Challenges and Opportunities for Innovation in Complex Generic Drug Product Development

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Disclaimer

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

Outline

- Regulatory pathways for New Drug Application(NDA) and Abbreviated New Drug Application (ANDA), and equivalence concepts
- Challenges for complex generic drug products
  - Bioequivalence and formulation considerations for complex generics
- Considerations for generic peptide products

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 references a listed drug; 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 refer to a listed drug (i.e., a reference listed drug (RLD)), contain information to demonstrate therapeutic equivalence, and may not be submitted if studies are necessary to establish the safety or effectiveness of the proposed drug product

Equivalence Concepts

- **Pharmaceutical Equivalence (PE)**
  - Same active ingredient(s) and
  - Same dosage form and
  - Same route of administration and
  - Same strength and more …
- **Bioequivalence (BE)**
  - No significant difference in rate and extent of the active ingredient at the site of action
- **Therapeutic Equivalence (TE) of Generic Products**
  - Generics must demonstrate PE and BE to the RLD
  - Generics rely on the safety and efficacy of the RLD
  - TE products can be substituted freely

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

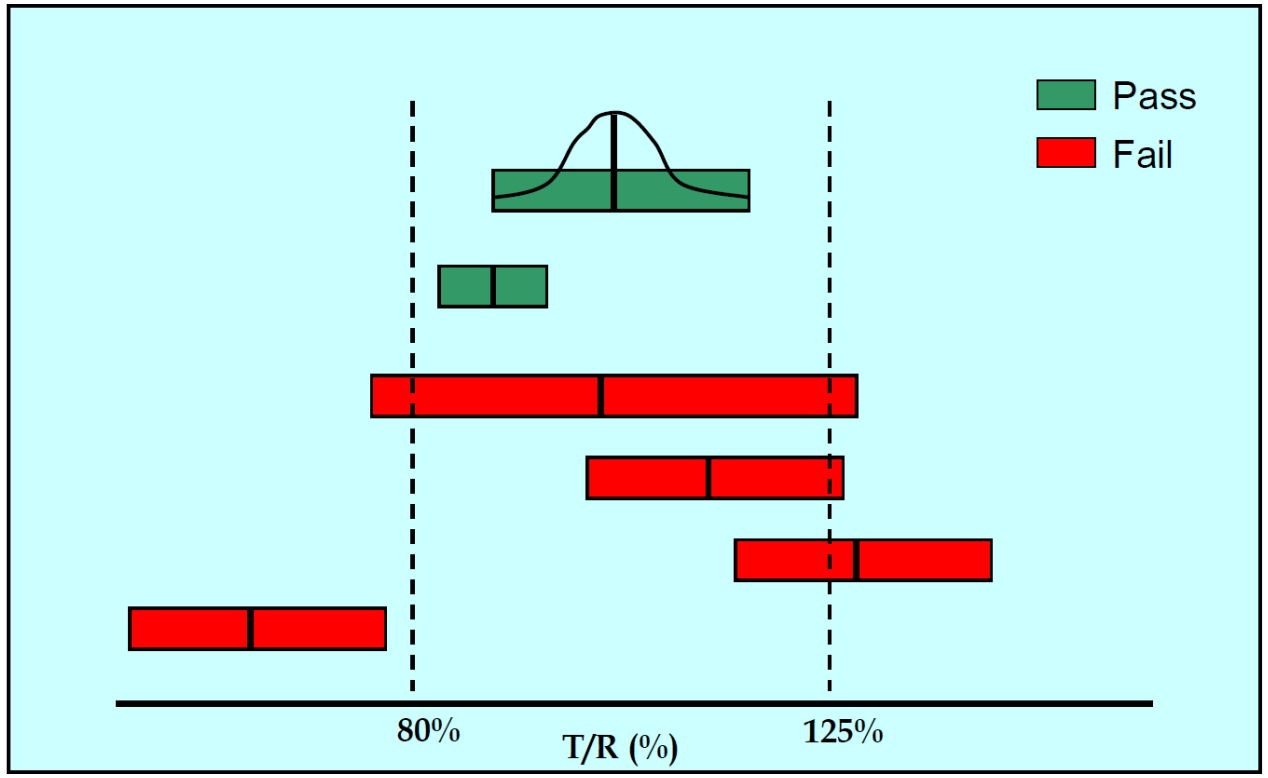
NDA	ANDA
1. Chemistry, Manufacturing & Controls (CMC)	1. Chemistry, Manufacturing & Controls (CMC)
2. Testing	2. Testing
3. Labeling	3. Labeling
4. Inspection	4. Inspection
5. Animal Studies	
6. Bioavailability	5. Bioequivalence
7. Clinical Studies	

What is Bioequivalence?

- ***Bioequivalence*** is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study … …

21 CFR 314.3

An Example of Bioequivalence



AUC and Cmax of T/R: 90% Confidence Intervals (CI) must fit between 80% - 125%

T = average of Test drug product

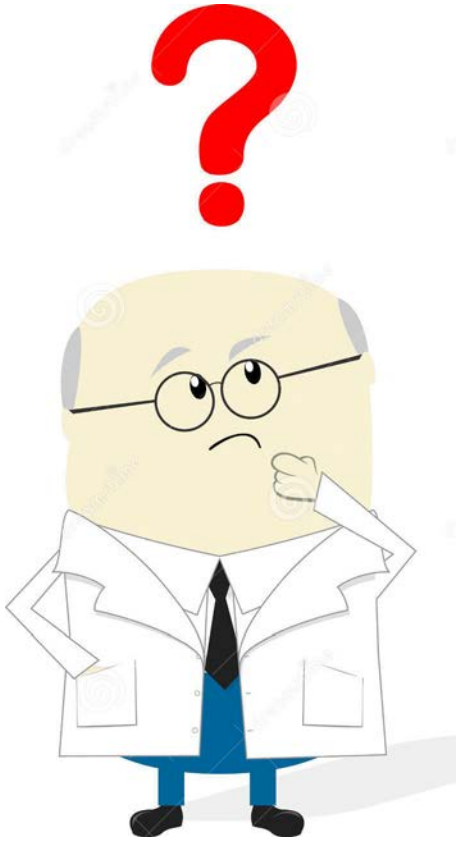
R = average of Reference drug product

Complex Products under GDUFA II

- Complex active ingredients
  - E.g., Complex mixtures of APIs, polymeric compounds, peptides
- Complex formulations
  - E.g., Liposomes, suspensions, emulsions, gels
- Complex routes of delivery
  - E.g., Locally acting such as ophthalmic, otic, dermatological and inhalational drugs
- Complex dosage forms
  - E.g., Long acting injectables and implantables
- Complex drug-device combinations
  - E.g., Metered Dose Inhalers and transdermals
- Other products where complexity or uncertainty concerning the approval pathway or other alternative approach would benefit from early scientific engagement

