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Committee for Veterinary Medicinal Products (CVMP)

Guideline on risk management requirements for elemental impurities in veterinary medicinal products

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This guideline replaces 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.

*The implementation of this guideline for immunological veterinary medicinal products is detailed in the separate document Implementation of submission of risk assessments to control elemental impurities required by the European Pharmacopeia in immunological veterinary medicinal products (EMA/CVMP/366323/2025).

[1] First day of the 7th month.

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Keywords	**Elemental impurities, risk management, veterinary medicinal products, novel therapy products**

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Executive summary

This guideline provides recommendations on how the risk management may be conducted for elemental impurities for veterinary medicinal products (VMPs) authorised or to be authorised in the European Union in order to comply with the requirement of the European Pharmacopeia (Ph. Eur.) General Monograph 2619 for Pharmaceutical Preparations.

This guideline also provides information on the documentation expected to be included in the dossier in order to address this requirement.

1. Introduction (background)

Elemental impurities in VMPs may arise from several sources; they may be residual catalysts that were added intentionally in synthesis or may be present as impurities (e.g. through interactions with processing equipment or container/closure systems or by being present in components of the medicinal product). Because elemental impurities do not provide any therapeutic benefit to the target species and may be a concern to them and also to the consumer, their presence and origins should be understood and their levels in the VMP controlled if necessary.

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 mentions that all monographs of the European Pharmacopoeia are applicable, also for immunological veterinary medicinal products (IVMPs) unless otherwise justified.
The Ph. Eur. 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. Therefore, manufacturers of VMPs remain responsible for controlling the levels of elemental impurities using these principles.

This guideline on risk management for elemental impurities in veterinary medicinal products provides recommendation on how to address this requirement for VMPs. It also highlights the expectations of regulators regarding the data to be submitted in the product dossier to support a quality risk management summary report for elemental impurities. Particularities for IVMPs and novel therapy VMPs are also considered in this guideline.

The separate document Implementation of submission of risk assessments to control elemental impurities required by the European Pharmacopeia in immunological veterinary medicinal products (EMA/CVMP/426245/2023) *outlines the phased implementation of submission of risk assessments required by the European Pharmacopeia for immunological VMP.*

2. Scope

This guideline applies to the following categories of products: VMPs other than biologicals, biological VMPs other than immunologicals and immunological VMPs.

This guideline also applies to novel therapy products.

This guideline does not apply to veterinary herbal products, radiopharmaceuticals or to elements that are intentionally included in the VMP for therapeutic benefit.

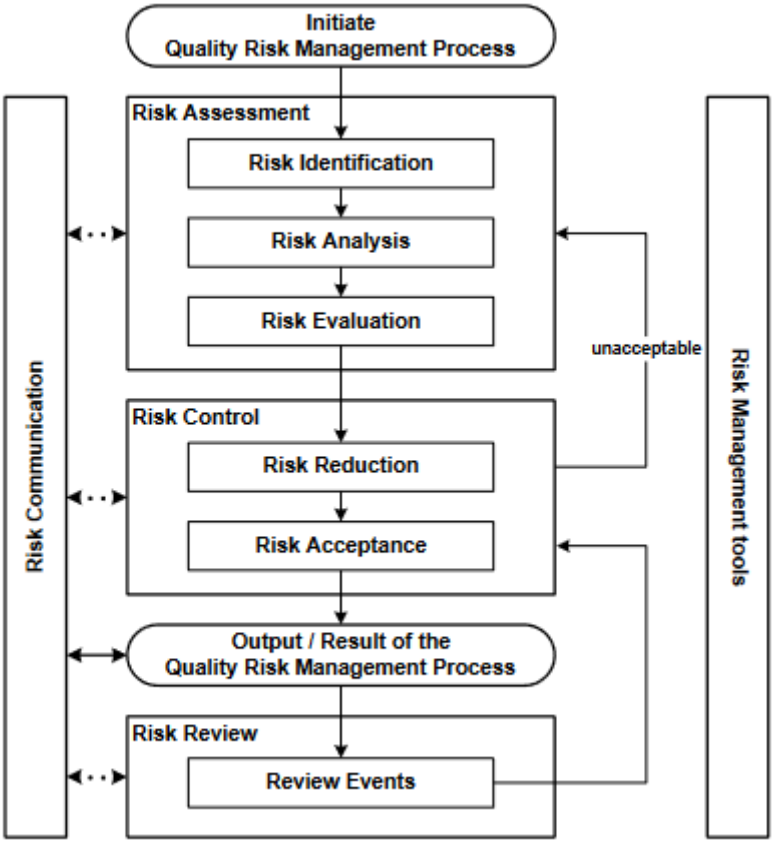
3. Risk Management

The control of elemental impurities in a VMP should be based on the principles of quality risk management.

