Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Loxapine

May 2023

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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.

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: Loxapine

Dosage Form; Route: Powder; Inhalation

Strength: 10 mg

Recommended Studies: Two in vitro bioequivalence studies and one in vivo bioequivalence study with pharmacokinetic endpoints

Two in vitro bioequivalence studies:

FDA recommends that prospective applicants conduct the following in vitro bioequivalences studies on samples from each of three or more batches of the test (T) product and three or more batches of the reference standard (RS) product 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 the drug substance and three different batches of device constituent part components (e.g., upper housing, lower housing assembly, and heat package). 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 using a flow rate of 20 L/min, 40 L/min, and 80 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 actuations per device 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 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 using flow rates of 20 L/min, 40 L/min, and 80 L/min. The Anderson Cascade Impactor, Next Generation Impactor, 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, 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 reference 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).[1] 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
   Strength: 10 mg
   Dose: 10 mg of loxapine (single inhalation)
   Subjects: Healthy males and non-pregnant females
   Additional comments: Loxapine inhalation powder is approved with a Risk Evaluation and Mitigation Strategy (REMS) with an Elements to Assure Safe Use (ETASU), which restricts its use. All pertinent elements of the REMS must be incorporated into the protocol and informed consent. Exclude subjects with current and history of bronchospasm, asthma, COPD, or any other acute or chronic pulmonary disease, and/or a history of hypotension or orthostatic hypotension.

Analyte to measure: Loxapine in plasma

Equivalence based on: $AUC_{0\text{-}30\ min}$ and $AUC_{0\text{-}\infty}$. The 90% confidence intervals for the geometric mean T/R ratios of $AUC_{0\text{-}30\ min}$ and $AUC_{0\text{-}\infty}$ should fall within the limits of 80.00% - 125.00%.

[1] 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 regarding the bioequivalence study with pharmacokinetic endpoints:
The following pharmacokinetic parameters will be evaluated: Log-transformed $AUC_{0\text{-}30\ min}$ and $AUC_{0\text{-}\infty}$. Applicants should submit C_{max}, T_{max} and partial AUC of early time points as supportive data to assess the onset of loxapine effect. Applicants should collect sufficient quantifiable pharmacokinetic samples to allow a comparison of exposure to loxapine between the T product and the RS product within the first 10 minutes, 30 minutes, and 30 minutes to 2 hours after administration.

Additional information:

Device:
The reference listed drug (RLD) is a single dose, disposable inhaler that produces a thermally generated aerosol. The disposable inhaler is a device constituent part.

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

- Passive (breath-actuated), single dose format of the RLD device
- Device activation system
- Indicator that the device is activated
- 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]

Unique Agency Identifier: PSG_022549

[a] For the most recent version of the 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												