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Draft Guidance on Calcitonin Salmon

December 2025

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In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient:	Calcitonin salmon
Dosage Form:	Injectable
Route:	Injection
Strengths:	100 IU/mL, 200 IU/mL
Recommended Studies:	Comparative characterization studies to support active ingredient sameness and request for waiver of in vivo bioequivalence study requirements

Recommendations to Support Active Ingredient Sameness and Impurity Assessment:

In addition to ensuring active ingredient sameness (i.e., same primary sequence and physicochemical properties) for the drug substance, it is recommended to conduct the following comparative analyses of the proposed generic calcitonin salmon and the designated reference standard (RS) on no less than three batches of the proposed drug product tested on or near release and at the end of the proposed shelf life and no less than three batches of the RS aged tested prior to expiry, after aging under conditions consistent with the label storage conditions:[1]

1. Secondary structure.
2. Oligomer/aggregation states: oligomer/aggregation propensity and the nature of the aggregates formed for the proposed product should be similar to that of the RS.

[1] Samples should be aged under conditions consistent with the worst-case label storage conditions.

3. Biological activities.[2]
4. Active ingredient-related impurity profile comparison: new impurities found in the proposed generic drug product but not in the RS and impurities found at a significantly higher level in the proposed generic drug product than in the RS, should be identified and characterized. If upon Agency assessment, an impurity is identified that has the potential to increase the immunogenicity risk, further immunogenicity assessments or studies may be recommended.
5. Comparative study demonstrating comparable innate immune response risk of the test product and RS.[3]

Non-clinical methods can be used to demonstrate comparable safety and efficacy profiles between a proposed generic peptide (recombinant or synthetically produced) and the RS. Unlike synthetic peptides, recombinant peptides may also contain impurities, such as host cell proteins and residual DNA, from the host cell. Therefore, FDA recommends that applicants demonstrate and justify these host cell related impurities are well controlled if the proposed generic peptide product is manufactured using a recombinant process.[4]

Waiver of in vivo bioequivalence study requirements:

To qualify for a waiver from submitting an in vivo bioequivalence study on the basis that bioequivalence is self-evident under 21 CFR 320.22(b)(1), a generic calcitonin salmon injection product should be qualitatively (Q1)[5] and quantitatively (Q2)[6] the same as the RLD.

An applicant may seek approval of a drug product that differs from the RLD in preservative, buffer, or antioxidant if the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.[7]

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[2] An applicant may provide justification for not characterizing biological activities as part of the comparative analyses if it can be demonstrated the formulated peptide active ingredient lacks functional secondary or higher order structure.

[3] Demonstrating comparable innate immune activities can be accomplished through analyzing aggregates and non-peptide process-related impurities, which may alter the product's immunogenicity profile. Differences found in comparability studies assessing aggregates should be mitigated using manufacturing strategies. Levels of non-peptide process-related impurities including particulate matter, microbial contaminants, residual organic solvents, elemental impurities and leachables, should meet compendial acceptance criteria and toxicological limits. If non-peptide process-related impurities meet these criteria and limits, and aggregation profiles are comparable to that of the RS, applicants should not conduct in vitro innate immune testing.

[4] For any inquiries regarding the use of non-clinical assays to assess risk in recombinant generic peptides, please submit pre-ANDA product development meeting requests. For additional information, refer to the most recent version of the guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*.

[5] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD.

[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 RLD.

[7] 21 CFR 314.94(a)(9)(iii).

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