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Committee for Veterinary Medicinal Products (CVMP)

Concept paper on the quality and safety aspects of RNA interference and RNA antisense oligonucleotide therapies as veterinary medicinal products

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

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1. Introduction

This concept paper addresses the need for a guideline on the quality and safety aspects of RNA interference and RNA antisense oligonucleotide therapies as veterinary medicinal products.

Regulation (EU) 2019/6 recognises RNA antisense therapy and RNA interference therapy products as novel therapies as defined in Article 4 (43). Section V.1 of Annex II of the Regulation (EU) 2019/6 stipulates the general requirements for marketing authorisation applications for novel therapy veterinary medicinal products, together with specific requirements for identified veterinary medicinal products related to the nature of the active substances contained therein. Moreover, point V.1.1.6 of Annex II lays out a requirement for a risk management plan for novel therapy veterinary medicinal products.

The specific quality and safety requirements for RNA antisense therapy and RNA interference therapy products are laid out in the point V.1.5.6 of the Annex II as follows:

V.1.5.6.1. Antisense therapy and interference therapy products may be generated by synthesis or through recombinant techniques.

V.1.5.6.2. Antisense RNA is a single stranded RNA that is complementary to a protein coding messenger RNA with which it hybridises, and thereby blocks its translation into protein.

V.1.5.6.3. RNA interference is a biological process in which RNA molecules inhibit gene expression or translation, by neutralising targeted mRNA molecules.

V.1.5.6.4. In addition to the data requirements set out in Sections II or III the following requirements shall apply:

(a) the minimum amount of RNA segments per volume needs to be established as part of control tests of the finished product, as well as the confirmation that the RNA segments present the correct sequence;

(b) for certain antisense therapy products falling under Section II of this Annex a potency bioassay may be needed for their release testing;

(c) stability studies shall include a test to monitor the degradation rate of the RNA segments over time;

(d) for RNA antisense therapy products, the possible harmful effects due to on- or off-target binding shall be addressed as well as possible non-antisense harmful effects due to, for example, accumulation, pro-inflammatory responses and aptamer binding;

(e) for RNAi therapy products, the possible harmful effects of off-target interference (due to the positive RNAi strand) shall be addressed, as well as the possibility of crossing the blood-brain barrier and causing central nervous system disorders;

(f) for RNA antisense therapy and RNA interference therapy products intended for gene therapy the requirements for gene therapy veterinary medicinal product shall be considered.

The guideline to be developed aims at providing further detailed specific requirements.

2. Problem statement

Based on a survey among industry stakeholders initiated by the Novel Therapies and Technologies Working Party (NTWP), RNA antisense and RNA interference therapies have been identified as the most

advanced class of novel therapies with regard to their stage of development. Thus, CVMP identified the need for the development of a guideline specifically focusing on the quality and safety aspects.

RNA interference and antisense oligonucleotide therapy products may be generated by synthesis or through recombinant techniques. As the chemical synthesis is already covered by the Draft Guideline on the development and manufacture of oligonucleotides (EMA/CHMP/CVMP/QWP/262313/202424), the quality part of the guideline to be developed will mainly focus on products manufactured by non-chemical synthesis, e.g. enzymatic synthesis. For the safety part of the guideline, products manufactured by both chemical and non-chemical synthesis will be taken into account.

Other relevant guidance documents and Ph. Eur. texts for veterinary and human medicinal products, that could overlap with the guideline to be drafted, will also be taken into consideration.

General safety requirements should be followed, e.g. requirements for the establishment of maximum residue limits (MRLs) for the active substances, (as laid down in Commission Regulation (EU) 2018/782), when the product is intended for use in food producing species; and toxicology, target animal safety, user and consumer safety aspects for marketing authorisations.

The guideline to be developed is expected to cover specific quality and safety aspects of these products that are not already covered in the general guidance documents applicable to veterinary medicinal products.

3. Discussion (on the problem statement)

The proposed guideline will address the following:

- Scope: RNA interference and antisense oligonucleotide therapies for veterinary use involving, for example, the exogenous introduction of small interfering RNA and microRNA. The guideline will also address delivery systems for the nucleic acids, with a focus on non-viral delivery systems.
- Gene constructs expressing short hairpin RNA, genetically modified cells (allogeneic or autologous somatic cells modified *ex vivo* or *in vitro* with a gene therapy vector prior to administration to the animal) or gene therapies that introduce genetic material into the genome will be out of scope of the guideline.
- Quality aspects: In line with the above-mentioned Annex II, and other possible quality aspects identified, the following points will be further developed in the guideline:
    - Guidance on rational oligonucleotide design to ensure target specificity and stability.
    - Selection of starting materials including a criticality assessment of their impurity profiles.
    - Characterisation (e.g. sequence analysis, sequence length, characterization of the 5’ and 3’ ends, quantification (assay), functional activity, impurities).
    - Critical parameters in the manufacturing process, including purity and sequence verification, modifications, conjugation processes (e.g. PEGylation, GalNAc conjugation).
    - Appropriate analytical tools for identity (sequence and length verification), purity, impurities (e.g. truncated sequences, synthesis by-products) and assay (high specificity, orthogonal analytical methods); stability-indicating methods.
    - Delivery system as part of the finished product to be included in the specifications.
    - Guidance on characterising delivery platforms (specificity of the delivery system to reach the target).

