Contains Nonbinding Recommendations

Draft Guidance on Beclomethasone Dipropionate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Active Ingredient: Beclomethasone dipropionate

Dosage Form; Route: Aerosol, metered; nasal

Strengths: 0.04 mg/Actuation
0.08 mg/Actuation

Recommended Studies: In vitro studies

FDA recommends the following in vitro studies to establish bioequivalence (BE) of the test (T) and reference (R) metered nasal aerosol products containing beclomethasone dipropionate.

In Vitro Studies

FDA recommends that applicants conduct the following in vitro studies for all strengths of the T and R products. For each strength, use at least three batches each of the T and R products, with no fewer than 10 units from each batch. FDA recommends that three primary stability batches be used to demonstrate in vitro BE, if appropriate. The three batches of T product should be manufactured from, at minimum, three different batches of container/closure system.

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[1] of the product, using a flow rate of 28.3 L/min. U.S. Pharmacopoeia (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. Please refer to the product-specific recommendation for Budesonide Inhalation Suspension for additional information regarding PBE.[2]

[1] 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.

[2] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM319977.pdf

2. Type of Study: Droplet size distribution by Laser Diffraction
Design: Droplet size distribution should be determined using laser diffraction or an appropriately validated alternate methodology. Droplet size distribution should be measured for fully developed phase only at B and E lifestages. It is recommended that the studies be performed within a range of 2 to 7 cm from the actuator orifice, with the two distances separated by 3 cm or more.
Additional Comments: Single spray droplet size distribution and span should be reported based on volume (mass). Mean D_{10}, D_{50}, D_{90} values for a given unit should be computed from the mean of up to three consecutive sprays from that unit at each lifestage. Span can be computed $((D_{90} - D_{10})/D_{50})$. To assess precision, the data of each spray should also be reported.

   Equivalence based on: PBE analysis of D_{50} and span at two selected distances.

3. Type of study: Particle/Droplet Size Distribution by Cascade Impactor
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. The APSD determination of each unit should be performed with a minimum number of actuations 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, 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).[3] 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.

4. 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.[4] 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

[3] 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.
[4] The distance between the actuator orifice and point of spray pattern measurement should be the same for T and R.

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}.

5. Type of study: Plume geometry
   Design: The plume geometry test should be performed at the B lifestage of the product. The timed-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 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 plume angle and width, which should fall within 90 - 111%.

6. 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 products 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.

Additional Information

Formulation:

FDA recommends that the T formulation be qualitatively (Q1)[5] and quantitatively (Q2)[6] the same as the R product.

Device:

Applicants should refer to the FDA Guidance for Industry entitled, Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA (January 2017), which provides 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 applicants consider the following characteristics of the R product in designing the T product:

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

In addition, studies should be conducted to support the functionality, accuracy, and robustness of the proposed T product

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

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												