USP-NF Packaging Standards Update

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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>

Packaging standards revision have high impact

- 40-50 year old standards
- New testing procedures and specifications
- New testing paradigm
- Impacts many currently approved drug products that use plastic, elastomeric and glass components in their packaging system

<661.1> Material Characterization Chapter

Goal of <661> revision

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

- **<661.1> Objective**: To 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> Objective:** To determine if packaging system is deemed chemically suited for its intended use.

<661.1> Plastic Materials of Construction (USP 41)

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>	Not required	Required
In Vivo per USP <88>	Not required	Required as needed to obtain plastic classification

<661.2> Plastic Packaging Systems for Pharmaceutical Use (USP 41)

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>	Not required	Required
In Vivo per USP <88>	Not required	Required as needed to obtain plastic classification

<661.1> and <661.2> 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
  - <661.1> should directly reference <232>
- USP perspective:
  - <232> elements list serves a different purpose than the list in <661.1>
  - Elemental analysis in <661> chapters can be used to:
    - Support the risk assessment option in <232>,
    - Obtain the necessary data to make a decision regarding the selection of a material for a new product or for a packaging material change.

Grandfather: currently approved products

Rationale

Suitability and safety of a packaging system, with it's 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 is needed
- One standard for all products is easier to manage

How?

- Revision Bulletin (May 1, 2017)
  - **<661>:** USP 38 (2015) version was reintroduced to the chapter, which will be official until May 1, 2020.
  - **<661.1> and <661.2>**: This chapter will become official on May 1, 2020 . Early adoption of the requirements in this chapter and its companion chapter <661.2> are permitted by USP. When early adoption is not used, <661> will apply and must be met wherever <661.1> or <661.2> is referenced in the USP-NF.

<661.1> and <661.2> Revision timeline

New implementation date –
Notice of Intent to Revise (October 26, 2018)

- Delay until December 1, 2025 the implementation of new requirements of General Chapters <661.1> and <661.2>.
- To make General Chapter <661> applicable until December 1, 2025.
- Clarify in General Chapter <659> that early adoption of the requirements of <661.1> and <661.2> is allowed by USP, and that packaging systems conforming to these requirements in advance of December 1, 2025 are considered by USP to be in conformance with the USP–NF.
- Reformat and clarify content in <661.1> and <661.2> to improve usability.
- Revise the extractable element testing approach in <661.1> and <661.2>.
- Revise <1661> to align with the changes that have occurred in <661.1> and <661.2>.

<661.1> and <661.2> Revision timeline

Proposed timeline:

- Pre-post updated chapters on the USP Website **January 1, 2019**
- Publish In Process Revision (IPR) in *Pharmacopeial Forum* 45(2) **March–April 2019**
- Comment period ends **May 31, 2019**
- Proposed IPR anticipated to become official **August 1, 2020**

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

Significant changes and impact of general chapter <381> Elastomeric Closures for Injections

- **Supplier-End User (Table 1)**
  - Removed from <381> added to <1381> as Guidance
- **Physicochemical Eliminated Pre-Wash prior to extraction**
  - Reduce unexpected but potential impact on Type 1&2
- **Extractable Elements**
  - Extraction procedure/analysis verified for recovery for specific elements
  - Report as found >0.05ug/g vs limits
- **Separated functionality chapter <382>/<1382>**
  - Testing a wider range of systems, based on the performance and functional properties needed by the end-user.

<1381>: Informational chapter

- **Purpose:** To support the planned revisions of *Elastomeric Closures for Injections* <381>
- **Topics Covers:**
  - Describes elastomeric components and their materials of construction for use in pharmaceutical packaging systems
  - Provides a high-level introduction to elastomer chemistry, manufacturing technology, and the post processing of components
  - Explains basic functional characteristics of components
  - Designates baseline requirements
  - Discusses identification testing

<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.
- Thus the new <382> is meant to addresses suitable for intended use (functionality) 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>: Functionality Test Categories

Section 3. General Test Requirements

Section 4. Package Integrity

Section 5. Needle and Spike Access Functionality Tests

- 5.1 Fragmentation
- 5.2 Penetration Force
- 5.3 Self-sealing Capacity
- 5.4 Spike retention and Sealability Capacity

Section 6. Plunger Functionality Tests

- 6.1 Plunger Break Force and Plunger Glide Force
- 6.2 Plunger Seal Integrity

Section 7. Tip Cap and Needle Shield Functionality Tests

Elastomers Chapters - 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

Status: PF 43 (3) revisions will not become official and chapters will be revised and republished Q2 2019

