Compendial Effort to Revise Packaging Material Standards: Glass, Plastic, Elastomer, and Other

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PNP Stakeholder Forum
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USP current efforts in revision of packaging standards

- Plastic
    - Plastic Materials of Construction - <661.1>
    - Plastic Packaging System for Pharmaceutical Use - <661.2>
    - Plastic Component and Systems Used in the Manufacturing of a Drug Product - <665>
- Elastomeric components used for pharmaceutical use
    - Injectable Drug Products - <381>
    - Functionality Testing - <382>
- Glass Containers Used for Pharmaceutical Use - <660>
- Metal Containers Used for Pharmaceutical Use - <662>
- Biocompatibility Testing of Plastic and Elastomeric Material
    - Biological Reactivity, In Vitro - <87>
    - Biological Reactivity, In Vivo - <88>
    - Biocompatibility of Materials - <1031>

A starting point for the revision of USP standards

- Building safety into a system by using well-characterized and safe materials of construction (Quality by Design).
- The testing required to select and qualify a packaging system is correlated with the risk that the packaging system or component will interact with the final drug product (Risk-based Approach).
- The USP standard serves as a baseline
  - Should have value in every situation of use, but may not necessarily address every individual situation of use

Plastic materials and packaging systems

<661.1>
Plastic Material of Construction

- Identification
- Biological Activity
- Physico-chemical Tests
- Extractable Metals
- Plastic Additives

<661.2>
Plastic Packaging Systems for Pharmaceutical Use

- Biological Activity
- Physico-chemical Tests
- Safety Assessment (Extractables/Leachables)

<661.1> Plastic Materials of Construction

Test Parameter	Oral and Topical Dosage Forms	All Other Dosage Forms
Chemical Tests		
Identification	DSC/IR	DSC/IR
Physicochemical Tests	Water extraction: • UV absorbance, • Acidity/alkalinity • TOC	Water extraction: • UV absorbance, • Acidity/alkalinity • TOC
Extractable Metals	Acid extraction: • ICP analysis for targeted and relevant metals	Acid extraction: • ICP analysis for targeted and relevant metals
Polymer Additives	Proper Reference to Indirect Food Additive Regulations, CFR 174-186	Direct chemical testing
Biological Reactivity		
In Vitro per USP <87>	Required	Required
In Vivo per USP <88>	Not required	Required as needed to obtain plastic classification

<661.1> Material Characterization Chapter

- **Objective**: gain as much information about a material of construction to determine potential suitability

- Requirements of <661.1> can be met by:
  - The materials of construction meeting requirements of <661.1>
  - The component or system meeting the requirements of <661.2>

<661.2> Plastic Packaging Systems for Pharmaceutical Use

Comparison of Testing Required for Various Dosage Forms		
Test Parameter	**Oral and Topical Dosage Forms**	**All Other Dosage Forms**
Chemical Tests		
Physicochemical Tests	Water extraction: • UV absorbance, • acidity/alkalinity • TOC	Water extraction: • UV absorbance, • acidity/alkalinity • TOC
Chemical Assessment—Extractables and Leachables	Risk-based testing*	Risk-based testing*
Biological Reactivity		
In Vitro per USP <87>	Required	Required
In Vivo per USP <88>	Not required	Required as needed to obtain plastic classification

<661.1> and <661.2> Sample comments

Biological Reactivity Testing

Comment/Concern: Biological reactivity testing for SODF does not seem to be appropriate for the level of risk.

USP Position: A cornerstone of suitability for use assessment of packaging systems and their materials of construction is the concept of orthogonal assessment. Individual means of assessment are generally insufficiently robust or broad in scope to provide rigorous and complete assessments on their own, thus orthogonal assessments are preformed to essentially “fill the gaps” in the individual assessments.

PF 42 (4) July 2016: Proposed the removal of the Biological reactivity testing for SODF and Topical Dosage Forms

<661.1> and <661.2> Sample comments (cont’ed)

TOC and Absorbance Testing

Comment: Materials that would not pass the test that could still be used for certain applications

Planned Revision:

“If the specification for absorbance or TOC is exceeded, then the material or packaging system can still be deemed acceptable if the chemicals responsible for the test results can be established (identity and concentration) and the chemicals are safety assessed to establish that the probable safety risk posed by all the chemicals, considered individually, is within acceptable parameters.”

<661.1> Comments

Extractable Metal Testing

- Comments:
  - Some of the metals specified in <661.1> are fundamentally misaligned to <232>
  - Metal specifications in the chapter are not based no clear basis from either a toxicological or quality perspective and should be removed
  - <661.1> should directly reference <232> because the chapter already discusses the contributions of packaging components to the final drug product.

