CHAPTER 1

Regulatory Considerations for Peptide Therapeutics

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1.1 Introduction

Being at the borderline between typical small molecules and large proteins, peptides have raised a series of regulatory challenges. Although the use of the term ''peptide'' varies in the scientific literature outside the regulatory framework, the currently used regulatory definition delineates that peptides are α-amino acid polymers with specific defined sequences, 40 amino acids or fewer in size, and regardless of their production method (synthetic or of recombinant DNA origin). Despite the pharmaceutical industry's interest in peptides as drug candidates, specific regulatory challenges persist, especially related to establishing their quality standards. Moreover, current US Food and Drug Administration (FDA) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines regarding the quality of pharmaceutical products do not include peptides. This chapter presents an overview of the approval process for New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs) as pertaining to the quality of peptide drugs.[1,2]

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1.2 Peptide Quality Assessment at the FDA

The FDA Center for Drug Evaluation and Research (CDER) is in charge of timely assessment of all data submitted by applicants relevant to the safety, efficacy and quality of peptide drug products. Within the CDER, the quality information in marketing applications [also known as the Chemistry, Manufacturing and Controls (CMC) section] is under the purview of the Office of Pharmaceutical Quality (OPQ). The OPQ assesses the identity, strength, quality and purity of peptide drug substances and products by integrating their review, inspection, surveillance, policy and research and creating the parity of quality between new drug products, generic drug products.[3]

1.3 Overview of the Current Drug Approval Process Employed for Peptide Applications

When a peptide drug product application is submitted to the FDA, it is the responsibility of the applicant to provide evidence that the peptide product under evaluation is safe, effective, and of high quality. Once an application has been submitted for review, OPQ regulators have the responsibility to assess the quality of the peptide drug with respect to its impact on the safety and efficacy by taking a stepwise risk analysis approach. This approach includes (1) understanding the complexity of the peptide and its clinical use, (2) evaluating the process- and product-related factors that may impact the safety and efficacy of the proposed peptide product and (3) determining whether additional studies (*in vitro* or *in vivo*) are needed to address any residual uncertainty related to the safety of the peptide product. This is not a ''one size fits all'' approach, but rather a case-by-case analysis depending on factors characteristic of each different peptide.[2]

As with any other drug product, the overall peptide drug development and approval process generally follows pre-defined steps: (1) preclinical investigation, (2) clinical investigation, (3) post-approval marketing surveillance and (4) life-cycle management.[1] An overview of the stages of drug development, relevant application submissions and corresponding regulatory paths as applicable to peptides is provided below.[4]

Before any clinical investigations regarding a new peptide may begin, the applicant must submit an Investigational New Drug (IND) application. Clinical investigations, as planned and documented through the IND process, generally consist of three phases: Phase I, in which safety studies are conducted in a small number of individuals (20–200 people); Phase II, in which efficacy studies begin in volunteers (up to several hundred people) of the target population; and Phase III, in which human testing continues in a significant number of patients (several hundred to several thousand people).[4] Once Phase III is complete, the applicant will submit an NDA under Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) including all collected clinical and nonclinical data. If an applicant intends to rely, to any extent, on safety or effectiveness investigations that were not

conducted directly by or for the applicant, the NDA may be submitted in accordance with FDCA Section 505(b)(2).[1]

Upon approval, the drug product can be marketed. Any subsequent modifications to an approved application should be submitted to the FDA for assessment as post-approval changes or supplements. After NDA approval, the next stage in the life cycle of a drug product happens when all forms of exclusivity (*e.g.* patent protection) have expired for the ''innovator'' or ''reference listed'' drug. At that point, under FDCA Section 505(j), the Reference Listed Drug (RLD) may be cited in an ANDA submitted for marketing a generic version of the drug product. An ANDA contains information to show that the proposed generic product is therapeutically equivalent and thus interchangeable with the RLD, specifically in terms of active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics and intended use. ''Bioequivalence,'' provides the basis for establishing product interchangeability. Through reliance on bioequivalence, generally, ANDAs do not require significant amounts of time and money that would be normally needed for the submission of NDAs.[1]

1.3.1 The New Drug Application Assessment Process

NDAs submitted to FDA for assessment should comprehensively provide all clinical and nonclinical data collected during drug development efforts that were undertaken by or on behalf of the applicant. CDER assessors will evaluate these data to decide whether adequate evidence has been established with regard to safety, efficacy, risk–benefit profile, proposed labeling and quality.[6]

1.3.1.1 INDs and Presubmission of NDAs

Before starting any of the clinical trials essential for providing data to be included in the NDA, applicants are required to have submitted an IND; the IND should summarize evidence of safety and efficacy from preclinical studies and should demonstrate the preparedness of investigators for clinical trials.[7] The most relevant INDs to broad discussions of drug development and regulations are ''investigator'' INDs. An investigator IND is initiated by a physician who leads the investigation and decides how the investigational drug is administered. An investigator IND can be submitted for an unapproved drug or to investigate an approved drug for a new indication or new patient population. Other IND types, such as emergency use INDs (for patients who do not meet enrollment criteria for an existing study protocol) and treatment INDs (for patients with serious and life-threatening conditions), are also essential in terms of public health as they expand access to experimental drugs.[1]

Good communication between an applicant and the FDA can greatly facilitate the process of ''filing'' an IND. A ''fileable'' IND must provide information about the investigational drug manufacture, data from animal pharmacology and toxicology studies, and the proposed clinical investigation

protocols, including investigator information. The IND should be submitted to the FDA at least 30 days before the in-human trials are initiated. If an answer is not received from the FDA within 30 days, the applicant may proceed with clinical trials according to the IND. If the FDA has any concerns about the way clinical trials are conducted or about their resultsin the IND, a ''clinical hold'' may be imposed. Successfully elaborated clinical development, per IND regulations, will typically originate from complete Phase I, II, and III clinical investigations.[5] The FDA assessment of Phase I focuses on product safety, whereas assessment of Phase II and III submissions includes evaluation of efficacy, clinical investigations, and the prospect of meeting the regulatory standards for marketing approval.[1]

In a peptide IND, FDA regulators evaluate the quality information by assessing whether chemistry and manufacturing data related to the peptide drug substance and peptide drug product may indicate health risks to subjects enrolled in IND trials.[8] Quality information related to peptide drug substance and peptide drug product is provided in a summary report, containing physical, chemical and biological characteristics relevant to the peptide, composition of the peptide drug product, a brief description of the manufacturing process, and acceptable controls and analytical methods used to assess peptide identity, strength, quality, purity and stability.[1] The applicant should also demonstrate that it can adequately produce and supply batches of the peptide drug product, that the proposed peptide drug product is reasonably safe for initial testing in humans, and that the clinical investigators are qualified to perform their responsibilities as assigned during the trial. The amount of the quality information usually varies with the phase and scope of the clinical investigation, but it is expected that this information will be thoroughly documented upon submission of a peptide NDA.[1]

