test (T) and reference (R) metered dose inhalers (MDIs) containing fluticasone propionate.

In Vitro Studies

FDA recommends that applicants conduct the following in vitro studies for all strengths of the T and R products. For each strength, use at least three batches each of the 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 a flow rate of 28.3 L/min. U.S. Pharmacopoeia (USP) <601> Apparatus A or another appropriate apparatus may be used to determine the SAC using a validated assay. The number of actuations per determination should be one.

   Equivalence based on: Population bioequivalence (PBE) analysis of SAC. Please refer to the product-specific recommendation for Budesonide Inhalation Suspension for additional information regarding PBE.[2]

2. Type of study: Aerodynamic particle size distribution (APSD)

[1] Based on the labeled number of actuations, the terms, B lifestage, M lifestage, and E lifestage represent the first actuation(s) following the labeled number of priming actuations, 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

Design: The APSD test should be performed at the B and E lifestages of the product using a flow rate of 28.3 L/min or 30 L/min. The USP <601> Apparatus 1, Apparatus 6, 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.

Additional comments: Drug deposition on individual sites, including the mouthpiece adapter, the induction port, 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 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.

3. Type of study: Spray pattern
   Design: The spray pattern test should be performed at the B lifestage of the product and at two different distances from the actuator orifice. The selected distances should be at least 3 cm apart and based on the range of 3 to 7 cm from the R actuator mouthpiece.[4] Impaction (thin-layer chromatography plate impaction), non-impaction (laser light sheet technology), or other suitable method may be used to determine the spray pattern.
   Additional comments: Spray pattern should be measured quantitatively in terms of ovality ratio and area within the perimeter of the true shape (to include a high proportion, e.g., 95% of the total pattern) for the automated analysis or ovality ratio and D_{max} for the manual analysis. Ovality ratio is defined as the ratio of D_{max} to D_{min}. D_{max} and D_{min} are the longest and shortest diameters, respectively, that pass through the center of mass or the center of gravity, as appropriate. The number of sprays per spray pattern would preferably be one.

   Equivalence based on: At two selected distances, (i) qualitative comparison of spray shape, and (ii) PBE analysis of ovality ratio and area within the perimeter of the true shape or ovality ratio and D_{max}.

4. Type of study: Plume geometry
   Design: The plume geometry test should be performed at the B lifestage of the product. The timed-sequence sound-triggered flash photography method, laser light sheet technology, or other suitable method may be used to determine the plume geometry at the appropriate post-actuation delay time.
   Additional comments: Plume geometry measurements should be reported at a single delay time while the fully developed plume is still in contact with the actuator mouthpiece. Plume geometry should be measured quantitatively in terms of plume angle

[3] 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.

[4] The distance between the actuator orifice and point of spray pattern measurement should be the same for T and R.

and width. The plume angle is based on the conical region of the plume extending from a vertex that occurs at or near the actuator mouthpiece. The plume width is measured at a distance equal to the greater of the two distances selected for characterization of the spray pattern.

Equivalence based on: Ratio of the geometric mean of the three batches of T to that of the three batches of R (based on log transformed data) for plume angle and width, which should fall within 90 - 111%.

5. Type of study: Priming and repriming
   Design: Priming and repriming tests should take into consideration the emitted dose (ex-actuator) of a single actuation immediately following the specified number of priming or repriming actuations specified in the R product labeling. The repriming test should be performed following storage for the specified period of non-use after initial use and/or other conditions (e.g., dropping), if the R product labeling provides such repriming information.
   Additional comments: For BE evaluation, we recommend priming and repriming tests be based on products stored in the valve upright position, with the exception of MDIs for which the R labeling recommends storage in the valve down position. The priming data can be based on the SAC data at the B lifestage.

   Equivalence based on: PBE analysis of the emitted dose of a single actuation immediately following the specified number of priming or repriming actuations specified in the R product labeling.

Pharmacokinetic (PK) BE Study

FDA recommends that applicants conduct the following PK BE study for all strengths of the T and R products.

