Complex Peptide ANDAs: Test and Reference Product Comparability Studies from a Quality Perspective

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Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

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A quality product of any kind consistently meets the expectations of the user.

Drugs are no different.


Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is

assuring *every* dose is safe and effective, free of contamination and defects.

It is what gives patients confidence in their *next* dose of medicine.

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Outline

- Regulatory Pathway for Synthetic Generic Peptides
- Therapeutic Equivalence
- Peptide Characterization
- Peptide Comparability Studies
  - Higher Order Structure
  - Aggregation Profile
  - Impurity Profile
  - Biological Activity
- Formulation Changes
- Container Closure System

Regulatory Pathway

- Agency considers a polymer composed of 40 or fewer amino acids to be a peptide regulated under the FD&C Act*
- A pathway for complex synthetic peptide generic drug development under section 505(j) has been facilitated by a number of factors
  - The development of solid phase peptide synthesis and highly selective and sensitive analytical techniques
  - Potential to assess immunogenicity risk if the peptide product has
    - Defined starting materials
    - Characterizable peptide-related impurities
    - No glycosylation
    - No host cell proteins
- Draft Guidance for Industry: *ANDAs for Certain Highly Purified Synthetic Peptide Drug Products that Refer to Listed Drugs of rDNA Origin*, dated October 2017
  - A pathway for generic synthetic peptide drug development under section 505(j) for glucagon, liraglutide, nesiritide, teriparatide, and teduglutide
  - For other peptide products not covered, immunogenicity risk, and hence eligibility for approval under section 505(j), is assessed on a case-by-case basis

* FDA Guidance for Industry: *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2)*, December 2018, pp 13-14.

Therapeutic Equivalence

- For an ANDA submitted under section 505(j), the applicant must demonstrate that the proposed generic drug has therapeutic equivalence with the reference listed drug (RLD)
  - Pharmaceutical Equivalence
    - Same active ingredient(s)
    - Same dosage form
    - Same route of administration
    - Same strength
  - Bioequivalence
    - Under 21 CFR 320.22(b)(1), a drug product's in vivo bioavailability or bioequivalence may be considered ***self-evident*** and can be waived if it
      i. Is a parenteral solution intended solely for administration by injection, … and
      ii. Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full NDA or ANDA
- Most peptide injectable products are eligible for a “biowaiver”

Peptide Characterization and Comparability Studies

- Applicant must provide evidence to ensure the identity, strength, quality, and purity of the peptide drug substance
  - Includes characterization of primary peptide structure and physicochemical properties
  - Could be provided by the DMF holder but should also be generated one-time in-house
- Evidence should be provided to ensure the peptide higher-order structure, aggregation profile, impurity profile and biological activity *in the proposed finished drug product* are comparable to those of the RLD
- These studies are important for demonstrating that the proposed product has the appropriate biological activity and an integral part of the assessment of immunogenicity risk

Types of Comparability Studies

- Higher-order structure
  - Secondary structure
    - α-helix, β-sheet, random coil, unordered
  - Tertiary structure
    - overall monomer structure
- Aggregation
  - Can range from small oligomers (e.g., dimers) to large assemblies (sub-visible or visible particles)
  - Can form during production, storage, shipment, or delivery
  - Can nucleate around foreign particles, e.g., steel or rubber particles
- Impurities
  - Generally risk is with process impurities because degradative impurities would be expected to be the same as for the RLD
- Bioassay

General Considerations for Drug Product Comparability Studies

- Most peptide drug products are parenteral products (sterile solutions or lyophilized products to be reconstituted for injection)
- Comparability studies should be conducted on the finished drug product where possible (reconstituted as per the label instructions if necessary)
- Justification should be provided if it is not feasible to conduct a study on the finished drug product; sample manipulation should be minimized
- Each study should be conducted on a statistically meaningful number of lots of both the proposed drug product tested on or near release and at or near the end of the proposed shelf life, and the RLD tested on or near release and at or near expiry, after aging under conditions consistent with the label storage conditions
- Multiple orthogonal validated methods should be used for each comparability study class
- Sample ages should be provided for the dates of all studies
- Provide drug substance lot # used for each proposed drug product lot

Higher Order Structure Comparability Studies

- Demonstrate that the higher order structure found in the proposed product is comparable to that of the RLD
- Examples of Methods
  - Secondary
    - Far-UV CD (190 – 250 nm) (Far-Ultraviolet Circular Dichroism)
    - FTIR (Fourier Transform Infrared Spectroscopy)
    - Raman Spectroscopy
  - Tertiary
    - Near-UV CD (250 – 350 nm) (Near-Ultraviolet Circular Dichroism)
    - Intrinsic Fluorescence
    - DSC (Differential Scanning Calorimetry)
    - NMR (Nuclear Magnetic Resonance Spectroscopy)

Aggregation Comparability Studies

- Demonstrate that levels of aggregation found in the proposed product are the same as or less than those of the RLD
- In addition to label storage conditions, aggregation comparability studies should also be conducted on samples that have been subjected to stressed conditions
- Examples of Methods
  - Light Scattering
    - SEC-UV/MALS (Size Exclusion Chromatography-Ultraviolet/Multi-angle Light Scattering)
    - CG-MALS (Composition-Gradient MALS)
    - DLS (Dynamic Light Scattering)
  - Analytical Ultracentrifugation
    - SE-AUC (Sedimentation Equilibrium-Analytical Ultracentrifugation)
    - SV-AUC (Sedimentation Velocity-Analytical Ultracentrifugation)
  - Gel Electrophoresis
    - Denaturing - SDS-PAGE (Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis)
    - Non-Denaturing or Native
  - FFF (Field Flow Fractionation)
    - AF4 (Asymmetric Field Flow Fractionation)
  - MFI (Micro-Flow Imaging)

