EUROPEAN MEDICINES AGENCY
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 Oligonucleotides

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 Oligonucleotides

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1. Introduction

This concept paper addresses the need to establish a Guideline on the Development and Manufacture of Synthetic Oligonucleotides. The number of clinical trial applications for human products and marketing authorisation applications for synthetic oligonucleotides for both human and veterinary products has significantly increased over the last few years. From an analytical and regulatory perspective, oligonucleotides are interesting since they present a link between products derived from biotechnology and small molecular chemical compounds. Furthermore, synthetic oligonucleotides 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 oligonucleotides 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 Peptides 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 oligonucleotides.

3. Discussion (on the problem statement)

Synthetic oligonucleotides are at the interface of small molecules and biologicals and, from a quality point of view, specific considerations apply to this class of therapeutics. The guideline will cover antisense and other single strand products, double strand products as siRNA and as a third subclass aptamers.

The proposed guideline will address the following:

- Development of an overall integrated control strategy to ensure consistent quality of synthetic oligonucleotides and the resulting medicinal products, based on relevant critical quality attributes (CQAs)
- Requirements specific for the solid-phase synthesis manufacturing pathway including requirements on batch definition and the description of splitting, pooling and re-processing steps applied in the purification process
- Selection of starting materials including a criticality assessment of their impurity profiles
- Characterisation approaches including investigation of the active substance impurity profile
- Purity control strategy: product-related impurities and process-related impurities; use of orthogonal purity methods, discussion of grouping strategies for impurities

- Differences in requirements between single strand, double strand and aptamer oligonucleotide products will clearly be outlined
- Oligonucleotides have potential to use prior knowledge and platform technologies. Recommendations on how to justify applicability of prior knowledge and platforms will be provided.
- Requirements for conjugation (e.g., GalNAc, PEG-ylation, monoclonal antibodies, peptides, proteins) approaches. Conjugation has emerged as a common mechanism to alter or enhance the properties of synthetic oligonucleotides.

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 formulations containing synthetic oligonucleotides will be addressed. Furthermore, considerations for active substances that are in solution (i.e. not isolated) will be provided.

In contrast to synthetic peptides no purity limits are stated in the Ph. Eur. Monograph 'Substances for pharmaceutical use' for synthetic oligonucleotides. Establishing harmonised limits could be considerd in this GL. However, additional discussions are needed as analytical methods and specific oligonucleotide type of products are not comparable per se. The public consultation may facilitate comments from different stakeholders in this regard.

First applications for generic oligonucleotides for human products will be submitted in the near future. Additional considerations regarding quality aspects may be applicable for such submissions including demonstration of comparability and will be covered in the guideline.

Initiatives for the development of personalised antisense oligonucleotides (either for one patient or a small group of patients) are currently on-going and may be considered in this guideline.

In regard to the products for human use, it is also intended to address specific requirements for synthetic oligonucleotides 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 Oligonucleotides.

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 oligonucleotides 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
- 'Ph. Eur. Monograph 'Substances for pharmaceutical use'