1.3.1.2 Format and Content of the NDA

The intent of the NDA is to provide FDA with documentation of data gathered during animal and human clinical investigations. The format and content of NDAs submitted to the FDA are specified in regulations (21 CFR 314.50) and reflected in the form FDA 356(h), used for all drug products including peptides.[9] The contents and the specifics of a peptide NDA are as follows.[1]

1. *Index* – The index guides the FDA regulators through the peptide NDA and describes the contents and location of each section.
2. *Labeling* – Peptide drug product labeling is a critical information and it must be submitted electronically using structured product labeling (SPL) formatting in compliance with the Physician's Labeling Rule (PLR) as described in 21 CFR 201.56 and 201.57.[10]
3. *Summary* – The peptide NDA summary delivers a general understanding of the peptide drug product. It provides an overview of the safety and efficacy of the peptide drug product for its proposed useand an indication of the overall quality and accuracy of the NDA.

4. *Chemistry, manufacturing and controls/pharmaceutical quality* – The pharmaceutical quality section provides detailed information on the composition, manufacture, test methods, specifications and stability of the peptide drug substance and the final peptide drug product.

   The peptide drug substance subsection should detail all relevant physical and chemical properties and tests performed to demonstrate the identity, purity, potency and stability of the peptide, as well as methods of its manufacture.[1] Information to be submitted in an application for a peptide drug substance is addressed in Section 1.3.2.3.2 (Drug Master Files).

   Similarly, the peptide drug product subsection must present a rigorous account of peptide drug product characterization, manufacture and packaging, peptide drug product specifications, microbiology, container closure system and stability. Recommendations on the quality information that should be included in a peptide drug application[11] are listed below.

   - *Description and composition of the peptide drug product* – Lists the active and inactive ingredients in the peptide drug product together with their functions and amounts and provides a description of the dosage form and container closure system proposed for marketing of the peptide drug product.
   - *Pharmaceutical development report* – Contains details of the development studies conducted by the applicant to establish that the proposed peptide dosage form, formulation, manufacturing process, container closure system, microbiological attributes and instructions for use of the product are appropriate for the purpose specified in the application.
   - *Manufacture* – Includes a list of the manufacturers with their addresses and responsibilities, and describes the manufacturing and packaging processes, by providing flowcharts and details on the equipment, materials, and in-process controls (*e.g.* operating parameters, environmental controls, process tests and in-process material tests) for the finished peptide drug dosage form.
   - *Control of excipients* – Describes the excipients and provides the proposed specifications and tests completed to confirm their quality. Also, it identifies novel excipients and excipients of human or animal origin.
   - *Control of the peptide drug product* – Provides the specifications and tests selected to assure the peptide drug product quality and lot-to-lot consistency of the finished product. It also presents sampling procedures and validation results, and it lists all peptide drug product impurities including expected peptide impurities, degradation products, and residual solvents.
   - *Reference standards* – Provides information on the reference standard(s) used to test the peptide drug product and its impurities.

- *Container closure systems* – Describes the proposed container closure system(s) in which the peptide drug product will be marketed, including the identity of materials of construction and their compatibility with the peptide.
- *Stability* – Describes the stability protocols and stability results supporting the proposed expiration date and storage conditions of the peptide, and provides the post-approval stability protocol and stability commitment.

In addition to the general CMC information as outlined above, an NDA for a peptide product should also include specific data capturing quality factors that affect the safety (including immunogenicity) of the peptide.[2]

The immunogenicity of peptide products can have clinical consequences, including production of antibodies working against the therapeutic peptide, loss of peptide efficacy, neutralization of the human peptide counterpart, and general effects impacting the immune system (including allergy and anaphylaxis).[12]

In general, the peptide primary structure (amino acid sequence) can be a determining factor for the peptide immunogenicity. Although immunogenicity inherent to the peptide sequence is unavoidable, peptide candidates with minimal potential to elicit an immune response can be selected during drug development through sequence analysis, used to predict the peptide immunogenicity.[2] A vast array of analytical methods can be used to capture the complexity of the peptide structure. Analysis of the primary structure of a peptide is, in fact, elucidation of its amino acid sequence using amino acid chromatographic analysis, or in conjunction with sequencing methods such as by Edman degradation (N-terminal residue identification) or peptide mapping coupled with mass spectrometry.[13,14] Furthermore, Edman sequencing and tandem mass spectrometry can be used together to elucidate the primary structure of complex peptides having disulfide bonds, which may not be identified from simple amino acid analysis and sequencing.[15] Peptides with less than 40 amino acids generally exhibit high conformational flexibility, triggered by a secondary structured consisting predominantly of random coils and limited degree of secondary structures (*e.g.* α-helices and β-sheets). For some peptides, their structural ordering may impact the biological activity; therefore, elucidation of secondary structure is needed when performing peptide structure characterization.[2] Commonly used methods to investigate peptide secondary structure include circular dichroism (CD), Fourier transform infrared (FTIR), Raman, fluorescence and nuclear magnetic resonance (NMR) spectroscopy and X-ray crystallography. Far-UV CD (170–250 nm) can be applied to analyze α-helices, whereas near-UV CD (250–320 nm) can detect environmental changes around aromatic amino acids.[16,17] FTIR spectroscopy can be used to estimate the β-sheet formation and further differentiate between parallel and antiparallel forms, and also aggregates.[18,19] Raman spectroscopy is less affected by water absorption and can be used to study local interactions

(involving Cys or Tyr groups) in addition to the peptide conformation. Furthermore, NMR spectroscopy and X-ray crystallography are currently the only methods that allow the characterization of the entire molecular structure of the peptide by elucidating the relative positions of all atoms (and thus all amino acids) within the peptide chain.[2]

Peptide structure can be characterized by various methods, including but not limited to those illustrated above; however, taken individually, each method can only capture limited features of higher-order structure, therefore orthogonal characterization methods are critical to correctly elucidate the peptide secondary structure. Moreover, an *in vitro* bioassay may be included as part of the characterization of higher-order structure and biological activity of complex peptides as it provides essential information on the peptide structure–activity relationship.[2]

In addition to the structure, peptide purity also impacts its safety.[20] Table 1.1 provides a compilation of peptide-related impurities resulting from synthesis (process related) or arising from degradation (product related) that may occur in peptide drug products regardless of the manufacturing process.

