Teriparatide Injection First Generic Approval: Quality-Related Review Considerations

Advancing Generic Drug Development 2024:
Translating Science to Approval

Day 2, Session 5A: Spotlight Generic Drug Review Challenges and Solutions

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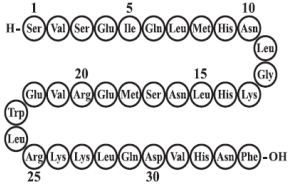
Outline

- Learning objective
- Quality related recommendations for Teriparatide Injection generic applications
- Immunogenicity risk mitigation for Teriparatide Injection generic applications
- Examples of common deficiencies for peptide products
- Summary
- Challenge questions

Learning Objectives

- Learn quality related recommendations for Teriparatide Injection generic approval
- Review examples of common deficiencies to highlight aspects where attention should be focused to facilitate ANDA approval

Teriparatide Injection, 0.25 mg/mL



- Teriparatide contains 34 amino acids with MW of 4117.8 daltons.
- Indicated for osteoporosis.
- Clear solution in a multi-dose injector pen for subcutaneous injection (20 µg dose each day for 28 days).

Component	RLD FORTEO™ (each mL contains)
Teriparatide	0.250 mg
Glacial Acetic Acid	0.41 mg
Sodium Acetate (Anhydrous)	0.1 mg
Mannitol	45.4 mg
Metacresol	3 mg
Water for Injection	q.s.
10% Sodium Hydroxide (if needed)	Adjust to pH 4
10% Hydrochloric Acid (if needed)	Adjust to pH 4

- Reference Listed Drug: N021318, Eli Lilly and Co, recombinant API
- 1st Generic ANDA:

  A208569, Teva Pharmaceuticals USA Inc, approved on 11/16/2023, synthetic API and Q1/Q2 to RLD

  A211097, Apotex Inc, approved on 11/16/2023, synthetic API and Q1/Q2 to RLD

Therapeutic Equivalence

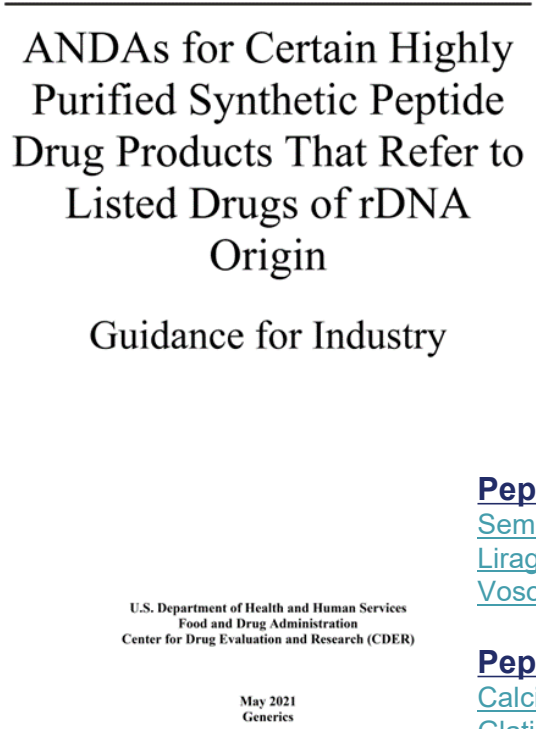
- For an ANDA submitted under section 505(j), the applicant must demonstrate that the proposed generic drug has therapeutic equivalence with the reference listed drug (RLD)
  - ❖ Pharmaceutical Equivalence
    - **Same active ingredient**(s)
    - Same dosage form
    - Same route of administration
    - Same strength
  - ❖ Bioequivalence

    Under 21 CFR 320.22(b)(1), a drug product's in vivo bioavailability or bioequivalence may be considered *self-evident* and can be waived if it

    i. Is a parenteral solution intended solely for administration by injection, … and

    ii. Contains **the same active** and inactive ingredients in the same concentration as a drug product that is the subject of an approved full NDA or ANDA

