SBIA-DMF Drug Substance Workshop

March 3 & 4, 2021 (Virtual)

Synthetic Peptide APIs of generic complex drug products: Recommendations for API sameness & related impurities

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Division Life Cycle API/Office of New Drug Products/Office of Pharmaceutical quality/CDER/FDA. March 3 & 4, 2021 Virtual

PURPOSE

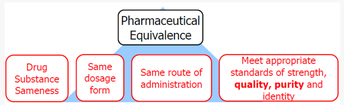
FDCA section 505j states that the Generic products must be therapeutically equivalent to the RLD, as established through the combined criteria of pharmaceutical equivalence and bioequivalence. For a generic peptide drug product, pharmaceutical equivalence signifies that the generic product and the RLD contain the identical peptide API and its strength, dosage form, route of administration, quality, performance characteristics and intended use are the same.[1,2] This presentation is to describe the components that are required to demonstrate the API sameness & qualification of related impurities for peptide API with respect to Drug Master File (DMF).

BACKGROUND:

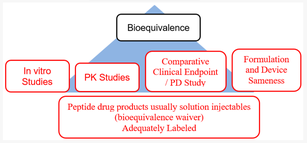
Therapeutic Equivalence

For an ANDA submitted under section 505(j), the applicant must demonstrate the following for the proposed generic drug compared to the reference listed drug (RLD)

Pharmaceutical Equivalence



Bioequivalence



Therapeutic Peptides : FDA considers any polymer composed of 40 or fewer amino acids to be a peptide.

Examples:

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 (S-S) CSNLSTCVLGKLSQELHKLQTYPRTNTGSGTP-NH_2 — **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**

FDA does not have a general guidance for peptide drugs. However, FDA has released draft guidance for industry ;ANDAs for Certain Highly Purified Synthetic Peptide Drug Products that Refer to Listed Drugs of rDNA Origin and product specific guidance (Glatiramer Acetate Injection and Semaglutide).[2-4] The FDA draft guidance, provides basic regulatory information about how to establish a generic product be therapeutically equivalent to the RLD through pharmaceutical equivalence and bioequivalence.

What are scientific considerations for generic API sameness with RLD?

1. **Active Ingredient Sameness**
   - Primary sequence and physicochemical properties- Drug Substance (DMF)
   - Secondary structure
   - Oligomer/Aggregation states
   - Biological activities (by in vitro or animal studies)

   → Drug Product (ANDA)

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SCOPE AND GENERAL REQUIREMENTS IN THE DMF

1. **Primary sequence and physicochemical properties [Drug Substance(DMF)]**

API Characterization (DMF)	API Physicochemical Properties (DMF)
Infra-red (IR) Spectroscopy	Description
Mass spectrometry (MS)	Solubility
Ultra-violet (UV) Spectroscopy	Hygroscopicity
Nuclear Magnetic Resonance (NMR) Spectroscopy	Potential Isomerism/Chirality/Specific Optical Rotation
Amino Acid Analysis (AAA)	Polymorphism (most peptides are amorphous)
Chiral Amino Acid Analysis (L- and D- amino acid content)	Melting Point (most peptides are amorphous)
Amino Acid Sequencing (AAS)	Edman Degradation and/or MS/MS
Other relevant studies, if necessary	Other relevant studies as per the API

2. **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% should be identified and justified.
   - 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. (LOQ is less than 0.10%)

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).
- Use multiple orthogonal validated methods.

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 and Solvents	Residual DNA & cellular proteins
Intermediates	Bacteria, fungi, mycoplasma, viruses, etc.
By-products	Column materials
Other related Degradation products	Other related Degradation products

POTENTIAL RELATED-IMPURITIES DUE TO SPPS (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)

Degradative impurities

Process impurities

Impurities may form during storage

Orthogonal analytical methods:

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)

Scenarios:

Generic DS impurities

Specified Impurities	AC
A	NMT 0%
B	NMT 0.20%
C	NMT 0.15%
D	NMT 0.20%
E	NMT 0.10%
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%
E	Not observed
Any unspecified	NMT 0.40%
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%

Limits of common Impurities ≤ RLD impurity levels

Any unspecified impurity ≤ 0.10%

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

Summary:

- API sameness as well as Impurity profile comparability studies on the proposed peptide drug substance are significant part in developing generic Peptide products.
- Each peptide API has its own challenges, DMF applicants need to evaluate individual situation and apply these recommendations accordingly.

