PSG Recommendations for Risk-based Comparative Immunogenicity and Impurity Profile Assessment

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Learning Objective

- Describe immunogenicity risk considerations for peptides
- Summarize comparative immunogenicity and impurity profile assessment (comparative profile assessment) that may be included in a peptide product-specific guidance (PSG)
- Correlate product-specific guidance recommendations for peptide products with different immunogenicity risk

Product-Specific Guidances (PSGs)

- PSGs contain FDA's recommended studies to demonstrate therapeutic equivalence
- For peptide PSGs, the studies recommended are based on the immunogenicity risk of the product
- PSGs are revised to reflect the Agency's current scientific understanding

Immunogenicity Risk Considerations for Peptide[1] Products

- Product considerations
  - Peptide size, route of administration, dosing frequency, homology to human protein sequences, half-life, etc.
- Patient population considerations
  - Indication, immune status, etc.
- Clinical experience of the reference listed drug (RLD)
  - Anti-Drug Antibody (ADA) levels found during clinical studies, adverse events, etc.

1. Footnote 7, Guidance for Industry: ANDAs for Certain Highly Purified Synthetic Peptide Drug Products that Refer to Listed Drugs of rDNA Origin. "FDA interprets the statutory definition of “biological product” in section 351 of the Public Health Service Act such that any alpha amino acid polymer composed of 40 or fewer amino acids (i.e., a “peptide”) is outside the scope of the term “protein.”“ https://www.fda.gov/media/107622/download

Overview of Comparative Profile Assessment

- Active pharmaceutical ingredient (API) sameness
- High order structure (HOS) and aggregation profile
- Impurity profile
  - Adaptive immunogenicity assessment
- Innate immune response assessment on the drug product

Recommended Studies Depends on the Risk of the Peptide Product

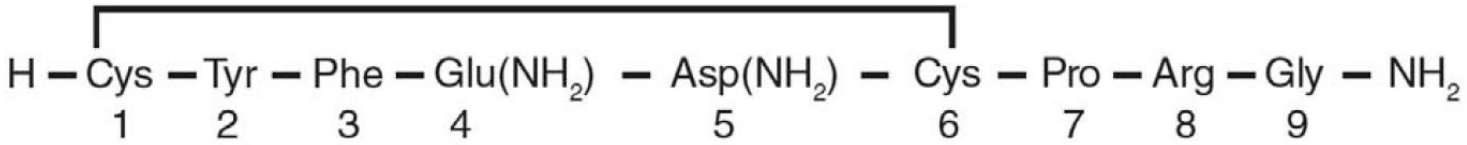
	API sameness	Impurity profile	Adaptive Immune	Innate Immune	HOS and oligomer (Aggregate)	Biologic activities
Octreotide Injectable	X				X	
bremelanotide	X				X	
Vasopressin	X	X			X	
Secretin	X	X			X	X
Dasiglucagon	X	X		X	X	X
Semaglutide injectable	X	X	X	X	X	X

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

Vasopressin

- Vasopressin is a nine amino acid polypeptide hormone that causes contraction of vascular and other smooth muscles and antidiuresis.

- Initially, there were concerns with the possibility of developing anti-vasopressin antibodies after chronic dosing
  - Recommended immunogenicity assessment for new impurities present in the proposed drug product and impurities present at elevated levels compared to the RLD



Vasopressin

- "When it became apparent that the review of a 505(b)(2) vasopressin application, which proceeded separately of the review of vasopressin ANDAs, had differed in the assessment of immunogenicity risk, the Agency initiated an internal reconsideration of its review practices for vasopressin products in general." – CP Response (Dec 28, 2021. FDA-2021-P-0898)

- After further studying the post marketing experience of the marketed vasopressin products, FDA arrived at the conclusion that this product is considered to have relatively low immunogenicity risk.

  – In general, immunogenicity risk assessment for impurities are not necessary

Vasopressin PSG

Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Vasopressin

February 2022

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.