In the context of this guideline, whilst VMPs are outside the scope of the guideline on Quality Risk Management (ICH Q9), its principles are applicable to medicinal products for veterinary use. ICH Q9 gives some guidance on the steps included in a risk assessment/management process (hazard identification, risk analysis and risk evaluation) and on how such a process can be performed.

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the VMP across the product lifecycle.

Figure 1: Overview of a typical quality risk management process



Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. Quality risk assessments begin with a well-defined problem description or risk question (risk identification).

Risk analysis consists of the estimation of the risk associated with the identified hazards. It is a qualitative or quantitative process of linking the likelihood of occurrence and the severity of harm.

Risk evaluation compares the identified and analysed risk against given criteria.

Quality risk management supports a scientific and practical approach to decision-making. It provides documented, transparent and reproducible methods to accomplish steps of the quality risk management process based on current knowledge about assessing the probability, severity and sometimes detectability of the hazards, and their associated risks.

4. Risk assessment for elemental impurities

The risk assessment to control elemental impurities in VMPs should be based on scientific knowledge and understanding of the product and its manufacturing process, while bearing in mind the safety of the target species and where relevant, of the consumer. The applicant should document the risk assessment and control approaches. The risk assessment can be described as a 3-step process:

1. Identification of known and potential sources of elemental impurities that may find their way into the VMP.
2. Evaluation of the presence of a particular elemental impurity in the VMP by determining the observed or predicted level of the impurity and comparing with the acceptable limits.
3. Summary and documentation of the risk assessment.

The data that support this risk assessment can come from a number of sources that include, but are not limited to:

- Prior knowledge;
- Published literature;
- Data generated from similar processes;
- Supplier information or data (suppliers of active substance(s), excipient(s), primary packaging and manufacturing equipment);
- Testing of the components of the VMP;
- Testing of the VMP.

During the risk assessment, several parameters can influence the level of the potential impurity in the VMP and should be considered. These include but are not limited to:

- Efficiency of removal of elemental impurities during further processing;
- Natural abundance of elements (especially important for the elements which are not intentionally added);
- Prior knowledge of elemental impurity concentration ranges from specific sources;
- The composition of the VMP.

Detailed information on risk assessment for elemental impurities can be found in section 5 of the ICH Q3D.

4.1. Potential sources of elemental impurities

Several broad categories of potential sources of elemental impurities should be considered:

- Residual impurities resulting from elements intentionally added (e.g. catalysts) during the synthesis of the active substance, excipients or other VMP components. The risk assessment should address the potential for inclusion of elemental impurities in the VMP;
- Elemental impurities that are not intentionally added and are potentially present in the active substance, water or excipients used in the preparation of the VMP;

- Elemental impurities that are potentially introduced into the VMP components and/or the VMP itself from manufacturing equipment;
- Elemental impurities that have the potential to be leached into the VMP components and to the VMP itself from primary packaging.

4.2. Identification of potential elemental impurities

Potential elemental impurities derived from intentionally added catalysts and inorganic reagents: If any element is intentionally added, it should be considered in the risk assessment.

Potential elemental impurities that may be present in active substances and/or excipients: While not intentionally added, some elemental impurities may be present in some active substances and/or excipients. The possibility for inclusion of these elements in the VMP should be reflected in the risk assessment.

Potential elemental impurities derived from manufacturing equipment: The contribution of elemental impurities from this source may be limited and the subset of elemental impurities that should be considered in the risk assessment will depend on the manufacturing equipment used in the production of the VMP. Application of process knowledge, selection of equipment, equipment qualification and GMP controls ensure a low contribution from manufacturing equipment. The specific elemental impurities of concern should be assessed based on knowledge of the composition of the components of the manufacturing equipment that come in contact with components of the VMP. The risk assessment of this source of elemental impurities can potentially be utilised for many VMPs using similar processes.

