Related-Impurities Assessment Considerations for APIs in Generic Complex Peptide Products

SBIA 2020: Advancing Innovative Science in Generic Drug Development Workshop

Session 1: Method Development/Validations for Non-traditional Analytical Methods

Topic 1: Complex Active Pharmaceutical Ingredients (APIs) Including Peptide Products

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Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

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A quality product of any kind consistently meets the expectations of the user.

Drugs are no different.


Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is

assuring *every* dose is safe and effective, free of contamination and defects.


FDA
It is what gives patients confidence in their *next* dose of medicine.

Learning Objectives

- Describe the components that are required to demonstrate API sameness for peptides with respect to Drug Master File (DMF)

- Know the common deficiency and Importance of the impurity Comparability Studies in DMF

- List a few comparability study scenarios

Relevant Terminology for Peptides

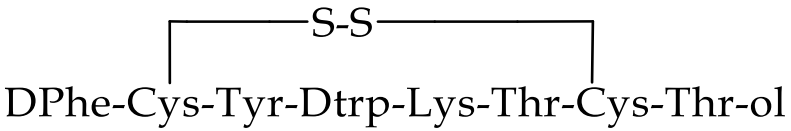
- ***Peptide* —** FDA considers a polymer composed of 40 or fewer amino acids to be a peptide regulated as a drug under the FD&C Act*
- ***Protein* —** FDA interprets the term “protein” to mean any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size
- Only Synthetic Peptides are eligible to be approved as generics under section 505(j) of the FD&C Act†

* FDA Guidance for Industry: *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2)*, December 2018, pp 13-14.

† Section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355)

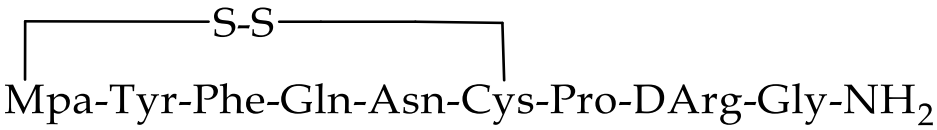
Examples of Therapeutic Peptides

Octreotide



8 AAs

Desmopressin



9 AAs

Bivalirudin

DPhe-Pro-Arg-Pro-Gly-Gly-Gly-Gly-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu-NH_2

20 AAs

Calcitonin

32 AAs

Teriparatide

Phe-Asn-His-Val-Asp-Gln-Leu-Lys-Lys-Arg-Leu-Trp-Glu-Val-Arg-Glu-Met-Ser-Asn-Leu-His-Lys-Gly-Leu-Asn-His-Met-Leu-Gln-Ile-Glu-Ser-Val-Ser-NH_2

34 AAs

Peptide Guidances

- No FDA general peptide guidance
- Draft Guidance for Industry: *ANDAs for Certain Highly Purified Synthetic Peptide Drug Products that Refer to Listed Drugs of rDNA Origin*

  [Liraglutide, Glucagon, Nesiritide, Teriparatide, and Teduglutide]
- Product-specific guidance (PSG)
  - Glatiramer Acetate Injection
  - Semaglutide

Draft Guidance for Industry:

(*ANDAs for Certain Highly Purified Synthetic Peptide Drug Products that Refer to Listed Drugs of rDNA Origin*)

i. Active ingredient sameness:

- Primary sequence and physico-chemical properties → **Drug Substance (DMF)**

- Secondary & Higher order structures
- Oligomer/Aggregation states; and
- Biological activities (by in vitro or animal studies).

} **Drug Product (ANDA)**

Draft Guidance for Industry:

(*ANDAs for Certain Highly Purified Synthetic Peptide Drug Products that Refer to Listed Drugs of rDNA Origin*)

ii. Related Impurities

- For the impurities that are common between your DS and the RLD, the acceptance criteria should be not more than those observed in the RLD (at the end of the shelf-life).

- For any new impurities in your DS, but not observed in the RLD, they should not exceed 0.5%. Furthermore, each of these new impurities present at 0.10% or greater should be identified and justified for not affecting the safety and efficacy.

