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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)
Committee for Veterinary Medicinal Products (CVMP)

Concept Paper on the Establishment of a Guideline on the Development and Manufacture of Synthetic Peptides

Agreed by Quality Working Party	29 June 2022
Adopted by CHMP for release for consultation	15 September 2022
Adopted by CVMP for release for consultation	8 September 2022
Start of public consultation	20 September 2022
End of consultation (deadline for comments)	20 December 2022

Comments should be provided using this template. The completed comments form should be sent to QWP@ema.europa.eu

Keywords	Guideline, Chemistry, Development and Manufacture, Drug Substance, New Active Substance, Synthetic Peptides

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1. Introduction

This concept paper addresses the need to establish a Guideline on the Development and Manufacture of Synthetic Peptides. The number of clinical trial applications for human products and marketing authorisation applications for synthetic peptides for both human and veterinary products significantly increased over the last few years. From an analytical and regulatory perspective, peptides are interesting since they present a link between products derived from biotechnology and small molecular chemical compounds. Furthermore, synthetic peptides are fully or partially excluded from the scope of ICH Q3A/B (VICH GL10/GL11), ICH Q6A/B (VICH GL39/GL40) and ICH M7 (EMA/CVMP/SWP/377245/2016). It is therefore proposed to establish a guideline addressing those specific aspects regarding the manufacturing process, characterisation, specifications and analytical control for synthetic peptides which are not covered in the Guideline on the Chemistry of Active Substances (EMA/454576/2016) and Chemistry of Active Substances for veterinary medicinal products (EMA/CVMP/QWP/707366/2017).

A second concept paper on the establishment of a Guideline on the Development and Manufacture of Synthetic Oligonucleotides will be published. There are numerous similarities between synthetic peptides and oligonucleotides. For both active substance classes, solid phase synthesis is well established and widely used, and is generally followed by chromatographic purification steps. However there are also some fundamental differences, for example starting material chemistry and impurity profiles. It is envisaged that two separate guidelines will be developed to address specific requirements for both synthetic peptides and oligonucleotides.

2. Problem statement

Currently there is no guideline which reflects the quality requirements for regulators and industry on synthetic peptides.

3. Discussion (on the problem statement)

Synthetic peptides are at the interface of small molecules and proteins and, from a quality point of view, specific considerations apply to this class of therapeutics. The proposed guideline will address the following:

- Development of an overall integrated control strategy to ensure consistent quality of synthetic peptides and the resulting medicinal products, based on relevant critical quality attributes (CQAs)
- Requirements specific for the solid-phase synthesis pathway including requirements on batch definition and the description of splitting, pooling and re-processing steps applied in the purification process
- Requirements for other synthesis pathways, in addition to solid phase synthesis
- Selection of starting materials
- Characterisation approaches including investigation of the impurity profile
- Purity control strategy: product-related impurities (in function of the molecule size) and process-related impurities; use of orthogonal purity methods (while distinct impurity peaks are typically observed for peptides, orthogonal purity methods are recommended to minimize the risk of undetected impurities coeluting with the main peak or with each other)

- Requirements for conjugation (e.g. PEG-ylation) approaches. Conjugation has emerged as a common mechanism to alter or enhance the properties of synthetic peptides.

The ‘‘Technical Guide for the Elaboration of Monographs on Synthetic Peptides and Recombinant DNA Proteins’’ (Edition 2018) published by the EDQM is intended to provide guidance to authors, contributors and users of the Ph. Eur. on the elaboration of active substance monographs for synthetic peptides and products of recombinant DNA (rDNA) technology. This guidance will need to be reflected during the drafting process of the proposed guideline. Ph. Eur. monographs are available for certain individual synthetic peptides and should be taken into account as relevant. Furthermore, specific limits are laid down in the Ph. Eur. Monograph ‘Substances for pharmaceutical use’ for synthetic peptides which need to be referred to/reflected in the guideline.

The proposed guideline will follow the structure of CTD Module 3 and the Guideline on the Chemistry of Active Substances where relevant. Additionally, finished product considerations (e.g. choice of excipients, formulation & sterilisation aspects) relevant to finished product formulations containing synthetic peptides will be addressed.

It can be assumed that the number of applications where a biological medicinal product is used as a reference product and the active substance (peptide) is manufactured by chemical synthesis will increase in the future. The biosimilar regulatory pathway is not possible for marketing authorisation applications for human products containing chemically synthesised peptides. Nevertheless, requirements for the demonstration of similarity of the synthetic product with the reference product will be described in the guideline.

In regard to the products for human use, it is also intended to address specific requirements for synthetic peptides to be used in clinical trials.

4. Recommendation

The Quality Working Party recommends the establishment of the Guideline on the Development and Manufacture of Synthetic Peptides.

5. Proposed timetable

The concept paper will be published for a three-month public consultation period.

QWP will take account of all comments received during the public consultation on the concept paper when preparing the draft guideline.

The draft guideline will be published for a six-month public consultation period.

QWP will take account of all comments received during the public consultation on the draft guideline when preparing the final guideline text. It is expected that the final guideline will come into operation six months after publication following adoption by CHMP and CVMP.

6. Resource requirements for preparation

The development of the guideline will involve the EMA-QWP Secretariat, the Joint CHMP/CVMP Quality Working Party, the CHMP, the CVMP, and GMP/GDP Inspectors Working Group, who would be consulted, as necessary. The QWP should appoint a rapporteur and a drafting group.

7. Impact assessment (anticipated)

No adverse impact on industry with respect to either resources or costs is foreseen.

The guideline will clarify requirements for regulators and industry with respect to the development and manufacture of synthetic peptides taking into account the concepts of recent development.

The guideline will not introduce new requirements on medicinal products already authorised and on the market.

8. Interested parties

Pharmaceutical Industry, EU Competent Authorities, GMP/GDP Inspectors Working Group

9. References to literature, guidelines, etc.

- ICH guideline Q8 (R2) on pharmaceutical development CHMP/ICH/167068/04
- Guideline on the development pharmaceutics for veterinary medicinal products EMEA/CVMP/315/98
- ICH guideline Q11 on development and manufacture of drug substances (chemical entities and biotechnological/ biological entities) CHMP/ICH/425213/2011
- Guideline on the chemistry of active substances EMA/454576/2016
- Guideline on the chemistry of Active Substances for veterinary medicinal products (EMA/CVMP/QWP/707366/2017)
- Guideline on Active Substance Master File procedure CHMP/QWP/227/02 Rev 4/ Corr., EMEA/CVMP/134/02 Rev 4/ Corr.
- Guideline on the Summary of Requirements for the Active substance in the Quality Part of the Dossier CHMP/QWP/297/97 Rev 1 corr., EMEA/CVMP/1069/02
- Manufacture of the finished dosage form (human) EMA/CHMP/QWP/245074/2015
- Manufacture of the finished dosage form (veterinary) EMA/CVMP/QWP/798401/2015
- Sterilisation of the medicinal product, active substance, excipient and primary container EMA/CHMP/CVMP/QWP/850374/2015
- Requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials EMA/CHMP/QWP/545525/2017 Rev
- Technical Guide for the Elaboration of Monographs on Synthetic Peptides and Recombinant DNA Proteins (Edition 2018), EDQM
- Ph. Eur. Monograph 'Substances for pharmaceutical use'

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