Assessing Immunogenicity Risk of Peptides: the Synthetic Peptide Guidance and PSGs

SBIA 2022: Advancing Generic Drug Development: Translating Science to Approval

Day (1), Session 1A: (Peptide Immunogenicity Risk and Impurity Assessment Considerations)

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Learning Objectives

- Describe Guidance for ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin
- Summarize immunogenicity and non-clinical assays
- Discuss product-specific guidances (PSGs) for peptide products
- Evaluate immunogenicity risk assessment for peptides

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) - recombinantly expressed peptide extracted from cells (e.g., yeast or bacteria)
- Extraction from natural sources

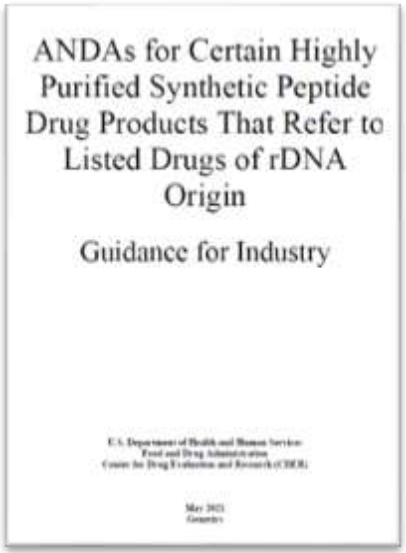
Different manufacturing process can result in different impurities, *which may give rise to different safety concerns*

- 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

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

FDA outlined current thinking to address potential immunogenicity risk for synthetic **Glucagon, Liraglutide, Nesiritide, Teriparatide, and Teduglutide** referencing recombinant RLDs



- 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 acceptable
  - Impurities at 0.10%- 0.5% identified, characterized and justified for not affecting the safety and efficacy, including comparative immunogenicity risk tests

Clarifications to the Synthetic ANDA Peptide Guidance

- Like PSG, the synthetic ANDA peptide guidance contains recommendations.
- Applicable for the five peptide products, however, the scientific principles and recommendations of the guidance may apply to other peptides depending on risk.
- Impurities greater than the RLD and new impurities greater than 0.5% may not be able to rely on non-clinical risk assessment. Reach out to us for these situations through controlled correspondence[1] or Pre-ANDA meeting[2] processes.

1. Guidance for Industry: Controlled Correspondence Related to Generic Drug Development. www.fda.gov/media/109232/download
2. Guidance for Industry: Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA. www.fda.gov/media/107626/download

Impurity-Related Immunogenicity Risk: Innate and Adaptive Immunities

Innate immunity

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

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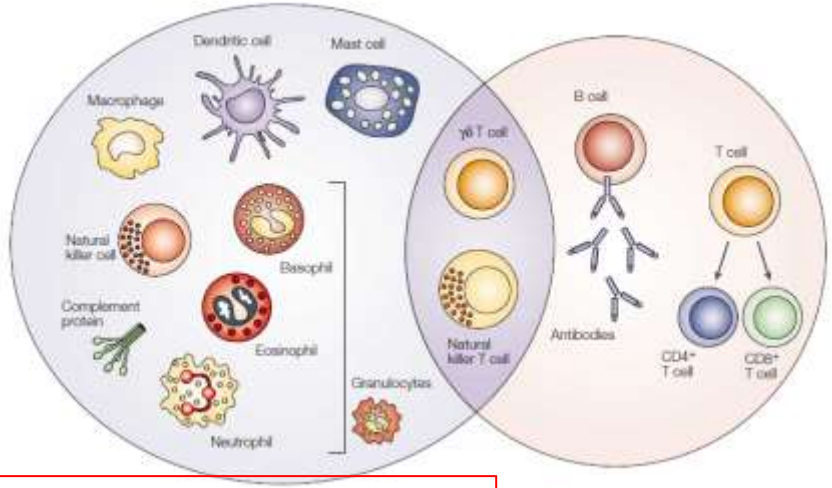
Testing on whole product (independent of presence of new impurities)



Innate immune response modulating impurities (IIRMI) assays

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

Adaptive immunity

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

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Testing on each isolated impurity:

- T-cell epitope in peptide-related impurities
- New impurities in proposed generic (0.10%-0.5%)

Dranoff, G., Nature Rev. Cancer, 2004

In silico assays

In vitro cell-based assays to assess MHC (Major Histocompatibility Complex) binding and/or identify responsive T cells

