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

Guidance for Industry

DRAFT GUIDANCE

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

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Generics

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ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 is intended to assist potential applicants in determining when an application for a synthetic peptide drug product (synthetic peptide) that refers to a previously approved peptide drug product of recombinant deoxyribonucleic acid (rDNA) origin (peptide of rDNA origin) should be submitted as an abbreviated new drug application (ANDA) under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) rather than as a new drug application (NDA) under section 505(b) of the FD&C Act. Specifically, this guidance covers the following five peptide drug products: glucagon, liraglutide, nesiritide, teriparatide, and teduglutide.

Given the current state of technology for peptide synthesis and characterization, FDA believes it is now possible for an ANDA applicant to demonstrate that the active ingredient in a proposed generic synthetic peptide drug product (proposed generic synthetic peptide) is the "same" as the active ingredient in a previously approved peptide of rDNA origin. For a synthetic peptide that is intended to be a "duplicate"[2] of a previously approved peptide of rDNA-origin, a determination of whether an application for the synthetic peptide should be submitted as an ANDA depends largely on its impurity profile as compared to the impurity profile for the peptide of rDNA origin. Differences in impurities, particularly peptide-related impurities, may affect the safety or effectiveness of a peptide drug product.

Submission of an ANDA for a proposed generic synthetic peptide for which the reference listed drug (RLD) is a peptide of rDNA origin generally would be appropriate if, among other things, the applicant can: 1) show that, for each peptide-related impurity that is found in both the proposed generic synthetic peptide and the RLD, the level of such impurity in the proposed generic synthetic peptide is the same as or lower than that found in the RLD; 2) show that the proposed generic synthetic peptide does not contain any new specified peptide-related impurity

[1] This guidance has been prepared by the Office of Generic Drugs (OGD) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] The term "duplicate" generally refers to a drug product that has the same active ingredient(s), dosage form, strength, route of administration, and conditions of use as a listed drug. See Abbreviated New Drug Application Regulations; Proposed rule (54 FR 28872 at 28877, July 10, 1989).

that is more than 0.5 percent of the drug substance; 3) characterize each new specified peptide-related impurity; and 4) justify for each new specified peptide-related impurity that is no more than 0.5 percent of the drug substance why such impurity does not affect the safety of the proposed generic synthetic peptide and does not affect its effectiveness.[3]

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. BACKGROUND

FDA considers any polymer composed of 40 or fewer amino acids to be a peptide regulated under the FD&C Act, rather than a protein regulated under the Public Health Service Act.[4] Accordingly, glucagon, liraglutide, nesiritide, teriparatide, and teduglutide are peptides subject to regulation under the FD&C Act.

In order for FDA to approve an ANDA, an applicant must demonstrate, among other things, that the proposed generic drug[5] has the "same" active ingredient(s), conditions of use, dosage form, route of administration, strength, and (with certain permissible differences) labeling as the RLD, and is bioequivalent to its RLD.[6] Additionally, FDA must find that the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the generic drug are adequate to assure and preserve its identity, strength, quality, and purity.[7]

In the past, analytical methods have not always been capable of adequately characterizing peptide products for submission in an ANDA. However, given the current state of technology for peptide synthesis and characterization, FDA now believes it is possible for an ANDA applicant to demonstrate that the active ingredient in a proposed generic synthetic peptide is the

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[3] For definitions of specified and unspecified impurities, see guidances for industry *ANDAs: Impurities in Drug Substances* and *ANDAs: Impurities in Drug Products*, and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidances *Impurities in New Drug Substances* (ICH Q3A(R2)) and *Impurities in New Drug Products* (ICH Q3B(R2)). The guidances referenced in this document are available at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[4] Guidance for industry *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* at 13-14. Unless a peptide otherwise meets the statutory definition of a *biological product* (e.g., a peptide vaccine), it will be regulated as a drug under the FD&C Act.

[5] Throughout this guidance we use the term *generic drug* to refer to a new drug product described in an ANDA submitted under section 505(j) of the FD&C Act.

