Follow up Discussion on FDA Peptide Guidance after Public Comments

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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.

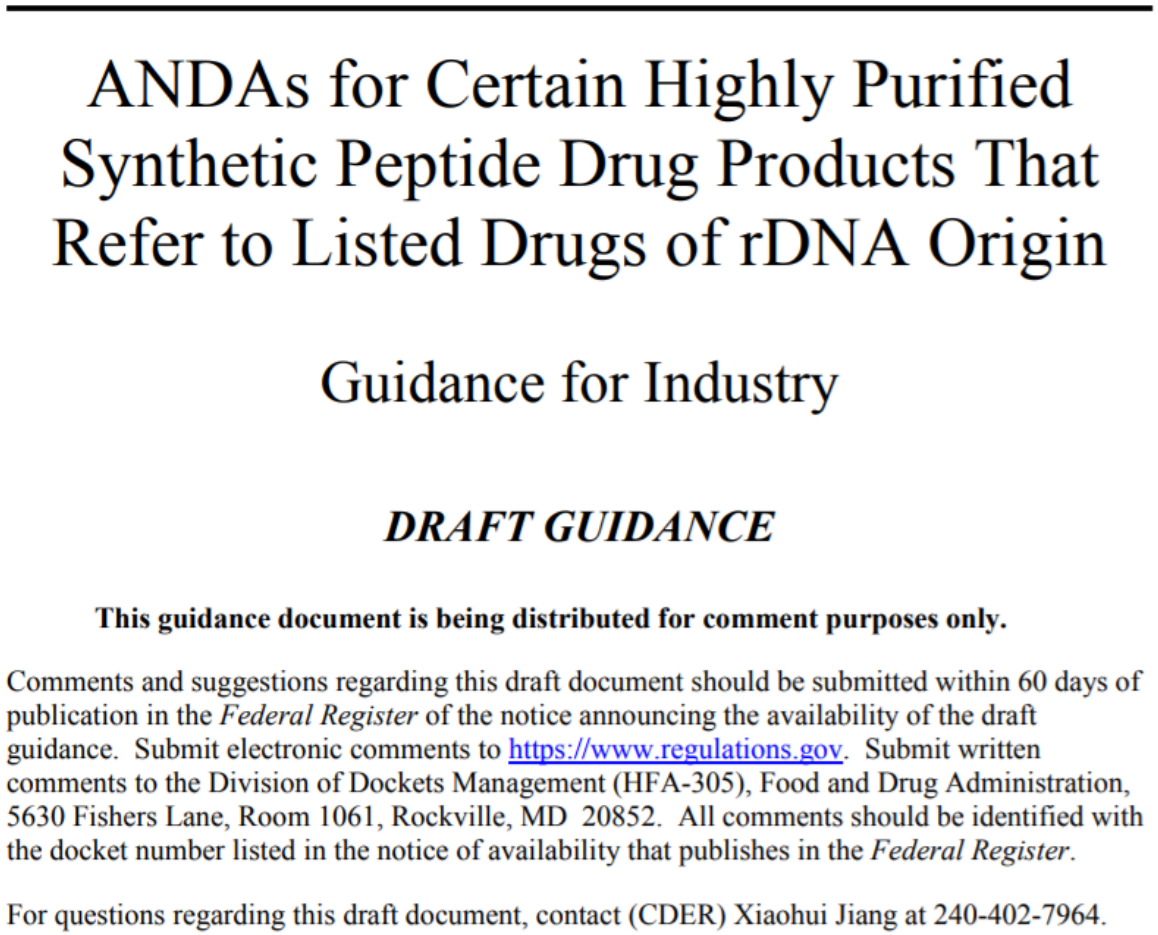
Outline

- Background of the FDA peptide guidance

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

- Discussion of
  1) Peptide drug vs biological product
  2) API and drug product characterization
  3) Peptide-related impurity analysis and control
  4) Risk mitigation strategy

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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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

Public Comments on the Peptide Guidance

- Guidance published on October 3, 2017
- Public comment period
  - Initially 60 days from October 3, 2017
  - Extended to February 4, 2018
- Total number of comments received: 22
- Public comments are available at:

  https://www.regulations.gov with docket number FDA-2017-D-5767

(1) Peptides Covered by the Guidance

Public Comments

- Asserted the five peptides should be regulated as biological products
- Asked why only include these five peptides? Why not include other peptide products of rDNA origin?

