Assessing Immunogenicity Risk of Peptide Drugs: Generic Drug Perspective

Eric Pang, Ph.D.

Team Lead (Acting)

ORS/OGD

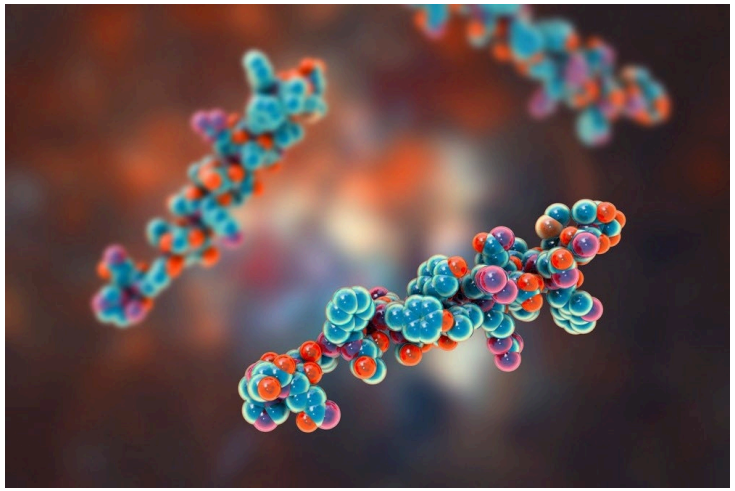
CDER | U.S. FDA

CRCG Workshop, Oct 2024

Disclaimers

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

Any representation of brand name drugs in this talk are for purposes of scientific discussion and specific comparison.



Topics

- Overview of peptide drugs and immunogenicity
- Synthetic peptide guidance and product-specific guidances (PSGs)
- In vitro in silico immunogenicity assays (IVISIA) and challenges
- Future development and directions

Peptide Features as Compared to Small Molecules and Biologics

Compared to small molecules, Peptides have high specificity, good efficacy and safety

However, peptides may have lower permeability and poorer stability

NDAs and ANDAs

Compared to proteins, Peptides are lower cost and generally lower immunogenicity risk

However, peptides may lack specificity

BLAs

Peptides[1]: Equal or less than 40 A.A.

1. Based on definition of "biological product" as defined in 85 FR 10057, February 21, 2020

Why Assessing Immunogenicity Risk for Peptide Products

Immunogenicity May Impact Safety and Efficacy

- Developing antibodies can affect the pharmacokinetics (PK) by enhancing or delaying clearance
- Neutralizing antibodies can diminish efficacy, and there is concern of cross-reactivity with endogenous non-redundant proteins
- Hypersensitivity responses

Generic peptides approval relies on the finding of safety and efficacy of the RLD and should have no greater risk than RLD

- Generic drug is essentially copies of the approved RLD

But…. what about the differences between proposed generic and RLD?

Differences in Manufacturing and Impurities of Peptide Drugs

Manufacturing pathways

- Chemical synthesis - made by chemical synthesis (e.g., step-by-step amino acid synthesis addition)
- Recombinant DNA (rDNA origin) - peptide extracted from recombinantly expressed yeast or bacteria cells
- Extraction from natural sources

Different manufacturing process can result in different impurities, *which may give rise to different safety risks*

