Clinical Pharmacology Considerations for Peptide Drug Products

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Office of Clinical Pharmacology Guidance and Policy at CDER_OCP_GPT@fda.hhs.gov.

U.S. Department of Health and Human Services
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Clinical Pharmacology

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Clinical Pharmacology Considerations for Peptide Drug Products Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations to assist industry in the development of peptide drug products. Specifically, this guidance, when finalized, will describe the FDA's current thinking regarding the impact of clinical pharmacology considerations, including hepatic impairment, drug-drug interactions (DDIs), QTc prolongation risk, and immunogenicity risk on a peptide drug product's pharmacokinetics (PK), safety, and efficacy.

This guidance specifically outlines clinical pharmacology considerations for development programs for proposed peptide drug products submitted in a new drug application (NDA) under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and references other relevant guidances when appropriate. The term *peptide*, for purposes of this guidance, refers to any polymer composed of 40 or fewer amino acids.[2] In general, if a peptide meets the definition of a drug and does not otherwise meet the statutory definition of a "biological product"[3] or a "device,"[4] it would be regulated as a drug under the FD&C Act and be subject to all the "drug" requirements under the FD&C Act and FDA's regulations, including the requirement that new drugs must be approved under section 505(c) of the FD&C Act before they can be marketed in interstate commerce.[5] However, peptide drug products can have product characteristics that may be similar, in certain respects, to biological products, and as such, this guidance includes references to other FDA guidances on biological products that discuss scientific principles that could also be applicable to peptide drug products.

[1] This guidance has been prepared by the Office of Clinical Pharmacology in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] See, e.g., FDA Final Rule "Definition of the Term 'Biological Product'" (85 FR 10057 March 23, 2020).

[3] See section 351(i)(1) of the Public Health Service Act (42 U.S.C. 262(i)(1)); see also FDA Final Rule "Definition of the Term 'Biological Product'" (85 FR 10057, February 21, 2020).

[4] See section 201(h) of the FD&C Act.

[5] This guidance does not to apply to considerations for development programs for proposed peptide drug products submitted in abbreviated new drug applications (ANDAs) under section 505(j) of the FD&C Act.

Peptides can be isolated from animal tissue, produced synthetically, or produced through recombinant expression, and often serve as signaling molecules for many physiological functions. Recent drug development efforts have focused on improving the absorption, distribution, metabolism, and excretion (ADME) properties of native peptides, such as increasing oral bioavailability, increasing half-life, decreasing general hydrophobicity, and increasing conformational flexibility to increase selectivity of the intended target. To obtain more favorable ADME characteristics in patients, peptide drug products under development have included certain alterations to the peptide structure and/or incorporated new formulation strategies (e.g., liposomes). These structural alterations can include cyclization, pseudo-peptide bonds, unnatural amino acids, and peptide conjugations (e.g., PEGylation). As such, peptide drug products can exhibit distinct combinations of characteristics of both small and large molecules regarding their chemistry, pharmacology, pharmacokinetic disposition, and pharmacodynamics (PD). Of note, this guidance does not focus on the development of any particular peptide drug product. Any questions about regulatory requirements for a particular peptide drug product should be addressed to the appropriate FDA review division.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. CLINICAL PHARMACOLOGY CONSIDERATIONS

Given that peptide drug products can have product characteristics similar to both small-molecule drugs and biological products, evaluating the clinical pharmacology of peptide drug products often incorporates aspects of both drug product and biological product development programs, which are discussed in the sections below.[6]

However, there are some clinical pharmacology topics where FDA guidance already exists as it relates to the development of peptide drug products, such as:

- ***Bioanalytical Approach:*** All bioanalytical methods should be validated and reported as recommended in the FDA guidance entitled *M10 Bioanalytical Method Validation and Study Sample Analysis* (November 2022).[7]

[6] This guidance pertains to whether a peptide drug product can be shown to be safe and effective for its intended use under section 505(d) of the FD&C Act and does not address the analyses or studies may be needed to support a therapeutic equivalence evaluation.

