

Guideline on the quality requirements of synthetic peptides

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Saudi Food & Drug Authority

Drug Sector

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Saudi Food and Drug Authority

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Vision

To be a leading international science-based regulator to protect and promote public health

Mission

Protecting the community through regulations and effective controls to ensure the safety of food, drugs, medical devices, cosmetics, pesticides and feed

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Acronyms and Abbreviations

ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
AAA	Amino Acid Analysis
API	Active pharmaceutical ingredient
CD	Circular Dichroism
CG-MALS	Composition gradient multi-angle light scattering detection
COA	Certificates of Analysis
CQA	Critical Quality Attribute
CTD	Common Technical Document
DP	Drug Product
FTIR	Fourier Transform Infra-Red
LC-HRMS	Liquid Chromatography-High-Resolution Mass Spectrometry
LC-MS	Liquid Chromatography-Mass Spectrometry
LC-MS/MS	Liquid Chromatography with Tandem Mass Spectrometry
LC-UV	Liquid Chromatography with Ultraviolet detection
LPPS	Liquid-Phase Peptide Synthesis
MS	Mass Spectrometry
NMR	Nuclear Magnetic Resonance
Ph. Eur.	European Pharmacopeia
QNMR	Quantitative Nuclear Magnetic Resonance
QTPP	Quality Target Product Profile
RP-HPLC	Reversed Phase High-Performance Liquid Chromatography
SEC	Size Exclusion Chromatography
SEC-MALS	Size-exclusion chromatography Coupled with Multi-angle Light-Scattering
SFDA	Saudi Food and Drug Authority
SMs	Starting Materials
SPPS	Solid-Phase Peptide Synthesis
USP	United States Pharmacopeia

1. INTRODUCTION

This guidance outlines the quality requirements for approving synthetic peptide products by the Saudi Food and Drug Authority (SFDA). Synthetic peptides are classified as complex active pharmaceutical ingredients. They are chain of amino acids linked to each other with amide bond. The length of this chain is varied from product to another, which consequently can affect its categorization in regulations or regulatory requirements. Due to size and structure, synthetic peptides fall in between small molecules and large proteins.

1.1.Scope

The guideline provides information to the applicant with some key regulatory considerations for the development, manufacture, and control of synthetic peptides intended for human use.

Synthetic peptides represent a unique class of substances, sharing characteristics of both small molecules and proteins, and thus require specialized regulatory approaches.

Therefore, this guideline addresses specific requirements concerning the manufacturing process, characterization, specification, including special considerations for analytical procedures.

This guideline does not cover peptides derived from biological or biotechnological sources, nor does it apply to recombinant technologies, radiopharmaceuticals, and radiolabeled peptide-containing products. Additionally, considerations related to the clinical safety and efficacy of synthetic peptides fall outside the scope of this document.

1.2.Related guidelines

This guideline should be read in conjunction with the data requirements for human drug submission and all other relevant International Council for Harmonization (ICH) guidelines, which are implemented by SFDA. These include, but are not limited to:

- ICH Q1 Stability testing of drug substances and drug products
- ICH Q2 Validation of analytical procedures
- ICH Q3A Impurities in new drug substances
- ICH Q3B Impurities in new drug products

- ICH Q3C Residual solvents
- ICH Q3D Elemental impurities
- ICH Q6A Specifications – Test Procedure and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances
- ICH Q8 Pharmaceutical development
- ICH Q9 Quality risk management
- ICH Q11 guideline on development and manufacture of drug substances (chemical entities and biotechnological/ biological entities)
- ICH Q13 Continuous manufacturing of drug substances and drug products
- ICH M7 Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk.

2. REGULATORY CONSIDERATION ON SYNTHETIC PEPTIDE

Quality requirements related to synthetic peptide drug substance and drug product should be submitted according to specific considerations. These includes all factors had an impact on the safety and efficacy of the product, which could be in manufacturing process, raw materials, characterization, analytical procedure, and development of the product. Control of impurities and aggregations should be considered when present in the drug substance and drug product due to potential immunogenicity issue. Evaluation of critical quality attributes and develop a suitable control strategy should be highlighted in the submission. Compatibilities of finished product with container closure systems, formulation composition including excipient and other parameters affect final product have to be justified and controlled.

