INTERNATIONAL CONSORTIUM *for*
INNOVATION & QUALITY
*in* PHARMACEUTICAL DEVELOPMENT

# USP Packing General Chapters <661.1>, <381>, <665>: An Industry Perspective on Elemental Impurities Compliance for Container/Closure

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# Presentation Outline

- Background information on USP General Chapters <661.1>, <381>, and <665>
- Review of ICH Q3D Section 5.3
- <661.1> Prescribed Elemental Impurities Testing Over-view and Summary of Compliance Challenges.
- <381> Prescribed Elemental Impurities Testing Over-view and Summary of Compliance Challenges.
- <665> Prescribed Elementa Impurities Testing Over-view and Summary of Compliance Challenges.
- Summary of Industry Comments.
- Final Statement

# USP Packaging Committee Series of General Chapters

- **<661.1> Plastic Materials of Construction**
  - **Scope:** To provide test methods and specifications for plastic materials of construction used in packaging systems…..establish potential safety effect
  - **Guidelines:** Materials that do not meet these requirements are not suitable for containers for these dosage forms unless the materials are established to be suitable by other means….
  - **Current status:** Officially Enacted Chapter on May 1, 2017. Delayed implementation date until May 1, 2020

# USP Packaging Committee Series of General Chapters

- **<381> Elastomeric Closures for Injection**
  - **Scope:** The chemical testing prescribed is orthogonal in that the physicochemical tests provide a general overview of extracted chemical entities and the extractable elements test provides a quantitative assessment of extractable elements of concern.
  - **Guidelines:** Antimony, arsenic, cadmium, cobalt, copper, lead, lithium, mercury, nickel, vanadium, and zinc are reported in amounts greater than 0.05 µg/g converted to µg/component with two significant figures. If the measured values are below these values, report the result as less than 0.05 µg/g.
  - **Current status:** Published in USP PF 43(3). Review period extended until 30-SEP-2017.

# USP Packaging Committee Series of General Chapters

- **<665> Polymeric Components and Systems Used in the Manufacturing of Pharmaceutical and Biopharmaceutical Drug**
  - **Scope:** …polymeric manufacturing materials, components, or systems should not release substances that accumulate in the pharmaceutical or biopharmaceutical product as process equipment-related leachables in quantities that could adversely affect product quality or the health of the patient. It is this patient safety aspect of suitability for use that is the specific focus of this chapter.
  - **Guidance:** Arsenic, cadmium, lead, mercury, cobalt, nickel, vanadium, zinc, platinum, aluminum: Report the measured value in Solution S3 at values above 0.01 mg/L (ppm), corresponding to 0.025 µg/g. If the measured values are below these values, report the result as less than 0.01 mg/L (ppm), corresponding to less than 0.025 µg/g.
  - **Current Status:** Published in USP PF 43(3). Review period extended until 30-SEP-2017.

# ICH Q3D Container Closure Statement

## 5.3 Identification of Potential Elemental Impurities

**Elemental impurities leached from container closure systems:** The identification of potential elemental impurities that may be introduced from container closure systems should be based on a scientific understanding of likely interactions between a particular drug product type and its packaging. ***When a review of the materials of construction demonstrates that the container closure system does not contain elemental impurities, no additional risk assessment needs to be performed.*** It is recognized 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 container closure system during the shelf- life of the product. ***Studies to understand potential leachables from the container closure system (after washing, sterilization, irradiation, etc.) should be performed. This source of elemental impurities will typically be addressed during evaluation of the container closure system for the drug product.***

