

Draft Guidance on Calcitonin Salmon

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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:** Calcitonin salmon
- Dosage Form; Route:** Spray, metered; nasal
- 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 calcitonin salmon.

In Vitro Option

If the T formulation is qualitatively (Q1)¹ and quantitatively (Q2)² the same as the R formulation,³ 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 calcitonin salmon in a metered nasal spray product can be established solely through in vitro performance tests in lieu of a pharmacokinetic (PK) BE study. FDA recommends that 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 T product should be manufactured from, at minimum, three different batches of drug substance(s), excipient(s), and device components. 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. Drugs in Small Particles/Droplets
4. Spray Pattern
5. Plume Geometry
6. Priming

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.

³ Refer to the following reference for recommendations regarding pharmaceutical equivalence for calcitonin salmon nasal spray: SL Lee, LX Yu, B Cai, et al. Scientific Considerations for Generic Synthetic Salmon Calcitonin Nasal Spray Products. *The AAPS Journal* 13(1): 14-19, 2011.

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.

In Vivo Option

If the T formulation 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: In vivo, regardless of food intake conditions

Design: Single-dose, partial or fully replicated crossover

Strength: 200 IU/spray

Subjects: Women of greater than 5 years post menopause with postmenopausal osteoporosis when alternative treatments are not suitable

Additional Comments: (1) Demonstrate that there is no cross-reactivity of the assay against human calcitonin; (2) Applicants may consider using a reference-scaled average BE approach. Provide evidence of high variability in the BE parameters, AUC and/or C_{max} (i.e., within-subject variability $\geq 30\%$) when using this approach. For general information on this approach, refer to the product-specific guidance for *Progesterone Oral Capsule*.

Analyte(s) to measure (in appropriate biological fluid): Calcitonin salmon in plasma

Equivalence based on: AUC and C_{max} for calcitonin salmon. The 90% confidence intervals for the geometric mean T/R ratios of AUC and C_{max} should fall within the limits of 80-125.00%.

Additional Information

Device:

Sponsors should refer to the FDA 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 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