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INTRODUCTION TO USP <381> ELASTOMERIC COMPONENTS USED IN INJECTABLE PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS

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USP <381>, A Whole New Ball-game?

⟨381⟩ Elastomeric Closures for Injections, USP 40 page 326:

The Packaging and Distribution Expert Committee is proposing the following revisions which will update and expand the scope of the current chapter.

- **In-Process Revision: <381> ELASTOMERIC COMPONENTS USED IN INJECTABLE PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS.**
- **In-Process Revision: <1381> ELASTOMERIC EVALUATION OF ELASTOMERIC COMPONENTS USED IN PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS.**
- **In-Process Revision: ⟨382⟩ ELASTOMERIC CLOSURE FUNCTIONALITY IN INJECTABLE PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS.**
- **In-Process Revision: ⟨1382⟩ ASSESSMENT OF ELASTOMERIC CLOSURE FUNCTIONALITY IN INJECTABLE PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS.**

Modifications to USP <381> (1)

Listed below are the key changes being proposed:

1.Change the title to “Elastomeric Components Used in Injectable Pharmaceutical Packaging/Delivery Systems”.

2.Emphasize the baseline requirements for the **selection** of thermoset and thermoplastic elastomeric components.

3.Expand the scope to include all elastomeric components used in an injection packaging system. 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.

4.Delete the *Heavy Metals* ⟨*231*⟩ testing and replace with a modern method for extractable element determination.

Modifications to USP <381> (2)

5. Move functionality tests and assessment to new chapters.

    a. Functionality tests appear in Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems ⟨382⟩.
    b. Baseline information for the assessment is provided in Assessment of Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems ⟨1382⟩.

6. Develop a new informational chapter, Elastomeric Evaluation of Elastomeric Components Used in Pharmaceutical Packaging/Delivery Systems ⟨1381⟩, that will support the revised <381> by:

    a. Describing elastomeric components and their materials of construction for use in pharmaceutical packaging systems
    b. Providing a high-level introduction to elastomer chemistry, manufacturing technology, and the post processing of components
    c. Explaining basic functional characteristics of components
    d. Discussing identification testing

Contents of the Proposed <381> Chapter

1. **INTRODUCTION**
2. **SCOPE**
3. SPECIFICATIONS
   - 3.1 **Biological Reactivity***
   - 3.2 Physicochemical
   - 3.3 **Extractable Elements**
4. TEST METHODS
   - 4.1 **Biological Reactivity***
   - 4.2 Physicochemical
   - 4.3 Appearance (Turbidity/Opalescence)
   - 4.4 Color
   - 4.5 Acidity or Alkalinity
   - 4.6 Absorbance
   - 4.7 Reducing Substances
   - 4.8 Volatile Sulfides
   - 4.9 Ammonium
   - 4.10 **Extractable Elements**

Bolded titles indicate sections which were significantly changed or are new.

* Changes to the Biological Reactivity sections are largely cosmetic and not substantial.

A Brief Introduction to <381> (1)

1. Every elastomeric component used in a pharmaceutical packaging/delivery system should be proven safe and compatible for its intended use.
2. The chapter provides baseline requirements for the selection of elastomeric components to be further qualified for use in a given system.
3. The chemical testing prescribed is orthogonal:
   - the physicochemical tests provide a general overview of extracted chemicals,
   - the extractable elements test provides a quantitative assessment of potential elements of concern,
   - Because chemical testing alone may not be adequate, it is augmented by establishing biological reactivity

A Brief Introduction to <381> (2)

4. 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⟩.

The Scope of <381> (1)

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.

2. Elastomeric components can be either thermoset or thermoplastic.

3. Tests are always conducted on the components after surface modifications.
   - chlorinated surface treatments,
   - fluoropolymer coatings and films,
   - cross-linked polydimethylsiloxane,
   - polydimethylsiloxane that has been applied to the component surface as a lubricant

The Scope of <381> (2)

4. Baseline testing (biological reactivity, physicochemical, and extractable elements) is to be performed on the finished components after completion of all manufacturing and processing (e.g., molding conditions, sterilization, etc.).