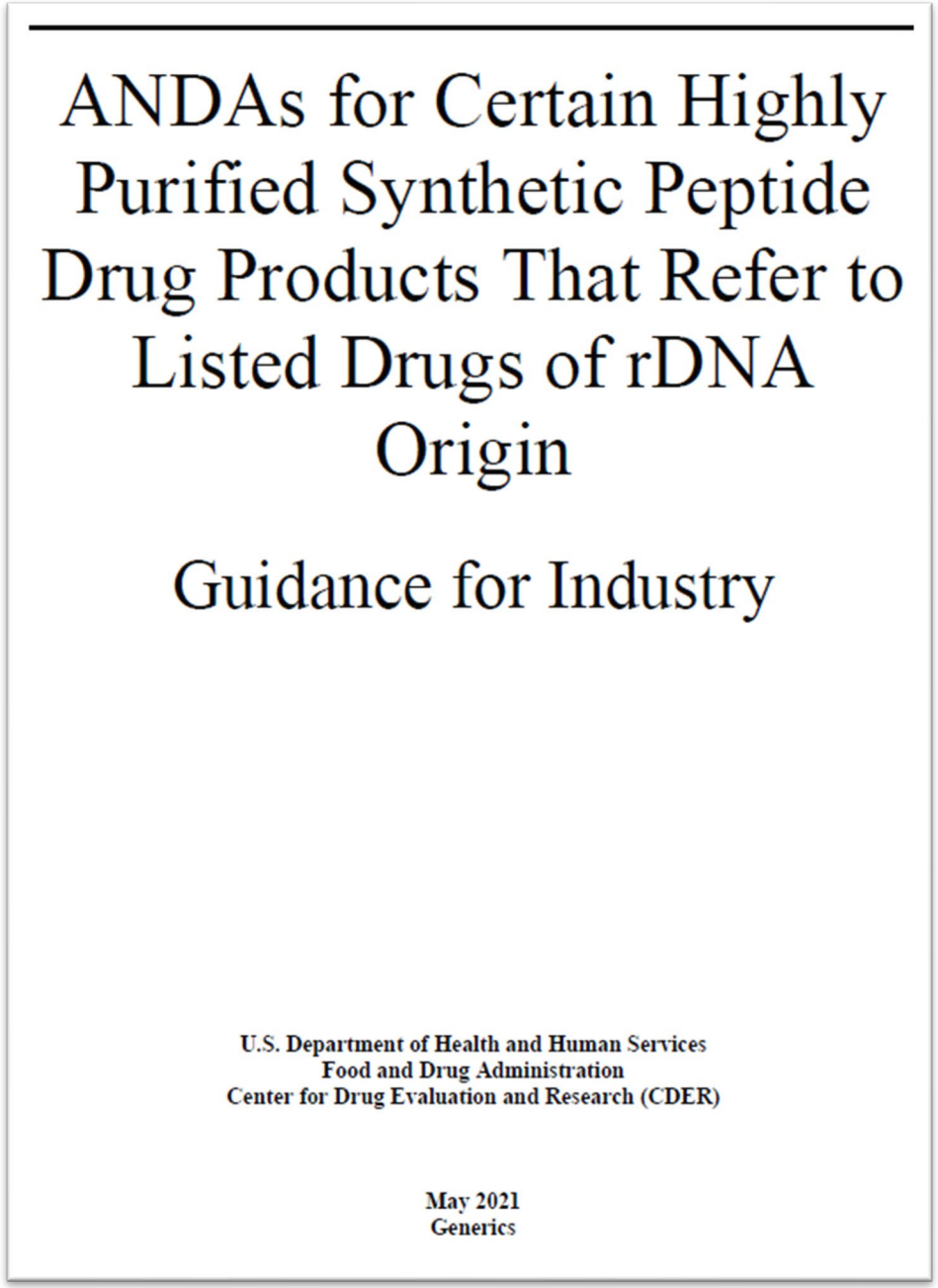
- Process-related (host cell proteins, leachable extractables, microbial contaminant, etc.)
- Peptide-related (impurities related to the API peptide, such as deletion, duplication, etc.)

Hence, generics should demonstrate differences in impurities would not increase a product's risk

API - active pharmaceutical ingredient

Peptide-related Impurities

- For specified impurities common to proposed generic and reference listed drug (RLD)
  - Level in proposed generic ≤ RLD
- For any new impurities in the proposed generic
  - > 0.5% is not recommended
  - Impurities at 0.1%- 0.5% identified, characterized and justified for not affecting the safety and efficacy, including comparative immunogenicity risk tests



for synthetic **Glucagon, Liraglutide, Nesiritide, Teriparatide, and Teduglutide** referencing recombinant RLDs

"ANDA applicant should provide justification for why the presence of such impurity would not be expected to affect the safety of the proposed generic synthetic peptide or its effectiveness as compared to that of the RLD, including with respect to the risk of **immunogenicity related to peptide-related impurities…**

…such data should demonstrate that each new impurity does not contain sequences that have an **increased affinity for MHC**, known as T-cell epitopes, and that the proposed generic synthetic peptide **does not alter the innate immune activity**."