- Safety aspects: In line with the above-mentioned Annex II, and other possible safety aspects identified, the following points will be further developed in the guideline:

  From the Annex II Regulation (EU) 2019/6:

  - For antisense therapy products, possible harmful effects due to on- or off-target binding shall be addressed as well as possible non-antisense harmful effects due to, for example, accumulation, pro-inflammatory responses and aptamer binding.
  - For RNA interference therapy products, off-target interference (due to the positive RNAi strand) shall be addressed, as well as the possibility of crossing the blood-brain barrier and causing central nervous system disorders.

  Other specific safety aspects applicable to veterinary medicines:

  - The possible deviations from the general target animal safety tests (VICH guidelines GL43 and GL 44) that could be accepted and/or recommended taking into account the specific characteristics of these products.
  - The specific need for short-term and/or long-term safety studies, depending on the target species, administration regimen and pharmacodynamic profile.
  - Specific aspects of these products for the establishment of MRLs (for active substances) when needed, and user and consumer safety aspects.
  - The guideline to be developed will not address environmental risk assessment requirements which are governed by Annex II of the Regulation (EU) 2019/6.

Taking also into account the experiences with already authorised human products, the following aspects will be specifically covered:

- Immunotoxicity (adverse effects on the immune system).
- Immunogenicity (including unintended or "exaggerated" immune responses; such as innate immune response (for example Toll-like receptor activation by RNAs), immunoconjugates, etc.).
- Toxicity on non-target organs (hepatotoxicity, renal toxicity, thrombocytopenia, etc.).
- Possible toxicity or accumulation of the delivery systems.
- Long term silence/oversilence/delay on physiological effects.

4. Recommendation

The NTWP recommends drafting a guideline on the quality and safety aspects of RNA antisense and RNA interference therapies as veterinary medicinal products after taking into account the issues identified above.

5. Proposed timetable

Q3 2026 Concept paper released for public consultation

Q4 2026 End of public consultation

Q3 2027 Draft guideline to be released for public consultation.

6. Resource requirements for preparation

The NTWP recommends drafting a guideline on the quality and safety aspects of RNA interference and RNA antisense oligonucleotide therapies as veterinary medicinal products. An operational expert group (OEG) on RNA antisense and RNA interference therapy products as veterinary medicinal products has been set up. The development of the guideline will involve the EMA-BIO-VET secretariat, the NTWP, CVMP, QWP, SWP-V, and the IWP who would be consulted, as necessary.

7. Impact assessment (anticipated)

It is anticipated that the guideline would benefit academia, industry and regulators, due to provision of a relevant guidance on data requirements for RNA antisense and RNA interference therapy products as veterinary medicinal products.

8. Interested parties

Academic organisations involved in research and development in the field of veterinary bacteriophage therapy.

Veterinary pharmaceutical industry and consultants.

EU Regulatory authorities involved in assessment of marketing authorisation applications.

Other European bodies.

9. References to literature, guidelines, etc.

EMA guidelines:

- Veterinary medicines:

  Guideline on the Development and Manufacture of Oligonucleotides (EMA/CHMP/CVMP/QWP/262313/202424)

  Concept paper (and future guideline) for the development of a guideline on the safety of nanoparticles – in the context of the establishment of maximum residue limits and veterinary marketing authorisations (EMA/CVMP/NTWP/143787/2023)

  Guideline on plasmid DNA vaccines for veterinary use (EMA/CVMP/IWP/365817/2022)

  VICH GL39: Test procedures and acceptance criteria for new veterinary drug substances and new medicinal products: Chemical substances (EMEA/CVMP/VICH/810/04-corrig)

  VICH GL40 Test procedures and acceptance criteria for new biotechnological/biological veterinary medicinal products (EMEA/CVMP/VICH/811/04-corrig)

  VICH GL43: Target animal safety for veterinary pharmaceutical products (EMEA/CVMP/VICH/393388/2006)

  VICH GL44: Target animal safety for veterinary live and inactived vaccines (EMEA/CVMP/VICH/359665/2005)

- Human medicines:

  Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014)

Guideline on the quality aspects of mRNA vaccines (EMA/CHMP/BWP/82416/2025)

- Ph. Eur. texts/monographs (human medicines):

  Ph. Eur. 3186. Gene therapy medicinal products for human use

  Ph. Eur. 53400. 5.34. Additional information on gene therapy medicinal products for human use

- International guidelines:

  ICH Final Concept Paper S13 EWG: Non-clinical Safety Evaluation of Oligonucleotide-based Therapeutics. 28 October 2024

  FDA Draft guidance: Non-clinical Safety Assessment of Oligonucleotide-Based Therapeutics Guidance for Industry. FDA-2024-D-4624. November 2024

- EFSA:

  EFSA FAF Panel (EFSA Panel on Food Additives and Flavourings), Younes, M., Aquilina, G., Degen, G., Engel, K.-H., Fowler, P., Frutos Fernandez, M. J., Fürst, P., Gundert-Remy, U., Gürtler, R., Husøy, T., Manco, M., Mennes, W., Passamonti, S., Moldeus, P., Shah, R., Waalkens-Berendsen, I., Wright, M., Barat Baviera, J. M., … Castle, L. (2023). Safety evaluation of synthesised DNA oligonucleotides as a food additive. EFSA Journal, 21(12), e8452. https://doi.org/10.2903/j.efsa.2023.8452

  EFSA (European Food Safety Authority), Barro, F., Braeuning, A., Goumperis, T., Lewandowska, A., Moxon, S., Papadopoulou, N., & Sánchez-Brunete, E. (2025). Risk assessment considerations for RNAi-based genetically modified plants. EFSA Journal, 23(3), e9321. https://doi.org/10.2903/j.efsa.2025.9321