Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 2199-2207 | ISSN:2251-6727

Scientific Considerations and Requirements for the Approval of Generic Synthetic Peptide Prefilled Syringe by Usfda.

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(Received: 07 January 2024 Revised: 12 February 2024 Accepted: 06 March 2024)

KEYWORDS

USFDA,
ANDA,
Solid Phase Peptide Synthesis,
OCP,
PMOA,
PFS.

ABSTRACT:

Introduction: Before drugs can be sold, they have to be proven safe and effective by law. USFDA oversees the safety of food and drugs. When it comes to approving drugs, there's a process, which includes submitting an application for generic drugs. Recently, the FDA has seen more requests for approval of generic versions of peptide medicines. Having these generic versions available is important for making sure people can access these essential medications. But, ensuring that generic versions are as good as brand-name ones can be tricky, especially for peptide drugs with specific amino acid sequences. Contaminants introduced during manufacturing can be a problem, as they might affect the safety of the generic medicine. These contaminants, which are similar to the medicine itself, can be tough to detect, analyze, and regulate. This study gives a detailed look at combination products, focusing on the scientific aspects of submitting generic versions of peptide prefilled syringes. It covers things like characterizing peptides, specifying drug substances and products, and studying impurities—all of which are important for getting approval from the FDA.

Objectives: To brief about the drug device combination products and overview what are generic drug products and Abbreviated New Drug Application. To study the submission requirements of USFDA for synthetic peptides and analytical techniques used for drug characterization. Also to get a basic understanding of prefilled syringe.

1. Introduction

Peptides:

Peptides are compounds made up of two or more amino acids linked together by a specific chemical bond called an amide formation. They differ from proteins in terms of their size, having fewer amino acid residues. Peptides can be either natural or man-made (synthetic). Synthetic peptides are designed to mimic naturally occurring ones and can be used to treat serious illnesses like cancer. They're also used in mass spectrometry (MS) applications as standards and reagents. These synthetic peptides play a crucial role in discovering, characterizing, and quantifying proteins, especially those

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 34-37 | ISSN:2251-6727

that are early indicators of diseases. According to FDA regulations, any synthetic amino acid polymer with 40 or fewer amino acids and a predetermined sequence is classified as a peptide medicine. This means it's regulated under the FD&C Act and requires either a NDA or an ANDA for approval, rather than being classified as a biologic under the PHS Act (1,2).

Chemical Synthesis of Peptide:
It involves creating chains of amino acids, which are the building blocks of proteins. Peptides are essentially short proteins, ranging from just 2 amino acids to about 100. They occur naturally and often have important roles in biological processes, such as transmitting signals in the body.

Chemical synthesis of peptides can be done by either: solution-phase and solid-phase. Each method has its own strengths and limitations. Standard solid-phase peptide synthesis (SPPS) is commonly used to make peptides containing five to sixty amino acids. On the other hand, solution-phase synthesis, also known as liquid-phase peptide synthesis, is preferred for producing shorter peptides, typically up to ten amino acids in length (3). Individual amino acids are linked in a solution during the traditional solid-phase synthesis (SPS) process. The fragment condensation process is used to create longer peptides. In this case, the shorter peptide segments are first synthesized independently and subsequently combined to generate the larger peptide. The main advantage of SPS in peptide synthesis is that the intermediate products may be purified and treated to remove protection, yielding a very pure version of the final desired peptide. (4,5).

Oxytocin, which plays a role in sexual reproduction, porcine gastrin releasing peptide, involved in stomach acid secretion, and human insulin, which regulates carbohydrate metabolism, are examples of peptide hormones synthesized using solid-phase synthesis (SPS). While SPS can be easily scaled up and is cost-effective, it does have the drawback of requiring long reaction times.

The developing peptide is supported by a resin in the solid-phase peptide synthesis (SPPS) technique. Initially, the first amino acid binds to the resin via its C-terminus. It has alpha amino groups to inhibit polymerization and transient protecting groups on its reactive side chain. The protecting group is removed after adding each amino acid, and the resin is cleaned before adding the next. The peptide is then separated from the resin and this cycle is repeated until the desired sequence is achieved. (6).

