Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Treprostinil

November 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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:	Treprostinil
Dosage Form:	Powder
Route:	Inhalation
Strengths:	0.016 mg/inh, 0.032 mg/inh, 0.048 mg/inh, 0.064 mg/inh
Recommended Studies:	Three in vitro bioequivalence studies, two in vivo bioequivalence studies with pharmacokinetic endpoints, and one comparative characterization study

To demonstrate bioequivalence using the recommendations in this guidance, 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.

Three 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

[1] Q1 (qualitative sameness) means that the T product uses the same inactive ingredient(s) as the RS product.
[2] Q2 (quantitative sameness) means that concentrations of the inactive ingredient(s) used in the T product are within ± 5% of those used in the RS product.

no fewer than 10 units from each batch.[3] 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 for the 0.016 mg and the 0.064 mg strength cartridges at the beginning (B), middle (M), and end (E) lifestages[4,5] of the product, using a flow rate of 15 L/min, 30 L/min, and 45 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 used 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 for the 0.016 mg and 0.064 mg cartridge strengths at B and E lifestages of the product using a flow rate of 15 L/min, 30 L/min, and 45 L/min. A cascade impactor 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 cartridges justified by the sensitivity of the validated assay. The volume of air drawn through the delivery system should be 4L.
   Additional comments: Drug deposition on individual sites, including the mouthpiece adapter, the induction port, the pre-separator, each stage of the cascade impactor, 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 cascade impactor 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.

[3] If bioequivalence of the 0.016 and 0.064 mg/inh strengths are acceptable, then SAC, APSD, and realistic APSD bioequivalence tests may not be needed for the 0.032 and 0.048 mg/inh strengths provided the T and RS devices have similar performance and functionality, including, but not limited to, cartridge size, cartridge outlet, and device resistance.

[4] 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 based on the use-life of the inhaler. For example, the B, M, and E lifestage for a 28-treatment inhaler (7 days of use) may correspond to actuations 1, 14, and 28.

[5] 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.

Bioequivalence based on: PBE analysis of impactor-sized mass (ISM).[6] The cascade impactor profiles representing drug deposition on the individual stages of the cascade impactor 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: Realistic APSD
Design: The realistic APSD test should be performed for the 0.016 mg and 0.064 mg cartridge strengths at the B lifestage of the product using mouth-throat models of different sizes (e.g., small and large) and breathing profiles (e.g., weak and strong) that are representative of the entire patient population. A cascade impactor 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 cartridges justified by the sensitivity of the validated assay.
Additional comments: Drug deposition on individual sites, including the mouthpiece adapter, the mouth-throat model, the mixing inlet, each stage of the cascade impactor, 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 cascade impactor data for the T and RS products, provide a table using the format in the appendix, and send them as part of the ANDA submission.

Bioequivalence based on: PBE analysis or other appropriate statistical analysis of ISM of the drug for each mouth-throat model-breathing profile combination. The cascade impactor profiles representing drug deposition on the individual stages of the cascade impactor along with the MMAD, GSD and FPM should be submitted as supportive evidence for equivalent APSD. If another statistical analysis is used, it should be adequately and scientifically justified considering the purpose of the study. Prospective applicants are encouraged to discuss other statistical analysis designs with FDA via a pre-ANDA meeting request. For additional information, refer to the most recent version of the FDA guidance for industry on *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*.[b]

Two in vivo bioequivalence study with pharmacokinetic endpoints:

FDA recommends that prospective applicants conduct the following pharmacokinetic bioequivalence study #1 for the lowest (0.016 mg/inh) and highest (0.064 mg/inh) strengths of the T and RS products and pharmacokinetic bioequivalence study #2 for the highest (0.064 mg/inh) strength of the T and RS products.

1. Type of study: Fasting
Design: Single-dose, two-way crossover
Dose: Minimum number of inhalations that is sufficient to characterize a pharmacokinetic profile by using a sensitive analytical method

[6] ISM is defined as a sum of the drug mass on all stages of the cascade impactor plus the terminal filter but excluding the top cascade impactor stage because of its lack of a specified upper cutoff size limit.

Subjects: Healthy males and non-pregnant, non-lactating females

Additional comments: (1) Subjects should adhere to the reference listed drug (RLD) product labeling for administration. (2) The analytical method should have sufficient sensitivity to adequately quantify the concentration of treprostinil in plasma. (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: Treprostinil in plasma

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

2. Type of study: Fasting
Design: Single-dose, two-way crossover with charcoal block
Dose: Minimum number of inhalations that is sufficient to characterize a pharmacokinetic profile by using a sensitive analytical method
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: (1) Subjects should adhere to the RLD product labeling for administration. (2) The analytical method should have sufficient sensitivity to adequately quantify the concentration of treprostinil in plasma. (3) A Bio-IND is required prior to conduct of the pharmacokinetic study if the dose exceeds the maximum labeled single dose. (4) Justification for the charcoal dose should be provided in the ANDA submission.

Analyte to measure: Treprostinil in plasma

Bioequivalence based on: AUC and C_{max} for treprostinil. The 90% CI for the geometric mean T/R ratios of AUC and C_{max} should fall within the limits of 80.00% - 125.00%.

One comparative characterization study:

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 and agglomeration behavior. Description for the sample collection method should be provided. Where applicable, chemical classification of the individual components in agglomerate particles and individual drug and/or excipients can be provided using an optimized and validated analytical method (e.g., morphologically-directed Raman spectroscopy) to further describe and/or support morphology characterization.

Additional information:

An optional computational modeling study may be used to support bioequivalence of the T and RS products. Refer to the most recent version of the FDA product-specific guidance on *Formoterol Fumarate; Glycopyrrolate Inhalation Metered Aerosol* (NDA 208294)[a] for additional information regarding the development and conduct of an optional computational modeling study.

In order to clarify the FDA's expectations for prospective applicants early in product development, and to assist applicants to submit an ANDA as complete as possible, FDA strongly encourages applicants to discuss their development program for any optional computational modeling study with the FDA via the pre-ANDA meeting pathway. For additional information on pre-ANDA meetings, refer to the most recent version of the FDA guidance for industry on *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*.[b]

Device:
The RLD is presented in drug cartridge 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 device including:

- Passive (breath-actuated), pre-metered, cartridge-based format
- Number of doses (number of cartridges)
- 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 November 2024

Unique Agency Identifier: PSG_214324

[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 RS	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 RS).
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												