Generic Peptide Guidance Update: Impurity Assessment and Control

Eric Pang, Office of Research and Standards, OGD
Cameron Smith, Office of Product Quality Assessment I, OPQ
CDER | U.S. FDA

AAM GRx+Biosims Conference
November 2-4, 2026

Agenda

- Recent updates to peptide PSGs/guidance
  - Active ingredient source
  - Active ingredient-related impurity thresholds
  - Innate Immunogenicity Risk Assessment
    - Non-active ingredient-related impurities
    - Aggregates
- Guidance revisions
- Background to these updates
- New submission expectations
- Revised impurity routine control strategies
- Common questions

Previous and Revised Recommendations for Peptides

Attribute	Previous	Revised[1]
Active Ingredient Source Scope	Synthetic active ingredients for ANDAs referencing a limited set of recombinantly manufactured peptide RLDs	Synthetic, recombinant, and semi-synthetic active ingredients for ANDAs referencing any peptide RLD
Active Ingredient-Related Impurity Thresholds:		
Reporting Threshold (RT)	≥ 0.10%	> 0.1%
Identification Threshold (IT)	≥ 0.10%	> 0.5%
Qualification Threshold (QT)	≥ 0.10% (with a maximum allowable qualification level of 0.5% using adaptive immunogenicity in vitro assay data)	> 1.0%
Total Impurities	Not defined	Total impurities in the proposed generic product should be ≤ the respective amount in the RLD
Innate Immunogenicity Risk Assessment	Risk mitigated using comparative innate immune response modulating impurity (IIRMI) in vitro assays	Risk mitigated if product meets certain USP/ICH compendial acceptance criteria and toxicological thresholds, and aggregates are comparable to or less than the RLD

[1] Per 15 peptide PSGs published in July 2026

Status of Guidance Revisions

- Generic peptide product PSGs
  - 15 PSGs, covering 17 peptide products were revised on 07/28/2026 with updated recommendations
- The final guidance *ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin* (May 2021) was withdrawn on 07/28/2026
- A new draft guidance *Considerations for Peptide Drug Products in ANDAs* is planned for publication in CY 2026

Recently Revised PSGs

Calcitonin salmon	(NDA 017769)
Calcitonin salmon	(NDA 017808)
Dasiglucagon	(NDA 214231)
Glucagon	(NDA 210134)
Glucagon	(NDA 020928)
Glucagon	(NDA 212097)
Liraglutide	(NDA 022341)
Liraglutide	(NDA 206321)
Pegcetacoplan	(NDA 217171)
Pegcetacoplan	(NDA 215014)
Semaglutide	(NDA 209637)
Semaglutide	(NDA 215256)
Teriparatide	(NDA 021318)
Teriparatide	(NDA 218771)
Tirzepatide	(NDA 215866)
Tirzepatide	(NDA 217806)
Vosoritide	(NDA 214938)

Background on Addition of Recombinantly Sourced Active Ingredient

- FDA has extensive experience with the review and approval of peptide and biosimilar applications
- Generic drug pathway is suitable for demonstrating sameness and ensuring safety and efficacy, irrespective of the manufacturing process used for the generic or the RLD, including synthetic, recombinant, or semi-synthetic means
  - Advances in analytical and manufacturing technologies demonstrate that robust control of the manufacturing process can be achieved
  - Control strategies that are used to address process-related impurities for biologics can generally be considered sufficient to address non-active-ingredient-related impurities in generic recombinant peptide products, e.g., host-cell proteins and DNA

Background on Active Ingredient-Related Impurity Thresholds

- Minor differences in the sequence of these peptides, such as single changes in amino acid sequence that are present in most active ingredient-related impurities are unlikely to have a significant impact on immunogenicity risk when compared to the parent active ingredient
- Impurities that contain multiple changes in amino acids and those present at greater than 1.0% of the active-ingredient are rare and unlikely in the context of the available drug substance manufacturing methods and degradation under conventional drug product storage conditions
- General toxicological testing for peptide active ingredient-related impurities below 1.0% is generally not warranted

- **Conclusion – Immunogenicity and general toxicity risk:**
  - **Impurities present at levels up to 1.0% are likely to have a similar immunogenicity and toxicological risk to the active ingredient itself**
  - **Total impurity load relative to the RLD should be controlled to ensure product quality**

