Elemental Impurities Update from CVM

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USP <232> and <233>

- The elemental impurity limits in USP <232> will not apply to veterinary products.
- CVM still expects sponsors of veterinary drug products to apply a risk-based control strategy for elemental impurities as described in USP <232> and draft ICH Q3D.
- Emphasis on supplier communication for identification of potential sources of elemental impurities in the drug product.
- No testing for elemental impurities is expected in cases where a material is deemed low risk.
- Where a test for specified elements is necessary, the method should be validated as described in USP <233>.

Sources of Elemental Impurities

- Potential sources of elemental impurities in a drug product:

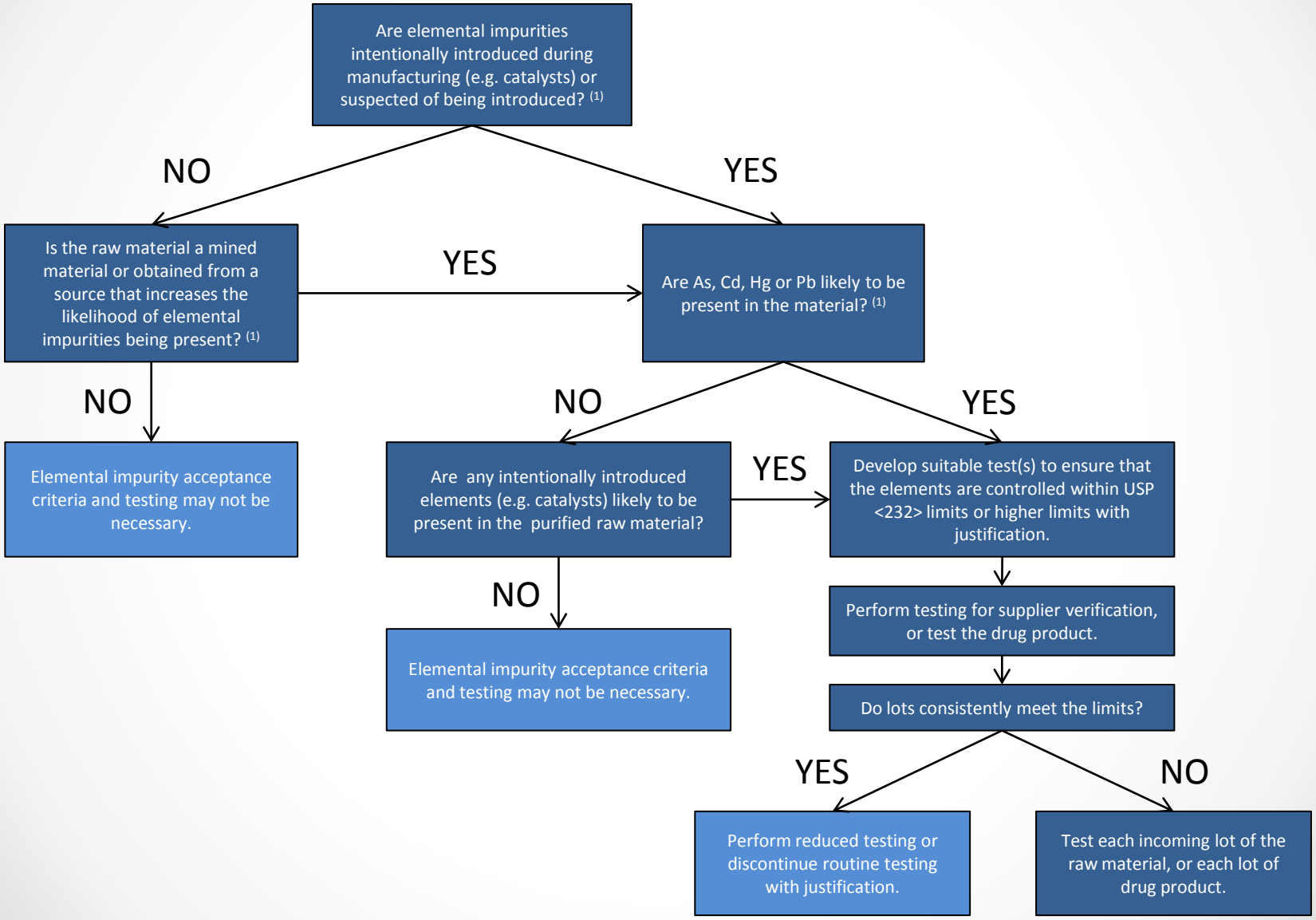
Higher Risk

1. Intentionally added (e.g. metal catalysts)
2. Known or suspected of being present based on the source of the material (e.g. a mined material)

Lower Risk

3. Known or suspected of being introduced by manufacturing equipment
4. Known or suspected of being introduced by the container closure system

Risk Assessment Decision Tree



(1) Denotes information to be obtained through communication with the supplier and/or the drug product sponsor's assessment of the raw material.

Limits for Veterinary Products

- Provide justification in cases where proposed limits exceed USP <232> limits.
- Justification may take into consideration the target species and relevant toxicological data. Information from the literature may be referenced where applicable.

USP <231> Heavy Metals

- You may continue to use the USP <231> test for heavy metals for low risk materials.
- USP <231> will be deleted.
- If the <231> heavy metals test will still be used, provide a copy of the test method in an annual report or in the CMC technical section for a new product.

What to Submit and How

- Approved Products:
  - Your elemental impurities risk assessment report for each product should be available for the Agency to review upon request during an inspection.
  - If USP <231> will still be used, submit the method in an annual report. The test may also be deleted in an annual report with justification.
    - Note: deletion of a test for a specific element (e.g. arsenic or lead) should be reported in a Prior Approval Supplement.
  - If a method is added for elemental impurities, provide the test method and justification for any limits that exceed <232> limits in your next annual report. The validation of the method should be kept on site.
    - Note: A new contract testing facility should be reported in a Supplement - Changes Being Effected.
  - CVM may request additional information on a case-by-case basis (e.g. for high risk materials).

What to Submit and How

- New Products:
  - Your elemental impurities risk assessment should be completed during product development and supplier verification. The risk assessment report should be available for the Agency to review upon request during an inspection.
  - Appropriate justification should be provided if test results for elemental impurities are listed on supplier certificates of analysis but not confirmed for supplier verification.
  - Submit the USP <231> test for heavy metals if it will be used.
  - Elemental impurity test methods should be submitted if applicable. The validation should be kept on site.
  - Provide justification if any elemental impurity limits exceed the USP <232> limits.
  - CVM may request additional information on a case-by-case basis (e.g. for high risk materials).

Implementation

- USP <232> and <233> are effective on December 1, 2015.
- CVM may develop guidance in the future.
- CVM Elemental Impurities Working Group:

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Questions?