Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Budesonide; Formoterol fumarate

May 2025

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Active Ingredients:	Budesonide; Formoterol fumarate
Dosage Form:	Aerosol, metered
Route:	Inhalation
Strength:	0.16 mg/inh; 0.0048 mg/inh
Recommended Studies:	Two options: (1) seven in vitro bioequivalence studies, one comparative characterization study, and two in vivo bioequivalence studies with pharmacokinetic endpoints, or (2) five in vitro bioequivalence studies, one comparative characterization study, one in vivo bioequivalence study with pharmacokinetic endpoints, and one comparative clinical endpoint bioequivalence study

I. Option I: Seven 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) 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 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.
[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.

Seven in vitro bioequivalence studies:

FDA recommends that prospective applicants conduct the following in vitro bioequivalence studies for the T product and RS. Use at least three batches each of the T product and RS, 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 a flow rate of 28.3 L/min or 30 L/min.[4] 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.

   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 a flow rate of 28.3 L/min or 30 L/min. A cascade impactor apparatus for inhalation aerosols 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 and co-suspending agent deposition on individual sites, including the mouthpiece adapter, the induction port, 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 product and RS, provide a table using the format in the appendix and send them as part of the abbreviated new drug application (ANDA) submission.

   Bioequivalence based on: PBE analysis of impactor-sized mass (ISM) of the drugs.[5] The cascade impactor profiles representing drug and co-suspending agent deposition on the individual stages of the cascade impactor along with the mass median aerodynamic

[3] 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.
[4] The selection of flow rate should match that of the flow rate chosen for APSD testing.
[5] 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.

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 RS actuator mouthpiece.[6] 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.

Bioequivalence 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.

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

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

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 reference listed drug (RLD) 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 RLD labeling provides such repriming information.

Additional comments: For the bioequivalence evaluation, the priming and repriming tests should be based on products stored in the valve upright position, with the exception of metered dose inhalers (MDIs) for which the RLD labeling recommends storage in the valve down position. The priming data can be based on the SAC data at the B lifestage.

Bioequivalence 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 RLD labeling.

6. 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 aerosols 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 and co-suspending agent 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 product and RS, 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 and co-suspending agent 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, *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*.[b]

7. 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 product and RS. Dissolution tests should be performed on samples with sufficiently similar drug mass for T product and RS.
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 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 budesonide 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 *M9 Biopharmaceutics Classification System-Based Biowaivers*.[b]

One comparative characterization study:

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

Two in vivo bioequivalence studies with pharmacokinetic endpoints:

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) 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 assure a relatively consistent inspiratory flow rate and inspiratory duration. (2) The subjects should adhere to the RLD labeling as follows: "Rinse your mouth with water

and spit the water out after each dose (2 puffs). Do not swallow the water." (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: Budesonide and formoterol in plasma

Bioequivalence 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%.

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 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 the RLD labeling as follows: "Rinse your mouth with water and spit the water out after each dose (2 puffs). Do not swallow the water." (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.

Analytes to measure: Budesonide and formoterol in plasma

Bioequivalence 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%.

Additional comments for the in vivo pharmacokinetic bioequivalence studies: Before conducting a charcoal block PK study, prospective applicants are encouraged to discuss their bioequivalence strategy with FDA via a pre-ANDA meeting request. For additional information, refer to the most recent version of the FDA guidance for industry, *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*.[b]

II. Option II: Five in vitro bioequivalence studies, one comparative characterization study, 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 #5, the comparative characterization study, and the in vivo pharmacokinetic bioequivalence study #1 as described in Option I. 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 product, or RS.
Strength: 0.16 mg/inh; 0.0048 mg/inh
Dose: 0.16 mg/inh; 0.0048 mg/inh, two inhalations twice daily
Subjects: Males and non-pregnant females with COPD
Inclusion criteria should, at minimum, include:
    a. Adult (≥ 40 y. o.) male or female subjects of non-child-bearing potential or of child-bearing potential but committed to consistent use of an acceptable method of birth control
    b. Diagnosis of COPD, as defined by American Thoracic Society (ATS) [GOLD criteria]
    c. Post-bronchodilator forced expiratory volume in one second (FEV_1) ≤ 80%
    d. Post-bronchodilator FEV_1/forced vital capacity (FVC) ratio ≤ 0.70
    e. Current or former smokers (e.g., with history of ≥ 10 pack-years)
    f. Willingness to give their written informed consent to participate in the study