<661.1> Comments

- 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

<661.1> Comments

Extractable Metal Testing

- Comments:
  - Metals specified in <661.1> are fundamentally misaligned to <232>
  - Metal specifications in the chapter are not based on either a toxicological or quality perspective

POLYVINYL CHLORIDE, PLASTICIZED

Arsenic, cadmium, lead, mercury, cobalt, nickel, and vanadium: Report the measured value in Solution S3 at values above 0.01 mg/L (ppm), corresponding to 0.025 mg/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 mg/g.

- Barium: S3 contains NMT 0.25 mg/L (ppm), corresponding to 5 mg/g.
- Calcium: S3 contains NMT 35 mg/L (ppm), corresponding to 0.07 weight %.
- Tin: S3 contains NMT 1 mg/L (ppm), corresponding to 20 mg/g.
- Zinc: S3 contains NMT 100 mg/L (ppm), corresponding to 0.2 weight %.

<661.1> Comments

Extractable Metal Testing

- Comments:
  - <661.1> should directly reference <232>
    - <232> already discusses the contributions of packaging components to the final drug product.
- USP Position:
  - <232> limits don’t apply to <661.1>
  - The focus has been on the risk assessment option in <232>
    - How to get the necessary data to make a decision regarding the selection of a material for a new product or for a packaging material change.
    - In the control of plastic materials, extractable metals is an important attribute to understand and testing seems to be the only way to obtain the necessary data.

Grandfather: currently approved products

Rationale

Goal of <661> revision

To aid in the selection and qualification of packaging materials and components that are deemed suitable and safe

Suitability and safety of a packaging system, with its drug product, is determined by regulatory authorities

- A packaging system, with a specific drug product, would meet the requirements of <661.1> and <661.2>, if it had gained regulatory approval.

Removal: Grandfathering exemption

Why?

- The standard, as written, states when the chapter is/is not applicable
  - Regulatory discretion
- One standard for all products is easier to manage

How?

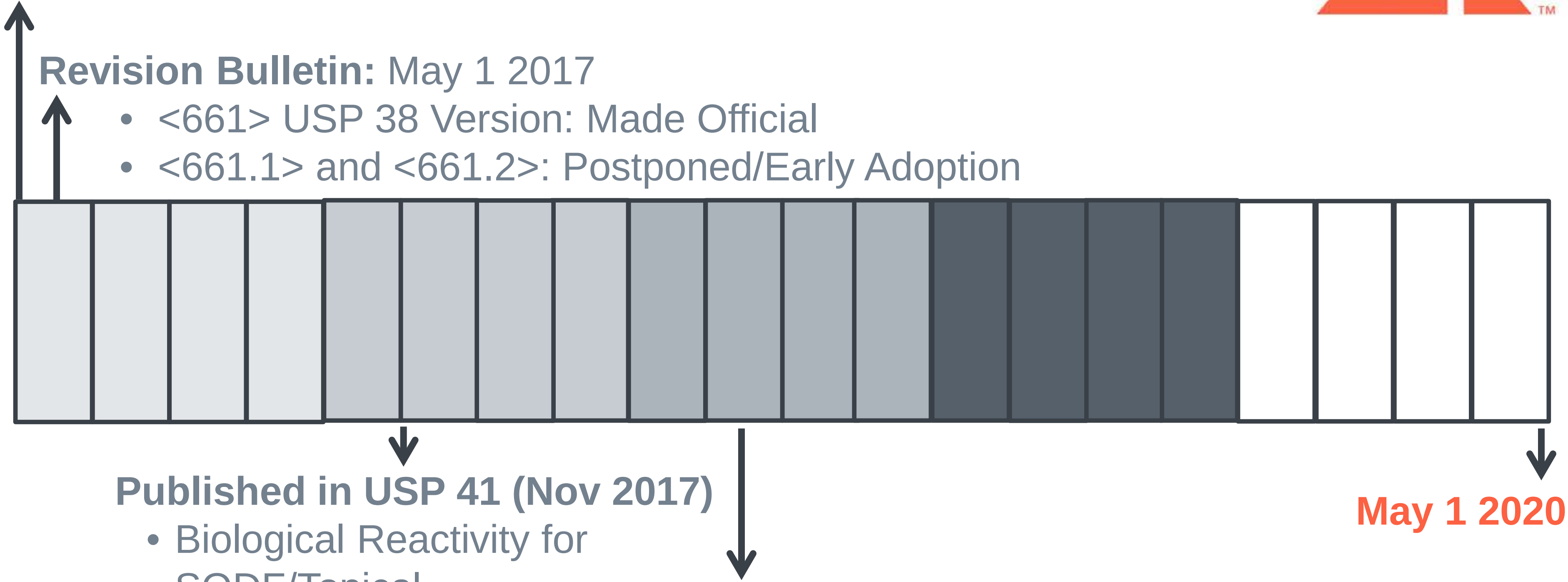
- Revision Bulletin
  - **<661>:** USP 38 (2015) version was reintroduced to the chapter, which will be official until May 1, 2020.
  - **<661.1> and <661.2>**: These chapters will become official on May 1, 2020 . Early adoption of the requirements in these chapters are permitted by USP. When early adoption is not used, <661> will apply and must be met wherever <661.1> or <661.2> are referenced in the USP-NF.