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 biological products under section 351 of the PHS Act
  - The Biologics Price Competition and Innovation Act (BPCIA) 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 BPCIA, 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) Transition Products

- The BPCIA amended the PHS Act to include in the term "biological product" proteins, except chemically synthesized polypeptides
  - **Proteins (generally any alpha amino polymer > 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)**

(2) API and Drug Product Characterization

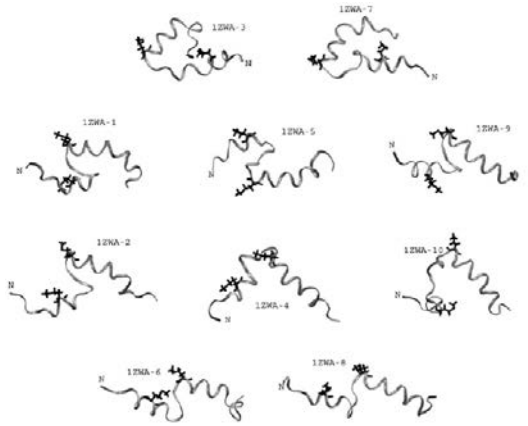
- Public comments questioned:
  - Whether sameness can be demonstrated without clinical trials
  - Impacts of excipients on characterizations
  - Use of comparative studies to the RLD or data from published literature
  - How to characterize and control peptide aggregation/fibrillation
  - Whether the bioactivity of peptide is determined by its primary sequence

Characterization of Peptide Product

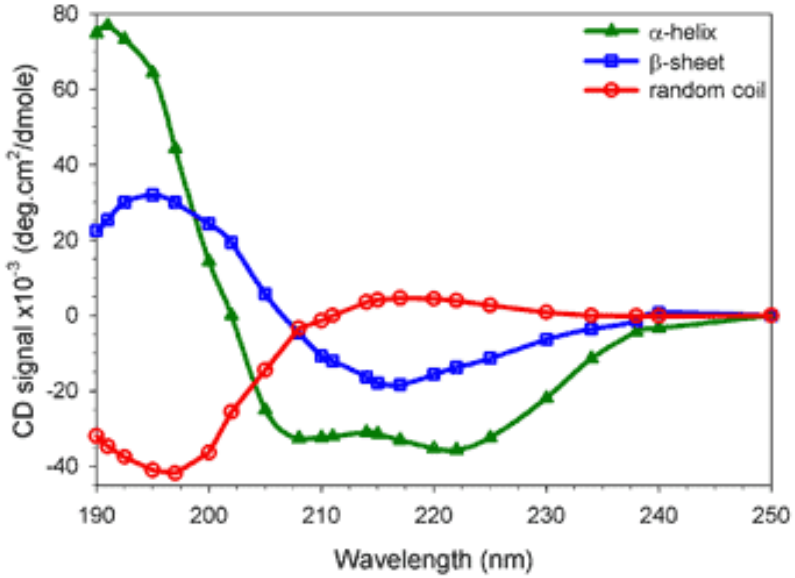
- Analytical characterizations of peptide properties
  - Primary sequence
  - Physico-chemical properties
  - Secondary and high-order structure
  - Oligomer and aggregation states
- Biological evaluations
  - Relevant to peptide's mechanism of action

