

Draft Guidance on Levodopa

May 2024

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Active Ingredient:	Levodopa
Dosage Form:	Powder
Route:	Inhalation
Strength:	42 mg
Recommended Studies:	Two options: (1) two in vitro bioequivalence studies and two comparative characterization studies, or (2) one comparative characterization study and one in vivo bioequivalence study with pharmacokinetic endpoints

I. Option 1: Two in vitro bioequivalence studies and two comparative characterization studies

To demonstrate bioequivalence by this option, the test (T) product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference standard (RS) product that may significantly affect the local or systemic availability of the active ingredient. For example, the T product can be qualitatively (Q1)¹ and quantitatively (Q2)² the same as the RS product to satisfy no difference in inactive ingredients.

¹ Q1 (qualitative sameness) means that the T formulation uses the same inactive ingredient(s) as the RS formulation.

² 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.

Two in vitro bioequivalence studies:

FDA recommends that prospective applicants conduct the following in vitro bioequivalence studies for the T and RS products. Use at least three batches each of the T and 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 a minimum, three different batches of drug substances, excipients, 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^{3,4} of the product using a flow rate of 28.3 L/min or 30 L/min,⁵ 60 L/min, and 90 L/min U.S. Pharmacopeia (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,⁶ 60 L/min, and 90 L/min. A cascade impactor (CI) apparatus 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 capsules justified by the sensitivity of the validated assay. The volume of air drawn through the delivery system should be 4 L.

³ 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. 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 92 capsule packaging configuration may correspond to actuations 1, 46, and 92. Prospective applicants intending to market additional packaging 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.

⁴ 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.

⁵ The selection of flow rate should match that of the lowest flow rate chosen for APSD testing.

⁶ A flow rate of 28.3 L/min or 30 L/min flow rate can be used depending on the apparatus selected for APSD testing.

Additional comments: Drug deposition on individual sites, including the mouthpiece adapter, the induction port, the pre-separator, and each stage of the 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).⁷ 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.

Two comparative characterization studies:

Comparative physicochemical characterization studies of the T product and the RS product should be performed on a minimum of three exhibit batches of the T product and three batches of the RS product. The comparative characterization studies should include:

1. Particle morphology of the emitted dose
 - a. Imaging comparisons of the deposited particles from the emitted dose at the B lifestage should be determined to assess particle morphology, crystalline content, and agglomeration behavior. Description for the sample collection method should be provided.
2. Evaluation of crystalline and amorphous content of the powder formulation
 - a. Characterization of the crystalline and amorphous content by X-ray powder diffraction or other appropriate method of the powder formulation from the capsules should be determined. Description for the sample collection method should be provided. Quantification of the % relative AUC of the crystalline content vs. amorphous content of the T and RS product should be compared.

II. Option 2: One comparative characterization study and one in vivo bioequivalence study with pharmacokinetic endpoints

To demonstrate bioequivalence by this option, it is recommended to conduct the comparative characterization study #2 as described in Option 1. In addition, it is recommended to conduct the in vivo bioequivalence study with pharmacokinetic endpoints described below:

1. Type of study: Fasting
Design: Single-dose, two-way crossover
Dose: Minimum number of inhalations that is sufficient to characterize the pharmacokinetic profiles by using a sensitive analytical method
Subjects: Healthy males and non-pregnant, non-lactating females

⁷ 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.

Additional comments: (1) The 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) Subjects should adhere to the reference listed drug (RLD) product labeling for administration. (3) A Bio-IND is required prior to conduct of the pharmacokinetic study if the dose exceeds the maximum labeled single dose.

Analyte to measure: Levodopa in plasma

Bioequivalence based on: AUC and C_{\max} for levodopa. The 90% confidence intervals (CIs) for the geometric mean T/R ratios of AUC and C_{\max} should fall within the limits of 80.00% - 125.00%.

Additional information:

Device:

The RLD is presented in drug capsules co-packaged with a 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 devices including:

- Passive (breath-actuated), pre-metered, capsule-based format
- Number of doses
- Device airflow resistance

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 May 2024

Unique Agency Identifier: PSG_209184

^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	MMA D	GSD	FPM
TEST	1234	1												
		2												
		3												
		4												
		5												
		6												
		7												
		8												
		9												
		10												