# <661.1> PLASTIC MATERIALS OF CONSTRUCTION

# Introduction Section of USP <661.1>



***Add the following:***

E

**▲⟨661.1⟩ PLASTIC MATERIALS OF CONSTRUCTION**

**INTRODUCTION**

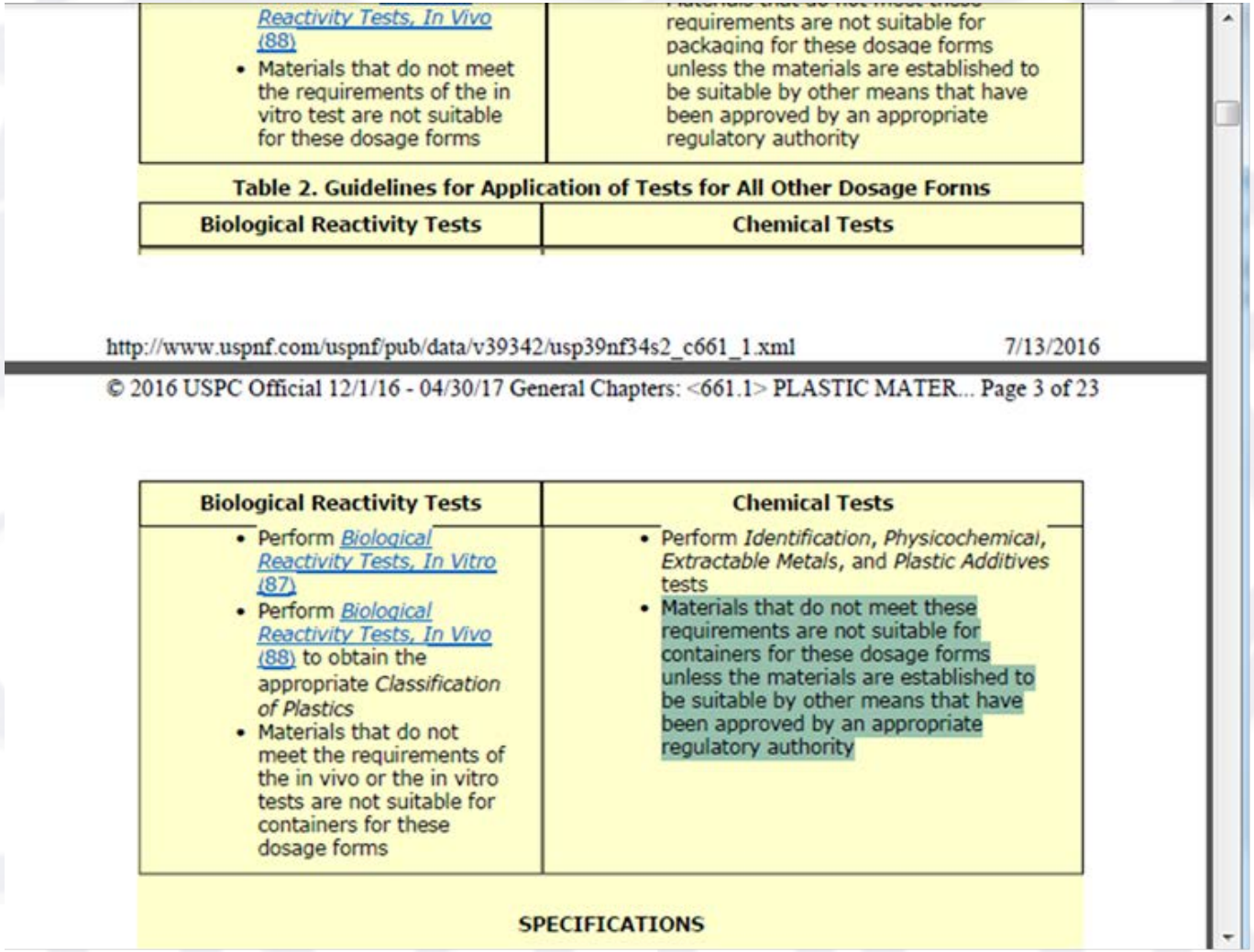
The use of well-characterized materials to construct packaging systems is a primary means of ensuring that the packaging system is suited for its intended use. Materials are characterized so that their properties and characteristics can be matched to the performance requirements of the packaging system, thus facilitating the intentional selection of appropriate materials. For the purposes of this chapter, a plastic material of construction is deemed to be well-characterized for its intended use if the following characteristics have been adequately established: its identity, biocompatibility (biological reactivity), general physicochemical properties, and composition (i.e., additives and extractable metals likely to be present).