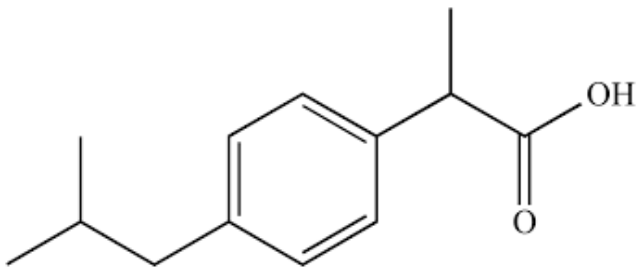
https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

Equivalence Determination
“Simple” vs “Complex”



Traditional Approach for Establishing Equivalence of an ANDA

- Active ingredient sameness — API characterizations
- Pharmaceutical equivalence — Same dosage forms …
- Bioequivalence — PK study …



Challenges for Complex Generics

- Active ingredient sameness
  - Characterizing mixture of APIs
- Pharmaceutical equivalence
  - Characterizing complex formulation
  - Comparing inactive ingredients if needed*
  - Comparing impurities if needed
- Bioequivalence
  - Locally acting …

➢ Same clinical effect and safety profile

How to demonstrate inactive ingredients, impurities and other allowed differences in a proposed drug product do not affect its safety or efficacy???

* If required under 21 CFR 314.94(a)(9) or recommended by a product specific guidance

CFR Requirements on Generic Formulations

Section 314.94 Content and format of an abbreviated applicant

- (a)(9) Chemistry, manufacturing, and controls

➢ (ii) Inactive ingredients. Unless otherwise stated in paragraphs (a)(9)(iii) through (a)(9)(v) of this section, an applicant must identify and characterize the inactive ingredients in the proposed drug product and provide information demonstrating that such inactive ingredients do not affect the safety or efficacy of the proposed drug product.

➢ (iii)–(v) Specific inactive ingredient requirements for parenteral, ophthalmic, otic, and topical drug products, and differences permitted for such products

Q1/Q2 Requirement for Generic Parenteral 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 must contain the same inactive ingredients (Q1) and in the same concentration (Q2) as the reference listed drug**.

However, 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.

Q1/Q2 Requirement for Generic Ophthalmic/Otic Products

21 CFR 314.94 (a)(9)(iv) – *Inactive ingredient changes permitted in drug products intended for ophthalmic or otic use.*

Generally, **a drug product intended for ophthalmic or otic use must contain the same inactive ingredients (Q1) and in the same concentration (Q2) as the reference listed drug**.

However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or substance to adjust tonicity, or thickening agent 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 … …

Q1/Q2 Requirement for Generic Topical Products

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

Generally, **a drug product intended for topical use, solutions for aerosolization or nebulization, and nasal solutions shall contain the same inactive ingredients (Q1) as the reference listed drug**.

However, an ANDA may include different inactive ingredients 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.

Q1/Q2 Assessments

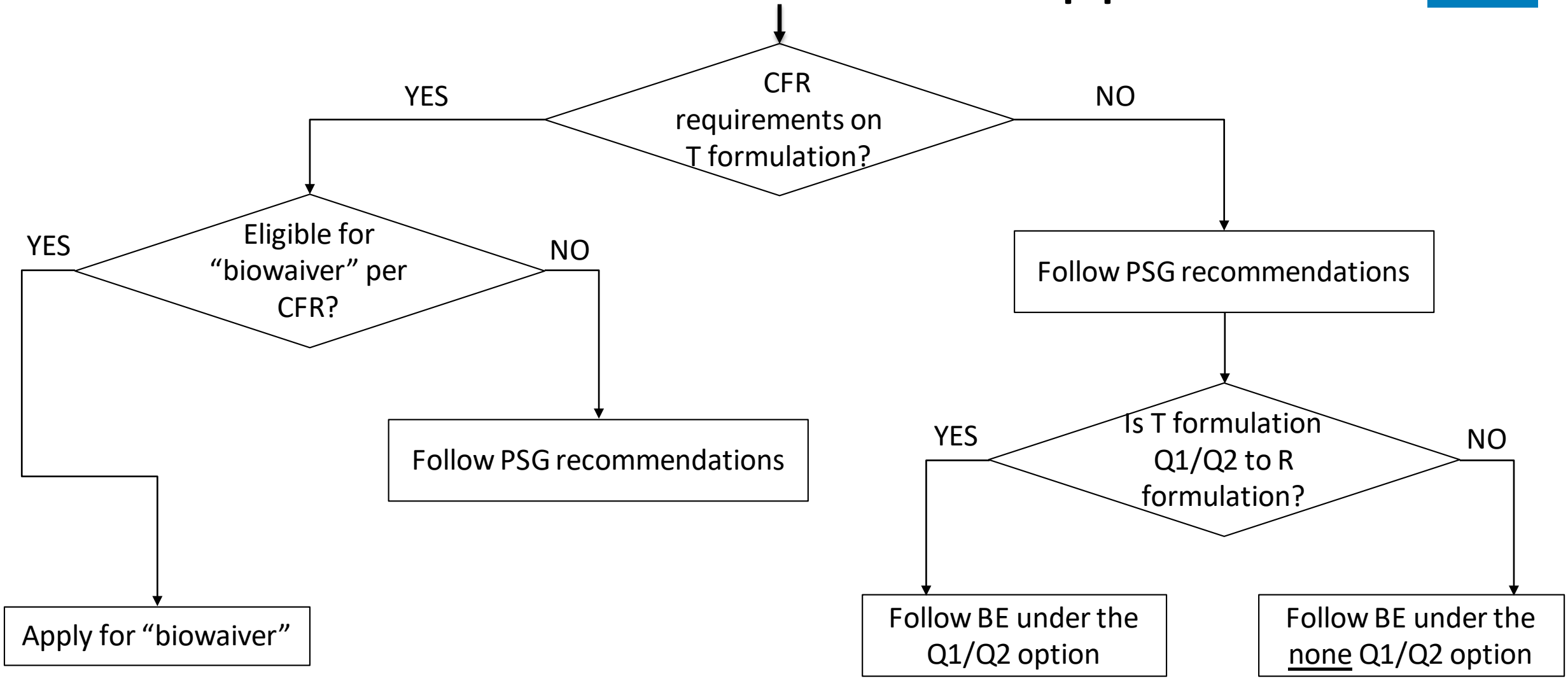
- Q1: identity of an inactive ingredient. An applicant should provide detailed information on the chemistry and grade of each inactive ingredient, and characterization data, if needed for inactive ingredients.
- Q2: determine the difference (%) of an inactive ingredient in the Test (T) and Reference (R) products (i.e., [(T-R)/R] x100). The difference should not exceed 5%.

