Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Calcitonin Salmon

November 2022

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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; Route: Injectable; injection

Recommended Study: Request for waiver of in vivo bioequivalence study requirements

In vivo bioequivalence study may be waived on the basis that bioequivalence is self-evident under 21 CFR 320.22(b), for a generic calcitonin salmon injection product that is qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the Reference Listed Drug (RLD).
An applicant may seek approval of a test product that differs from the RLD in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the test product.[3]

In addition to ensuring Active Pharmaceutical Ingredient (API) sameness (i.e., same primary sequence and physiochemical properties)for the drug substance, it is recommended to conduct the following comparative analyses of the proposed generic calcitonin salmon and the RLD product 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 RLD aged tested prior to expiry, after aging under conditions consistent with the label storage conditions.[4]

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[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference listed drug.
[2] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ± 5% of those used in the reference listed drug.
[3] 21 CFR 314.94(a)(9)(iii)
[4] Samples should be aged under conditions consistent with the worst-case label storage conditions.

1. API-related impurity profile comparison: new impurities found in the proposed generic drug product but not in the RLD, and impurities found at a significantly higher level in the proposed generic than the RLD, that are found at levels greater than or equal to 0.10% and less than or equal to 0.5%[5], should be identified and characterized and their levels justified using non-clinical immunogenicity assays.
    a. Innate immune activities: the proposed generic synthetic peptide drug product does not alter the innate immune activity in comparison to the RLD
    b. Secondary structure
    c. Oligomer/aggregation states: oligomer/aggregation propensity and the nature of the aggregates formed for the proposed product should be similar to that of the RLD
    d. Biological activities

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[5] For new peptide-related impurities found at levels greater than 0.5% that cannot be qualified using comparative RLD data, please discuss with the Agency regarding the suitability of using non-clinical immunogenicity assays for assessing the immunogenicity risk of these impurities.