Establishing the potential safety effect of a material of construction cannot rely on a single testing strategy, because a single testing strategy cannot cover all of the material's attributes that have a potential safety impact. The chemical testing prescribed in the chapter is orthogonal in that the *Physicochemical Tests* sections provide a general overview of extracted substances, the *Extractable Metals* sections address potential sources of elemental impurities; and the information provided by the *Plastic Additives* tests addresses potential organic extractables. Because chemical testing alone may not be adequate to establish a material's suitability for use, chemical testing is augmented by the orthogonal approach of establishing biological reactivity.

**SCOPE**

The purpose of this chapter is to provide test methods and specifications for plastic materials of construction used in packaging systems. This chapter solely applies to individual plastic materials and should not be applied to packaging systems or components consisting of multiple individual plastic materials. The testing and qualification of plastic packaging systems and

# Guidelines for Application of Tests. USP <661.1



| | |
|---|---|
| Reactivity Tests, In Vivo (88)<br>• Materials that do not meet the requirements of the in vitro test are not suitable for these dosage forms | requirements are not suitable for packaging for these dosage forms unless the materials are established to be suitable by other means that have been approved by an appropriate regulatory authority |

**Table 2. Guidelines for Application of Tests for All Other Dosage Forms**

| Biological Reactivity Tests | Chemical Tests |
|---|---|

http://www.uspnf.com/uspnf/pub/data/v39342/usp39nf34s2_c661_1.xml 7/13/2016

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| Biological Reactivity Tests | Chemical Tests |
|---|---|
| • Perform *Biological Reactivity Tests, In Vitro* (87)<br>• Perform *Biological Reactivity Tests, In Vivo* (88) to obtain the appropriate *Classification of Plastics*<br>• Materials that do not meet the requirements of the in vivo or the in vitro tests are not suitable for containers for these dosage forms | • Perform *Identification*, *Physicochemical*, *Extractable Metals*, and *Plastic Additives* tests<br>• Materials that do not meet these requirements are not suitable for containers for these dosage forms unless the materials are established to be suitable by other means that have been approved by an appropriate regulatory authority |

**SPECIFICATIONS**

# Scope Section of USP <661.1>

**SCOPE**

The purpose of this chapter is to provide test methods and specifications for plastic materials of construction used in packaging systems. This chapter solely applies to individual plastic materials and should not be applied to packaging systems or components consisting of multiple individual plastic materials. The testing and qualification of plastic packaging systems and components for pharmaceutical use are covered in *Plastic Packaging Systems for Pharmaceutical Use* ⟨661.2⟩.

This chapter contains tests, methods, and specifications for the following materials: cyclic olefins, polyethylene, polypropylene, polyethylene terephthalate, polyethylene terephthalate G, and plasticized polyvinyl chloride. Other plastic materials of construction can be used in packaging systems if their suitability for use has been established by testing that is consistent with the general procedures and specifications provided in this chapter for the above-mentioned materials. Alternatively, individual plastic materials of construction are deemed to be well characterized and appropriate for use if they are used in a packaging system that meets the requirements in ⟨661.2⟩ or if the packaging system has been deemed appropriate for pharmaceutical use by the appropriate regulatory authority. Such a conclusion is only valid for the specific packaging system that meets the requirements of ⟨661.2⟩ and cannot be extended to other packaging systems using the same material (or materials) of construction. If the same material of construction is used in another packaging system, then its suitability for use in that packaging system must be established.

Given the wide variety of materials and packaging systems available, and the potential for new developments in materials and packaging systems, it is possible that plastic packaging



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# Comparison of ICH Q3D Permitted Concentrations (100mL) and <661.1> Specifications