5. The tested components need to be representative of the final components as intended for use in a packaging or delivery system.

What is outside the Scope of <381>

Elastomer evaluation requirements that are beyond the scope of this chapter:

- Verification of elastomer interactions with the packaged drug product
- Identification and safety qualification of component leachables found in a packaged product
- Verification of packaged product component functionality under actual storage and use conditions
- Specific test conditions for performing all relevant functionality studies

Identification tests are also beyond the scope of this chapter.

An Important Distinction; Type I vs Type II

Current Text: Type I closures are those used for aqueous preparations. Type II closures are typically intended for non-aqueous preparations and are those which, having properties optimized for special uses, may not meet all requirements listed for Type I closures because of physical configuration, material of construction, or both.

All elastomeric closures suitable for use with injectable preparations must comply with either Type I or Type II test limits. However, this specification is not intended to serve as the sole evaluation criteria for the selection of such closures.

Proposed Text: Type I components have stricter physicochemical test limits than Type II components. If a component fails to meet one or more of the Type I requirements, but still meets the Type II requirements, the component is assigned a final classification of Type II. Meeting the specifications, or the designations of Type I and Type II, is not intended to serve as the sole criterion for the selection of the elastomeric component.

The Major Chemical Modification to <381>; Extractable Elements

Because the <231> Heavy Metals is being discontinued, a new approach, based on recent (more rigorous) expectations around material characterization and modern analytical capabilities, for dealing with extracted metals and other relevant elements was required.

Major Changes:

1. A new extraction and analysis methodology was established based on extensive laboratory investigations,
2. Specifications were replaced with “report as found” requirements.

Extractable Elements - Extraction

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 (HNO3), 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.

Extractable Elements - Analysis

Analysis: 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.

Method 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.

Extractable Elements - Reporting

Test Results: 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.

Method Suitability (Extraction recovery): Refer to *Elemental Impurities—Procedures ⟨233⟩* for system suitability requirements.

Key User Questions Concerning <381>

1. **What were they thinking?**
2. **How do I use these chapters?**

Answers provided in:

<1381> ELASTOMERIC EVALUATION OF ELASTOMERIC COMPONENTS USED IN PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS

The Purpose of <1381>

The new chapter:

1. Describes elastomeric components and their materials of construction for use in pharmaceutical packaging systems
2. Provides a high-level introduction to elastomer chemistry, manufacturing technology, and the post processing of components
3. Explains basic functional characteristics of components
4. Designates baseline requirements
5. Discusses identification testing

Elastomeric Components: Compounds of Concern (Table 4)

Compound of Concern	Source	Concern	Comment
Latex	Associated with compounds containing dry natural rubber or derivatives	Allergic reaction	—
Materials of animal origin	Stearic acid salts and esters used as slip agents	Transmissible spongiform encephalopathies (TSEs) including bovine spongiform encephalopathy (BSE)	Equivalent materials from vegetable origin are not associated with BSE/TSE risks.
MBT (2-mercapto-benzothiazole) and derivatives	Associated with cure system	Carcinogenic	—
Phthalates: [bis(2-ethylhexyl) phthalate (DEHP), diisononyl phthalate (DINP), diisodecyl phthalate (DIDP)]	Used as a plasticizer in polymers used in TPEs	Toxicity	—
PNAs (polynuclear aromatic compounds)	Associated with carbon black (colorant)	Carcinogenic	The PNA content of carbon black depends on its production process.

Key Points in <1381>, Section 6.1, Test Requirements and Responsibilities (1)

- Elastomeric closures should conform both when they are shipped by the closure supplier to the injectable product manufacturer (the end user) and in their final state, ready for use by the end user.
- For elastomeric closures processed by the supplier before distribution to the end user, the supplier should demonstrate compendial conformance of closures exposed to such processing and/or sterilization steps.
- If elastomeric closures are subsequently processed or sterilized by the end user, the end user is responsible for demonstrating the continued conformance of the closures to compendial requirements after such processing and/or sterilization conditions (i.e., in their ready-to-use state).

