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Draft – Not for Implementation

## Draft Guidance on Tiotropium Bromide

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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.

<b>Active Ingredient:</b>	Tiotropium bromide
<b>Dosage Form; Route:</b>	Spray, metered; inhalation
<b>Strengths:</b>	EQ 0.0025 mg Base/inh EQ 0.00125 mg Base/inh
<b>Recommended Studies:</b>	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) inhalation sprays containing tiotropium bromide.

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### In Vitro BE Studies

FDA recommends that prospective applicants conduct the following in vitro studies for all 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. FDA recommends that three primary stability batches be also used to demonstrate in vitro BE. The three batches of T product should be manufactured from, at minimum, three different batches of drug substance(s), excipient(s), and device 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<sup>1</sup> of the product, using a flow rate of 28.3 L/min. U.S. Pharmacopoeia (USP) <601> Apparatus A or other 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 product-specific guidance for *Budesonide Inhalation Suspension* for additional information regarding PBE analysis procedures.

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<sup>1</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.

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. The USP <601> Apparatus 1, Apparatus 6, or other 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. Water evaporation should be minimized by performing the APSD test under high humidity conditions (as close as possible to 100% relative humidity) or by cooling the cascade impactor (CI) to low temperatures (e.g., 5°C) or by any other suitable method.

Additional comments: Drug deposition on individual sites, including the mouthpiece adapter, the induction port, each stage of the 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>2</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 at two different distances from the nozzle. The selected distances should be at least 3 cm apart and based on the range of 3 to 7 cm from the R mouthpiece edge.<sup>3</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: The spray pattern test should be measured quantitatively in terms of ovality ratio and area within the parameter 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. 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 the B lifestage of the product. The timed-sequence sound-triggered flash photography method, laser light sheet

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<sup>2</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>3</sup> The distance between the nozzle and point of spray pattern measurements should be the same for T and R.

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 mouthpiece edge. 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 the vertex that occurs at or near the edge of the 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 plume angle and width, which should fall within 90-111%.

5. Type of study: Priming and repriming

Design: The priming and repriming tests should take into consideration the emitted dose (ex-mouthpiece) 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 upright 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.

6. Type of study: Spray duration

Design: The spray duration test should be performed at the B and E lifestages of the product. Video recording with a high-speed camera, laser light diffraction, particle image velocimetry or other suitable method may be used to determine the spray duration.

Equivalence based on: PBE or other appropriate statistical analysis of the time interval when the spray begins to develop, to the last moment when a spray is formed at the nozzle. If other statistical analysis is used, it should be adequate considering the purpose of the study and scientifically justified.

7. Type of study: Spray velocity

Design: The spray velocity test should be performed at the B and E lifestages of the product. High speed imaging, particle image velocimetry, phase doppler anemometry or other suitable method may be used to determine spray velocity.

Equivalence based on: PBE or other appropriate statistical analysis of plume front velocity<sup>4</sup> at one selected distance between 8 to 12 cm from the nozzle. If other statistical analysis is used, it should be adequate considering the purpose of the study and scientifically justified. Full plume front velocity vs. distance data should be submitted as supportive evidence for equivalent spray velocity.

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

FDA recommends that prospective applicants conduct the following PK BE study for all strengths of the T and R products.

8. 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: Adult 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 sprays in a standard fashion, prior to each treatment session, to assure a relatively consistent inspiratory flow rate and inspiratory duration. (2) A Bio-IND is required prior to conduct of the PK study if the dose exceeds the maximum labeled single dose.

Analyte to measure: Tiotropium in plasma

Equivalence based on: AUC and  $C_{max}$  for tiotropium. 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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### **Additional information**

Formulation:

FDA recommends that the T formulation be qualitatively (Q1)<sup>5</sup> and quantitatively (Q2)<sup>6</sup> the same as the R formulation.

Device:

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<sup>4</sup> Velocity at the front edge of the aerosol cloud.

<sup>5</sup> Q1 (qualitative sameness) means that the test formulation uses the same inactive ingredient(s) as the reference formulation.

<sup>6</sup> Q2 (quantitative sameness) means that the concentrations of the inactive ingredient(s) used in the test formulation are within  $\pm 5\%$  of those used in the reference formulation.

Prospective applicants should refer to FDA's guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January 2017), which, when finalized, will provide the Agency's current thinking on the identification and assessment of any differences in the design of the user interface for a proposed generic drug-device combination product when compared to its RLD.

FDA recommends that prospective applicants consider the following characteristics of the R product when designing the T product:

- Active, metered, multi-dose device
- Size and shape of the R product
- Number of doses in the R product
- External operating principles and external critical design attributes of the R product
- Dose indicator/counter

## 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												