Federal Institute
for Drugs
and Medical Devices

# European Quality Guidelines for Synthetic Peptides and Oligonucleotides

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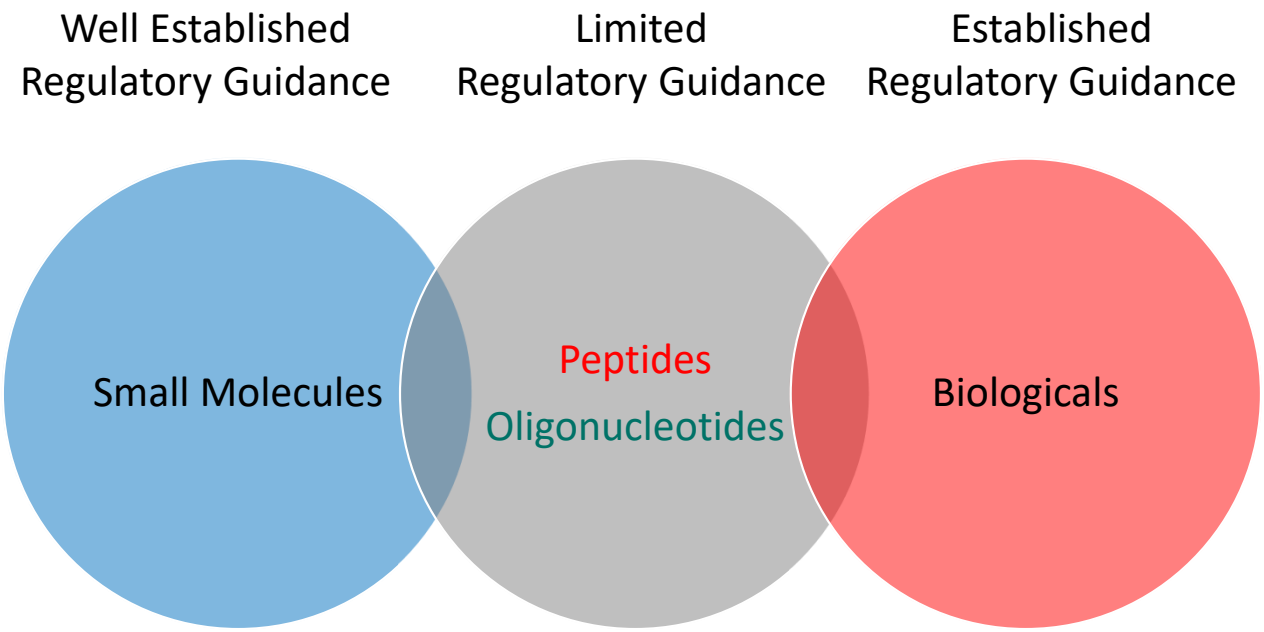
USP Workshop on Peptide and Oligonucleotide Therapeutics: Regulations and Quality Standards, Rockville
9th April 2024

# Disclaimer

**The views expressed in this presentation are those of the speaker and do not necessarily represent those of the BfArM and other European Regulatory Agencies.**

# The Grey Area



# EMA Guideline on the Development and Manufacture of Synthetic Peptides

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 October 2023
EMA/CHMP/CVMP/QWP/387541/2023
Committee for Medicinal Products for Human Use (CHMP)
Committee for Veterinary Medicinal Products (CVMP)

## Guideline on the Development and Manufacture of Synthetic Peptides

Draft

| | |
|---|---|
| **Draft agreed by Quality Working Party** | 6 September 2023 |
| **Adopted by CHMP for release for consultation** | 12 October 2023 |
| **Adopted by CVMP for release for consultation** | 5 October 2023 |
| **Start of public consultation** | 18 October 2023 |
| **End of consultation (deadline for comments)** | 30 April 2024 |

A second concept paper on the establishment of a Guideline on the Development and Manufacture of Synthetic Oligonucleotides has been published. There are numerous similarities between synthetic peptides and oligonucleotides, however also fundamental differences. Therefore it has been decided to develop two separate guidelines.