| Elemental Impurity | ICH Q3D, Parenteral Permitted Concentration, 100mL Dose, µg/mL | USP <661.1> Limit, µg/mL in Extraction Solution S3[1] (polyethylene), µg/mL | USP <661.1> Limit in Extraction Solution S3 (cyclic olefins), µg/mL | USP <661.1> Limit in Extraction Solution S3 (polypropylene), µg/mL | USP <661.1> Limit in Extraction Solution S3 (PET and PET G), µg/mL | USP <661.1> Limit in Extraction Solution S3 (Plasticized PVC), µg/mL |
|---|---|---|---|---|---|---|
| Al | None | 0.4 | 0.4 | 0.4 | 0.4 | N/A |
| As | 0.15 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 |
| Ba | 7 | N/A | N/A | N/A | 0.4 | 0.25 |
| Ca | None | N/A | N/A | N/A | N/A | 35 |
| Cd | 0.02 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 |
| Co | 0.05 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 |
| Cr | 11 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 |
| Ge | None | N/A | N/A | N/A | 0.4[2] | N/A |
| Hg | 0.03 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 |
| Mn | None | N/A | N/A | N/A | 0.04 | 0.04 |
| Ni | 0.2 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 |
| Pb | 0.05 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 |
| Sb | 0.9 | N/A | N/A | N/A | 0.4[2] | N/A |
| Sn | 6 | 1 | 1 | 1 | N/A | 1 |
| Ti | None | 0.4 | 0.4 | 0.4 | 0.4 | N/A |
| V | 1 | 0.04 | 0.04 | 0.04 | 0.04 | 0.01 |
| Zn | None | 0.4 | 0.4 | 0.4 | 0.4 | 100 |
| Zr | None | 0.04 | 0.04 | 0.04 | N/A | N/A |

[1]Solution S3 (Acid Extraction): 100-g material/250mL 0.1N HCl
[2]Solution S4 (Alkali Extraction): 20-g material/50mL 0.01N NaOH

# Industry Challenges for CCS EI Compliance: Inconsistencies between <661.1> and <232>/ICH Q3D

- EI list in <661.1> is not consistent with Q3D:
  - (Aluminum, Calcium, Germanium, Manganese, Titanium, Zinc and Zirconium are added)
- EI list in <661.1> is not consistent with Q3D Risk Assessment for Parenteral Drug Products:
  - Class 3 elements Cu, Li are missing entirely. Antimony included for one extraction solution.
- Specifications in <661.1> for EI limits are not consistent with PDE based permitted concentrations in <232>/Q3D and appear to be completely arbitrary.
- Product safety based <661.1> EI Specifications are not self-consistent amongst four polymers. No explanation provided.

# <381> ELASTOMERIC CLOSURES FOR INJECTION

# Introduction of USP <381>



For the establishment of the potential safety of a component, one cannot rely on a single testing strategy, because one strategy cannot cover all of the component's attributes that have a potential safety impact. The chemical testing prescribed is orthogonal in that the physicochemical tests provide a general overview of extracted chemical entities and the extractable elements test provides a quantitative assessment of extractable elements of concern. Because chemical testing alone may not be adequate to establish a component's safety and compatibility, it is augmented with the orthogonal approach of establishing biological reactivity.

In addition, evaluation of the suitability of a component to function properly requires that the complete system be considered, and testing must be designed to meet the requirements for intended use, as described in *Assessment of Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems* (1382). If components comply with requirements outlined in the chapter, studies should then be designed to determine safety and compatibility as recommended in *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems* (1663) and *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems* (1664).

Establishing the suitability of packaging systems for pharmaceutical products involves multiple tests and testing procedures including:

- **Component screening:** The baseline requirements described in this chapter comprise characterization of the elastomer's biological reactivity, physicochemical properties, and extractable elements.
- **Controlled extraction (simulation) study:** The worst-case controlled extraction (simulation) study is performed so that applicants can determine the extent to which extractables may become probable leachables. (For additional information, see (1663).)
- **Pharmaceutical product assessment:** This type of testing is actual-case measurement of confirmed leachables in the pharmaceutical product in the packaging/delivery system intended for the commercial market. (For additional information, see (1664).)

## 2. SCOPE

Elastomeric packaging components are used in packaging systems for various parenteral preparations as defined in *Injections and Implanted Drug Products* (1). Elastomeric components include, but are not limited to, those used for vials, bottles, prefilled syringes (plungers, needle shields, and tip caps), cartridges (plungers and seal liners), injection ports for flexible bags and infusion sets, and plungers for single-use syringes. Packaging systems, also referred to as container–closure systems, are defined in *Packaging and Storage Requirements* (659); these systems are the sum of packaging components that together contain, protect, and in certain cases, deliver the drug product.