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

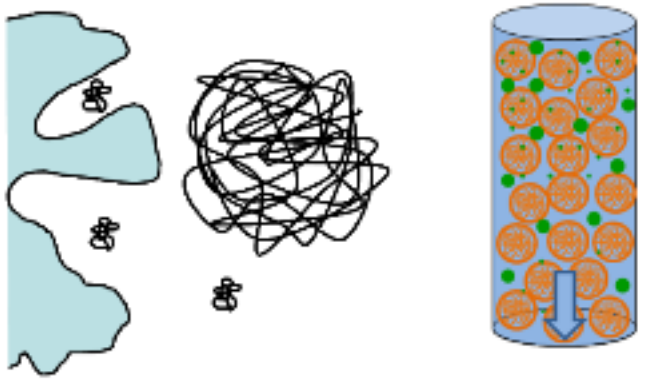


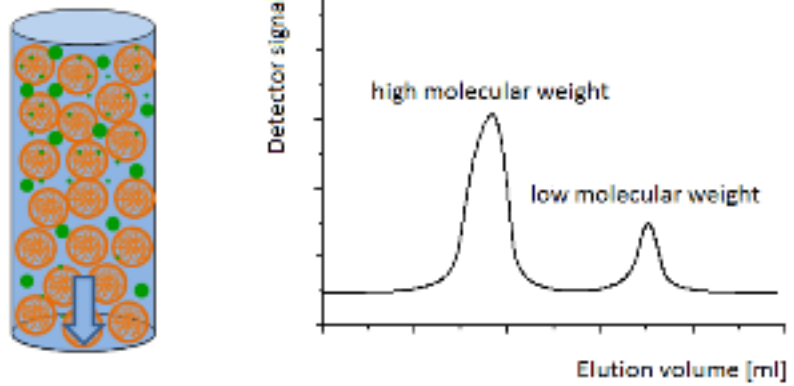
NMR structures of teriparatide
Chu, et al., Biochemistry 43 (2004) 14139.



