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Draft Guidance on Levalbuterol Tartrate

November 2023

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Active Ingredient:	Levalbuterol tartrate
Dosage Form:	Aerosol, metered
Route:	Inhalation
Strength:	EQ 0.045 mg Base/inh
Recommended Studies:	Five in vitro bioequivalence studies, one in vivo bioequivalence study with pharmacokinetic endpoints, and one in vivo pharmacodynamic bioequivalence study

FDA recommends the following in vitro and in vivo studies to establish bioequivalence of the test (T) and reference (R) metered dose inhalers (MDIs) containing levalbuterol tartrate.

Five in vitro bioequivalence studies:

FDA recommends that prospective applicants conduct the following in vitro bioequivalence studies using at least three batches each of 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 a 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] of the product, using a flow rate of 28.3 L/min or 30 L/min.[2] U.S. Pharmacopoeia (USP) <601> Apparatus A or another 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 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 a flow rate of 28.3 L/min or 30 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 inhalations justified by the sensitivity of the validated assay.
Additional comments: Drug deposition on individual sites, including the mouthpiece adapter, the induction port, 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.

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.

3. Type of study: Spray pattern
Design: The spray pattern test should be performed at the B lifestage of the product and at two different distances from the actuator orifice. The selected distances should be at least 3 cm apart and based on the range of 3 to 7 cm from the R actuator mouthpiece.[4] 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: Spray pattern should be measured quantitatively in terms of ovality ratio and area within the perimeter 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

[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] The selection of flow rate should match that of the flow rate chosen for APSD testing.
[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 cutoff size limit.
[4] The distance between the actuator orifice and point of spray pattern measurement should be the same for T and R.

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, that pass through the center of mass or the center of gravity, as appropriate. 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 actuator mouthpiece. 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 a vertex that occurs at or near the actuator 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: Priming and repriming tests should be based on the emitted dose (ex-actuator) 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.
Additional comments: For bioequivalence evaluation, the priming and repriming tests should be based on products stored in the valve upright position, with the exception of MDIs for which the R labeling recommends storage in the valve down 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.

One in vivo 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, randomized, two-way crossover
   Dose: EQ 0.09 mg Base (two inhalations)
   Subjects: Healthy males and non-pregnant females
   Additional comments: (1) The 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 assure a relatively consistent inspiratory flow rate and inspiratory duration. (2) Prospective applicants may consider using a reference-scaled average bioequivalence approach. Provide evidence of high variability in the bioequivalence parameters, AUC, and/or C_{max} (i.e., within-subject variability ≥ 30%) when using this approach. For general information on this approach, refer to the most recent version of the FDA product-specific guidance on *Progesterone Oral Capsule* (NDA 019781).[a]

Analyte to measure: Levalbuterol in plasma

Equivalence based on: AUC and C_{max} for levalbuterol. 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 in vivo pharmacodynamic bioequivalence study:

FDA recommends that prospective applicants conduct the following pharmacodynamic bioequivalence study using a bronchoprovocation study design for the T and R products.

1. Type of study: Pharmacodynamic bioequivalence study
   Design: A bronchoprovocation study using a single-dose, double-blind, double-dummy, randomized, crossover design that is recommended at minimum to consist of the following treatment periods:
   a. Zero dose: One actuation each from two different placebo R inhalation aerosols and one actuation each from two different placebo T inhalation aerosols
   b. EQ 0.045 mg Base dose of R: One actuation each from the R inhalation aerosol and the placebo R inhalation aerosol and one actuation each from two different placebo T inhalation aerosols
   c. EQ 0.090 mg Base dose of R: One actuation each from two different R inhalation aerosols and one actuation each from two different placebo T inhalation aerosols
   d. EQ 0.045 mg Base dose of T: One actuation each from the T inhalation aerosol and the placebo T inhalation aerosol and one actuation each from two different placebo R inhalation aerosols
   Subjects: Males and non-pregnant females with asthma

Inclusion criteria should, at minimum, include:

a. Male and non-pregnant female subjects (18-65 years of age).
b. Stable mild asthmatics based on National Asthma Education and Prevention Program[5,6] guidelines.
c. Pre-bronchodilator forced expiratory volume in one second (FEV_1) ≥ 80% of predicted.
d. Airway responsiveness to methacholine demonstrated by a pre-levalbuterol dose (baseline) $PC_{20} \leq 8$ mg/mL.
e. Nonsmokers for at least six months prior to the study and a maximum smoking history of five pack-years (the equivalent of one pack per day for five years).
f. Written informed consent.