2.1. Drug substances:

2.1.1. General information

Part of the submitted common technical document (CTD) should include structure, nomenclature, and general properties of synthetic peptides, such as optical rotation, solubility, water content, and hygroscopicity, etc... The applicant should provide product-specific physical properties. The three-letter amino acid code can be used for a structural

formula. A full name should be included in case of the use of a non-natural amino acid or d-amino acid.

2.1.2. Chemistry, Manufacturing and Control

2.1.2.1. Manufacturing process:

Narrative description of the manufacturing process by either using solid-phase peptide synthesis (SPPS), liquid-phase peptide synthesis (LPPS), or a hybrid SPPS/LPPS process should be provided. In the LPPS process, the description of purification used in each step should be submitted, intermediates have to be identified, and suitable control should be provided. In the SPPS process, in which a peptide chain is built by coupling, deprotection, and elongation through repeated cycles in a solid support, the purification, isolation, and control can be provided at the end of the manufacturing process. Thus, observed impurities that formed during SPPS cycles should be discussed along with appropriate controls.

For products manufactured using continuous manufacturing approaches, the requirements outlined in ICH Q13 regarding the description of the manufacturing process shall be considered.

2.1.2.2. Raw Material considerations:

Material used in the synthesis of peptide could be;

a. Starting Materials (SMs):

Starting materials include resin preloaded with linkers coupled with the first amino acid, amino acids, protected amino acid derivatives, and protected dipeptides, which may be accepted when justified. Following ICH Q11, the selection of starting materials should be considered. Providing name and site of starting material manufacturer, as well as manufacturing process of each SM, along with specifications, certificates of analysis (COAs) from both the SM supplier and the active pharmaceutical ingredient (API) manufacturer, and justification of selecting these starting materials are required.

Specifications of SMs should include quality attributes that reflect acceptable quality. As amino acids and their derivatives are used as building blocks of peptides, they will have an effect to the quality of the final API, which is presented by impurities that may be difficult

to be removed in the purification step, leading to low yield or decreased API purity.

Impurities in starting materials may include: free amino acids or amino acid derivatives (des-Fmoc), amino acid contaminants (foreign amino acids), i.e., amino acids other than the desired one, amino acid enantiomers and diastereomers, dipeptides or oligopeptides, and β -alanine containing contaminants from using Fmoc-succinimide (Fmoc-OSu) as the reagent. Any other impurity, such as reagents, solvents, etc., may be presented.

b. Resin

Resin itself is not considered an SM unless it is preloaded with the first amino acid or amino acid derivative. Besides appearances and identification, resin should have an acceptable particle size that permits ease of handling and removal of solvent. Resin is generally considered inert, but having adequate swelling capability is essential since it will affect loading the first amino acid, and also inefficient swelling will have an impact on the purity of the final active ingredient by leading to C-terminal deletion/truncated impurity.

c. Solvents and Reagents

Other materials used in the peptide manufacturing process are solvents and reagents, which function as coupling, activation, cleavage, and deprotection, should be listed in control of materials along with their specifications and COAs. The minimum requirements to be provided in the specification of reagents and solvents are appearance, identification, and purity, including possible impurities.

2.1.2.3. In-process control and intermediates:

Developing an appropriate control strategy for each manufacturing step is important due to its effect on the purity and potency of the final product. The critical process parameters for the following manufacturing steps should be identified: deprotection, coupling, washing, capping, and cleavage. Providing a well-established control strategy in a submission for each critical step, for example, a color test, such as the Kaiser Test (Ninhydrin test), can be used to determine the coupling completion.

The purification step is crucial for the quality of the synthetic peptide and should be carefully controlled. The selection of the purification method needs to be adequately

validated and described. Other steps, e.g., lyophilization, post-cleavage work-up, etc., involved in the synthesis should be well controlled as well.

Intermediates should be identified in the manufacturing process as defined by ICH Q7: “A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated.”, and specification and analytical data of these intermediates are expected to be provided. However, in LPPS, fragments are synthesized and isolated; these intermediates may require more special control than SPPS.

2.1.2.4. Characterization consideration:

a. Elucidation of structure

Elucidation of structure is performed using different analytical methods to confirm primary, secondary, tertiary, and quaternary structures of peptides, where applicable (**Table 1**). The primary structure, which indicates amino acid sequence and secondary structure that identifies the arrangement of amino acid residues adjacent in sequence, is required for all synthetic peptides that might affect the safety and efficacy of the final product. Tertiary structure indicates the three-dimensional conformation of amino acid residues that are far apart in sequence. In addition, a complex peptide represents a quaternary structure that indicates the assembly of peptides, which are called higher-order structure/aggregates.