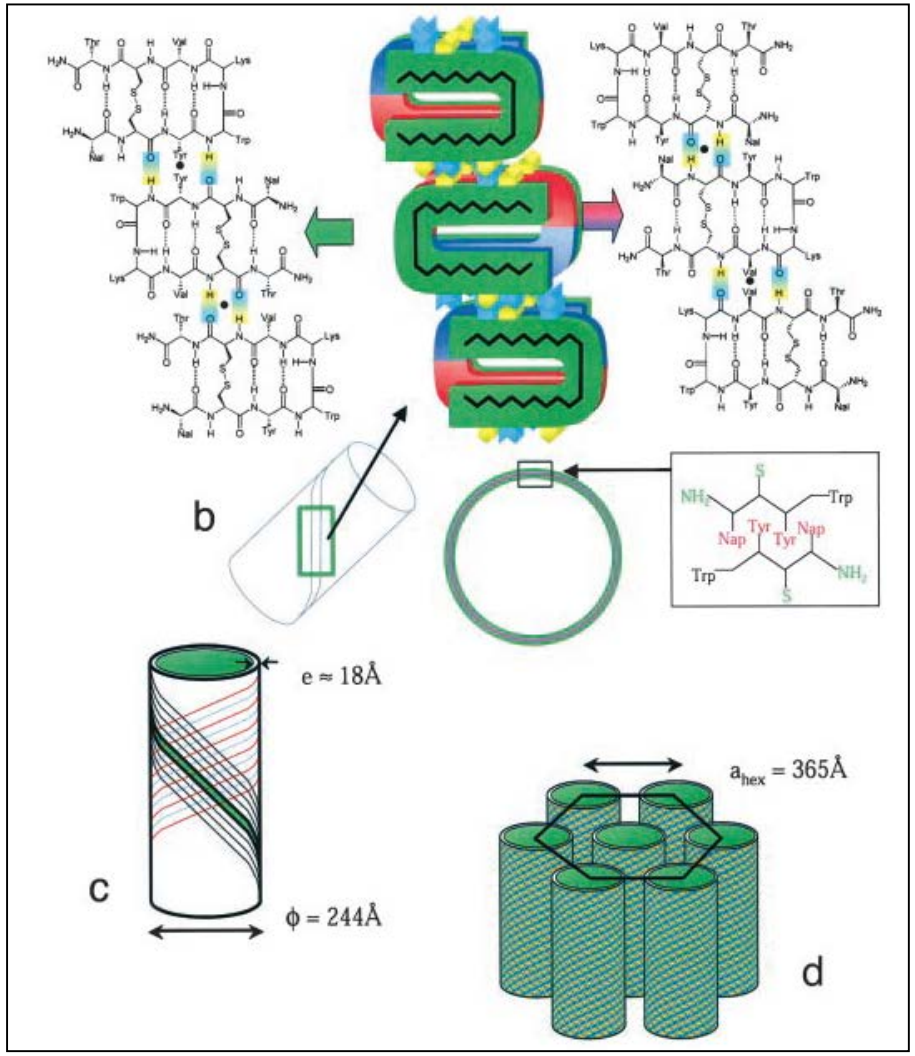
Oligomer and Aggregation States

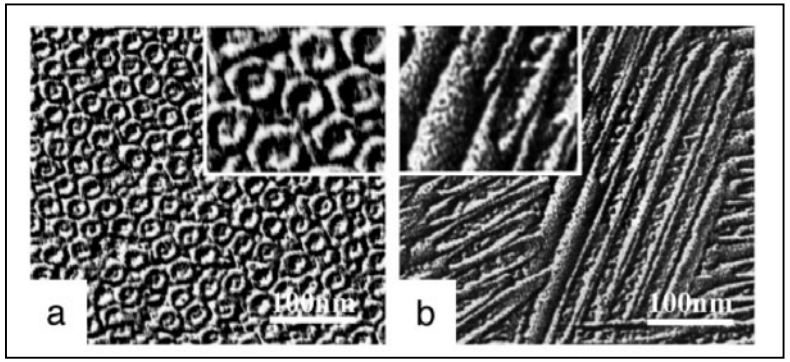
- Measurement
  - Size-exclusion chromatograph (SEC), analytical ultracentrifuge (AUC), particle size measuring methods(e.g., DLS, MALS, NMR), imagining methods (e.g. Cryo-TEM, AFM), …
- Under stress and stability conditions
  - Freeze-thaw, high temp

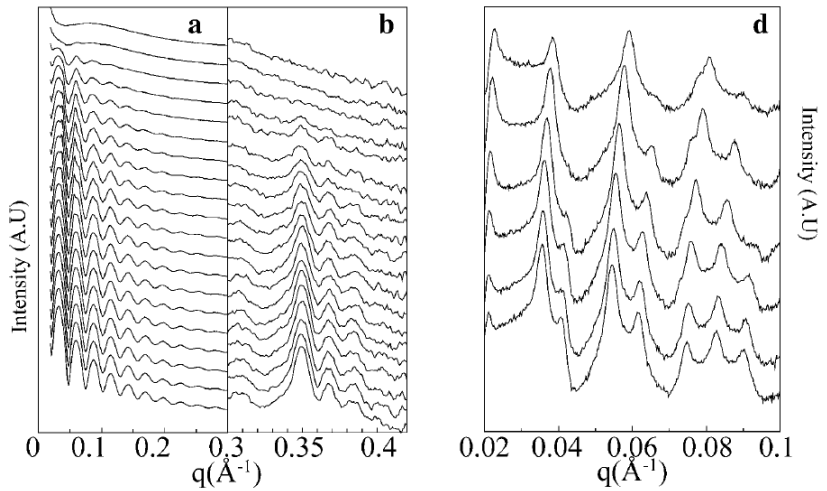




Somatulin Depot: Self Assembled Lanreotide Acetate Nanotubes







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

(3) Peptide-related Impurity Analysis and Control

- Identification threshold: justify impurities ≥ 0.10%
- Public comments asserted the value of 0.10% is too low (several proposal for 0.3%)
  - Difficult to measure such impurities between 0.1% - 0.5%
  - Difficult to control in manufacturing process
- Arguments questioning whether degradation impurities would be expected to be the same where the RLD and the proposed generic products have the same API, generally the same excipients, and the same labeled storage conditions

