Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Mannitol

February 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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:	Mannitol
Dosage Form:	Powder
Route:	Inhalation
Strengths:	N/A, 5 mg, 10 mg, 20 mg, 40 mg
Recommended Studies:	Three in vitro bioequivalence studies, one in vivo bioequivalence study 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 the formulation relative to the reference standard (RS) product that may significantly affect the local or systemic availability of the active ingredient.

Three in vitro bioequivalence studies:

FDA recommends that prospective applicants conduct the following in vitro bioequivalence study on samples from each of three or more batches of the T product and three or more batches of the RS product, with no fewer than 10 units from each batch.[1] 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, a minimum, three different batches of drug substance(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] If bioequivalence of the 5 and 40 mg strength is acceptable, then SAC, APSD, and realistic APSD bioequivalence tests may not be needed for the 10 and 20 mg strength provided the T and RS devices have similar performance and functionality, including, but not limited to, capsule size, piercing mechanism and device resistance.

1. Type of study: Single actuation content (SAC)
Design: The SAC test should be performed for the 5 mg strength capsule and the last 40 mg strength capsule for each unit of the drug product, using the same device.[2] The SAC test for each strength should be performed using a flow rate of 30 L/min, 60 L/min, and 90 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 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 5 mg strength capsule and the last 40 mg strength capsule for each unit of the drug product, using the same device. The APSD test for each strength should be performed using a flow rate of 30 L/min,[3] 60 L/min, and 90 L/min. Cascade impaction devices 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.

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 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).[4] 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: Realistic APSD
Design: The realistic APSD (rAPSD) test should be performed for the 5 mg strength capsule and the last 40 mg strength capsule for each unit of the drug product, using the

[2] When conducting in vitro bioequivalence studies, capsules before (i.e., the 0 mg strength capsule) and between those tested should be actuated using the device. For example, prospective applicants testing at the last 40 mg strength capsule should actuate all capsules leading up to the last 40 mg strength capsule tested.
[3] Depending on the apparatus selected, a prospective applicant can use a flow rate of 28.3 L/min in lieu of the 30 L/min flow rate. The same flow rates used for SAC testing should be used for APSD testing.
[4] 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.

same device. The rAPSD study should be performed using mouth-throat models of different sizes (e.g., small and large) and breathing profiles (e.g., weak and strong) representative of the entire patient population. CI devices 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.

Additional comments: Drug deposition on individual sites, including the mouthpiece adapter, the mouth-throat model, the mixing inlet, 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 ANDA submission.

Bioequivalence based on: PBE analysis or other appropriate statistical analysis of ISM of the drugs for each mouth-throat model-breathing profile combination. The CI profiles representing drug deposition on the individual stages of the CI 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]

One in vivo bioequivalence study with pharmacokinetic endpoints:

1. Type of study: Fasting
   Design: Single-dose, two-way crossover with charcoal block
   Strength: 40 mg
   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 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 mannitol in serum. (3) Justification for the charcoal dose should be provided in the ANDA submission. (4) A Bio-IND is required prior to conduct of the pharmacokinetic study if the dose exceeds the maximum labeled dose.

   Analyte to measure: Mannitol in serum

   As mannitol is widely present in food that can be consumed by subjects, the serum concentrations of mannitol should be corrected for baseline endogenous levels by subtracting the mean pre-dose baseline value (average of at least three pre-dose values,

e.g., -1.0, -0.5, and 0 hours). Any negative values obtained from baseline correction at time 0 hour, should be designated as zero (0) and any subject with pre-dose concentration more than 5% of their C_{max} should be excluded from bioequivalence statistical analysis and the 90% confidence intervals based on the remaining subjects. Refer to the most recent version of the FDA guidance on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*[b] for additional information regarding endogenous compounds.

Bioequivalence based on: Baseline-corrected AUC and C_{max} for mannitol. 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 comparative characterization study:

A comparative physicochemical characterization study 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 study should include:

1. Particle morphology of the emitted dose
    a. Imaging comparisons of the deposited particles from the emitted dose of the 5 mg strength capsule should be determined to assess particle morphology and agglomeration. Description for the sample collection method should be provided.

Additional information:

An optional computational modeling study may be used to support establish 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 for any 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 conducting the recommended studies with the FDA via the pre-ANDA meeting pathway. 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]

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, single-unit dose, 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]

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Unique Agency Identifier: PSG_022368

[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												