# Section 3.3 of USP <381>



Antimony, arsenic, cadmium, cobalt, copper, lead, lithium, mercury, nickel, vanadium, and zinc are reported in amounts greater than 0.05 µg/g converted to µg/component with two significant figures. If the measured values are below these values, report the result as less than 0.05 µg/g.

## 4. TEST METHODS

### 4.1 Biological Reactivity

In vitro and in vivo biological tests are performed on components according to test procedures described in ⟨87⟩ and ⟨88⟩.

### 4.2 Physicochemical

**Solution S:** Place whole, uncut closures corresponding to a surface area of 100 ± 10 $cm^2$ into a suitable glass container. Cover the closures with 200 mL of *Purified Water* or *Water for Injection*. If it is not possible to achieve the prescribed closure surface area (100 ± 10 $cm^2$) using uncut closures, select the number of closures that will most closely approximate 100 $cm^2$ and adjust the volume of water used to the equivalent of 2 mL/1 $cm^2$ of actual closure surface area used.

Place the washed closures into a Type I glass wide-necked flask (see *Containers—Glass* ⟨660⟩), add the same quantity of *Purified Water* or *Water for Injection* initially added to the closures, and weigh. Cover the mouth of the flask with a Type I glass beaker. Heat in an autoclave so that a temperature of 121 ± 2° is reached within 20–30 min, and maintain this temperature for 30 min. Cool to room temperature over a period of about 30 min. Add *Purified Water* or *Water for Injection* to bring it up to the original mass. Shake, and immediately decant and collect the solution. [NOTE—This solution must be shaken before being used in each of the tests.]

**Blank:** Prepare a blank solution similarly, using 200 mL of *Purified Water* or *Water for Injection*, omitting the closures.

### 4.3 Appearance (Turbidity/Opalescence)

The determination of turbidity may be performed using either a visual or instrumental comparison. For a discussion of turbidimetry, see *Nephelometry, Turbidimetry, and Visual Comparison* ⟨855⟩. Instrumental assessment of clarity provides a more discriminatory test

# Industry Challenges for CCS EI Compliance: Inconsistencies between <381> and <232>/ICH Q3D

- EI list in <381> is not consistent with <232>, Q3D or <661.1>:
  - Zinc is required. Aluminum, Germanium, Zirconium, Calcium, Manganese, and Titanium are not included.
- Specifications in <381> for EI limits are not consistent with PDE based permitted concentrations in <232>/Q3D and appear to be completely arbitrary.

# ⟨665⟩ POLYMERIC COMPONENTS AND SYSTEMS USED IN THE MANUFACTURING OF PHARMACEUTICAL AND BIOPHARMACEUTICAL DRUG PRODUCTS

# Scope Section of USP <665>



## 1. INTRODUCTION

Pharmaceutical and biopharmaceutical manufacturing processes are the sum of those steps that convert raw materials into an active pharmaceutical ingredient (API), biopharmaceutical drug substance (DS), or drug product (DP). Manufacturing processes utilize components and parts that may either be fully or partially constructed with polymeric materials.

It is likely that one or more polymeric components will come into contact with all process streams associated with the manufacturing process, from raw materials through to the drug product. Such an interaction could result in the accumulation of process equipment-related leachables (PERLs), which have the potential to alter a key quality attribute of a DS, a DP, and their associated intermediates should the PERLs persist through the manufacturing process.

## 2. SCOPE

This chapter is applicable to all manufactured APIs, DSs, and DPs, including pharmaceuticals, biopharmaceuticals, biologics, and small molecule products defined as drugs with a molecular weight of <500 Da. This chapter is applicable solely to those processes that involve liquid streams since the propensity of polymeric components and liquid process streams to interact is greater than with solid, or gaseous process streams (see *Figure 1*). While this chapter does not address the absorption of ingredients, APIs, DSs, or DPs onto polymeric components or systems during manufacturing, this issue should be considered in the selection and qualification of manufacturing materials, components, and systems.