Peptide Injectables:
Since the synthesis of insulin in 1921 and the introduction of synthetic oxytocin in 1962, the field of peptide drugs has boomed. In the US, Europe, and Japan, more than 60 peptide medications have received approval; over 150 are presently undergoing clinical development, and over 260 have undergone testing on humans. This has made peptide medications one of the most talked-about areas in pharmaceutical research.

Advancements in protein purification, synthesis methods, and structural elucidation have played a significant role in accelerating the development of peptide drugs. These advancements have led to the approval of nearly 40 peptide drugs worldwide. Alongside natural peptides, synthetic versions like oxytocin and vasopressin, as well as recombinant human insulin, have been successfully produced (7).

Due to their simplicity and enhanced absorption into the body, peptide medications are predominantly administered via injection, known as parenteral administration. This method holds the largest market share for protein and peptide-based therapies, with approximately 75% of peptide medicines being delivered this way.

FDA's Organization and the Office of Combination Products:
Each type of product, whether it's a biological product, drug, or device, falls under the jurisdiction of a specific center within the regulatory agency. These centers, such as the CBER, the CDER, and the CDRH, have their own regulations, management structures, and review processes tailored to their respective products.

For combination products, which combine different types of products like drugs and devices, a single center may not have all the necessary expertise to handle all legal, regulatory, and scientific aspects. The OCP determines which center will take the lead in reviewing and regulating a combination product based on its PMOA. OCP also acts as a central hub for coordinating activities related to combination products across the agency and assists both industry and agency reviewers in the review process (8,9).

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 34-37 | ISSN:2251-6727

Combination Products and Single Entity Combination Product:

A combination product (CP)is essentially a blend of two or more different medical products, like a drug, device, or biological product, all combined together. The individual components, whether they're drugs, devices, or biological products, are called "constituent parts" of the combination product.

There are several types of CP:

1. Single-entity combination product: This includes products like a prefilled syringe, where all the components are physically integrated into one unit.
2. Co-packaged combination product: These are products like surgical or first-aid kits, where multiple medical items are packaged together but remain separate entities.
3. Cross-labeled combination product: In this type, products like a light-emitting device and a light-activated drug are packaged and labeled separately but are intended to be used together for a specific purpose.
4. Another type of cross-labeled combination product: This encompasses similar combinations of products that are labeled separately but meant to be used together for their intended purpose (10,11).

2. Methods

SCIENTIFIC CONSIDERATIONS FOR ANDAS FOR PROPOSED GENERIC SYNTHETIC PEPTIDES:

There are 2 main factors considered by FDA which are as follows;

A) Active Ingredient Sameness:

The applicant must demonstrate that the proposed generic medication is nearly equivalent to the RLD in a number of ways in order for the FDA to authorize an ANDA. This entails having the same active components, use guidelines, dose form, administration method, potency, and labeling (with a few permitted deviations). Additionally, the generic medication needs to show that it functions in the body in a manner identical to that of the RLD, or bioequivalency.

The FDA must also guarantee that the facilities, processes, and controls employed in the generic drug's production, processing, and packaging are adequate to preserve its uniqueness, potency, quality, and purity. This guarantees patients may take the generic medication safely and effectively.

Numerous techniques for physicochemical characterization and biological assessment are used to prove that the active component in a proposed generic synthetic peptide is same. The proposed generic synthetic peptide undergoes characterization to demonstrate its similarity to the RLD in terms of the following properties:

- Primary sequence
- Secondary structure
- Physicochemical properties
- Oligomer/aggregation states
- Biological activities (by in vitro or animal studies)

Previously, analytical methods often fell short in fully characterizing peptide products for submission in an Abbreviated New Drug Application (ANDA). However, with advancements in peptide synthesis and characterization technology, such as high-resolution mass spectrometry, liquid chromatography, and NMR, the FDA now believes it's feasible for an ANDA applicant to show that the active ingredient in a proposed generic synthetic peptide is identical to that of the Reference Listed Drug (RLD) (12). Additionally, applicants can demonstrate that these products are pharmaceutical equivalents. These advancements allow for a more thorough understanding and comparison of the active ingredients, ensuring the safety and efficacy of generic synthetic peptides.