- Utilize sensitive and high resolution analytical methods (e.g., UHPLC-HRMS*) to detect and characterize peptide-related impurities in a proposed generic synthetic peptide in comparison to RLD. Identify and report each specified and unspecified peptide-related impurity that is 0.10% of the drug substance or greater. (LOQ is less than 0.10%)

*Zeng et al. AAPS J. 2015, *17*, 643-651

API Sameness & Related Impurities in DMF

- Structure confirmation or comparative structural signature analysis
  - Primary structure of peptide; structural features and fingerprints, etc.
- Comparative physicochemical property analysis
  - spectroscopic analysis, etc.
- Comparative impurity profile analysis
  - peptide-related impurities in synthetic peptides

Totality of Evidence approach

Origin of Impurities (DMF)

Differences in manufacturing process may result in differences in related impurities:

Chemical Synthesis	Recombinant Synthesis
Starting materials (AAs)	Fermentation & cell culture media components
Reagents, Catalysts, Solvents	Residual DNA & cellular proteins
Intermediates	Bacteria, fungi, mycoplasma, viruses, etc.
By-products	Column materials
Other Degradation products	Other Degradation products

Peptide Related-Impurities: SPPS

SPPS:

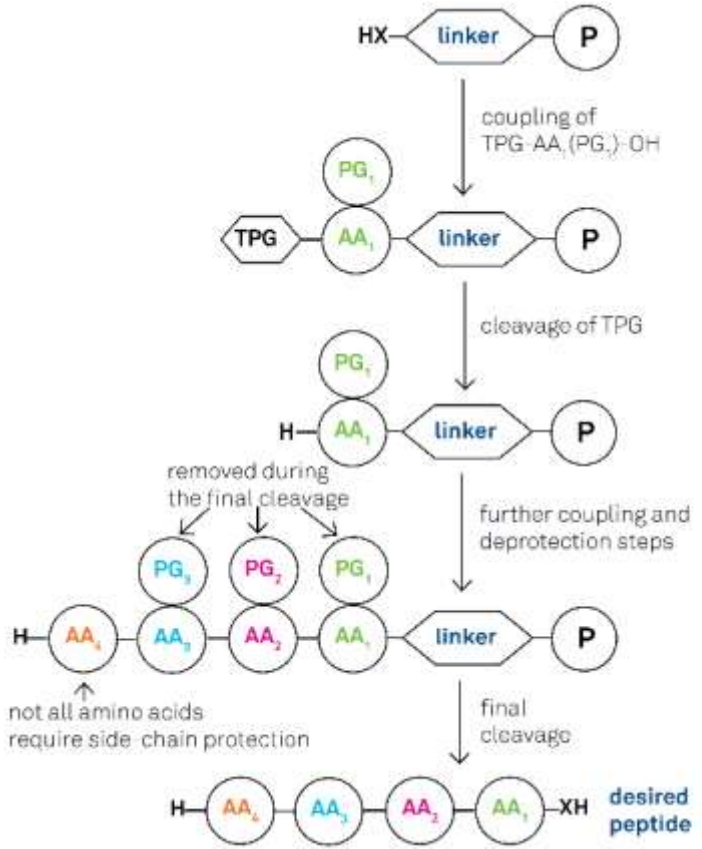
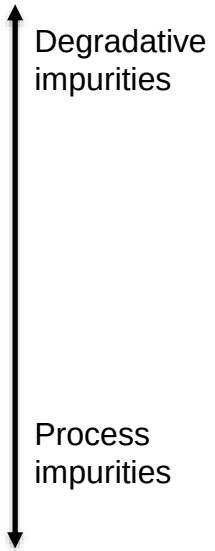


Fig. 1.
General scheme of SPPS.
X = O, NH
AA = Amino Acid
PG = Protecting Group
P = Polymer Support
TPG = Temporary Protecting Group

Adopted from Bachem Solid-Phase Peptide Synthesis white paper

Potential Related-Impurities (DMF)

- Impurities may result from the insertion, deletion, or modification of amino acid sequences or residues; can be process or degradative in origin or both
  - Proteolysis (e.g., peptide hydrolysis to form fragments)
  - Deamidation (hydrolysis of primary amide to carboxylic acid)
  - Oxidation (e.g., oxidation of methionine sulfur to sulfoxide/sulfone)
  - Reduction (e.g., reduction of cystine to cysteine)
  - Racemization (e.g., epimerization of amino acid residue α-stereocenter)
  - Deletion (incomplete coupling)
  - Truncation (missing amino acids)
  - Insertion (additional amino acids)
  - Incomplete deprotection (attached protective groups)
  - Disulfide exchange (e.g., cystine isomerization)
- Impurities may form during storage



General Considerations for Impurity Comparability Studies (DMF)

- Conduct a comparative impurity profiling of the RLD and proposed generic DS to
  i. Demonstrate that impurities common to both the proposed DS and the RLD are present in the proposed DS at the same or lower levels than in the RLD
  ii. Analyze and characterize new impurities in the proposed DS that are not common to the RLD
- Conduct each study on a statistically meaningful number of batches (generally at least three) of both the proposed drug substance and the RLD
- It is recommended the proposed DS be tested on or near release and at the end of the proposed shelf life, and RLD batches of different ages be tested prior to expiry (as available). Provide sample ages for the dates of all studies
- Use multiple orthogonal validated methods

Orthogonal Analytical methods (DMF)

