Resolving Peptide Drug Challenges through Pre-ANDA Processes

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Disclaimer

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

During Your Complex Drug Product Development

Have you had the following symptoms:

- Confusion

  "If we propose an alternative formulation, would that be acceptable?"

- Headache

  "We are having technical difficulties when conducting necessary studies to comply with the product specific guidance (PSG). Help?"

- Fatigue

  "The PSG requirements are extensive. Can we propose to use alternative study design?"

- Depression

  "This is too difficult, we are abandoning this project."

Did you know you can ask the Agency for help?!

Outline

- Introduction: peptide drug products
  - Regulatory pathways
  - Guidance: Generic synthetic peptides referencing RLD of rDNA origin
- Case studies
  - Case 1: API characterization
  - Case 2: alternative formulation
  - Case 3: immunogenicity assessment

Goal: To show how you can utilize the Pre-ANDA processes to address challenges and obtain the Agency's guidance

Regulatory Paths for Peptide Drug Products

- Peptides (≤ 40 amino acids) and fully synthetic peptides (<100 amino acids) are regulated as drug under FD&C Act
  - 505(b)2 or 505(j)
- Guidance for Industry: ANDAs for Certain Highly Purified Synthetic Peptide Drug Products that Refer to Listed Drugs of rDNA Origin*
  - A pathway for generic synthetic peptide development under section 505(j) for glucagon, liraglutide, nesiratide, teriparatide, and teduglutide

* https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM578365.pdf

Sameness Consideration for Generics

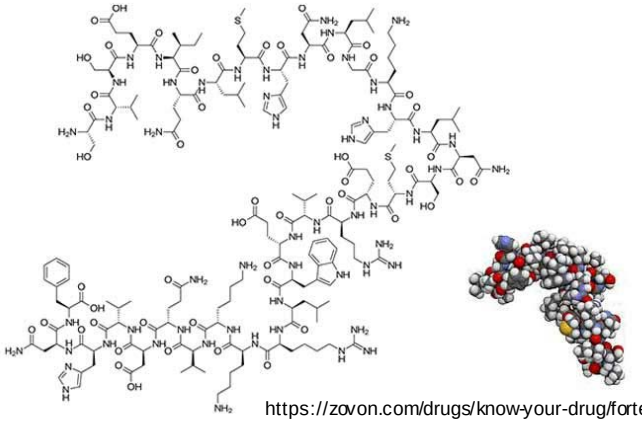
Generics are therapeutically equivalent to the reference listed drugs (RLDs)

- Freely substitutable with RLD
- Have the same clinical effect and safety profile when administered under conditions specified in the labeling

Pharmaceutical Equivalence

Active Pharmaceutical Ingredient

- Physiochemical properties
- Primary sequence
- Secondary structure



https://zovon.com/drugs/know-your-drug/forteo/

- Oligomer and higher order structures (& aggregates)
- Biological activities (*in vitro* or *in vivo*)

Impurities in Peptide Drug Products

- Peptide-related impurities
  - Degradation related
    - would be expected to be same between RLD and generic
  - Process related
    - Synthetic process related: deletion, insertion, etc.
- Host-cell related impurities (rDNA origin only)
- Residual chemicals
  - Follow FDA and ICH guidelines

Next…

Case Study 1: API Characterization

Question from firm A

We have performed the comparative studies (for primary and secondary structures) to demonstrate drug substance sameness to the RLD, we seek the agency's guidance on any additional characterization methods and considerations needed to demonstrate API sameness.

Response:

The studies you have proposed are insufficient in demonstrating API sameness.

In addition to ensuring primary and secondary structure sameness, attention also should also be given to higher order structures, possible aggregates, and bioactivities.

We recommend that you refer to *Guidance for Industry: ANDAs for Certain Highly Purified Synthetic Peptide Drug Products that Refer to Listed Drugs of rDNA Origin.*

After some product development, applicant returned with meeting request

Question: An excipient X interferes with the NMR analysis (data provided). To demonstrate API sameness, we propose the following studies

1. Extract the peptide, and conduct NMR in absence of the excipient.
2. Use alternative methods (including CD, SEC, IMS) in the presence of the excipient.