References:

1. Drugs: Abbreviated New Drug Application (ANDA) (2018). http://www. fda.gov/Drugs/Development Approval Process/ How Drugs are Developed and Approved/Approval Applications/ Abbreviated New Drug Application ANDA Generics/default.htm.
2. FDA Guidance for Industry: ANDAs for certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin
3. https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_209637.pdf
4. https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_209637.pdf

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Division of Lifecycle API
Office of New Drug Products
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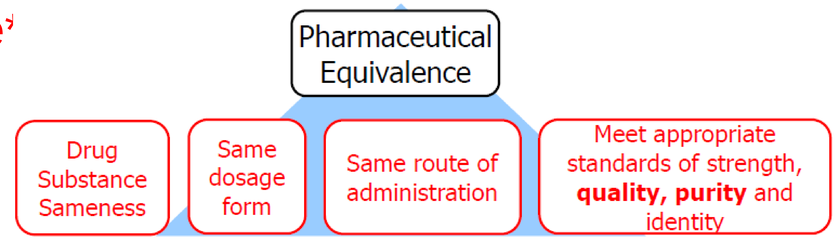
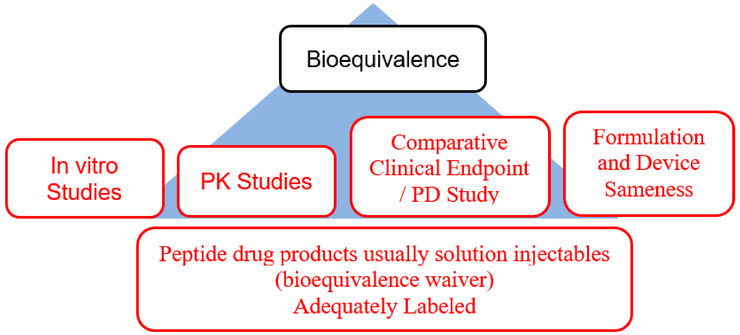
Therapeutic Equivalence*

- For an ANDA submitted under section 505(j), the applicant must demonstrate the following for the proposed generic drug compared to the reference listed drug (RLD)
  - Pharmaceutical Equivalence[$]



  - Bioequivalence



  - Adequately Labeled

***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[$]
FDA believes at this time that only Synthetic Peptides are eligible to be approved as generics under section 505(j) of the FD&C Act[†]

* For definition, see 21 CFR 314.3(b); certain differences may be permitted if the petition is submitted and approved per 21 CFR 314.93
[$] 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

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

S-S

CSNLSTCVLGKLSQELHKLQTYPRTNTGSGTP-NH_2

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 ICH guidelines for Peptides
- 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
  - Linaclotide

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. (impurity profile comparability studies)

- 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). Minimum 3 batches of Generic DS and 3 batches of RLD are recommendable.

- For any new impurities in your DS, but not observed in the RLD, they should not exceed 0.50%. Furthermore, each of these new impurities present at > 0.10% should be identified and justified.

- 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. (LOQ is less than 0.10%)

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

API Physicochemical Properties (DMF)

- Physicochemical Properties at the API level
  - Description
  - Solubility
  - Hygroscopicity
  - Potential Isomerism/Chirality/Specific Optical Rotation
  - Polymorphism (most peptides are amorphous)
  - Melting Point (most peptides are amorphous)
  - Other relevant studies as per the API

API Characterization (DMF)

- Characterization of Peptide Structure at the API Level
  - Infra-red (IR) Spectroscopy
  - Mass spectrometry (MS)
  - Ultra-violet (UV) Spectroscopy
  - Nuclear Magnetic Resonance (NMR) Spectroscopy
  - Amino Acid Analysis (AAA)
  - Chiral Amino Acid Analysis (L- and D- amino acid content)
  - Amino Acid Sequencing (AAS)
    - Edman Degradation and/or MS/MS
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Origin of Impurities (DMF)

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Thank you!

- Send questions regarding this poster to: DMFWorkshop2021@fda.hhs.gov by 2/15/2021 for inclusion in the poster Q&A session on *March 3rd, 2021.*

- Follow-on webinar for both posters/presentations on April 9, 2021. Questions can be sent to the above email by 3/19/2021 for the webinar.

- Please refer to the following presentations on March 3rd and 4th for additional information:
  1. *"Regulatory Considerations in Demonstrating Complex API Sameness".*
  2. *"Safety Evaluation of Drug Substances impurities in Generics"*