Current Thinking on Synthetic Peptides in Abbreviated New Drug Applications

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Disclaimer

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

Outline

- US FDA's regulations related to peptide drug products
- Peptide characterization and quality control
- Peptide-related impurities and in vitro immunogenicity assessment for generic peptide products

Drug Products vs. Biological Products

- Federal Food Drug and Cosmetic Act (FD&C Act)
  - Gives authority to FDA to regulate drug products
  - The Abbreviated New Drug Application process in section 505(j) was established through the Hatch-Waxman Amendments, which were part of the Drug Price Competition and Patent Term Restoration Act of 1984
- Public Health Service Act (PHS Act)
  - Gives authority to FDA to regulate biological products
  - Historically, some proteins have been approved as drugs under section 505 of the FD&C Act and other proteins have been licensed as biologics under section 351 of the PHS Act
  - The Biologics Price Competition and Innovation Act (BPCI Act) creates an abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with an FDA-licensed reference product [section 351(k) of the PHS Act].
  - Under the BPCI Act, a protein, except any chemically synthesized polypeptide, will be regulated as a biological product

FDA's Interpretation of Relevant Terms

- Protein
  - FDA has interpreted this term to mean any alpha amino polymer with a specific defined sequence that is greater than 40 amino acids in size
- Chemically synthesized polypeptide
  - FDA has interpreted this term to mean any alpha amino acid polymer that (1) is made entirely by chemical synthesis; and (2) is less than 100 amino acids in size

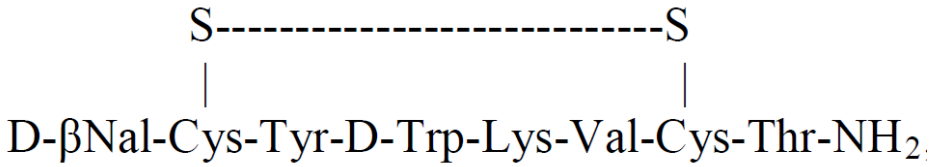
Guidance for Industry: Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009

Biologics Price Competition and Innovation Act (BPCIA) Transitional Products

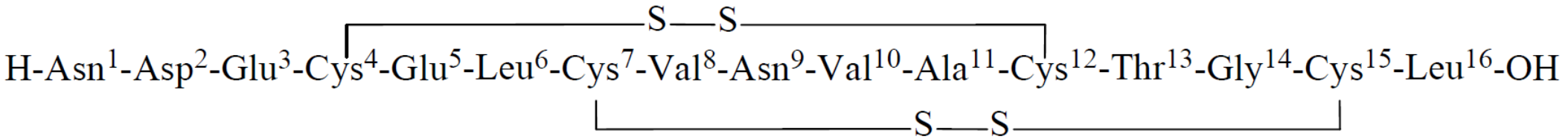
- BPCIA expanded "biologicals" to include proteins, except chemically synthesized polypeptides
  - **Proteins (generally any peptide > 40 amino acids (A.A.) except > 40 and < 99 A.A. if chemically synthesized)**
- For a BPCIA transitional application
  - **On March 23, 2020**: Approved NDAs for biological products will be deemed to be BLAs
  - **After March 23, 2020**:
    - Pending NDAs for biological products can not be approved
    - **A product deemed to be licensed cannot be an RLD for an ANDA or 505(b)(2)**

Examples of Synthetic Peptides

Lanreotide (8 aa)



Plecanatide (16 aa)

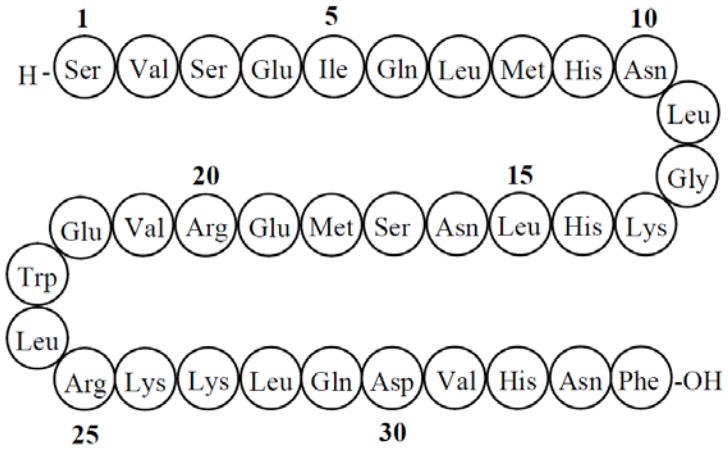


Exenatide (39 aa)

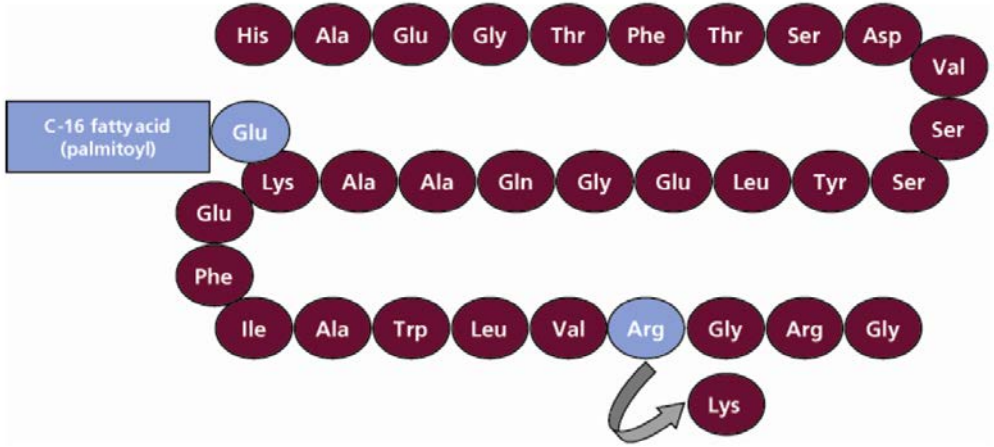
H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-
Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2

How About Recombinant Peptides?

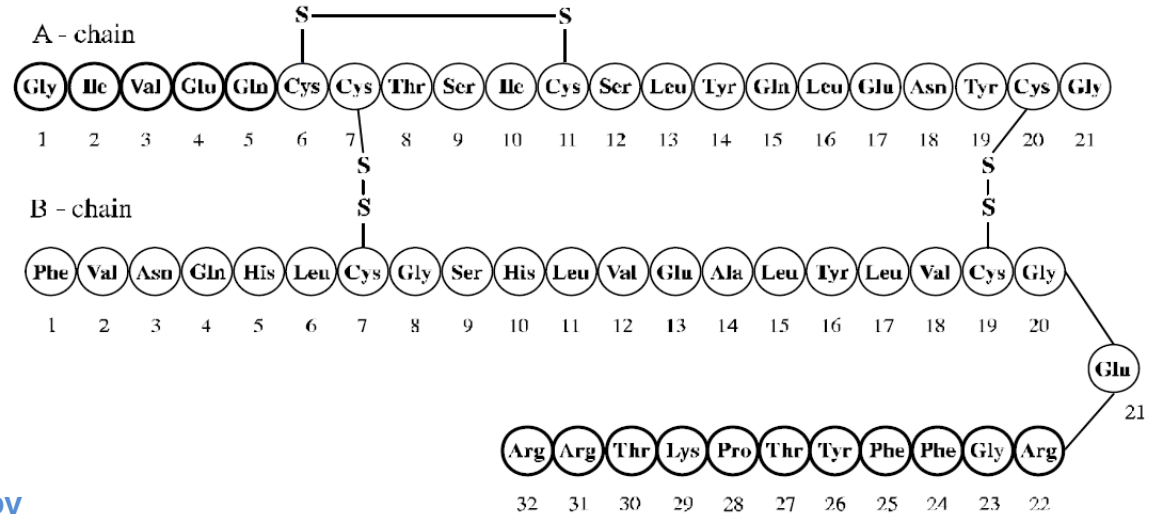
Teriparatide (34 aa)