Examples of Non-Clinical Assays for Assessing Adaptive Immunogenicity Risk

In silico immunogenicity assessment to assess the presence of MHC binding

- A quick way to screen and predict the presence of binding epitope without experimentally test the individual impurities
- However, may need to be confirmed with results from in vitro studies

In vitro assays to assess T cells responses to the impurities

- HLA Binding studies
- Cell-based assays such as T cell proliferation assays

In vivo animal assays

- Transgenic mouse model

In Vitro Assays for Innate Immune Response Modulating Impurities

Cell line		Origin	Commercial Availability
PBMC/whole blood	Proliferation Cytokines	Human macrophages, dendritic cells, monocytes and lymphocytes	Yes
RAW-BLUE	NFkB	Mouse macrophages	Yes
Macrophage-like-MonoMac6 (MM6)	Cytokines	Human monocytic cell	Yes
THP-1	NFkB or Cyt.	Human monocyte	Yes
HEK 293-Receptor	NFkB	Human embryonic kidney	yes
Dendritic cells activation	Activation markers	Fresh or frozen human DC	Yes

Common Challenges with In-Vitro Assays

- Sufficient demonstration of assay sensitivity
- Sufficient justification on the type of assay and methodology
- Sufficient detail on methodology (concentration tested, number of subjects, etc.)

Product-Specific Guidances (PSGs)

- FDA develops PSGs to provide its current thinking on the information/studies recommended to support generic approval (e.g. studies demonstrating pharmaceutical equivalence and/or bioequivalence)
- Per GDUFA II Commitment Letter, FDA agreed to publish PSGs for a new complex products as soon as scientific recommendations are available
- PSG recommendations for peptide products is based on considerations for immunogenicity potential and demonstrating product sameness

Recommended Studies Depends on the Risk of the Peptide Product

	RLD/RS	API sameness	Impurity profile	Adaptive Immune	Innate Immune	HOS and oligomer	Biologic activities
Semaglutide, SubQ-Solution	209637	X	X	X	X	X	X
Vasopressin, IV Solution	204485	X	X			X	
Secretin Synthetic Human, IV Solution	021256	X	X			X	X
Bremelanotide, SubQ-Solution	210557	X				X	
Octreotide, SubQ-Solution	213224	X				X	

- Not recommending a study in a PSG does not mean it will not be requested during review process.

Initial Immunogenicity Risk Assessment for Peptide Products

- Peptide product consideration:
  - Peptide size, route of administration, dosing frequency, homology to human protein sequences, half-life, etc.
- Intended patient consideration
  - Indication, immune status, etc.
- Clinical experience of the RLD
  - Anti-drug antibody levels found during clinical studies, adverse events, etc.

Summary

- PSG recommended studies depend on the current thinking and understanding of associated risk of the peptide product
  - The synthetic peptide guidance targets specific five peptides where immunogenicity is a concern
  - PSGs support the development of generic peptides products
- Nonclinical immunogenicity assays may be utilized to assess the comparable risks of the generic to the RLD
- There is a need to establishing best practices and standards for conducting nonclinical assays

GDUFA Funded Research

- IAA-224-19-3008S Evaluating Innate Immune Response of Generic Peptide Drugs and Impurities
  - Holley et al. *Molecules.* 2021
- 75F40120C00157 Immunogenicity Risk of Peptide Drug Generics and their Impurities: In Silico and In Vitro Assessment and Validation Methods
- HHSF223201810186C In-silico and In-vitro Methods for Evaluating Generic Peptide Drug Immunogenicity

Please submit new research proposals at https://www.fda.gov/drugs/generic-drugs/generic-drug-research-collaboration-opportunities

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Challenge Question #1

Which of the following peptide products is not covered by the Guidance: ANDAs for Certain Highly Purified Synthetic Peptide Drug Products that Refer to Listed Drugs of rDNA Origin

A. Nesiritide
B. Teduglutide
C. Glucagon
D. Secretin

Challenge Question #2

Which of the following statements is NOT true?

A. PSGs contain recommended studies to demonstrate product sameness for both pharmaceutical equivalence and bioequivalence

B. Immunogenicity risk assessment using nonclinical assays is recommended for all peptide products regardless of their risk

C. Adaptive and innate immune response assays are typically recommended for certain peptide products with immunogenicity concern

D. Peptide products not covered by the synthetic peptide guidance may still reference parts of the recommendations outlined in that guidance

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Questions?

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