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Draft – Not for Implementation

Draft Guidance on Umeclidinium Bromide

February 2024

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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:	Umeclidinium bromide
Dosage Form:	Powder
Route:	Inhalation
Strength:	EQ 0.0625 mg Base/inh
Recommended Studies:	Two in vitro bioequivalence studies, one in vivo bioequivalence study with pharmacokinetic endpoints, and one comparative clinical endpoint bioequivalence study

Two in vitro bioequivalence studies:

FDA recommends that prospective applicants conduct the following in vitro bioequivalence studies using at least three batches each of the test (T) and reference standard (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 30 L/min, 60 L/min and 90 L/min. U.S.

[1] 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.

Pharmacopoeia (USP) <601> Apparatus B or another appropriate apparatus may be used to determine the SAC using a validated assay. The number of actuations per determination should be one. The volume of air drawn through the delivery system 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 on *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 flow rates of 28.3 L/min or 30 L/min, 60 L/min and 90 L/min. Cascade impaction devices 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 inhalations 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 (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 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).[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.

One 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: Normal healthy 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 powder 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.

[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.

Analyte to measure: Umeclidinium in plasma

Bioequivalence based on: AUC and Cmax for umeclidinium. The 90% confidence intervals for the geometric mean T/R ratios of AUC and Cmax should fall within the limits of 80.00% - 125.00%.

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, and placebo-controlled, at minimum consisting of a 2-week run-in period (to allow for washout of anticholinergic agents, as well as chronic long-acting beta-agonists and chronic inhaled corticosteroids) followed by a one-day treatment period of the placebo, T, or RS product.
Strength: EQ 0.0625 mg Base/inh (umeclidinium bromide inhalation powder)
Dose: EQ 0.0625 mg umeclidinium, single-dose
Subjects: Males and non-pregnant females with COPD. 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)

   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 FEV1 ≤ 70%
   d. Post-bronchodilator FEV1/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 hypertrophy, 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 umeclidinium-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 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 recommendations:

a. 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.
b. All spirometry should be conducted in accordance with ATS standards.
c. 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).
d. 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 and to establish FEV1 baseline values.
e. 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.
f. 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.
g. 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.

h. 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.
i. 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.

Bioequivalence study endpoints: Area under the serial FEV1-time curve calculated from time zero to 24 hours (AUC0-24h) following the treatment.

The above bioequivalence 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, 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 (Tmax) and FEV1 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 BE study endpoint should fall within 80.00% - 125.00%.

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)[3] and quantitatively (Q2)[4] the same as the RS product to satisfy no difference in inactive ingredients.

Device:
The reference listed drug (RLD) is presented as a blister-based 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 T

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

device. In addition, T device design should take into consideration the following characteristics of the RLD:

- Passive (breath-actuated), pre-metered, multi-dose format
- Number of doses
- Device airflow resistance
- 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 October 2016; Revised February 2024

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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 Name**	**Variable Name**	**Variable Name**
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	FPM

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												