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# Elemental Impurities in Animal Drug Products
# Questions and Answers

# Guidance for Industry

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For further information regarding this document, contact AskCVM@fda.hhs.gov.

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**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Veterinary Medicine (CVM)**
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# Guidance for Industry

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## I. INTRODUCTION

This guidance is intended to assist sponsors of animal drug products in addressing changes in the United States Pharmacopeia (USP)[1] requirements for the control of elemental impurities in drug products marketed in the United States.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency's guidances means that something is suggested or recommended, but not required.

## II. BACKGROUND AND SCOPE

USP General Chapter <231>, Heavy Metals, was deleted with the implementation of General Chapters <232>, Elemental Impurities – Limits, and <233>, Elemental Impurities – Procedures. While USP <232> does not apply to animal drug products, the Center for Veterinary Medicine (CVM) expects sponsors of animal drug products to continue to apply a risk-based control strategy for elemental impurities and establish appropriate acceptance criteria and test methods for elemental impurities where necessary. Ensuring that elemental impurities in the final drug product are controlled within safe limits remains the responsibility of the sponsor of the animal drug product.

This document provides recommendations to sponsors regarding the control of elemental impurities in animal drug products, including pending and approved applications for all dosage forms and routes of administration. The information to be maintained on-site and information to be submitted to CVM is also clarified. The submission of information regarding components and composition, as well as manufacturing methods, facilities, and controls is required under 21 CFR 514.1(b)(4) and (5) for new animal drug applications and under section 512(n)(1)(G) of the Federal Food, Drug, and Cosmetic Act for abbreviated new animal drug applications. The

[1] http://www.usp.org/

submission of manufacturing changes to an approved application is required under 21 CFR 514.8(b)(1)(i).

Approaches other than those set forth in this guidance may be applicable and acceptable.

## III. RECOMMENDATIONS

CVM recommends that animal drug product sponsors perform a thorough evaluation of the component materials of the drug product (e.g., drug substance, excipients, and primary packaging), including communication with the suppliers of sourced materials, and an evaluation of the manufacturing process for the drug product to identify risk factors that could potentially lead to significant levels of one or more elemental impurities in the drug product. CVM will only expect test methods and limits for elemental impurities in cases where a specific risk is identified based on the evaluation of the components, including the primary packaging, and the manufacturing process for the product.

This section includes CVM's answers to the following questions regarding control of elemental impurities.

### Q1. What elements should be evaluated?

A. Typically, the greatest emphasis should be placed on arsenic, lead, mercury, cadmium, and any additional elements used in the excipient, drug substance, and drug product manufacturing process, such as catalysts; however, any elements that could be present at levels that may be of toxicological concern for the target species and, where relevant, the consumer, should be considered. Refer to International Council for Harmonisation (ICH) Q3D, "Elemental Impurities,"[2] for details.

### Q2. Is it necessary to test investigational and approved animal drug products for elemental impurities?

A. CVM recommends that animal drug product sponsors evaluate the components of the drug product, including the primary packaging, and the drug product manufacturing process to identify any risk factors that could potentially lead to significant levels of one or more elemental impurities in the drug product (see Q3 and Q4 below). Some examples of risk factors for introduction of elemental impurities into the drug product include the use of a catalyst or inorganic reagent in the manufacture of a component or the drug product, and the use of high concentrations of inorganic components, including mined materials, in the drug product formulation. See ICH Q3D for more information on performing risk assessments. In cases where a specific risk factor has been identified based on this assessment, CVM would expect a test method and limit for elemental impurities in either the component or the drug product to ensure that they are adequately controlled (see Appendix I for more information).

[2] https://www.fda.gov/media/135956/download.

**Q3. How should drug product components be evaluated for their potential to introduce elemental impurities into the finished drug products?**

A. The considerations may include, but are not limited to:

- Knowledge of the source and production process for drug product components (drug substance, excipients, and primary packaging), including information or data from suppliers;
- The concentration of the component (drug substance or excipient) in the drug product formulation;
- The quality of any water used in the production of the component;
- Published data;
- Test results generated by the animal drug product sponsor.