Active Ingredient:	Vasopressin
Dosage Form; Route:	Solution; intravenous
Strength:	20 units/mL (20 units/mL), 20 units/100 mL (0.2 units/mL), 40 units/100 mL (0.4 units/mL), 60 units/100 mL, (0.6 units/mL), and 200 units/10 mL (20 units/mL)
Recommended Study:	Request for waiver of in vivo bioequivalence study requirements

Waiver:

In vivo bioequivalence (BE) study may be waived on the basis that BE is self-evident (21 CFR 320.22(b)), for a generic vasopressin injection solution product that is qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the Reference Listed Drug (RLD). An applicant may seek approval of a drug product that differs from the RLD in preservative, buffer, or antioxidant if 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.[3]

In addition to ensuring active pharmaceutical ingredient API sameness (i.e., same primary sequence), the following comparative analyses of the proposed generic vasopressin and the RLD product should be provided on at least three batches each of the proposed generic and the RLD aged under various conditions.[4]

1. API related impurity profile comparison: new impurities found in the proposed generic product but not in the RLD and impurities found at a significantly higher level in the proposed generic product than in the RLD, should be identified[5]
2. Comparative comparison of aggregation profile and any secondary structure

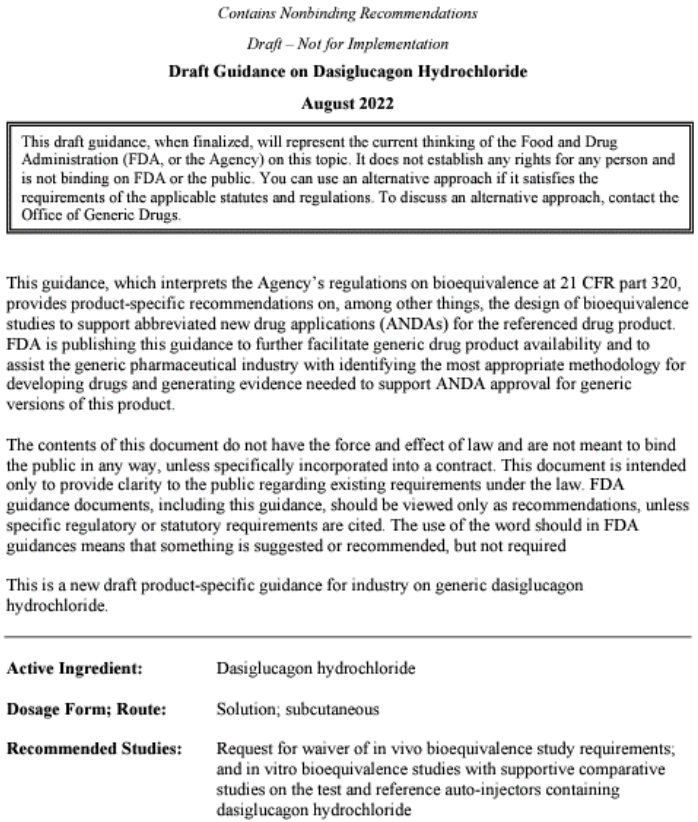
- Q1/Q2
- API sameness
- Peptide related impurity profile comparison*
- Comparative aggregation profile

*Immunogenicity assessment may be requested in situations where the comparative impurity or aggregation profile indicates the presence of an unusual new impurity or aggregation state, or a markedly elevated level of an impurity or aggregation state in the proposed generic product relative to the RLD.

Dasiglucagon

- Synthetic 29 amino acids human glucagon analog
- Dasiglucagon is similar to glucagon sequence and indication
- RLD is synthetic and indicated for emergency use
- Immunogenicity risk appears to be lower
  - Based on labeling, less than 1% developed anti-drug antibodies in clinical trials
  - Allergic reactions have been reported, although rare

Dasiglucagon PSG



Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Dasiglucagon Hydrochloride

August 2022

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.