Pharmaceutical and biopharmaceutical manufacturing suites may contain both single-use systems (SUS) and multiple-use systems (MUS). Polymeric materials and components are used, in all or in part, in both SUS and MUS and must be suitable for their intended use. That is, the manufacturing system should be:

- Composed of materials and components that are safe for use with the pharmaceutical or biopharmaceutical product and all process intermediates and/or process streams
- Compatible with the pharmaceutical or biopharmaceutical product and all process intermediates and process streams
- Functional

Focusing on the first aspect of compatibility, polymeric manufacturing materials, components, or systems should not release substances that accumulate in the pharmaceutical or biopharmaceutical product as PERLs in quantities that could adversely affect product quality or the health of the patient. It is this patient safety aspect of suitability for use that is the specific focus of this chapter.

Polymeric manufacturing components and systems are chemically suited for their intended use if:

# Section 4.10 of USP <665>

**Test solution:** Dilute 5 mL of *Solution S* with water to 14 mL. Make alkaline, if necessary, by adding 1 N sodium hydroxide, and dilute with water to 15 mL. Add 0.3 mL of *Alkaline potassium tetraiodomercurate solution* and close the container.

**Ammonium standard solution:** Prepare a solution of ammonium chloride in water [1 ppm of ammonium ($NH_4$)]. Mix 10 mL of the 1 ppm ammonium chloride solution with 5 mL of water and 0.3 mL of *Alkaline potassium tetraiodomercurate solution*. Close the container.

**4.10 Extractable Elements**

**Extraction solution:** Prepare a solution of a mixture of acids with gold (Au) to stabilize mercury (Hg) in the following ratio: 0.2 N nitric acid ($HNO_3$), 0.05 N hydrochloric acid (HCl), and 200 ppb gold (Au). Prepare the solution in a volume sufficient to prepare all standards, blanks, spikes, and extractions. Care should be taken to use high-purity reagents.

**Extraction:** Place whole, uncut components equivalent to 1 g/2.5 mL of the *Extraction solution* into a suitable plastic container and record the weight. Prepare two extraction blank solutions (one for spiking) using a container of the same type as that used for the samples, omitting the closures. Seal the containers and place in an oven at 70°. Remove containers after 24 h and allow to cool. Analyze within 48 h. Extracts, spikes, and blanks are to be analyzed by inductively coupled plasma–mass spectrometry (ICP–MS) and/or inductively coupled plasma–optical emission spectroscopy (ICP–OES). Refer to *Elemental Impurities—Procedures* ⟨233⟩ for analytical procedures and system suitability.

**Extraction recovery:** Prepare a 10 µg/mL solution of antimony (Sb), arsenic (As), cadmium (Cd), cobalt (Co), copper (Cu), lead (Pb), lithium (Li), mercury (Hg), nickel (Ni), vanadium (V), and zinc (Zn) in *Extraction solution* [0.2 N nitric acid ($HNO_3$), 0.05 N hydrochloric acid (HCl), and 200 ppb gold (Au)]. Using a suitable pipet, spike one of the blank extraction solutions with the appropriate volume of the 10-µg/mL solution, resulting in a concentration of 0.05 µg/g.

Calculations:

# Section 4.2.2 Specifications of USP <665>



*Solution S3* is analyzed for extractable metals using the instrumentation and methods that are specified in *Elemental Impurities—Procedures* (233) including an inductively coupled plasma–atomic emission spectrophotometer and an inductively coupled plasma–mass spectrophotometer (see *Plasma Spectrochemistry* (730)), as directed.

4.2.2 SPECIFICATIONS

•**IDENTIFICATION**

Determine the infrared spectrum from 3800 $cm^{-1}$ to 650 $cm^{-1}$ (2.6–15 µm). The specimen exhibits an absorption spectrum that is substantially equivalent to that of USP Silicone Elastomer RS. Substantial, as opposed to exact, equivalence allows for minor spectral differences arising from the natural compositional and/or physical variation among polymers of this class. Substantial equivalence is achieved when all differences between the sample and Reference Standard spectra can be explained in the context of such natural compositional and/or physical variations.

•**PHYSICOCHEMICAL TESTS**

**Acidity or alkalinity:** NMT 2.5 mL of 0.01 N sodium hydroxide is required to change the color of the indicator to blue. NMT 1.0 mL of 0.01 N hydrochloric acid is required to reach the beginning of the color change of the indicator from yellow to orange.