Allowable Formulation Changes

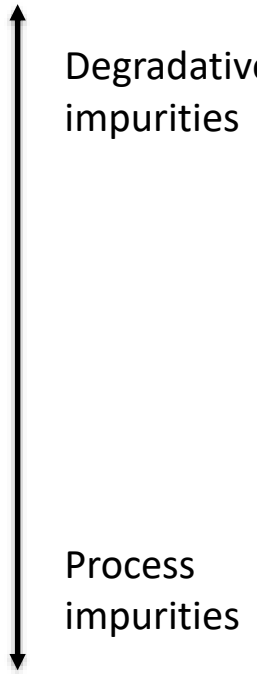
- As per 21 CFR 314.94 (a)(9)(iii):
- *Inactive ingredient changes permitted in (ANDA) drug products intended for parenteral use.* ... an applicant may seek approval of a drug product that differs from the reference listed drug in **preservative, buffer, or antioxidant** provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product
- The risk of changes such as these should be mitigated by additional higher order structure and aggregation comparability studies with the RLD

Proposed Changes to Buffer

- Deletion of or changes to the RLD buffer could potentially result in fluctuations of the pH outside of the proposed pH range and/or changes to the peptide conformation in solution and aggregation levels
- In this situation, comparative higher order structure and aggregation studies should also be conducted on test product samples whose pH is adjusted across and outside the proposed pH limits

Peptide Impurities

- Impurities and degradants may form during manufacture and storage
- Impurities may result from the insertion, deletion, or modification of amino acid sequences or residues; can be process or degradative in origin or both
  - Proteolysis
  - Deamidation
  - Oxidation
  - Reduction
  - Racemization
  - Deletion (incomplete coupling)
  - Truncation (missing amino acids)
  - Insertion (additional amino acids)
  - Incomplete deprotection (attached protective groups)
  - Disulfide exchange



Impurity Comparability Studies

- A comparative impurity profiling of the RLD and proposed generic product should be conducted to
  i. Demonstrate that impurities common to both the proposed product and the RLD are present in the proposed product at the same or lower levels than in the RLD
  ii. Analyze and characterize new impurities in the proposed product that are not common to the RLD
- Study should be conducted on a statistically meaningful number of lots of both the proposed product tested on or near release and at or near the end of the proposed shelf life, and the RLD tested on or near release and at or near expiry, after aging under conditions consistent with the label storage conditions (reconstituted as per the label instructions if necessary)
- Samples should be analyzed using multiple orthogonal validated analytical methods
  – Use of UHPLC-HRMS/MS should be considered to facilitate peak identification and ensure peak purity (see *Liquid Chromatography-High Resolution Mass Spectrometry for Peptide Drug Quality Control* by Zeng *et al*. *AAPS J.* **2015**, *17*, 643-651)
- Impurity limits
  – ICH Q3A/Q3B guideline states it does not apply to peptide drug products
  – Proposed limits should be justified by levels observed in the RLD or by safety evaluation (evaluation of toxicology and immunogenicity as appropriate)

Synthetic Peptide Drug Product ANDAs That Refer to RLD of rDNA Origin

- Draft Guidance for Industry: *ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin* dated October 2017
- Guidance covers the following five peptide drug products: glucagon, liraglutide, nesiritide, teriparatide, and teduglutide
- To submit an ANDA via 505(j) pathway:
  - Identify each peptide related impurity present in the proposed product at a level of 0.10% of the drug substance or greater
  - For each peptide-related impurity found in both the proposed product and the RLD, the proposed product level of such an impurity should be the same as or lower than that found in the RLD
  - Demonstrate that the proposed product does not contain any new peptide related impurities (i.e. not present in the RLD) at levels greater than 0.5% of the drug substance
  - Characterize any peptide related impurity found at levels ≥ 0.10% and ≤ 0.5% of the drug substance that is either not present in the RLD or is present in the proposed product at higher levels than that of the RLD, and provide justification as to why such an impurity does not affect the safety, effectiveness or potential for immunogenicity of the proposed product

Immunogenicity Risk

- For any new or elevated level peptide-related impurities found at levels of ≥ 0.10% and ≤ 0.5%, the risk of immunogenicity should be evaluated
  - T-cell activation via binding of peptide-related impurities to Major Histocompatibility Complex (MHC)
    - *In silico* studies of MHC binding, and
    - *In vitro* binding and functional assays of specific impurities
- Innate immune activity comparison between proposed generic and RLD formulated products
  - *In vitro* cell-based assays
  - Animal models

* Draft Guidance for Industry: *ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin*, dated October 2017

Container Closure System

- Evaluate proposed CCS with respect to protection (e.g., photostability), compatibility, safety, and performance
- Perform extractables and leachables studies
  - using sensitive analytical methods such as GC/MS and/or HPLC/MS
- Use CCS compatible with the drug product to minimize the amount of leachables
  - Demonstrate the absence of significant levels of leachables, or
  - Demonstrate comparability of leachable profiles between the proposed generic product and multiple batches of the RLD throughout the product shelf life

Summary

- Comparability studies should be conducted on samples of the proposed finished drug product and RLD
- Assessment of the following should be provided
  - Higher order structure
  - Aggregation profile
  - Impurity profile
  - Biological activity
  - Container closure system
- Allowable formulation changes will likely require further comparability studies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