Different analytical techniques are used to determine peptide structure. A combination of different methods is required to confirm the structure, especially for complex peptides. Using the chromatographic method for amino acid sequence, besides N-terminal Edman degradation or peptide mapping coupled with mass spectrometry, is a beneficial way to determine primary structure. The evidence of chemical structure shall be provided under Section 3.2.S.3.1. For identification of the peptide as part of the specification and release, at least two orthogonal methods shall be employed.

Elucidation of secondary structure is considered a part of peptide characteristics. The interaction between the atoms of the peptide backbone through hydrogen bonding results in a certain degree of folding (i.e. α -helix and/or β -sheet). Elucidation of secondary

structure can be performed by using circular dichroism (CD), Fourier Transform Infra-Red (FTIR), Raman spectroscopy, fluorescence spectroscopy, Nuclear Magnetic Resonance (NMR), and X-ray crystallography, where relevant.

The information/data of higher order structure should be submitted on a case-by-case basis, i.e., complex peptides and cyclic peptides.

Table 1: Examples of analytical technique used in synthetic peptide characteristics:

Characteristic	Analytical Technique
Primary structure	- Molecular Mass Determination - Peptide mapping (Using chemicals or enzymes to produce peptide fragments, then these fragments separated and analyzed using LC-UV or with LC-MS) - Peptide sequencing (N-terminal Edman degradation) - Amino acid analysis - Determination of d-Amino acids
Secondary structure	- Far-UV CD Spectroscopy - FTIR Spectroscopy - Raman Spectroscopy - NMR Spectroscopy - Fluorescence spectroscopy
Tertiary structure	- Near-UV CD Spectroscopy - Intrinsic Fluorescence Spectroscopy - Differential Scanning Calorimetry - Disulfide Bonds
Quaternary structure/ Self association/ Aggregation	- Size-exclusion (gel filtration) chromatography with UV detection. - Size-exclusion (gel filtration) chromatography coupled with Multi-angle Light-Scattering Detection (SEC-MALS). - Composition gradient multi-angle light scattering detection (CG-MALS) - Thioflavin test (ThT test)
Biological Activity	- Cell-based and other biological assays

b. Impurities

Peptides impurities can be classified as: peptide-related impurities and non-peptide-related impurities. Understanding of impurities present in the drug substances and drug product of synthetic peptides and providing adequate control strategy is important to assure the safety by the mean of immunogenicity.

Peptide-related impurities usually originate from raw materials impurities, manufacturing processes such as amino acid deletion or amino acid insertion, truncation, etc., and are formed by different degradation processes. **Table. 2** provides examples of possible process-related impurities and degradants that may occur during storage. Discussion on the possible impurities should be submitted, the control of them based on reporting, detection, and quantification thresholds should be provided with the justifications by toxicological studies, clinical studies, or other relevant information whenever applicable.

Non-peptide-related impurities include solvents, reagents, metals, catalysts, counter ions and others and should be controlled by following the relevant guidance, i.e., ICH Q3A - Q3D, and M7.

An appropriate analytical procedure should be developed to adequately separate, identify, and qualify each type of impurity. For example, Liquid Chromatography-High-Resolution Mass Spectrometry (LC-HRMS) or Liquid Chromatography with tandem mass spectrometry (LC-MS/MS) is commonly used for several types of peptide-related impurities. Another example is using size-exclusion chromatography (SEC) or SEC–multi-angle light scattering (SEC–MALS) for aggregation impurities. However, utilizing two orthogonal methods should be considered for some cases to provide better control.

Table 2: Process-related impurities and degradants that may occur during storage:

Impurity	Mechanism
Denaturation	- Modification of the peptide structure that changes its physical, chemical and biological properties; occurs in the presence of denaturing agents
Aggregation and precipitation	- Association of hydrophobic amino acid residues to form aggregates; precipitation occurs if on a macroscopic scale
Oxidation and reduction	- Induced by temperature, pH, metal ions and buffers during synthesis and/or storage
Proteolysis	- Upon exposure to harsh conditions, extreme pH, high temperature or enzymes
Deamination	- Hydrolysis of the side-chain amide linkage of an amino acid residue with formation of a free carboxylic acid
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
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
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
By-products generated by incomplete deprotection	- Results in protecting groups covalently attached to peptide sequences
β -Elimination	- Proceeds through a carbanion intermediate; susceptible residues under alkaline conditions are Cys, Lys, Phe, Ser and Thr
Truncation	- Missing one or more amino acid residues at either the N- or C-terminal end due to precipitation of resin beads during synthesis
Dimers	- Self-association of hydrophobic amino acids residues in peptides to form aggregates - Chemical reactions
Side- and end-chain impurities	- Amination of side chain of Arg with a mass difference of +15 Da. Other examples include acetylation, histamine-substituted guanidine with a mass difference of +126 Da
Diketopiperazine, pyroglutamate	- Diketopiperazine formation occurs if Pro or Gly residues are at position 1 or 2. Pyroglutamic acid forms if Gln is the N-terminal amino acid residue.

