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Draft Guidance on Tiotropium Bromide

August 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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:	Tiotropium bromide
Dosage Form:	Spray, metered
Route:	Inhalation
Strengths:	EQ 0.0025 mg Base/inh, EQ 0.00125 mg Base/inh
Recommended Studies:	Seven in vitro bioequivalence studies and one in vivo bioequivalence study with pharmacokinetic endpoints

Seven in vitro bioequivalence studies:

FDA recommends that prospective applicants conduct the following in vitro studies for all strengths of the test (T) and reference standard (RS) products. For each strength, use at least three batches each of the T and RS 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 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[1] of the product, using a flow rate of 28.3 L/min or 30 L/min.[2] U.S.

[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

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.

Bioequivalence based on: Population bioequivalence (PBE) analysis of SAC. Refer to the most recent version of the product-specific guidance for *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 sprays as per USP <601> Table 2 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 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 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 and RS products, 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).[3] 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. 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 RS mouthpiece edge.[4] Impaction (thin-layer chromatography plate impaction), non-impaction (laser light sheet technology), or other suitable method may be used to determine the spray pattern.

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the labeled number of actuations, and the actuation(s) corresponding to the labeled number of actuations, respectively.

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

[3] 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.

[4] The distance between the nozzle and point of spray pattern measurements should be the same for T and RS.

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.

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 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.

Bioequivalence based on: Ratio of the geometric mean of the three batches of T to that of the three batches of RS (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 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 bioequivalence 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.

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: 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.

Bioequivalence 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.[5] 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.

Bioequivalence based on: PBE or other appropriate statistical analysis of plume front velocity[6] at one selected distance between 8 to 12 cm from the nozzle.[7] 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.

One in vivo study with pharmacokinetic endpoints:

FDA recommends that prospective applicants conduct the following pharmacokinetic bioequivalence study for all strengths of the T and RS 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, non-lactating females
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 pharmacokinetic study if the dose exceeds the maximum labeled single dose.

Analyte to measure: Tiotropium in plasma

Bioequivalence 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%.

[5] The distance between the nozzle and point of measurement for the start and end of the spray should be the same for T and RS.
[6] Velocity at the front edge of the aerosol cloud.
[7] The distance between the nozzle and point of plume front velocity measurement should be the same for T and RS.

Additional information:

Formulation:
To demonstrate bioequivalence, the T product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the RS product that may significantly affect the local or systemic availability of the active ingredient. For example, the T product can be qualitatively (Q1)[8] and quantitatively (Q2)[9] the same as the RS product to satisfy no difference in inactive ingredients.

Device:
The RLD is presented as a drug cartridge co-packaged with an inhalation spray device. The inhalation spray device is the device constituent part.

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 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 November 2020; Revised August 2024

Unique Agency Identifier: PSG_021936

[8] Q1 (qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RS.
[9] Q2 (quantitative sameness) means that the concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the RS.

[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												