[6] See section 505(j)(2)(A) of the FD&C Act. An applicant may submit a petition seeking permission to submit an ANDA for a change in route of administration, dosage form, strength, or one active ingredient in a fixed combination drug product. See 21 CFR 314.93.

[7] Section 505(j)(4) of the FD&C Act.

same as the active ingredient in the RLD that is of rDNA origin, and demonstrate that such products are pharmaceutical equivalents.

All ANDAs must contain a description of the composition, manufacture, and specifications of the drug substance and the drug product.[8] An ANDA applicant is required to submit a full description of the drug substance including its physical and chemical characteristics and stability; the method of synthesis (or isolation) and purification of the drug substance; and, the specifications necessary to ensure the identity, strength, quality, and purity of the drug substance and the bioavailability of the drug products made from the substance.[9] To ensure purity, applicants should propose and justify appropriate limits on the impurities in their drug substances and drug product.[10]

In reviewing an ANDA, FDA considers the types and amounts of impurities present in a proposed generic drug in comparison to its RLD.[11] While certain differences in impurity profiles between a proposed generic drug and the RLD may be permissible, FDA evaluates whether a generic drug contains impurities at levels greater than those found in the RLD and whether the impurities, including new impurities, are otherwise justified to help ensure, among other things, that the generic drug does not pose a greater safety risk than the RLD.

Whether a peptide is produced by a recombinant or synthetic process, impurities may result from the insertion, deletion, or modification of amino acid sequences or residues. These impurities generally pose minimal safety or efficacy risks and can be controlled. However, in some circumstances, peptide-related impurities may create the potential for differences in immunogenicity or may otherwise affect the safety or effectiveness of a peptide drug product. Because of these concerns about the potential for immunogenicity for glucagon, liraglutide, nesiritide, teriparatide, and teduglutide, the type of application that should be submitted for a proposed synthetic peptide that refers to a peptide of rDNA origin depends largely on the type of data that would be necessary to evaluate the differences in impurities between the proposed product and the previously approved product.[12]

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[8] 21 CFR 314.94(a)(9) and 314.50(d)(1).

[9] 21 CFR 314.94(a)(9)(i) and 314.50(d)(1)(i).

[10] FDA may refuse to receive an ANDA that is incomplete because it does not on its face contain information required under section 505(j) of the FD&C Act or 21 CFR 314.94, which includes a demonstration of the purity of the drug substance and drug product and information on the impurities and residues (21 CFR 314.101(d)(3) and 314.94(a)(9) (requiring ANDA to contain the information required under 314.50(d)(1)). See guidance for industry *ANDA Submissions – Refuse to Receive for Lack of Proper Justification of Impurity Limits*.

[11] See, e.g., guidances for industry: *ANDAs: Impurities in Drug Substances* and *ANDAs: Impurities in Drug Products*.

[12] Based on the types of data permitted to be submitted in an ANDA, FDA does not believe that an ANDA could include sufficient evidence for approval of a proposed peptide of rDNA origin at this time (see section 505(j)(2)(A) of the FD&C Act). This reflects the Agency's view, based on currently available technologies, that clinical data would be needed to assess potential immunogenicity risks associated with a proposed generic peptide of rDNA origin. An applicant may file a 505(b)(2) application if it is seeking approval for a drug product that is ineligible for approval under section 505(j) of the FD&C Act (e.g., because clinical studies would be required to demonstrate the safety or effectiveness of the proposed drug product). An applicant seeking approval of a proposed peptide of rDNA origin may also consider a "stand-alone" NDA submitted under section 505(b)(1) of the FD&C Act.

The recommended conditions for submission of an ANDA for the peptides covered by this guidance are designed primarily to help ensure that the risk of immunogenicity due to peptide-related impurities will not differ from that of the RLD of rDNA origin.

