Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Palopegteriparatide

May 2026

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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:	Palopegteriparatide
Dosage Form:	Solution
Route:	Subcutaneous
Strengths:	EQ 0.168 mg teriparatide/0.56 mL (EQ 0.168 mg teriparatide/0.56 mL) | EQ 0.294 mg teriparatide/0.98 mL (EQ 0.294 mg teriparatide/0.98 mL) | EQ 0.42 mg teriparatide/1.4 mL (EQ 0.42 mg teriparatide/1.4 mL)
Reference Listed Drug:	NDA 216490
Recommended Studies:	Request for waiver of in vivo bioequivalence study requirements and comparative characterization studies to support active ingredient sameness

Waiver request of in vivo bioequivalence study: 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 palopegteriparatide subcutaneous solution product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD).

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

An applicant may seek approval of a drug product intended for parenteral use 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]

Recommendations to support active ingredient sameness and impurity assessment:
Provide data and information on same primary sequence and physicochemical properties to ensure active ingredient sameness. In addition, conduct the following comparative analyses of the test product and the designated reference standard (RS). Testing should be performed on no less than three batches of the test product. These test product batches should be tested on or near release and at the end of the proposed shelf life. Testing should also be performed on no less than three batches of the RS product aged prior to expiry. The RS batches should be aged under conditions consistent with the label storage conditions.[4]

1. Secondary structure.
2. Oligomer/aggregation states: Oligomer/aggregation propensity and the nature of the aggregates formed for the test product should be similar to that of the RS.
3. Biological activities[5].
4. Active ingredient-related impurity profile comparison: New impurities found in the test product but not in the RS and impurities found at a significantly higher level in the test 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 risk of the product, further assessments or studies may be recommended.
5. Comparative study demonstrating comparable innate immune response risk of the test product and RS.[6]

Non-clinical methods can be used to demonstrate comparable safety and efficacy profiles between a test product (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 test product is manufactured using a recombinant process.

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[3] 21 CFR 314.94(a)(9)(iii).

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

[5] 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.

[6] 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.

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

Device: The RLD is presented in a prefilled pen injector co-packaged with needles. The pen injector and needles are the device constituent parts. FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD devices when designing the test devices including:

- Single-patient-use, disposable pen injector with variable-dose format
- Dose selector and dose button
- Needle gauge and length

User interface assessment: An abbreviated new drug application (ANDA) for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the test product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a]

Document History: Recommended May 2026

[a] We update guidances periodically. For the most recent version of a guidance, refer to the FDA guidance webpage at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.