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Draft Guidance on Ipratropium Bromide

August 2023

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Active Ingredient:	Ipratropium bromide
Dosage Form:	Aerosol, metered
Route:	Inhalation
Strength:	0.021 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 ipratropium bromide.

Five in vitro bioequivalence studies:

FDA recommends that prospective applicants conduct the following in vitro bioequivalence studies for the T and R products. 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 substance(s), excipient(s), 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. The 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. 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).[2] 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.[3] 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

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

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 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 tip. 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 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 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 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: Subjects 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. A Bio-IND is required prior to conducting the pharmacokinetic study if the dose exceeds the maximum labeled single-dose.

Analyte to measure: Ipratropium in plasma

Equivalence based on: AUC and C_{max} for ipratropium. 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 T and R products.

1. Type of study: Comparative clinical endpoint bioequivalence study
   Design: This study could be either of crossover or parallel-group design, taking into consideration the patient population, the current standard of care treatment for Chronic Obstructive Pulmonary Disease (COPD) and should include appropriate justification for the design chosen. The study should be randomized, single-dose, double-blind, and placebo-controlled, at minimum consisting of a 2-week run-in period followed by a one day treatment period of the placebo, T or R product.
   Strength: 0.021 mg/inh
   Dose: 0.042 mg, single-dose (i.e., two inhalations)
   Subjects: Males and non-pregnant females with COPD

Inclusion criteria should, at a minimum, include:

a. Adult (≥40 y.o.) male or female subjects of non-child bearing potential or of child bearing potential committing to consistent use of an acceptable method of birth control
b. Diagnosis of COPD, as defined by American Thoracic Society (ATS) [GOLD criteria]
c. Current or former smoker (e.g., with history of ≥10 pack-years)
d. Post-bronchodilator forced expiratory volume in one second (FEV_1)≤65% of predicted
e. Post-bronchodilator FEV_1/forced vital capacity (FVC) ratio ≤0.70
f. Willingness to give their written informed consent to participate in the study

Exclusion criteria should at a minimum include:

a. Known respiratory disorder 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, or interstitial lung disease
b. Evidence or history of other clinically significant disease or abnormality (such as congestive heart failure, uncontrolled hypertension, uncontrolled coronary artery disease,

myocardial infarction, stroke, glaucoma or cardiac dysrhythmia) 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 exacerbated during the study

c. Patients with known active tuberculosis
d. History of narrow angle glaucoma, prostatic hypertrophy, or bladder neck obstruction, which, in the Investigator's opinion, would contraindicate the use of an anticholinergic agent
e. History of allergy or hypersensitivity to anticholinergic/muscarinic receptor antagonist agent, beta-2 agonists, or specific intolerance to aerosolized ipratropium bromide-containing products, or known hypersensitivity to any of the proposed ingredients
f. Hospitalization for COPD or pneumonia within 12 weeks prior to the initiation of study
g. Treatment for COPD exacerbation within 12 weeks prior to the initiation of 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 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 the 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 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 for study).
b. A clear list of permitted and restricted medications should be provided, including justification for use (or restriction) of certain classes of respiratory therapies, which considers the current standard-of-care for COPD.
c. All spirometry should be conducted in accordance to ATS standards.
d. The 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 long-acting anti-cholinergic agents and to establish FEV_1 baseline values.
f. 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.
g. 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.
h. 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 date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution.
i. 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.
j. 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.

k. 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 primary endpoint: Area under the serial FEV_1-time curve calculated from time zero to 6 hours ($AUC_{0\text{-}6h}$) following the treatment.

The above bioequivalence study endpoint should be baseline-adjusted (change from baseline). FEV_1 measurements should be performed and interpreted in accordance with ATS guidelines.

Serial spirometry (FEV_1) should be measured at 0, 10, 15, 30, 60, 90, and 120 minutes, and 3, 4, 5, and 6 hours post-dose.

For each treatment group, time to peak bronchodilator response (T_{max}) and FEV_1 values at all measurement times within each evaluation period should be included in the final study report.

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

Alternative approach to the comparative clinical endpoint bioequivalence study:

A comparative clinical endpoint bioequivalence study is recommended for the T ipratropium bromide inhalation aerosol, metered product. The T product is not an aqueous-based formulation, but rather is a liquefied propellant-based formulation in which the volatile excipients are expected to rapidly volatilize upon actuation. As such, the drug forms that reach the local sites of action in the lungs are likely nonvolatile residual drug particles which may have a complex morphology due to the high relative humidity in the respiratory tract. Within this context, and considering the existing in vitro and in vivo pharmacokinetic bioequivalence studies recommended in this guidance, a comparative clinical endpoint bioequivalence study between T and R products is currently the recommended tool that provides information on the equivalence in clinical effect at the local sites of action in the lungs.

However, the FDA is supportive of the development of novel bioequivalence approaches. The FDA expects that these approaches, in order to support an ANDA submission, should be scientifically justified with a comprehensive, significant body of data, and evaluated as statistically meaningfully as possible; this may include in vitro, in vivo and/or in silico studies. For this particular drug product, which contains a solution-based formulation, if the T formulation is Q1 and Q2 the same as the R formulation, and if the T device is sufficiently similar to the R device with respect to critical design attributes and user interface, additional supportive data may provide a foundation to help ensure the equivalence of T and R products at the local sites of action in the lungs, and thus, could be considered as a potential alternative to the

currently recommended comparative clinical endpoint bioequivalence study, in the context of the weight-of-evidence approach.

Additional supportive in vitro studies may include, but are not limited to, (i) more predictive APSD testing using representative mouth-throat models and breathing profiles, (ii) characterization of emitted aerosol sprays with respect to velocity profiles and evaporation rates, (iii) dissolution, and (iv) morphology imaging comparisons, including characterization of the full range of residual drug particle sizes. Additional studies may be considered to characterize the impact of the nonvolatile excipients in the test product formulation on the rate and extent of evaporation of volatile excipients and the final state of the forms (e.g., dry particles, semi-dry particles, droplets) that deposit in the lungs. Prospective applicants may also consider the use of quantitative methods and modeling (for example, physiologically-based pharmacokinetic and computational fluid dynamic studies) and alternative in vivo pharmacokinetic bioequivalence studies.

In order to clarify the FDA's expectations for prospective applicants early in product development, and to assist prospective applicants to submit an ANDA as complete as possible, FDA strongly encourages prospective applicants to discuss their development program for an alternative approach to bioequivalence 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]

Additional information:

Formulation:
FDA recommends that the T formulation be qualitatively (Q_1)[4] and quantitatively (Q_2)[5] 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

[4] Q_1 (qualitative sameness) means that the T product uses the same inactive ingredient(s) as the R product.
[5] Q_2 (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.

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]

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[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	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												