III. SCIENTIFIC CONSIDERATIONS FOR ANDAS FOR PROPOSED GENERIC SYNTHETIC PEPTIDES

A. Active Ingredient Sameness

A crucial factor in determining whether an ANDA meets the statutory requirements for approval is whether the active ingredient in the proposed generic drug is the "same" as that of the RLD.[13] The sameness of active ingredient in a proposed generic synthetic peptide can be established through physicochemical characterization and biological evaluation. Although compendial standards may be available for some peptides covered by this draft guidance, comparative testing of the proposed generic synthetic peptide and RLD product is recommended, as applicable. ANDA applicants are encouraged to apply orthogonal analytical methods to characterize the following properties and other properties, as appropriate:

- Primary sequence and physicochemical properties
- Secondary structure
- Oligomer/Aggregation states
- Biological activities (by in vitro or animal studies)

Where data demonstrate that the proposed synthetic peptide's active ingredient is the "same as" the active ingredient in the RLD, whether an application should be submitted as an ANDA or as an application submitted pursuant to section 505(b)(2) of the FD&C Act, may depend on the proposed product's impurity profile, because differences in impurities may affect, among other things, the potential for immunogenicity.

B. Impurities

In reviewing an ANDA, FDA considers the types and amounts of impurities present in a proposed generic drug in comparison to its RLD.[14] In general, a proposed generic synthetic peptide should not contain impurities at levels greater than those found in the RLD. Any impurities, including new impurities, should be justified to help ensure, among other things, that the generic drug does not pose a greater safety risk, including with respect to immunogenicity, than the RLD.

Regardless of whether a peptide drug product is produced by a recombinant or synthetic process, it may contain impurities resulting from degradation during product storage or from the method of producing the peptide. Impurities that result from degradation during storage of the product, rather than from how the peptide is produced, would be expected to be the same where the RLD

[13] Section 505(j)(2)(A)(ii)(I) of the FD&C Act. *Active ingredient* is defined at 21 CFR 314.3(b).

[14] See, e.g., guidances for industry *ANDAs: Impurities in Drug Substances* and *ANDAs: Impurities in Drug Products*.

and proposed generic synthetic peptide have the same active ingredient, generally the same inactive ingredients[15], and the same labeled storage conditions. FDA will generally consider the sameness of active ingredient, inactive ingredients, storage conditions, and impurities that result from degradation in its evaluation of an ANDA for a peptide drug product in the same manner it does for ANDAs for non-peptide drug products.

Impurities may also occur as a result of the specific process used to produce the peptide. The impurities produced by rDNA technology can be divided into three categories:

- Peptide-related impurities
- Host cell-related impurities
- Other (non-peptide-related) impurities

Peptide-related impurities include amino acid sequences related to, but different from, that of the active ingredient, as a result of insertion, deletion, or other modifications (e.g., oxidation or glycosylation) to the amino acid sequence, and residues of the peptide. Host cell-related impurities include host cell DNA and host cell proteins. Other impurities include residual solvents, reagents, and metals. Peptide-related impurities and other (non-host cell-related) impurities may result from the production of a peptide by both recombinant and synthetic processes. Host cell-related impurities, however, occur only in rDNA-origin peptide drug products.

Differences between the peptide-related impurities in a proposed generic synthetic peptide and those in an RLD of rDNA origin could produce different impurity profiles which could adversely affect the safety or effectiveness of a synthetic peptide product, if uncontrolled. The peptide-related impurity profiles for approved peptides of rDNA origin have been well characterized for the peptides covered by this guidance. Therefore, it may be feasible to compare the peptide-related impurity profile of a proposed generic synthetic peptide to its RLD. Further, FDA believes it is possible to identify and reduce or mitigate risks related to peptide-related impurities considering the advances in analytical chemistry, synthetic peptide manufacturing and purification technology, and biological assays.[16]

FDA recommends that applicants apply sensitive and high resolution analytical procedures (e.g., UHPLC-HRMS)[17] to detect and characterize peptide-related impurities in a proposed generic synthetic peptide in comparison to the RLD. In general, for the peptides covered by this guidance, applicants should identify each peptide-related impurity that is 0.10 percent of the drug substance or greater. Depending on the potential immunogenicity risk of a particular product,

[15] At present, approved drug products for the five peptides covered by this guidance are all intended for parenteral use. A parenteral drug product generally must contain the same inactive ingredients and in the same concentration as the reference listed product. See 21 CFR 314.94(a)(9)(iii); see also guidance for industry *ANDA Submissions—Refuse-to-Receive Standards*.

