

Draft Guidance on Budesonide

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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:	Budesonide
Dosage Form; Route:	Powder; inhalation
Strength:	0.09 mg/INH 0.180 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) dry powder inhalers (DPIs) containing budesonide.

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 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.

- 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 30 L/min, 60 L/min and 90 L/min. 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.

Equivalence based on: Population bioequivalence (PBE) analysis of SAC. Please refer to the draft Budesonide Inhalation Suspension BE Guidance for additional information regarding PBE.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 priming, 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 flow rates of 28.3 L/min or 30 L/min, 60 L/min and 90 L/min. The USP <601> Apparatus 3, Apparatus 5, 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 (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.

Pharmacokinetic Study

FDA recommends that applicants conduct the following pharmacokinetic (PK) BE study for both strengths of the T and R products.

3. **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 non-pregnant females, general population

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 and spit the water out after each dose. Do not swallow the water.” (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): Budesonide in plasma

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

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.

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

4. 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: 0.09 mg/INH (budesonide)

Dose: 0.09 mg/INH, four inhalations twice daily

Inclusion and exclusion criteria:

Inclusion criteria should, at minimum, include:

- a. Adult male or female subjects of non-childbearing potential, or of childbearing 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)⁴ at least 12 weeks prior to screening
- c. Pre-bronchodilator FEV₁ of $\geq 45\%$ and $\leq 85\%$ of predicted value during the screening visit and on the first day of treatment
- d. $\geq 12\%$ and 0.20 L reversibility of FEV₁ within 30 minutes following 360 mcg of salbutamol/albuterol inhalation (pMDI)
- e. Patients should be stable on their chronic asthma treatment regimen for at least 4 weeks prior to screening
- f. Currently non-smoking; having 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 -agonist (SABA) 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) during the run-in period and for 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 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 prior to the screening or during the run-in period
- b. Significant respiratory disease other than asthma (COPD, interstitial lung disease, 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, or

⁴ 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.

- 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. Viral or bacterial, fungal or parasitic, upper or lower respiratory tract infection, or sinus, or middle ear infection within 4 weeks prior to the screening, during the run-in period, or on the day of treatment
 - e. Hypersensitivity to any sympathomimetic drug (e.g., albuterol), or to any inhaled, intranasal, or systemic corticosteroid therapy, or to milk proteins, or to excipients in the DPI
 - f. Patients receiving systemic, oral, parenteral or depot corticosteroids, or Anti-IgE therapy, or other immunosuppressive medications within 12 weeks prior to screening and during the study
 - g. Patients receiving β 2-blockers, anti-arrhythmics, and cytochrome P450 3A4 inhibitors, within 4 weeks prior to the screening

Additional recommendations:

- 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).
- 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.
- Subjects who discontinue from the study early should be identified, and the protocol should clearly, prospectively state how missing data will be handled in the statistical analysis and provide appropriate justification for the method chosen. The protocol should also include subject retention strategies and other plans to minimize missing data.
- 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 and/or 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.
- 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 a 4-week treatment period.

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 period.

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 product be qualitatively (Q₁)⁵ and quantitatively (Q₂)⁶ the same as the R product.

If a sponsor uses a Q₂-different formulation for its T product, the sponsor should explain the reason(s) for not using a T formulation that is Q₂ the same as the R formulation. In addition, the sponsor should provide pharmaceutical development data, involving in vitro testing of multiple drug-to-excipient ratios that encompass combinations below and above the ratios used in the T and R products.

Device

Sponsors are encouraged to submit a working model and engineering drawings to the Office of Generic Drugs (OGD) prior to the abbreviated new drug application (ANDA) submission.

FDA recommends that the T product have the following characteristics:

- Passive (breath-actuated) device
- Device-metered multi-dose format

⁵ Q₁ (qualitative sameness) means that the T product uses the same inactive ingredient(s) as the R product.

⁶ 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.

- Same number of doses as the R product
- Similar external operating procedures as the R product
- Similar size and shape to the R product
- Comparable device resistance to 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												