2.1.2.5. Specification consideration:

Establishing specifications should be based on critical quality attributes (CQAs) along with justification. These CQAs are assumed to have an impact on safety, efficacy and quality. In addition, pharmacopoeial monographs should be used as references (where available).

The specification of the synthetic peptide should cover, but not be limited to, physical properties, identification, assay, peptide content, impurities, optical rotation, counter ion, loss on drying, water content, bacterial endotoxins, pH, and any other specific test for the product should be submitted along with justification (**Table. 3**).

Identification as per ICH Q6A: “identification testing should optimally be able to discriminate between compounds of closely related structure which are likely to be present” should indicate the conformation of identity for the synthetic peptide, and this will be established by using two independent tests. Reversed phase high-performance liquid chromatography (RP-HPLC) and mass spectrometry (MS) are useful methods for synthetic peptides. Other tests, such as amino acid analysis (AAA), peptide mapping, nuclear magnetic resonance (NMR), and tandem mass (MS-MS), are also considered acceptable.

Assay of the synthetic peptide product can be presented on an anhydrous or counter-ion-free basis. The method should include a reference standard and well-established calculations that take into consideration the differences in each peptide.

For purity/related impurities highlighted in the synthetic peptide, they can be classified into peptide-related impurities and non-peptide-related impurities. For process-related or degradation impurities, they should be evaluated and analyzed using appropriate methods, and orthogonal separation techniques are recommended. These methods could be Reversed Phased HPLC, Ion Exchange chromatograph, or Liquid Chromatography-Mass Spectrometry (LC-MS), depending on nature of impurities. Aggregation/oligomerization should be considered in setting the specification of synthetic peptides. The aggregation of peptides may be separated using methods that can cover a different range of aggregate sizes, such as Size Exclusion Chromatography (SEC). Controlling other impurities from

the manufacturing process, such as residual solvents, elemental impurities, and genotoxic impurities from possible non-peptide related substances, should follow the ICH Q3A - Q3D and ICH M7 guidance.

Identification of counter-ion is important due to its effect in the secondary structure of peptides and consequently their biological activity. Mostly, acetic acid/acetate or chloride is used in peptide preparation. Other counter- ions can be used, such as trifluoroacetic acid. The determination of ions is performed mostly by using high-performance liquid chromatography or ion chromatography.

Table 3:Example of most common specification test with its proposed example method:

Test	Method
Appearance	Visual inspection
Identification	Examples; HPLC, MS, AAA, MS-MS, NMR, Peptide mapping by chemical or enzymatic cleavage method, enantiomeric purity, N-terminal sequence analysis, IR and higher order structures tests. Bio-identity can be considered for complex and long peptides.
Assay	By HPLC or other suitable identification test.
Peptide content	Peptide content by AAA UV spectroscopy QNMR
Impurities	
Peptide related substances	Specific method such as; LC-MS and can be used more than method independently capabilities.
Residual solvents	Considering ICH Q3C
Elemental analysis	Considering ICH Q3D
Other small-molecule impurities	Followed ICH Q3A & Q3B guidance. Could include potential mutagenic impurities that required additional evaluation considering ICH M7.
Aggregation/ Oligomerization	SEC method.
Specific tests	
Counter ion (e.g. Trifluoroacetate, format, hydrochloride)	RP-HPLC or ion-exchange chromatography.
Water content	Example: Coulometric method
Specific optical rotation	Example: Using polarimeters
Ellman test	Required if the reduced form(s) of a peptide containing disulfide bonds cannot be determined using the method for related substances

The proposed acceptance criteria should be based on toxicological and clinical data, real batch analysis, including stability data to justify an adequate safety level. The scientific thinking and approaches described in ICH Q6A can be used for small-sized synthetic peptides, along with special consideration regarding characteristic attributes resulting from the peptide synthesis pathway and development process. The pharmacopeia, i.e., USP or Ph. Eur., can be used to justify the development of quality control of the same active pharmaceutical ingredient, including limit establishment.