Liraglutide (31 aa)



Remain as NDAs



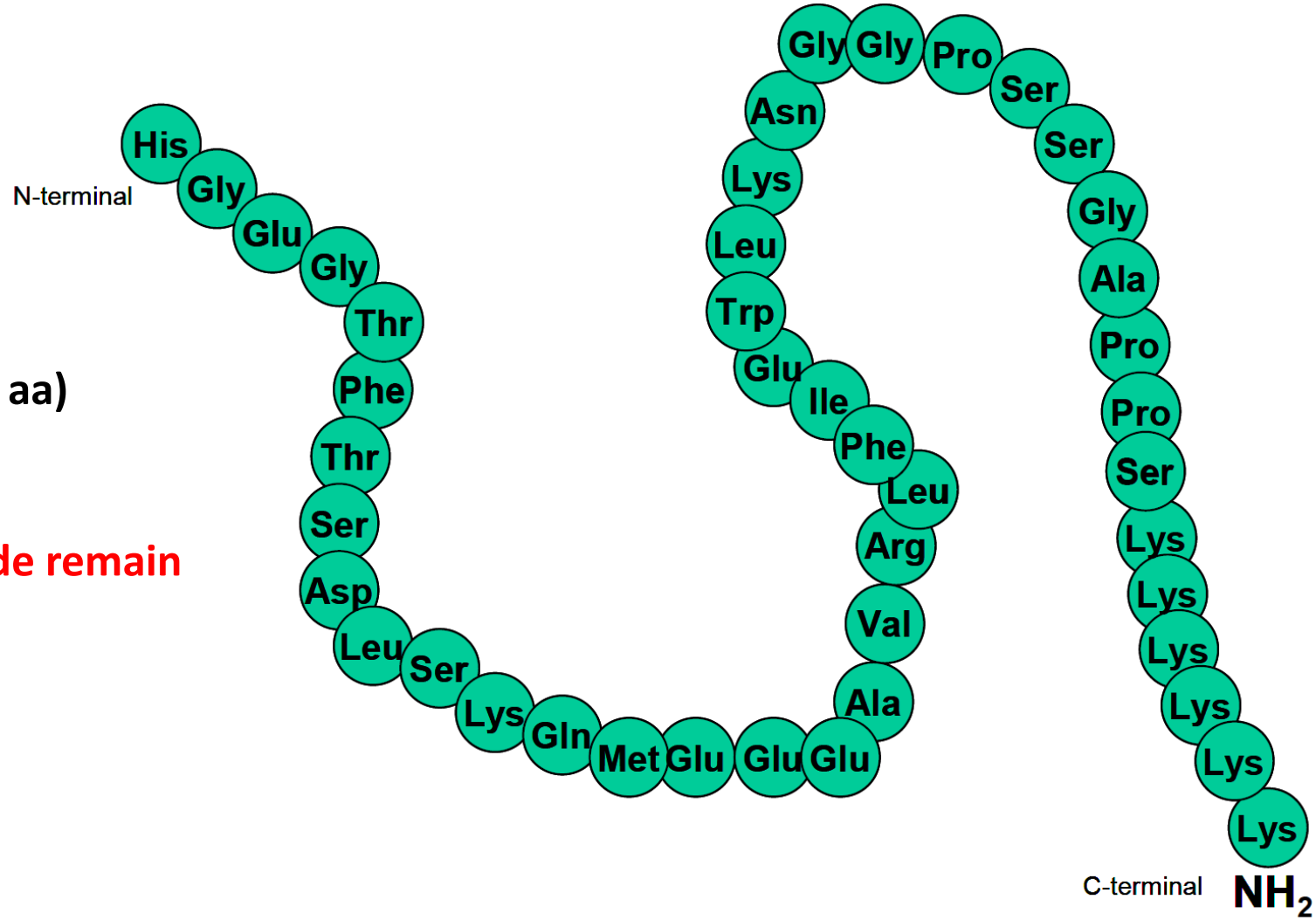
Insulin glargine (53 aa)

Transitional product NDA -> BLA
If not chemically synthesized

Should This One Remain as a NDA or Transition into a BLA?

Lixisenatide (44 aa)

Synthetic peptide remain as a NDA



Regulatory Pathways of New Drug Application

- 505(b)(1)
  - "stand-alone" New Drug Application (NDA), usually a New Molecular Entity (NME)
  - Contains full reports of investigations of safety and effectiveness of a proposed drug product
- 505(b)(2)
  - NDA
  - Usually have a Refence Listed Drug (RLD); some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use
- 505(j)
  - Abbreviated NDA (ANDA, i.e., duplicate of a previously approved drug product)
  - Must have a RLD, contain information to establish therapeutic equivalence, and may not be submitted if studies are necessary to establish the safety or effectiveness of the proposed drug product

New Drug Application (NDA) vs. Abbreviated New Drug Application (ANDA)

NDA	NDA
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Testing	3. Testing
4. Labeling	4. Labeling
5. Inspection	5. Inspection
6. Animal Studies	
7. Clinical Studies	6. Bioequivalence
8. Bioavailability	

Same CMC Requirements

Therapeutic Equivalence of ANDA

- Pharmaceutical Equivalent (PE)
  - Contain identical amounts of the identical active ingredient(s)
  - Identical dosage form
  - Identical route of administration
  - Meet identical compendial or other applicable standards
  - May differ in characteristics such as shape, excipients, packaging ...
- Bioequivalent (BE)
  - Absence of a significant difference in the rate and extent to which the active ingredient or active moiety in PEs becomes available at the site of drug action when administered under similar conditions

Q1/Q2 Requirement for Generic Parenteral Products

- Demonstration of qualitative (Q1) and quantitative (Q2) sameness of inactive ingredients in parenteral drug products

21 CFR 314.94 (a)(9)(iii) – *Inactive ingredient changes permitted in drug products intended for parenteral use.*

Generally, a drug product intended for parenteral use shall contain the same inactive ingredients (qualitatively the same – "Q1") and in the same concentration (quantitatively the same – "Q2") as the reference listed drug.

An applicant may seek approval of a drug product that differs from the reference listed drug in **preservative, buffer, or antioxidant** provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

A formulation which contains an excipient not contained in the RLD and not considered to be an "exception excipient" cannot be submitted as an ANDA.