- Primary Sequence : The process of identifying a peptide starts with figuring out what makes it up chemically. This entails figuring out which amino acids are in it and how they are arranged in the peptide chain, or fundamental structure. The peptide's safety and efficacy are directly impacted by the primary structure, which contains essential information for the peptide to assume its proper secondary shape.

Analyzing the primary structure of a peptide essentially means figuring out the sequence of its amino acids. This can be achieved using chromatography techniques, which can be quite straightforward. By understanding the primary structure, scientists can ensure that the peptide is correctly formed and can function as intended in the body. In reality, analyzing a peptide's main structure involves determining its amino acid sequence by chromatography, which may be done using basic;

1. Mass spectrometry (MS) - It is a powerful technique used to analyze peptides. In this method, charges are added to molecules within a drug product, and these charged molecules are then subjected to an electric field. The resulting movement of these molecules depends on the ratio of their charge to their mass. This

Journal of Chemical Health Risks

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JCHR (2024) 14(2), 34-37 | ISSN:2251-6727

allows for the identification of individual molecular species among the hundreds of components present in a sample (13).

2. Edman Sequencing and Tandem Mass Spectrometry Combination– It is a highly effective method for determining the primary structure of complex peptides, especially those with disulfide bonds. Traditional amino acid analysis and sequencing may not always identify these bonds accurately. A method for figuring out a peptide's amino acid sequence is called Edman sequencing. Tandem mass spectrometry, on the other hand, disassembles and further analyzes peptides into tiny pieces to provide more structural details about the peptide..

When used together, Edman Sequencing and Tandem Mass Spectrometry complement each other, allowing for a more comprehensive analysis of complex peptides, including those with disulfide bonds. This combined approach enhances the accuracy and efficiency of determining the primary structure of peptides, ensuring a thorough understanding of their composition and functionality (14,15).

3. Peptide Mapping coupled with Mass Spectrometry –

Peptide mapping is a commonly employed method for studying the primary structure of biopharmaceuticals. It typically involves three main steps: enzymatic digestion of the protein, separation of the resulting peptides, and analysis using mass spectrometry (MS).

Several mass analyzer types are used to distinguish ionized molecules: quadrupoles, time-of-flight (TOF), magnetic sectors, Fourier transform, and quadrupole ion traps. Quadrupole and TOF analyzers are the most often used tools in the field of proteomics. For peptide mapping, quadrupole analysis is frequently included into mass spectrometry using an electrospray ionization (ESI) instrument.(16).

4. Amino Acid Analysis (AAA) is a valuable technique for determining both the relative amounts (ratios) and absolute content of amino acids in a peptide. It serves as a powerful tool for identifying and quantifying peptides. AAA has played a pivotal role in uncovering the structure of peptides and proteins.

In the process of AAA, peptide samples are purified and then hydrolyzed to break them down into their individual amino acids. This hydrolysis is achieved by subjecting the samples to strong acid and heat. By analyzing the concentrations of the individual amino acids and considering the molecular weight of the protein, the amino acid composition of the peptide can be determined accurately. This method provides essential insights into the composition and structure of peptides, aiding in their characterization and understanding (17).

Numerous chromatographic techniques have been employed to separate and quantify amino acids, each with its unique advantages and applications such as paper chromatography, thin-layer chromatography (TLC), low-pressure ion-exchange chromatography, ion-exchange HPLC, reversed-phase HPLC, gas chromatography (GC), capillary electrophoresis (CE), infrared (IR) spectroscopy, ultraviolet (UV) spectroscopy.

Each of these techniques offers different levels of sensitivity, resolution, and selectivity, making them suitable for various analytical needs in amino acid analysis (18).

Secondary Sequence - Less than 40 amino acid peptides usually exhibit a great deal of conformational flexibility. The primary characteristic of this flexibility is a random coil form, while secondary structures like alpha helices or beta sheets may occasionally be present. It is essential to comprehend these peptides' secondary structure as it has a significant impact on their biological function. Therefore, determining secondary structure ought to be a crucial component of characterizing peptide structures.

1. Circular Dichroism (CD) is a method for examining the folding characteristics and secondary and tertiary structures of proteins in solution. It measures the differential in the absorption of circularly polarized light, which is a function of the structural asymmetry in the molecule, from left- and right-handed sources. This method is very helpful for researching how a protein's structure varies in response to environmental conditions like pH or temperature. (19).