Related Impurities	Complementary methods*
Deletion	LC-HRMS(MS)
Insertion	LC-HRMS(MS)
Truncation	LC-HRMS(MS)
proteolysis	LC-HRMS(MS)
Substitution	LC-HRMS(MS)
FG modification	LC-HRMS(MS)
Disulfide modification	LC-HRMS(MS)
Deamidation	LC-HRMS(MS)
Acetylation of amino functions	LC-HRMS(MS)

*Zeng et al. AAPS J. 2015, 17, 643-651

Scenario: 1 (in DMF)

Generic DS Impurities

Specified Impurities	AC
A	NMT 1.0%
B	NMT 0.20%
C	NMT 0.15%
D	NMT 0.15%
Any unspecified	NMT 0.10%
Total Impurity	NMT 2.0%

RLD impurities

Specified Impurities	AC
A	NMT 0.50%
B	NMT 0.20%
C	NMT 0.15%
D	NMT 0.20%
Any unspecified	NMT 0.10%
Total Impurity	NMT 2.0%

Impurities-A, B, C, & D are common impurities (may be Process and /or degradants)

If the common impurity A is higher than the RLD, you propose to control it at the same or lower levels than in the RLD.

Limits of Common Impurities ≤ RLD impurity levels

Scenario: 2 (in DMF)

Generic DS Impurities

Specified Impurities	AC
A	NMT 0.50%
B	NMT 0.20%
C	NMT 0.15%
D	NMT 0.20%
E	NMT 0.40%
Any unspecified	NMT 0.10%
Total Impurity	NMT 2.0%

RLD impurities

Specified Impurities	AC
A	NMT 0.50%
B	NMT 0.20%
C	NMT 0.15%
D	NMT 0.20%
Any unspecified	NMT 0.10%
Total Impurity	NMT 2.0%

Impurities-A, B, C, & D are common impurities (may be Process and/or degradants)
Impurity –E could be specific for Generic process

New Impurities ≤ 0.50%

Additional data to qualify impurity-E may be requested from an ANDA applicant referencing this DMF.

Scenario: 3 (in DMF)

Generic DS Impurities

Specified Impurities	AC
A	NMT 0.50%
B	NMT 0.20%
C	NMT 0.15%
D	NMT 0.20%
Any unspecified	NMT 0.10%
Total Impurity	NMT 2.0%

RLD-DS impurities

Specified Impurities	AC
A	NMT 0.50%
B	NMT 0.20%
C	NMT 0.15%
D	NMT 0.20%
Any unspecified	NMT 0.40%
Total Impurity	NMT 2.0%

Impurities-A, B, C, & D are common impurities (may be Process and/or degradants)

The 'any unspecified impurity' limit, in your DS, is recommended to be controlled at the level of 0.10% (or based on MDD) or else justification should be provided.

This general approach may be considered when developing other peptide API products.

Typical Deficiency (DMF)

If you provide insufficient information regarding related-impurities…

Deficiency: Please provide one-time comparison of the impurity profile of your Drug Substance (DS) with the RLD Drug product (DP) and provide data. Please perform these studies taking into account the following.

a. Demonstrate that impurities common to both the proposed DS and the RLD DP are present in the proposed DS at the same or lower levels than in the RLD.
b. In general, any new impurities not common to the RLD that are present in your proposed DS at a level above 0.10% should be identified and reported by RRT and their limit should be justified.
c. Samples should be analyzed using at least two orthogonal validated analytical methods. Use of UHPLC-HRMS/MS should be considered to facilitate peak identification and matching between the RLD DP and proposed DS samples and to 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).
d. Ensure that sample analysis dates and batch manufacturing or expiry dates are provided for all studies to facilitate calculation of sample ages.

Justification: Risk analysis data, safety mitigation data, based on manufacturing capability, literature data, statistical analysis, existing specifications, etc.

Challenge Question #1

Which one of the following Amino acid polymers is considered by the FDA to be regulated as a peptide drug under the FD&C Act?

A. Amino acid polymer contains <100 & >40 amino acids

B. Amino acid polymer contains ≤40 amino acids

C. Amino acid polymer contains >100 amino acids

D. Amino acid polymer with the size of >15,000 Da.

Challenge Question #2

Which one of the following is not considered to be synthetic peptide related-impurities :

A. Amino acid Insertion impurities

B. Amino acid Deletion impurities

C. Residual DNA & cellular protein impurities

D. Incomplete deprotection impurities

Summary

- Impurity profile comparability studies on the proposed peptide drug substance with RLD is a key part in qualifying related impurities in the Peptide API (in DMF).

- Each peptide API has its own challenges, DMF applicants need to evaluate individual situation and apply these recommendations accordingly.

U.S. FOOD & DRUG ADMINISTRATION

Thank you