Manufacturing Components Chapters - Status

- <665> Polymeric Components and Systems Used in the Manufacturing of Pharmaceutical and Biopharmaceutical Drug Products
- <1665> Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products

Publication: PF 43 (3) May 1, 2017

Comment deadline: July 31, 2017

Workshop: April 16, 2019

Biocompatibility Chapters

- The Biocompatibility Expert Panel was established to modernize the following:
- <87> Biological Reactivity, In Vitro
- <88> Biological Reactivity, In Vivo
- <1031> The Biocompatibility of Materials Used in Drug Containers, Medical Devices and Implants
- <1184> Sensitization Testing

Biocompatibility Revision Objectives

- Objectives of the Expert Panel:
  - **REDUCE** the amount of redundant testing of existing components/systems and limit the testing of new components/systems to in vitro biocompatibility testing
  - **REFINE** the type of testing performed to align with the potential risk
  - **REPLACE** in vivo testing with a risk based QbD approach based on the knowledge of the component/system

Biocompatibility Workshop 2016 – User input

- Scope of chapters should be clarified with respect to device types
- Metal materials should not be ignored
- Risk-based testing approaches should be incorporated into <87> and <88>
- A decision tree for application of <87>,<88> should be considered
- Testing materials of construction to a targeted application should be considered
- Consideration should be given to the use of test results from “equivalent or better” tests
- Reduction of animal testing should be considered
- Definition of “Medical Grade” should be considered

