Extractable Element Testing in USP Packaging Chapters: Current Perspective

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Extractable elements testing

- The testing of extractable metals in USP Packaging standards dates back to the 1980's
  - <231> Heavy Metal in the plastic and elastomers standards
  - <211> Arsenic in the glass standard.
- A relevant quality attribute of a material or component is its propensity to leach metals and other substances that are measured as extractable elements.
  - There are numerous instances when metallic or elemental leachables had a discernible and sometimes undesirable effect on product safety and/or quality
- As the PDEC revises the various packaging standards a major discussion point has been around extractable element testing and what form it should take in the future.

Extractable elements testing

- The major considerations for testing materials or components discussed
  - Sample preparation
  - How to test the sample
  - What elements to measure
  - What specification, if any

Sample preparation

- Packaging materials and components used in final packaging systems do not dissolve under the conditions of use.
- Inorganic and organics substances from packaging systems accumulate in the drug product by the process of leaching (extraction).
- Thus, the appropriate and relevant sample-preparation process for assessing extractable elements is extraction, as opposed to complete digestion

How to test the sample

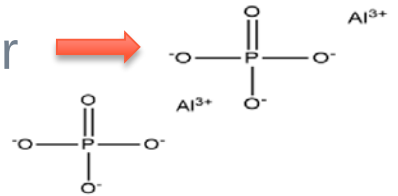
- For testing the extract, atomic absorption spectroscopy and emission spectroscopy (ICP–AES or ICP–OES) were chosen due to their performance capabilities and their wide application and availability.

What elements to measure

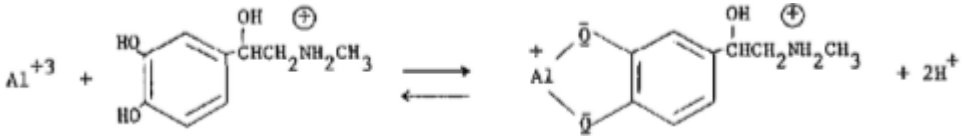
- The concept of relevant elements
  - a relevant element is one which is a known constituent of the material or component that could potentially arise from a starting material, additive, or manufacturing process and elements of known toxicological concern as outlined in <232>.
  - Nontoxic elements that are intentionally added because of potential drug product sensitivities and interactions

Nontoxic elements

- Cause of visible particulates:
  - Leached aluminum + sodium phosphate buffer
  - Leached barium + sodium sulfate buffer



- Cause of drug product degradation :
  - Leached aluminum catalyzed bisulfite reaction Leached aluminum catalyzed bisulfite reaction



- Cause of protein aggregation:
  - Tungsten oxide leached from process to insert needle into glass barrel

$$WO_3 \rightarrow Na_2WO_4 \cdot 2H_2O$$

Toxic elements

- Pb, Hg, As, Cd
- Others elements associated with materials used in packaging are under discussion

What specification, if any

Current position

- Moving forward there will not be a pass/fail specification for specific elements, but just a reporting threshold
  - This allows generated data to be more effectively used in the final assessment
- Approach was used in the revision of <381> in 2017, but not in the revision of <661.1> in 2015
  - The decision to include certain element with specification in <661.1> was to align with other long standing polymer standards (European Pharmacopeia)
    - PD EC will propose a revision 2018 to remove all specification tied to extractable elements in <661.1>

Extractable elements testing: Summary

- The major considerations for testing materials or components discussed
  - Sample preparation
    - **extraction**
  - How to test the sample
    - **atomic absorption spectroscopy and emission spectroscopy (ICP–AES or ICP–OES)**
  - What elements to measure
    - **relevant elements**
  - What specification, if any
    - **reporting threshold**

Proposed USP <381> Extractable Elements

Considerations for replacement method

- Target potential elemental impurities required as per ICH Q3D
- Provide selective and specific elemental data
- Provide quantitative data
- Appropriate sensitivity
- To enable decision about SUITABILITY FOR USE

Extractable elements targets

Elemental Impurities Guidance for Industry
Route of Administration: Parenteral

Class	Elements	Included in Risk Assessment
Class 1	As, Cd, Hg, Pb	Yes
Class 2A	Co, Ni, V	Yes
Class 3	Cu, Li, Sb	Yes
Other	Zn	Not Required

Source: ICH Q3D Elemental Impurities Guidance

Extractable elements – Method considerations

- Extraction solvents
  - Water, pH adjusted
  - Acid solutions
  - Concentration
- Extraction ratios
  - Surface area
  - Weight
  - Solvent volume
- Extraction technique and conditions
  - Reflux
  - Sealed vessel

Evaluation of extraction efficiencies

- Spike aqueous solutions spanning pH range
- Identified most efficient recovery solvent
- Spiked using acidic extraction conditions
- Testing by Inductively Coupled Plasma - Mass Spectrometry (ICP-MS)

Stimuli Article: The Rationale and Proposed Changes to the Revision of *Elastomeric Closures for Injections ⟨381⟩, PF 43 (5)*

Final proposed extraction conditions

- Extraction Solution
  - 0.2 N Nitric Acid
  - 0.05 N Hydrochloric Acid
  - 200 ppb Gold
- Sample Size
  - Component to Solvent Ratio 1:2.5
  - Weight to volume Ratio
- Extraction Conditions
  - Sealed Container
  - 70°C for 24h