“Biowaiver” for Peptide Products

- Under 21 CFR 320.22(b)(1):

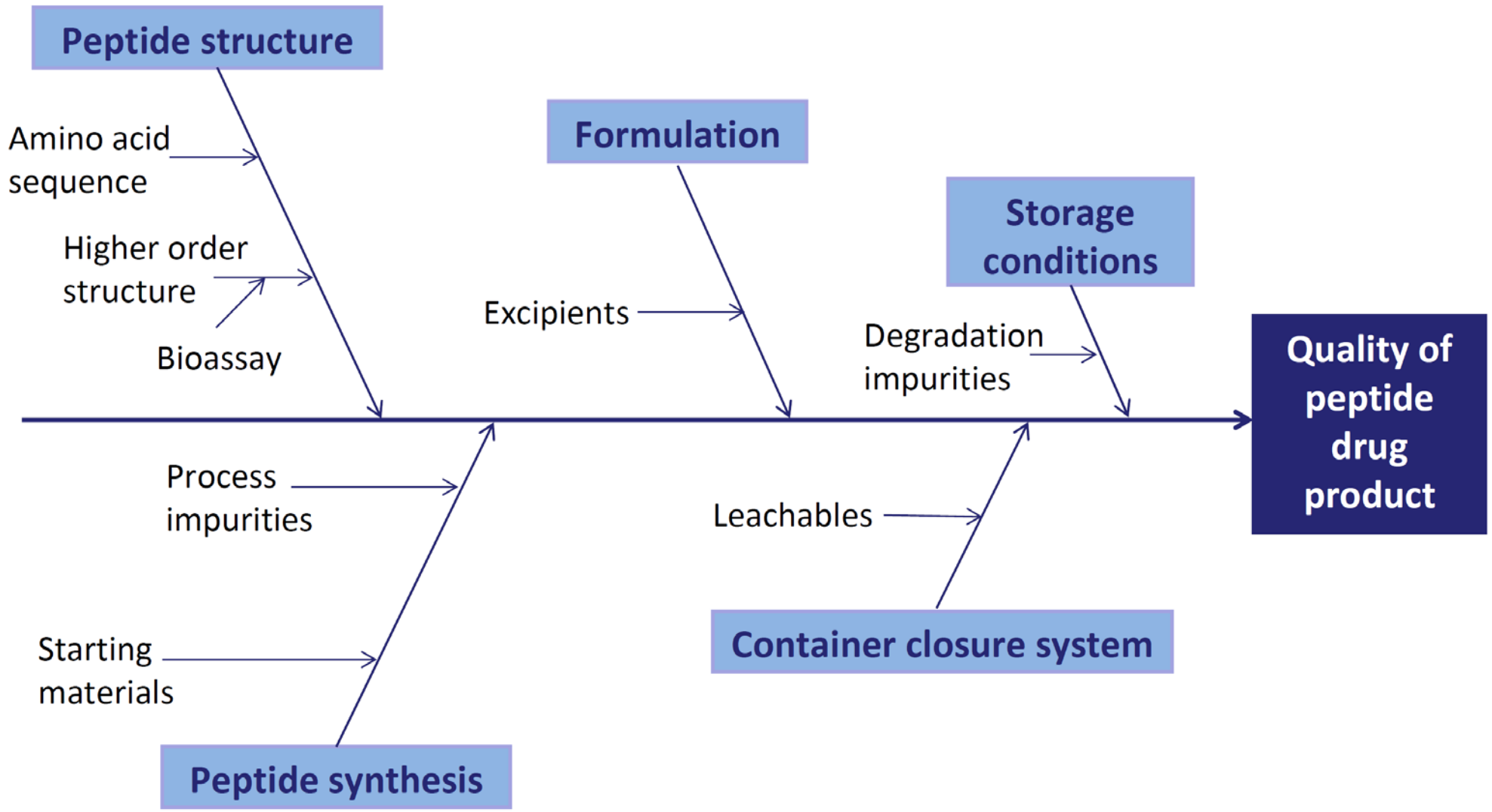
  “A drug product's in vivo bioavailability or bioequivalence may be considered ***self-evident*** …” if it

  (i) Is a *parenteral* solution intended solely for administration by injection, or an ophthalmic or otic solution; and

  (ii) Contains the *same active and inactive ingredients* in the *same concentration* as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

- Most peptide injection solution products are eligible for “biowaiver”

Risk Assessment for Quality of Peptide Drugs

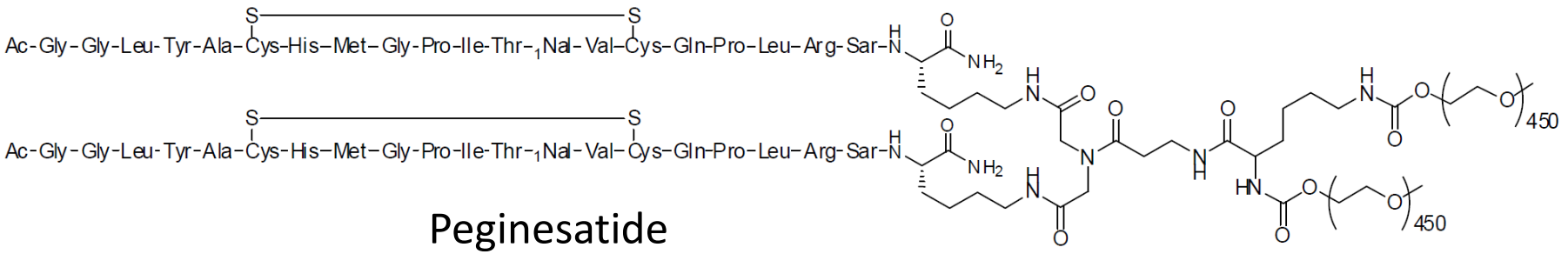


Characterization of Peptide Product

- Analytical characterizations of peptide properties
  - Primary sequence
  - Physico-chemical properties
  - Secondary and high-order structure
  - Oligomer and aggregation states
- Biological evaluations
  - Relevant to peptide's mechanism of action
  - Risk assessment for peptide-related impurities
- Impurity analysis
  - Process impurities
  - Degradation impurities

Primary Sequence and Physico-chemical Properties

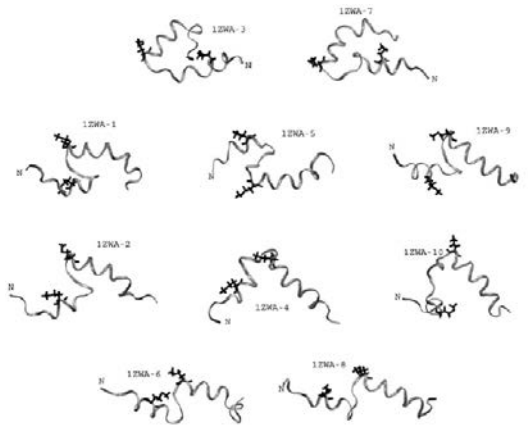
- Primary sequence
  - Amino acid(AA) analysis(chiral AA analysis as appropriate), MS/MS sequencing, peptide mapping, NMR, …
  - Disulfide configuration(s)
  - Structural determination of unnatural amino acids and other modifications
- Physico-chemical
  - Salt form, molecular weight, solubility, isoelectric point, and other spectroscopy properties



