

## Draft Guidance on Ipratropium Bromide

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- Active Ingredient:** Ipratropium bromide
- Dosage Form; Route:** Aerosol, metered; inhalation
- Recommended Studies:** In vitro and in vivo studies

The following in vitro and in vivo studies are recommended to establish bioequivalence (BE) of the test (T) and reference (R) metered-dose inhalers (MDIs) containing ipratropium bromide.

### In vitro studies

The FDA recommends that applicants conduct the following in vitro studies, using at least three batches<sup>1</sup> 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) lifestages<sup>2</sup> of the product using a flow rate of 28.3 L/min. 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.

**Equivalence based on:** Population bioequivalence (PBE) analysis of SAC. Refer to the draft budesonide inhalation suspension be guidance for additional information regarding PBE analysis.<sup>3</sup>

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. The APSD determination of each unit should be performed with a minimum number of inhalations justified by the sensitivity of the validated assay.

<sup>1</sup> A single batch of solution can be split-filled into three equal-size sublots of product.

<sup>2</sup> 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.

<sup>3</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM319977.pdf>

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).<sup>4</sup> 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 mouthpiece. 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.<sup>5</sup> 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 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 tip. The plume width is measured at a distance equal to the greater of the two distances selected for characterization of the spray pattern.

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<sup>4</sup> 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.

<sup>5</sup> The distance between the actuator orifice and the point of spray pattern measurement should be same for T and R.

**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.

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### **Pharmacokinetic (PK) BE Study**

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 sensitive analytical method

Subjects: Normal healthy males and nonpregnant females, general population

Additional comments: The healthy 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

**Analyte(s) to measure (in appropriate biological fluid):** 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%.

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### **Clinical pharmacodynamic (PD) study**

**Type of study:** Bioequivalence study

**Design:** This study could be either of crossover or parallel-group design, taking into consideration the patient population and the current standard-of-care treatment for 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 run-in period (to

allow for wash-out of anticholinergic agents) followed by a one-day treatment period of the placebo, T, or R product.

**Strength:** 21 mcg ipratropium bromide

**Dose:** 42 mcg, single dose (i.e., two inhalations from 21 mcg ipratropium bromide metered-inhalation aerosol)

**Subjects:** Males and non-pregnant females with COPD. The study may enroll all COPD patients who meet inclusion and exclusion criteria, or may be enriched with patients who demonstrate  $\geq 15\%$  reversibility to bronchodilator therapy (appropriate justification should be included for the population chosen for study)

**Additional comments:**

1. Inclusion criteria should, at a minimum, include:
  - a. Adult ( $\geq 40$  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. Current or former smoker (e.g., with history of  $\geq 10$  pack-years)
  - d. Post-bronchodilator FEV<sub>1</sub>  $\leq 65\%$  of predicted
  - e. Post-bronchodilator FEV<sub>1</sub>/FVC ratio  $\leq 0.70$
2. 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. 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 study
  - g. Treatment for COPD exacerbation within 12 weeks prior to study
  - h. Acute (viral or bacterial) upper or lower respiratory tract infection or illness within 6 weeks prior to study
  - i. Lung volume reduction surgery within the previous 12 months
  - j. Chronic oxygen use for  $>12$  hours/day
3. 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.
4. All spirometry should be conducted in accordance with ATS standards.

5. 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).
6. The study should begin with a placebo run-in period (at least 2 weeks in duration) to wash out any pre-study long-acting anti-cholinergic agents.
7. 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.
8. 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.
9. All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of an AE should include date of onset, description of AE, severity, relation to study medication, action taken, outcome, and date of resolution.
10. 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.

**BE study primary endpoint:** Area under the serial FEV1-time curve calculated from time zero to 6 hours ( $AUC_{0-6h}$ ) following the treatment.

The above BE study endpoint should be baseline-adjusted (change from baseline). FEV1 measurements should be performed and interpreted in accordance with ATS guidelines.

Serial spirometry (FEV1) should be measured at 0, 10, 15, 30, 60, 90, and 120 minutes, and 3, 4, 5, 6, and 7 hours post-dose.

For each treatment group, time to peak bronchodilator response ( $T_{max}$ ) and FEV1 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 interval for the T/R ratio for the BE study endpoint should fall within 80.00-125.00%.

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## Additional information

### Formulation and Device

The T product is recommended to be qualitatively (Q1)<sup>6</sup> and quantitatively (Q2)<sup>7</sup> 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 if the R product has a dose counter. In vitro and in-use robustness studies should be conducted to support the functionality, accuracy, and robustness of the proposed dose counter of the T product.

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<sup>6</sup> Q<sub>1</sub> (qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.

<sup>7</sup> Q<sub>2</sub> (quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within  $\pm 5\%$  of those used in the reference product.

**APPENDIX**

<b>Variable Name</b>	<b>Variable Type</b>	<b>Content</b>	<b>Notes</b>
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												