Bioequivalence Approaches

- In vivo PK study or a correlated in vitro study
- In vivo urine study
- In vivo PD study
- In vivo comparative clinical endpoint BE study
- In vitro test acceptable to FDA (usually dissolution rate test)
- Any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence

21 CFR 320.24(b)

Formulation Variations and BE Approaches



T: Test Product R: Reference Product

Current Status of Peptide Drugs

- World-wide approvals: 80+
- Advantages:
  - Exceptional specificity and high potency
  - Low toxicity and side effects, well-tolerated
  - Established manufacturing process, and suitability for engineering
- Disadvantages:
  - Susceptible to proteases and poor absorption across GI membranes
  - Labile and need low temperature storage
- Dosage forms:
  - Solution injection: most of peptide drug products on market
  - Long-acting injectable: PLGA microspheres (e.g., leuprolide, exenatide)
  - Oral capsules and tablets: linaclotide and plecanatide (local GI acting)

Recent Peptide Drug Approvals by US FDA

Approval date	Generic name	Brand name	Indication	Manufacture method	No. of AA
2005	Exenatide	Byetta	Type 2 Diabetes Mellitus	synthetic	39
2007	Pramlintide	Symlin	Type 1 or type 2 diabetes	synthetic	37
2007	Lanreotide	Somatuline	Gastroenteropancreatic Neuroendocrine Tumors	synthetic	8
2008	Teriparatide	Forteo	Osteoporosis	recombinant	34
2008	Degarelix	Firmagon	Treatment of advanced prostate cancer	synthetic	10
2010	Liraglutide	Victoza	Improve glycemic control (type2 diabetes)	recombinant	31
2012	Linaclotide	Linzess	Irritable Bowel Syndrome with IBS-C and CIC	synthetic	14
2012	Teduglutide	Gattex	Short Bowel Syndrome (SBS)	recombinant	33
2014	Vasopressin	Vasostrict	Increase blood pressure in adults with vasodilatory shock	synthetic	9
2016	Lixisenatide	Adlyxin	To improve glycemic control	synthetic	44
2017	Plecanatide	Trulance	To treat Chronic Idiopathic Constipation	synthetic	16
2017	Etelcalcetide	Parsabiv	To treat secondary hyperparathyroidism with CKD	synthetic	8
2017	Semaglutide	Ozempic	Improve glycemic control (type2 diabetes)	recombinant	29

Drug Products vs. Biological Products

- Federal Food Drug and Cosmetic Act (FD&C Act)
  - Giving 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 definition
  - 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) Transition 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 fully convert to BLAs
  - **After March 23, 2020**: Pending NDAs may not be approved; **There will not be an RLD for an ANDA or 505(b)(2) to reference**

“Biowaiver” for Peptide Products

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

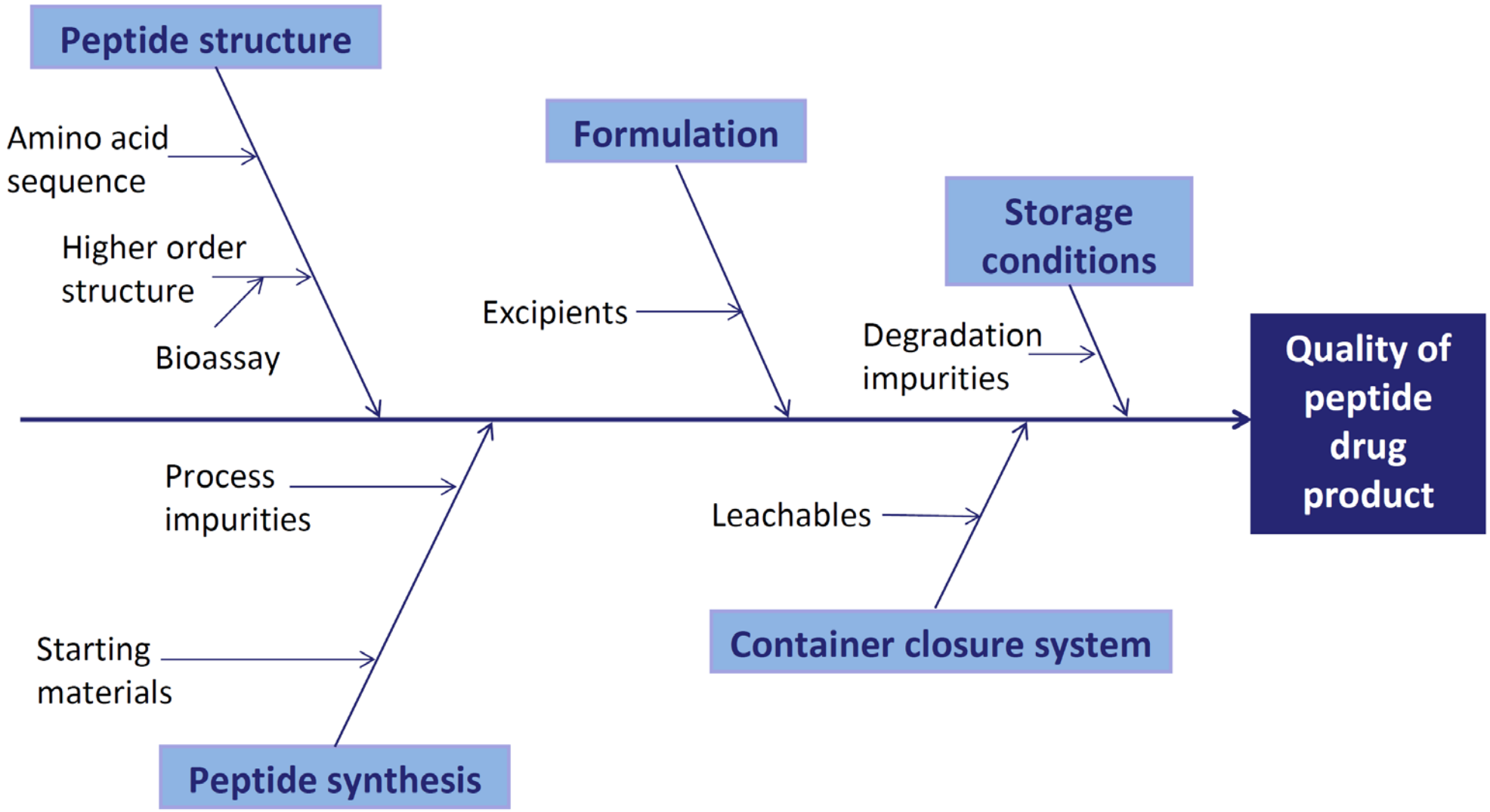
  “A drug product's in vivo bioavailability or bioequivalence may be considered ***self-evident*** …”