Biocompatibility Revision <1031>

- (OLD) USP<1031> Biocompatibility Decision Tree

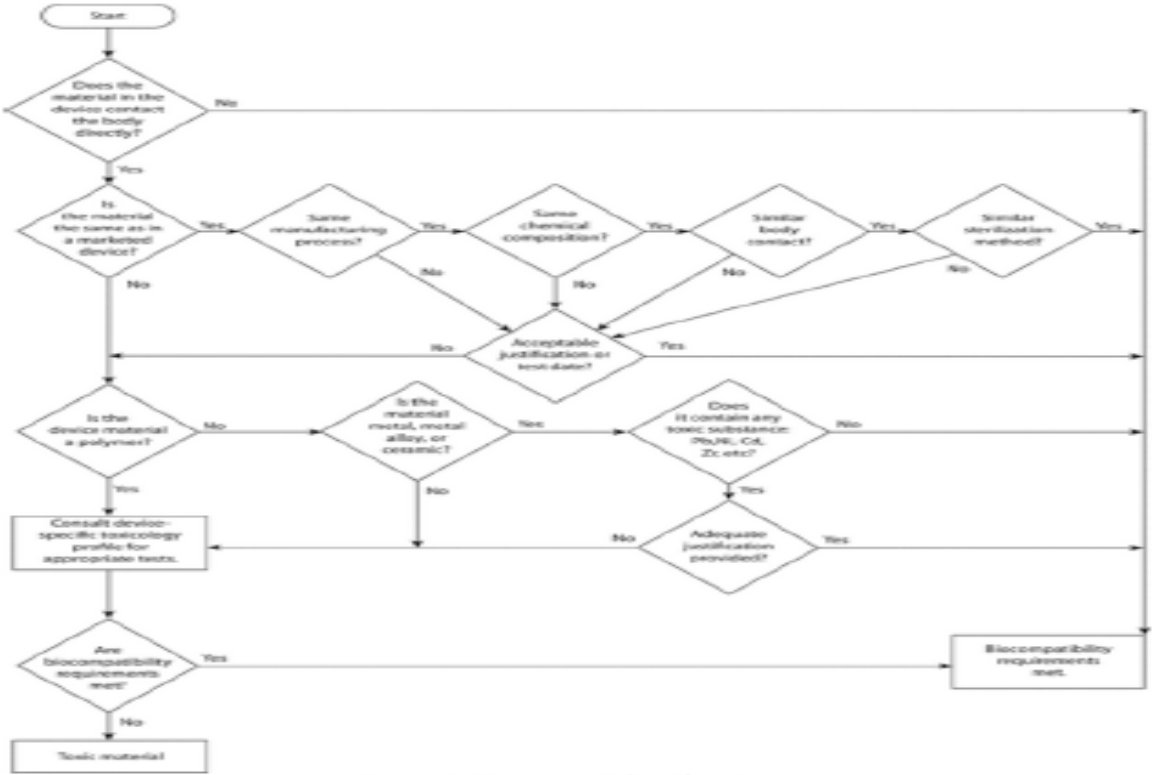
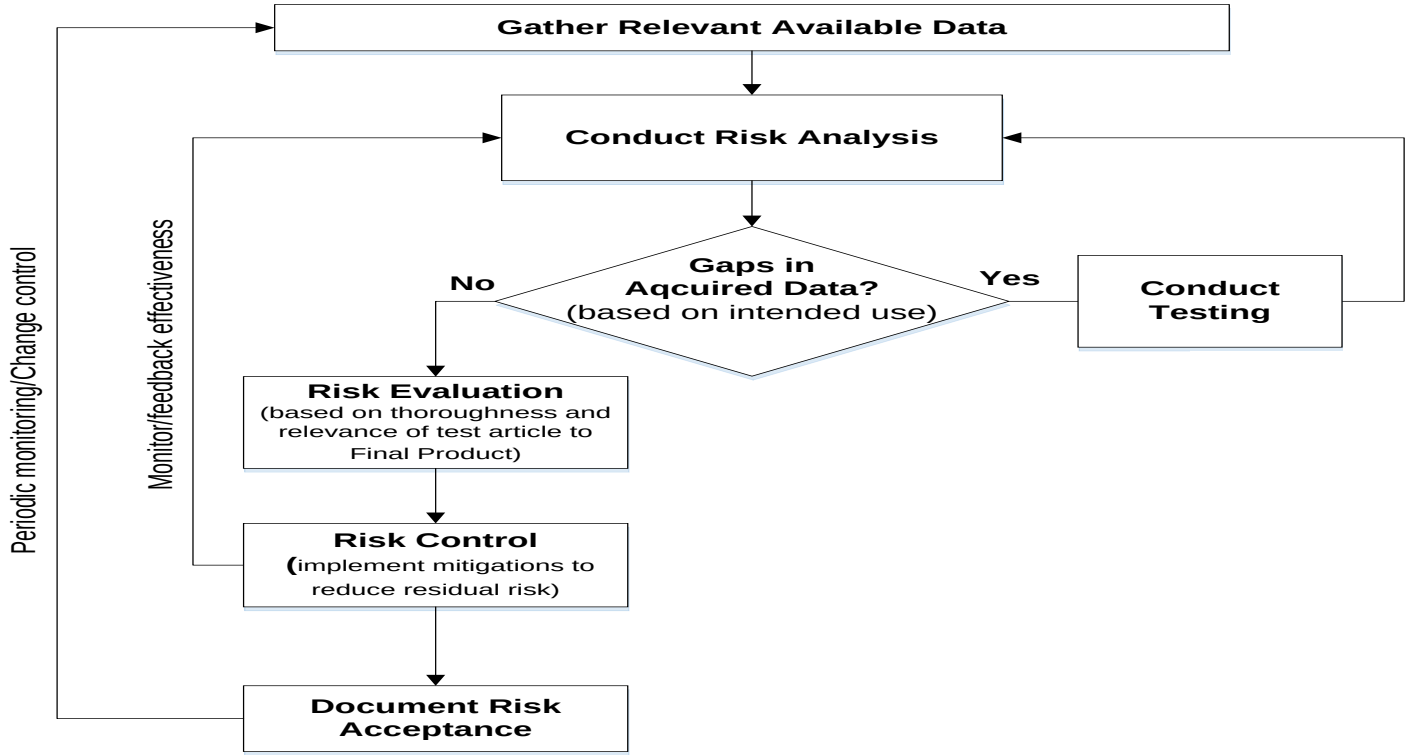


Figure 1. Biocompatibility flowchart.

Biocompatibility Revision <1031>

- (NEW) USP<1031> Biocompatibility Evaluation Process



Biocompatibility Revision Process

- Chapters transferred to Packaging, Storage and Distribution Expert Committee in 2014
- Expert Panel formed late in 2014
- Initial face to face meeting of panel in 2014
- Expert Panel continued into a new Expert Committee cycle (2015)
- Various Working Groups formed (Chemical Characterization; Biological Testing)
- Workshop held in 2016
- Regular meetings of Expert Panel in 2017 and 2018
- Targeting revision publication in PF in 2019

Questions

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Thank You

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