# Draft GL on Synthetic Peptides Background and History

15 December 2023
EMA/54514/2023
Human Medicines Division

## 3-year work plan for the joint CHMP/CVMP Quality Working Party

- Guideline on synthetic peptides (H/V) – publication of guideline by Q4 2025
- Guideline on synthetic oligonucleotides (H/V) – publication of draft guideline for public consultation in Q4 2024

Part of QWP workplan:

**CP adopted by QWP and CHMP/CVMP**
Sep 2022

**Industry Consultation**
until 20/12/2022

Concept Paper on the Establishment of a Guideline on the Development and Manufacture of Synthetic Peptides (europa.eu)
89 comments received from 9 industry stakeholders

**Preparation of draft GL**

Drafting Group meetings with experts from EU network

**IP meeting with industry stakeholders on 27/06/2023**
Draft GL discussed with QWP

Topics discussed with industry stakeholders:
- Starting materials
- Orthogonal/
- Complementary methods to control difficult to detect impurities
- Peptide definition / when are Ph. Eur. impurity limits (not) applicable

**QWP comments addressed**

Extra DG meeting

**Draft GL Adopted by QWP Sep 2023**
by CVMP /CHMP
Oct 2023

+ Clinical Trial Coordination Group informed

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# Next Steps


Please take the opportunity to provide your comments to the draft guideline

*full text:* Guideline on the Development and Manufacture of Synthetic Peptides (europa.eu)

# Executive summary

This guideline addresses 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) or Chemistry of Active Substances for Veterinary Medicinal Products (EMA/CVMP/QWP/707366/2017). It also contains requirements and considerations related to conjugation, to medicinal product development, to synthetic peptide development using biological peptides as European reference medicinal product, and to clinical trial applications (human products only).

- Introduction (background)
- Scope
- Legal Basis and Relevant Guidelines
- Active Substance
- -> further structure according to the 3.2.S eCTD structure (S1 to S7) + Extra Chapter on Conjugation
- Medicinal Product Considerations
- Synthetic Peptide Development Programmes Using a Biological Medicinal Product as a European Reference Medicinal Product
- Requirements for Clinical Trial Applications

# Scope

- Addresses specific aspects regarding the manufacturing process (solid phase peptide synthesis, fragment condensation), characterisation, specifications and analytical control for synthetic peptides which are not covered in the

  - Guideline on the Chemistry of Active Substances (EMA/454576/2016)
  - Chemistry of Active Substances for Veterinary Medicinal Products (EMA/CVMP/QWP/707366/2017)

and is to be considered complementary to the latter guidelines

# S 2.2 Description of Manufacturing Process and Process Controls

- For repeated synthesis cycles in SPPS : [PARs + reaction conditions] x N
    - Splitting & pooling
    - Repurification of side fractions
    - Repetition of coupling reaction
- Hybrid approaches e.g. SPPS + fragment condensation step
- Lyophilisation process parameters

# S 2.3 Control of Materials

- Starting materials
  - ICH Q11 applies
  - Starting material manufacturers (name + address), subject to lifecycle management

  - Protected AAs and/or protected dipeptide building blocks (if justified)
    - Flowchart of SM synthesis
    - Criticality assessment : impact of SM impurities on impurity profile of peptide
    - SM specifications based on fate- and purge studies

  - Non-peptidic structural moieties

- Other materials used in manufacturing process
  - E.g. resins, solvents, chromatographic materials

# S 2.4 Control of Critical Steps and Intermediates

- Criticality of manufacturing steps to be established as per ICH Q9 – 11 for
  - SPPS steps (control of deprotection, washing, coupling, capping, cleavage)
  - Purification steps
  - Pooling strategy with purity acceptance criteria for:
    - Main fractions
    - Side fractions that are allowed to undergo secondary purification (if applicable)
    - Fractions to be discarded
  - LPPS and hybrid approaches with fragment condensation processes

- IPCs

- Intermediate specifications

# S 3 Elucidation of Structure and Other Characteristics / Impurities

- Primary, secondary, tertiary, quaternary structure – as relevant
- A number of typical characterisation techniques are provided

- Peptide-related impurities – not in scope of ICH M7
  - From starting materials:

  e.g. incorrect enantiomers, AAs with incorrect or without protecting groups, dipeptides in single AA SMs (or vice versa)
  - From manufacturing process

  e.g. stereoisomers due to racemisation of AAs, deletion sequences and truncated sequences, insertion sequences, related substances formed during cleavage
  - From degradation (e.g. due to oxidation, hydrolysis, deamidation, aggregation…)

- Process-related impurities – in scope of ICH M7 or ICH Q3C

  e.g. process reagents, by-products, residual solvents, elemental impurities

# S. 4 Control of the Active Substance

- Typical specification tests are provided as a non-exhaustive list
- Ph. Eur. general monograph `Substances for Pharmaceutical Use` applies:

Table 2034.-2. – *Reporting, identification and qualification of organic impurities in peptides obtained by chemical synthesis*

| Reporting threshold | Identification threshold | Qualification threshold |
|---|---|---|
| > 0.1 per cent | > 0.5 per cent | > 1.0 per cent |

- Identification test(s) should unambiguously confirm the sequence of the peptide (2 orthogonal methods are recommended)
- Purity methods: Analytical development might be challenging due to co-eluting impurities. If one method is not appropriate to separate all peaks, additional independent methods may be needed Stability indicating properties and mass balance need to be studied. Specific chiral methods might be needed to control diastereomers
- Absence of biological assay should be justified
- Acceptance criteria for peptide-related impurities should be based on batch data
- Assay limits to be expressed in terms of counter-ion free, anhydrous substance

# Conjugation Considerations

- Synthesis of conjugate moiety and (if applicable) the linker is to be part of S 2.2
- Starting material for the conjugation component (and/or the linker): ICH Q11 applies
- In case of multiple manufacturers of conjugate moiety and (if applicable) the linker: peptide-conjugated material from all suppliers to be manufactured -> batch results and stability data to be generated
- Impurities of conjugate moiety and (if applicable) the linker: ICH M7 applies
- Control of unconjugated peptide (as intermediate) is key
- In the final active substance: unconjugated components, multi-conjugated components to be controlled as impurities

# Medicinal Product Considerations

- Thresholds from Ph. Eur. general monograph `Substances for Pharmaceutical Use` also apply to medicinal product
- Impurity acceptance criteria to be justified considering batch results and qualification data
- ICH Q3D and risk considerations for nitrosamine impurities apply
- Need for potency assay, for measurement of secondary and tertiary structure, and for aggregates / oligomers needs to be considered, and presence/absence of such tests in routine specification needs to be justified
- The decision trees in the ‘Guideline on the Sterilisation of the Medicinal Product, Active Substance, Excipient and Primary Container’ apply

# Synthetic Peptide Development using a Biological Medicinal Product as a European Reference Medicinal Product

- The biosimilar regulatory pathway is not possible for chemically synthesized peptides since these fall outside the definition of a biological substance
- Nevertheless, the basic principles to demonstrate biosimilarity – high similarity in terms of structure, biological activity and efficacy, safety and immunogenicity profile – should be considered
- Analytical comparability testing, comprising physicochemical (structural) and biological (functional) assays and conventional analytical testing, forms the basis of the demonstration of similarity
- A broad panel of analytical methods to demonstrate the similarity is requested
- The applicants will need to fully quantify all differences in peptides produced by chemical synthesis with the reference product
- Pre-defined comparability acceptance criteria should be defined
- Characterization of purity should be addressed using an orthogonal approach

# Synthetic Peptide Development using a Biological Medicinal Product as a European Reference Medicinal Product

- Aggregation propensity should also be investigated
- In principle Ph. Eur. Limits for synthetic peptides are also relevant for these products
- Process-related impurities from the cell construct [e.g. host cell protein (HCP), DNA] or resulting from the manufacturing process (e.g. antibiotics and other media components) do not need to be part of the comparability studies
- Clearance of reagents, residual solvents, elemental impurities and potential genotoxic impurities for the synthetic peptides should be addressed
- Functional assays (e.g. cell based assays using appropriate cell lines) should be developed and used in the comparability studies
- The absence of a biological activity test in the release specifications for drug substance and drug product should be appropriately justified

# Synthetic Peptide Development using a Biological Medicinal Product as a European Reference Medicinal Product

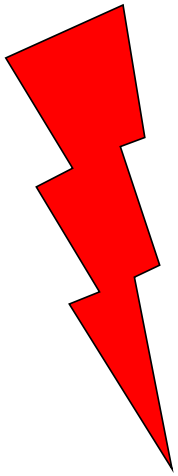
- The analytical methods used in the comparability exercise should be suitable, sufficiently qualified and/or validated and sensitive to detect potential differences between both products
- The number of batches used in the comparability studies should be adequately justified (see also: ‘Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development’ - EMA/CHMP/138502/2017)
    - EMA product-specific bioequivalence guidance for lanreotide acetate (reference product is not a biological) requires comparability data from at least 5 batches of the test and reference product. It is also stated that more batches may be needed in case of higher variability of the reference product results
- Comparative stability studies can be useful for detecting potential differences in the stability profile of the peptides manufactured either by chemical synthesis or by recombinant techniques
- Stability and shelf-life claims cannot be derived from the reference product without their own data

# Requirements for Clinical Trial Applications

- Phase-appropriate requirements, focus on safety, especially in early development
- Impurities in starting materials should be monitored already in early development, setting of limits for certain impurities may be expected for later development
- Changes in manufacturing process during development should be assessed for potential impact on the quality of the active substance, especially the impurity profile
- Primary structure should be characterised, as well as propensity to aggregation and racemisation
- Orthogonal/complementary analytical procedures should be employed to allow adequate characterisation of the impurity profile
- Impurities in the peptide active substances should be identified in the course of development. Peptide-related impurities above the threshold of 1.0%, should be identified and qualified in preclinical studies

# The Guideline Dilemma

Please provide specific guidance on…..