Key Points in <1381>, Section 6.1, Test Requirements and Responsibilities (2)

- For closures that are normally lubricated with silicone prior to use, it is permissible to perform physicochemical testing on non-lubricated closures to avoid potential method interference and/or difficulties in interpreting test results.
- For closures supplied with other lubricious non-barrier coatings, all tests are to be performed using the coated closure.

Key Points in <1381>, Section 6.1, Test Requirements and Responsibilities (3)

- For closures coated or laminated with coatings intended to provide a barrier function, physicochemical compendial tests apply to the uncoated base elastomer, as well as to the coated closure.
  - Suppliers are responsible for demonstrating physicochemical compendial compliance of the coated closure, as well as of the uncoated closure, processed or treated in a manner simulating conditions typically followed by the supplier for such coated closures before shipment to the end user.
  - End users of coated closures are also responsible for demonstrating the continued physicochemical compendial conformance of the coated closure, processed or treated in a manner simulating conditions typically employed by the end user prior to use.

Key Points in <1381>, Section 6.1, Test Requirements and Responsibilities (4)

Identification Tests:

it is the responsibility of the closure supplier and the injectable product manufacturer (the end user) to verify the closure's elastomeric formulation and any coating or laminate material used according to suitable identification tests.

Tests to Use:

- specific gravity,
- percentage of ash analysis,
- sulfur content determination,
- Fourier transform infrared spectroscopy-attenuated total reflectance (FTIR-ATR) test,
- thin-layer chromatography of an extract,
- UV absorption spectrophotometry of an extract,
- infrared absorption spectrophotometry of a pyrolysate.

Key Points in <1381>, Function of the Various Physicochemical Tests (1)

Determination of turbidity (opalescence): a nonspecific test for all the extractable species in a rubber formulation that are not soluble in an aqueous solution. A high turbidity is the indication of a high extractable potential. Species promoting turbidity have numerous origins in a rubber formulation, including fatty acid derivatives, residues of curing systems, and oligomers from the elastomer.

Acidity/alkalinity: a nonspecific test indicative of the acidic, basic, or buffering power of the aqueous extractables from the rubber formulation. High values in the acidity/alkalinity test may need to be evaluated in conjunction with the specifics of a drug solvent vehicle and anticipated specification of the drug product for pH.

Key Points in <1381>, Function of the Various Physicochemical Tests (2)

Color: a nonspecific test indicative of the presence of extractable species in a rubber formulation that have the capacity of attributing color to an aqueous solution. Species that cause color may have several origins in a rubber formulation. Aqueous solutions are common in pharmaceutical packaging/delivery systems.

Absorbance: The UV spectrum of an aqueous extract from a rubber formulation is indicative of the unsaturated or aromatic character of the chemical species extracted. Unsaturated compounds in the extracts may originate from many raw materials and additives of a rubber formulation such as antioxidants, preservatives, and curing or dying agents.

Key Points in <1381>, Function of the Various Physicochemical Tests (3)

Reducing substances: a nonspecific test. Extracted species from a rubber formulation with potential reducing power may originate from most raw materials of a rubber formulation (polymer, curing system, preservatives, antioxidants, etc.).

Ammonium: a specific test for rubber formulations with nitrogen-containing raw materials. Ammonium ions can be generated during the curing process. Thiurams and thiazoles are examples of nitrogen-containing curing systems used.

Volatile sulfides: a specific test for rubber formulations containing sulfur. Sulfur and sulfur precursors are often used as components of curing systems for rubber.

Current Status, <381> and <1381>

- **In-Process Revision: <381> ELASTOMERIC COMPONENTS USED IN INJECTABLE PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS.**
- **In-Process Revision: <1381> ELASTOMERIC EVALUATION OF ELASTOMERIC COMPONENTS USED IN PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS.**

Both these documents were published in the Pharmacopeial Forum; 43(3), 2017.

Both these documents are currently in their review/revision stage (first cycle). The public review stage ended in September 30, 2017 and the comments received are currently under USP review. Although I expect the document will change based on the comments received, the changes will be more like “clarification and adjustment” and less like “remove and replace”.

Thank You!

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