

Draft Guidance on Budesonide; Formoterol fumarate dihydrate

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Active Ingredient: Budesonide; Formoterol fumarate dihydrate

Dosage Form; Route: Aerosol; metered; inhalation

Strength: 0.08 mg/INH; 0.0045 mg/INH
0.160 mg/INH; 0.0045 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 budesonide and formoterol fumarate dihydrate.

In Vitro Studies

FDA recommends that applicants conduct the following in vitro studies for both strengths of the T and R products. For each strength, use at least three batches each of T and R products, with no fewer than 10 units from each batch.

1. **Type of study:** Single actuation content (SAC)
Design: The SAC test should be performed at the beginning (B), middle (M), and end (E) lifestages¹ of the product using a flow rate of 28.3 L/min. U.S. Pharmacopeia (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. The budesonide inhalation suspension BE guidance provides additional information regarding PBE.²

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. The USP <601> Apparatus 1, Apparatus 6, or another appropriate method may be used to determine APSD using a validated assay.

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>

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 B lifestage of the product. The time 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

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 same for T and R.

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 both 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 BE 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.

Pharmacokinetic BE Study

FDA recommends that applicants conduct the following pharmacokinetic (PK) BE study for both 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 males and nonpregnant females, general population

Additional comments: The 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 ensure a relatively consistent inspiratory flow rate and inspiratory duration. 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): 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%.

Clinical Endpoint Study

The Agency recommends that applicants conduct the following BE study with a clinical endpoint for the lowest strength of the T and R products.

7. Type of study: Clinical endpoint study

Design: A randomized multiple-dose, placebo-controlled, parallel group design consisting of a 2-week run-in period followed by a 6-week treatment period of the placebo, T product, or R product

Strength: 80/4.5 (budesonide 80 mcg and formoterol 4.5 mcg)

Dose: 80/4.5, two inhalations twice daily

Additional comments:

- Inclusion criteria should, at minimum, include:
 - a. Adult male or female subjects of non-childbearing or of childbearing potential committed 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 6 months prior to screening
 - c. Moderate-to-severe asthma with a pre-bronchodilator FEV₁ of $\geq 45\%$ and $\leq 85\%$ of predicted normal, measured at least 6 hours after short-acting β agonist (SABA) and at least 24 hours after the last dose of long-acting β agonist (LABA), at the screening visit and on the day of treatment
 - d. $\geq 15\%$ and ≥ 0.20 L reversibility of FEV₁ 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; having not used tobacco products (i.e., cigarettes, cigars, pipe tobacco) within the past year, and having ≤ 10 pack-years of historical use
 - g. Able to replace current regularly scheduled short-acting β agonists (SABAs) with salbutamol/albuterol inhaler for use only on an as-needed basis 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. Willing to discontinue their asthma medications (inhaled corticosteroids and long-acting β agonists) during 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 hypercapnoea, respiratory arrest or hypoxic seizures, asthma-related syncopal episodes(s), or hospitalizations within the past year or during the run-in period
 - b. Significant respiratory disease other than asthma (chronic obstructive pulmonary disease (COPD), interstitial lung disease, etc.)

⁵ 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

- 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 exacerbated during the study
 - d. Patients who required systemic corticosteroids (for any reason) within the past 4 weeks
 - e. Hypersensitivity to any sympathomimetic drug (e.g., formoterol or albuterol) or any inhaled, intranasal, or systemic corticosteroid therapy
 - f. Patients currently receiving β -blockers
- All spirometry should be conducted in accordance with American Thoracic Society standards.
 - The study should 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.
 - 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 adequate study sensitivity, the T and R products should both be statistically superior to placebo ($p < 0.05$) with regard to the BE study primary endpoints.
 - 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.
 - 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 date of onset, description of AE, severity, relation to study medication, action taken, outcome, and date of resolution. This information will assist FDA in determining whether the incidence and severity of adverse reactions is different between the T and R products.

BE study endpoints: (i) Area under the serial FEV₁-time curve calculated from time zero to 12 hours (AUC_{0-12h}) 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 the 6-week treatment.

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 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, FEV₁ 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 endpoints. The 90% confidence intervals for the T/R ratios for the primary endpoints should fall within the limits of 80.00-125.00%.

Additional information

Formulation and Device

FDA recommends that the T product be qualitatively (Q₁)⁶ and quantitatively (Q₂)⁷ the same as the R product, and be similar in shape and size to the R product. The T product should have a dose counter. The Agency encourages sponsors to submit a working model of the MDI to the Office of Generic Drugs prior to the ANDA submission, in order to ensure the eligibility of a T device under the 505(j) pathway.

⁶ Q₁ (qualitative sameness) means that the T product uses the same inactive ingredient(s) as the R product.

⁷ 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												