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Reflection paper on risk management requirements for elemental impurities in veterinary medicinal products

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1. Introduction

Revision of the European Pharmacopoeia General Monograph 2619: Pharmaceutical Preparations which came into effect in January 2018, requires manufacturers of products outside the scope of the General Chapter 5.20 to control the levels of elemental impurities in the products using the principles of risk management. These changes to the European Pharmacopoeia have been introduced to align with requirements of the ICH Q3D guideline for elemental impurities that came into effect for existing human medicinal products in December 2017.

Elemental impurities in medicinal products 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 also be a concern to the consumer, their presence and origins should be understood and their levels in the medicinal product controlled if necessary.

The document “implementation of risk assessment requirements to control elemental impurities in veterinary medicinal products” (EMA/CVMP/QWP/631010/2017-Rev.1) outlines the phased implementation of submission of risk assessments required by the European Pharmacopeia. By 2023, a risk assessment should be performed for all products for veterinary use that will be on the European Union market.

As no guidance is currently available for marketing authorisation holders, active substance, medicinal product and excipient manufacturers for veterinary medicinal products, the purpose of this reflection paper is to provide information on how such risk management may be conducted for elemental impurities in products authorised or to be authorised in the European Union. It also highlights the expectations of regulators regarding the data to be submitted in the product dossier for those risk managements/assessments. In accordance with European Pharmacopoeia General Monograph 2619, the responsibility for the conduct of the risk management rests with the medicinal product manufacturer.

2. Scope

This reflection paper applies to veterinary medicinal products containing chemical and biological/biotechnological substances. Veterinary medicinal products containing synthetic and semi-synthetic antibiotics and synthetic peptides of low molecular weight are also within the scope of this reflection paper.

This reflection paper does not apply to veterinary herbal products, radiopharmaceuticals and immunological products.

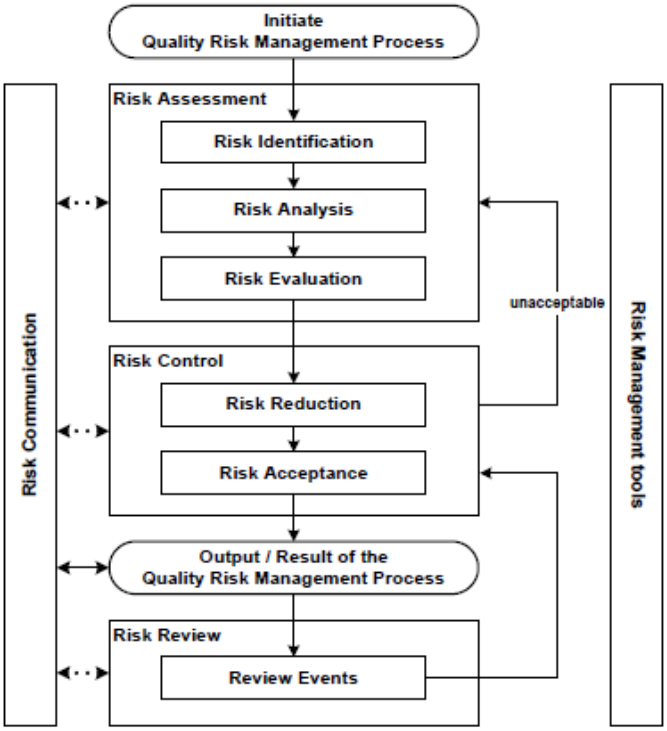
3. Risk management

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

In the context of this reflection paper, whilst veterinary medicinal products 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 (risk 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 medicinal product 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 a quantitative process of linking the likelihood of occurrence and the severity of harm.

Risk evaluation compares the identified and analyzed 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 risk.

4. Risk assessment for elemental impurities

The risk assessment to control elemental impurities in veterinary medicinal products should be based on scientific knowledge and understanding of the 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 medicinal product.

2. Evaluation of the presence of a particular elemental impurity in the medicinal product by determining the observed or predicted level of the impurity and comparing with the acceptance 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 medicinal product;
- Testing of the medicinal product.