  (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”

How to Ensure Quality of Peptide Drugs

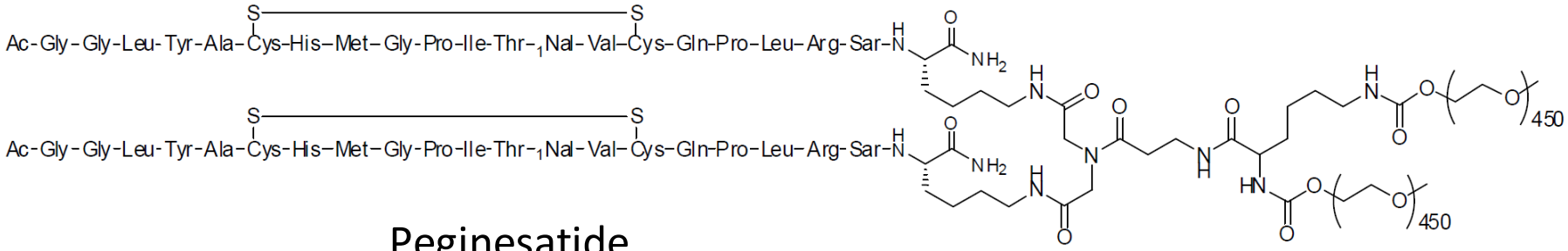


Characterization of Peptide Product

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

Primary Sequence and Physico-chemical Properties

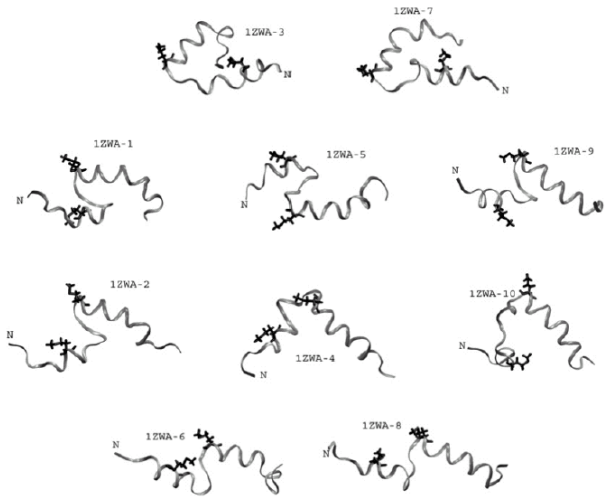
- Primary sequence:
  - Amino acid (AA) analysis (chiral AA analysis as appropriate), MS/MS sequencing, peptide mapping, NMR, …
  - Disulfide configuration(s)
  - Structural determination of unnatural amino acids and other modifications
- Physico-chemical:
  - Salt form, molecular weight, solubility,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



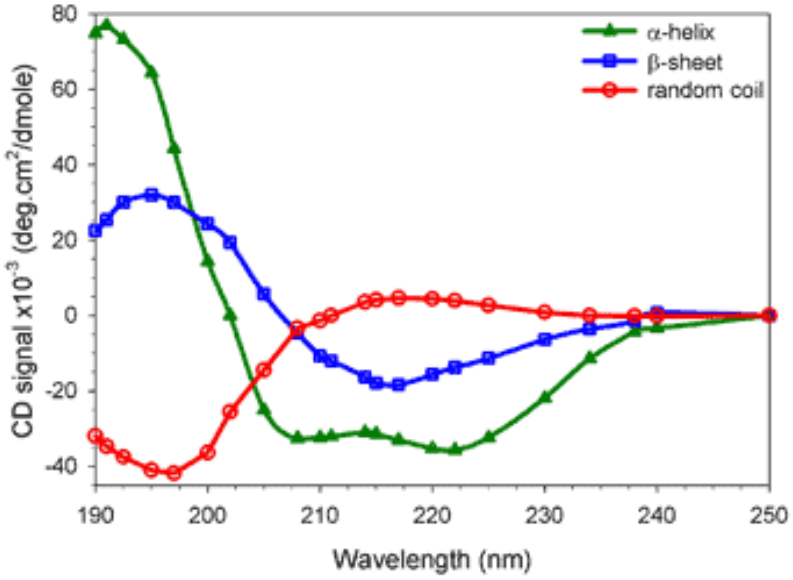
Peginesatide

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

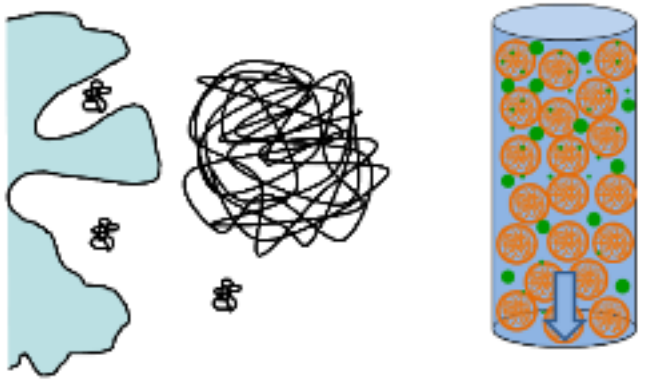


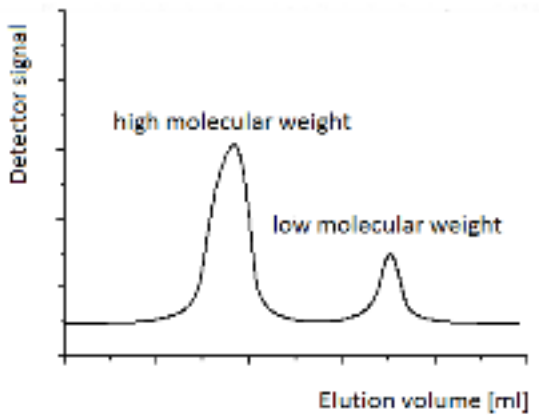
NMR structures of teriparatide
Chu, et al., Biochemistry 43 (2004) 14139.



