Regulatory Considerations for Peptide Drug Products

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This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies.
Peptide Team introduction

Products we reviewed and approved

Key considerations
- Drug substance manufacturing and controls
- Drug substance characterization
- Drug product manufacturing and controls
- Drug product stability
- Safety (immunogenicity)

Focus of the talk:
Generic chemically synthetic peptides (with less than 40 amino acids in size, for injectable solutions) with chemically synthetic RLDs
Peptide Team at OGD

- Formed in June 2012, initially with 1 TL and 3 FTE
- Currently with 1 TL and 6 FTE with background in peptide chemistry, peptide characterization and formulation, drug delivery systems (including liposomes), biochemistry and biology

Work purpose

- Review ANDA, DMF, and supplements for peptides and complex drug substances
- Develop scientific criteria for review and approval of ANDAs for complex drug substances
- Answer controlled correspondence related to peptide drugs and other complex drug substances.
Definitions

- **Biological product**
  - a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product ... applicable to the prevention, treatment, or cure of a disease or condition of human beings

- **Protein**
  - any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size

- **Chemically synthesized polypeptide**
  - any alpha amino acid polymer that is (a) made entirely by chemical synthesis, and (b) is less than 100 amino acids in size

- **Peptide**
  - any alpha amino acid polymer with specific defined sequence that is 40 amino acids or less in size

BPCI Act, section 351(i) PHS Act, 21 CFR 600.3(h); FDA Draft Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product, Feb. 2012; MAPP 5016.3
Peptides and Complex Drug Products We Reviewed and Approved

- Chemically synthesized peptide products with less than 40 aa (e.g., salmon calcitonin, cosyntropin, desmopressin, leuprolide, octreotide, oxytocin, etc.)
- Other complex naturally-derived/semi-synthetic products (heparin, LMWH, protamine sulfate)
- Liposome (doxorubicin HCl)
Review and Approval of Generic Peptides

- No official guidelines for peptide drugs
- Demonstration of the same active ingredients from two different manufacturers more difficult than conventional “small molecule” drugs
- Depending on the peptide complexity, dosage form and route of administration, potential immunogenicity concerns for some peptide products
- Peptide drug products usually solution injectables (bioequivalence waiver)

Pharmaceutical Equivalence

- Drug Substance Sameness
- Same dosage form
- Same route of administration
- Meet appropriate standards of strength, quality, purity and identity
Review and Approval of Generic Peptides

- Key areas to consider
  - Complexity of the peptide, its clinical use, and the origin of its potential immunogenicity
  - Sameness of peptide structures (i.e., primary and possibly higher order structures)
  - Process- and product-related factors (e.g., formulation and CCS) that may impact safety and efficacy of the proposed peptide product

- Case-by-case analysis
ANDA CTD Format

2.3.S. DRUG SUBSTANCE
2.3.S.1. General information
2.3.S.2. Manufacture
2.3.S.3. Characterization
2.3.S.4. Control of drug substance
2.3.S.5. Reference standards or materials
2.3.S.6. Container closure system
2.3.S.7. Stability

2.3.P. DRUG PRODUCT
2.3.P.1. Description and composition of the drug product
2.3.P.2. Pharmaceutical development
2.3.P.3. Manufacture
2.3.P.4. Control of excipients
2.3.P.5. Control of drug product
2.3.P.6. Reference standards or materials
2.3.P.7. Container closure system
2.3.P.8. Stability
Drug Substance

- CMC information about peptide API provided by reference to a DMF
  - Letter of Authorization signed by the DMF holder
- Choice of a drug substance supplier
  - Peptides in the proposed generic and the RLD preferably synthesized by similar methods (e.g., to minimize differences in impurity profiles and have high purity)
Peptide Manufacture and Controls (2.3.S.2)

- Most peptides manufactured by solid-phase peptide synthesis
  - Peptide assembled on a solid support (resins) one amino acid at a time in a predetermined sequence
  - Solution-phase peptide synthesis also possible
- Each step of the synthesis described in detail
  - Amounts of reactants, solvents and reagents, reaction conditions, yields, deprotection method, circumstances requiring repeated coupling of certain amino acids, etc.
- Purification described in detail
  - Chromatographic conditions
  - Counter-ion used during the final step if peptide isolated as a salt
  - Yields
Peptide Manufacture and Controls (2.3.S.2)

Issues commonly encountered during the review of peptide DMFs and ANDAs for lack of:

- Control of materials (resin, amino acids, reagents and solvents)
  - Resin - substitution level, swelling properties, particle size, and density
  - Amino acids – impurities, chiral purity, etc.
- Testing coupling and tBoc/Fmoc deprotection by color tests
  - Kaiser, TNBS, chloranil; two independent tests are encouraged!
- Testing disulfide by Ellman test
- For longer peptides, cleavage and analysis by MS small amount of intermediate at different time points during synthesis
- Calculation of synthesis yields
  - Based on loading efficiency
Peptide Characterization
(2.3.S.3 and 2.3.P.2)

