US FDA Regulatory Framework for Generic Peptides Referring to rDNA Origin Reference Products

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Review Article

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 recombinant DNA 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 recombinant DNA 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 recombinant DNA Origin". This guideline provides recommendations for evaluating whether an Abbreviated New Drug Application submission is appropriate for a synthetic peptide referring to previously approved glucagon, liraglutide, nesiritide, teriparatide, and teduglutide of recombinant DNA origin. The requirements for Abbreviated New Drug Application submissions for synthetic generic peptides and 505(b) (2) submissions for generic peptides of recombinant DNA origin are compared.

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ABBREVIATIONS

US FDA   : United States Food and Drug Administration
rDNA   : Recombinant deoxyribonucleic acid
RLD   : Reference Listed Drug
NDA   : New Drug Application
ANDA   : Abbreviated New Drug Application
IND   : Investigational New Drug

1. INTRODUCTION

Peptides are defined by the US FDA as polymers of α-amino acid with defined sequences having 40 amino acids or less [1]. Therapeutic usage of peptides dates back to 1920s with the advent of insulin for the treatment of diabetes. Since then, more than 80 peptides have been approved for the treatment of various diseases related to endocrinology, oncology, neurology and musculoskeletal disorders [2]. Manufacturing of peptides has moved from extractions from animal tissues in the initial years, to chemical synthesis and recombinant DNA technology [3].

Structurally the peptides are in between small molecules and proteins, lacking tertiary structure and have molecular weight in the range of 500-500 Daltons [4,5]. The simpler structure also means that the peptides are less immunogenic [6] and also have lower production cost [7] than recombinant proteins. Fig. 1 represents the size comparison between small molecule, peptide and monoclonal antibody.

This also reflects in the regulatory requirements for peptides which are generally more than therapeutic small molecules and less than recombinant therapeutic proteins [10].

The approval pathways for therapeutic peptides in US FDA are summarized in Fig. 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 clinical efficacy studies are completed, the applicant needs to submit New drug application (NDA) under Section 505(b)(1) [11]. Upon approval, the new drug is given market exclusivity of 3 to 7.5 years based on drug type [12].
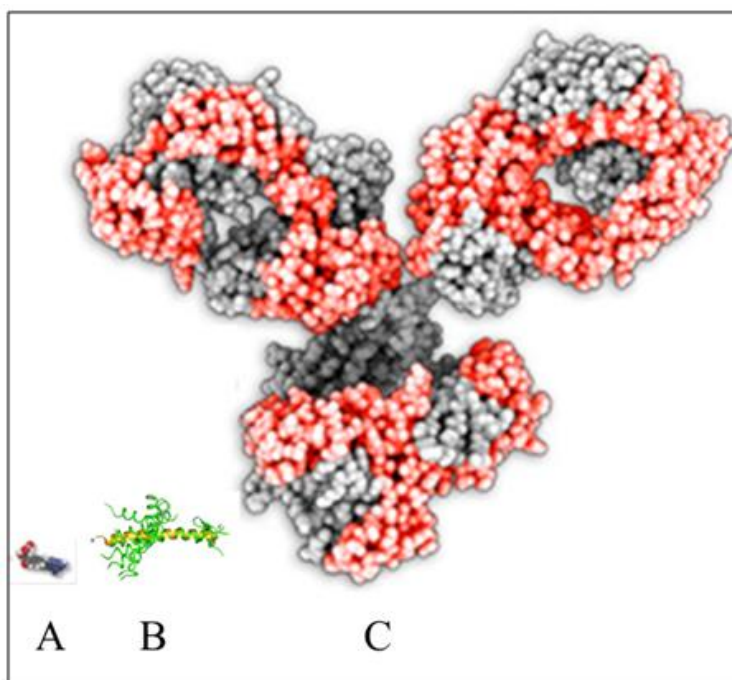

Fig. 1. Size comparison of A: Methotrexate (454 Da), B: Teriparatide (4118 Da) and C: Monoclonal antibody (150 kDa) [8,9]
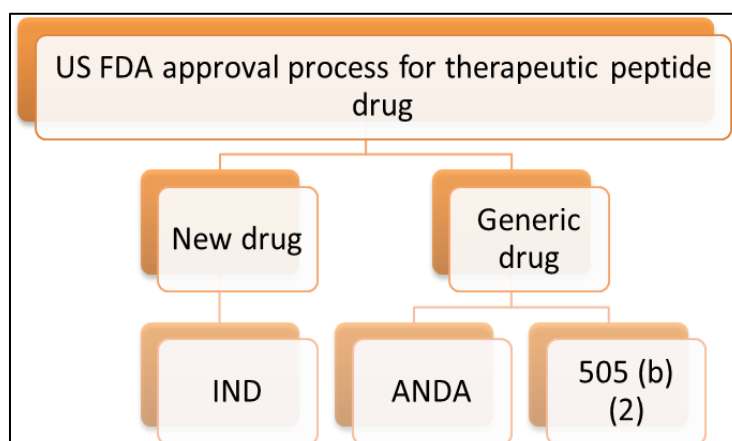
Fig. 2. Approval pathways for therapeutic peptides in US FDA

After four years of approval of a reference listed drug, a 505(b)(2) application can be submitted for a generic peptide [10]. 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" [13]**.**

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 [10].

1.1 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 [10].

1.2 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 via 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 the published literature available in public domain.

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 [14].

1.3 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

2. US FDA GUIDANCE ON ANDAS FOR PEPTIDES

US FDA has followed a case by case approach for the approval of generic peptides based on degree of similarity with the RLD and robustness of the manufacturing product [15]. 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 [16]. This guidance 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.

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

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 referring to the five mentioned peptides. Bonsity® is a generic teriparatide of rDNA origin and is approved via 505(b)(2) pathway in April, 2019 [17], whereas Gvoke®, a synthetic glucagon approved via 505(b)(2) pathway in September, 2019 [18]. There has been no approval of mentioned synthetic generic peptides since the publication of this guidance.

This guidance recommends an ANDA application for synthetic generic peptide referring RLD of rDNA origin if the applicant can:

- Demonstrate that the level of each peptide related impurity in the proposed generic synthetic peptide is same as or lower than that found in the RLD.
- Demonstrate that the level of any new specified peptide-related impurity is not more than 0.5 percent of the drug substance.
- Characterize each new peptide-related impurity.
- 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.

2.1 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)

2.2 Impurity Profile

Peptide related impurities such as aggregates and oligomers may impact product safety and result in immunogenicity [19]. 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 (not present in 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 not different significantly than the RLD by comparing the affinity for major histocompatibility complex (MHC) or T-cell epitopes.

Any new peptide related impurity at levels 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.

3. DISCUSSION

Therapeutic peptides constitute a significantly large group of drugs, both in terms of numbers and market size. The niche acquired by the peptides between small molecules and proteins has resulted in the regulatory requirements which are more stringent than the small molecules. US FDA has recommended to reduce the regulatory requirements for five synthetic generic peptides which refer to the reference listed drugs of rDNA origin. The candidate synthetic generic peptide needs to demonstrate similarity of active ingredients and comparable impurity profile with the reference listed drug to eliminate the requirement for clinical efficacy studies. There is a possibility to apply this approach to other well characterized peptides and biosimilars such as semaglutide, filgrastim and Pegfilgrastim.

4. CONCLUSION

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.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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