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Draft – Not for Implementation

Draft Guidance on Tiotropium Bromide

November 2024

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Active Ingredient:	Tiotropium bromide
Dosage Form:	Powder
Route:	Inhalation
Strength:	EQ 0.018 mg Base/inh
Recommended Studies:	Two options: (1) three in vitro bioequivalence studies, one comparative characterization study, and two in vivo bioequivalence studies with pharmacokinetic endpoints, or (2) two in vitro bioequivalence studies, one in vivo bioequivalence study with pharmacokinetic endpoints, and one comparative clinical endpoint bioequivalence study

I. Option 1: Three in vitro bioequivalence studies, one comparative characterization study, and two in vivo bioequivalence studies with pharmacokinetic endpoints

To demonstrate bioequivalence by this option, the test (T) product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference standard (RS) product that may significantly affect the local or systemic availability of the active ingredient. For example, the T product can be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the RS product to satisfy no difference in inactive ingredients.

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

Three in vitro bioequivalence studies:

FDA recommends that prospective applicants conduct the following in vitro bioequivalence studies for the T and RS products. 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 also be 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 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[3,4,5] of the product using flow rates of 20 L/min, 39 L/min and 60 L/min. U.S. Pharmacopeia (USP) <601> Apparatus B or another appropriate apparatus may be used to determine the SAC using a validated assay. The number of capsules used per determination should be one. The number of actuations per capsule should be two. The volume of air drawn through the delivery system per actuation should be 2 L.

   Bioequivalence based on: Population bioequivalence (PBE) analysis of SAC. Refer to the most recent version of the FDA product-specific guidance for *Budesonide Inhalation Suspension* (NDA 020929)[a] for additional information regarding PBE analysis procedures.

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[3] Based on the labeled number of actuations, the terms, B lifestage, M lifestage, and E lifestage represent the first actuation(s), 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. In vitro lifestage testing should be conducted on the to be marketed packaging configuration with the highest number of doses. For example, the B, M, and E lifestage for a 90 capsule packaging configuration may correspond to actuations 1, 45, and 90. Prospective applicants intending to market additional packing configurations with a lower number of doses than the configuration used in the recommended in vitro bioequivalence studies may establish their bioequivalence based on (1) acceptable in vitro bioequivalence studies on the configuration with the highest number of doses, (2) same formulation composition across all configurations, and (3) same container/closure system components critical to the product performance across all configurations. Considerations for lifestage are not applicable for the recommended in vivo bioequivalence studies.

[4] At minimum, at least one T batch and RS batch each should be used across all in vitro and in vivo studies, whenever feasible. The T and RS batch packaging configurations used for the in vitro and in vivo bioequivalence studies should be the same. However, a lower packaging configuration for the T and RS batches may be used for in vivo bioequivalence studies if adequate justification is provided and the lower packaging configuration batch is included as one of the three batches used in the in vitro bioequivalence studies. Combination of units for the lower packaging configuration may be needed to ensure consistency in in vitro lifestage testing with the lifestages of the highest packaging configuration intended to be marketed. Prospective applicants proposing to use batch multiple packaging configurations for the in vitro and in vivo bioequivalence studies are strongly encouraged to discuss the proposed study designs with FDA through a controlled correspondence or as part of a pre-ANDA product development meeting request. For additional information, refer to the most recent versions of the FDA guidances for industry on *Controlled Correspondence Related to Generic Drug Development* and on *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*.[b]

[5] When conducting in vitro studies at different lifestages, doses between those tested at each lifestage should be actuated using the device. For example, prospective applicants testing at the E lifestage should actuate all doses leading up to the dose used to test the E lifestage.

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 flow rates of 20 L/min, 39 L/min, and 60 L/min. A cascade impactor apparatus for inhalation powders 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 capsules justified by the sensitivity of the validated assay. The volume of air drawn through the delivery system should be 4 L.

Additional comments: Drug deposition on individual sites, including the mouthpiece adapter, the induction port, the pre-separator, and 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 for bioequivalence evaluation.

Bioequivalence based on: PBE analysis of impactor-sized mass (ISM).[6] 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: Realistic APSD
Design: The realistic APSD test should be performed at the B lifestage of the product using mouth-throat models of different sizes (e.g., small and large) and breathing profiles (e.g., weak and strong) that are representative of the entire patient population. A cascade impactor apparatus for inhalation powders 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 capsules justified by the sensitivity of the validated assay.

Additional comments: Drug deposition on individual sites, including the mouthpiece adapter, the mouth-throat model, the mixing inlet, and 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 ANDA submission.

Bioequivalence based on: PBE analysis or other appropriate statistical analysis of ISM of the drug for each mouth-throat model-breathing profile combination. The cascade impactor profiles representing drug deposition on the individual stages of the cascade impactor along with the MMAD, GSD, and FPM should be submitted as supportive evidence for equivalent APSD. If another statistical analysis is used, it should be adequately and scientifically justified considering the purpose of the study. Prospective

[6] 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 cut-off size limit.

applicants are encouraged to discuss other statistical analysis designs with FDA via a pre-ANDA meeting request. For additional information, refer to the most recent version of the FDA guidance for industry, *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*.[a]

One comparative characterization study:

The comparative physicochemical characterization study of the T product and the RS product should be performed on a minimum of three exhibit batches of the T product and three batches of the RS product. The comparative characterization study should include:

1. Particle morphology of the emitted dose
    a. Imaging comparisons of the deposited particles from the emitted dose at the B lifestage should be determined to assess particle morphology and agglomeration. Description for the sample collection method should be provided. Where applicable, chemical classification of the individual components in agglomerate particles and individual drug and/or excipients can be provided using an optimized and validated analytical method (e.g., morphologically-directed Raman spectroscopy) to further describe and/or support morphology characterization.

