

Contains Nonbinding Recommendations
Draft Guidance on Ketorolac Tromethamine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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:** Ketorolac tromethamine
- Dosage Form; Route:** Spray, metered; nasal
- Strength:** 15.75 mg/spray
- Recommended Studies:** Two options: in vitro or in vivo studies

FDA recommends the following in vitro or in vivo studies to establish bioequivalence (BE) of the test (T) and reference (R) nasal sprays containing ketorolac tromethamine.

In Vitro BE Option

If the T formulation is qualitatively (Q1)¹ and quantitatively (Q2)² the same as the R formulation, and the nasal spray device (e.g., pump and actuator design) of the T product is appropriate for approval in an abbreviated new drug application (ANDA) (as demonstrated by comparative analyses further described below), BE of the T ketorolac tromethamine metered nasal spray product to the R ketorolac tromethamine metered nasal spray product can be established solely through in vitro performance tests in lieu of a pharmacokinetic (PK) BE study. 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. 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 final drug constituent formulation intended to be marketed. The following in vitro BE tests are recommended:

1. Single actuation content
2. Droplet size distribution by laser diffraction
3. Drug in small particles/droplets
4. Spray pattern

¹ Q1 (qualitative sameness) means that the T product uses the same inactive ingredient(s) as the R product.

² Q2 (quantitative sameness) means that concentrations of the inactive ingredient(s) used in the T product are within $\pm 5\%$ of those used in the R product.

5. Plume geometry
6. Priming

Additional Comments: Refer to the product-specific guidance on *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.

In Vivo BE Option

If the T product is not Q1 and Q2 the same as the R formulation and the nasal spray device (e.g., pump and actuator design) of the T product is appropriate for approval in an ANDA (as demonstrated by comparative analyses further described below), the following PK study is recommended to establish BE between the T and R product:

Type of Study: Fasting

Design: Single-dose, two-way crossover in vivo

Strength: 15.75 mg/spray (dose: 31.5 mg, administer as one spray in each nostril)

Subjects: Adult males and non-pregnant, non-lactating females, general population

Additional Comments: Subjects should adhere to the R drug product labeling for administration.

Analyte to measure: Ketorolac in plasma

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

Additional Information

Device:

Prospective applicants should refer to FDA's guidance for industry entitled, *Comparative Analyses and Related Comparative Use Human Factors Studies* (January 2017), 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.

FDA recommends that prospective applicants consider the following characteristics of the R product when 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