In general, the processes used to prepare a given active substance are considerably more aggressive than processes used in preparing the VMP given the relatively limited potential to leach or remove elemental impurities from manufacturing equipment. Contributions of elemental impurities from VMP manufacturing equipment would be expected to be lower than contributions observed for the active substance. However, when this is not the case based on process knowledge or understanding, the applicant should consider the potential for incorporation of elemental impurities from the VMP manufacturing equipment in the risk assessment (e.g. hot melt extrusion).

Elemental impurities leached from primary packaging of the VMP: The identification of potential elemental impurities that may be introduced from primary packaging should be based on a scientific understanding of likely interactions between a particular VMP type and its packaging. When a review of the materials of construction demonstrates that the primary packaging does not contain elemental impurities, no additional risk assessment needs to be performed. It is recognised that the probability of elemental leaching into solid dosage forms is minimal and does not require further consideration in the risk assessment. For liquid and semi-solid dosage forms there is a higher probability that elemental impurities could leach from the primary packaging during the shelf-life of the product. Studies to understand potential leachables from the primary packaging (after washing, sterilisation, irradiation, etc.) might be performed if necessary. This source of elemental impurities will typically be addressed during the evaluation of the primary packaging for the VMP.

4.3. Possible approaches to the risk assessment

Two approaches can be considered to construct the risk assessment: the medicinal product approach and the component approach. A combination of both approaches can also be appropriate.

4.3.1. The medicinal product approach

This approach focuses on the measured levels of potential elemental impurities in the VMP. However, in addition to analytical data, a risk assessment is also required.

Implicit in the medicinal product approach is the availability of quantitative data concerning the levels of elemental impurities in the VMP. Preliminary element screening can establish the elements of interest. The manufacturer will analyse batches of the VMP for the presence of elemental impurities. The observed level of elemental impurities will need to be compared with the acceptable limit. The level of variability of an elemental impurity can generally be established by providing data from at least three representative production scale batches or six representative pilot scale batches of the VMP. When the risk is demonstrated to be low, data on at least one representative production scale batch and two representative pilot scale batches of the VMP may be provided (the equipment used for the pilot scale batches should be representative of the equipment used at the production scale). More batch data may be necessary for example in case of components from multiple sources (e.g. multiple active substance sources), inherent variability for some components (e.g. mined active substances or excipients) or if the observed level is close to the limit. Where necessary the control strategy will include a limit for the relevant elemental impurities on the specification(s) for the VMP.

4.3.2. The component approach

In the component approach, the contribution of elemental impurities from each component is identified, evaluated and summarised. All potential sources of elemental impurities should be taken into account e.g., active substance, excipients, primary packaging, equipment and environment. Examples are given in sections 4.1 and 4.2 above. The potential contributions from each of these sources should be considered to determine the overall contribution of elemental impurities to the VMP. If necessary, a control strategy is established for the elemental impurities.

4.4. Possible outcome of the risk assessment

As the potential elemental impurity identification process is concluded, there are two possible outcomes:

The risk assessment process does not identify any potential elemental impurities. The conclusion of the risk assessment and supporting information and data should be documented.

The risk assessment process identifies one or more potential elemental impurities. For any elemental impurities identified in the process, the risk assessment should consider if there are multiple sources of the identified elemental impurity or impurities and document the conclusion of the assessment and supporting information.

5. Elemental impurities to be considered in the risk management

The most important elemental impurities to consider are those listed in ICH Q3D:

Cd, Pb, As, Hg, Co, V, Ni, Tl, Au, Pd, Ir, Os, Rh, Ru, Se, Ag, Pt, Li, Sb, Ba, Mo, Cu, Sn, Cr.

Based on their likelihood of occurrence in the medicinal product and their toxicity, the elements have been classified in 3 classes in ICH Q3D. This classification and the recommendation on the elements to be considered in the risk assessment given in table 5.1 of ICH Q3D and table A 5.1 for cutaneous and

transcutaneous products are considered acceptable when conducting the risk assessment for elemental impurities in VMPs.

