

US FDA regulatory framework for generic peptides referring to rDNA origin reference products

Abstract:

Peptides are polymeric molecules having 40 or less amino acids. Peptides have been used as therapeutic compounds for the treatment of various disorders since 1920s. Initially, these were isolated from animals. Currently, most of the therapeutic peptides are either synthetic or produced by rDNA technology. Given the continuously improving synthesis technology and availability of robust characterization tools, it is now possible to synthesize a generic therapeutic peptide for a reference product which is of rDNA origin. The manufacturing of synthetic generic peptides is generally considered more advantageous than recombinant generic peptides due to low risk of immunogenicity and absence of host cell derived biomolecules. This article compares the approval process of generic peptides for a reference product of rDNA origin in the United States especially in light of US FDA guideline “ANDAs for certain highly purified synthetic peptide drug products that refer to listed drugs of rDNA Origin”. This guideline provides recommendations for evaluating whether an ANDA submission is appropriate for a synthetic peptide referring to previously approved glucagon, liraglutide, nesiritide, teriparatide, and teduglutide of rDNA origin. The requirements for ANDA submissions for synthetic generic peptides and 505(b) (2) submissions for generic peptides of rDNA origin are compared.

Background:

Peptides are defined by the US FDA as polymers of α -amino acid with defined sequences having 40 amino acids or less. Therapeutic usage of peptides dates back to 1920s with the advent of insulin for the

treatment of diabetes. Since then, peptides manufacturing has moved from extractions from animal tissues, to chemical synthesis and recombinant DNA technology (1). Structurally the peptides are in between small molecules and proteins (Figure 1).

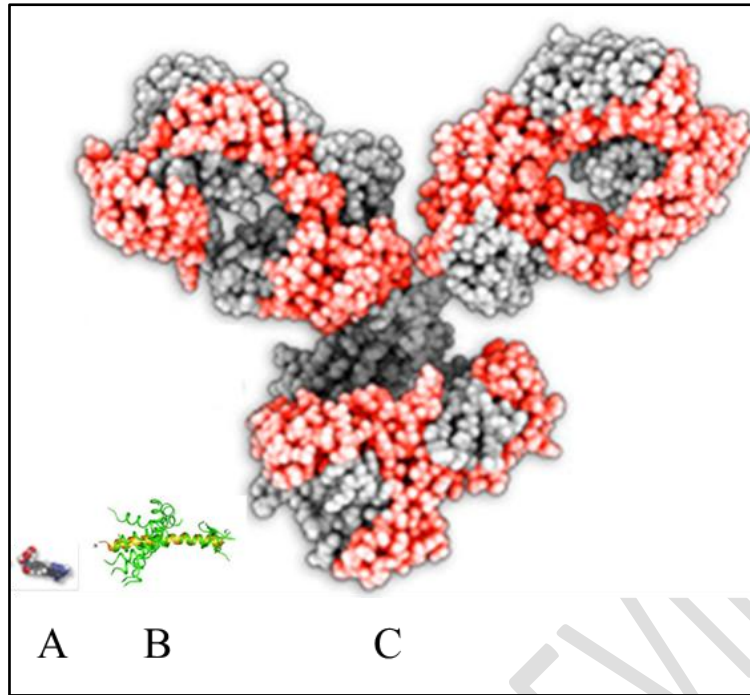


Figure 1: Size comparison of A: Methotrexate (454 Da), B: Teriparatide (4118 Da) and C: Monoclonal antibody (150 kDa) (3), (4)

This also reflects in the regulatory requirements for peptides which are generally more than therapeutic small molecules and less than recombinant therapeutic proteins (2).

The approval pathways for therapeutic peptides in US FDA are summarized in Figure 2. Center for Drug Evaluation and Research (CDER) is responsible for evaluation of safety, efficacy and quality of therapeutic peptides. Applicant needs to submit Investigational New Drug (IND) application before clinical investigations for any new peptide. After the phase III efficacy studies are completed, the applicant needs to submit New drug application (NDA) under Section 505(b)(1) (5). Upon approval, the new

drug is given market exclusivity of 3 to 7.5 years based on drug type (6).

