Peptides as Radiopharmaceuticals: CMC Perspectives

Ravindra K. Kasliwal, Ph.D.
Office of New Drug Products (ONDP)
Office of Pharmaceutical Quality (OPQ)
Center for Drug Evaluation and Research (CDER)
Food and Drug Administration
Outline

• Definitions
• Radiopharmaceutical Drugs
  – Monoclonal Antibodies (Ab), including various modifications
  – Peptides and Proteins
• CMC related Considerations
  – Ab based radiopharmaceuticals
  – Peptide based radiopharmaceuticals
    • Starting materials for peptide, characterization, specifications and safety.

Focus of the talk:
Chemically synthesized peptide radiopharmaceuticals (with ≤ 40 amino acids, for injectable solutions)
Definitions

• **Peptide** – any alpha amino acid polymer with specific defined sequence that is 40 amino acids or less 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

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

• **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 .......
## Radionuclide Examples

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>(^{89}\text{Zr})</th>
<th>(^{177}\text{Lu})</th>
<th>(^{68}\text{Ga})</th>
<th>(^{90}\text{Y})</th>
<th>(^{111}\text{In})</th>
<th>(^{64}\text{Cu})</th>
<th>(^{131}\text{I})</th>
<th>(^{18}\text{F})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Form</td>
<td>(^{89}\text{Zr-oxalate})</td>
<td>(^{177}\text{LuCl}_3)</td>
<td>(^{68}\text{GaCl}_3)</td>
<td>(^{90}\text{YCl}_3)</td>
<td>(^{111}\text{InCl}_3)</td>
<td>(^{64}\text{CuCl}_2)</td>
<td>Na(^{131}\text{I})</td>
<td>Na(^{18}\text{F})</td>
</tr>
<tr>
<td>Production</td>
<td>Cyclotron</td>
<td>Reactor</td>
<td>Generator</td>
<td>Reactor</td>
<td>Cyclotron</td>
<td>Cyclotron</td>
<td>Reactor</td>
<td>Cyclotron</td>
</tr>
<tr>
<td>Half-Life</td>
<td>3.3 days</td>
<td>6.73 days</td>
<td>68 Minutes</td>
<td>2.67 days</td>
<td>2.8 days</td>
<td>12.7 Hrs.</td>
<td>8.02 days</td>
<td>109.77 minutes</td>
</tr>
<tr>
<td>Decay Product</td>
<td>(^{89}\text{Y})</td>
<td>(^{177}\text{Hf})</td>
<td>(^{68}\text{Zn})</td>
<td>(^{90}\text{Zr})</td>
<td>(^{111}\text{Cd})</td>
<td>(^{64}\text{Zn};^{64}\text{Ni})</td>
<td>(^{131}\text{Xe})</td>
<td>(^{18}\text{F})</td>
</tr>
</tbody>
</table>
Ab Based Radiopharmaceuticals

- Radiolabeling of Ab with conjugated bifunctional chelate (e.g., with $^{90}$Y, $^{89}$Zr)
- Direct radiolabeling of Ab (e.g., with $^{131}$I)
- Other methods.
Antibody Based Radiopharmaceutical

Specifications for:
- Starting Materials
- Ab intermediate
- Linker
- Moab Conjugate
- Radionuclide precursor
- Radiolabeled product (drug substance and drug product)

An NDA for a radionuclide may not be approved without the corresponding Ab NDA.

Information may be provided in DMF / NDA
Ab Based Radiopharmaceuticals-Considerations

• Preservation of antibody characteristics:
  – Ab $\rightarrow$ Ab-Conjugate $\rightarrow$ Radiolabeled Ab.
  – Need adequate characterization (primary and higher order structures).

• Reproducibility of conjugation and radiolabeling reaction
  – Ab – linker / chelate ratio
  – Characterization of site of attachment of linker / chelate
  – Ab – radioisotope ratio; amount of naked antibody

• Impurity control at each stage of the process
  – e.g., free linker / chelate, other protein related impurities, aggregates, etc.

• IND - Relationship of preclinical batches to the clinical batch(es)
• NDA - Relationship of clinical batches to the commercial product
Peptide Radiopharmaceuticals

• Radiolabeling of peptide with conjugated bifunctional chelate (e.g., $^{89}$Zr, $^{68}$Ga, $^{111}$In)
  – Lyophilized powder formulation (for injection)
  – Solution formulation (injection)

• Direct radiolabeling of peptide (e.g., $^{18}$F, $^{131}$I)
Lyophilized Powder Formulation

Starting Material(s)

(CGMP)

Peptide

(CGMP)

Conjugated Peptide

(CGMP)

Formulated Lyophilized Peptide (DP)

(CGMP)

Radionuclide Precursor

(CGMP)

Radiolabeled Peptide Drug Substance & Product

Specifications for:
• Starting Materials
• Peptide
• Conjugated peptide
• Radionuclide precursor
• Formulated lyophilized product
• Radiolabeled product

Details of each step of the synthesis / manufacture for peptide, conjugated peptide precursor, radionuclide precursor, drug substance and drug product

Information may be provided in DMF

An NDA for a radionuclide may not be approved without the “Kit for the peptide” NDA.