FDA Guidance for Industry


ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2021
Generics

FDA Guidance for Industry (draft published October 2017, finalized May 2021)

- Describes a pathway for generic synthetic peptide drug approval under section 505(j) of the FD&C Act for Glucagon, Liraglutide, Nesiritide, **Teriparatide**, and Teduglutide

Peptide PSG that reference the above guidance:
Semaglutide (Subcutaneous, Ozempic), Semaglutide (Subcutaneous, Wegovy), Liraglutide (Subcutaneous, Victoza), Liraglutide (Subcutaneous, Saxenda), Vosoritide

Peptide PSG that recommend active ingredient (AI) sameness:
Calcitonin Salmon, Dasiglucagon Hydrochloride, Degarelix Acetate, Etelcalcetide, Glatiramer Acetate, Glucagon (Nasal), Glucagon (Subcutaneous), Lanreotide Acetate, Octreotide Acetate, Pegcetacoplan, Tirzepatide, Vasopressin

Active Ingredient Sameness

- As per the ANDA peptide guidance*, comparative characterization of the following for the proposed product and RLD is recommended using orthogonal analytical methods
  - Primary sequence and physicochemical properties
  - Secondary structure
  - Oligomer/aggregation states
  - Biological activities

*FDA Guidance for Industry: *ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin* (May 2021)

AI Characterization and Comparability Studies

- **Characterization**:
  - Characterization of drug substance primary peptide structure and physicochemical properties
    - Provide evidence to ensure the identity, strength, quality, and purity of the peptide drug substance
    - DMF can be referenced for the AI characterization information
- **Comparability**:
  - Provide evidence to ensure the peptide higher-order structure, oligomer/aggregation profile and biological activity *in the proposed finished drug product* are comparable to those of the RLD

Drug Substance Characterization

Attribute	Examples of Characterization/Comparability Studies	Examples of Methods
Primary sequence and physicochemical properties	➢ Primary peptide structure/sequence ➢ Solubility as a function of pH ➢ Hygroscopicity ➢ log P ➢ Isoelectric point (pI) ➢ specific optical rotation	➢ Infra-red (IR) Spectroscopy ➢ Mass spectrometry (MS) ➢ Ultra-violet (UV) Spectroscopy ➢ Nuclear Magnetic Resonance (NMR) Spectroscopy ➢ Circular Dichroism (CD) Spectroscopy ➢ Amino Acid Analysis (AAA) ➢ L- and D- amino acid content ➢ Amino Acid Sequencing (AAS) (Edman Degradation and/or HRMS/MS)

Comparability Studies at the Drug Product Level

Attribute	Examples of Characterization/ Comparability Studies	Examples of Methods
Higher Order Structure	Secondary: α-helix, β-sheet, random coil, unordered	Secondary: Far-UV CD, FTIR, Raman Spectroscopy
	Tertiary: overall monomer structure	Tertiary: Near-UV CD, Intrinsic Fluorescence, DSC, NMR
Oligomer/ Aggregation States	➢ Reversible non-covalent soluble oligomers ➢ Irreversible soluble/insoluble aggregates (may exist as sub-visible or visible particles)	➢ Light Scattering: SEC-UV/MALS, CG-MALS, DLS ➢ Analytical Ultracentrifugation: SE-AUC, SV-AUC ➢ Gel Electrophoresis: SDS-PAGE, Native ➢ Field Flow Fractionation: AF4 ➢ MFI (Micro-Flow Imaging)
Biological Activity	Therapeutically relevant bioassay	Bioidentity Tests per USP monograph for Teriparatide Injection