After 4 years of approval of an RLD, a 505(b)(2) application can be submitted for generic peptide (2). This NDA contains safety and efficacy data, where at least some of the study is not conducted by the applicant. The applicant is expected to perform bridging studies with Reference Listed Drug (RLD) to ensure the “sameness” (7).

An Abbreviated New Drug Application (ANDA) is submitted for the generic peptide which is shown to be therapeutically equivalent to the RLD by the means of pharmaceutical equivalence and bioequivalence.(2)

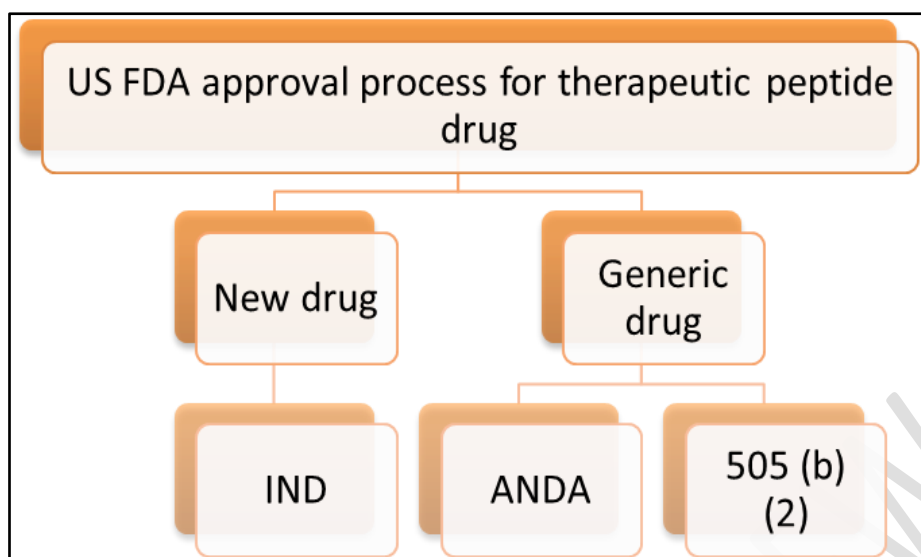


Figure 2: Approval pathways for therapeutic peptides in US FDA

Requirements for IND application

An IND application submitted under section 505(b)(1) should contain full safety and efficacy data from the study / studies conducted by the applicant. This should include details of manufacturing procedure and analytical methods, specifications and data for structure, impurity profile and stability. In addition, data for quality attributes which may impact product safety, efficacy and immunogenicity should be provided. Nonclinical pharmacology and toxicology data from relevant animal models, and clinical pharmacology, safety and efficacy data from human subjects are necessary for new drug application (2).

Requirements for 505(b) (2) application

New drug which differs from the RLD in terms of formulation, administration routes and proposed use can be approved by the 505(b)(2) pathway. This approval may be based on the previous results of safety and efficacy of an approved drug; and/or clinical and preclinical data from published literature.

A bridging is required with the RLD to establish similarity in terms of bioavailability and bioequivalence. Some additional studies to support safety and efficacy may also be required (8).

Requirements for ANDA

An ANDA is an application submitted and approved under section 505(j) for a generic peptide that is same to the RLD with respect to their active ingredients, dosage form, route of administration,

strength and conditions of use. ANDA relies on the safety and efficacy data of the RLD and a bioequivalence study is considered sufficient to prove the similarity

US FDA guidance on ANDAs for peptides

US FDA published its guidance for the industry on ANDAs for certain highly purified synthetic peptide drug products that refer to listed drugs of rDNA origin in May, 2021 (9). This guidance is specifically refers to highly purified synthetic peptides referring to RLD of rDNA origin. The scope of this guidance includes previously approved glucagon, liraglutide, nesiritide, teriparatide, and teduglutide of rDNA origin.

This guidance provides recommendations to determine when an application for a synthetic peptide referring to RLD of rDNA origin should be submitted as ANDA instead of a 505(b)(2) application.

This guidance states that the advancements in peptide synthesis technology and availability of state of the arts characterization methods enable the applicants to demonstrate that the generic synthetic peptide is a “duplicate” of a previously approved peptide of rDNA origin.