Peptide-related impurities and degradants are tightly controlled during the development and manufacturing of the peptide products. In general, the recommendations for reporting, identifying, and qualifying impurities for peptides differ from those cited in the guidelines for small molecules because peptide active pharmaceutical ingredients (APIs) can have many peptide-related impurities. Proposed thresholds for peptide-related impurities resulting from the peptide synthesis or arising from its degradation are usually established on a case-by-case basis considering the risk of immunogenicity and depending on the clinical use of the peptide(*e.g.*, therapeutic use, vaccine, *in vivo* or *in vitro* diagnostics). As such, ICH guidelines for impurities may be suitable for peptides with fewer than 10 amino acids in length. Such peptides usually can be treated as small molecules as they are highly pure, and less likely to cause severe adverse immune events.[2] For all others, levels of impurities should be justified [by clinical and toxicology data for innovator peptides, or by reference to available United States Pharmacopeia (USP), European Pharmacopoeia (EP), British Pharmacopoeia (BP) and Japanese Pharmacopoeia (JP) monographs, the scientific literature, development and stability data, toxicological data, significant metabolites of the drug substance and/or RLD for generic drugs].[2]

A special case of peptide degradants is aggregates. Aggregates of therapeutic peptides/proteins that are made of minimum 10–20 epitopes at a repetitive spacing of ~100 Å and having a molecular weight greater than 100 kDa can induce immune responses by efficiently activating T-cell help for antibody production.[21,22] Aggregates lead to serious problems in the development of peptide drugs, and they may form as a result of various stress factors (*e.g.* temperature fluctuations, light, shaking, surfaces, pH adjustments) during manufacturing, processing, and shipping. Aggregates may also appear upon storage as a result of denaturation (through thermal, pH, dielectric constant

Table 1.1 Process-related impurities and degradants that may occur in peptide drug products. Reproduced from ref. 2 with permission from Elsevier, Copyright 2017.

Impurity	Mechanism
Denaturation	Modification of the peptide structure that changes its physical, chemical and biological properties; occurs in the presence of denaturing agents
Proteolysis	Upon exposure to harsh conditions, extreme pH, high temperature or enzymes
Aggregation and precipitation	Association of hydrophobic amino acid residues to form aggregates; precipitation occurs if on a macroscopic scale
Deamination	Hydrolysis of the side-chain amide linkage of an amino acid residue with formation of a free carboxylic acid
Oxidation and reduction	Induced by temperature, pH, metal ions and buffers during synthesis and/or storage
Disulfide exchange	Change in conformation due to reaction between disulfides within a peptide chain
Diastereoisomerization (racemization)	Alteration of L-amino acids to D,L mixtures, with formation of peptide bonds sensitive to proteolytic enzymes
β-Elimination	Proceeds through a carbanion intermediate; susceptible residues under alkaline conditions are Cys, Lys, Phe, Ser and Thr
Deletion (incomplete coupling)	Incomplete coupling due to incomplete removal of the protecting group of the last coupled amino acid or insufficient activation of the incoming amino acid
Truncation	Missing one or more amino acid residues at either the N- or C-terminal end due to precipitation of resin beads during synthesis
Amino acid insertion	Insertion of an additional amino acid into the peptide sequence due to excess of 9-fluorenylmethoxycarbonyl (Fmoc)-protected amino acids and improper washing
Dimers	Self-association of hydrophobic amino acids residues in peptides to form aggregates
By-products generated by incomplete deprotection	Results in protecting groups covalently attached to peptide sequences

and/or ionic strength changes), or peptide modification (through oxidation, deamidation and primary sequence changes). Some of these factors (*e.g.* temperature, pH, light) can be easily controlled during manufacture and storage, but control is more challenging for others (*e.g.* mechanical stress, surfaces[23–26]). Knowing that a high content of aggregates can be correlated with increased safety risks, including immunogenicity, it becomes necessary to evaluate the aggregate profiles by using a combination of orthogonal analytical methods to cover a wide range of aggregates sizes, such as size-exclusion chromatography (SEC), analytical ultracentrifugation (AUC), dynamic light scattering (DLS) and field-flow fractionation (FFF).[2]

Excipients can also play an important role in the safety of peptide drug products. It has been reported that interactions of some peptides and small proteins with preservatives (such as phenylethyl alcohol, chlorobutanol, benzalkonium chloride and benzyl alcohol) may be responsible for conformational changes and aggregation,[27] which may lead to increased immunogenicity, allergic reactions, and even anaphylactic shocks (*e.g.*, salmon calcitonin peptide).[28] Also, peptide interaction with Tween 80 (polysorbate) micelles and exposure of peptide epitope to the micellar surface may induce antibodies.[29] Based on these observations, it can be concluded that the formulation of a peptide drug product can change the propensity of the peptide to aggregate, deaminate, oxidize, *etc.*; therefore, it can enhance or reduce its immunogenic potential. An appropriate design of the peptide product formulation may affect the product safety and immunogenicity by stabilizing the peptide against physical and chemical degradation, and minimizing its interactions with the excipients.[2,30]

Another factor that affects the safety of the peptide drug product is the interaction of the drug product formulation with the container closure system (especially rubber components), which may produce extractables and leachables. To this regard, organic compounds leached from the uncoated chlorobutyl rubber plunger of a syringe in contact with erythropoietin formulations (Eprex®) containing polysorbate 80 may have been a factor enhancing immunogenicity.[31] Leachables from the rubber components of the container closure system may impact peptide immunogenicity by acting as adjuvants for peptide crosslinking and antibody induction. Leachables must be studied as part of stability studies according to ICH and FDA stability guidance for drug products.[32]

The remaining information in the pharmaceutical quality section of a peptide NDA refers to samples of the peptide drug substance and/or finished peptide product, validation of analytical methods, and environmental impact information provided with adequate detail so that FDA quality assessors can thoroughly evaluate any impact on the peptide drug product performance.[1]

The rest of the peptide NDA contents are outlined below.