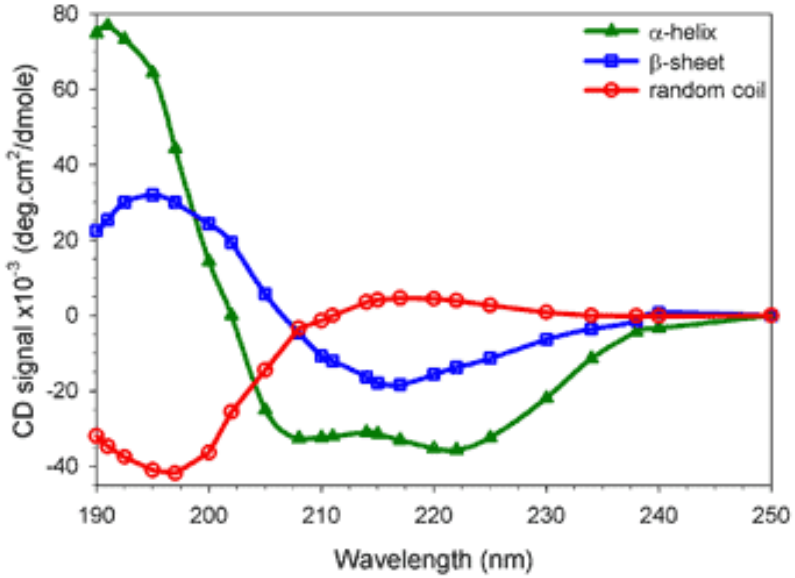
Peginesatide

Secondary and High-order Structure

- Measurement
  - Circular dichroism (CD), fluorescence, FTIR/Raman, 2D NMR, X-ray, …
  - Media: preferable in the drug product formulation
- Stability
  - Kinetic process vs thermodynamically stable

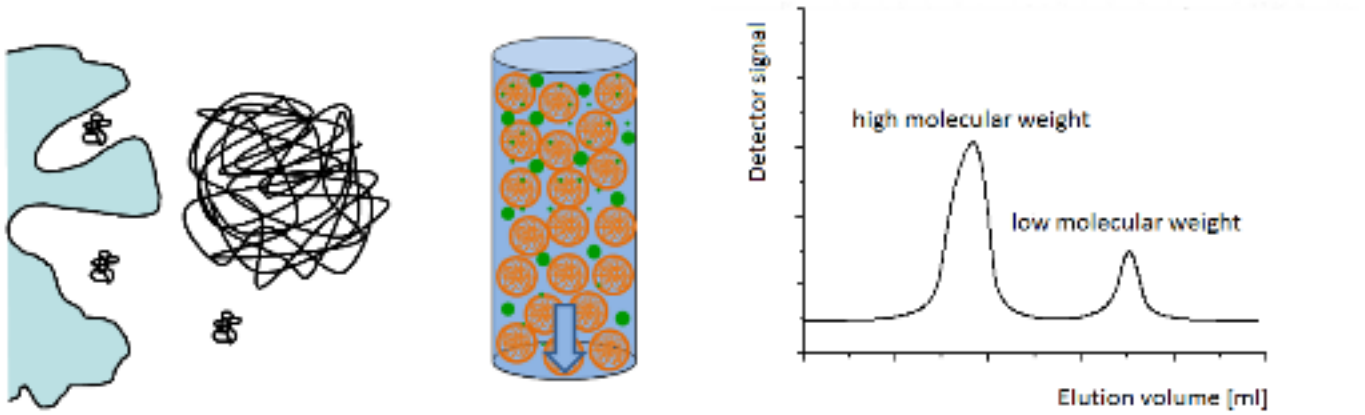


NMR structures of teriparatide
Chu, et al., Biochemistry 43 (2004) 14139.