The method details and preliminary data showing the discriminating power of the proposed methods are provided.

Response:

We would grant your meeting request.

- We may request additional information to help us understand the methods you used and proposed

- Depending on the amount of information provided, we may provide concrete suggestions or general recommendations to your proposed study plan/design

Next…

Case Study 2: Alternative Formulations

Allowed Variation in Formulation

- Most of the peptide products are parenteral products, therefore, Q1/Q2 sameness to the RLD is generally expected.

- Per 21 CFR § 314.94 (a)(9)(iii), inactive ingredient changes permitted in parental drugs are limited to "preservatives, 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."

Question from firm B

We propose to use an **alternative buffer** in our proposed generic product. We believe the alternative buffer would **not affect the physiochemical** (pH and viscosity) properties of the drug product.

Is our proposed alternative buffer acceptable?

Response:

Per 21 CFR § 314.94 (a) (9) (iii), you may seek approval of a product that differs from the RLD in buffer provided that you identify and characterize the differences and provide information to demonstrate that the differences do not affect the safety or efficacy of the drug product.

Please conduct studies characterizing your proposed buffer's effect on API's properties, such as higher-order structures, aggregation, bioactivity and stability.

If any differences between the RLD and your drug product are observed due to the buffer difference, please provide justifications for how these differences would not affect efficacy and safety (including immunogenicity) of the drug product.

Lastly…

Case Study 3: Impurity Assessment

for the five products in the Guidance

Peptide-related Impurities

- For specified impurities common to proposed generic and RLD
  - Level in proposed generic ≤ RLD
- For any new impurities in the proposed generic
  - > 0.5% is not acceptable for submitting 505(j)
  - Impurities at 0.10%- 0.5% identified, characterized and justified for not affecting the safety and efficacy

Need to know RLD's impurity profile range

Immunogenicity Risk Assessment

Immunogenicity Risk Assessment

The risk of immunogenicity (both T-cell modulated and innate) for any new impurities found at impurity level of 0.1% - 0.5% should be evaluated

- T-cell activation through MHC binding by peptide-related impurities
  - *In silico* studies MHC binding
  - *in vitro* binding and functional assays of specific impurities
- Innate immune activity comparison between proposed generic and RLD products
  - *In vitro* cell-based assays
  - Animal models

Question from firm C

We found no new impurities in our proposed generic product, based on our LC-UV profiles of the RLD and our proposed product.

Does the Agency agree that we do not need to conduct immunogenicity assessment on our product, since we did not observe any new impurity.

Response

Your proposed LC-UV method is insufficient for comparing the impurity profiles of your product and the reference product.

The peptide impurities can co-elute with API and impurity peaks*, thus LC-UV based method would not be able to detect the low abundant co-eluting impurities.

Please conduct the impurity profiling using a highly sensitive (LOQ ≥ 0.1%) and selective method, such as UPLC-MS.

*Zeng et al. (AAPS Journal, 17, 643-651, 2015)

After method development, applicant returned with meeting request

An impurity unique in our proposed product is identified, and this impurity is detected at **NMT 0.3%**.

We conducted in silico **MHC binding** prediction and found the binding propensity to be no greater than that of the API peptide.

We seek the Agency's comment on the following:

1. Is our in silico MHC binding assessment sufficient?
2. If both in silico and in vitro MHC binding assessment show no increased immunogenicity risk with the new impurity, do we still need to evaluate innate immune activity, for the impurity as well as for the drug product?

Response:

1. The acceptability of your MHC binding assessment will be determined during the ANDA review. Please provide data and validation report in your submission to show your MHC predication model and algorithms have been properly validated.

2. Yes, you would need to demonstrate **both** the impurity and the whole product do not alter the innate immune activities, despite the predicated low MHC binding affinity.

Final Thoughts

- Developing complex generics can be challenging at times
- When in doubt, ask the Agency through pre-ANDA process
- Be prepared and do the necessary R&D
- Submit a complete package (e.g. rationale, experimental design and preliminary data)

Ultimately, we want to help you

- address some of these issues early, prior to submission
- to speed up the review of these complex generic application

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