The principles described in ICH Q9, "Quality Risk Management,"[3] and ICH Q3D should be considered. Control approaches should be proportional to the level of risk (see Q5, Q9, Q10, and Appendix I).

**Q4. How should the potential for the container closure and manufacturing equipment to leach elemental impurities into the drug product be addressed?**

A. CVM considers the risk of elemental impurities from the container closure to be low in most cases. The probability of elemental leaching into solid dosage forms is minimal and does not require further evaluation in the risk assessment. For liquid and semi-solid dosage forms, if the primary container closure components may introduce elemental impurities into the drug product at levels that present a safety concern, adequate controls should be in place. If the supplier certifies that the materials of construction of the primary packaging meet the applicable requirements of the USP and the U.S. Code of Federal Regulations (CFR), the animal drug product sponsor will not be asked to confirm the COA results for extractable metals. If a statement or data are unavailable from the manufacturer of the primary packaging regarding elemental impurities, CVM recommends performing at a minimum a test for heavy metals, such as the procedure previously described in USP <231>, for containers used for liquid and semi-solid dosage forms. The probability of elemental leaching into solid dosage forms is minimal and does not require further evaluation in the risk assessment. If the primary container closure components are expected to introduce elemental impurities into the drug product at levels that present a safety concern, adequate controls should be in place or testing of the drug product may be necessary.

CVM considers the risk from manufacturing equipment to be low in most cases if appropriate, qualified equipment is selected for the process and GMP requirements (21 CFR parts 210, 211, and 226) are met. Unless an unusual amount of chemical corrosion

[3] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q9-quality-risk-management.

or mechanical erosion of equipment results from the manufacturing process, no further assessment is expected.

**Q5. Can a non-specific test, such as the test for heavy metals previously described in USP <231>, be used to test a component, or should instrumental methods, such as those described in USP <233> be used?**

A. Procedures with selectivity and sufficient sensitivity for individual elements, such as the procedures described in USP <233>, should be used where controls for individual elements are necessary based on the risk assessment (see Appendix I for additional guidance). Non-specific tests, such as the procedures previously described in USP <231>, are unsuitable for controlling elemental impurities below acceptable limits. Non-specific tests for components determined to be low risk based on the risk assessment may be maintained at the sponsor's discretion. Previously reported non-specific tests can typically be deleted (see Q6 below). If you choose to maintain a non-specific test, it can be kept on site and should not be submitted to the file.

**Q6. For approved products, should we continue to perform the USP <231> test for heavy metals where it is included in the approved specifications for components of a drug product?**

A. The USP <231> test for heavy metals has significant limitations and we therefore do not recommend that it be used for controlling elemental impurities below acceptable limits where controls for individual elements are necessary based on the risk assessment. The heavy metals test and limit may be deleted, and the change may be reported in the next Minor Changes and Stability Report (MCSR). If the test method is maintained, it can be kept on site and should not be submitted to the file.

**Q7. Some USP monographs contain limits for specific elements and, in some cases, a different general chapter, such as USP <211>, Arsenic, or USP <251>, Lead, is referenced. Do these limits apply to veterinary products?**

A. At a minimum, these materials should continue to meet the requirements in the monograph, including the limits for specified elements, unless a risk-based justification supports their omission. An instrumental method consistent with those described in USP <233> may be used as an alternative to the referenced procedure.

**Q8. If a certificate of analysis for an excipient or drug substance contains test results for specific elements using an instrumental method per USP <233>, do these tests need to be confirmed as part of vendor qualification?**

A. This depends on the risk assessment. Communication with the supplier regarding the reason for including limits for specific elements is recommended. The results should be confirmed by the animal drug product sponsor only when deemed necessary by the risk assessment (see Q10 and Appendix I).

**Q9. When specified elements are known to be present in one or more of the excipients or the drug substance, how should the elemental impurity daily exposure from the drug product be assessed?**

A. The daily exposure to the elements should be calculated based on the supplier's limit, the amount of the excipient or drug substance in the drug product, and the maximum daily dose. If the same element may be introduced by more than one component of the drug product, the total exposure should be calculated. CVM generally considers the Permitted Daily Exposures (PDEs) for humans established in ICH Q3D in units of µg/day acceptable for the safety of animal drug products. The calculated elemental impurity daily exposure should result in a level equal to or below the ICH Q3D PDE for the drug product; however, CVM recognizes that the PDEs in ICH Q3D are for humans. If the calculated elemental impurity content of the animal drug product exceeds the PDE in ICH Q3D, the animal drug product sponsor may provide a justification or contact CVM to discuss the product and veterinary-specific considerations.