5. *Nonclinical pharmacology and toxicology* – This section includes all relevant animal and laboratory studies to be evaluated by the FDA with respect to inconsistent or inadequate toxic effects, acute, subacute and chronic toxicity, pharmacological activities and potential carcinogenicity and teratogenicity.[1,33]
6. *Human pharmacokinetics and bioavailability* – This section of the peptide NDA includes clinical pharmacokinetic and bioavailability data and analyses, and relevant analytical and statistical methods.[1]
7. *Clinical microbiology* – This section is provided only when effects on the physiology of a targeted microorganism are relevant to the NDA.[1] It reports the drug action on microbial physiology, the antimicrobial spectrum affected, resistance mechanisms, and laboratory methods used.[34]

8. *Clinical data section* – The clinical dataset is the basis of the efficacy and safety of the proposed peptide drug product. A wide range of FDA and ICH guidelines address different aspects of the clinical studies in NDA submissions that cannot be covered in detail here.
9. *Safety update* – The first safety update report is usually filed as an amendment to the NDA at 4 months after the submission of the original NDA and contains safety information that arises from ongoing studies, animal studies, and other sources.[1]
10. *Statistical* – This section of the peptide NDA is closely linked to the clinical data section and contains statistical analyses with a format and content agreed upon by the applicant and the FDA.[1]

11–12. *Case reports* – This section includes tabulations of cases of patient data and data elements with proper case report forms (CRFs). The CRFs for patients who died during a clinical study and for patients who discontinued because of an adverse event should also be included.[1,35]

13–14. *Patent information and certification* – Patent certification is mandatory for any relevant patents that claim the listed peptide drug on which the investigations relied, or that claim a use for the listed peptide drug.[1]

15. *Establishment description* – This section provides general information about the organization, physical plant and major equipment, in addition to quality assurance functions.[1]
16. *Debarment certification* – The FDA is authorized to debar individuals convicted of crimes related to the development, approval, or regulation of drugs; these individuals should not provide any type of services to the applicants of a peptide drug application.[1,36]
17. *Field copy certification* – Applicants based in the USA must submit a "field" copy of the pharmaceutical quality section, application form, and summary of the peptide NDA to FDA. This information will be used during the preapproval inspection (PAI) at the manufacturing site.[1]
18. *User fee cover sheet* – Form FDA 3397 is used to determine the applicability of a user fee and indicate whether a payment has been made to an FDA account concurrent with the submission of the peptide NDA.[1,37]
19. *Financial information* – This section includes clinical investigator financial disclosures (form FDA 3455) and certification (form FDA 3454), describing financial interests of the investigator and applicant–investigator financial arrangements.[1,38]
20. *Other information* – Any information that was submitted to FDA before the peptide NDA submission should be referenced in this section. An applicant may propose other uses of this section at the pre-NDA meeting.

1.3.1.3 NDA Assessment

1.3.1.3.1 Filing. Prior to submitting a peptide NDA to the FDA, applicants are strongly encouraged to request a meeting with the FDA to discuss

the planned content of the application and ensure that the submitted application is complete and fileable. The date of receipt by the FDA ''central document room'' of the peptide NDA starts the review time clock for that application. When the NDA is ready for assessment, a regulatory project manager (RPM) manages the assessment process and coordinates all communications with the applicant. After payment of all required fees and submission of complete administrative information, the peptide NDA is assigned to a multidisciplinary team of FDA assessors, who by day 45 of the review (day 30 for priority reviews) will discuss their respective decisions regarding the fileability of the application. All filing review issues identified by the assessment team are communicated in writing to the applicant. Applications failing to provide necessary information may result in a refuse-to-file (RTF) letter by day 60. Otherwise, the application is accepted for filing and the applicant receives a 74 day letter, confirming the application action date and the review choice (standard or accelerated).[1,39]

1.3.1.3.2 Assessment. The overall NDA assessment and approval process (or ''cycle'') usually takes place in six major steps: (1) presubmission activities, (2) process submission, (3) review plan, (4) conduct review, (5) take official action and (6) post-action feedback.[40,41]

Once the application is filed, a planning meeting is held with the assessment team to discuss timelines, high-level labeling revisions, need for advisory committees, and/or inspections and review activities. The review timeline for NDAs, including New Molecular Entities (NMEs), is 10 months from receipt for standard reviews, and 6 months for priority reviews. During the main review phase, each assigned FDA assessor, according to discipline (*e.g.* medical officer, pharmacologist, chemist, statistician, microbiologist, clinical pharmacologist), evaluates the pertinent portion of the peptide application, proposes labeling revisions, and writes an assessment document.[1]

All approvability and high-level labeling issues are identified by the time the mid-cycle meeting is held (*i.e.* month 5 for standard reviews, and month 3 for priority reviews). Deficiencies identified by respective discipline assessors are usually communicated to the applicant after the mid-cycle meeting through a mid-cycle Information Request (IR). The conclusions of all assessment and inspection activities are integrated during the wrap-up meeting; the medical officer takes the lead to reconcile observations and written summaries, after which the action package is finalized.[1]

In the event that the peptide NDA is approved, the applicant receives a letter that authorizes the manufacturer to distribute the peptide product in accordance with any pre-established agreements and post-marketing commitments. If the agency decides on the basis of its assessment not to issue an approval letter, a complete response (CR) letter will be issued, citing deficiencies and offering recommendations to the applicant. Applicants who receive a CR letter may request an end-of-review meeting with the FDA to discuss deficiencies and further steps to be taken, including resubmission, withdrawal, or request an opportunity for a hearing.[1,42]

1.3.1.3.3 Labeling. Final discussions about the package insert will usually take place near the end of the NDA assessment, possibly 2–5 weeks before the PDUFA (Prescription Drug User Fee Act) action date. At this time, the FDA will communicate recommendations concerning the peptide product label to the applicant; the agency and applicant will work to reach agreement on the final wording of the package insert prior to the action date.[1]

1.3.1.3.4 FDA–Applicant Communications During NDA Review. While evaluating the quality, safety and efficacy of the peptide drug product, based on a thorough scientific examination of the submitted application, the FDA may choose to seek clarification from the applicant through an information request (IR) email or teleconference, discipline review letter (DRL), or face-to-face meeting. Any information needed in support of the peptide application review must be officially submitted as an amendment to the application.[1]

1.3.1.3.5 Advisory Committee. If significant issues arise during the peptide NDA assessment, the FDA can seek advice from an advisory committee. An advisory committee comprises a specialized group of external experts, identified by the FDA, that convenes to provide advice to the agency concerning any number of matters,[43] including NME, novel clinical trial designs or the use of surrogate endpoints, particular safety issues or drug effectiveness.[1]

1.3.1.4 Special Approval Pathways

1.3.1.4.1 Expedited Approval Pathways. In order to increase the availability of drugs intended to treat serious and/or life-threatening conditions, four expedited drug approval pathways have been created: Priority Review Designation, Accelerated Approval, Fast Track Designation, and Breakthrough Therapy Designation.[44] Drug products evaluated and approved by these expedited approval pathways have efficacy, safety, and quality held at the same rigorous regulatory standards as drugs evaluated and approved in the FDA regular review programs.