This guidance, which interprets the Agency's regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required

This is a new draft product-specific guidance for industry on generic dasiglucagon hydrochloride.

Active Ingredient:	Dasiglucagon hydrochloride
Dosage Form; Route:	Solution; subcutaneous
Recommended Studies:	Request for waiver of in vivo bioequivalence study requirements; and in vitro bioequivalence studies with supportive comparative studies on the test and reference auto-injectors containing dasiglucagon hydrochloride

- Q1/Q2
- API sameness (include biological activities)
- Comparative impurity profile*
- Comparative aggregation
- Innate immune response
- Comparative Device Analysis

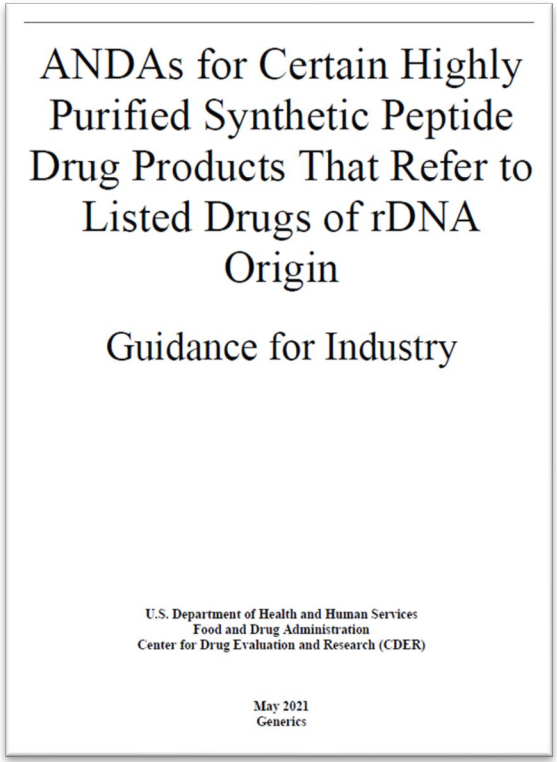
*Identify new and higher common impurities. If upon Agency assessment, an impurity has potential to increase immunogenicity, further immunogenicity studies may be required

Semaglutide Injection

- RLD is a recombinant 31 amino-acid GLP-agonist
- Similar to liraglutide for sequence, intended patient population, and indication
- Chronically used through subcutaneous injection and a homologue of non-redundant endogenous peptide/hormone
- Immunogenicity risk appears to be similar to the five peptides outlined in the synthetic peptide guidance

Semaglutide PSG

Refers to the Synthetic Peptide Guidance


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

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2021
Generics

- Although specific to the five peptide products listed in the guidance, the scientific principles and elements of the guidance may be applied to other follow-on higher risk peptide products, such as semaglutide
- This guidance provides recommendations on addressing the potential immunogenicity risk for peptide-related impurities
  - Comparative impurity profile
  - Adaptive immune response (MHC binding)
  - Innate immunogenicity of the product

Summary

- Different risks of the peptide products warrants different set of studies recommended through PSG
- With the Agency's scientific understandings advances, the regulatory recommendations may evolve as well
  - PSGs provide the Agency's current thinking on the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval
  - Reach out to the Agency through controlled correspondence[1] and pre-ANDA[2] process to discuss scientific studies that may deviate from guidance

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

Acknowledgement

DTP/ORS/OGD

- Rob Lionberger
- Lei Zhang
- Markham Luke
- Darby Kozak
- Yan Wang
- Complex API and Formulation Team

OBP/OPQ

- Steve Kozlowski
- Daniela Verthelyi

OLDP/OPQ

- Bing Cai
- Pahala Simamora
- Cameron Smith

Challenge Question #1

True or false: PSGs only contains recommended studies for demonstrating BE studies for generic products

A. True

B. False

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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"When I reach for the medicine cabinet, I know I am safe, I am a patient, too!"
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