**Q10. Even in cases where the COA includes results for elemental impurities and a specific risk factor has been identified, often the excipient or drug substance make up a small percentage of the drug product or the COA results demonstrate that the elements are controlled at low levels. Is there a threshold at which we would not be expected to confirm the COA results?**

A. If the elemental impurity content listed on the COA will lead to a daily exposure that is not more than 30% of the PDE for an element, the risk from the component can usually be considered below the threshold at which additional testing by the drug product manufacturer is necessary (see Appendix I), and confirmation of the COA values for elemental impurities will not be requested. If the 30% control threshold will be applied, the total daily exposure should not exceed 30% of the PDE in cases where the same element may be introduced by multiple components of the drug product.

If the 30% threshold is exceeded but the elements are below the PDE, the drug product manufacturer should confirm the component COA results for vendor qualification, or, alternatively, test every lot of the drug product to ensure that the element does not exceed the PDE. A test that is selective for the element should be used unless an alternative approach can be justified. The test method(s) and limit(s) should be submitted to the file (see Q11 below). Reduced testing may be appropriate for a qualified supplier in accordance with 21 CFR 211.84(d)(2). The test may also be discontinued if sufficient data are generated to support that the element remains below 30% of the PDE.

**Q11. What information should be submitted to the file?**

A. If test methods and limits for elemental impurities in components or the drug product are deemed necessary based on the risk assessment, they should be submitted to the file. If the drug product will be tested for elemental impurities, the method validation should also be submitted to the file. If one of the compendial procedures described in USP <233> is used, the animal drug product sponsor may simply reference that chapter for the method.

The risk assessment, any calculations, and any method validations for methods for elemental impurities in components, where applicable, should be kept on site to provide to an investigator upon request (see 21 CFR parts 210, 211, and 226). CVM may request additional information on a case-by-case basis.

**Q12. How should updates to the test methods and limits be reported to the file?**

A. For approved products, this information can be provided in an annual MCSR unless a new testing facility is requested. A new testing facility should be reported in a supplement (please see CVM Guidance for Industry #83, "Chemistry, Manufacturing, and Controls Changes to an Approved NADA or ANADA"[4]).

**Q13. Does this guidance apply to Type A medicated articles?**

A. Yes. When a specific risk factor has been identified that may lead to introduction of elemental impurities into the Type A medicated article, any calculations of the daily exposure should take into account the ultimate dilution of the Type A to produce a medicated feed.

**Q14. What if the drug product contains elements that are for therapeutic benefit?**

A. This guidance does not apply to elements that are present in a form that is for therapeutic benefit (e.g., as part of the active pharmaceutical ingredient). However, the sponsor's risk assessment should consider the potential for elemental impurities to be present at elevated levels based on the composition of the active pharmaceutical ingredient.

**Q15. When is it necessary to reassess the risk for the drug product?**

A. The potential sources of elemental impurities in the drug product should be reevaluated where necessary throughout the product lifecycle, for example:

- With changes to the components and composition of the drug product;
- With changes to the drug product manufacturing process;
- With changes to the drug product manufacturing facility or equipment;
- With changes to the source or manufacturing process for the drug substance or excipients; or
- With changes to the primary packaging components.

**Q16. By what date should we have completed risk assessments for elemental impurities in our products?**

[4] https://www.fda.gov/media/70323/download

A. We ask that completed risk assessments for investigational and approved products be available on site to provide upon request by January 2023. Potential sources of unsafe levels of elemental impurities in the product should be controlled even prior to this requested date, and CVM may request additional information from drug product sponsors in cases where there appears to be an inadequately controlled potential source of elemental impurities in a product.

## IV. Appendix I – Example decision tree for the components of the animal drug product.