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Committee for Veterinary Medicinal Products (CVMP)

Concept paper on a guideline on risk management requirements for elemental impurities in veterinary medicinal products, including immunological veterinary medicinal products

Agreed by QWP	September 2022
Agreed by IWP	October 2022
Adopted by CVMP for release for consultation	08 December 2022
Start of public consultation	19 December 2022
End of consultation (deadline for comments)	31 March 2023

The proposed guideline will replace the Reflection paper on risk management requirements for elemental impurities in veterinary medicinal products, EMA/CVMP/QWP/153641/2018 and the Implementation of risk assessment requirements to control elemental impurities in veterinary medicinal products, EMA/CVMP/QWP/631010/2017-Rev.2.

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

Keywords	Elemental impurities, risk management, veterinary medicinal products, immunological veterinary medicinal products

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1. Introduction

The European Pharmacopoeia General Monograph 2619 for Pharmaceutical Preparations requires manufacturers of products outside the scope of the General Chapter 5.20 to control the levels of elemental impurities in the products by using the principles of risk management. This requirement was introduced into the 3rd supplement of the 9th Edition of the European Pharmacopeia (published in July 2017, with an implementation date of 1st January 2018) to align with requirements of the ICH Q3D guideline for elemental impurities that came into effect for existing human medicinal products in December 2017.

In the 9th Edition, the wet chemical testing for heavy metals (General Chapter European Pharmacopeia 2.4.8) was also deleted from individual monographs. This test was maintained within individual monographs for veterinary use only.

To provide advice on these new requirements, two documents, not applicable to immunological veterinary medicinal products were published initially on the EMA website: "Implementation of risk assessment requirements to control elemental impurities in veterinary medicinal products" and "Reflection paper on risk management requirements for elemental impurities in veterinary medicinal products".

In 2021, the remaining wet chemical testings for heavy metals were deleted from the monographs on substances "for veterinary use only". These revised monographs will become applicable in January 2023.

In order to address these new requirements, the development of a guideline on risk management for elemental impurities in veterinary medicinal products including immunological veterinary medicinal products is needed.

2. Problem statement

The 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 and containing the technical documentation necessary for demonstrating the quality, safety and efficacy of the veterinary medicinal product (VMP) states in section I.2.2:

"All monographs, including specific monographs, general monographs and general chapters of the European Pharmacopoeia are applicable. For immunological veterinary medicinal products, all monographs, including specific monographs, general monographs and general chapters of the European Pharmacopoeia are applicable, unless otherwise justified."

This requirement was already present in the COMMISSION DIRECTIVE 2009/9/EC of 10 February 2009 amending Directive 2001/82/EC of the European Parliament and in the Council on the Community code relating to medicinal products for veterinary use.

Considering the European Pharmacopoeia General Monograph 2619 applies to all veterinary medicinal products, risk management of elemental impurities in all VMPs in the EU market is expected.

Currently, limited recommendation is available on the risk management of elemental impurities for non-immunological VMPs and no guidance is available for immunological VMPs.

3. Discussion (on the problem statement)

The revised General Monograph 2619 was implemented for medicinal products outside the scope of the general chapter 5.20 in January 2018, but a phased implementation was agreed by the CVMP at the end of 2017 for VMPs as no guidance on that requirement was available and time was needed by regulators to develop the document.

As no guidance was available for marketing authorisation holders, active substance, medicinal product and excipient manufacturers for VMPs, a "Reflection Paper on risk management requirements for elemental impurities in veterinary medicinal products (EMA/CVMP/QWP/153641/2018)" was developed and published in 2020 on the EMA website. This reflection paper provides information on how risk assessment of elemental impurities may be conducted, which elemental impurities should be considered in the risk management, how to set acceptable limits and which data/results should be available in a dossier.

The phased implementation, as detailed in the document "Implementation of risk assessment requirements to control elemental impurities in veterinary medicinal products (EMA/CVMP/QWP/631010/2017-Rev.2)" published on the EMA website, requires for new VMPs containing a new active substance a full risk assessment should be performed by January 2021 and for new VMPs containing existing active substances a full risk assessment should be performed by January 2022. By January 2023 a risk assessment should be performed for all products for veterinary use which are authorised in the European Union.

