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Draft – Not for Implementation

Draft Guidance on Glycopyrrolate; Indacaterol Maleate

May 2023

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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 Ingredients:	Glycopyrrolate; Indacaterol maleate
Dosage Form; Route:	Powder; Inhalation
Strength:	15.6 mcg/inh; 27.5 mcg/inh
Recommended Studies:	Two in vitro bioequivalence studies, one in vivo bioequivalence study with pharmacokinetic endpoints, and one comparative clinical endpoint bioequivalence study

FDA recommends the following in vitro and in vivo studies to establish bioequivalence of the test (T) and reference (R) dry powder inhalers (DPIs) containing glycopyrrolate and indacaterol maleate.

In vitro bioequivalence studies:

FDA recommends that prospective applicants conduct the following in vitro bioequivalence studies for the 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 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[1,2] of the product, using a flow rate of 30 L/min, 60 L/min and 90 L/min. 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 capsules and number of actuations per capsule used per determination should be one. The volume of air drawn through the delivery system should be 2 L.

Equivalence based on: Population bioequivalence (PBE) analysis of SAC. Refer to the most recent version of the FDA product-specific guidance for *Budesonide Inhalation Suspension*[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 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 (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 bioequivalence evaluation.

Equivalence based on: PBE analysis of impactor-sized mass (ISM).[3] 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 priming, 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 60 capsule packaging configuration may correspond to actuations 1, 30, and 60. 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 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.

[2] 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.

[3] 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 cut-off size limit.

In vitro bioequivalence study with pharmacokinetic endpoints:

FDA recommends that prospective applicants conduct the following pharmacokinetic bioequivalence study for the T and R products.

1. Type of Study: Fasting
   Design: Single-dose, two-way crossover
   Dose: Minimum number of capsules that is sufficient to characterize a pharmacokinetic profile by using a sensitive analytical method
   Subjects: Healthy males and non-pregnant females
   Additional comments: (1) Subjects enrolled for in vivo studies should be trained in the use of the inhalation powders 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.

Analytes to measure: Glycopyrronium and indacaterol in plasma

Equivalence based on: AUC and C_{max} for glycopyrronium and indacaterol. 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%.

Comparative clinical endpoint bioequivalence study:

FDA recommends that prospective applicants conduct the following comparative clinical endpoint bioequivalence study for the T and R products.

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) followed by a one-day treatment period of the placebo, T, or R product.
   Strength: 15.6 mcg/inh; 27.5 mcg/inh
   Dose: 15.6 mcg/inh; 27.5 mcg/inh, one inhalation
   Subjects: Adult 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 and exclusion criteria:

a. Inclusion criteria should, at minimum, include:
    - 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
    - Diagnosis of COPD, as defined by American Thoracic Society (ATS) [GOLD criteria]
    - Post-bronchodilator forced expiratory volume in one second (FEV_1) ≤ 80%
    - Post-bronchodilator FEV_1/forced vital capacity (FVC) ratio ≤ 0.70
    - Current or former smokers (e.g., with history of ≥ 10 pack-years)
    - Willingness to give their written informed consent to participate in the study

b. The exclusion criteria should, at minimum, include:
    - 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
    - Evidence or history of other clinically significant cardiovascular disease or abnormality (such as, but not limited to, congestive heart failure, uncontrolled hypertension, uncontrolled coronary artery disease, myocardial infarction, arrhythmia, long QT syndrome, paroxysmal atrial fibrillation), renal, neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or hematological disease or abnormality 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 exacerbates during the study
    - Known active tuberculosis
    - History of paradoxical bronchospasm, narrow-angle glaucoma, prostatic hyperplasia, bladder neck obstruction, or severe renal impairment or urinary retention or any other condition, which, in the opinion of the investigator, would contraindicate the use of an anticholinergic or long-acting beta-agonist agent
    - History of allergy or hypersensitivity to anticholinergic/muscarinic receptor antagonist agents, long- or short-acting beta-2 agonists, sympathomimetic amines, lactose/milk proteins, or specific intolerance to aerosolized glycopyrrolate or indacaterol-containing products or known hypersensitivity to any of the proposed ingredients or components of the delivery system
    - Hospitalization for COPD or pneumonia within 12 weeks prior to the initiation of the study
    - Treatment for COPD exacerbation within 12 weeks prior to study
    - Inability to discontinue COPD medications during the run-in and treatment periods

- 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
- Abnormal and significant electrocardiogram (ECG) finding prior to the screening, during the run-in and treatment periods
- Lung volume reduction surgery within 12 months prior to the initiation of the study
- 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 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 or long-acting beta-agonist agents and to establish FEV1 baseline values.
e. To ensure adequate study sensitivity, the T and R products should both be statistically superior to placebo ($p < 0.05$) with regard to the BE study endpoint.
f. It is the prospective applicant's responsibility to enroll a sufficient number of subjects for the study to demonstrate BE of the T to the R 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, at minimum, 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. 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.

Bioequivalence study primary endpoint: Area under the serial FEV_1-time curve calculated from time zero to 12 hours (AUC_{0_12h}) on the first day of treatment.

The above BE study endpoint should be baseline-adjusted (change from baseline). FEV_1 measurements should be performed and interpreted in accordance with ATS guidelines.

On the first day of treatment, serial FEV_1 should be determined at 0, 5 and 15 min, 1, 2, 4, 6, 8, 10 and 12 hours post-dose.

Equivalence based on: T/R ratio for the primary endpoints. The 90% confidence intervals for the T/R ratio for the primary endpoint should fall within the limits of 80.00% - 125.00%.

Additional information:

Formulation:
FDA recommends that the T product be qualitatively (Q1)[4] and quantitatively (Q2)[5] the same as the R formulation.

If a prospective applicant uses a Q2-different formulation for its T product, the prospective applicant should explain the reason(s) for not using a T formulation that is Q2 the same as the R formulation. In addition, the prospective applicant should provide pharmaceutical development data, involving in vitro testing of multiple drug-to-excipient ratios that encompass combinations below and above the ratios used in the T and R products.

Device:
The reference listed drug (RLD) is presented in drug capsules co-packaged with a dry powder inhaler. The inhaler 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 of the RLD device
- Number of doses of the RLD product
- Device resistance of the RLD product

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]

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

Revision History: Recommended June 2020; Revised May 2023

Unique Agency Identifier: PSG_207930

[a] For the most recent version of a product-specific guidance, check the FDA product-specific guidance web page at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.
[b] For the most recent version of a guidance, check the FDA guidance web page 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												