Oligomer and Aggregation States

- Measurement:
  - Size-exclusion chromatography (SEC), analytical ultracentrifugation (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





Impurities in Peptide Drug Products

- Process impurities
  - Residual chemicals
  - Peptide-related impurities
  - Host-cell related impurities for recombinant peptides
- Degradation impurities
  - Peptide-related impurities

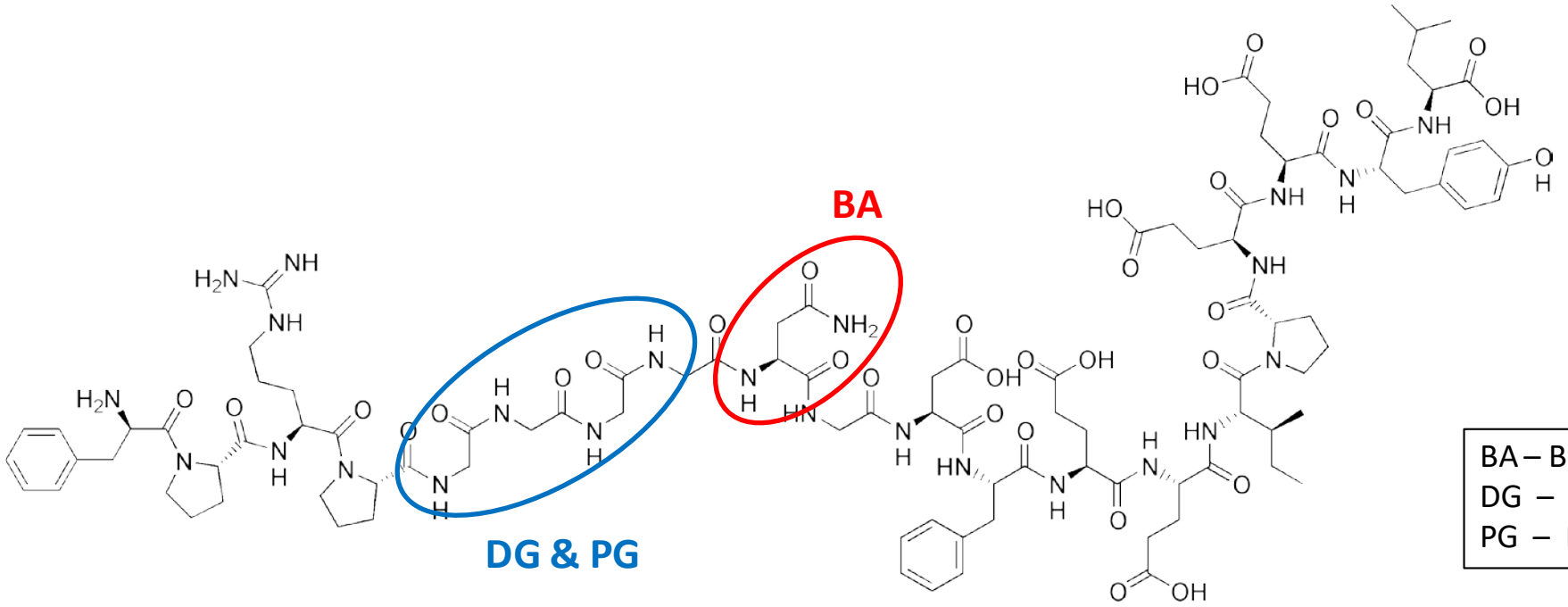
Peptide-related Impurities

Amino acid sequences related to, but different from, the active ingredient, as a result of *insertion*, *deletion*, *truncation* and 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

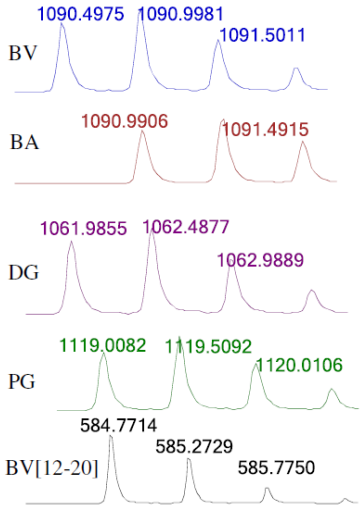
D-Phe-Pro-Arg-Pro-Gly-Gly-Gly-Gly-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu



BA – Beta-aspartic acid-bivalirudin
DG – Des-glycine-bivalirudin
PG – Plus-glycine-bivalirudin

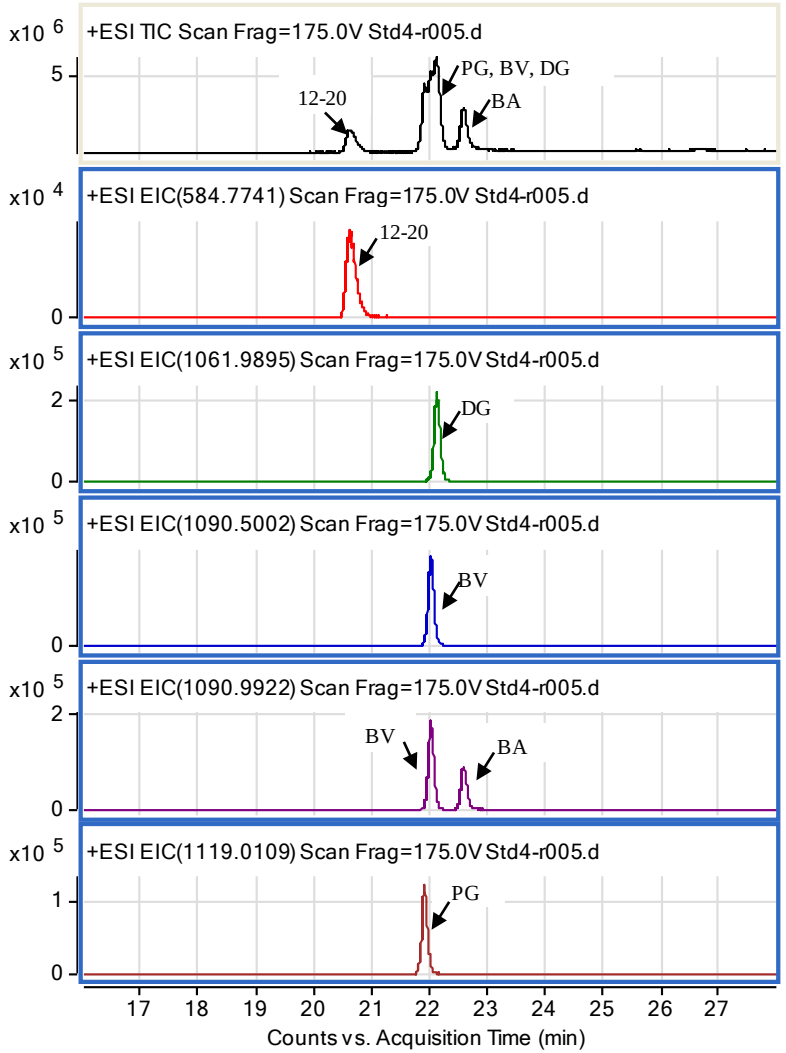
Peptide-related Impurity Analysis

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.

Considerations for Peptide-related Impurities

- Better control in manufacturing and purification process
  - Different coupling strategies, 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*.