2. X-ray crystallography is an effective technique for figuring out how the atoms are arranged in a crystallized substance. It is often used to investigate the three-dimensional structure and operation of different biological molecules, such as nucleic acids and proteins. Through the use of this technology, scientists may get a comprehensive understanding of the spatial arrangement of atoms and the molecular interactions and functions that occur within these molecules.

3. 2D NMR methods like Nuclear Overhauser Effect Spectroscopy (NOESY) and Total Correlation Spectroscopy (TOCSY) are used to determine the peptides' fingerprint structure. They are also helpful in identifying any possible alterations in the peptide structure brought about by modifications to the surrounding environment, such the addition of new excipients. As a result, candidates can utilize these

Journal of Chemical Health Risks

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JCHR (2024) 14(2), 34-37 | ISSN:2251-6727

methods to show how the higher-order structure of the generic peptide and its Reference Listed Drug (RLD) are comparable (20).

4. Fourier Transform Infrared Spectroscopy (FTIR) is a valuable tool for estimating the formation of β-sheets in peptides and can further distinguish between parallel and antiparallel forms, as well as aggregates. This technique works by measuring the absorption of infrared light by molecules, providing information about their chemical composition and structure. By analyzing the characteristic absorption peaks associated with β-sheet structures, FTIR can help researchers understand the conformational changes and aggregation states of peptides (21).

- Physiochemical properties - Physicochemical properties refer to the observable physical and chemical characteristics of a substance, which describe how it behaves under various conditions. When evaluating the similarity between the Active Pharmaceutical Ingredient (API) of a proposed generic drug and the reference standard specifications provided in the Drug Master File (DMF) issued by the API vendor, physicochemical properties play a crucial role.

These properties serve to identify, classify, and compare different substances. Some key physicochemical properties that are often considered include:

1. Physical description: This refers to the appearance and physical state of the substance, such as color, texture, and form (e.g., solid, liquid, powder).
2. Solubility: Solubility indicates the ability of the substance to dissolve in a solvent, such as water or organic solvents.
3. Aqueous solubility (as a function of pH): This measures how the solubility of the substance changes with varying pH levels in an aqueous solution.
4. Specific optical rotation (α): Specific optical rotation is a measure of the rotation of plane-polarized light by a substance, which can provide information about its chirality and structural characteristics.
5. Hygroscopicity: Hygroscopicity describes the tendency of a substance to absorb moisture from the surrounding environment.
6. Physical form: This refers to the crystalline or non-crystalline structure of the substance and its physical appearance.
7. Chirality: Chirality indicates the presence of asymmetric carbon atoms in the molecule, leading to different spatial arrangements of its mirror image forms (enantiomers).

By comparing these physicochemical properties of the proposed generic drug's API with those specified in the DMF, manufacturers can assess the similarity between the two formulations. This evaluation is essential for ensuring the quality, safety, and efficacy of the generic drug.

Specifications should be considered according to ICH Q6 for drug product and drug substance for the data to be submitted.

- Aggregates - One of the most common challenges in pharmaceutical peptide formulations is the association of peptides, which can occur through various processes such as dimerization, oligomerization, the formation of high-order structures, self-association, and irreversible aggregate formation. To address this issue, multiple techniques are available for the characterization of peptides and the determination of aggregates and their structures.

Some of the techniques commonly used for characterizing peptide aggregates include:

1. Size-exclusion chromatography (SEC): This technique separates molecules based on their size, allowing for the detection and quantification of peptide aggregates.
2. Dynamic light scattering (DLS): DLS measures the fluctuations in scattered light caused by the Brownian motion of particles, providing information about the size distribution of peptide aggregates in solution.
3. Analytical ultracentrifugation (AUC): AUC separates particles based on their sedimentation rates, allowing for the determination of the size, shape, and concentration of peptide aggregates.
4. Transmission electron microscopy (TEM): TEM provides high-resolution images of peptide aggregates, allowing for the visualization of their size, shape, and morphology.
5. Nuclear magnetic resonance (NMR) spectroscopy: NMR can provide insights into the structure and dynamics of peptide aggregates at the atomic level.
6. Fourier-transform infrared (FTIR) spectroscopy: FTIR can be used to characterize the secondary structure of peptide aggregates, providing information about their conformation.

