Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Flunisolide

May 2026

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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 Ingredient:	Flunisolide
Dosage Form:	Aerosol, metered
Route:	Inhalation
Strength:	0.078 mg/inh
Reference Listed Drug:	NDA 021247
Recommended Studies:	Two options: (I) Three in vitro bioequivalence studies and one in vivo bioequivalence study with pharmacokinetic endpoints or (II) two in vitro bioequivalence studies, one in vivo bioequivalence study with pharmacokinetic endpoints, and one comparative clinical endpoint bioequivalence study

Option I: In vitro bioequivalence studies and an in vivo bioequivalence study with pharmacokinetic endpoints

Eligibility: To demonstrate bioequivalence by this option, the test 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 test 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 test 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 test product are within ± 5% of those used in the RS.

1. Class of study: Bioequivalence
Type of study: Single actuation content (SAC)
Design: The SAC study 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] The 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.
Strength: 0.078 mg/inh

Bioequivalence based on: Population bioequivalence (PBE) analysis of SAC. Refer to the product-specific guidance on *Budesonide Inhalation Suspension* (NDA 020929)[a] for additional information regarding PBE analysis procedures.

2. Class of study: Bioequivalence
Type of study: Aerodynamic particle size distribution (APSD)
Design: The APSD study 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.
Strength: 0.078 mg/inh
Study design recommendations:
   - Drug 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 test 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).[5] The cascade impactor profiles representing drug deposition on the individual stages of the cascade impactor 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] 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.

3. Class of study: Bioequivalence
Type of study: Realistic APSD
Design: The realistic APSD study 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 patient population. A cascade impactor apparatus for inhalation aerosols as per USP <601> Table 2 or another appropriate method may be used to determine realistic APSD using a validated assay. The realistic APSD determination of each unit should be performed with a minimum number of actuations justified by the sensitivity of the validated assay.
Strength: 0.078 mg/inh
Study design recommendations:
    - Drug deposition on individual sites, including the mouthpiece adapter, the mouth-throat model, the mixing inlet, 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 test 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 deposition on the individual stages of the cascade impactor along with the MMAD, GSD and FPM should be submitted as supportive evidence for equivalent realistic APSD.

    Meeting recommendations: 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 guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*.[b]

Study design recommendations for all in vitro bioequivalence studies:

- FDA recommends that prospective applicants conduct the following in vitro bioequivalence studies for the test product and RS using at least three batches each of the test 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 test product should be manufactured from, at a minimum, three different batches of drug substances, excipients, and device constituent part components.
- The test product should consist of the final device constituent part and final drug constituent formulation intended to be marketed.

4. Class of study: Bioequivalence
Type of study: Bioequivalence study with pharmacokinetic endpoints
Design: Fasting, single-dose, two-way crossover, in vivo
Strength: 0.078 mg/inh
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, non-lactating females
Safety recommendation:

- A Bio-IND is required prior to conduct of the pharmacokinetic study if the dose exceeds the maximum labeled single dose.

Study design recommendations:

- 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.
- Subjects should adhere to the reference listed drug (RLD) labeling for administration, including "Rinse your mouth thoroughly with water and spit it out."
- Refer to the guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*[b] for additional information regarding the analysis of the bioequivalence study with pharmacokinetic endpoints.

Analyte to measure: Flunisolide in plasma

Bioequivalence based on (90% confidence interval [CI]): $AUC0_{-t}$, AUC_{0-inf}, and C_{max}

Option II: In vitro bioequivalence studies, an in vivo bioequivalence study with pharmacokinetic endpoints, and a comparative clinical endpoint bioequivalence study

1.-3. Refer to Option I, Studies #1, #2, and #4.

4. Class of study: Bioequivalence
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, test product, or RS
Strength: 0.078 mg/inh
Dose: 0.078 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 of 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,[6,7] at least 12 months prior to screening.

c. Pre-bronchodilator forced expiratory volume in one second (FEV_1) of ≥ 45% and ≤ 85% of predicted 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 screening.
e. Currently non-smoking, has not used tobacco products (i.e., cigarettes, cigars, pipe tobacco) within the past year, and having had ≤ 10 pack-years of historical use.
f. ≥ 12% reversibility of FEV_1 within 30 minutes following 360 mcg of albuterol inhalation (e.g., from a metered dose inhaler (MDI)).
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 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., chronic obstructive pulmonary disease (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, 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 any inhaled, intranasal, or systemic corticosteroid therapy or any of the excipients in the study drugs or rescue medication formulation.
e. Patients receiving non-selective β-blockers, anti-arrhythmics, anti-depressants, and 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, during the run-in period, or on the day of treatment.

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[6] 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.

[7] 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.

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).

Study design recommendations:

a. 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).
b. 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 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.
c. All spirometry should be conducted in accordance with American Thoracic Society (ATS) standards.
d. 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.
e. 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.
f. 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).
g. To ensure adequate study sensitivity, the test product and RS should both be statistically superior to placebo ($p<0.05$) with regard to the bioequivalence study endpoint.
h. It is the prospective applicant's responsibility to enroll a sufficient number of subjects for the study to demonstrate bioequivalence of the test product to the RS.
i. A clear list of permitted and restricted medications should be provided, including justification for use (or restriction) of certain classes of respiratory therapies, considering the current standard of care for asthma.
j. 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.
k. 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 test product and RS.

l. Refer to the 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 primary endpoint: 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 primary endpoint 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 period.

Bioequivalence based on (90% CI): T/R ratio for the primary endpoint

Additional information for both options:

Computational model(s) for regional drug delivery: An optional computational modeling study may be used to support bioequivalence of the test product and RS. Refer to the 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 guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*.[b]

Device: The RLD is presented as an MDI. The device constituent part is the actuator with attached spacer, and canister 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 test device including:

- Active, metered, multi-dose format
- Number of doses
- Attached spacer

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 guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[b]

Document History: Recommended November 2025, Revised May 2026

[a] We update guidances periodically. For the most recent version of a product-specific guidance, refer to the FDA guidance webpage at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.
[b] We update guidances periodically. For the most recent version of a guidance, refer to the FDA guidance webpage 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).
Mouthpiece Adapter	Numeric	Numeric Values	MA
Induction Port/Mouth-Throat	Numeric	Numeric Values	IP/MT
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	FPM

Example:

PRODUCT	LOT	Unit	MA	IP/ MT	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														