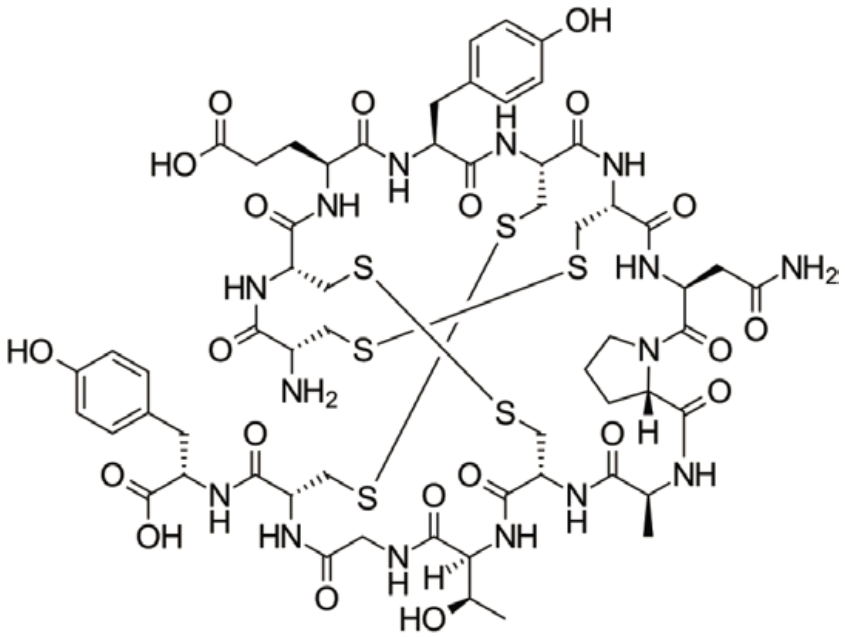
For questions regarding this draft document, contact (CDER) Xiaohui Jiang at 240-402-7964.

Biological Evaluations

- Purpose
  - Active ingredient bio-identity: relevant to peptide's mechanism of action
  - Potency assay: currently for Repository Corticotropin Injection (USP) only
  - Peptide-related impurities: risk assessment
- Types of assays
  - In vitro binding
  - In vitro functional assays
  - In vivo animal studies

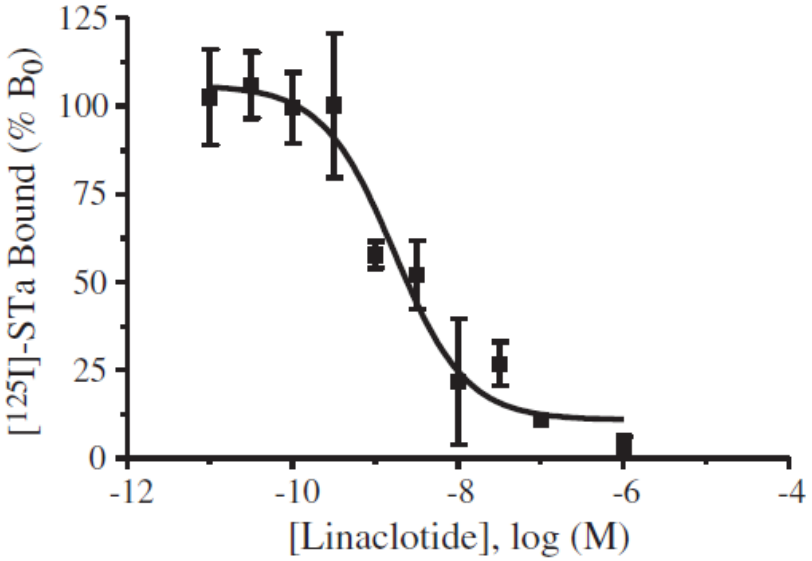
Example : Linaclotide (1)

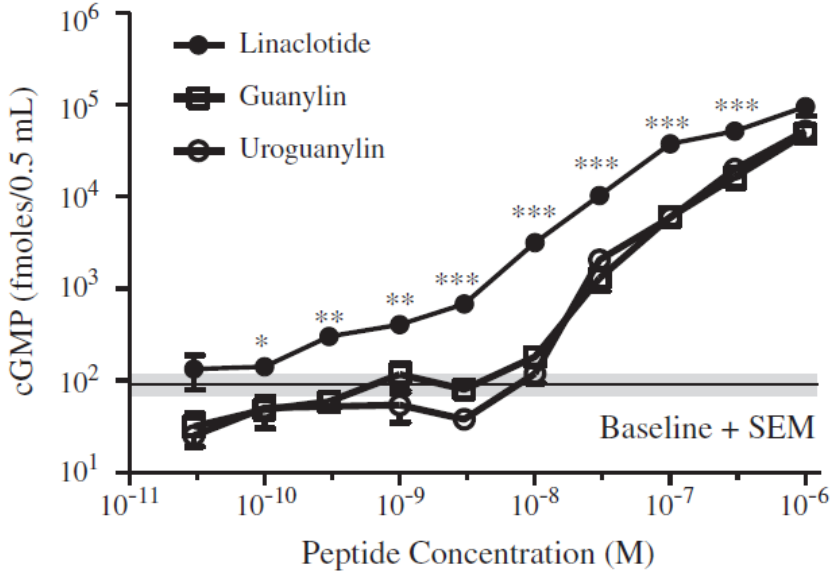
- Linaclotide, oral capsules
- Indications: irritable bowel syndrome with constipation and chronic idiopathic constipation
- 14 amino acid peptide



Example : Bioassay of Linaclotide (2)

- Mechanism of action: Guanylate cyclase type C (GC-C) agonist
- Binding and functional assays available