By employing these techniques, researchers can gain a comprehensive understanding of peptide aggregation phenomena, which is crucial for the development of stable and effective peptide formulations in pharmaceuticals (22).

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 34-37 | ISSN:2251-6727

- Biological activities (by in vitro or animal studies) – Not considered in ANDA submission.

B) Impurities:

In the review process of an Abbreviated New Drug Application (ANDA), the FDA carefully considers the types and levels of impurities present in a proposed generic drug compared to its Reference Listed Drug (RLD). The impurity profile is a crucial factor in determining whether the application follows the 505(j) pathway or the 505(b)(2) pathway.

Generally, a proposed generic synthetic peptide should not contain impurities at levels higher than those found in the RLD. Any impurities, including new ones, must be justified to ensure that the generic drug doesn't pose a greater safety risk, especially concerning immunogenicity, compared to the RLD.

Impurities in synthetic peptide drugs can result from degradation during product storage or from the manufacturing process. These impurities can be broadly categorized into:

1. Peptide-related impurities: These are impurities directly related to the peptide structure and may include degradation products or incomplete synthesis products.
2. Other impurities: This category encompasses residual solvents, elemental impurities, and other organic impurities that are not directly linked to the peptide structure.

Thorough assessment and control of impurities are essential for ensuring the safety, efficacy, and quality of generic synthetic peptide drugs.

For further information related to impurities refer ICH guideline on impurities (23).

What are prefilled syringes? :

Prefilled syringes are pre-filled with medication during manufacturing and packaging, eliminating the need for drug withdrawal and filling at the time of administration. Unlike traditional methods where drugs are stored in glass ampoules or vials and then transferred to a syringe for injection, prefilled syringes offer several advantages. Firstly, they enhance convenience by providing ready-to-use doses, eliminating the need for additional steps before administration. This not only saves time but also reduces the risk of errors during drug preparation.

Secondly, prefilled syringes improve affordability by reducing wastage of medication, as only the required dose is withdrawn for administration. This helps in optimizing drug usage and minimizing unnecessary expenses.

Moreover, prefilled syringes enhance accuracy by providing precise doses, reducing the likelihood of dosing errors. This is particularly important in critical care settings where accuracy is paramount for patient safety.

Additionally, prefilled syringes ensure sterility as the medication is filled under controlled conditions during manufacturing, minimizing the risk of contamination. This helps in maintaining the integrity of the medication and reduces the chances of infections associated with administration.

Overall, prefilled syringes offer a convenient, affordable, accurate, sterile, and safe method of drug administration, making them increasingly popular in healthcare settings.

Table 3. Components of prefilled syringe-

Component	**Material**
Barrel	Plastic/Glass
Piston	Elastomer
Tip cap	Elastomer
Plunger rod	Plastic
Needle	Stainless steel
Needle cover	Plastic

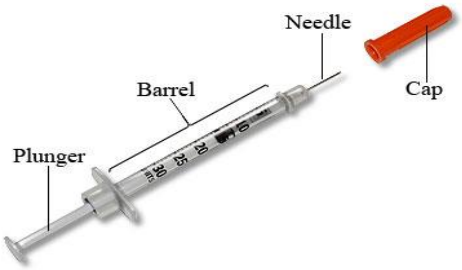

Fig.1: Prefilled Syringe.

PFS benefits include:

- Lower danger of contamination;
- Less handling needed.
- Self-administration capability for the patient;
- Enhanced patient compliance;
- Assurance of sterility;
- Added convenience when used in conjunction with autoinjectors

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 34-37 | ISSN:2251-6727

• Less waste is produced by not having to overfill pricey medications, and dose mistakes are minimized as a result of fewer steps being required (24).

Threshold Analysis and Human Factors Study Submission:
Threshold analyses, as defined by the FDA, are aimed at comparing two drug products to identify any differences, particularly focusing on the user interface of the proposed combination product compared to the reference product. Human factors studies play a crucial role in demonstrating the safe and effective use of the device component within a combination product.
There are two main types of human factors studies:
1. Formative studies: These studies are conducted early in the development process of a product and are intended to provide insights and feedback to inform further development and validation studies. They help identify potential issues with the user interface and usability of the device component.
2. Validation studies: These studies are conducted at the end of the development process, once the product is finalized. They aim to validate the usability and effectiveness of the final combination product, ensuring that it can be safely and effectively used by users.

