Scientific Considerations in Submitting Synthetic Peptide Drug Products as ANDAs Referencing Peptide Drug Products of rDNA Origin

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

Scope

For rDNA-sourced peptide drug products, currently FDA considers any polymer composed of 40 or fewer amino acids to be a peptide, thus they are regulated as drugs rather than biologics

Why Now?

- With the advancement of SPPS, chemical synthesis of therapeutic peptides becomes one of the most mature technology available
- Development of analytical technology makes detailed characterizations of the APIs and impurities possible
- Exclusivity coverage on rDNA-sourced peptide drugs has either expired or is approaching expiration

Outline

- Key regulatory requirements for submitting ANDA
- Active ingredient sameness for peptide drug products
- Control of impurities
- Evaluation of immunogenicity risk
- Summary

Key Requirements for Submitting Abbreviated New Drug Application (ANDA)

Demonstrating Therapeutic Equivalence of Test Product to Reference Listed Drug (RLD)

- Pharmaceutical Equivalence (PE)
  - Same active ingredient(s)
  - Same dosage form and route of administration
  - Identical in strength or concentration
  - May differ in characteristics such as shape, excipients, packaging, etc.
- Bioequivalence (BE)
  - Same rate and extent of absorption when administered at the same molar dose under similar experimental conditions

Regulatory Requirements for Parenteral Solution Injection Products

- Pharmaceutical Equivalence (PE)
  - Same active ingredient(s)
  - Same dosage form and route of administration
  - Identical in strength or concentration
  - Same inactive ingredients and in the same concentration (CFR 314.94(a)(9))
  - May differ in preservative, buffer, or antioxidant
    - Needs to demonstrate the differences do NOT affect the safety and efficacy of the proposed drug product
- Bioequivalence (BE)
  - In vivo BE may be self-evident when the product contains the same active and inactive ingredients in the same concentration as the RLD. In vivo BE waiver can be requested. (CFR 320.22(b)(1))

Sameness of Active Ingredient

Recommended characterizations for generic peptides:*

- Primary sequence including amino acid composition, optical purity and physicochemical properties
- Secondary structure
- Oligomers and aggregation states (including under stress and stability conditions)
- Biological activity

* Comparative testing should be performed on generic and RLD products, as applicable

Control of Impurities

Impurities in Peptide Drug Products

- Product-related impurities
  - Degradation products of active ingredient
  - Independent of manufacturing method

- Process-related impurities
  - Process-dependent peptide-related impurities
  - Host-cell related impurities (in peptides of rDNA origin)
  - Residual chemicals (FDA and ICH guidelines)

Peptide-related Impurities

- Amino acid sequences related to, but different from the active ingredient:
  - Insertion
  - Deletion
  - D-Amino acid
  - Acylation
  - Oxidation
  - Deamidation
  - Glycosylation

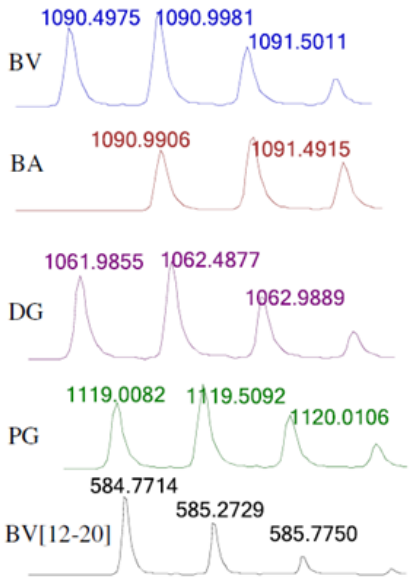
Peptide-related Impurities

- Specified impurities
  - Characterized and quantified with LC/MS/MS and other analytical technologies
- Unspecified impurities
  - Low level peptide impurities whose identity and amount may change from batch to batch
  - Acceptance limit is set for the largest amount of such an impurity
  - Total amount is controlled by “Total peptide-related impurities”

Example: Analysis of Peptide Impurities

Bivalirudin: 20 amino acid (aa) peptide (BV)

D-Phe-Pro-Arg-Pro-Gly^{5}-Gly-Gly-Gly-Asn-Gly^{10}-Asp-Phe-Glu-Glu-Ile^{15}-Pro-Glu-Glu-Tyr-Leu^{20}