1.3.1.4.2 Orphan Drug Designation Program. An orphan designation signifies that a drug indication applies to a rare disease, which by definition affects fewer than 200 000 American patients per year. The Orphan Drug Act (1983) and amendments (1992 and 2013) established several incentives to encourage the development of orphan drugs, including market exclusivity for 7 years after approval, fee waivers, tax credit on clinical research, technical assistance during the review process, and other federal research grants.[45]

1.3.1.4.3 Pediatric Exclusivity. There have been a few FDA initiatives to improve medical product research and availability for children, including the Food and Drug Administration Modernization Act (FDAMA) of 1997,

Best Pharmaceuticals for Children Act of 2002, Food and Drug Administration Amendments Act (FDAAA) of 2007 and Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012. Pediatric exclusivity is a 6-month extension of exclusivity, added to existing periods of marketing exclusivity or patent protection.[46]

1.3.2 Abbreviated New Drug Application Assessment Process

Abbreviated New Drug Applications (ANDAs) contain information submitted to CDER for the assessment of generic drug products. Generic drug applications are ''abbreviated'' because they generally allow the applicant to rely on preclinical (animal) and clinical (human) data used to establish the safety and effectiveness of an approved drug product (RLD). Generic products must be therapeutically equivalent to the RLD, as established through the combined criteria of pharmaceutical equivalence and bioequivalence.[1] For a generic peptide drug product, pharmaceutical equivalence signifies that the generic product and the RLD contain the identical peptide API and its strength, dosage form, route of administration, quality, performance characteristics and intended use are the same for the generic product and the RLD.[47] Bioequivalence signifies that the generic product exposes the patient to the same amount of API in the same time course as does the RLD; in general, generic peptide drugs formulated as parenterals with the same active and inactive ingredients in the same concentration [qualitatively and quantitatively (Q1/Q2) the same] as the RLD receive a biowaiver.[48] Generic peptide applications are filed under FDCA Section 505(j) and authorized for marketing only after all forms of exclusivity for the innovator peptide drug product have expired.[1]

1.3.2.1 Format and Content of the ANDA

The format and content of ANDA submissions to the FDA are specified in regulations (21 CFR 314.94) and reflected in the ''harmonized'' application form FDA 356(h). The list of contents of a peptide ANDA and the difference between the required contents of peptide NDA and ANDA submissions are provided below.[1]

1. *Index/table of content*s.
2. *Basis for ANDA submission* – This section shows that the peptide ANDA refers to the RLD selected by the agency and documents a comparison between the generic peptide drug and the RLD, including a statement that the peptide API, the route of administration, dosage form, and strength of the proposed peptide drug product are the same as those of the RLD.
3. *Labeling* – According to 21 CFR 314.94(8), it includes a side-by-side comparison of the applicant's proposed labeling (container and carton) and the labeling approved for the RLD for each strength and package size; any differences should be explained in annotation.[1]

4. *Chemistry, manufacturing and controls/pharmaceutical quality* – The quality section contains information as required under 21 CFR 314.50(d) and detailed below as applicable for generic peptides.

The quality section of a peptide ANDA, like that of a peptide NDA, covers raw materials, manufacturing facility, manufacturing of the peptide API and in-process controls, a master production record and a description of the equipment to be used in the manufacture of the commercial batch of the peptide drug product, materials used in peptide API packaging, controls for the finished dosage form, analytical methods, stability of the finished dosage form, sterility assurance data, and samples and environmental considerations.[1] Stability requirements for generic and new drug peptides are identical, according to ICH and FDA guidelines.[49,50]

Differences between peptide ANDA and NDA quality sections are usually related to the peptide API information; because the peptides that are used in the manufacture of generic peptide drug products are usually obtained from third-party external manufacturers, the ANDA applicant must typically reference a Drug Master File (DMF), previously submitted to the FDA, containing proprietary information (see Section 1.3.2.3.2). Additional requirements for peptide ANDAs as compared with peptide NDAs include but are not limited to the following:[1]

- Any inactive ingredient in the proposed peptide generic product that differs from the RLD must be identified and demonstrated to have no effect on safety and efficacy.
- Specifications should be justified with reference to compendia (*e.g.* USP, JP) and/or analysis of the RLD.
- Release characteristics of the proposed generic peptide must parallel those of the RLD.

Similarly to peptide drugs submitted as NDAs, generic peptides undergo extensive characterization with respect to primary and secondary structure, oligomer and aggregation states, and biological activity. For generic peptides, the primary structure and the position of disulfide bonds are critical determinants of the peptide API sameness as compared with the RLD. When comparing peptides, the two-dimensional NMR methods can be used to identify the fingerprint peptide structure and detect any alterations in the peptide structure caused by environmental changes (such as new excipients), and demonstrate sameness of higher-order structure between the generic peptide and its RLD.[2] Most generic peptide drug products have formulations that are Q1/Q2 the same as the RLD, thus presenting a low risk. However, there are situations when differences in formulations introduced by new excipients may affect peptide conformation or interact with the peptide. These new excipients could lead to the formation of dimers and higher-order aggregates, which may alter the stability, safety (including immunogenicity), and efficacy of the peptide drug product, rendering a peptide drug product

essentially different from the RLD. Nonetheless, for generic peptides that have the same amino acid sequence and are formulated Q1/Q2 the same as the RLD, it can be generally inferred that they have the same higher-order structure as the RLD. Assessment of the biological activity is particularly important in cases where a synthetic peptide is used as the API, if an additional confirmatory test is needed for demonstrating sameness between the proposed generic and RLD products.[2]

Different factors including modification and degradation resulting from the manufacture or storage conditions, residual solvents, formulations or leachables from the container closure system can potentially change the quality of the peptide API and affect the safety (including immunogenicity) of the peptide products.[51] Clearly, the potential for immunogenicity should be taken into consideration but, especially for generic peptides, the safety concerns can be mitigated by controlling the peptide drug quality through optimizing the manufacturing, drug formulation, and assuring proper storage conditions.

For the peptide API in a proposed generic drug product, a one-time study making a direct comparison of peptide-related impurity profiles between the proposed generic drug product and multiple batches of its RLD is beneficial to show comparably low levels of peptide-related impurities under long-term storage and accelerated/stress conditions. In particular, when evaluating the quality of a generic peptide, it is expected that impurities will differ between a generic peptide and its RLD, especially if the peptide manufacture pathways use different synthetic methods (chemical synthesis *versus* recombinant DNA technology).[2] To diminish the risks to patients, these specified impurities, different from those of the RLD, should be strictly controlled at low levels established based on prior knowledge and supported by risk assessment, and/or, depending on the peptide, as indicated by guidelines.[52] Recently, the FDA developed a draft guidance according to which, for synthetic peptide drug products (including glucagon, liraglutide, nesiritide, teriparatide and teduglutide) referencing a recombinant-derived peptide drug product, the risk of immunogenicity due to impurities in the generic product should not differ from that of the RLD.[52] Mitigation of the immunogenicity risk can be achieved by providing data to demonstrate that the impurities in the generic peptide product, different from those in the RLD, do not produce a stimulation of innate immune activity greater than that caused by the RLD. Such data can be obtained from *in silico* and *in vitro* studies that determine the binding affinities of the peptide to the major histocompatibility complex (MHC), which can be used to identify the peptide impurities responsible for prompting an immune response and, hence, to inform the relative immunogenicity risk of these impurities different from those of the RLD.[53–55]

Comparison of the aggregation profiles between a proposed generic peptide drug product and its RLD should be done throughout the product shelf-life, and also in accelerated/stress conditions. This comparison uses orthogonal analytical methods (such as SEC, AUC, DLS, and FFF) to cover a wide range of aggregates sizes.[2] Demonstrating the comparability between the generic product and its RLD in peptide aggregate profiles in terms of

aggregates sizes and levels can sufficiently address the safety/immunogenicity concerns due to aggregation.

