Elemental Impurities and Animal Drugs – An Update from CVM

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Michael Brent, Ph.D.
Center for Veterinary Medicine (CVM)
Division of Manufacturing Technologies (DMT)

This presentation summarizes CVM's current thinking on this topic. The specifics of the policy are only preliminary and are subject to change.

USP <232>

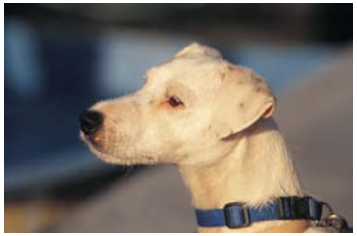
- Does not apply to articles intended for veterinary use. However:
  - **The Center for Veterinary Medicine (CVM) still expects applicants to continue to apply a risk-based control strategy for elemental impurities and establish appropriate controls for elemental impurities where necessary.**
  - **The animal drug product applicant is responsible for ensuring that elemental impurities in the drug product are controlled within safe limits.**

Recommendations

- Start by identifying risks based on the available information such as:
  - Supplier communication
  - The manufacturing process
  - Literature and database information
- Establish controls, where necessary, proportional to the level of risk.
- No testing for elemental impurities is expected in cases where a material is deemed low risk.
- We will also continue to accept a heavy metals test for low risk materials.
- **Methods and limits for specific elements are expected only for materials or finished products deemed high risk. For example:**
  - Elements are used in the process (e.g. catalysts).
  - Mined or other high risk materials make up a significant percentage of the formulation.

PDEs

- As part of the risk assessment, evaluate supplier limits in the context of the product.
  - See ICH Q3D, section 7, Converting Between PDEs and Concentration Limits, Option 2b.
  - The 30% of PDE control threshold from ICH Q3D may be applied in the risk assessment and used in justifications.
- If limits for elements are established:
  - The USP <232>/ICH Q3D PDEs for humans can usually be applied.
  - Alternatively, it may be acceptable to propose an alternate PDE for the target species. However, need to consider the food versus non-food status of the animal.