Exclusion criteria should, at minimum, include:
    a. Known respiratory disorders other than COPD including, but not limited to the following: alpha-1 antitrypsin deficiency, cystic fibrosis, significant asthma, active bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, pulmonary edema, or interstitial lung disease
    b. Evidence or history of other clinically significant cardiovascular disease or abnormality (such as, but not limited to, congestive heart failure, uncontrolled hypertension, uncontrolled coronary artery disease, myocardial infarction, stroke, glaucoma, cardiac dysrhythmia, arrhythmia, long QT syndrome, paroxysmal atrial fibrillation), renal, neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or hematological disease or abnormality which, 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
    c. Known active tuberculosis
    d. History of paradoxical bronchospasm, narrow-angle glaucoma, prostatic hyperplasia, bladder neck obstruction, or severe renal impairment or urinary retention or any other condition, which, in the opinion of the investigator, would contraindicate the use of an anticholinergic or long-acting beta-agonist agent
    e. History of allergy or hypersensitivity to inhaled, intranasal, or systemic corticosteroid therapy, anticholinergic/muscarinic receptor antagonist agents, long- or short-acting beta-2 agonists, sympathomimetic amines, lactose/milk proteins, or specific intolerance to aerosolized budesonide or formoterol fumarate containing products or known hypersensitivity to any of the proposed ingredients or components of the delivery system

f. Hospitalization for COPD or pneumonia within 12 weeks prior to the initiation of the study
g. Treatment for COPD exacerbation within 12 weeks prior to study
h. Inability to discontinue COPD medications during the run-in and treatment periods
i. Acute (viral or bacterial) upper or lower respiratory tract infection, sinusitis, rhinitis, pharyngitis, urinary tract infection or illness within 6 weeks prior to the initiation of the study
j. Abnormal and significant electrocardiogram (ECG) finding prior to the screening, during the run-in and treatment periods
k. Lung volume reduction surgery within 12 months prior to the initiation of the study
l. Chronic oxygen use for >12 hours/day

Additional comments:

a. The study may enroll all COPD patients who meet the inclusion and exclusion criteria or may be enriched with patients who demonstrate ≥ 15% reversibility to bronchodilator therapy (appropriate justification should be included for the population chosen).
b. 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 COPD.
c. All spirometry should be conducted in accordance with ATS standards.
d. The study protocol should list appropriate withholding times prior to spirometry for permitted concomitant medications (e.g., 4 hours for short-acting beta-agonists, 12 or 24 hours for long-acting beta-agonists).
e. The study is recommended to begin with a placebo run-in period (at least 2 weeks in duration; appropriate justification should be included for the duration chosen) to wash out any pre-study corticosteroids, long-acting anticholinergic or long-acting beta-agonist agents and to establish FEV_1 baseline values.
f. To ensure adequate study sensitivity, the T product and RS should both be statistically superior to placebo ($p < 0.05$) with regard to the bioequivalence study endpoint.
g. 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).
h. It is the prospective applicant's responsibility to enroll a sufficient number of subjects for the study to demonstrate bioequivalence of the T product to the RS.
i. 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.
j. All adverse events (AEs) should be reported whether or not they are considered to be related to the treatment. The report of AEs should include, at minimum, date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution.

k. Appropriate pre-defined withdrawal criteria should be described for patients who may require withdrawal during washout period due to COPD exacerbation or inability to tolerate withdrawal of baseline therapy.
l. 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.
m. 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 treatment, and (ii) FEV_1 measured in the morning prior to the dosing of inhaled medications on the last day of the 4-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 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 treatment, FEV_1 should be determined at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours post-dose.

Bioequivalence 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:

An optional computational modeling study may be used to support bioequivalence of the T product and RS. Refer to the most recent version of the FDA product-specific *Guidance on Formoterol Fumarate; Glycopyrrolate Inhalation Aerosol, Metered* (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 an MDI. The device constituent parts are the actuator and the canister with metering valve.

FDA recommends that prospective applicants examine the size and shape, external critical design attributes, and 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 May 2025

Unique Agency Identifier: PSG_216579

[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												