Two in vivo bioequivalence study with pharmacokinetic endpoints:

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 powder in a standard fashion prior to each treatment session to assure a relatively consistent inspiratory flow rate and inspiratory duration. (2) Subjects should adhere to the reference listed drug (RLD) product labeling for administration, including the following: "Must breathe in 2 times from the same capsule." (3) A Bio-IND is required prior to conduct of the pharmacokinetic bioequivalence 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%.

2. Type of study: Fasting
   Design: Single-dose, two-way crossover with charcoal block
   Dose: Minimum number of inhalations that is sufficient to characterize the pharmacokinetic profiles by using a sensitive analytical method.

Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: (1) The subjects enrolled for in vivo studies should be trained in the use of the inhalation powder in a standard fashion prior to each treatment session to assure a relatively consistent inspiratory flow rate and inspiratory duration. (2) Subjects should adhere to the RLD product labeling for administration, including the following: "Must breathe in 2 times from the same capsule." (3) A Bio-IND is required prior to conduct of the pharmacokinetic study if the dose exceeds the maximum labeled single dose. 4) Justification for the charcoal dose should be provided in the ANDA submission.

Analyte to measure: Tiotropium in plasma

Bioequivalence based on: AUC and C_{max} for tiotropium. The 90% confidence intervals (CIs) for the geometric mean T/R ratios of AUC and C_{max} should fall within the limits of 80.00% - 125.00%.

II. Option 2: Two in vitro bioequivalence studies, one in vivo bioequivalence study with pharmacokinetic endpoints, and one comparative clinical endpoint bioequivalence study

To demonstrate bioequivalence by this option, it is recommended to conduct the in vitro bioequivalence studies #1 through #2 and the in vivo pharmacokinetic bioequivalence study #1 as described in Option 1. In addition, it is recommended to conduct the comparative clinical endpoint bioequivalence study described below.

One comparative clinical endpoint bioequivalence study:

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 and 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, blinded (where possible) 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 RS product.
Strength: EQ 0.018 mg base/inh
Dose: 0.018 mg tiotropium, single dose (i.e., two inhalations from the same capsule)
Subjects: Males and non-pregnant females with COPD

   Inclusion criteria should, at minimum, include:
   a. Adult (≥ 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. Post-bronchodilator forced expiratory volume in one second (FEV_1) ≤ 80%
   d. Post-bronchodilator FEV_1/forced vital capacity (FVC) ratio ≤ 0.70
   e. Current or former smokers (e.g., with history of ≥ 10 pack-years)

f. Willingness to give their written informed consent to participate in the study

Exclusion criteria should, at minimum, include:

a. Known respiratory disorders 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, pulmonary edema, 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 paradoxical bronchospasm, narrow-angle glaucoma, prostatic hyperplasia, bladder neck obstruction, or any other condition, which, in the opinion of the investigator, would contraindicate the use of an anticholinergic agent
e. History of allergy or hypersensitivity to anticholinergic/muscarinic receptor antagonist agents, beta-2 adrenergic agonists, lactose/milk proteins, or specific intolerance to aerosolized tiotropium-containing products or known hypersensitivity to any of the proposed ingredients or components of the delivery system
f. Hospitalization for COPD or pneumonia within 12 weeks prior to the initiation of the study
g. Treatment for COPD exacerbation within 12 weeks prior to 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 the 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 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 the 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).
b. 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.
c. All spirometry should be conducted in accordance with ATS standards.

d. The study 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 should begin with a placebo run-in period (at least 2 weeks in duration; appropriate justification should be included for the duration chosen) to washout any pre-study long-acting anticholinergic agents, chronic long-acting beta-agonists or chronic inhaled corticosteroids and to establish FEV_1 baseline values.
f. To ensure adequate study sensitivity, the T and RS products should both be statistically superior to placebo ($p < 0.05$) with regard to the bioequivalence study primary endpoint.
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 RS 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 24 hours ($AUC_{0\text{-}24h}$) 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, 5 and 30 min, 1, 2, 4, 6, 8, 10, 12, 23, and 24 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.

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

Additional information:

Computational model(s) for regional drug delivery:
An optional computational modeling study may be used to support bioequivalence of the T and RS products. Refer to the most recent version of the FDA product-specific guidance on *Formoterol Fumarate; Glycopyrrolate Inhalation Metered Aerosol* (NDA 208294)[a] for additional information regarding the development and conduct of an optional computational modeling study. In order to clarify the FDA's expectations for prospective applicants early in product development, and to assist applicants to submit an ANDA as complete as possible, FDA strongly encourages applicants to discuss their development program and plans for conducting an optional computational modeling study 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]

Device:
The RLD is presented in drug capsules co-packaged with a dry powder inhaler (DPI). The DPI 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 test devices including:

- Passive (breath-actuated), pre-metered, single-unit dose, capsule-based format
- Number of doses
- Device airflow resistance

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]

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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												