Proposed analysis and reporting

- Solutions analyzed by ICP-MS or ICP-OES
  - Appropriate interference corrections are critical
- Evaluate blank solutions
  - Check for reagent contamination
- Evaluate spike recoveries
  - Verify recovery at Sensitivity Threshold (0.05 µg/g)
- Data evaluation
  - Analysis: Sensitivity Threshold of 0.05 µg/g of component
  - Reporting: result to be converted to µg/component

Analytical considerations

- Extraction
  - Suitable container (must be free of detectable elements)
- Instrumentation
  - Must be capable of achieving Sensitivity Threshold of 0.05 µg/g of component (0.02 µg/mL in extract)
- Interferences
  - Transition metals prone to interferences
  - Arsenic will suffer interference due to matrix
  - Sample may give rise to interferences

Reporting

- Analytical results obtained in µg/g of component
  - Sensitivity Threshold of 0.05 µg/g of component must be achieved
- Results need to be converted to µg/component for reporting
- Report Results “as found”
  - No limit applied

Example extractable elements data

Component	Size (mm)	Average Weight (g)	Zn (µg/component)
Stopper	13	0.5	< LOQ
Stopper	13	0.5	3.5
Stopper	20	1.8	0.16
Stopper	20	1.7	0.11
Stopper	20	0.6	16
Lyo Stopper	13	0.7	< LOQ
Plunger	n/a	0.2	< LOQ
Needle Shield	n/a	0.2	4.1
Tip Cap	n/a	0.6	0.25

< LOQ = As, Cd, Co, Cu, Hg, Li, Ni, Pb, Sb, V
LOQ = 0.05 µg/g of material extracted

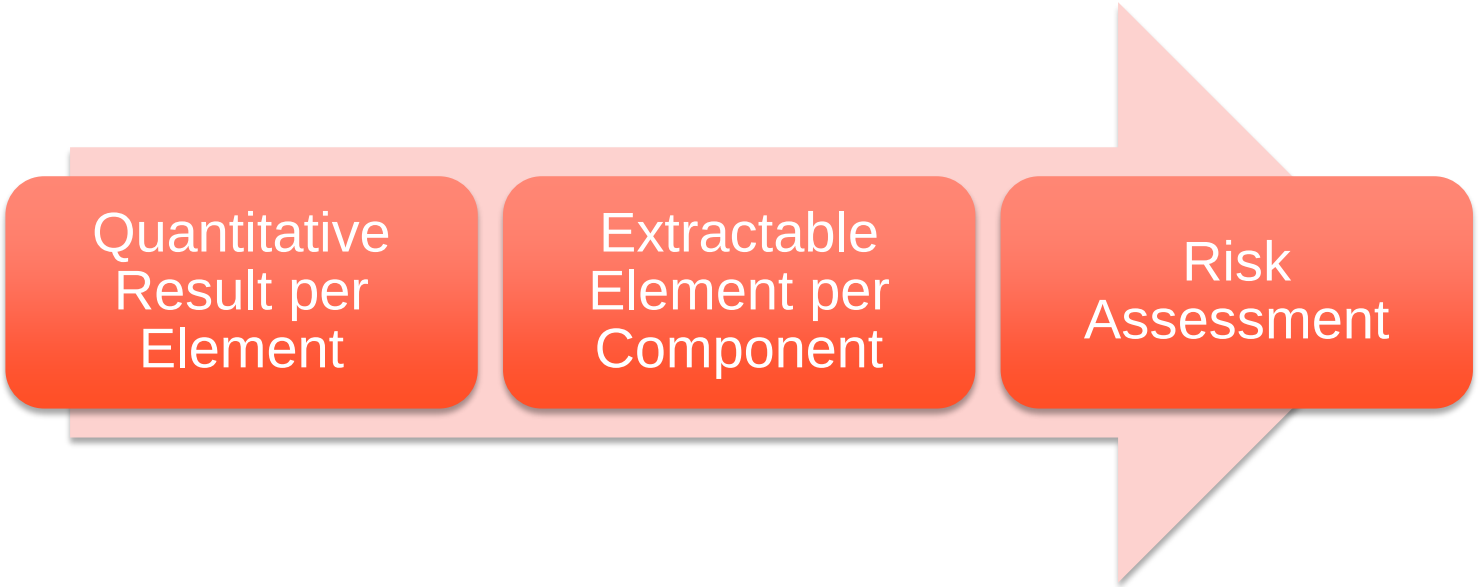
Source: FDA Laboratory

Component conversion examples

Component	Weight (g)	Element (µg/g)	Element (µg/component)
Plunger	0.2	0.05	0.01
Stopper	0.6	0.05	0.03
Stopper	1.8	0.05	0.09
Plunger	3.3	0.05	0.17

Sensitivity Threshold = 0.05 µg/g

Data Interpretation



Conclusion

- USP <381> “Heavy Metals” will be replaced with “Extractable Elements”
- Extractables Elements provides:
  - Element specific data
  - Quantitative data
  - Sensitivity Threshold of 0.05 µg/g of component
  - Data to be converted to µg/component for Risk Assessment
- USP <381> “Extractable Elements” data is suitable to be used in ICH Q3D Risk Assessments

Questions

Empowering a healthy tomorrow

Thank You

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