Overall, human factors studies, including both formative and validation studies, are essential for assessing and ensuring the usability and safety of combination products, particularly focusing on the device component Listed below are the different threshold analysis and human factors submission types:

1)Use-Related Risk Analysis

2) HF Validation Study Protocol

3) HF Validation Study Results Report

4) Comparative Use HF Study Protocol

5) Comparative Use HF Study Results Report

6) Threshold Analysis including, Labelling comparison, Comparative task analysis, Physical comparison, Design difference, Product samples (25,26).

Reliable Report Submission – Fault Tree Analysis:
Reliability is crucial for ensuring that an injector functions as intended without failure for a specified time interval and under specific conditions. To establish the safe and effective performance of an emergency-use injector, the marketing application should include information verifying and validating that the device meets its reliability specifications. This information is typically provided in the form of a Reliability Report.
A Reliability Report encompasses various analyses and assessments, including Fault Tree Analysis (FTA). FTA is an analytical approach that identifies potential failure modes within a product or process. It involves systematically mapping out all possible failure scenarios and determining their root causes. By understanding these failure modes, manufacturers can implement measures to prevent or mitigate them, thereby enhancing the reliability of the injector.
Overall, the Reliability Report, which includes Fault Tree Analysis, is a critical component of demonstrating the reliability and performance of an emergency-use injector, ensuring its safe and effective use in real-world scenarios (27).

3. Results

This document summarises the various components of peptide drug product quality that are considered throughout development and manufacture, as well as during regulatory review of a peptide medicine. Because there is no "formal" regulation regarding peptides, to assess the risk of peptide quality to safety (including immunogenicity) and efficacy, producers and regulators employ a risk-based approach. If a potential risk is detected, a thorough analysis of product and process-related aspects must be done to assure the peptide drug's safety and efficacy. The researched factors and analytical portfolio techniques appropriate for a certain peptide must be selected on a case-by-case basis based on knowledge of the intricacy of the peptide structure and awareness of its production process.

4. Discussion

Brand-to-generic switching is a common practice across all therapeutic areas with the main aim of cost savings. According to the FDA, the cost of a generic drug can be 80%–85% lower than the innovator’s branded product; hence generic drugs can be rapidly substituted after patent expiration with estimated cost savings to consumers of $8 to $10 billion a year.

Many novel peptide medications have been approved for the US market in recent years as a result of increased

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JCHR (2024) 14(2), 34-37 | ISSN:2251-6727

focus on peptide pharmaceutical discovery and development.

Abbreviated New Drug Application for the generic drug product should be submitted according to 21 CFR § 314.94 - Content and format of an ANDA

Furthermore, the recent industry move towards generic peptide drug product submissions has increased the necessity for prompt evaluation of generic peptide drug product submissions as well as the application of the same quality standards to both brand-name and generic drug products.

Peptides fall somewhere between conventional small molecules and large proteins in terms of chemical complexity. As a result, peptides have sparked a slew of regulatory squabbles. Peptides are the small and complex in structure and hence it is difficult to show the structural sameness between two products. Peptides/protein medications have been governed as traditional chemical entity drugs in some circumstances and biologics in others, depending on their structure, properties, and production.

The main issue with parenteral drug delivery is a lack of convenience, price, accuracy, sterility, and safety, among other things. Because of these disadvantages, this distribution strategy is less desirable. This widespread acceptance of prefilled syringes is not surprising given the variety of compelling benefits such as ease, suitability for home use, less waste, and higher dose precision. Prefilled forms are convenient and aid in the administration process. The patient does not have to be concerned about transferring a medicine from a vial to a syringe, and hence does not have to be concerned about leaving a small fraction of the dose behind. As a result, the use of prefilled syringes can readily overcome all of the limitations of these methods.

The stability studies for drug product are performed in PFS rather than in vials in other cases. Human factor study and threshold analysis is done on the peptide PFS so as to identify any risk associated with the product.

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