<661.1> and <661.2> Revision timeline

Intent to Revise: March 31,2017

Revision Bulletin: May 1 2017

- <661> USP 38 Version: Made Official
- <661.1> and <661.2>: Postponed/Early Adoption



Published in USP 41 (Nov 2017)

- Biological Reactivity for SODF/Topical
- TOC and Absorbance

USP 41: May 1, 2018

- Official

May 1 2020

<660> Containers – Glass

Extractable Tests:

- Glass Grains Test measures the amount of extracted alkali from glass matrix to determine Glass Type
  - Type I Borosilicate glass
  - Type II Treated soda-lime-silica glass
  - Type III Soda-lime-silica glass

Inner Surface Test

- Surface Glass Test measures the amount of extracted alkali from the glass inner surface
- Arsenic test measures the amount of extracted arsenic from the glass inner surface

Spectral Transmission Test:

- For colored glass containers

Phase I revision for glass containers - <660>

PF 43 (3) May 2017

- The chapter title has been changed to “Glass Containers Used in Pharmaceutical Packaging/Delivery Systems”.
- A *Scope* section has been added.
- Table 1 and Table 2 have been consolidated into one table which contains the specifications for the *Surface Glass Test*, *Glass Grains Test* and *Surface Etching Test* for a glass container to be classified as Type I, II, or III.
- The list of ancillary equipment required to execute the chapter has been expanded.
- The *Purified Water* requirement has been aligned with the *Pharm Europa* General Chapter 3.2.1 "Glass Containers for Pharmaceutical Use".

Phase I revision for glass containers - <660>

PF 43 (3) May 2017

- Additional information on the *Autoclaving Procedure* has been added to the chapter, including *Reference temperature curve*, *Autoclave calibration*, and *Routine autoclave runs*.
- Additional requirements for the autoclave used for the various tests have been added to the chapter.
- Additional information on how to titrate the test and blank samples has been added to the chapter.

Phase II revision for glass containers - <660>

- Inclusion of other glass composition:
  - How can the standards be revised to include other glass materials, beyond borosilicate and soda-lime glass, that conform to the chapter specifications?
- Analytical Methods:
  - The titration method for Glass Grains and Inner Surface Tests measures the sum of alkali oxides. It does not quantitate individual elements.
    - Quantify individual extracted alkali elements by inductively coupled plasma optical or atomic emission spectroscopy (ICP-OES or ICP-AES)
  - The method to determine extractable Arsenic is outdated (colorimetric)
    - Quantify extractable Arsenic by ICP-OES or ICP-AES
  - Can a test be developed to differentiate between internal surface areas, e.g. heel, side wall, neck, in tubular containers (ampules, vials)?

Status

- <660> Containers-Glass
- <1660> Evaluation of the Inner Surface Durability of Glass Containers

Publication: PF 43 (3) May 1, 2017

Comment Deadline: ~~July 31, 2017~~ (September 30, 2017)

Changes for elastomeric closures for injections - <381>

- Title Changes
  - Elastomeric Components Used in Injectable Pharmaceutical Packaging/Delivery Systems
- Emphasis on baseline requirements for the selection of thermoset and thermoplastic elastomeric components.
- Expand the scope to include all elastomeric components used in an injection packaging system, included 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.
- Deleted the Heavy Metals ⟨231⟩ testing, added new method for extractable elements.
- Moved functionality tests and assessment to new chapters
- Develop a new informational chapters

<382> Elastomeric Closure Functionality Testing

- Physicochemical, biological reactivity and extractable elements test in <381> are intended for testing individual components
  - Functional testing can only be done on the whole packaging system.
- Functionality testing in current <381> is limited to testing closures intended to be pierced by a hypodermic needle for penetrability, fragmentation and self-sealing capacity.
- <382> is meant to addresses suitability for intended use (functionality) of the various packaging/delivery systems intended for injectable dosage forms
  - Elastomeric Component should work with packaging system to
    - protect and contain packaged contents
    - enable safe and effective product access at the time of use

<382>: Scope

- Bottle and vial stoppers intended to be accessed with a needle or spike
- Prefilled syringe or cartridge plungers, needle shields, tip caps
- Pen, jet or related injector system components
- Blow-fill-seal plastic container lined caps
- Plastic bags or blow-molded infusion container access ports

Status

- <381> Elastomers Used in Pharmaceutical Packaging/Delivery Systems
  - Elastomeric Components Used in Injectable Drug Product Packaging/Delivery Systems
- <1381> Evaluation of Elastomeric Components Used in Pharmaceutical Packaging/Delivery Systems
- <382> Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems
- <1382> Assessment of Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems

Publication: PF 43 (3) May 1, 2017

Comment Deadline: ~~July 31, 2017~~ (September 30, 2017)

Questions

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Thank You

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