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Draft Guidance on Ipratropium Bromide

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

This guidance, which interprets the Agency's regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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This is a new draft product-specific guidance for industry on generic ipratropium bromide.

Active Ingredient:	Ipratropium bromide
Dosage Form; Route:	Spray, metered; nasal
Strength:	0.021 mg/spray 0.042 mg/spray
Recommended Studies:	In vitro studies

FDA recommends the following in vitro studies to establish bioequivalence (BE) of the test (T) and reference (R) nasal sprays containing ipratropium bromide.

In Vitro BE Studies

FDA recommends that prospective applicants conduct the following in vitro BE studies on samples from each of three or more batches of the T product and three or more batches of the R

product, with no fewer than 10 units from each batch.[1,2] FDA recommends that three primary stability batches be also used to demonstrate in vitro BE. The three batches of the T product should be manufactured from, at minimum, three different batches of the drug substance, three different batches of critical excipients, and three different batches of the device components (e.g., pump and actuator) proposed for the final device configuration of the commercial product. The T product should consist of the final device constituent part and the final drug constituent formulation intended to be marketed.

1. Single actuation content
2. Droplet size distribution by laser diffraction
3. Drug in small particles/droplets
4. Spray pattern
5. Plume geometry
6. Priming and repriming

Additional Comments: Refer to the product-specific guidance for *Fluticasone Propionate Nasal Spray Metered* for recommendations on design and equivalence criteria for the aforementioned in vitro BE studies, and general recommendations on the conduct of the in vitro BE studies and data submission.

Additional Information

Formulation:

FDA recommends that the T product be qualitatively (Q1)[3] and quantitatively (Q2)[4] the same as the R product.

Device:

Prospective applicants should refer to the FDA guidance for industry, *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*, which, when finalized, will provide 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.

[1] If bioequivalence of the 0.042 mg/spray strength product is acceptable, then abbreviated in vitro BE studies may be conducted for the 0.021 mg/spray strength product provided the 0.021 mg/spray strength product is manufactured without changing the actuator and metering valve or pump (other than dip tube, due to different volumes of product or other factors) used in the 0.042 mg/spray strength product. FDA recommends that the same protocols and the acceptance criteria used to establish BE of the 0.042 mg/spray strength product be used for the 0.021 mg/spray strength product.
[2] If conducting abbreviated in vitro BE studies for the 0.021 mg/spray strength product, the droplet size distribution by laser diffraction test may be conducted at the beginning of lifestage only, and the drug in small particles/droplets test and plume geometry test may not be conducted.
[3] Q1 (qualitative sameness) means that the T product uses the same inactive ingredient(s) as the R product.
[4] Q2 (quantitative sameness) means that concentrations of the inactive ingredient(s) used in the T product are within ±5% of those used in the R product.

FDA recommends that prospective 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

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