LC-MS Analysis of Teriparatide

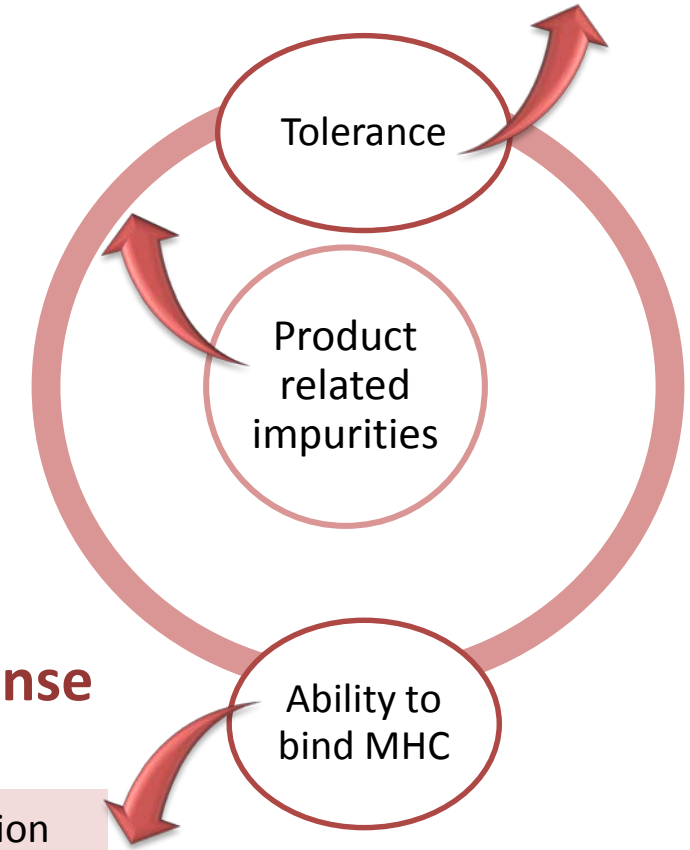
Compound Name	Monoisotope MW	RT, min	RRT	C470473C	C587623C	C644202D	C650452G	C616383C	C658878C	**Avg**	Std
Teriparatide(1-34)	4115.1305	45.92	1.00	95.94	96.21	96.79	96.26	97.01	97.19	**96.57**	0.50
Teriparatide(1-34) Met +O (8, 18)	4147.1203	38.89	0.85	0.00	0.00	0.00	0.00	0.00	0.00	**0.00**	0.00
Teriparatide(1-34) Met +O (8)	4131.1254	41.85	0.91	0.79	0.51	0.65	0.55	0.36	0.32	**0.53**	0.18
Teriparatide(1-34) Met +O (18)	4131.1254	43.47	0.95	1.28	1.15	1.27	1.30	0.92	0.86	**1.13**	0.19
rhPTH(1-30)	3617.8919	42.52	0.93	0.79	0.57	0.40	0.44	0.47	0.42	**0.51**	0.15
rhPTH(1-34) Succinimide(30)	4097.1199	45.71	1.00	0.82	0.66	0.54	0.58	0.59	0.54	**0.62**	0.11
Val-Arg rhPTH (1-34)	4370.3000	45.49	0.99	0.10	0.11	0.09	0.08	0.10	0.11	**0.10**	0.01
N-ac rhPTH (1-34)	4157.1410	45.92	1.00	0.02	0.02	0.02	0.02	0.02	0.02	**0.02**	0.00
rhPTH(1-33)	3968.0621	43.27	0.94	0.20	0.43	0.11	0.23	0.22	0.19	**0.23**	0.11
rhPTH (1-29)	3502.8649	42.19	0.92	0.02	0.31	0.02	0.40	0.29	0.24	**0.21**	0.16
Teriparatide(4-34)	3841.9980	45.13	0.98	0.03	0.02	0.11	0.15	0.03	0.11	**0.07**	0.05

Zeng, K. et al, Poster presentation at American Society for Mass Spectrometry Annual Conference (2018)