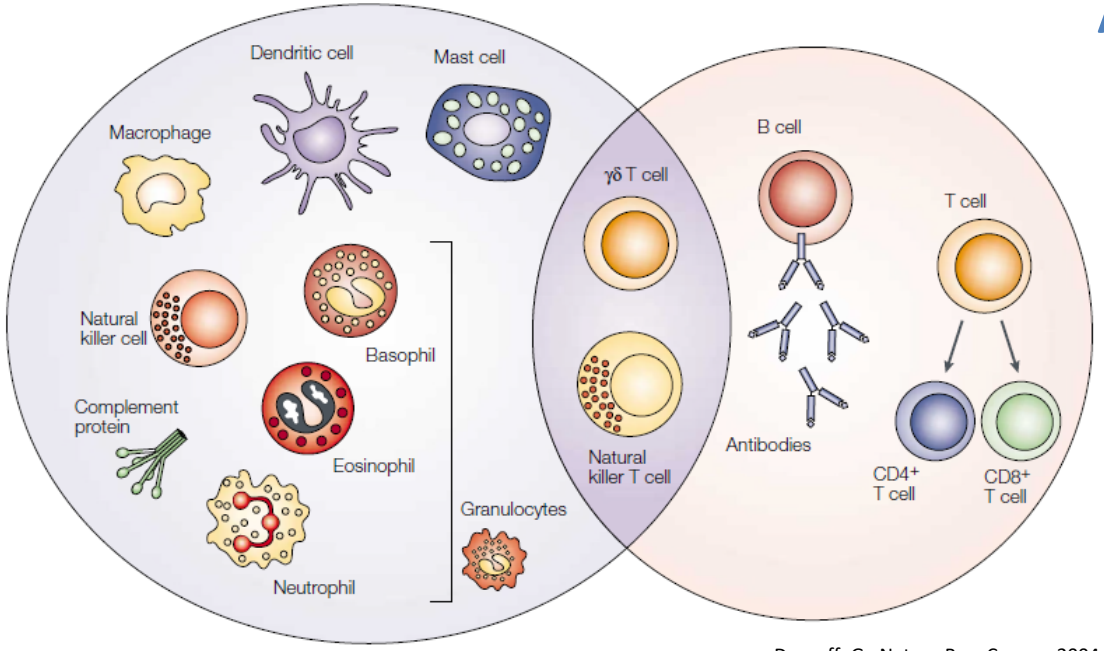
Potential for Impurity-related Immunogenicity Risk: Innate and Adaptive Immunities

Innate immunity

All **process-related impurities**
(contaminants, leachables)

⇩

Testing on whole product



Dranoff, G., Nature Rev. Cancer, 2004

Adaptive immunity

Peptide-related impurities
(e.g., deletions, insertions…)

⇩

Testing on individual impurity: T-cell epitope in peptide-related impurities

Innate immune response modulating impurities (IIRMI) assays

Detect innate immunogenic potential of low levels of process and product-related impurities

In silico assays

In vitro cell-based assays to identify responsive T cells

In Vitro In Silico Immunogenicity Assessment (IVISIA)

Evaluating the Risk of Immunogenicity through IVISIA

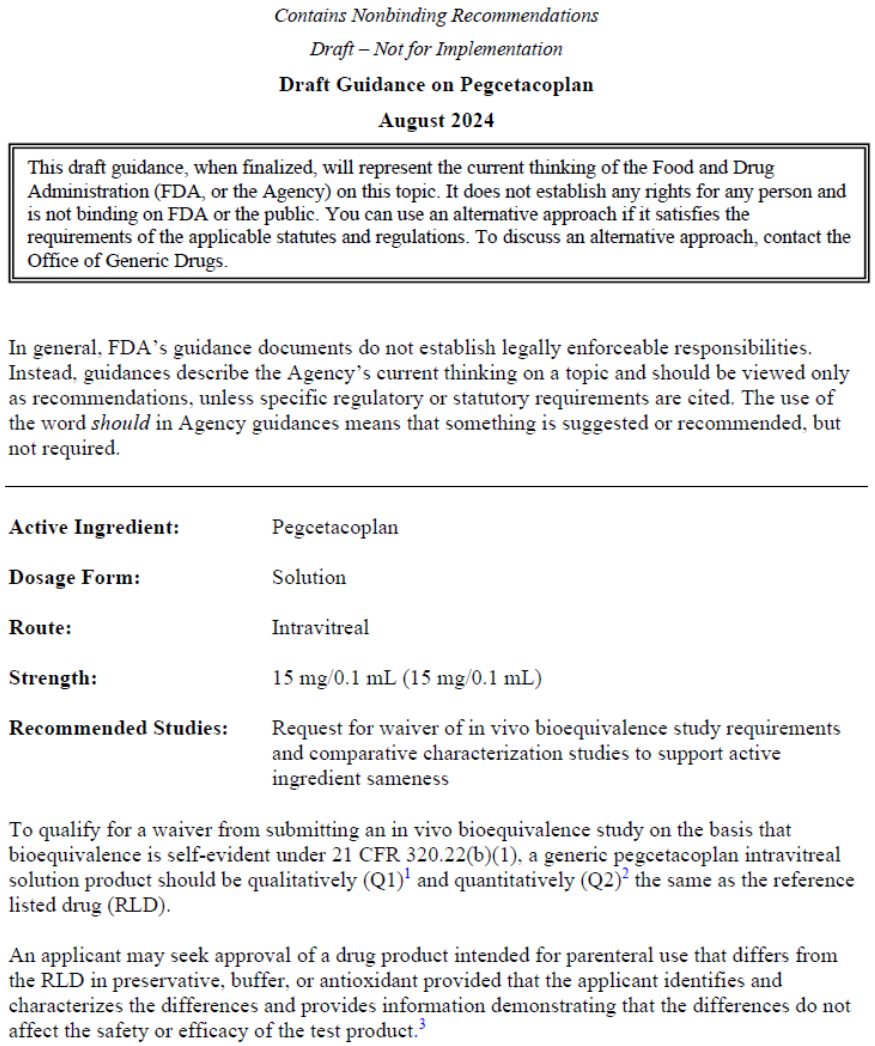
- Adaptive immunogenicity assessment (orthogonal assays) for T-cell activation potential of peptide-related impurities
  - *in silico* studies MHC binding,
  - *in vitro* binding and functional assays
- Innate immune activity comparison between proposed generic and RLD products
  - *in vitro* cell-based assays