Moreover, the peptide–excipient interactions and the impact of excipients on the peptide stability should be assessed in real-time and forced degradation studies. In this regard, in generic peptide products that have formulations that are Q1/Q2 the same as the RLD, the peptide–excipient interactions are expected to be the same as for the RLD. However, when Q1/Q2 the same formulations of a proposed generic peptide and its RLD differ with respect to preservative, buffer, and/or antioxidant (as an allowed difference in excipients of injectable generic products),[56] the effect of the new excipient on the peptide stability is to be evaluated by real-time and/or forced degradation stability studies performed in comparison with the RLD. The possible interactions between the peptide and the new excipient can be determined using a range of techniques including surface plasmon resonance (SPR), NMR spectroscopy, differential scanning calorimetry (DSC), and/or bioassay.[2]

5. *Human pharmacokinetics and bioavailability/bioequivalence* – This section contains information that shows that the drug product is bioequivalent to the RLD, but waivers of *in vivo* bioequivalence studies are available in certain cases.[57] Most of the injectable peptide drugs are subject to receiving a biowaiver if their formulation is Q1/Q2 the same as the RLD.
6. *Case report forms* – See case reports for NDAs (Section 1.3.1.2).
7. *Patent information and certification* – This section contains all relevant patents for the peptide drug product, method of use, licensing agreements, disputed patent information, amended certifications, *etc.* Brand peptide NDA applicants must confirm patent certification under one of the following criteria (*i.e.* Paragraphs):
   I. patent information on the peptide drug product that is the subject of the ANDA has not been submitted to the FDA;
   II. the patent has expired;
   III. the date the patent expires; or
   IV. the patent is invalid or not infringed by the peptide drug product proposed in the submitted ANDA.[1]
8. *Financial certification or disclosure statement* – See certification and financial information for NDAs (Section 1.3.1.2).

An applicant may amend a peptide ANDA under review to revise submitted information, or respond to information requests, which generally tend to involve the quality section of the application.

1.3.2.2 ANDA Assessment

1.3.2.2.1 Pre-ANDA (pANDA). The demonstration of equivalence for complex generic products including peptides is challenging enough that many complex products currently do not have generic competition. The FDA established the Regulatory Science Program in the Generic Drug

User Fee Amendments of 2012 (GDUFA) to address this challenge through research and funding of studies specifically addressing difficult problems in demonstration of equivalence. The GDUFA II program established a pre-ANDA (pANDA) meeting pathway route as a means through which industry could meet with the FDA to clarify regulatory expectations, assist applicants to develop more complete submissions and discuss new or alternative methods for establishing bioequivalence for complex generic drug products. The ultimate goal of this effort is to increase efficiency and effectiveness of the ANDA assessment process and to reduce the number of review cycles required to obtain ANDA approval for complex drug products. Another modality of discussing with the FDA prior to ANDA submission is in the form of a controlled correspondence requesting information on product development, especially for first generics.[58]

1.3.2.2.2 Filing. Once a peptide ANDA is submitted, the FDA determines whether that ANDA is sufficiently complete to allow a substantive assessment. If the submission is incomplete, the FDA can issue a refuse-to-receive (RTR) letter, which prevents a lengthy assessment period, multiple cycles, and/or waste of resources. Complete peptide ANDA submissions may be filed under Paragraph I, II, III and IV certifications depending on the related patent status as listed in the ''Orange Book'' for the brand peptide RLD. An ANDA applicant who files a Paragraph IV certification must, within 20 days of filing, notify the innovator, who will have 45 days to take action upon receiving the notification. The FDA may hold the peptide ANDA up to 30 months, depending on the outcome of the litigation between the innovator and the ANDA applicant, if any.[1,59]

1.3.2.2.3 Assessment. As more and more peptide RLDs have come off patent and as more companies have begun generic peptide drug manufacture, the volume of peptide ANDAs has been growing over the past decade. According to the GDUFA II, the FDA is committed to review and act, within 10 months from submission, on 90% of those original ANDAs from the date of submission, and within the applicable review goals on 90% of certain priority ANDAs and their amendments.[60] To assist ANDA applicants in improving the quality of submissions, the FDA has issued a number of GDUFA-related guidance documents[61] and is working on issuing product-specific guidelines.[62]

The quality section of a peptide ANDA is the major component of the peptide ANDA assessment. Quality reviewers organized within a number of disciplines work as a team to assess the quality of the peptide drug substance and drug product, manufacturing and controls, batch formulation and records, facilities, product specifications, packaging and stability. A number of assessment enhancement initiatives are under way to ensure the timely review of ANDAs; these focus on efficient communication with the applicant or on efficient assessment (*e.g.* through knowledge management). If all disciplines find the ANDA acceptable and if all facilities are in

satisfactory standing as evaluated and inspected, the ANDA receives approval. If the ANDA assessment is completed prior to the expiration of innovator peptide drug product exclusivity, the ANDA applicant will receive tentative approval (TA) but is not allowed to distribute the peptide product. An approval letter is contingent upon the resolution of litigation and issues related to peptide product exclusivity.[1]

1.3.2.3 Special Considerations for ANDAs

1.3.2.3.1 ANDA Filing and Market Exclusivity. New drug product exclusivity is provided by FDCA Sections 505(c)(3)(E) and 505(j)(5)(F). Peptide NDAs seeking to market a new peptide receive a 5 year period of exclusivity; but after 4 years, information from such an NDA approval may be used as part of the submission of Section 505(b)(2) NDA or an ANDA, on condition that the new submission supplies evidence of no infringement.[1] Follow-on peptide drug products containing a previously approved active moiety and approved on the basis of new clinical investigations are granted a 3 year period of exclusivity, whereas the first generic version of a peptide drug product may be eligible for a 180-day period of exclusivity. Orphan drug exclusivity extends 7 years, and pediatric exclusivity provides a 180 day extension period to existing patents or exclusivity.[1]