+ Gly: PG

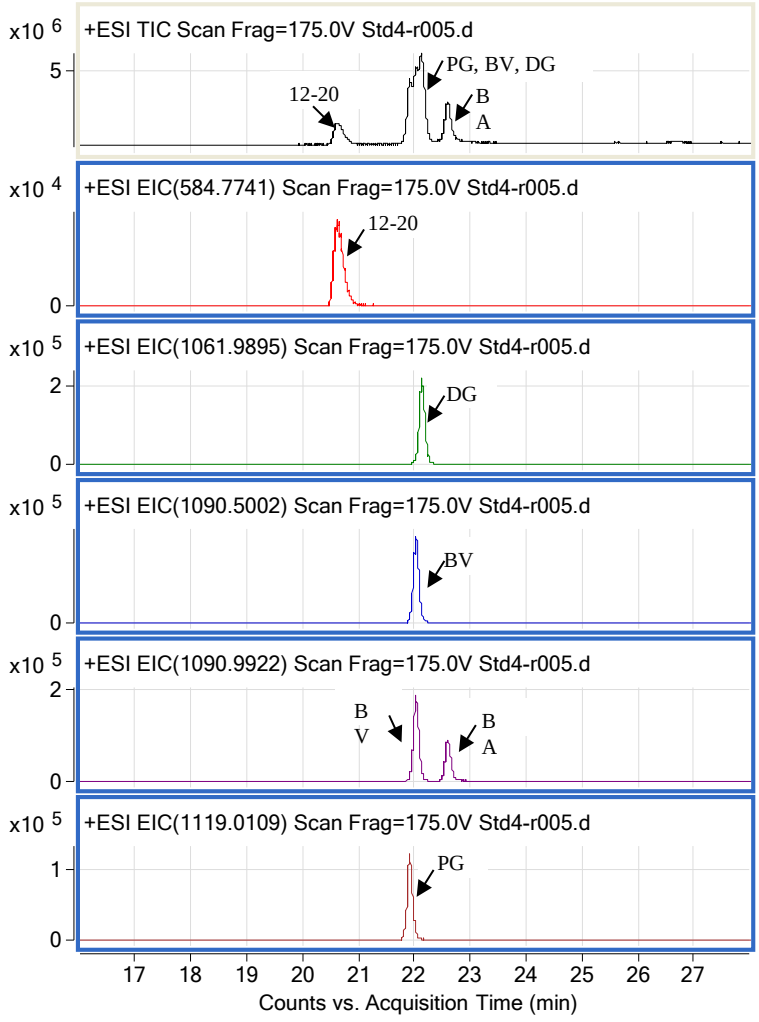
- Gly: DG

β-Asp: BA

BV [12-20]

High resolution mass spectra (+2 charge states) of BV and related impurities

Example: Analysis of Peptide Impurities



- Baseline separation in total ion chromatogram (TIC) for BV[12-20] and BA, but BV, DG and PG co-eluted
- LC-HRMS extracted ion chromatogram (EIC) allows for baseline separation of all components

AAPS J. 2015 May;17(3):643-51.

Control of Impurities

- Better control of manufacturing and purification process
- Orthogonal and high-resolution comparative analysis of generic and RLD products
- Justification on new peptide-related impurities
  - Why each of such impurity does not affect the safety and efficacy of the proposed generic synthetic peptide
    - Identity and amount of the impurity
    - Impact on physicochemical properties
    - Impact on biological activities
    - Potential safety concern (e.g., **immunogenicity**)

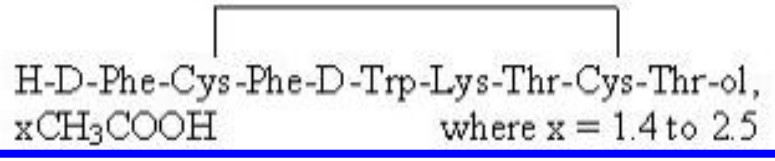
Immunogenicity

- Immunogenicity is the ability of a particular substance, such as an antigen or epitope, to provoke an immune response in the body of a human or animal
- Immunogenicity is the ability to induce a humoral and/or cell-mediated immune responses.
- Proteins are significantly more immunogenic than polysaccharides
- Host cell proteins (impurities) in rDNA peptides may be immunogenic

Immunogenicity of Peptides

- Longer chain peptides tend to be more immunogenic, but shorter ones like Octreotide (8 aa) also can induce anti-peptide antibody formation in patients

Octreotide



- NO detection level of antibodies found in 20 patients treated for 6 months
- Antibody titers to octreotide subsequently reported in 3 patients, prolonged duration of action reported in 2 patients
- Patients receiving octreotide reported anaphylactic shock

Immunogenicity of Peptides

- Teriparatide (34 aa):
  - For osteoporosis at high risk for fracture (postmenopausal women, etc.)
  - Human parathyroid hormone analog (N-terminal 34 aa of the 84 aa hPTH) which increase [Ca^{2+}] in blood
  - Formation of anti-drug antibody (ADA) observed in 3% women patient (15/541) following 12 months treatment at 20 mcg
  - ADAs had no impacts on serum calcium and bone mineral density

Immunogenicity of Peptide Products

Active Ingredient related

- API sequence, API degradation (oxidation, deamidation, etc.)

Treatment related

- Dose
- Route
- Frequency of administration
- Duration of therapy

Patient related

- Age
- Gender
- Genetic make-up
- Immune status
- Disease

Product related

- Impurities (process-related)
- Formulation difference, aggregation state

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In vitro tools to Mitigate Immunogenicity Risk

- For each new Impurity: T cell epitopes
  - In silico or in vitro tools
  - Peptide-related impurities do not have T cell epitopes
- For drug product:
  - Synthetic peptide does not produce greater stimulation of innate immune activity as compared to the RLD

See: Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products, FDA 2014

Summary

- Technology advancement opens the possibility for ANDA submission of synthetic peptide products referencing rDNA peptide products
  - Synthesis, purification and analytical technology
- Active ingredient sameness
  - structure analysis (primary, secondary), physicochemical characterization and bioactivity evaluation
- Impurity control and characterization to ensure the impurities will not affect the safety and efficacy of the generic products
  - peptide-related impurities, aggregates
  - immunogenicity evaluation

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