Impurity Comparability Studies

- Impurities should not be greater in a test product than that in the RLD
- Conduct a comparative peptide-related impurity profiling of the RLD and proposed generic product

  i. Identify each peptide-related impurity at level ≥ 0.10%

  ii. Demonstrate no new peptide related impurities > 0.5%

  iii. For impurity found in both the proposed drug product and the RLD, demonstrate the level in the test product is the same as or lower than that of the RLD

  iv. For impurity found at levels ≥ 0.10% and ≤ 0.5%:
    - not present in the RLD, or
    - in the test product at higher levels than that of the RLD

  provide justification as to why such an impurity does not affect the safety, effectiveness or potential for immunogenicity

- Consider the use of UHPLC-HRMS/MS to facilitate peak identification and ensure peak purity (see *Liquid Chromatography-High Resolution Mass Spectrometry for Peptide Drug Quality Control* by Zeng *et al*. *AAPS J.* **2015**, *17*, 643-651)

Immunogenicity Risk Mitigation for Teriparatide Injection

- Adaptive immune response
  - For any new or elevated level impurities found at levels of ≥ 0.10% and ≤ 0.5%, adaptive immunogenicity risks for such impurities should be evaluated individually
- Innate immune response
  - Innate immune response evaluation should be conducted on the fully formulated DP in comparison with the RLD to ensure the generic product does not contain anything, such as impurities, aggregates, contaminants, or leachables, that may increase immunogenicity risk

Common Deficiencies (for peptide products)

- You performed an impurity profile characterization of the test product samples aged near release using the HPLC Related Substance Method.
- We recommend you
  - Update the study using test product samples aged at the end of your proposed shelf life.
  - Perform the characterization study using orthogonal methods that use different chromatographic separation principles.
  - Use UHPLC-HRMS/MS to facilitate peak identification and matching between the RLD and proposed product samples and to characterize peak purity (specificity).

Common Deficiencies Cont'd

- You identified some impurities in the specification table with relative retention times (RRTs)
- We recommend you
  - Characterize the structure of those impurities identified by RRTs as per the ANDA peptide guidance*
  - Update the specification tables with identified names based on your characterization.

**FDA Guidance for Industry: ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin (May 2021)*

Common Deficiencies Cont'd

- You proposed a limit of NMT 0.10% for Any Unspecified Impurity
- We recommend you
  - Revise the limit from NMT 0.10% to less than 0.10% to be consistent with the ANDA peptide guidance*, which states that all impurities present at 0.10% or greater should be identified and characterized.

Common Deficiencies Cont'd

- The proposed limit for Impurity I is more relaxed than NMT 0.5% and not supported by the comparative RLD data.
- We recommend you
  - Tighten the limit consistent with and supported by the observed RLD level, or
  - Tighten the limit to 0.10%-0.5% and supported by immunogenicity study results suggesting Impurity I does not add immunogenicity risk to the product at the proposed limit

Common Deficiencies Cont'd

- You reported a greater level of aggregates in the test product than those found in the RLD.
- We recommend you
  - Perform an investigation to identify the root cause and improve your product aggregation profile. The aggregation profile of your test product should be comparable to the RLD
  - Demonstrate capability of manufacturing DS or DP exhibit batches as necessary with acceptable control of aggregates across the proposed shelf life

Challenge Question #1

Consistent with the ANDA peptide guidance*, when conducting a comparative impurity profiling of the generic product and RLD, identify all peptide-related impurities at a level of:

A. > 0.10%

B. > 0.5%

C. ≥ 0.10%

D. ≥ 0.1%

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Challenge Question #2

Which of the following statements is NOT true?

A. ICH Q3A & Q3B guideline is generally applicable to all drug products, including peptide drug products

B. The limit for each peptide-related impurity can be qualified by the observed RLD level for the same impurity

C. A comparative characterization of the impurity profile of the generic product and RLD is recommended to establish acceptance impurity limits

D. Peptide-related impurities and aggregates may pose immunogenicity risks

Summary

- Overview of quality related recommendations relevant to Teriparatide Injection generic approval
- Examples of common deficiencies communicated to ANDA applicants regarding compliance with the ANDA peptide guidance*

**FDA Guidance for Industry: ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin (May 2021)*

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