**Total organic carbon:** The TOC concentration of *Solution S1* is NMT 5 mg/L.

**Substances soluble in hexane:** The difference in weight of the glass evaporating disk, before and after drying of the residue, is less than 15 mg (3% by weight).

**Phenylated compounds:** The absorbance is NMT 0.4.

**Volatile matter:** For silicone elastomer prepared using peroxides, the volatile matter is NMT 0.5%. For silicone elastomer prepared using platinum, the volatile matter is NMT 2.0%.

•**EXTRACTABLE METALS**

**Arsenic, cadmium, lead, mercury, cobalt, nickel, vanadium, zinc, platinum, aluminum:** Report the measured value in *Solution S3* at values above 0.01 mg/L (ppm), corresponding to 0.025 µg/g. If the measured values are below these values, report the result as less than 0.01 mg/L (ppm), corresponding to less than 0.025 µg/g.

**5. POLYMERIC COMPONENTS AND SYSTEMS**

# Industry Challenges for CCS EI Compliance: Inconsistencies between <665> and <232>/ICH Q3D

- EI list in <665> is not consistent with Q3D or <661.1>:
  - Aluminum, Zinc and Platinum (a Class 2B EI) is included.
  - Additional elements mandated in <661.1> are not included in <665> (Calcium, Germanium, Manganese, Titanium, Zirconium)
  - Class 3 elements Sb, Cu, Li not included
  - Specifications in <665> for EI limits are not consistent with PDE based permitted concentrations in <232>/Q3D and appear to be completely arbitrary.

# Summary of Comments

Specific inconsistencies in proposed USP chapters <661.1>, <381> and <665> are as follows:

- Chapters <661.1>, <381> and <665> mandate arbitrary prescribed limits for elemental impurities of packing components with no consideration for drug product dose, route of administration or relative toxicity. The proposed specifications appear to be completely arbitrary.
- Chapter <661.1> introduces specifications for the elements aluminum, calcium, germanium, manganese, titanium, zinc and zirconium that are ***not*** identified as elements of toxicological concern in <232>/ICH Q3D.
- The elements aluminum and zinc are included as targeted elemental impurities in <665> and zinc is included as a targeted elemental impurity in <381>.
  - ✓ These elements are not defined as elemental impurities of toxicological concern in either USP <232> or ICH Q3D.
  - ✓ Regulations for controlling aluminum in large volume parenteral nutrition and dialysates appropriately assure patient safety.
  - ✓ Why zinc would be included at such a low acceptable concentration in both chapters is not explained.

# Summary of Comments, Continued…

Specific inconsistencies in proposed USP chapters <661.1>, <381> and <665> are as follows:

- Proposed chapter <665> includes prescriptive platinum analysis even though as a USP <232>/ICH Q3D Class 2B element, measurement is not required unless intentionally included in the process.
- Elemental impurities listed in <661.1> are ***not*** included in the prescribed targets lists in <381> or <665>, namely germanium, zirconium, titanium, manganese or calcium.
- Elemental impurities specifications are ***not*** assigned to other sources of elemental impurities by USP or ICH, such as excipients and water, that are included in the overall EI control strategy for drug products.
    - Why mandated testing would be prescribed for container/closer components at such low acceptable concentrations in these packaging chapters is not explained, is inconsistent and does not appear appropriate.
    - If evidence exists that container/closure components represent a heightened risk to patient safety, then that evidence needs to be brought forward.

# Final Statement

- The IQ Consortium ICH Q3D Implementation Working Group has grave concerns about the below 1000 chapters being proposed by the USP Packaging Committee with respect to elemental impurities control.

- The fundamental misalignment of USP <661.1>, <381> and <665> with USP <232> and ICH Q3D, as proposed, will result in extensive analyses being conducted across the entire pharmaceutical industry for no additional assurance to patience safety.

- Prescribed testing per a below 1000 USP chapter to these levels in container/closure components simply makes no sense from either or safety or quality perspective.

- The working group recommends that the sections pertaining to prescribed elemental impurities testing in these three chapters be stricken entirely and replaced with a reference to <232> with instructions to adhere to the risk assessment paradigm for elemental impurities control and monitoring from ***ALL*** sources including CCS.

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