[7] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

- ***Radiolabeled Mass Balance Studies:*** Unless clinical concerns suggest otherwise, human radiolabeled mass balance studies might not be recommended in certain circumstances, such as for drugs with known metabolism and elimination pathways based on basic pharmacology and nonclinical ADME information.[8]

- ***Impaired Renal Function***: Studies to characterize the impact of renal impairment on the PK are recommended for therapeutic proteins and peptides with a molecular weight less than 69 kDa.[9]

A. Considerations for Assessing Immunogenicity

1. Performing the Immunogenicity Risk Assessment

Most peptide drug products have the potential for immunogenicity; as such, sponsors should generally assess the immunogenicity risk for all peptide drug products. Assessing the immunogenicity risk for peptide drug products is similar to therapeutic proteins and involves understanding certain product-specific factors (e.g., molecular size and structure), process-specific factors (e.g., host cell proteins), subject-specific factors (e.g., disease state), and factors related to study design and product use (e.g., dosing regimen, route(s) of administration, and concomitant drugs). Factors related to immunogenicity risk of peptides are consistent with the scientific principles outlined in the FDA guidance for industry entitled *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014). In general, peptide drug products that are less than eight amino acids are not expected to be immunogenic unless there is an immunogenicity risk due to product impurities or aggregates.

Sponsors are encouraged to discuss their assessment of their product's immunogenicity risk (e.g., immunogenicity risk assessment) and how that risk will inform their evaluation of the anti-drug antibody (ADA) incidence, titers, and neutralizing activity and their impact on PK, PD, efficacy, and safety (e.g., clinical immunogenicity assessment) early in the development program with the Agency.

2. Performing the Clinical Immunogenicity Assessment

A multitiered clinical immunogenicity assessment of a peptide drug product should be informed by the immunogenicity risk assessment and conducted in a manner consistent with the scientific principles described in the FDA guidances *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014) and *Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection* (January 2019). For a peptide drug product with multiple domains, it might be appropriate to develop multiple assays

[8] For more information, see the draft FDA guidance for industry entitled *Clinical Pharmacology Considerations for Human Radiolabeled Mass Balance Studies* (May 2022). When final, this guidance will represent the Agency's current thinking on this topic.

[9] For more information, see the draft FDA guidance for industry entitled *Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing* (September 2020). When final, this guidance will represent the Agency's current thinking on this topic.

to measure the immune responses to the different domains. For a peptide product with sequence homology to an endogenous protein or peptide counterpart, it might also be appropriate to develop an assay to measure cross-reactivity of ADAs between the peptide drug product and endogenous counterpart. The need for and design of these assays should be informed by the immunogenicity risk and clinical concerns and should be discussed with the Agency.

3. Conducting the Immunogenicity Clinical Impact Analysis

The clinical immunogenicity assessment should be designed to assess the clinical impact of ADAs on the peptide drug product's PK, PD, efficacy, and safety. Specifically, both between-subject (i.e., between subjects who test ADA positive and those who test ADA negative) and within-subject comparisons (i.e., before ADA positive and after ADA positive) should be assessed. For all individual subjects who test ADA positive, further evaluation on the effects of antibody titers and neutralizing antibodies on the peptide drug product's PK, PD, efficacy, and safety should be assessed.

B. Characterizing the Impact of Hepatic Impairment

Peptides are generally metabolized by endopeptidases, then further degraded to amino acids by exopeptidases. Due to the ubiquitous availability of proteases and peptidases throughout the body, proteolytic degradation of many peptides is rapid and not limited to organs typically associated with drug elimination, such as the liver. Therefore, hepatic metabolism rarely plays a significant role in the clearance of peptides. However, emerging evidence suggests that under certain circumstances it might be important to characterize the impact of hepatic impairment on the PK of some peptide drug products. Below are some characteristics that could result in a recommendation for a hepatic impairment assessment, such as conducting a dedicated hepatic impairment study:

- Peptide drug products that are found to be substantially metabolized by liver enzymes (> 20 percent of the systemically available drug) based on nonclinical models could have increased plasma exposure due to hepatic impairment.

- Peptide drug products that result from certain modifications, such as cyclic peptides (e.g., cyclosporine and voclosporin), could render them susceptible to substantial metabolism by liver enzymes.

- Peptide drug products that are substantially eliminated through biliary excretion ($\geq$ 20 percent of systemically available drug or active metabolite is eliminated unchanged in the bile), as determined by basic pharmacology and nonclinical ADME studies (i.e., bile-duct cannulated animal models), could have increased plasma exposure due to hepatic impairment, even if hepatic metabolism is not significant.