Nevertheless, the phased implementation and the reflection paper mentioned above only apply to VMPs containing chemical and biological/biotechnological substances including VMPs containing synthetic and semi-synthetic antibiotics and synthetic peptides of low molecular weight. They do not apply to veterinary herbal products, radiopharmaceuticals, immunological VMPs, VMPs designed for gene therapy, regenerative medicine, tissue engineering, blood product therapy and phage therapy or to elements that are intentionally included in a VMP for therapeutic benefit.

As the requirements of the European Pharmacopeia also apply to immunological VMPs, there is a need to revise this reflection paper to convert it into a guideline and to include in the scope of this guideline non-immunological and immunological VMPs. This is reflected in the CVMP work plan for 2022 published in December 2021, and that mentions in section 1.4.4 Quality non-biologicals:

"Revise the reflection paper on risk management requirements for elemental impurities in veterinary medicinal products: release concept paper for consultation to convert into a guideline and to include IVMPs within its scope."

The general principles for risk assessments for elemental impurities are applicable to non-immunological VMPs and immunological VMPs likewise and the approaches developed for the non-immunological VMPs would also be applicable to Immunological VMPs. Nevertheless, some particularities could apply and it is necessary to develop relevant changes and additions to differentiate between non-immunological VMPs and immunological VMPs and make it clear for assessors and applicants, which particular requirements only apply to one of the two.

Clear guidance for appropriate risk assessment is considered crucial specifically for immunological VMPs since, in general, elemental impurity testing is not foreseen in the context of manufacturing control and final product testing of immunological VMPs. This makes it the only way for applicants to balance the potential risk factors. Therefore, this new guideline can also be seen as contributing to the Network action plan on availability of vaccines.

4. Recommendation

The Quality Working Party (QWP) and the Immunological Working Party (IWP) recommend revision and conversion of the Reflection Paper into a guideline with the inclusion of non-immunological and immunological VMPs into the scope of this guideline.

The guideline will also consider the definitions of Regulation (EU) 2019/6 when defining the scope of the VMPs concerned and the requirements.

5. Proposed timetable

September / November 2022 – discussion and adoption of the Concept Paper by the QWP and IWP.

November 2022 /January 2023 – adoption of the Concept Paper by the CVMP.

December 2022/February 2023 - release the Concept Paper for a 3-month consultation.

It is anticipated that the draft guideline could be available within 6 months after adoption of the concept by the CVMP. The draft guideline will then be released for external consultation for 3 months before its finalisation within 6 months.

It is expected that the guideline will come into operation 6 months after adoption at the CVMP.

6. Resource requirements for preparation

The revision will involve the EMA-QWP Secretariat, the Joint CHMP/CVMP Quality Working Party, the IWP and the CVMP.

The QWP should appoint a rapporteur within the members of the QWP.

7. Impact assessment (anticipated)

The revision of the reflection paper to a guideline and the inclusion of the non-immunological VMPs and immunological VMPs into the scope are expected to provide clearer and up-to-date guidance to industry and assessors in relation to applications of the requirements for risk management for elemental impurities in VMPs mentioned in the European Pharmacopoeia Monograph 2619.

8. Interested parties

Veterinary pharmaceutical industry and consultants, EU Regulatory authorities.

9. References to literature, guidelines, etc.

- European Pharmacopeia
- 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
- ICH guideline Q3D on elemental impurities Step 5, 25 July 2016 EMA/CHMP/ICH/353369/2013
- Implementation of risk assessment requirements to control elemental impurities in veterinary medicinal products, EMA/CVMP/QWP/631010/2017-Rev.2

- Reflection paper on risk management requirements for elemental impurities in veterinary medicinal products, EMA/CVMP/QWP/153641/2018
- CVMP work plan 2022 Committee for Veterinary Medicinal Products (CVMP) Work Plan 2022, EMA/CVMP/476954/2021