[16] Because peptide-related and other impurities come from the starting materials, reagents, solvents, and the process used, an ANDA applicant would be able to determine what impurities might occur and could take steps (e.g., follow FDA and ICH guidances) to ensure that such impurities in a proposed synthetic peptide are within allowed limits.

[17] See, e.g., Zeng K, et al., Liquid Chromatography-High Resolution Mass Spectrometry for Peptide Drug Quality Control, AAPS J, 17(3), 643-51 (2015).

applicants may be asked to also identify peptide-related impurities present at levels below this threshold. Applicants should ensure for each peptide-related impurity that is found in both the proposed generic synthetic peptide and the RLD the level of the peptide-related impurity in the proposed generic synthetic peptide is not more than that found in the RLD (e.g., by adjusting synthetic route or purification strategies).

Based on an understanding of the peptide-related impurities that could be present in the peptides covered by this guidance, and given current analytical capabilities and current manufacturing capabilities to control peptide-related impurities, FDA believes that filing of an ANDA for one of the peptides covered by this guidance would be generally appropriate if, among other things, the new specified peptide-related impurity level for the proposed generic synthetic peptide is no more than 0.5 percent of the drug substance. A new specified peptide-related impurity level higher than 0.5 percent of the drug substance raises concerns about the potential risk of immunogenicity that FDA believes could not be adequately addressed in an ANDA (e.g., assessment of the risk of immunogenicity would require clinical data under these circumstances).

A new specified peptide-related impurity level of no more than 0.5 percent of the drug substance for purposes of filing an ANDA is consistent with the small amount of unspecified peptide-related impurities observed in finished peptide drug products due to batch-to-batch variability, which occurs regardless of whether the peptide is produced by a recombinant or synthetic process. This allowance is, however, subject to subsequent scientific review upon the filing of an ANDA and FDA may ask the ANDA applicant to further reduce the level of a specified peptide-related impurity depending on the risks associated with a particular impurity as well as with the proposed drug product.

For each new specified peptide-related impurity that is not more than 0.5 percent of the drug substance, the ANDA applicant should characterize the impurity. Further, the ANDA applicant should provide justification for why such impurity does not affect the safety of the proposed generic synthetic peptide (including with respect to immunogencity) and why it does not affect its effectiveness. This justification should take into consideration, among other things, the identity and amount of an impurity, the impurity's impact on the physicochemical and biological properties of the peptide, and the potential risks specific to the peptide.[18] The justification should include data showing that any differences in impurities between the proposed generic synthetic peptide and the RLD do not modify each of the following: the physicochemical property, biological activity, or immunogenicity risk of the product. Such data should demonstrate for each new impurity that the impurity does not contain sequences that have an increased affinity for major histocompatibility complex (MHC), known as *T-cell epitopes.* Further, the data should demonstrate that the proposed generic synthetic peptide does not increase the aggregation propensity or the quality of the aggregates formed, especially under stress conditions, and does not contain impurities or contaminants that produce a greater or distinct stimulation of innate immune activity as compared to the RLD. Based on the

[18] For example, where a peptide drug has a sequence identical to part of a human endogenous protein, and some function(s) of the protein is non-redundant, if an immunogenic response that leads to antibodies directed against the endogenous protein occurs it could have far reaching consequences.

information provided, FDA may recommend that additional non-clinical immunogenicity evaluations be completed for the proposed generic synthetic peptide.