(4) Risk Mitigation Strategy
"New" Peptide-related Impurities

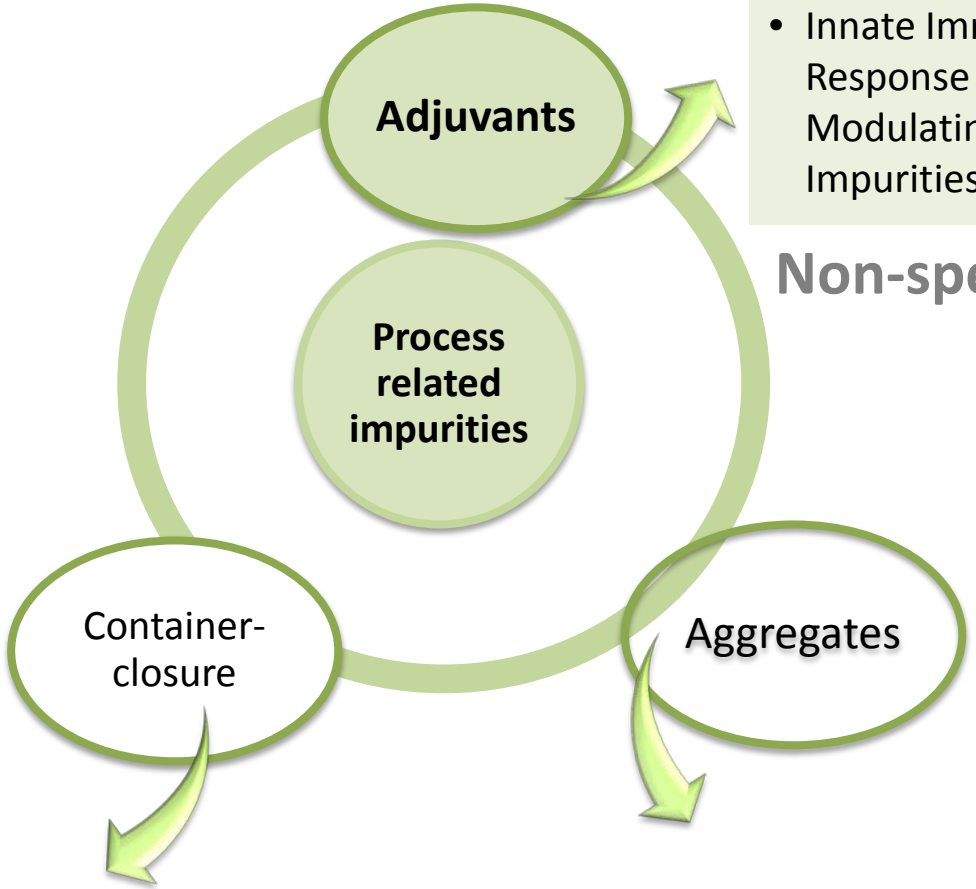
- Received comments questioning what studies are needed to support approval, but the purpose of this guidance is to recommend when to submit an application under 505(j) may be appropriate
- Risk of "new" peptide-related impurities
  - Low dose, low level impurity similar to API should have minimum risk
  - Different impurity needs clinical study for safety and efficacy
- Asked FDA provide examples or more guidance on studies to mitigate risks of "new" impurities between 0.1 – 0.5%

Immune-response from Impurities of Peptide Drug Product



Specific Response

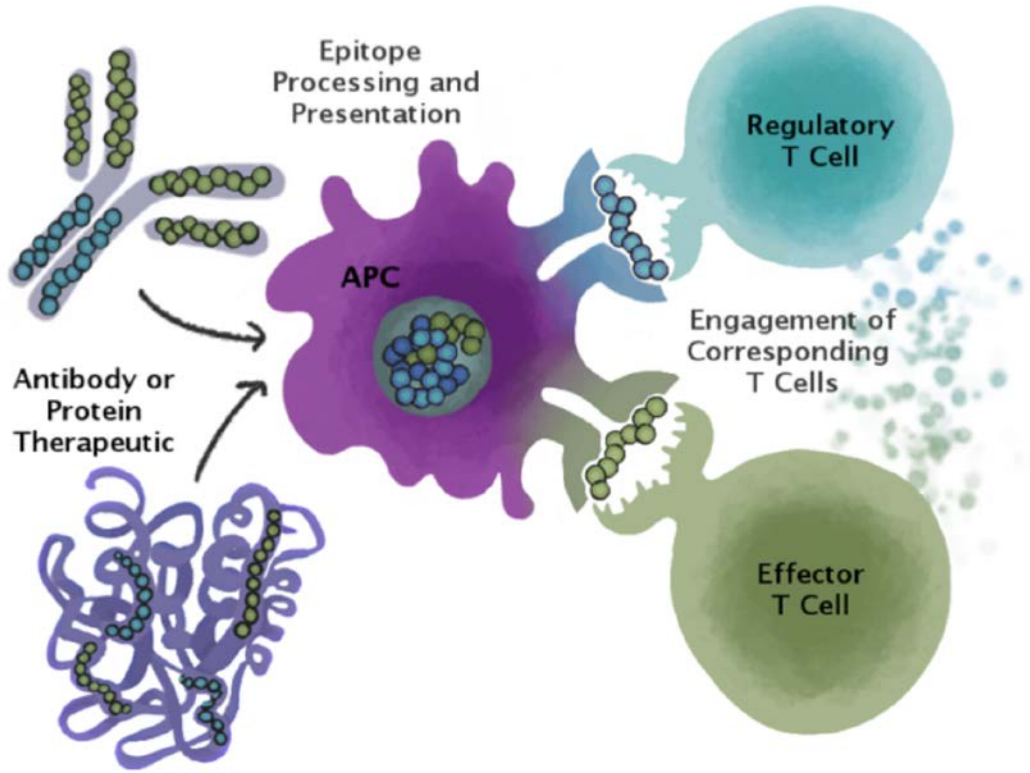
- T cell activation
- Specific amino acid sequences and length