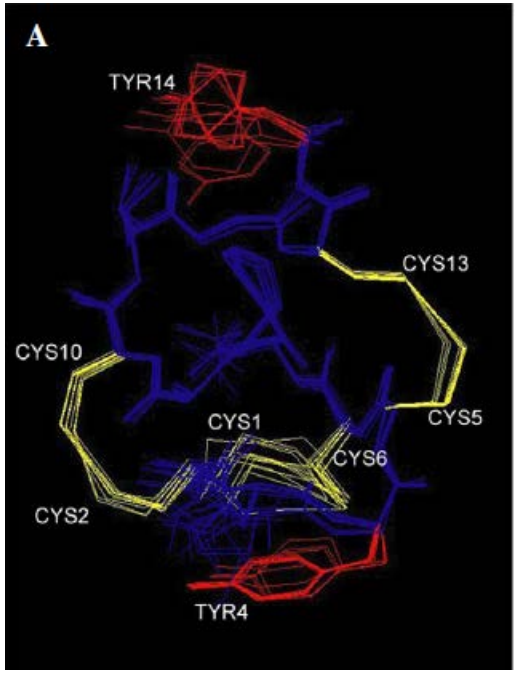


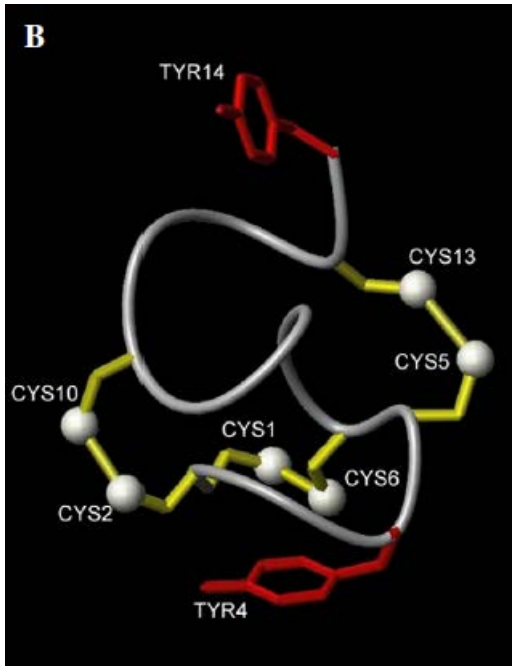


European Journal of Pharmacology 649 (2010) 328–335

Example : Bioassay of Linaclotide (3)

- 15 possible isomers due to disulfide configurations
- Bioassay can be used for bio-identity and impurity justification





European Journal of Pharmacology 649 (2010) 328–335

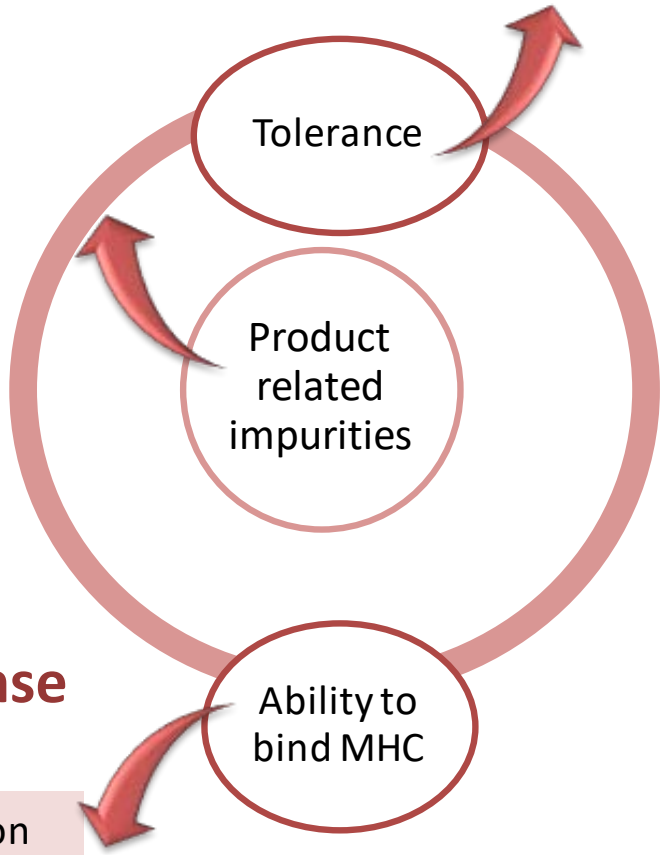
Immunogenicity May Impact Drug Product's Safety and Efficacy

- 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

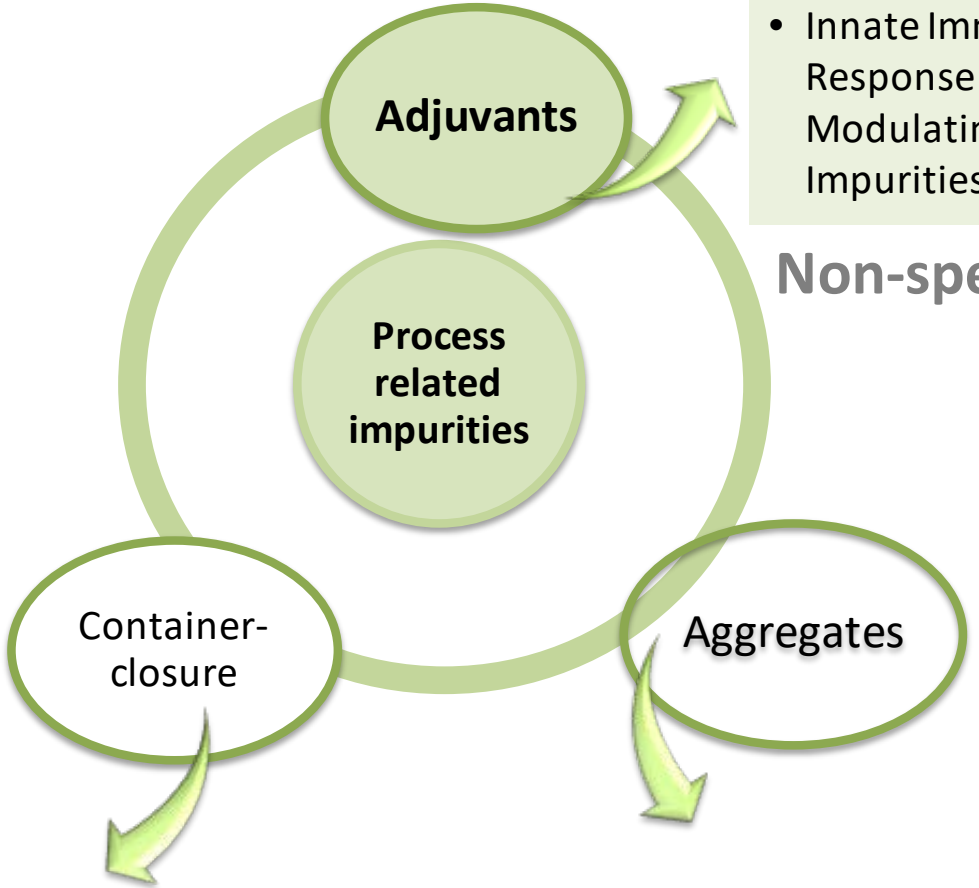
Refer to Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products (Aug 2014)