SNMMI - June 2016
Solution Formulation (Injection)

Starting Material(s)

\[ \downarrow \text{CGMP} \]

Peptide

\[ \downarrow \text{CGMP} \]

Conjugated Peptide Precursor

\[ \downarrow \text{CGMP} \]

Radionuclide precursor

Starting Material

\[ \downarrow \text{CGMP} \]

Radiolabeled Peptide (Drug Substance)

\[ \downarrow \text{CGMP} \]

Formulation

Radiolabeled Peptide Drug Product

Information may be provided in DMF

- Starting Materials - Identified in application
- Details of each step of the synthesis / manufacture for peptide, conjugated peptide precursor, radionuclide precursor, drug substance and drug product.

Specifications for:
- Starting Materials
- Peptide
- Conjugated peptide
- Radionuclide precursor
- Radiolabeled product (drug substance is controlled in the drug product)
Direct Radiolabeling of Peptide

Starting Material(s) (CGMP)
- Peptide

Starting Material (CGMP)
- Radionuclide precursor

Radiolabeled Peptide (Drug Substance)

Formulation (CGMP)

Radiolabeled Peptide Drug Product

Specifications for:
- Starting Materials
- Peptide
- Radionuclide precursor
- Radiolabeled product (drug substance is controlled in the drug product)

Information may be provided in DMF

Starting Materials - Identified in application
Details of each step of the synthesis / manufacture for peptide, radionuclide precursor, drug substance and drug product

SNMMI - June 2016
Considerations For Starting Materials for Peptide

• Amino acids and derivatives
  – Name and address of the vendor
  – Specifications – identification, assay, optical rotation, chemical and **chiral purity**, impurities, water content, microbial control (if appropriate).
  – Certificate of Analyses (COA) with test results.
  – Uncommon amino acid derivatives / use of novel synthesis method
    • Provide details of synthesis and characterization
Peptide and Peptide Conjugate Characterization

• Primary structure – amino acid sequence (method of synthesis)
• Use a combination of analytical methods
  – Amino acid analysis, Edman degradation, MS, CD, fluorescence spectroscopy, fragment mapping, Ellman test (for disulfides), NMR, test to check chirality of the amino acid
• Higher order structure characterization and/or in vitro bioassay which is relevant to the mechanism of action may be needed.
• Information and characterization on potential peptide related impurities that can arise from peptide synthesis, cyclization (if cyclic peptide), and degradation (oxidation, deamidation, hydrolysis, isomerization)
  – Mainly for addressing immunogenicity concerns of certain peptide drugs
  – Important to choose a supplier carefully to minimize differences in impurities (e.g., D-amino acids)
Controls for Peptide and Peptide Conjugate

• Well characterized reference standard for peptide, peptide conjugate and drug substance (non-radioactive)

• Generally applicable tests;
  – Appearance
  – Peptide identity by amino acid analysis, HPLC/MS (identity of conjugate)
  – Purity, individual impurities (e.g., free conjugate molecule or related impurities), largest single unknown impurity, and total impurities by HPLC (HPLC method discriminative in detecting all potential related impurities- D amino acids)
  – Peptide assay by HPLC (or by quantitative aa analyses), Water content, residual solvents, inorganic impurities (ICP analysis)
  – Counter ion content, other relevant ionic impurities
  – Specific optical rotation
  – Bioassay
  – Microbiological attributes
Radiolabeled Peptide Attributes

- Appearance
- Identity - Identity of radiolabeled peptide; Identity of radionuclide
- Identity of higher order structure and/or in vitro bioassay which is relevant to the mechanism of action
- Purity - Radiochemical purity; Chemical purity
- Specific activity
  - Mass of radiolabeled peptide; mass of unlabeled peptide
- Assay of radioactivity
- pH
- Osmolality
- Impurities (specified, unspecified and total)
  - Peptide related impurities, degradation products, residual solvents (as appropriate)
- Identity and assay of functional excipients (e.g., antimicrobials, stabilizers)
- Microbiological attributes (sterility, bacterial endotoxins, etc.)
Safety Considerations

• Immunogenicity
  – Peptide, proteins, antibodies
  – Related impurities

• Peptide excipient interactions – safety and potency

• Guidance for Industry -Immunogenicity Assessment for Therapeutic Protein Products
  
Conclusion

• Various radiopharmaceutical drugs
  – Peptides, Proteins, Antibodies

• Considerations for peptide radiopharmaceuticals
  – Starting materials
  – Characterization,
  – Attributes to test
  – Safety.

Thank-you
SUPPLEMENTARY MATERIAL
Drug Master Files

• When referencing a DMF, you must include a letter of authorization (LOA) obtained from DMF holder in your application.

• Identify what the DMF is being referenced for.
  – Type II - Drug substance, drug substance intermediate, and materials used in their preparation, or drug product
    • Examples - Radionuclide (including generator produced radionuclide), Precursor, Synthesizer cassettes, etc.
  – Type III - Packaging materials
  – Type IV - Excipient, colorant, flavor, essence, or materials used in their preparation
  – Type V - FDA accepted reference information (You must get permission to submit type V DMF)
    http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm