

Draft Guidance on Calcitonin-Salmon

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

- Active ingredient:** Calcitonin-Salmon
- Form/Route:** Spray, Metered / Nasal
- Recommended studies:** 2 Options: In Vitro or In Vivo Studies

In Vitro Option

If the test product formulation is qualitatively (Q1) (i.e., contain all of the same inactive ingredients) and quantitatively (Q2) the same as the reference listed drug (RLD), and the nasal spray device (e.g., the pump and actuator design) of the test product is comparable to that of the RLD, bioequivalence (BE) can be established solely by comparative in vitro performance tests.

Please refer to “*Scientific Considerations for Generic Synthetic Salmon Calcitonin Nasal Spray Products*”¹ by SL Lee for recommendations regarding pharmaceutical equivalence.

The following in vitro studies should be conducted using at least 3 batches of each of T and R products with no fewer than 10 units of each batch.

1. Single Actuation Content (SAC) through Container Life
2. Droplet Size Distribution by Laser Diffraction
3. Droplet Size Distribution by Cascade Impactor
4. Spray Pattern
5. Plume Geometry
6. Priming

Please refer to the Draft guidance for industry: *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (Issued on April 3, 2003) for more details regarding the in vitro studies.

¹ 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.

In Vivo Option

If the test product formulation is not Q1 and Q2 the same as the RLD with respect to inactive ingredients, BE should be established by conducting an in vivo study.

7. Type of study: in vivo, regardless of food intake conditions
Design: Single-dose, partial or fully replicated crossover in-vivo
Strength: 200 IU/spray
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments: (1) Please demonstrate that there is no cross-reactivity of the assay against human calcitonin; (2) Applicants may consider using a reference-scaled average bioequivalence approach for this highly variable drug substance/product. Provide evidence of high variability in the bioequivalence parameters, AUC and/or Cmax (i.e., within-subject variability $\geq 30\%$) when using this approach. For general information on this approach, please refer to the Draft Guidance on Progesterone Capsules. However, prior to using the alternative approach, the firm is encouraged to submit the study protocols for review by the Division of Bioequivalence.
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Analytes to measure (in appropriate biological fluid): Calcitonin in plasma

Bioequivalence based on (90% CI): Calcitonin

Waiver request of in-vivo testing: Not Applicable

Dissolution test method and sampling times: Not Applicable