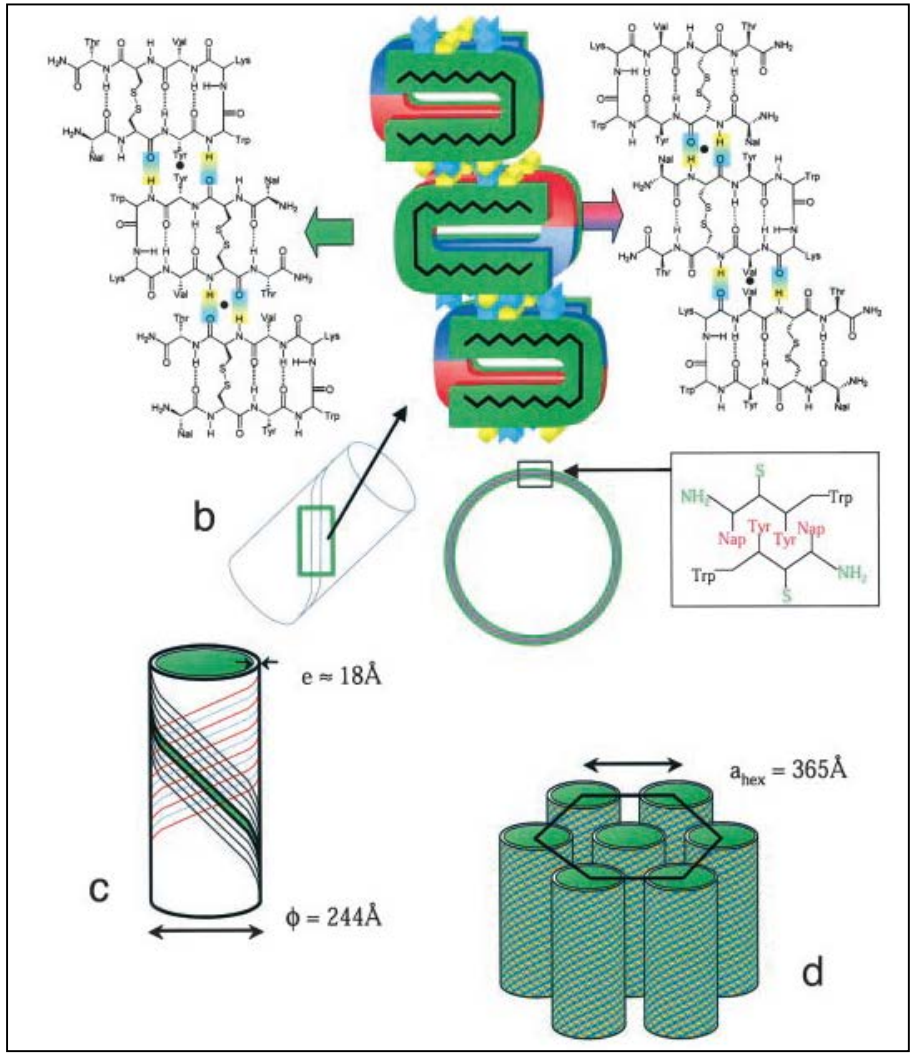


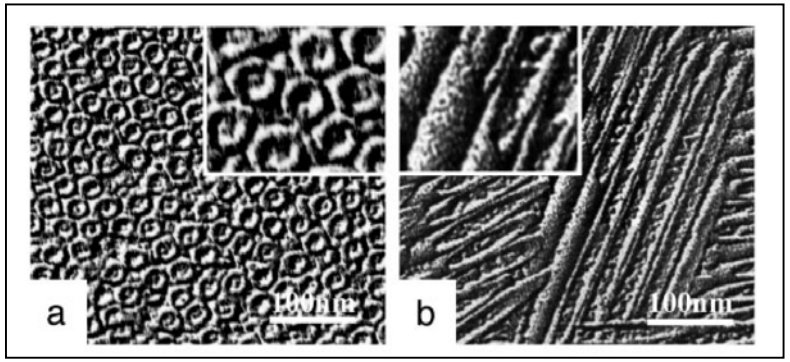
Oligomer and Aggregation States

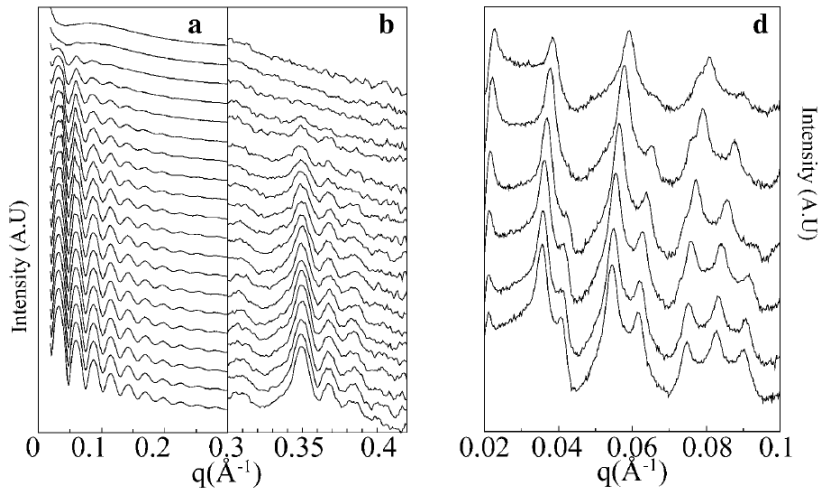
- Measurement
  - Size-exclusive chromatograph (SEC), analytical ultracentrifuge (AUC), particle size measuring methods(e.g., DLS, MASLS, NMR), imagining methods (e.g. Cryo-TEM, AFM), …
- Under stress and stability conditions
  - Freeze-thaw, high temp



Somatulin Depot: Self Assembled Lanreotide Acetate Nanotubes







Cryo-EM & SAXS analysis to demonstrate reversible nanotube structure
PNAS 100(2003) 10258.

Biological Evaluations

- Purpose
  - API identity: relevant to peptide's mechanism of action
  - Potency assay: e.g. Repository Corticotropin Injection (USP)
  - Peptide-related impurities: risk assessment
- Types of assays
  - In vitro binding
  - In vitro functional assays
  - In vivo animal studies

Impurities in Peptide Drug Products

- Process impurities
  - Residual chemicals
  - Peptide-related impurities
  - Host-cell related impurities for recombinant peptides
- Degradation impurities
  - Mostly API related and would be expected to be the same where the RLD and generic have the same API, Q1/Q2 and the same labeled storage conditions

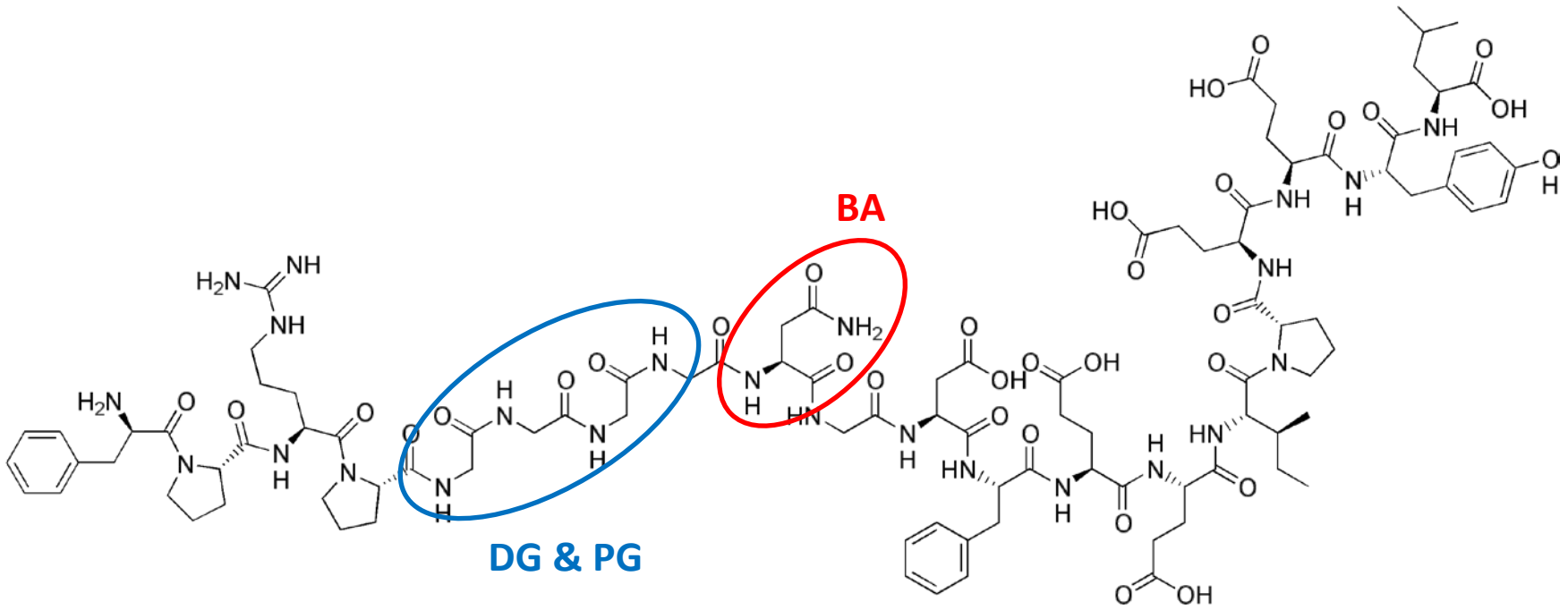
Peptide-related Impurities

Amino acid sequences related to, but different from, the active ingredient, as a result of *insertion*, *deletion*, or other modifications (e.g., *oxidation*, *glycosylation*, *deamidation*, *racemization*) to the amino acid sequence, and residues of the peptide

Example: Peptide-related Impurities

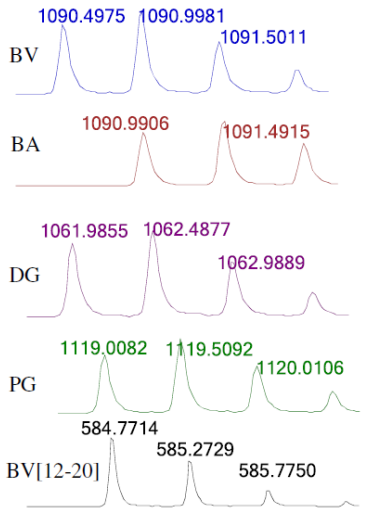
Bivalirudin: 20 amino acid peptide

D-Phe-Pro-Arg-Pro-Gly-Gly-Gly-Gly-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu



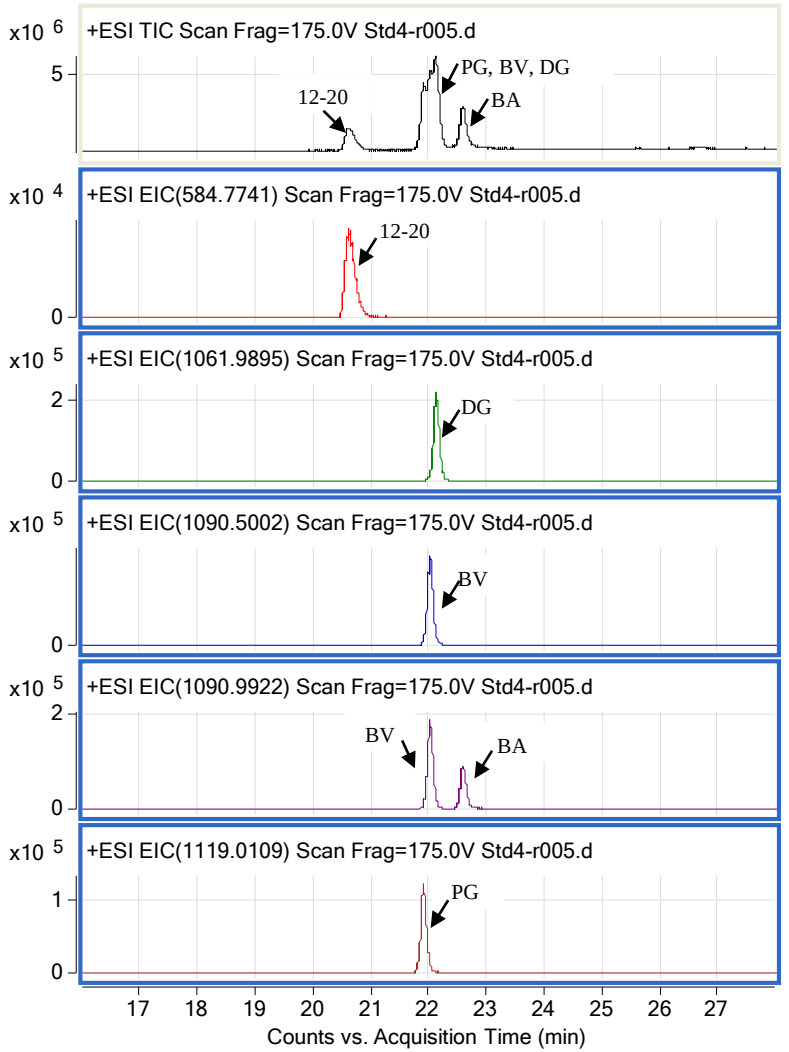
Peptide-related Impurity Analysis (LC-MS)

Bivalirudin: synthetic peptide (20 aa)



Mass-to-charge (m/z) +2 charge states of BV and its related impurities

BA – Beta-aspartic acid-bivalirudin
BV – Bivalirudin
BV[12-20] – 12-20 fragment of bivalirudin
DG – Des-glycine-bivalirudin
PG – Plus-glycine-bivalirudin



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

Summary: Impurity Profiling using LC-MS

- LC-MS analysis is capable of detecting and quantifying peptide impurities below 0.10%
- LC-MS method needs to be validated
  - Guidance for Industry: Analytical Procedures and Methods Validation for Drugs and Biologics (July, 2015)
- Orthogonal LC-MS methods (ex. different columns, different MS instruments) and experiments (top down, bottom up) may be used to verify the results
- Impurity profiles from multiple lots of the RLDs, throughout the product's shelf life, should be evaluated

Considerations for Peptide-related Impurities

- Better control in manufacturing and purification process
  - Fine-tune manufacturing process, alternative purification method, …
- High-resolution analytical method under different conditions
  - Determine identity and quantity if possible
- Justifications
  - Impacts on drug product properties
  - Impacts on bioactivities
  - Any safety concerns (e.g., immunogenicity)

Host-cell Related Impurities

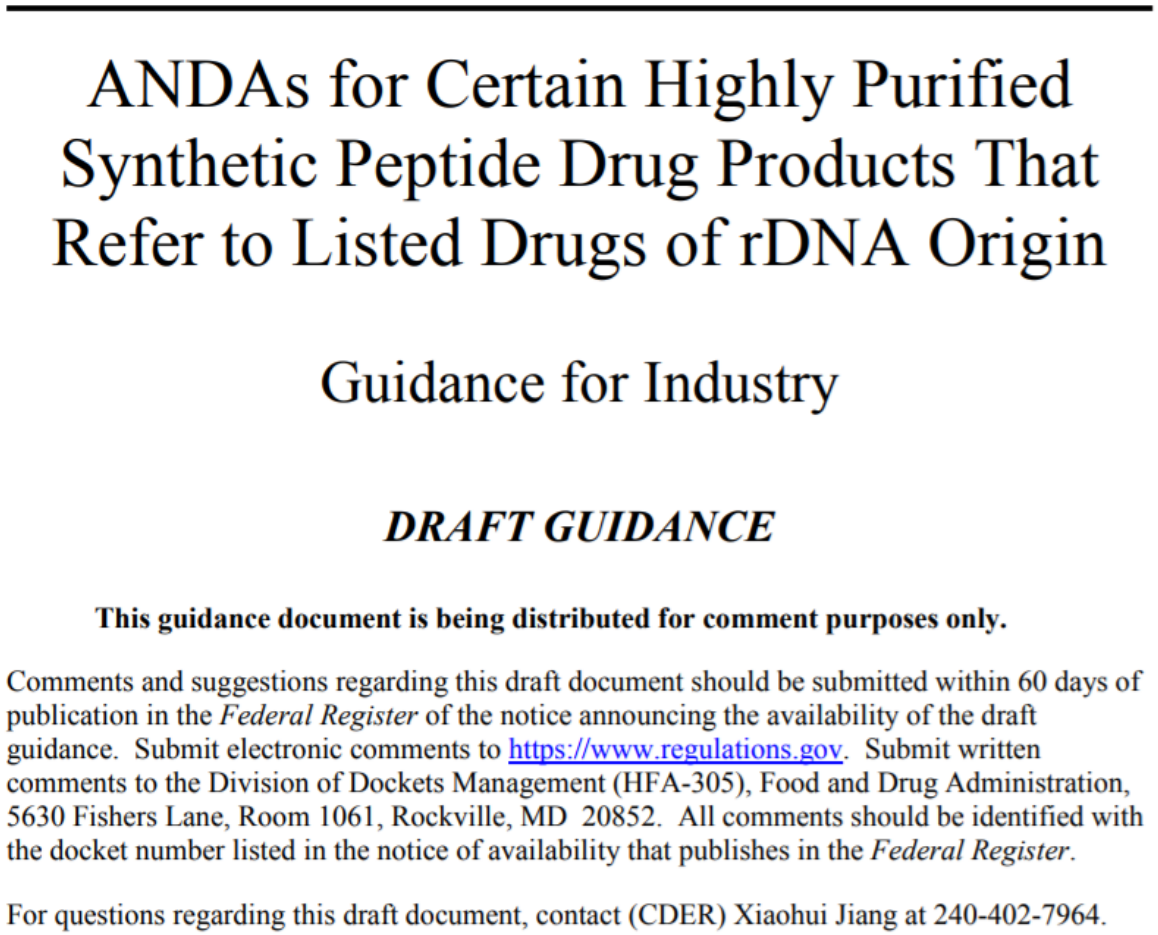
Host-cell protein (HCP) is an important process related impurity produced by host organisms used to produce recombinant peptides.