1.3.2.3.2 Drug Master Files (DMFs). A Drug Master File (DMF) is a document prepared and submitted by a manufacturer to support an IND, NDA, ANDA, another DMF, or their amendents and supplements. A type II DMF is commonly used to support the peptide API information in ANDAs; although it provides detailed information about the facilities, manufacturing process, packaging, and storage of a peptide API, the peptide DMF is neither a regulatory requirement nor a substitute for a marketing application.[1] Before the FDA can assess the peptide DMF submitted in support of an application, the DMF holder must provide a letter of authorization (LOA) that allows the applicant to reference that DMF. Because the information submitted in the peptide DMF is proprietary, deficiencies as identified during assessment of that DMF are communicated by the FDA to the DMF holder only, and cannot be disclosed to the applicant. Instead, the applicant referencing that peptide DMF is notified by the FDA if the DMF is deficient; it is then the DMF holder's responsibility to inform the applicant if the deficiencies in the DMF have been resolved. A DMF submission is never ''approved''; it is assessed to determine whether it is adequate to support a particular application that references it.[1]

A type II peptide DMF is subject to GDUFA fees, an initial ''Completeness Assessment'' (CA), and communications with DMF holders.[62] The CA determines whether the peptide DMF is substantially complete and ready to undergo a comprehensive scientific evaluation, but does not guarantee that the DMF will be found adequate.[1] A type II peptide DMF must cover characterization of the peptide API, manufacturing and controls of the

intermediates and final peptide API, including a list of the organic impurities, reference standards or materials, container closure system used for packaging the peptide API, and stability data and storage conditions. A type II peptide DMF must pass the initial CA to be referenced in an ANDA.[1] A list of DMFs that have passed the CA and are available for reference by ANDAs under GDUFA is available on the FDA website.[63]

As pertaining to the peptide DMF, an increased regulatory focus has been placed lately on the control of starting materials used in the manufacture of synthetic peptides, and also control of the synthetic steps.[64] Some details regarding information submitted in a type II DMF for a chemically synthesized peptide are presented below.

Control of Starting Materials. Starting materials for solid-phase peptide synthesis (SPPS) include resins used as solid supports, amino acids and protected amino acid derivatives, peptide fragments, reagents used in coupling, deprotection and cleavage steps of the synthesis and solvents.[2]

Resins

The selection of the resin itself affects the outcome of the SPPS. The resin should have an appropriate particle size that allows ease of handling and removal of solvents used during the SPPS, and it should be inert. The extent of the amino acid initial loading onto the resin is determined by the resin swelling ($mL\,g^{-1}$) properties, and also by its substitution ratio ($mmol\,g^{-1}$); an inefficient loading may lead to C-terminal deletion/truncated peptide impurities, and may directly impact the purity and the yield of the final peptide drug substance.[65] The substitution of the resin can be determined after loading of the first amino acid, for example, by common color or UV tests.[2]

Amino Acids and Amino Acid Derivatives

With respect to the quality of the amino acids and amino acid derivatives, particular attention is given to their chiral properties and impurities. Impurities in raw materials, including (i) free amino acids or amino acid derivatives, (ii) amino acid contaminants, (iii) incorrect enantiomers, *i.e.* D-isomer,[66] (iv) dipeptides or oligopeptides, and (v) β-alanine containing contaminants,[67] are likely carried over into the final peptide drug substance and, therefore, should be tightly controlled.[2]

Reagents and Solvents

Generally, there is limited concern regarding the quality attributes of the reagents and solvents used in the initial stages of the peptide manufacturing process as they are unlikely to be incorporated in the final peptide drug substance. These materials are tested in-house for vendor qualification and at the minimum should be pure to avoid side reactions. Nevertheless, solvents and reagents (*e.g.* acetonitrile, methanol, 2-propanol, acetic acid, trifluoroacetic acid) typically used in the purification or precipitation of peptides can be carried over and should be quantified in the final peptide drug substance.[2]

In-process Control Strategies. Special attention is given to each step of the SPPS, including initial coupling, final deprotection and cleavage, and in-process controls. Appropriate in-process controls are important for SPPS in order to avoid augmentation of peptide impurities from one synthesis step to the next. The control strategy developed during manufacturing process design refers to the identification of potential side reactions and impurities, and steps undertaken to minimize their levels.[2] Following the selection and control of the raw materials and attachment of the first amino acid, the peptide chain is built through a repeated cycle, involving first the deprotection of the N^{α}-amino protecting group (Fmoc), activation, and coupling of the next amino acid.[2]

Deprotection Control Strategies

The removal of the Fmoc protecting group is normally achieved through short exposure to a solution of 20–30% piperidine in dimethylformamide. Although in most cases deprotection strategies are effective, for long peptides incomplete deprotection leading to deletion peptide impurities can occur even at high concentrations of piperidine and after repeated trials. In this case, increased time allocated to the deprotection step or a stronger base, *e.g.* DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) are used.[2] Moreover, a washing step is introduced between deprotection and the next coupling step to remove the piperidine reagent and thus avoid premature deprotection of the next amino acid and generation of insertion impurities. In-process tests to ensure complete removal of piperidine are usually employed, including measurement of the pH of the washing solvent and a chloranil test.[68]

Coupling Control Strategies

In the coupling step, the coupling reagents are transforming the free carboxyl terminus of the incoming amino acid into an active electrophilic form. The selection of the activation reagent is a critical variable; an optimal reagent allows efficient acylation of the amino function, thus increasing the coupling efficiency and limiting the side reactions, such as racemization. In principle, racemization can occur in any step of the SPPS; however, the risk is higher during activation and coupling.[2] Extra caution is still needed for certain amino acids that are prone to racemization (*e.g.* Hys, Cys, Asp[69–71]) and also under reaction conditions with elevated temperature[72] or with excess of base.[73] Racemization impurities may not be readily detected and separated by high-performance liquid chromatography (HPLC); therefore, it is important to minimize their levels as they may cause aggregation of the peptide product, and also potential biological consequences.[74–76]

Another side reaction that is common during coupling is insertion. An insertion peptide impurity can be generated when an incoming amino acid first acylates an amide bond of the resin bond peptide, and then inserts itself into the peptide sequence during the next round of coupling.[77] The insertion can be caused by an excess amount of Fmoc-protected amino acid and is more likely to occur at locations on the peptide sequence where the amide

bond is further away from bulky side chains that introduce steric hindrance.[78] For certain difficult-to-react amino acids, recoupling may be necessary to reach completion of the reaction; however, if needed, a capping step may also be introduced to prevent the generation of deletion sequences. Capping itself will generate a truncated sequence; but truncated sequences are much easier to separate than the deletion sequences.[2] The completion of coupling can be determined and controlled using suitable in-process color tests such as Kaiser, trinitrobenzenesulfonate (TNBS), chloranil or Bromophenol Blue tests, which are able to detect the presence of residual amine. Each of these tests has its limitations; therefore, two independent tests are recommended to monitor the completion of the coupling reaction against negative controls (with protected amino function) and positive controls (with deprotected amino function).[2]

The deprotection–coupling cycle is repeated until the last amino acid is attached to the resin-bound peptide.