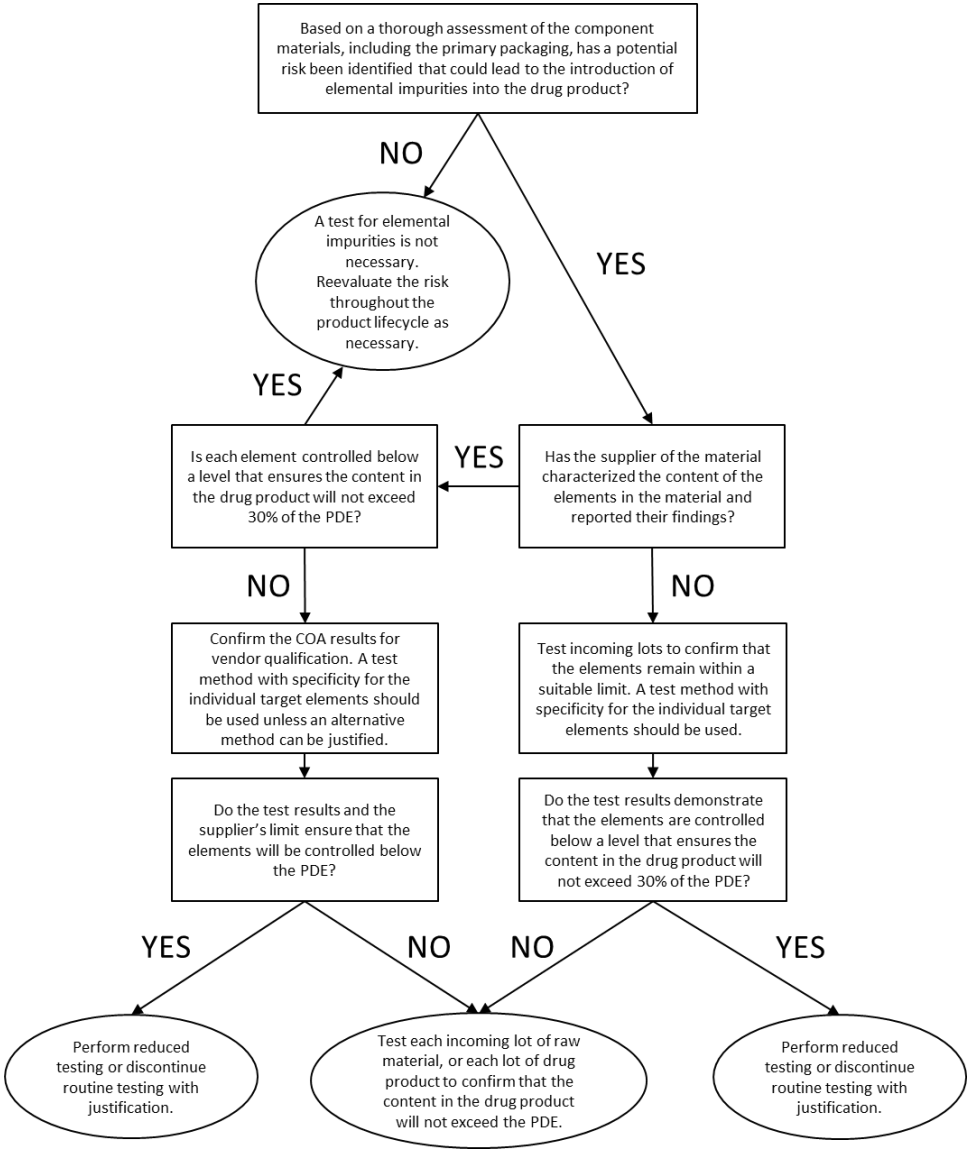




Other Potential Sources of EI

- Container/Closure:
  - CVM considers the risk to be low in most cases.
  - If the supplier certifies that the materials of construction of the primary packaging meet the applicable requirements of the USP and the CFR, the animal drug product applicant will not usually be asked to confirm COA results for EI.
  - The risk for solid dosage forms is usually minimal and does not require further evaluation in the risk assessment.
- Manufacturing Equipment:
  - CVM considers the risk to be low in most cases.
  - Unless an unusual amount of equipment corrosion or wear is anticipated as a result of the manufacturing process, no further assessment is expected.

Example Decision Tree



Updates to Monographs

- USP <231> limits for heavy metals are to be deleted.
- Depending on the animal drug product applicant's risk assessment, limits for heavy metals may be:
  - Replaced by controls for elemental impurities.
  - Maintained in the file.
  - Deleted in an annual report **only with a scientific, risk-based justification.**
- Continue to perform tests for specified elements, such as arsenic per USP <211> and lead per USP <251>, where they are listed in raw material monographs.
  - Alternatively, the test methods may be replaced by the methods described in USP <233>.

Filing Expectations

- For Approved Animal Drugs (NADAs and ANADAs):
  - The risk assessment should be available to provide upon request.
  - Methods and Validations:
    - If a method for elemental impurities is added, provide the test method and justification for proposed limits in the next annual report.
    - Contract testing facilities should be requested in a Supplement – Changes Being Effected.
    - EI method validations may be kept on site and provided upon request.
    - If a heavy metals/<231> method will be used, submit the method in the next annual report.
  - Limits for heavy metals may be deleted in an annual report with a scientific, risk-based justification.
  - Reviewers will request the risk assessment and additional justifications for elemental impurities on a case-by-case basis.

Filing Expectations

- For New Animal Drugs (INADs/JINADs/NADAs/ANADAs):
  - The risk assessment should be available to provide upon request.
  - Methods and Validations:
    - If a method for elemental impurities will be used, provide the test method and justification for the proposed limits.
    - EI method validations may be kept on site and provided upon request.
    - If a heavy metals/<231> method will be used, submit the method to the file.
  - Reviewers will request the risk assessment and additional justifications for elemental impurities on a case-by-case basis.

EI and the Product Lifecycle

- Re-evaluate the potential sources of elemental impurities in the animal drug product where necessary throughout the product lifecycle.
- For example with changes to the:
  - Components and composition of the drug product;
  - Drug product manufacturing process;
  - Drug product manufacturing facility or equipment;
  - Source or manufacturing process for the drug substance or excipients;
  - Primary packaging components.

Guidance

- CVM is working on releasing a guidance for elemental impurities in animal drug products.
- CVM Elemental Impurities Working Group:

  Michael Brent

  James Hoffman

  Kate Ciesienski

Thank you!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