MHC = Major Histocompatibility Complex

Common Challenges with IVISIA

- Lack of standardized approaches and working standards for validating the performance of assays is one of the most common challenges developing and assessing in vitro immunogenicity assays
- Some common product-related challenges include:
  - To synthesize highly purified impurities in enough quantity to perform the adaptive immunogenicity assays
  - Excipient interference to cell viability and assay performance
- Unclear recommendation on when in vitro immunogenicity assessment is needed for some products

PSGs Provide Recommended Studies for Peptide Products



Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Pegcetacoplan

August 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient:	Pegcetacoplan
Dosage Form:	Solution
Route:	Intravitreal
Strength:	15 mg/0.1 mL (15 mg/0.1 mL)
Recommended Studies:	Request for waiver of in vivo bioequivalence study requirements and comparative characterization studies to support active ingredient sameness

To qualify for a waiver from submitting an in vivo bioequivalence study on the basis that bioequivalence is self-evident under 21 CFR 320.22(b)(1), a generic pegcetacoplan intravitreal solution product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD).

An applicant may seek approval of a drug product intended for parenteral use that differs from the RLD 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 test product.[3]

PSGs reflect the current thinking on the information/studies recommended to support generic approval

- **Active pharmaceutical ingredient (API) sameness**
  - Sequence, structure, high order structure (HOS), aggregation profile, and bioactivities, if applicable
- **Impurity profile comparison**
- **Adaptive immune assessment**
- **Innate immune assessment**

Recommended Studies in Selected Peptide PSGs

NOT all peptide drugs need IVISIA

	HOS and oligomer (Aggregate)	Impurity profile	Biologic activities	Innate Immune	Adaptive Immune
Octreotide Injectable (NDA 213224)	X				
Bremelanotide (NDA 210557)	X				
Vasopressin (NDA 204485)	X	X			
Secretin (NDA 021256)	X	X	X		
Dasiglucagon (NDA 214231)	X	X	X	X	
Semaglutide injectable (NDA 215256)	X	X	X	X	X

Work in Progress…

- Recommend working standards for validating the performance of innate and adaptive immunogenicity assays on peptide products
- Continue to improve regulatory transparency by publishing PSGs to include recommended immunogenicity studies
- Explore new review process of in silico algorithms – Model Master File
- Fund research and publish on the best practices for conducting in vitro studies

We fund GDUFA-related research!

https://www.fda.gov/drugs/generic-drugs/generic-drug-research-collaboration-opportunities

Acknowledgement

OGD/ORS

- Jennifer Lee
- Deyi Zhang
- Andrew Clerman
- William Chong
- Darby Kozak
- Markham Luke
- Lei Zhang
- Rob Lionberger

OPQ/OPQR

- Daniela Verthelyi
- Mohanraj Manangeeswaran
- Seth Thacker
- Montserrat Puig
- David Keire

OCP

- Sophie Shubow
- Mohsen Rajabiabhari

OPQ/OPQA

- Cameron Smith
- Bing Cai
- Pahala Simamora
- Andre Raw
- Steve Kozlowski