Cleavage Control Strategies

During the cleavage step, the entire peptide chain, together with the side-chain protecting groups of the amino acid residues, are cleaved simultaneously. Concentrated trifluoroacetic acid (TFA) (95%) cocktail containing water and triisopropylsilane (TIS) scavengers is the most commonly used cleavage reagent in Fmoc-protected SPPS. Scavengers are added to protect sensitive nucleophilic side groups (such as Trp, Met, Tyr and Cys) by converting the cations generated during the reaction into corresponding hydrocarbons.[79] Scavengers containing sulfur, such as ethanedithiol (EDT), dithioerythritol (DTE), and thioanisole, are helpful for trapping carbocations and preventing oxidation and disulfide bond formation for Met and Cys residues,[80,81] whereas TIS can replace EDT to protect Arg and Trp residues.[82] Failure to properly shield these sensitive amino acids may cause unwanted impurities, which can further produce peptide aggregation.[83] The cleavage time and temperature need to be optimized during the development stage and be strictly monitored in peptide production.[2]

Post-cleavage Work-up Control Strategies

Certain peptides may need to undergo cyclization through the formation of oxidative intramolecular disulfide bridges. In this regard, a regioselective strategy with orthogonal Cys protecting groups can be employed for peptides with multiple disulfide bonds[84] and the oxidation conditions (temperature, duration) can be controlled to minimize the formation of intermolecular disulfide bonds responsible for the formation of dimers and aggregates.[85,86] In addition, controls (*e.g.* Ellman test) can be established to assess the extent of formation of disulfide linkages in these peptides.[2]

Finally, selection of the peptide purification route takes into account the size, polarity, and ionic character of the desired peptide and process-related impurities, including diastereomeric, deletion, truncated, deaminated, isomerized and oxidized peptides, disulfide exchange products, oligomers/aggregates,

by-products generated by incomplete deprotection of amino acid side-chain protecting groups, and reagents and solvents used in the peptide synthesis. Commonly used separation methods are reversed-phase chromatography (RPC) and ion-exchange chromatography (IEC).[2]

Owing to concerns regarding stability in aqueous solutions, many peptides are supplied as lyophilized (freeze-dried) products. Lyophilization conditions (temperature, pressure, rate and duration) in all stages and the residual moisture in the lyophilized peptide are strictly controlled throughout the product shelf-life because high concentrations (5–20%) of residual moisture reduce the glass transition temperature (T_g) of the product, resulting in instability issues.[2]

As an alternative to SPPS, small peptides composed of several amino acids can be efficiently prepared by solution-phase peptide synthesis (SPS) through the coupling of single orthogonally protected amino acids in solution, thus avoiding unwanted side reactions and overcoming synthetic difficulties.[87,88] The core chemistry of SPS, including deprotection, activation, and coupling, is similar to that of SPPS. The prime advantages of SPS are related to ease of scale-up, fewer side reactions, high purity of the final peptide, and convenient, flexible control methods applicable throughout the entire synthetic process.[2,89,90] However, the long reaction time in SPS,[91] combined with the need for purification steps after each coupling and deprotection reaction are major disadvantages. Because no solid support is used in SPS, extensive extraction, precipitation, and washing are needed to yield a relatively pure peptide intermediate. Consequently, the number of solution-phase stages and isolations needed increases with the length of the peptide, which considerably complicates its synthesis process.[92] To this end, combination of SPPS and SPS methods is the most effective approach to synthesize long peptides; specifically, short fragments of the required peptide are first synthesized by SPPS, then coupled together in solution to form the final long peptide. In this case, quality control of the intermediate peptide segments becomes critical and quantitative HPLC methods should be established to ensure segment purity.[2]

1.3.3 Post-approval Activities and Life-cycle Management

Whereas ''amendments'' are submitted to update or modify unapproved peptide applications, ''supplements'' are submitted to modify approved peptide applications. Supplements must address post-approval changes to peptide drug product components and composition, manufacturing sites and/or processes, specifications, container closure systems, stability protocols and expiration dates, or labeling. Supplement submissions list all changes that may affect the peptide drug product, with sufficient detail for the FDA to determine the scope of change readily.[1] Post-approval changes to an approved peptide NDA or ANDA are classified as major, moderate, or minor and should be reported using one of four reporting categories:[93] prior-approval supplements, Changes Being Effected (CBE-30 and CBE) supplements, or annual reports.[1]

1.3.3.1 Prior-approval Supplements (PASs)

PASs describe major changes, having the substantial potential to affect adversely peptide drug product quality, safety, and effectiveness; such changes require approval by the FDA before they are implemented in any distributed peptide drug product. Prior-approval changes described in a PAS include changes in the formulation (*e.g.* dosage or ingredient-release form), components and composition of the peptide drug product, changes in the manufacturing site that could trigger an FDA inspection, or placement of aseptic sterilization or various manufacturing processes (including packaging and closure systems) within new locations.[1] Other changes described in a PAS include changes affecting the impurity profile or the physical, chemical, or biological properties of the peptide drug product, changes affecting specifications or analytical processes, or changes to peptide drug product labeling (*e.g.* based on post-marketing study results).[1]

1.3.3.2 Changes Being Effected (CBE-30 and CBE) Supplements

CBE-30 supplements to an approved peptide application describe changes having moderate potential to impact the safety and effectiveness of the peptide drug product adversely; if, within 30 days of receiving a CBE-30 supplement, the FDA informs the applicant that a PAS is required, no peptide drug product affected by the change may be distributed. CBE supplements without the 30-day specification may also be used to describe moderate changes. Moderate changes reported in the CBE-30/CBE supplements may pertain to manufacturing facilities or packaging sites for the peptide API or peptide drug product, manufacturing processes, equipment, starting materials, specifications, analytical procedures, container closure systems or labeling. Examples can be found in FDA guidelines.[1,93]

1.3.3.3 Annual Reports

Annual reports submitted to an approved peptide application report minor changes, with little potential to affect the peptide drug product adversely. Changes reported in annual reports may be related to new manufacturing sites for peptide intermediates, new packaging sites for secondary packaging, new labeling sites, new equipment of the same design and operating principles, new specifications made to comply with an official peptide compendium, tightening of specifications, and minor labeling edits. Examples of each type of change that is appropriate for reporting in an annual report can be found in FDA guidelines.[1,93]

Disclaimer

The views and opinions expressed in this chapter are only those of the author and do not necessarily reflect the views and policies of the FDA.

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