Immune-response from Impurities of Peptide Drug Product



Specific Response

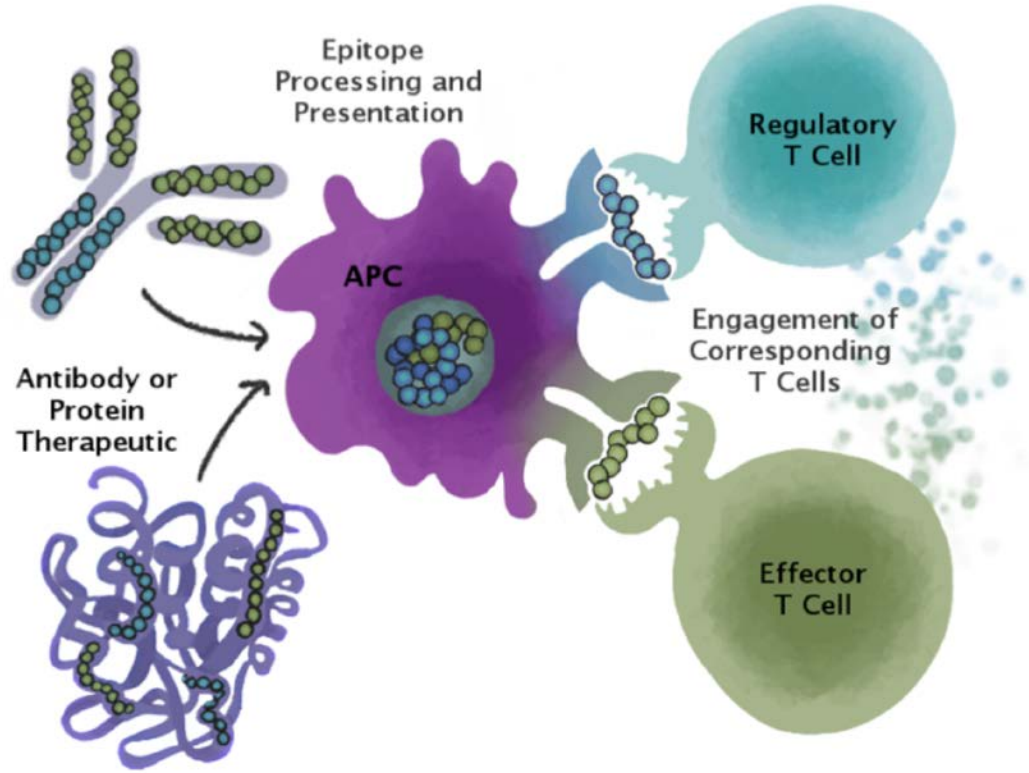
- T cell activation
- Specific amino acid sequences and length



- Innate Immune Response Modulating Impurities (IIRM)

Non-specific Response

Activation of T Cell

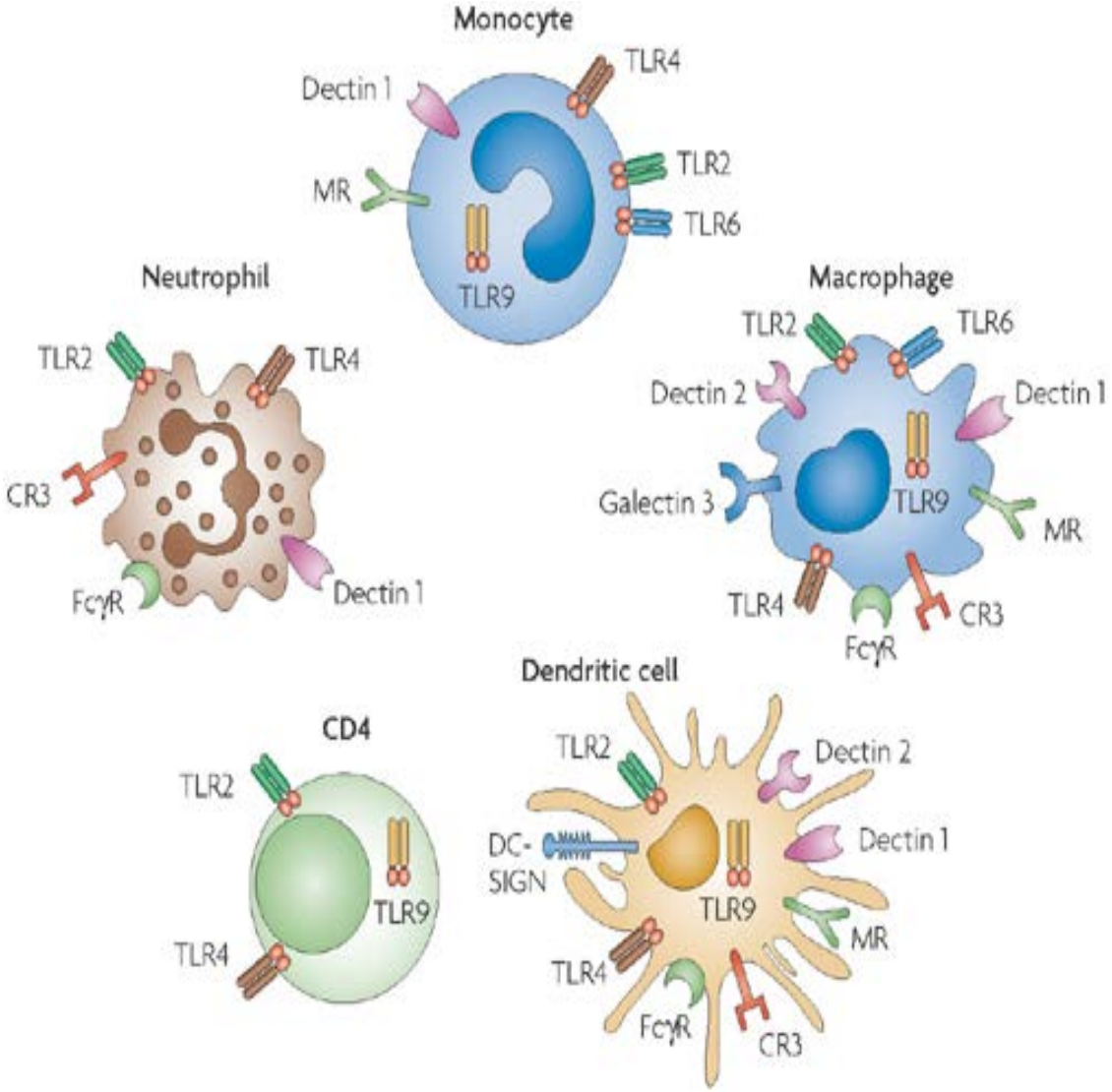


De Groot A.S., et al., Activation of Natural Regulatory T cells by IgG Fc-derived Peptide "Tregitopes". Blood, 2008,112: 3303. http://tinyurl.com/ASDeGroot-Blood-2008

- >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

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 assay
  - In vitro functional assay 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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    - Team of parenteral, ophthalmic, otic and implant products
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Questions?


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