- HCPs are considered as critical quality attributes (CQAs), and their associated risks may include:
  - Impact safety and efficacy of a drug product
  - Affect immunogenicity
  - Have other biological activities
  - Impact drug product stability
- HCPs are removed to the lowest feasible extent, and their levels are monitored in process and at release
- Low ppm-level HCPs are typically present in a peptide drug substance and drug product following purification processes

HCP Characterization Methods

Method	Strength	Weakness
SDS-PAGE/Silver stain	➢ Good sensitivity (100pg/band) ➢ Resolves multiple components	➢ Subjective interpretation ➢ Not quantitative ➢ Technique-dependent
HPLC/UV-fluorescent	➢ High resolution ➢ Quantitative	➢ Subjective interpretation ➢ Low sensitivity ➢ Non-specific
Western blot	➢ High sensitivity (0.1-1ng/band) ➢ Semi-quantitative ➢ Immunological identity ➢ Resolves multiple components	➢ Antibody may fail to detect some contaminants ➢ Technique-dependent
ELISA (gold standard)	➢ High sensitivity (1ppm) ➢ Semi-quantitative ➢ Easy to perform	➢ Objective endpoint ➢ Summed value ➢ Bias toward only immunoreactive species ➢ Not transferable (process related)
LC-MS/MS (in developing)	➢ Identification of individual HCPs ➢ High sensitivity (1ppm) ➢ Quantitative ➢ Process transferable ➢ Useful info for risk assessment	➢ Potential bias towards high abundant species ➢ Technique dependent ➢ Instrument high maintenance

FDA Guidance on Synthetic Generic Peptides Referencing NDA Peptides of rDNA Origin



ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Xiaohui Jiang at 240-402-7964.

Specific recommendations for synthetic peptides referencing:

Glucagon

Liraglutide

Nesiritide

Teriparatide

Teduglutide

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM578365.pdf

Peptide-related Impurities and Submission of an ANDA

- For specified impurities common to a proposed synthetic peptide and RLD
  - Level in Test ≤ RLD
- For any specified impurities unique in the proposed generic
  - > 0.5% is not acceptable
  - Impurities at 0.1% - 0.5% of drug substance should be identified
  - For impurities at 0.1% - 0.5%, characterize and justify impurity doesn't affecting the safety or efficacy

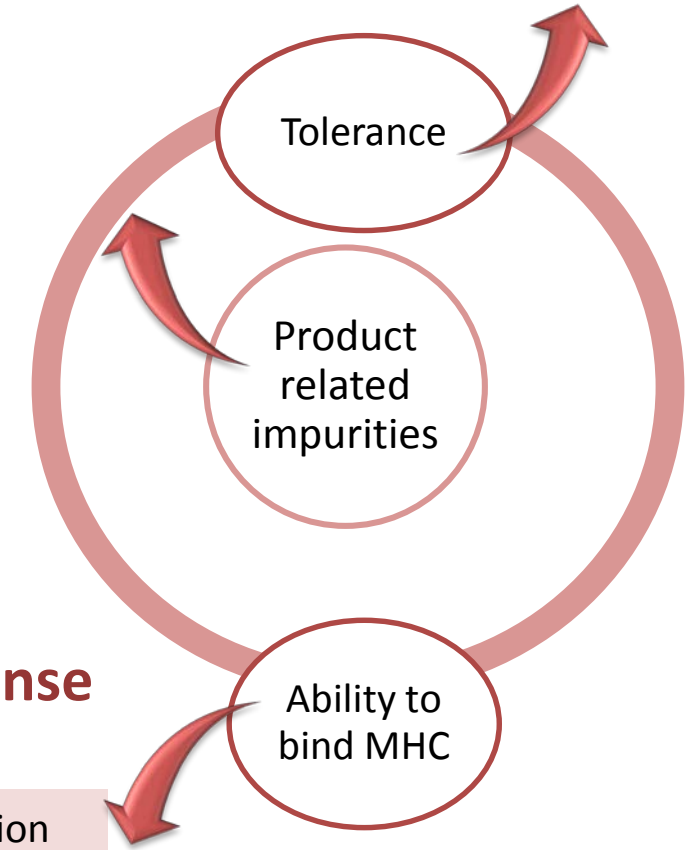
Immunogenicity May Impact Drug Product's Safety and Efficacy

- Developing antibodies
  - Affect the PK by enhancing clearance or delay clearance
  - Neutralizing antibodies can diminish efficacy
  - Anti-drug antibodies (ADA) may cross-react to endogenous proteins, and may cause deficiency syndrome

- Hypersensitivity responses
  - Cytokine Release Syndrome: rapid release of proinflammatory cytokines
  - Anaphylaxis: serious, acute allergic reactions

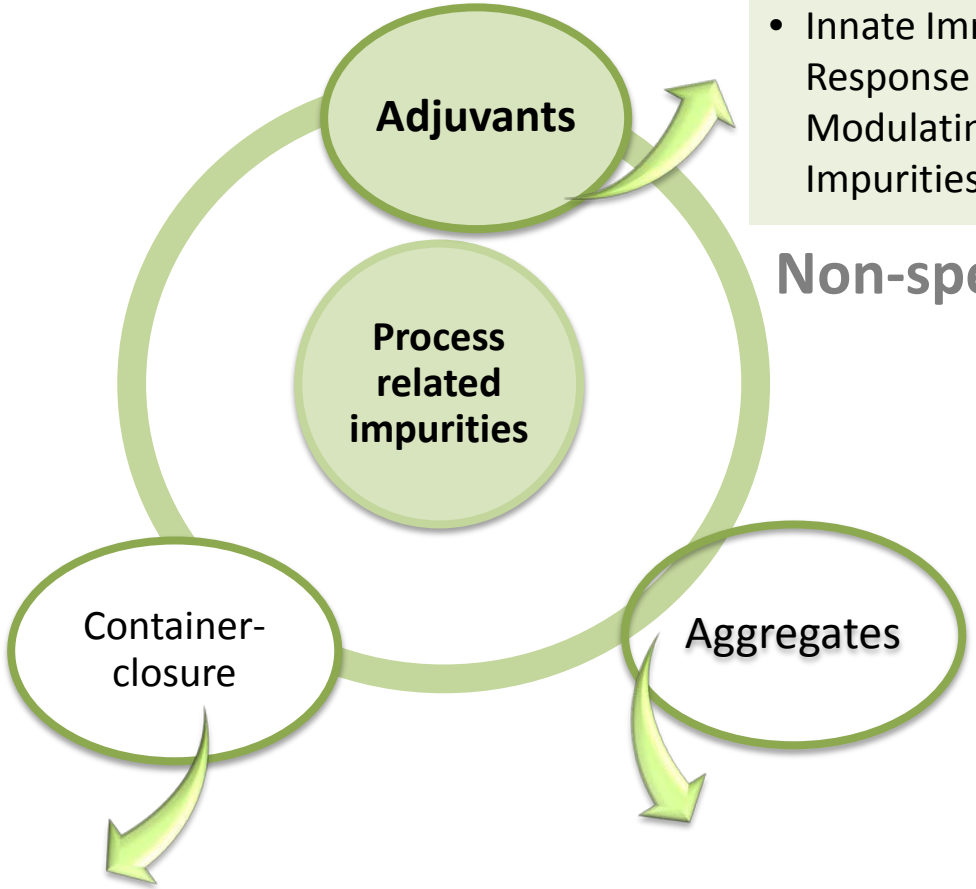
Refer to Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products (Aug 2014)