During the risk assessment, several parameters can influence the level of the potential impurity in the medicinal product 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 medicinal product.

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 medicinal product components. The risk assessment should address the potential for inclusion of elemental impurities in the medicinal product;
- Elemental impurities that are not intentionally added and are potentially present in the active substance, water or excipients used in the preparation of the medicinal product;
- Elemental impurities that are potentially introduced into the medicinal product components and/or the medicinal product itself from manufacturing equipment;
- Elemental impurities that have the potential to be leached into the medicinal product components and to the medicinal product 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 medicinal product 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 medicinal product. 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 medicinal product. The risk assessment of this source of elemental impurities is one that can potentially be utilised for many medicinal products using similar processes.

In general, the processes used to prepare a given active substance are considerably more aggressive than processes used in preparing the medicinal product given the relatively limited potential to leach or remove elemental impurities from manufacturing equipment. Contributions of elemental impurities from medicinal product 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 medicinal product manufacturing equipment in the risk assessment (e.g. hot melt extrusion).

Elemental impurities leached from primary packaging: 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 medicinal product 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, sterilization, irradiation, etc.) should be performed. This source of elemental impurities will typically be addressed during evaluation of the primary packaging for the medicinal product.

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 medicinal product. 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 medicinal product. Preliminary element screening can establish the elements of interest. The manufacturer will analyse batches of the medicinal product 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 be established by providing data from at least three representative production scale batches or six representative pilot scale batches of medicinal product. 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 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 medicinal product.

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 in to 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 medicinal product. 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 drug 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 are considered acceptable when conducting the risk assessment for elemental impurities in veterinary medicinal products.

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 acceptable limits

The permitted daily exposure (PDE) values detailed in ICH Q3D are considered acceptable to ensure the quality of the veterinary medicinal products 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 medicinal product. It is useful to convert the PDE to the concentration of the elemental impurity in medicinal product to establish the appropriate limit that should be applied to the medicinal product. Options 1, 2 or 3 detailed in ICH Q3D (Section 7) may be used to establish the concentrations of elemental impurities in drug products or components that ensure that the drug product does not exceed the PDE.

If a limit above the PDE is proposed for a specific elemental impurity, additional measures should be considered to bring the levels below the PDE. When additional measures are either not technically feasible or have been unsuccessful, any proposed level higher than the PDE should be justified on a case by case basis. 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, dose and duration of treatment. In certain circumstances, a toxicological evaluation may be required.

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.

Results can be presented in a tabulated format (an example can be found below). The table should be accompanied by details (an example can be found in the training materials of the ICH Q3D, module 8-1b case study) of how the elemental impurities were considered in the risk assessment. A table alone, without any other justification/explanation is not considered acceptable.

Example of a tabulated summary report

Element	Intentionally added?	Other potential source(s)	Considered in the risk assessment	Conclusion
Element xx	Yes/no	Specify/No	Yes*/no	Absent**/No control needed/ level observed/ limit: ≤ xx ppm

* information on how the elemental impurity was considered in the risk assessment should be provided

** an elemental impurity will be considered absent if it has been demonstrated that the level of that particular impurity is 30% below the acceptable limit in three representative commercial batches or 6 representative pilot batches

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.

For products already on the market at the time of the reflection paper coming into effect, if the outcome of the assessment shows that a change in the dossier is required, the appropriate variation(s) should be submitted. The summary report should be provided in the supportive documentation and the relevant section of the dossier updated.

The risk assessment should be reviewed if significant changes are introduced in the manufacturing process or in the supply chain of the components of the finished product. Existing controls may need to be reviewed accordingly.

9. References

- Implementation of risk assessment requirements to control elemental impurities in veterinary medicinal products (EMA/CVMP/QWP/631010/2017)
- ICH guideline Q3D on elemental impurities (EMA/CHMP/ICH/353369/2013)
- ICH guideline Q9 on quality risk management (EMA/CHMP/ICH/24235/2006)
- European Pharmacopoeia General Monograph 2619: Pharmaceutical Preparations