6. 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
   Subjects: Normal healthy adult males and non-pregnant females, general population
   Additional comments: (1) Subjects enrolled for in vivo studies should be trained in the use of the inhalation aerosols 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 PK study if the dose exceeds the maximum labeled single dose.

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

Equivalence based on: AUC and C_{max} for fluticasone propionate. 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 BE Study

FDA recommends that applicants conduct the following comparative clinical endpoint study for the lowest strength of the T and R products.

7. Type of study: Comparative clinical endpoint BE 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 R product
   Strength: 0. 044 mg/INH
   Dose: 0.044 mg/INH, two inhalations twice daily

   Inclusion and exclusion criteria:
   Inclusion criteria should, at a 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)[5] at least 12 months prior to screening
   c) Pre-bronchodilator FEV1 of ≥ 45% and ≤ 85% of the predicted normal value during the screening visit and on the first day of treatment
   d) Patients should be stable on their chronic asthma treatment regimen for at least 4 weeks prior to enrollment
   e) 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
   f) ≥15% reversibility of FEV1 within 30 minutes following 360 mcg of albuterol inhalation (pMDI)
   g) Ability to discontinue their asthma medication (inhaled corticosteroids and long-acting β agonist) during the run-in period and for remainder of the study
   h) 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 study visits
   i) Willingness to give their written informed consent to participate in the study

   Exclusion criteria should, at a minimum, include:

[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.

a) Life-threatening asthma, defined as a history of asthma episode(s) requiring intubation, and/or was 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, 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, cardiovascular, endocrine, 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) Hypersensitivity to any sympathomimetic drug (e.g., albuterol) or to any inhaled, intranasal, or systemic corticosteroid therapy, or to excipients in the MDI
e) Patients receiving β2-blockers, anti-arrhythmics, anti-depressants, and/or monoamine oxidase inhibitors within 4 weeks prior to the screening.
f) Viral or bacterial, upper or lower respiratory tract infection, or sinus, or middle ear infection within 4 weeks prior to the screening visit, during the run-in period, or on the day of treatment
g) Patients who required systemic or oral corticosteroids (for any reason) within the past 6 months prior to screening
h) Evidence or history of oral candidiasis, tuberculosis, hypercorticism, adrenal suppression, or eye problems (e.g., increased intraocular pressure, glaucoma, or cataracts)

Additional comments:

- 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).
- 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.
- All spirometry should be conducted in accordance with American Thoracic Society Standards.
- The study should begin with a placebo run-in period at least two weeks in duration, to wash out any pre-study corticosteroids/long-acting bronchodilators and to establish FEV1 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.

- 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).
- To ensure 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 BE of the T to the R product.
- 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.
- 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 sponsor should clearly explain whether the medication was used prior to baseline visit, during the study, or both.
- 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 the date of onset, description of AE, severity, relation to study medication, action taken, outcome, and date of resolution. The information will assist FDA in determining whether the incidence and severity of adverse reactions is different between the T and R products.

BE study endpoint: FEV1 measured in the morning prior to the dosing of inhaled medications on the last day of the 4-week treatment.

The above primary endpoint 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 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.

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

Additional Information

Formulation:

FDA recommends that the T product be qualitatively (Q_1)[6] and quantitatively (Q_2)[7] the same as the R product.

[6] Q_1 (qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.
[7] 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.

Device:

Sponsors should refer to FDA's Guidance for Industry entitled, *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January 2017), which, when finalized, will provide the Agency's current thinking on the identification and assessment of any differences in the design of the user interface for a proposed generic drug- device combination product when compared to its RLD.

FDA recommends that applicants consider the following characteristics of the R product when designing the T product:

- Size and shape of the R product
- Number of doses in the R product
- External operating principles and external critical design attributes of the R product
- Dose indicator/counter

In addition, in vitro and in use studies should be conducted to support the functionality, accuracy and robustness of the proposed T 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	FRM

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												