- Peptide drug products that are conjugated with a lipid group (e.g., fatty acids or cholesterol) can be highly bound to serum albumin and lipids, and their elimination rate could be affected by the levels of serum albumin and lipids. Patients with chronic liver diseases, because of the potential for lower levels of serum albumin, could have an

increased elimination rate for certain types of peptide drug products (e.g., alkylated or acylated peptides).

- Peptide drug products that are being developed for an indication with the liver as a target organ or in cases when the peptide drug product can be characterized as targeting the liver (e.g., GalNAc residues in the molecule) could be affected by hepatic impairment. As changes in liver function can result in pharmacodynamic changes that are independent of systemic pharmacokinetic changes, whenever appropriate and feasible, pharmacodynamic assessments should be included.

- Peptide drug products that are subject to target-mediated drug disposition may have altered PK in patients with hepatic impairment as a result of changes in target expression. Whenever appropriate and feasible, pharmacodynamic assessments should be included.

Regardless of the above characteristics, there could be special considerations when the peptide drug product is being developed for a liver disease where hepatic impairment is common.[10] For peptide drug products being developed for this population, the sponsor should assess the need for performing a hepatic impairment assessment and provide adequate justification for not performing an assessment based on the characterization of the peptide drug product.

Sponsors are encouraged to discuss the hepatic impairment assessment with the Agency early in development to determine the most appropriate approach. Recommendations describing the design of hepatic impairment assessments can be found in FDA guidances entitled *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling* (May 2003) and *Population Pharmacokinetics* (February 2022).

C. Considerations for Assessing Drug Interactions

1. Pharmacokinetic Interactions

a. Peptide drug product as substrates for CYP enzymes and transporters

In general, peptide drug products are primarily metabolized by proteolytic or hydrolytic enzymes such as endopeptidases, aminopeptidases, and carboxypeptidases, or are chemically modified to resist degradation, and are not metabolized by cytochrome P450 (CYP) enzymes. Therefore, the disposition of peptide drug products is not anticipated to be affected by inhibitors or inducers of CYP enzymes. Similarly, modulation of efflux transporters, such as P-gp and BCRP, or hepatic uptake transporters such as OATP1B1 and OATP1B3, or renal uptake or efflux transporters, such as OAT1, OAT3, OCT2, MATE1, and MATE2/K are generally not anticipated to have a significant impact on the PK of peptide drug products. There are cases when peptide drug products can be substrates of certain peptide transporters or amino acid transporters and could be subject to drug interactions.

[10] A dedicated hepatic impairment study should be conducted for a drug candidate developed for nonalcoholic steatohepatitis to characterize the effects of hepatic impairment on the drug's PK. See the FDA draft guidance *Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment* (December 2018). When final, this guidance will represent the Agency's current thinking on this topic.

However, there are structural modifications to peptide drug products, such as cyclic peptides (e.g., cyclosporine and voclosporin) that could render them susceptible to CYP enzyme-mediated metabolism and transporter-mediated disposition. In vitro experiments related to CYPs and transporters may be scientifically appropriate when hepatic and/or biliary excretion accounts for ≥20 percent of the overall elimination and/or the drug's target organ is the liver. For more information, see the FDA guidance entitled *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry* (January 2020). Additionally, in vitro experiments to evaluate a drug as a substrate of renal transporters may be appropriate for drugs with renal active secretion that accounts for ≥25 percent of systemic clearance of the drug and/or a drug that has renal toxicity. Sponsors should provide their plans and rationale early in development to evaluate whether peptide drug products are substrates of CYP enzymes and drug transporters.

b. Peptide drug products as inhibitors and inducers of CYP enzymes and transporters

In general, peptide drug products are not expected to significantly modulate CYP enzymes and drug transporters. However, there are structural modifications to peptide drug products (e.g., cyclosporine and voclosporin) that could lead to modulation of CYP enzymes and drug transporters. In addition, there are cases where peptides indirectly affect CYP enzymes or transporters. One example is somatostatin analogs (e.g., lanreotide and octreotide) that reduce or are suspected to reduce the clearance of co-administered drugs indirectly by modulating the expression of CYP enzymes. For each development program, sponsors should provide their plans to evaluate the drug interaction liability of peptide drug products, as recommended in the FDA guidance entitled *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry* (January 2020). Regarding the recommendations for clinical assessment of DDIs, refer to the FDA guidance entitled *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry* (January 2020).

