Contains Nonbinding Recommendations

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Draft Guidance on Semaglutide

July 2026

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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:	Semaglutide
Dosage Form:	Solution
Route:	Subcutaneous
Strengths:	2 mg/1.5 mL (1.34 mg/mL) | 2 mg/3 mL (0.68 mg/mL) | 4 mg/3 mL (1.34 mg/mL) | 8 mg/3 mL (2.68 mg/mL)
Reference Listed Drug:	NDA 209637
Recommended Studies:	Comparative characterization studies to support active ingredient sameness, impurity assessment, and waiver request for in vivo bioequivalence study requirements

Recommendations to support active ingredient sameness and impurity assessment:
In addition to evaluating active ingredient sameness for the drug substance itself (same primary sequence and physicochemical properties), it is recommended to conduct the following comparative analyses of the proposed generic peptide product and the reference listed drug (RLD) 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 prior to expiry, after aging under conditions consistent with the label storage conditions, to support either active ingredient sameness and/or impurity assessment:[1]

1. Higher order structure (HOS) (e.g. secondary and tertiary structure, and aggregates), where applicable.

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

2. Comparable biological activity, where appropriate
   Biological and functional assays (e.g., enzymatic, ligand binding, or cell based) are not always needed. An abbreviated new drug application (ANDA) applicant may provide justification for not characterizing biological activities as part of the comparative analyses if it can be demonstrated that the formulated peptide active ingredient lacks functional secondary or higher order structure.

3. Active ingredient-related impurity comparison
   Active ingredient-related impurities may result from the manufacturing of a peptide by recombinant, synthetic or semi-synthetic processes. The following thresholds and controls of active-ingredient-related impurities may be applied.
   a. Report all active ingredient-related impurities present in the proposed generic peptide drug product at a level above 0.1% of the drug substance.
   b. Identify all active ingredient-related impurities present in the proposed generic peptide drug product at a level above 0.5% of the drug substance.
   c. For each active ingredient-related impurity found in both the proposed generic peptide drug product and in the RLD, the level of the active ingredient-related impurity in the proposed generic peptide drug product should not be greater than that found in the RLD or 1.0% of the drug substance, whichever is greater. Efforts should be made to reduce the levels of these impurities by implementing appropriate manufacturing and control strategies.
   d. For new active ingredient-related impurities found in the generic peptide drug product, efforts should be made to reduce the levels of these impurities to below 1.0% of the drug substance by implementing appropriate manufacturing and control strategies.
   e. The total amount of active ingredient-related impurities in the proposed generic peptide product, including new active ingredient-related impurities, should not be greater than the amount in the RLD. All active ingredient-related impurities at a level greater than the reporting threshold of 0.1% should be summed and reported as total active ingredient-related impurities.

   The presence of a new or elevated common impurity outside of the specified levels above does not preclude an application from being submitted as an ANDA. However, the potential risks associated with a particular impurity at higher levels are subject to scientific review upon submission of the ANDA, and the Agency may ask the ANDA applicant to reduce the level of a specified active-ingredient-related impurity. In addition, the ANDA applicant should provide justification for why the presence of such impurity at higher than the levels specified above would not be expected to affect the safety of the proposed generic peptide drug product or its efficacy as compared to that of the RLD. Prospective ANDA applicants should contact the Office of Generic Drugs (OGD) if they have specific questions regarding what information should be provided as part of the justification.

An evaluation of innate immune activities can be accomplished through analyzing aggregates and non-active ingredient-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-active ingredient-related impurities including particulate matter, microbial contaminants, residual organic solvents, elemental impurities and leachables, should meet compendial acceptance criteria and toxicological limits. If non-active ingredient-related impurities meet these criteria and limits, and aggregation profiles are comparable to that of the RLD, in vitro innate immune testing may not be scientifically necessary.

Non-clinical methods can be used to support a conclusion that the proposed generic peptide (recombinantly, synthetically, or semi-synthetically produced) and the RLD can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. 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. This can be done using appropriate manufacturing and process controls combined with targeted comparative analytical studies, and meeting compendial standards (where appropriate).

Meeting recommendations: 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 guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*.[a]

Waiver of in vivo bioequivalence studies: To request 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 semaglutide subcutaneous solution product should be qualitatively (Q1)[2] and quantitatively (Q2)[3] the same as the RLD.

Considerations for non-Q1/Q2 formulations: 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 proposed drug product.[4]

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 device when designing the test device including:

- Multi-use disposable pen injector with fixed- or variable-dose format
- Dose selector and dose button
- Needle gauge and length

[2] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD.
[3] 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.
[4] 21 CFR 314.94(a)(9)(iii).

User interface assessment: An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic 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 March 2020; Revised November 2023, July 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.