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Committee for Veterinary Medicinal Products (CVMP)

Concept paper 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

Agreed by Novel Therapies and Technologies Working Party	June 2023
Adopted by CVMP for release for consultation	18 April 2024
Start of public consultation	26 April 2024
End of consultation (deadline for comments)	31 July 2024

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

Keywords	novel therapies, nano, safety, veterinary regulation, persistent nanoparticles, nano-toxicology, nanoparticles, nanotechnology, veterinary medicinal products issued from nanotechnologies

1. Introduction

This concept paper addresses the need for a specific guideline on the establishment of maximum residue limits (MRLs) for pharmacologically active nanoparticles, as well as on safety for veterinary medicinal products (VMPs) containing nanoparticles. There is currently no guidance for the establishment of MRLs for pharmacologically active nanoparticles, or for the safety of VMPs containing nanoparticles. A need to clarify the establishment of MRLs for nanoparticles and the safety requirements of VMPs containing nanoparticles was specifically recognised by requests for scientific advice from applicants received by EMA. Consequently, to address this issue, the CVMP initiated the development of a specific safety guideline.

The specific properties and functions of nanoparticles might differ from those of "conventional" active substances and therefore, this guideline will elaborate on safety aspects, including consumer safety of

an application for VMPs containing nanoparticles within the framework of Commission Regulation (EU) 2018/782 and Regulation (EU) 2019/6 including additional specific safety data requirements for particular veterinary medicinal products such as products issued from nanotechnologies, which are addressed in Section V.1.5.5. of Annex II. The guideline to be developed is intended to address these aspects for both pharmacologically active nanoparticles and nanoparticles without pharmacological activity (excipients) within the VMP.

The guideline to be developed should focus on the elaboration of guidance on specific data requirements and assessment for target animal safety, user safety, consumer safety and the environment for VMPs containing nanoparticles. The legal framework concerns Regulation (EC) 470/2009, Commission Regulation (EU) 2018/782 and Regulation (EU) 2019/6 and includes both biological and non-biological VMPs. This concept paper intends to describe and discuss the scientific approach as a basis for the guideline to be developed.

2. Problem statement

VMPs may contain nanoparticles which fulfil a variety of purposes, either as active substances or as excipients. The physico-chemical properties of nanoparticles might differ significantly from those of non-nanoparticles. More specifically, properties and functions of nanoparticles depend on the type of material (e.g. inorganic, organic or combinations of different materials or compounds), physical structure, morphology and composition. Therefore, nanoparticles might need specific data requirements and assessment considerations. As these properties and functions are not specifically limited to those particles up to 100 nm in size, the guideline is intended to also be applicable to larger particles (up to approximately 1000 nm) if the specific characteristics and functions thereof require such an approach.

Furthermore, the guideline to be developed will need to address the safety of both persistent and non-persistent nanoparticles. While it is generally expected that the use of non-persistent nanoparticles might prevail in veterinary use, special concern might be associated with nanoparticles with the potential for persistence in the treated animals, the environment, foodstuffs from animal origin or the consumers and this also needs to be taken into account during the assessment.

Generally, to adequately assess the safety of nanoparticles a thorough characterisation/identification with suitable and validated analytical test methods is necessary. Only under this condition a reliable correlation of the safety with its physico-chemical properties and quality aspects will be possible. It should be noted, however, that general aspects of the quality part of applications will not be addressed in the guideline. Nevertheless, also with regard to pharmacokinetic properties, the necessary parameters (characteristics) to define, to identify and to classify VMPs containing nanoparticles need to be determined.

Safety of VMPs must be ensured for target animals, users, consumers and the environment. This is required due to different or new characteristics and hazards compared to conventional active substances or excipients. For example, the toxicity profile of an active substance may differ because of altered physico-chemical characteristics (such as size, structure, shape, active surface) or properties of nanoparticles, with potential influence on the pharmacokinetic parameters (ADME). Furthermore, due to nanoparticle-specific hazards, it might be necessary to address safety studies that specifically take these into consideration (cytotoxicity, inflammation, immunotoxicity, ecotoxicity, long-term toxicity studies). In addition, the presence of nanoparticles may have significant influence on the safety profile of the VMP. For example, the bioavailability might be significantly increased, or the non-nanocomponent(s) might transfer through physiological barriers they would not be able to cross in a conventional formulation or individually. For products issued from nanotechnologies specific safety data

requirements are addressed within Section V.1.5.5. of Annex II of Regulation 2019/6. In the Annex, nanotechnologies are primarily seen as a technology to generate carriers. Therefore, it may be possible that certain VMPs might not be specifically covered in the Annex II. With a view to guide prospective developers, the guideline will aim to generally cover safety aspects for nanomaterials – as defined by the 2022 Commission Recommendation on the definition of nanomaterials – that are used in veterinary medicinal products. In addition, the guideline will also address other particles up to 1000 nm that are considered to require additional safety assessment within the framework of Regulation (EU) 2019/6 and Regulation (EU) 2018/782.