Immune-response from Impurities of Peptide Drug Product



Specific Response

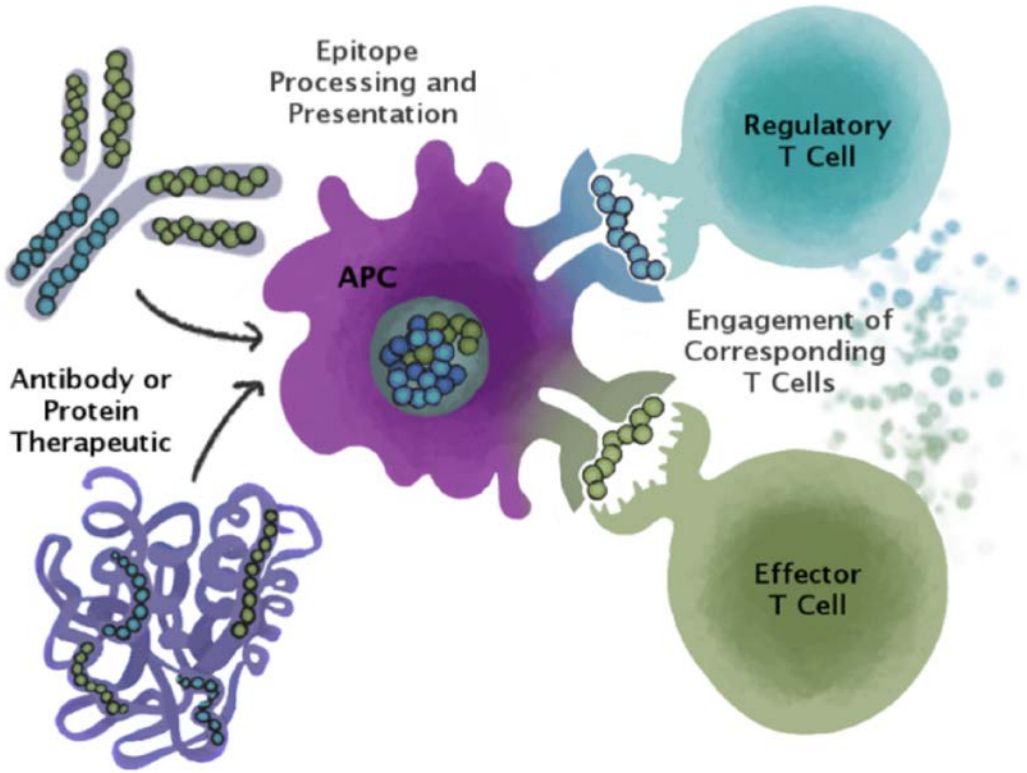
- T cell activation
- Specific amino acid sequences and length



- Innate Immune Response Modulating Impurities (IIRM)

Non-specific Response

Activation of T Cell

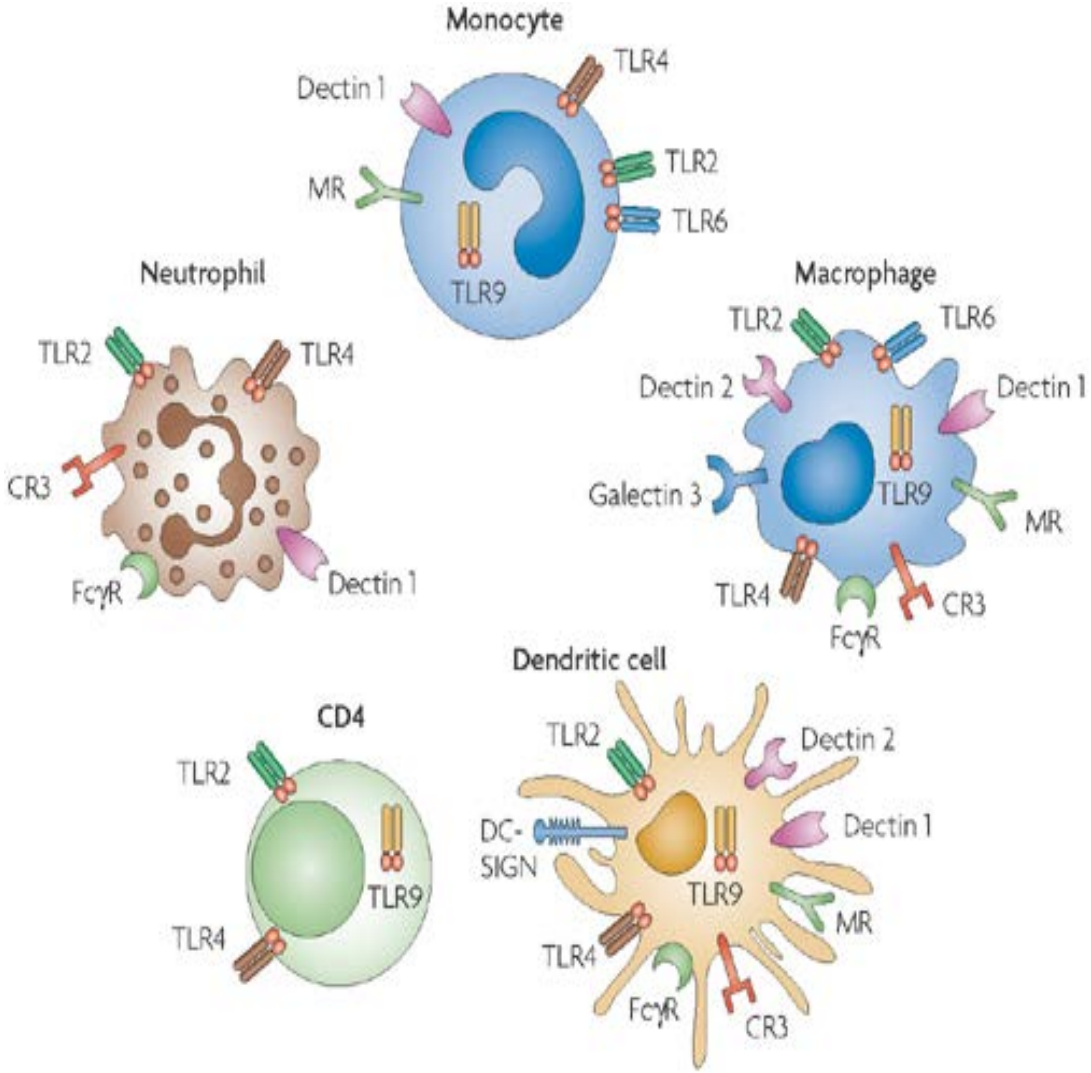


De Groot A.S., et al., Activation of Natural Regulatory T cells by IgG Fc-derived Peptide "Tregitopes". Blood, 2008,112: 3303. http://tinyurl.com/ASDeGroot-Blood-2008

- >4000 MHC combinations
- MHC* I: 8-9 AA
- MHC II: 11-17 AA, more flexible

*MHC: Major Histocompatibility Complex

Innate Immune Receptors (PRR) Can Recognize Process Related Impurities



- Macrophages and dendritic cells have the most PRR
- Different cells types have different PRR
- Non-immune cells also have PRR

Suggestions on Evaluating Risks of Immunogenicity in a Peptide Drug Product

- T cell activation assessment using specific peptide sequence
  - In silico model based prediction
  - In vitro HLA binding assays
  - In vitro functional assays (e.g., using isolated human PBMCs)
- Innate immune activity assessment using peptide drug product
  - In vitro cell-based assays
- Clinical immunogenicity studies with peptide drug product
  - Gold standard
  - Repeat dosing and monitor ADA among other endpoints

Acknowledgement

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- Eric Pang
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- Jane Chang
- Bing Cai
- Andre Raw

Questions?


FDA
U.S. FOOD & DRUG
ADMINISTRATION