Common Deficiencies Associated with Comparative Peptide Impurity Profile Studies and Qualification of Impurity Levels and Proposed Limits

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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September 20, 2022

Outline

- Learning objectives
- Introduction
- Quality considerations associated with:
  - Peptide-related impurities
  - Aggregates
  - Immunogenicity risks

  for peptides covered by the peptide guidance, or for those that immunogenicity might be a concern*
- Common deficiencies
- Summary

*FDA Guidance for Industry: ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin (May 2021)

Learning Objectives

- Describe regulatory challenges for synthetic peptide generic drugs:
  - Risk mitigation strategies for peptide-related impurities
  - Risk mitigation strategies for higher molecular weight peptide aggregates
- Review examples of common deficiencies to highlight aspects where attention should be focused to facilitate ANDA approval

Introduction

- Peptide drugs are specifically excluded from ICH Q3A/Q3B guidelines for impurity qualification
- Qualifying peptide-related impurity and aggregation levels and proposing appropriate limits is a regulatory challenge
- Additionally, peptide-related impurities and aggregates may pose immunogenicity risks
- Given this complexity, it is important to focus on these attributes to facilitate peptide ANDA approval

ANDA Peptide Guidance*

- Active Pharmaceutical Ingredient (API) sameness of generic and reference peptide drugs can be established by:
  - Primary sequence and physicochemical properties
  - Oligomer/aggregation states
  - Secondary structures
  - Biological activities
- Peptide-related impurity profile

** FDA Guidance for Industry: ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin (May 2021)*

Impurities and Oligomers/Aggregates

- Comparative study requirement for peptide related impurities:
  - Orthogonal chromatographic methods with different separation principle
  - UHPLC-HRMS/MS for peak identity and matching with the RLD*
- Comparative study requirement for oligomers/aggregates:
  - Orthogonal methods
  - Study directly on DP formulation, minimize sample manipulation, provide justification if manipulation is necessary
  - Comparative data under stress conditions

*Liquid Chromatography-High Resolution Mass Spectrometry for Peptide Drug Quality Control by Zeng et al. AAPS J.2015, 17, 643-651

Impurity Level Qualification

- Impurities should not be greater in a test product than that in the RLD:
  - Identify each peptide-related impurity at level ≥ 0.10%
  - Demonstrate no new peptide related impurities > 0.5%
  - For impurity found in both the test and RLD products, demonstrate the level in the test product is the same as or lower than that of the RLD
  - For impurity found at levels ≥ 0.10% and ≤ 0.5%:
    - not present in the RLD, or
    - in the test product at higher levels than that of the RLD

    provide justification as to why such an impurity does not affect the safety, effectiveness or potential for immunogenicity

Impurity Limits

- Limits for each peptide-related impurity can be established such that they are either
  - Less than 0.10%, or
  - Qualified by observed RLD levels for each impurity, or
  - The proposed limit is 0.10%-0.5%, and supported by immunogenicity study results suggesting the impurity does not add immunogenicity risk to the product

Aggregation Level Qualification

- A generic product should not contain aggregates at a greater level than that observed in the RLD:
  - Qualified by observed RLD levels, and
  - Supported by innate immune response studies demonstrating the aggregates do not add immunogenicity risk to the product
- If a generic product contains a greater level of aggregates, an investigation is recommended to identify the root cause and implement appropriate manufacturing process control as necessary

Immunogenicity Risk Mitigation

- Innate immune response evaluation should be conducted on the fully formulated DP in comparison with the RLD to ensure the generic product does not contain anything, such as impurities, aggregates, contaminants, or leachables, that may increase the immunogenicity risks
- For any new or elevated level impurities found at levels of ≥ 0.10% and ≤ 0.5%, adaptive immunogenicity risks for such impurities should be evaluated individually

Samples for Comparative Studies

- Batch requirements for comparative studies of impurity profile, aggregation profile and innate immune response:
  - At least three batches of test product that are manufactured from at least two batches of the DS, tested on or near release and at the end of shelf life
  - At least three batches of the RLD of different ages prior to expiry (as available)
  - Provide a table: DS/DP batch number, manufacturing date, testing date, and sample age on the date of testing

Common Deficiencies

- You performed an impurity profile characterization of the test product samples aged near release using the HPLC Related Substance Method
- **Deficiencies:**
  - Update the study using test product samples aged at the end of your proposed shelf life.
  - Perform the characterization study using orthogonal methods that use different chromatographic separation principles.
  - Use UHPLC-HRMS/MS to facilitate peak identification and matching between the RLD and proposed product samples and to characterize peak purity (specificity).

Common Deficiencies Cont'd

- You proposed to control some of the specified impurities as mixtures in the DP specification
- **Deficiencies:**

  For impurities that coelute in the chromatogram:

  - Improve the analytical method to resolve all specified impurities and control each with individual limit
  - Use multiple methods to control subsets of impurities

Common Deficiencies Cont'd

- You identified some impurities in the specification table with relative retention times (RRTs)
- **Deficiencies**
  - Characterize the structure of those impurities identified by RRTs as per the ANDA peptide guidance*
  - Update the specification tables with identified names based on your characterization

** FDA Guidance for Industry: ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin (May 2021)*

Common Deficiencies Cont'd

- You proposed a limit of NMT 0.10% for Any Unspecified Impurity
- **Deficiencies**
  - Revise the limit from NMT 0.10% to less than 0.10% to be consistent with the ANDA peptide guidance*, which states that all impurities present at 0.10% or greater should be identified and characterized.

** FDA Guidance for Industry: ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin (May 2021)*

Common Deficiencies Cont'd

- The proposed limit for Impurity I is more relaxed than NMT 0.5% and not supported by the comparative RLD data
- **Deficiencies:**
  - Tighten the limit consistent with and supported by the observed RLD level, or
  - Tighten the limit to 0.10%-0.5% and supported by immunogenicity study results suggesting Impurity I does not add immunogenicity risk to the product at the proposed limit

Common Deficiencies Cont'd

- You reported a greater level of aggregates in the test product than those found in the RLD
- **Deficiencies:**
  - Perform an investigation to identify the root cause and improve your product aggregation profile. The aggregation profile of your test product should be comparable to the RLD
  - Demonstrate capability of manufacturing DS or DP exhibit batches as necessary with acceptable control of aggregates across the proposed shelf life

Challenge Question #1

Consistent with the ANDA peptide guidance*, when conducting a comparative impurity profiling of the generic product and RLD, identify all peptide-related impurities at a level of:

A. > 0.10%

B. > 0.5%

C. ≥ 0.10%

D. ≥ 0.1%

* FDA Guidance for Industry: *ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin* (May 2021)

Challenge Question #2

Which of the following statements is NOT true?

A. ICH Q3A & Q3B guideline is generally applicable to all drug products, including peptide drug products.

B. The limit for each peptide-related impurity can be qualified by the observed RLD level for the same impurity.

C. A comparative characterization of the impurity profile of the generic product and RLD is required to establish acceptance impurity limits.

D. Peptide-related impurities and aggregates may pose immunogenicity risks.

Summary

- Overview of some of the regulatory requirements for synthetic peptide generic drugs covered by the ANDA peptide guidance*
  - Comparative peptide-related impurity and aggregation profile characterization studies
  - Qualification of impurity levels and proposed specification limits based on the comparative impurity profile data
- Examples of deficiency language commonly communicated to ANDA applicants regarding compliance with the ANDA peptide guidance*

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Acknowledgement

Thank You !

DLBP/OLDP/OPQ

- *Cameron Smith*
- *Bing Cai*
- *Pahala Simamora*

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Questions?

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