Submission Expectations and Impurity Routine Control Strategies

Recombinantly Sourced Active Ingredient – Submission Expectations

- Expectation for demonstrating sameness in active ingredient is the same regardless of manufacturing process
- Non-active ingredient-related impurities associated with recombinantly sourced active ingredients, e.g., host cell proteins (HCPs), host cell DNA, should be routinely controlled with justified acceptance criteria generally in the drug substance specification
  - If specification uses an ELISA assay, which may not detect certain individual HCPs, results of testing using an orthogonal method such as LC-MS, should be provided to justify why the proposed ELISA acceptance criterion (e.g., NMT 100 ppm) is appropriate

Revised Active Ingredient-Related Impurity Thresholds – Submission Expectations

Recommend applicants compare the active ingredient-related impurities of the proposed generic and the RLD. The following revised thresholds and controls are recommended.

1. Report all impurities present in the proposed generic at a level above 0.1% of the DS.
2. Identify (characterize) all impurities present in the proposed generic at a level above 0.5% of the DS.
3. For each impurity common to the proposed generic and the RLD, the level of the impurity in the proposed generic should not be greater than that found in the RLD or 1.0% of the DS, whichever is greater. Efforts should be made to reduce the levels of these impurities by implementing appropriate manufacturing and control strategies.
4. For new impurities found in the proposed generic, efforts should be made to reduce the levels of these impurities to below 1.0% of the DS by implementing appropriate manufacturing and control strategies.
5. The total amount of impurities in the proposed generic, including new impurities, should not be greater than the amount observed in the RLD.
   - All impurities at a level greater than the reporting threshold of 0.1% should be summed and reported as total impurities.

Adaptive vs. Innate Immunogenicity Risk Factors

- Adaptive immunogenicity risk assessment
  - Peptide active ingredient-related impurities
- Innate immunogenicity risk assessment
  - Aggregates
  - Non-active ingredient (non-peptide) process-related impurities
    - Particulate matter
    - Microbial contaminants (e.g., bacterial endotoxins)
    - Residual organic solvents
    - Elemental impurities
    - Leachables
    - Host cell proteins, host cell DNA
- Recommend implementation of manufacturing controls to control impurities at acceptable levels
- Adaptive and innate immunogenicity in vitro assays are no longer recommended as the primary tools to mitigate risk

Active Ingredient-Related Impurity Routine Controls

- Limits for each active ingredient-related impurity may be established such that they are either
  1. Qualified by observed RLD levels, or
  2. Not more than 1.0% (or tighter) (no general toxicology or adaptive immunogenicity risk mitigation necessary), or
  3. More relaxed than 1.0% and qualified for general toxicological and adaptive immunogenicity risk at the proposed limit
- Limits for any unspecified impurity may be established consistent with the identification threshold of 0.5%
- Limits for total impurities should be established consistent with the total impurities observed in the RLD
- Drug substance manufacturing process related impurities controlled in DS specification
- Degradants controlled in DP specification and as appropriate in the DS specification

Aggregate and Non-Active Ingredient-Related Impurity Routine Controls

- Aggregates
  - Generally controlled using a size-exclusion chromatography (SEC) analytical method in the DP specification with a limit qualified by observed RLD levels
  - Sometimes test is also included in the DS specifications
- Non-active ingredient (non-peptide) process-related impurities (DS and/or DP specification as appropriate)
  - Particulate matter per USP⟨788⟩
  - Microbial contaminants (e.g., bacterial endotoxins per USP⟨85⟩)
  - Residual organic solvents per USP⟨467⟩ or ICH Q3C(R8)
  - Elemental impurities per USP⟨232⟩ or ICH Q3D(R2)
  - Leachables per USP⟨1664⟩
  - Host cell proteins, host cell DNA per justified acceptance criteria

Common Questions

- Can the recommendations in the revised PSGs be applied to other generic peptide products?
- If an individual active ingredient-related impurity is found above 1.0%, and greater than in the RLD what justification is needed?
- If total active ingredient-related impurities is found to be greater than that found in the RLD, but all individual active ingredient-related impurities are each found to be below 1.0%, what justification is needed?


FDA
U.S. FOOD & DRUG
ADMINISTRATION