Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Budesonide; Formoterol Fumarate Dihydrate

November 2023

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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:	Budesonide; Formoterol fumarate dihydrate
Dosage Form:	Aerosol, metered
Route:	Inhalation
Strengths:	0.08 mg/inh; 0.0045 mg/inh, 0.16 mg/inh; 0.0045 mg/inh
Recommended Studies:	Five 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) metered dose inhalers (MDIs) containing budesonide and formoterol fumarate dihydrate.

Five in vitro bioequivalence studies:

FDA recommends that prospective applicants conduct the following in vitro bioequivalence 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. 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[1] of the product, using a flow rate of 28.3 L/min or 30 L/min.[2] 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. 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 a flow rate of 28.3 L/min or 30 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 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.

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.

---

[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] The selection of flow rate should match that of the flow rate chosen for APSD testing.

[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.

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 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 be based on 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 bioequivalence evaluation, the priming and repriming tests should 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.

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 R products.

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 females
   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. Spit out the water. Do not swallow it." A Bio-IND is required prior to conduct of the pharmacokinetic study if the dose exceeds the maximum labeled single dose.

Analytes to measure: Budesonide and formoterol in plasma

Equivalence based on: AUC and C_{max} for budesonide and 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%.

One comparative clinical endpoint bioequivalence study:

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

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 6-week treatment period of the placebo, T product, or R product
   Strength: 0.08 mg/inh; 0.0045 mg/inh
   Dose: 0.08 mg/inh; 0.0045 mg/inh, two inhalations twice daily
   Subjects: Males and non-pregnant females with asthma

   Inclusion criteria should, at minimum, include:
   a. Adult male or female subjects (non-childbearing or of childbearing potential committing to consistent and correct use of an acceptable method of birth control)

b. Diagnosis of mild to severe asthma as defined by the National Asthma Education and Prevention Program[5,6] at least 6 months prior to screening
c. Pre-bronchodilator forced expiratory volume in one second (FEV_1) of ≥ 45% and ≤ 85% of predicted normal
d. ≥ 12% and ≥ 0.20 L reversibility of FEV_1 within 30 minutes following 360 mcg of albuterol inhalation (pMDI)
e. Patients should be stable on their chronic asthma treatment regimen for at least 4 weeks prior to enrollment
f. Currently non-smoking; had not used tobacco products (i.e., cigarettes, cigars, pipe tobacco) within the past year, and having had ≤ 10 pack-years of historical use
g. 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)
h. Ability to discontinue their asthma medications (inhaled corticosteroids and long-acting β-agonists) from the run-in period and for the remainder of the study
i. Willingness to give their written informed consent to participate in the study

Exclusion criteria should, at minimum, include:

a. 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
b. Significant respiratory disease other than asthma (e.g., COPD or interstitial lung disease)
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. Patients who required systemic corticosteroids (for any reason) within the past 4 weeks prior to screening
e. Hypersensitivity to any sympathomimetic drug (e.g., formoterol or albuterol) or to any inhaled, intranasal, or systemic corticosteroid therapy or any of the excipients in the study drugs or rescue medication formulation
f. Patients receiving non-selective β-blockers, anti-arrhythmics, anti-depressants, and monoamine oxidase inhibitors within 4 weeks prior to the screening

[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.
[6] 2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. 2020. https://www.nhlbi.nih.gov/resources/2020-focused-updates-asthma-management-guidelines.

Additional comments:

a. All spirometry should be conducted in accordance with American Thoracic Society (ATS) standards.
b. The study is recommended to begin with a placebo run-in period (at least two weeks in duration; appropriate justification should be included for the duration chosen) to wash out any pre-study corticosteroids/long-acting bronchodilators and to establish FEV_1 baseline values.
c. 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.
d. 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).
e. 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 endpoints.
f. 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.
g. 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.
h. 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.
i. 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 endpoints: (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) FEV_1 measured in the morning prior to the dosing of inhaled medications on the last day of the 6-week treatment period.

The above two primary endpoints should be baseline adjusted (change from baseline). An 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 6-week treatment period. Sampling should correspond to the same time of day as used on the last day of a 6-week treatment. On the first day of the treatment, FEV_1 should be determined at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours post-dose.

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

Additional information:

Formulation:
FDA recommends that the T formulation be qualitatively (Q1)[7] and quantitatively (Q2)[8] the same as the R formulation.

Device:
The reference listed drug (RLD) is presented as a metered dose inhaler. The device constituent part is the actuator with metering valve.

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 device including:

- Active, metered, multi-dose format
- Number of doses
- 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]

Document History: Recommended June 2015; Revised November 2023

Unique Agency Identifier: PSG_021929

[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.

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