Need for flexible risk-based approaches: a flexible guidance document leveraging risk-based decisions is preferable to a highly prescriptive guidance document.

# Impurities vs. Sterility Assurance

- Terminal sterilisation of the final drug product is preferred to sterilisation by filtration and/or aseptic processing
- Aseptic processing is generally acceptable for biologicals
- In Europe sterile filtration was generally accepted for liquid synthetic peptide/oligonucleotide formulations in the past
- Decision trees for the selection of sterilisation methods as described in the ‘Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container` are relevant for synthetic peptides and oligonucleotides
- Terminal sterilisation should not be ruled out purely on the basis of an increase in degradation products without additional justification. If impurities are either metabolites or are generated at levels already qualified, then terminal sterilisation is still considered feasible
- Convincing data should be provided to allow the selection of sterile filtration and aseptic processing for future submissions
- Numerous scientific advice applications regarding this topic have been received recently. In several cases justification and provided/proposed data package is not considered sufficient!

# EMA Guideline on the Development and Manufacture of Synthetic Oligonucleotides

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 September 2022
EMA/CHMP/QWP/735423/2022
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 |

A second concept paper on the establishment of a Guideline on the Development and Manufacture of Synthetic Peptides has been published. There are numerous similarities between synthetic peptides and oligonucleotides, however also fundamental differences. Therefore it has been decided to develop two separate guidelines.

# Draft Concept Paper on the Establishment of a Guideline on the Development and Manufacture of Synthetic Oligonucleotides

- 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 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 drug substance impurity profile

# Draft Concept Paper on the Establishment of a Guideline on the Development and Manufacture of Synthetic Oligonucleotides

- 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 platform technologies will be provided
- Requirements for conjugation (e.g. GalNAc, PEG-ylation, monoclonal antibodies, peptides, proteins) approaches will be addressed
- The proposed guideline will follow the structure of 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

# Draft Concept Paper on the Establishment of a Guideline on the Development and Manufacture of Synthetic Oligonucleotides

- 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 considered 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
- Considerations for active substances that are in solution (i.e. not isolated) will be provided
- First applications for generic oligonucleotides 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
- End of consultation phase: 20 December 2022

# Public Consultation Outcome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# Extract of some Key Messages from Public Consultation

- Clear definition of scope (which molecule classes are within / without of the scope)
- International harmonisation
- No additional regulatory burden
- Consideration of white papers published by EPOC
- How to address mutagenic impurities?
- Discussion and requirements for specifications
- Several comments on analytical techniques
- Clarity on expectations for benefit-risk analysis for sterilization method selection (sterile filtration vs terminal sterilization)
- Discourage from trying to establish generic purity limits – these are too dependent on chemistry, sequence (even within the same chemistry) and method
- Phase-appropriate approaches to CMC development during clinical development

# Future Trends - Platform Technologies

- Oligonucleotides may have enormous potential to use prior knowledge and platform technologies
- Highly automated process / similar syntheses
- Most of the applicants have developped a specific type of chemistry
- These specific ‚chemistries' need to be considered in platform technologies
- Common CQAs
- Same starting materials and other materials are used for different development programmes
- Approaches to use stability data from other sequences could be discussed with regulatory agencies
- Currently there is only a limited number of CMOs available for commercial API manufacturing → how to involve this prior knowledge into individual applicant's filings
- Boundaries of the platform should be defined

# Coming Soon

**Generics**

- Starting to get into the focus of regulatory agencies
- Legal considerations
- Comparability requirements
- Impurities profiles
- Issues regarding sterochemistry will be in the focus of future regulatory discussions
- Comparative stress test studies?

**Personalised oligonucleotides (N-of-1)**

- Considerable number of initiatives
- Milasen developed for Mila a child in the USA
- Interaction with European Agencies recently initiated
- Numerous open questions for CMC

Thanks to my EMA colleagues

Hilde Bastaerts and Brian Dooley

and all members of the Guideline Drafting Group

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# Thank you very much for your attention!

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