- Characterize peptide structure and demonstrate sameness with the RLD
  - Primary structure – amino acid sequence
- Use a combination of analytical methods
  - Amino acid analysis, Edman degradation, MS, CD, fluorescence spectroscopy, fragment mapping, Ellman test, and/or NMR
- For drug products, perform higher order structure characterization and/or in vitro bioassay which is relevant to the mechanism of action
  - e.g., Chromogenic human thrombin inhibition assay for bivalirudin
Peptide Drug Product (2.3.P.1)

- Q1/Q2 sameness (e.g., for injectables)
  - Q1: proposed generic uses the same inactive ingredients as the RLD
  - Q2: concentrations of the inactive ingredients used in the proposed generic are within $\pm 5\%$ of those used in the RLD

- If difference in an excipient (e.g., preservative):
  - Assess effect of the new excipient on peptide stability - evaluate stability from comparative real time and/or forced degradation stability studies
  - Study peptide-excipient interactions - SPR, NMR, DSC, immunoassays (e.g., enzyme-linked immunosorbent assay) and/or bioassays
Peptide Drug Product Manufacture and Controls (2.3.P.3)

- Peptide drug products mostly injectables
- Issues commonly encountered during the review of peptide ANDAs:
  - Order of addition of ingredients, dissolution, and pH adjustment during compounding
  - Holding time and storage conditions for the bulk solutions before packaging
  - Lyophilization (freeze-drying) conditions
  - Peptide-equipment compatibility
  - In-process controls (pH, temperature, exposure to light, etc.)
  - Overage
Control of Peptide Drug Product (2.3.P.5)

- Specifications set up by comparison with multiple batches of RLD and if applicable, in agreement with USP (if compendial)
- No official guidelines regarding qualification levels for peptide-related impurities
  - Provide adequate information and characterization on potential peptide related impurities that can arise from peptide synthesis, cyclization (if cyclic peptide), and degradation (oxidation, deamidation, hydrolysis, isomerization)
  - Levels of impurities justified by those observed in the RLD
    - Mainly for addressing immunogenicity concerns of certain peptide drugs
    - Important to choose a API supplier carefully to minimize differences in impurities (e.g., D-amino acids)
Control of Peptide Drug Product (2.3.P.5)

- Tests generally applicable to all synthetic peptide based drug products
  - Peptide identity by amino acid analysis, HPLC/MS
  - Purity, individual impurities, largest single unknown impurity, and total impurities by HPLC
  - Peptide assay by HPLC and/or bioassay

- Dosage form specific tests
  - Injectables: testing according to USP<1>
  - Nasal sprays: testing according to FDA guidance

- Validation of non standard quantitative analytical methods (e.g., HPLC method discriminative in detecting all potential drug substance related impurities – D amino acids)

Container Closure System
(2.3.P.2 and 2.3.P.7)

- Evaluate CCS with respect to protection (e.g., photostability), compatibility, safety, and performance
- Perform extractable studies
- Use CCS compatible with the formulation to minimize the amount of leachables
  - Absence of significant levels of leachables (based on sensitive analytical method(s)) or comparability of leachable profiles between the proposed generic product and multiple batches of the RLD throughout the product shelf life
  - Analysis of leachables by GC/MS and/or HPLC/MS

FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics, from May 1999
**Stability (2.3.P.8)**

- Depending on the complexity of the peptide API, follow ICH and FDA stability guidance
  - 3 batches
  - 6 months long term and accelerated
- One time photostability study in photo-sensitive peptides
- Leachables included in the stability specifications (dosage form specific)
- Temperature cycling
- In-use stability

Factors - Immunogenicity

Factors That May Impact Immunogenicity

- Active Ingredient
- Route of Administration
- Dosage and Administration
- Patient Characteristics
- Peptide Related Impurities
- Aggregates
- Excipients
- Leachables

One Time Study: Comparability of Purity Profiles and Peptide Related Impurities Levels (2.3.P.2)

- Characterize peptide-related impurities
  - Under long-term storage and accelerated/stress conditions
  - By comparing impurity profiles between proposed generic and multiple batches of the RLD product (overlaid HPLC chromatograms)
  - Using analytical methods discriminative to detect all possible impurities, including those containing D-amino acids
One Time Study: Comparability of Peptide Aggregate Profiles (2.3.P.2)

- Characterize aggregates
  - Under long-term storage and accelerated/stress conditions (e.g., elevated temperatures)
  - By SEC, AUC, DLS, and/or FFF to cover a wide range of aggregate sizes
  - By comparison to the RLD product (multiple batches) in terms of the sizes of aggregates and their corresponding levels
Summary

- Choice of a peptide manufacturer
- Key review issues related to peptide drug products including comprehensive characterization and control strategy
- Key review issues pertaining to peptide immunogenicity:
  - Sameness of the active ingredient with the RLD
  - No active ingredient-excipient interactions
  - Comparable peptide-related impurity profile with the RLD
  - Absence of significant levels of leachables
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