3. Discussion (on the problem statement)

The guidance to be developed intends to focus on the following items:

- consider aspects of persistency or biodegradability of nanoparticles (either active substance or excipient) and/or VMPs containing such nanoparticles;
- provide guidance on the necessary parameters for the identification and characterisation of nanoparticles and in VMP formulation. This is relevant to ensure that the material tested is the same to which the target animals, users, consumers and the environment are exposed;
- provide guidance on pharmacokinetic considerations and the degradation process, including accumulation and potential persistence of the particles as well as fate of non-nano substances in VMPs containing nanoparticles, and quantitative and qualitative information on excretion;
- provide guidance on nano-specific safety and residue data requirements and assessment (consumer safety in regard to MRL and VMP authorisation, toxicity, user safety, target animal safety and environmental safety) within the framework of Commission Regulation (EU) 2018/782 and Annex II of Regulation 2019/6 for nanoparticles and VMPs containing nanoparticles including the specific data requirements and assessment for VMPs issued from nanotechnologies. This includes exposure of consumers, issues related to administration route for users and the target animals, consideration of toxicity (individual substance vs. formulation), impurities, environmental fate and ecotoxicity and also taking in consideration pharmacokinetic and potential pharmacodynamic properties;
- provide guidance on the influence of nanoparticles on the pharmacodynamics, pharmacokinetics and toxicity of non-nano component(s) in a VMP formulation.

In drafting the guideline, the NTWP will take existing international guidance on nanoparticles (e.g. OECD guidelines, EFSA guidance) as well as general guidance and their potential adaption for nano-specific consideration into account.

4. Recommendation

The Committee for Veterinary Medicinal Products (CVMP) recommends that the Operational Expert Group (OEG) on nanomedicines, a subgroup of the Novel Therapies and Technologies Working Party (NTWP), drafts a guideline on safety of nanoparticles in the context of MRLs and VMPs authorisations.

The scope of the guideline is to give clear advice to applicants and assessors on the safety data requirements and assessment of nanoparticles and other particles of concern (up to about 1000 nm).

5. Proposed timetable

Q2 2024	Concept paper released for public consultation
Q3 2024	End of public consultation
Q4 2025	Draft guideline to be released for public consultation

6. Resource requirements for preparation

The development of the new guideline will involve the OEG, the NTWP, the SWP-V, IWP, the QWP, EWP-V, ERAWP and the CVMP.

The OEG drafting group will meet virtually as required (e.g. 4-6 virtual meetings). Comments will be sought from SWP-V, QWP, IWP, ERAWP and EWP-V. Discussion/endorsement is foreseen at 3-5 NTWP meetings and 4 CVMP plenary meetings.

7. Impact assessment (anticipated)

The guidance will clarify requirements for regulators and industry with respect to nanoparticle safety and so will encourage consistent and predictable decisions. This is expected to have a positive impact on the development of veterinary medicines containing such substances.

8. Interested parties

Veterinary pharmaceutical industry, EU regulatory authorities involved in assessment of marketing authorisation applications.

9. References to literature, guidelines, etc.

Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32019R0006&from=EN (non-consolidated version)

Commission Delegated Regulation (EU) 2021/805 of 8 March 2021 amending Annex II to Regulation (EU) 2019/6 of the European Parliament and of the Council https://eur-lex.europa.eu/eli/reg_del/2021/805/oj

Commission Recommendation of 10 June 2022 on the definition of nanomaterial https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32022H0614%2801%29

Commission Regulation (EU) 2018/782 establishing the methodological principles for the risk assessment and risk management recommendations referred to in Regulation (EC) No 470/2009 https://eur-lex.europa.eu/legal-content/DE/TXT/?uri=CELEX%3A32018R0782

Regulation (EC) No 470/2009 of the European Parliament and of the Council laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin https://eur-lex.europa.eu/legal-content/DE/TXT/?uri=CELEX%3A32009R0470.