This list is not exhaustive and if there are other elemental impurities that may be of toxicological concern for the target species, these should be included in the risk assessment. If any element is known to be added, it should always be considered in the risk assessment.

6. Setting permitted concentrations

The permitted daily exposure (PDE) values and cutaneous and transcutaneous concentration limits (CTCL) detailed in ICH Q3D are considered acceptable to ensure the quality of a VMP in respect of elemental impurities.

The PDE is given in micrograms per day (µg/day) and gives the maximum permitted quantity of each element that may be contained in the maximum daily intake of a VMP. It is useful to convert the PDE to the concentration of the elemental impurity in the VMP to establish the maximum permitted concentration that should be applied to the VMP. Options 1, 2a, 2b or 3 detailed in ICH Q3D (Section 7) may be used to establish the concentrations of elemental impurities in VMPs or components that ensure that the VMP does not exceed the maximal permitted concentrations. If required, the PDE specific to a target species may be recalculated using the calculation formula A.1.1 in appendix 1 of the ICH Q3D.

When the level of an elemental impurity in the VMP is above the PDE, additional measures should be implemented to assure that the level does not exceed the PDE. Approaches that an applicant can pursue include but are not limited to:

- Modification of the steps in the manufacturing process that result in the reduction of elemental impurities below the PDE through specific or non-specific purification steps;
- Implementation of in-process or upstream controls, designed to limit the concentration of the elemental impurity below the PDE in the finished product;
- Establishment of specification limits for excipients or materials (e.g., synthetic intermediates), and/or the active substance, and/or for the finished product;
- Selection of appropriate container closure systems.

When additional measures are either not technically feasible or have been unsuccessful to bring down the elemental impurity content, any proposed level higher than the acceptable limit should be scientifically justified.

When a control is required, periodic testing may be applied to elemental impurities according to the principles described in VICH GL 39.

Levels of elemental impurities higher than the established PDE may be justified in certain circumstances, for example with reference to the route of administration, target species, weight of the target species, dose and duration of treatment. In certain circumstances, a toxicological evaluation may be required. Such higher levels are subject to authority approval.

When PDEs are necessary for other routes of administration than those mentioned in the ICH Q3D, the principles described in the ICH Q3D may be used to derive PDEs. An assessment may either increase or decrease an established PDE. Detailed information can be found in section 3.2 of the ICH Q3D.

7. Presentation of results

The conclusion of the risk assessment should be presented in a summary report. There are different acceptable approaches to summarise and document the risk assessment. The summary should specify the source for each elemental impurity and how the decision (to control or not) has been taken. If a limit is set, it should be justified how the limit has been established and demonstrated that it is appropriate.

An elemental impurity will be considered absent if it has been predicted or demonstrated that the level of that particular impurity is consistently below 30% of the acceptable limit.

The summary report should be accompanied by details on how the elemental impurities were considered in the risk assessment, including the following information: summary of identified elemental impurities with observed or predicted levels, data (numerical results to be reported), source(s) contributing to elemental impurity levels in the VMP, supportive data (e.g. from representative commercial or pilot scale batches), details on how acceptable limits and observed or predicted elemental impurity levels have been calculated, conclusion and justification of the control strategy based on the observed/predicted elemental impurity levels and applicable acceptable limits.

Example on how summary reports could be presented can be found in the training materials of the ICH Q3D, module 8 on case studies. Illustrated examples on how elemental impurities results can be managed and presented can be found in appendix 4 of ICH Q3D.

8. Information to be provided in regulatory submissions

The summary report of the risk management should always be provided in part 2E of the dossier to justify the presence/absence of control strategy for elemental impurities.

If a specific control is necessary following the conclusions of the risk assessment, the details of the test method and its validation should be provided in the section of the dossier where control of the elemental impurities is addressed. The method to control any elemental impurity should be selective. A non-specific compendial test for heavy metals will not be accepted.

During lifecycle of the VMP, the risk assessment should be reviewed when change(s) which could have the potential to change the elemental impurity content are introduced for the finished product and or its components. Such changes could include, but are not limited to: changes in synthetic routes, excipient suppliers, raw materials, processes, equipment, container closure systems or facilities.

When the change does lead to modification of the control strategy, submission of the summary report of the risk assessment should be provided in the submission package of the variation(s) as foreseen in the variation guidances.