IV. SUBMISSION OF ANDAS FOR PROPOSED GENERIC SYNTHETIC PEPTIDES

The submission of an ANDA for a synthetic glucagon, liraglutide, nesiritide, teriparatide, or teduglutide that references an approved peptide of rDNA origin would be generally appropriate if the statutory and regulatory requirements for an ANDA are met and, with respect to active ingredient sameness and impurities,[19]:

- The proposed generic synthetic peptide is characterized to show the sameness of the active ingredient to that of the RLD with respect to the following properties:
  - Primary sequence and physicochemical properties,
  - Secondary structure,
  - Oligomer/aggregation states, and
  - Biological activity/function (by in vitro or animal studies);
- For each peptide-related impurity that is found in both the proposed generic synthetic peptide and the RLD, the level of such impurity in the proposed product is the same as or lower than that found in the RLD;
- The proposed generic synthetic peptide does not contain any new specified peptide-related impurity (i.e., an impurity that is not also present in the RLD) that is more than the acceptance threshold for a new impurity (i.e., 0.5 percent of the drug substance); and
- For any new specified peptide-related impurity that is no more than 0.5 percent of the drug substance, the applicant has characterized the impurity (e.g., the amino acid sequence and structure) and provided a justification for why each such impurity does not affect the safety of the proposed generic synthetic peptide drug product (including with respect to immunogenicity) and does not affect its effectiveness.

For such applications, FDA recommends that the applicant identify in the ANDA each peptide-related impurity that is 0.10 percent of the drug substance or greater.

Also for each new specified impurity that is no more than 0.5 percent of the drug substance, the applicant should provide justification, including data, to show that any differences in impurity profiles between the proposed generic synthetic peptide and the RLD do not modify each of the following: the physicochemical properties, biological activity, or immunogenicity risk of the

[19] Determinations as to whether FDA will receive for substantive review or approve an ANDA will be made subsequent to submission. Applicants are encouraged to review the following guidances for industry for more information: *ANDA Submissions – Content and Format of Abbreviated New Drug Applications*, *ANDA Submissions – Refuse-to-Receive Standards*, *ANDA Submissions – Refuse-to-Receive for Lack of Justification of Impurity Limits*, and *Immunogenicity Assessment for Therapeutic Protein Products*, (noting that "[a]lthough this guidance focuses on therapeutic protein products, the scientific principles may also apply to … peptides").

product. For example, such data should demonstrate that each new impurity does not contain sequences that have an increased affinity for MHC, known as T-cell epitopes, and that the proposed generic synthetic peptide does not alter the innate immune activity.

FDA may recommend conducting additional comparative studies that can be required under section 505(j) of the FD&C Act (e.g., in vitro, in vivo animal, pharmacokinetic/pharmacodynamic equivalence), as appropriate, to assess whether a proposed generic synthetic peptide meets relevant approval standards, including that the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the drug are adequate to assure and preserve its identity, strength, quality, and purity.

If it is necessary to conduct clinical studies to establish the safety or effectiveness of a proposed synthetic peptide that seeks to rely, in part, on FDA's finding of safety or effectiveness for a previously approved product, submission of an application under the abbreviated pathway described in section 505(b)(2) of the FD&C Act would be necessary. Once an application for a synthetic peptide product has been approved under section 505(c) of the FD&C Act, subsequent applications for that synthetic peptide product may be submitted as ANDAs.

VI. REQUESTING ASSISTANCE FROM FDA

An applicant developing a proposed generic synthetic peptide for one of the peptides covered by this guidance may contact the Office of Generic Drugs (OGD) to confirm whether the application may be submitted as an ANDA. An applicant may submit a controlled correspondence[20] to or request a pre-ANDA meeting with OGD. Controlled correspondence is appropriate if an applicant has a specific and targeted inquiry about the generic drug development process. The pre-ANDA meeting is appropriate for a prospective applicant seeking a dialogue with the Agency on a particular matter outside the scope of controlled correspondence. Requests for pre-ANDA meetings should be submitted to GenericDrugs@fda.hhs.gov.

[20] See guidance for industry *Controlled Correspondence Related to Generic Drug Development* for information on the types of inquiries accepted as controlled correspondence and submission of controlled correspondence to OGD.