

*Contains Nonbinding Recommendations*  
**Draft Guidance on Levalbuterol Tartrate**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

<b>Active Ingredient:</b>	Levalbuterol tartrate
<b>Dosage Form; Route:</b>	Aerosol, metered; inhalation
<b>Strength:</b>	EQ 0.045 mg Base/Inh
<b>Recommended Studies:</b>	In vitro and in vivo studies

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

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### **In Vitro Studies**

FDA recommends that prospective applicants conduct the following in vitro 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 BE. 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<sup>1</sup> of the product using a flow rate of 28.3 L/min. The 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 product-specific guidance for *Budesonide Inhalation Suspension* 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. The USP <601> Apparatus 1, Apparatus 6, or another appropriate method may be used to determine APSD using a validated assay.

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<sup>1</sup> 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.

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, please provide a table using the format in the Appendix, and send them as part of the abbreviated new drug application (ANDA) submission for BE evaluation.

**Equivalence based on:** PBE analysis of impactor-sized mass (ISM).<sup>2</sup> 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.<sup>3</sup>

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 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 B lifestage of the product. The time 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

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<sup>2</sup> 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.

<sup>3</sup> The distance between the actuator orifice and point of spray pattern measurement should be same for T and R.

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 both 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 BE 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.

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## Pharmacokinetic (PK) BE Study

FDA recommends that prospective applicants conduct the following PK BE study for the T and R products.

6. Type of Study: Fasting

Design: Single-dose, randomized, two-way crossover

Dose: 0.09 mg (two inhalations)

Subjects: Adult males and non-pregnant females, general population.

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 BE approach.

Provide evidence of high variability in the BE parameters, AUC, and/or C<sub>max</sub> (i.e., within-subject variability  $\geq 30\%$ ) when using this approach. For general information on this approach, refer to the product-specific guidance on *Progesterone Oral Capsule*.

**Analyte(s) to measure (in appropriate biological fluid):** Levalbuterol in plasma

**Equivalence based on:** AUC and C<sub>max</sub> for levalbuterol. The 90% confidence intervals for the geometric mean T/R ratios of AUC and C<sub>max</sub> should fall within the limits of 80.00-125.00%.

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## Pharmacodynamic (PD) BE Study

FDA recommends that prospective applicants conduct a method using a bronchoprovocation study for the T and R products for this part of in vivo requirements.

### 7. Type of Study: Bronchoprovocation study

Design: Single-dose, double-blind, double-dummy, randomized, crossover study. FDA recommends that the study consist of, at minimum:

- Zero dose: One actuation each from two different placebo R inhalation aerosols and one actuation each from two different placebo T inhalation aerosols
- 0.045 mg 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
- 0.090 mg of R: One actuation each from two different R inhalation aerosols and one actuation each from two different placebo T inhalation aerosols
- 0.045 mg 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

No less than a 24-hour washout period should be allotted between treatments.

Subjects: Males and non-pregnant females with asthma

Additional comments:

- 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 (NAEPP) guidelines.
  - c.  $FEV_1 \geq 80\%$  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 other respiratory diseases.
  - d. History of cardiovascular, renal, neurologic, liver, or endocrine dysfunction, including ECG with evidence of ischemic heart disease.
  - 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.
- The study day evaluation should take into consideration the following:
  - a. Drug administration should begin within two weeks following screening for admission to the study.
  - b. Baseline FEV<sub>1</sub> should not be less than 70% of predicted normal value and within 88-112% of qualifying day FEV<sub>1</sub> value. If either occurs, the study should be rescheduled.
  - c. FEV<sub>1</sub> due to the saline control should fall no more than 10% from the baseline FEV<sub>1</sub>, or the study should be postponed. This limits the drop in FEV<sub>1</sub> shown by some subjects due to the saline control vehicle in which the challenge agent is dissolved.
  - d. A subject failing three consecutive visits should be dropped from the study.
- A Bio-IND is required prior to conduct of the PD 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., 0.090 mg) where 25.0 mg/mL methacholine chloride may not lead to a 20% reduction in FEV<sub>1</sub>.
- Firms 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<sub>max</sub> dose-response curve. The method for blinding should be described.

**PD endpoint(s):** Post-dose PC<sub>20</sub> or PD<sub>20</sub>, which are the provocative concentration or dose, respectively, of the methacholine challenge agent required to reduce the forced expiratory volume in one second (FEV<sub>1</sub>) by 20% following administration of differing doses of levalbuterol (or placebo) by inhalation. The 20% reduction in FEV<sub>1</sub> is determined relative to the saline FEV<sub>1</sub> measured before the placebo or levalbuterol administration.

**Equivalence based on:** Dose-scale analysis of the PD data. For details regarding the dose-scale analysis, refer to the product-specific guidance for *Orlistat Oral Capsule*. The 90% confidence intervals for the relative bioavailability (F) should fall within 67.00-150.00% to establish equivalence in the PD study.

**Additional comments:**

- The PD BE 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).
- All spirometry should be conducted in accordance with the American Thoracic Society (ATS) standards.
- 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.

- It is the prospective applicant's responsibility to enroll a sufficient number of subjects for the study to demonstrate BE of the T product to the R product.
- 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.
- 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.
- 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 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.
- Log transformation of the PD data before fitting the  $E_{\max}$  model is recommended for dose-scale analysis.

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## Additional Information

### Formulation

The T formulation is recommended to be qualitatively (Q1)<sup>4</sup> and quantitatively (Q2)<sup>5</sup> the same as the R formulation.

### Device

Prospective applicants should refer to FDA's Guidance for Industry, *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January 2017), which, when finalized, will provide the Agency's current thinking on the identification and assessment of any differences in the design of the user interface for a proposed generic drug- device combination product when compared to its RLD.

FDA recommends that prospective applicants consider the following characteristics of the R product when designing the T product:

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<sup>4</sup> Q<sub>1</sub> (qualitative sameness) means that the T product uses the same inactive ingredient(s) as the R product.

<sup>5</sup> Q<sub>2</sub> (quantitative sameness) means that concentration of the inactive ingredient(s) used in the T product are within  $\pm 5\%$  of those used in the R product.

- Size and shape of the R product
- Number of doses in the R product
- External operating principles and external critical design attributes of the R product
- Dose indicator/counter

## 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												