When the change does not lead to modification of the control strategy, submission of the updated risk assessment or its conclusion is not foreseen, nor a confirmation that the risk assessment for elemental impurities has been reviewed.

All changes should be subject to internal change management processes as part of the quality system, and available for inspection.

If, at the time of the guideline coming into effect, the outcome of an assessment shows that a change in the dossier is required for products[2] already on the market the appropriate variation(s) should be submitted. In this case, the summary report should be provided in the supportive documentation and

[2] Products previously outside the scope of the Reflection paper on risk management requirements for elemental impurities in veterinary medicinal products and now in the scope of this guideline

the relevant section(s) of the dossier shall be updated. Routine submission of risk assessments via variations, or otherwise, which conclude that no change is required, is not envisaged. The risk assessment should be available at the manufacturing site for inspection.

9. Specific considerations/Particularities for immunological veterinary medicinal products

For IVMPs, the risks of elemental impurities being present in the VMP at levels that raise target species safety or, where relevant, consumer safety concerns are considered low.

This is because:

- Elements are not typically used as catalysts or reagents in the manufacturing of IVMPs;
- Elements are present only at very low levels in media feeds used during cell culture processes, without accumulation and with significant dilution/removal during further processing;
- Purification processes used in IVMP manufacturing such as e.g. extraction, chromatography and centrifugation steps and ultrafiltration-diafiltration (UF/DF) have the capacity to clear elements introduced in cell culture/fermentation/media preparation steps or from contact with manufacturing equipment to negligible levels;
- IVMPs are not used for long-term treatment but are administered only a few times in the lifetime of an animal and administration is repeated infrequently;
- The administered volume is generally low.

As such, specific controls on elemental impurities up to the active substance level are generally not needed unless otherwise justified.

However, potential elemental impurity sources in finished product manufacturing (e.g. excipients) and other environmental sources should be considered for IVMPs. The contribution of these sources to the finished product should be evaluated in a risk assessment because they are typically introduced in the finished product manufacture at a step in the process where subsequent elemental impurity removal is not generally performed.

Risk factors that should be considered in this assessment should include:

- The type of excipients and adjuvants used;
- The primary packaging;
- The manufacturing process conditions;
- Their susceptibility to contamination by environmental sources (e.g. controlled areas for sterile manufacturing and use of purified water) and
- Overall dosing frequency.
- When no elemental impurity is intentionally added in the manufacture of the active substance, the inclusion of the active substance in the risk assessment is generally not necessary unless data from prior knowledge show that there is a risk for elemental impurities.

Section 4.3 above gives examples on how the risk assessment for IVMPs could be established. However, any other approach providing relevant information can also be used.

Data from leachable/extractable studies or relevant literature may be used.

The information generally expected in regulatory submissions are detailed in section 8, with the possibility to adapt the level of information in the summary of the risk assessment to the importance of the risk identified.

If testing is necessary, this should be performed using suitable analytical procedures according to the requirements of Ph. Eur. chapter 2.4.20 "Determination of elemental impurities".

10. Specific considerations/Particularities for novel therapy products

A similarly low level of risk is expected for novel therapy products derived from biological production processes (i.e. bacteriophages, cell therapy products) as for IVMP.

Risk factors that should be considered in this assessment for novel therapy products should include but are not limited to those listed for IVMP.

References

- European Pharmacopoeia General Monograph 2619: Pharmaceutical Preparations.
- ICH guideline Q9 on quality risk management (EMA/CHMP/ICH/24235/2006).
- ICH guideline Q3D on elemental impurities (EMA/CHMP/ICH/353369/2013).
- Training Module Materials for the implementation of the guideline ICH Q3D (https://www.ich.org/page/quality-guidelines)
- Implementation strategy of ICH Q3D guideline (EMA/CHMP/QWP/115498/2017)
- Reflection paper on risk management requirements for elemental impurities in veterinary medicinal products (EMA/EMA/CVMP/QWP/153641/2018).
- Implementation of risk assessment requirements to control elemental impurities in veterinary medicinal products (EMA/CVMP/QWP/631010/2017-Rev.2).
- European Pharmacopoeia chapter 2.4.20: Determination of elemental impurities.
- European Pharmacopoeia General chapter 5.20: Elemental impurities.