2.1.2.6. Analytical procedure and validation considerations

Analytical methods used in either release or stability tests should be adequately validated. For the development of analytical procedures for identity, peptide-related impurities, and other tests, refer to the discussion in the **sections 2.1.2.4 and 2.1.2.5**. With consideration of the complexity of the structure, application of an advanced method other than that used for small molecules may be needed, in some cases, orthogonal analytical methods should be utilized. Referring to ICH Q2 and ICH Q14 might be considered during the development of the analytical method and validation.

2.2.Stability

The general principle of ICH Q1 and SFDA Guidelines for Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products can be applicable to synthetic peptides. Special consideration regarding degradation impurities studies or specific control for aggregation, another degradant impurity, or other product-specific parameters, such as water content or pH control, needs to be provided where applicable. Other biophysical stability parameters detected during development of the drug product should be added.

2.3.Peptide drug products (DPs) Considerations:

During drug product development, a Quality Target Product Profile (QTPP) as per ICH Q8 (R2) guidance should be provided. This would be designed based on the CQAs, considering

route of administration, dosage form, bioavailability, strength, and stability.

The main concern in the quality of synthetic peptide drug products is related to the immunogenicity of the peptide product, which results from impurities related to aggregation/oligomerization. Risk factors, such as pH, that affect the level of impurities should be included in the drug product specification.

Assessing the compatibilities of drug product with formulation composition, such as excipients, preservatives, and any other excipients, should be documented and submitted. A study of extractables and leachables from the container/closure system must be submitted, as it can interact with the drug product, affecting the safety and efficacy of the drug product.

Other synthetic peptide drug products with reference drug that chemically or biologically synthesized comparability studies will be considered (Refer to sections 2.3.1 and 2.3.2).

2.3.1. Consideration for generic drugs with chemically synthesized reference drug

Major concerns for generic drugs are the differences in the purity profile. As the methods of synthesis are usually the same for both generic and reference drug products, similar impurity profiles are expected in a submission, especially for complex peptides. Peptide-related impurities at comparable levels in generic drug products under long-term storage and accelerated study should be submitted.

Considering the reference, drug limits in the establishment of impurities, including aggregation limits, can be applicable.

The stability requirements of a generic peptide drug are the same as those of the reference peptide drug.

In case of differences in the formulation of the peptide drug product, compatibility studies should be provided.

2.3.2. Consideration of synthetic peptides with biological reference drug

As biological products contain active substances from biological sources or produced using biotechnology approaches, some biological substances, such as a small protein, can be chemically synthesized.

The biosimilar regulatory pathway is not possible for chemically synthesized peptides since they fall outside the definition of a biological substance.

Characterization and analytical comparability studies, physicochemical properties, assay, and other parameters related to quality are required. The characterization and analytical comparability testing should be placed in section (Characterisation 3.2.S.3). A broad panel of analytical methods to demonstrate the comparability between the recombinant reference product and the synthetic version is required for the side-by-side analytical comparability studies. The extent of comparative non-clinical and clinical studies to confirm a comparable safety and efficacy profile is determined based on the outcome of side-by-side analytical comparability testing. It is important to note that the reference product used in the analytical comparability studies should be sourced from the Saudi market or markets under the regulation of reputable regulatory authorities outlined in the SFDA regulatory framework for drug approval.

It is predicted that impurities in the biological reference drug are different from those in chemically synthesized ones, due to the change of source and synthetic pathway. Whenever possible include comparative studies between a chemically synthesized peptide and its biologically sourced reference. These include aggregate profiles in terms of aggregate sizes and levels, which might adequately address immunogenicity concerns due to aggregation. Peptide-related impurities present in both products should be at the same level or less for the chemically synthesized product.

It is recommended to provide comparative forced degradation studies and demonstrate the suitability of the analytical purity methods to fully characterize the impurity profile of both products.

Suitable analytical methods that are qualified, validated, and sensitive to detect possible differences between both products should be used in the analytical comparability studies.

It is recommended that at least 10 commercial batches be used for the side-by-side analysis in the comparability testing, or the number of batches used in the analytical comparability studies should be adequately justified.

In-silico prediction of immunogenic impurities arising from synthesis or degradation processes, should be performed when applicable.