This 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.

This guidance, which interprets the Agency’s regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required.

This is a new draft product-specific guidance for industry on generic olodaterol hydrochloride; tiotropium bromide.

**Active Ingredient:** Olodaterol hydrochloride; Tiotropium bromide

**Dosage Form; Route:** Spray, metered; inhalation

**Strength:** EQ 0.0025 mg Base/inh; EQ 0.0025 mg Base/inh

**Recommended Studies:** 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 olodaterol hydrochloride and tiotropium bromide.

### In Vitro BE Studies

FDA recommends that prospective applicants conduct the following in vitro studies for 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 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\(^1\) 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.

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).\(^2\) 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.

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\(^1\) 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. 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. 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 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.

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3 The distance between the nozzle and point of spray pattern measurements should be the same for T and R.
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\(^4\) 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 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-

\(^4\) Velocity at the front edge of the aerosol cloud.
IND is required prior to conduct of the PK study if the dose exceeds the maximum labeled single dose.

**Analytes to measure:** Olodaterol and tiotropium in plasma

**Equivalence based on:** AUC and $C_{\text{max}}$ for olodaterol and tiotropium. The 90% confidence intervals for the geometric mean T/R ratios of AUC and $C_{\text{max}}$ 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) and quantitatively (Q2) the same as the R formulation.

**Device:**

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

**Unique Agency Identifier:** PSG_206756

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

6 Q2 (quantitative sameness) means that the concentrations of the inactive ingredient(s) used in the test formulation are within ±5% of those used in the reference formulation.
# APPENDIX

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