Exclusion criteria should, at minimum, include:

a. Conditions that could alter the airway reactivity to methacholine (e.g., pneumonia, upper respiratory tract infection, viral bronchitis and/or sinobronchitis) within the past six weeks.
b. If a history of seasonal asthma exacerbations, the subject should be studied outside of the relevant allergen season.
c. History of cystic fibrosis, bronchiectasis, or significant respiratory diseases other than asthma (e.g., COPD, interstitial lung disease).
d. Evidence or history of clinically significant disease or abnormality including: congestive heart failure, uncontrolled hypertension, uncontrolled coronary artery disease, myocardial infarction, cardiac dysrhythmia, or ECG with evidence of ischemic heart disease. In addition, historical or current evidence of significant hematologic, hepatic, neurologic, psychiatric, renal, or other diseases that, 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.
e. Treatment in an emergency room or hospitalization for acute asthmatic symptoms or need for daily oral corticosteroids within past three months.
f. Known intolerance or hypersensitivity to any component of the levalbuterol MDI.

Additional comments:

a. No less than a 24-hour washout period should be allotted between treatments.
b. The study day evaluation should take into consideration the following:
    - Drug administration should begin within two weeks following screening for admission to the study.
    - Baseline FEV_1 should not be less than 70% of predicted normal value and within 88% - 112% of qualifying day FEV_1 value. If either occurs, the study should be rescheduled.

[5] Guidelines for the Diagnosis and Management of Asthma: Expert Panel Report 3. National Asthma Education and Prevention Program; National Institute of Health; National Heart, Lung, and Blood Institute. 2007, Publication No. 07-4051.
[6] 2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. 2020. https://www.nhlbi.nih.gov/resources/2020-focused-updates-asthma-management-guidelines.

- FEV_1 due to the saline control should fall no more than 10% from the baseline FEV_1, or the study should be postponed. This limits the drop in FEV_1 shown by some subjects due to the saline control vehicle in which the challenge agent is dissolved.
- A subject failing three consecutive visits should be dropped from the study.

c. A Bio-IND is required prior to conduct of the pharmacodynamic bioequivalence study as the concentration of methacholine chloride solution may exceed the labeled 25.0 mg/mL concentration, particularly at the higher levalbuterol dose (e.g., EQ 0.090 mg Base) where 25.0 mg/mL methacholine chloride may not lead to a 20% reduction in FEV_1.

d. Prospective applicants are encouraged to consider the conduct of a pilot study to refine the study design (e.g., inclusion and exclusion criteria) and estimate the study power based on intra- and inter-subject variability and slope of the E_{max} dose-response curve. The method for blinding should be described.

e. The pharmacodynamic bioequivalence study may enroll all asthma patients who meet the inclusion and exclusion criteria, or may be enriched by using a sub-population of patients predicted to respond well to the study treatment (appropriate justification should be included for the population chosen for the study).

f. All spirometry should be conducted in accordance with the American Thoracic Society (ATS) standards.

g. The study protocol should include pre-specified definitions of asthma exacerbation, as well as pre-specified and appropriate escape criteria with consideration to patient safety.

h. The study protocol should provide a definition of compliant subjects (e.g., used at least 75% and no more than 125% of study drug doses) and specify how compliance will be verified (e.g., by the use of subject diaries).

i. It is the prospective applicant's responsibility to enroll a sufficient number of subjects for the study to demonstrate bioequivalence of the T product to the R product.

j. The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use. The prospective applicant should clearly explain whether the medication was used prior to baseline visit, during the study or both.

k. All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of each AE should include the date of onset, description of AE, severity, relation to study medication, action taken, outcome, and date of resolution. The information will assist FDA in determining whether the incidence and severity of adverse reactions is different between the T and R products.

l. Subjects who discontinue from the study early should be identified, and the protocol should clearly prospectively state how missing data will be handled in the statistical analysis and provide 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 F estimation. Detailed information for all subjects who are discontinued from the study should be provided.

m. Log transformation of the pharmacodynamic data before fitting the E_{max} model is recommended for dose-scale analysis.

Pharmacodynamic bioequivalence endpoints: Post-dose PC_{20} or PD_{20}, which are the provocative concentration or dose, respectively, of the methacholine challenge agent required to reduce the FEV_1 by 20% following administration of differing doses of levalbuterol (or placebo) by inhalation. The 20% reduction in FEV_1 is determined relative to the saline FEV_1 measured before the placebo or levalbuterol administration.

Equivalence based on: Dose-scale analysis of the pharmacodynamic data. For details regarding the dose-scale analysis, refer to the most recent version of the FDA product-specific guidance for *Orlistat Oral Capsule* (NDA 020766; NDA 021887).[a] The 90% confidence intervals for the relative bioavailability (F) should fall within 67.00% - 150.00% to establish equivalence in the pharmacodynamic study.

Additional information:

Formulation:
FDA recommends that the T formulation be qualitatively (Q1)[7] and quantitatively (Q2)[8] the same as the R formulation.

Device:
The reference listed drug (RLD) is presented as a metered dose inhaler. The device constituent part is the actuator with metering valve.

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 device including:

- Active, metered, multi-dose format
- Number of doses
- Dose indicator/counter

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

[8] 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.

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 June 2015; Revised March 2020, November 2023

Unique Agency Identifier: PSG_021730

[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												