- Innate Immune Response Modulating Impurities (IIRM)

Non-specific Response

Activation of T Cell

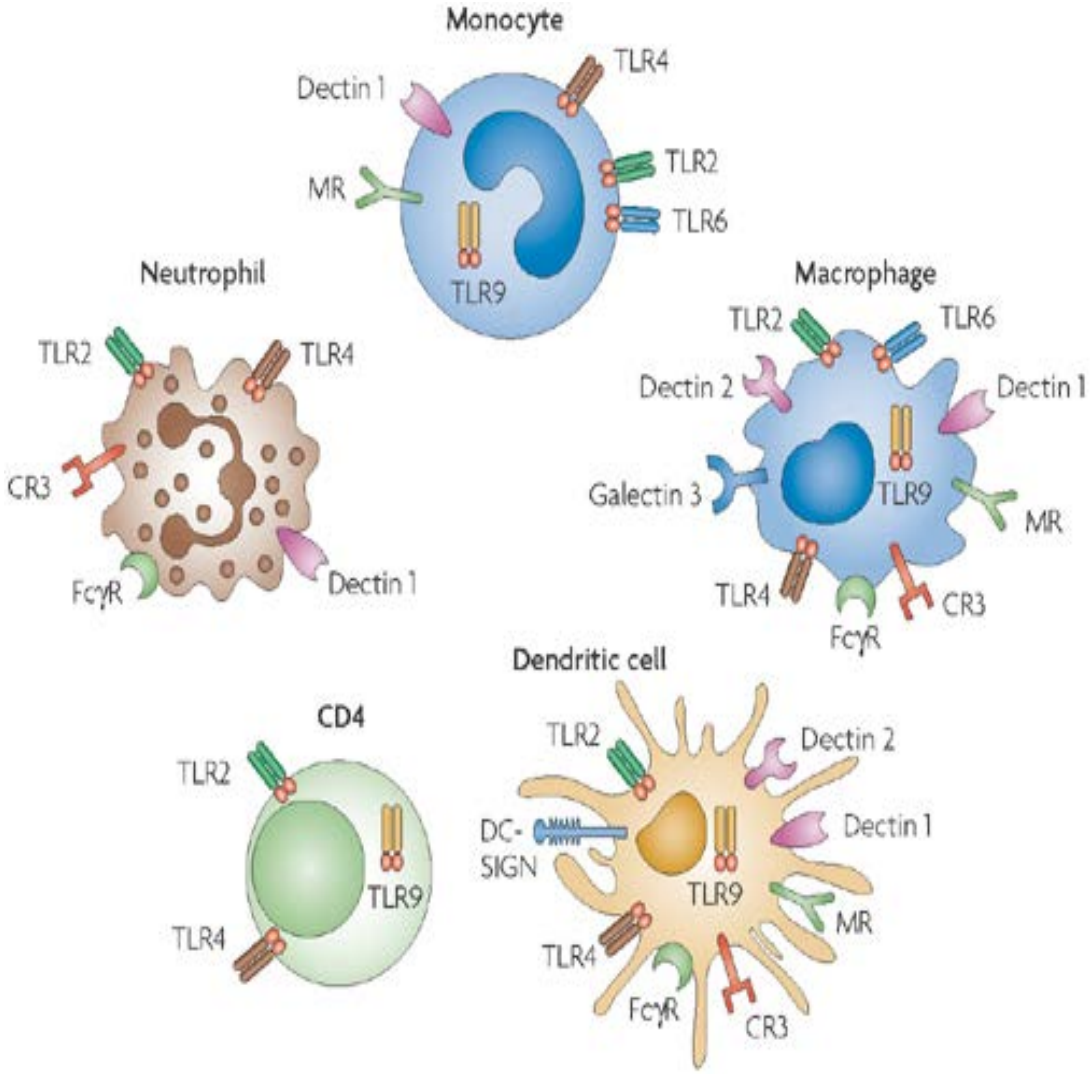


De Groot A.S., et al., Activation of Natural Regulatory T cells by IgG Fc-derived Peptide "Tregitopes". Blood, 2008,112: 3303. http://tinyurl.com/ASDeGroot-Blood-2008

- >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

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Questions?


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