Additionally, certain peptide drug products could alter the PK of concomitant drugs as a result of their mechanism of action. For example, glucagon-like peptide-1 (GLP-1) receptor agonists (e.g., exenatide and liraglutide) could delay gastric emptying of co-administered oral drugs. Also, in situations where the mechanism of action of the peptide drug product could affect the PK of co-administered products, the sponsor should evaluate the peptide drug product as a perpetrator.

2. Pharmacodynamic Interactions

Peptide drug products can exhibit pharmacodynamic interactions with a concomitant drug when the pharmacological effect of one drug is altered by that of another drug (e.g., concomitant use of vasopressin with catecholamines can result in an additive effect on mean arterial pressure and other hemodynamic parameters). Sponsors are encouraged to consult with the FDA regarding assessment of pharmacodynamic drug interactions.

D. Characterizing QT Interval Prolongation

Peptides comprised of only naturally occurring amino acids have a low likelihood of direct ion channel interactions, and a thorough QT study is generally not scientifically warranted, unless the potential for proarrhythmic risk is suggested by mechanistic considerations or data from clinical or nonclinical studies.

When indicated, an assessment of QTc prolongation risk and a proposed QTc assessment plan should be submitted as described in the FDA guidances entitled *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (October 2012), the *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs Questions and Answers (R3)* (June 2017), and *E14 and S7B Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential--Questions and Answers (*August 2022*).* All proposals in the QTc assessment plan should contain a rationale and be discussed with the Agency. The timing and extent of the clinical QTc assessment depend upon the overall risk/benefit profile of the peptide drug product.

III. LABELING CONSIDERATIONS

For all prescription drug products, labeling must contain a summary of the essential scientific information needed for the safe and effective use of the product,[11] and the labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular.[12]

The Prescribing Information must include information about the PK and PD of the peptide drug product to inform its safe and effective use by the health care provider.[13,14] The labeling for peptide drug products – which are primarily metabolized by proteolytic or hydrolytic enzymes – should include the following (or similar) statement under the Metabolism subheading under the Elimination heading in the *Pharmacokinetics* subsection of the CLINICAL PHARMACOLOGY section:

> [Insert Drug Name] is expected to be metabolized into small peptides by catabolic pathways.

It is not necessary to include a statement in the CLINICAL PHARMACOLOGY section that peptide drug products do not have a clinically significant drug interaction with CYP inhibitors or CYP inducers because the catabolic metabolism of peptides is expected to be understood by

[11] 21 CFR 201.56(a)(1).

[12] 21 CFR 201.56(a)(2).

[13] See 21 CFR 201.57(c)(13).

[14] For more information, see the FDA guidance for industry entitled *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (December 2016).

healthcare providers; therefore, such information is not needed for the safe and effective use of the drug product.[15]

Given the potential for immunogenicity generally associated with peptide drug product administration, the labeling for such products should include immunogenicity information, consistent with the principles proposed in FDA's draft guidance *Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling — Content and Format* (February 2022).[16] In general, the labeling for peptide drug products that are less than eight amino acids that are without concerns for impurities and/or aggregates do not need to include immunogenicity information because an immunogenicity assessment would likely not be relevant to the assessment of a drug's safety and effectiveness.[17]

The recommendations in other Prescribing Information guidances for drug products generally apply to peptide drug products and the principles from other Prescribing Information guidances for biological products may also be relevant.[18,19,20,21] For additional human prescription drug labeling guidance documents, see the FDA's Labeling Resources for Human Prescription Drugs website.[22]

[15] 21 CFR 201.56(a)(1).

[16] For proposed recommendations on how to incorporate immunogenicity information into the labeling of peptide drug products, see the FDA draft guidance for industry entitled *Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling — Content and Format* (February 2022). When final, this guidance will represent the FDA's current thinking on this topic.

[17] See 21 CFR 201.56(a).

[18] For more information, see the draft FDA guidance for industry entitled *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023). When final, this guidance will represent the Agency's current thinking on this topic.

[19] For more information, see the FDA guidance for industry entitled *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (December 2016).

[20] For more information, see the FDA guidance for industry entitled *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Prescription Drug and Biological Products — Content and Format* (October 2011).

[21] For more information, see the FDA guidance for industry entitled *Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (December 2014).

[22] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources. Accessed August 2023.