US FDA approved peptides which are covered in this guidance are listed in Table 1.

As on February 2022, two generic peptides have been approved by US FDA for the five mentioned peptides. Bonsity a generic teriparatide is of rDNA origin and is approved by 505(b)(2) pathway in April, 2019 (10), whereas Gvoke, a synthetic glucagon approved by 505(b)(2) pathway in September, 2019 (11). There has been no approval of mentioned synthetic generic peptides since the publication of this guidance.

An ANDA for synthetic generic peptide RLD of rDNA origin is recommended if the applicant can:

1. Demonstrate that the level of each peptide related impurity in the proposed generic synthetic peptide is the same as or lower than that found in the RLD.
2. Demonstrate that the level of any new specified peptide-related impurity is not more than 0.5 percent of the drug substance.
3. Characterize each new peptide-related impurity.
4. Justify why the presence of new peptide-related impurities (less than 0.5 percent) will not adversely impact the safety and efficacy of the peptide.

Generally, the type of application for approval depends on the similarity of

active ingredients and the impurity profile of the synthetic peptide.

Table 1: US FDA approved peptides

Peptide	RLD	Generic peptide
Teriparatide	Forteo	Bonsity
Liraglutide	Victoza	NA
Glucagon	Glucagen	Gvoke
Nesiritide	Natrecor	NA
Teduglutide	Gattex	NA

Similarity of active ingredients:

The similarity of active ingredient in a proposed generic synthetic peptide and RLD is essential. This can be established through physicochemical characterization and biological evaluation in a comparative study with the RLD. Applicants are recommended to use orthogonal methods for characterization of following characteristics:

- Primary sequence
- Physicochemical properties
- Secondary structure
- Biological activities (*in vitro* or *in vivo*)
- Clinical pharmacokinetics (PK)
- Clinical pharmacodynamics (PD)

Impurity profile:

Peptide related impurities such as aggregates and oligomers may impact product safety and result in immunogenicity (12). Generally, the levels of impurities in the proposed generic

synthetic peptide should be less than that of the RLD. Any difference including the presence of new impurities should be justified for the safety and lack of immunogenicity of the proposed synthetic peptide.

This guidance considers the similarity in terms of active ingredients, inactive ingredients, and storage conditions with the RLD as the basis of similarity in impurities generated during product storage.

Host cell impurities such as host cell proteins and host cell DNA are not a concern for synthetic generic peptides as they occur only in rDNA-origin peptide drug products.

Peptide-related impurities include differences in amino acid sequences due to insertion, deletion and oxidation.

Different impurity profiles for peptide related impurities could impact the safety and efficacy of the drug. Since the peptide-

related impurity profiles for approved peptides of rDNA origin covered in this guideline have been well characterized; hence, it is recommended to compare the peptide-related impurity profile of synthetic generic peptide and RLD. Applicants are suggested to evaluate the levels of each peptide-related impurity in synthetic generic peptide and RLD. The level of such impurities in the synthetic generic peptide should be less than the RLD. Any high level impurity should be mitigated by change in synthesis or purification process.

Applicants should identify any new peptide related impurity (different from the RLD) and ensure that the level of such impurities is below 0.5 percent level. All new peptide related impurities should be well characterized to ensure that these do not have adverse impact on product safety and efficacy. This justification should include the identity and level of these impurities, their impact on physicochemical and biological properties and stability of the peptide especially with regard to aggregation under stress condition. The immunogenicity should be demonstrated to be non-significantly different than the RLD by comparing the affinity for major histocompatibility complex (MHC) or T-cell epitopes.

Any new peptide related impurity level higher than 0.5 percent is considered to be

a potential risk for immunogenicity and may result in 505(b)(2) pathway to accommodate the clinical investigation.

Discussion: manufacturing and controls of synthetic generic peptides have become very robust due to advanced synthesis procedure and characterization methods. This has resulted in redundancy of clinical efficacy evaluation. FDA has relaxed the regulatory requirements for certain highly purified peptides by enabling the ANDA application instead of 505(b)(2) pathway. This would result in timely, efficient and low cost development of synthetic generic peptides ultimately benefitting the patients.

Reference:

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