

Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Acridinium Bromide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:	Acridinium bromide
Dosage Form:	Powder, metered
Route:	Inhalation
Strength:	0.4 mg/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) lifestages¹ of the product, using a flow rate of 31.5 L/min, 63 L/min and 94.5 L/min.

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.

U.S. 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 31.5 L/min, 63 L/min and 94.5 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 adult males and non-pregnant females, general population
Additional comments: The healthy subjects enrolled for in vivo studies should be trained in the use of the inhalation aerosols in a standard fashion prior to each treatment session to ensure a relatively consistent inspiratory flow rate and inspiratory duration.

Analyte to measure: Acclidinium in plasma

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.

Bioequivalence based on: AUC and C_{\max} for acclidinium. 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%.

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 run-in period (to allow for wash-out 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: 0.4 mg/inh
Dose: 0.4 mg, single dose (i.e., one inhalation)
Subjects: Males and non-pregnant females with COPD. The study may enroll all COPD patients who meet inclusion and exclusion criteria, or may be enriched with patients who demonstrate $\geq 15\%$ reversibility to bronchodilator therapy (appropriate justification should be included for the population chosen for study).

Inclusion criteria should, at minimum, include:

- a. Adult (>40 -year-old) male or female subjects of non-childbearing potential or of childbearing potential but committed to consistent use of an acceptable method of birth control
- b. Diagnosis of COPD, as defined by American Thoracic Society (ATS) or Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria
- c. Current or former smoker (e.g., with history of >10 pack-years)
- d. Post-bronchodilator $FEV_1 < 80\%$ of predicted
- e. Post-bronchodilator FEV_1/FVC ratio ≤ 0.70

Exclusion criteria should, at minimum, include:

- a. Known respiratory disorder 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, 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 narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction, which, in the investigator's opinion, would contraindicate the use of an anticholinergic agent

- e. History of allergy or hypersensitivity to anticholinergic/muscarinic receptor antagonist agent, beta-2 agonists, or specific intolerance to acclidinium bromide-containing products, or known hypersensitivity to any of the proposed ingredients
- f. Hospitalization for COPD or pneumonia within 12 weeks prior to study
- g. Treatment for COPD exacerbation within 12 weeks prior to study
- h. Acute (viral or bacterial) upper or lower respiratory tract infection or illness within 6 weeks prior to study
- i. Lung volume reduction surgery within the previous 12 months
- j. Chronic oxygen use for >12 hours/day

Additional comments:

- 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 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) to wash out any pre-study long-acting anti-cholinergic agents, corticosteroids, and long-acting bronchodilators.
- 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 endpoints.
- 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 an AE should include date of onset, description of 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. The study protocol should include pre-specified definitions of COPD exacerbation, as well as pre-specified and appropriate escape criteria with consideration to patient safety.

Bioequivalence study primary endpoint: Area under the serial FEV₁-time curve calculated from time zero to 6 hours (AUC_{0-6h}) 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, 10, 15, 30, 60, 90, and 120 minutes, and 3, 4, 5, and 6 hours post-dose.

For each treatment group, time to peak bronchodilator response (T_{max}) 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% CI for the T/R ratio for the bioequivalence 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 reservoir-based dry powder inhaler (DPI). The DPI is the device constituent part.

FDA recommends that prospective applicants examine the size and shape, external critical design attributes, and external operating principles of the RLD device when designing the T device. In addition, T device design should take into consideration the following characteristics of the RLD:

- Passive (breath-actuated) device, device-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

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 $\pm 5\%$ of those used in the RS formulation.

Document History: Recommended September 2015; Revised February 2024

Unique Agency Identifier: PSG_202450

^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												