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BRIEFING

〈1381〉 Assessment of Elastomeric Components Used in Injectable Pharmaceutical Product Packaging/Delivery Systems, *PF* 43(3) [May–June 2017]. The previous proposal for this chapter, published in *PF* 43(3) under a different title, *Elastomeric Evaluation of Elastomeric Components Used in Pharmaceutical Packaging/Delivery Systems* was canceled and an updated version is being proposed. The Packaging and Distribution Expert Committee is enacting this new general chapter to support the planned revisions to Elastomeric Closures for Injections 〈381〉, which are also proposed in this issue of *PF*. This new chapter:

1. Describes elastomeric components and their materials of construction for use in pharmaceutical product packaging/delivery systems.
2. Provides a high-level introduction to elastomer chemistry, manufacturing technology, and the post-processing of components.
3. Designates and expands on baseline requirements.
4. Discusses identification testing.
5. Describes requirements and responsibilities.
6. Provides a summary of required and recommended test methods.

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Add the following:

▲〈1381〉 ASSESSEMENT OF ELASTOMERIC COMPONENTS USED IN INJECTABLE PHARMACEUTICAL PRODUCT PACKAGING/DELIVERY SYSTEMS

1. INTRODUCTION

Risk to drug product quality may exist when elastomeric components come into direct or indirect contact with pharmaceutical products. Elastomeric components used in pharmaceutical packaging/delivery systems must be proven suitable for their intended use based on aspects of protection, compatibility, and performance.

Tests and specifications applicable to elastomeric components used in packaging/delivery systems for injectables are referenced in conjunction with *Injections and Implanted Drug Products* 〈1〉 .

Elastomeric Closures for Injections 〈381〉 presents a body of test procedures and acceptance criteria for elastomeric components employed in injectable product packaging/delivery systems. The biological reactivity tests and physicochemical tests provide baseline information on a component's suitability. The test methods and acceptance criteria are detailed in their description but lack an explanation as to their relevance to the composition of the elastomers. Due to the large and diverse nature of the pharmaceutical marketplace, it may not be intuitive to stakeholders as to the proper use and application of 〈381〉. Therefore, a primary purpose of this chapter is to communicate the key concepts that form the foundation of 〈381〉 and to establish and clarify its application and applicability.

Beyond the baseline requirements provided in 〈381〉, elastomers will need to be qualified for intended use commensurate with the level of risk to drug product quality. These evaluations would encompass studies for extractables and leachables. Recommendations for conducting these studies are found in *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems* 〈1663〉 and *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems* 〈1664〉 .

Finally, elastomeric component functional suitability as part of the finished product packaging/delivery system must be demonstrated. Relevant information is found in *Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems* 〈382〉 and *Assessment of Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems* 〈1382〉.

2. SCOPE

This chapter serves as a supplement to the elastomeric component baseline requirements in 〈381〉. This chapter seeks to 1) describe elastomeric components and their materials of construction for use in pharmaceutical packaging/delivery systems; 2) provide a high-level introduction to elastomer chemistry, manufacturing technology, and the post-processing of components; 3) designate and expand on baseline requirements; 4) discuss identification testing; 5) discuss test requirements and responsibilities; and 6) provide a summary of required and recommended test methods.

Elastomeric components utilized for injectable pharmaceutical products within the scope of this chapter include, but are not limited to, those used for vials and bottles (stoppers and cap liners), prefilled syringes (plungers, needle shields, and tip caps), cartridges (plungers and seal liners), flexible bags (injection ports), and blow-fill-seal containers (cap liners). Also within the scope are elastomeric components of systems or packages that are intended for transient product storage and/or delivery intended for specific pharmaceutical products (e.g., the elastomeric components of an infusion set or a single-use syringe included as part of a co-packaged combination product or linked by way of labeling for use with a specific pharmaceutical product). Components of similar systems intended for general product use are out of the scope of this chapter. All elastomeric components in direct or indirect contact with the pharmaceutical product are within the scope.

3. DESCRIPTION OF ELASTOMERIC COMPONENTS IN PACKAGING SYSTEMS

Certain components used in pharmaceutical packaging/delivery systems must have elastic properties for the system to function properly. Elastomers are a unique family of polymers with properties including the ability to recover from being stretched or deformed beyond their original state. This allows components to be flexible, maintain a seal, and be able to reseal after puncturing. In the following sections, typical elastomer materials, compositions, and physical attributes are summarized. Various compounding ingredients, including curing systems, are required to produce optimal elastomeric performance. In thermoset elastomers, the physical attributes will depend on polymer cross-linking, achieved during the vulcanization process. The cured polymer will produce a chemical reaction and by-products that will impact the chemical makeup of the elastomeric formulation. The compounding ingredients, reaction by-products, and post-processing effects, such as sterilization, will influence the outcome of the component's chemical characterization.

Given the complex nature of packaging systems and their manufacturing and development processes, multiple testing procedures are needed to establish their suitability for use with a specific pharmaceutical product. The logical manufacturing and development process for packaged drug products—starting with the packaging system's materials of construction, continuing with the packaging system itself, and ending with the packaged drug product—forms the basis of the following three-stage approach to packaging/delivery systems qualification:

- **Component screening:** The baseline requirements for biological reactivity and physicochemical testing described in this chapter.
- **Controlled extraction studies:** Studies as described in 〈1663〉 to create extractables profile(s) of particular pharmaceutical packaging/delivery systems, packaging components, or materials of construction.
- **Pharmaceutical product assessment:** 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〉).

Assessment of elastomeric component functionality is performed within the context of the intended product packaging system. (For additional information, see 〈382〉 and 〈1382〉.)

4. ELASTOMERIC COMPONENTS—MATERIALS OF CONSTRUCTION

4.1 Thermoset and Thermoplastic Elastomeric Components

4.1.1 THERMOSET COMPOSITION (TYPICAL)

A thermoset elastomer is a polymer system in which the elastomeric properties are derived from chemical cross-linking that is irreversible. This cross-linking is created between a curative (cross-linking agent) and a polymer (elastomer) when the materials are subjected to heat and pressure. In thermoset elastomers de-cross-linking is not possible without destruction of the material. Other ingredients that typically are part of the thermoset rubber formulation are shown in *Table 1*.

Table 1. Thermoset Elastomeric Components: Typical Rubber Ingredients

Ingredient	Function
Polymers (elastomers)	Provide elastic properties after curing
Curatives (cross-linking agents)	Form cross-links to provide elasticity and strength
Fillers/extenders	Impart hardness, modulus/deformation, strength, reinforcement
Processing aids	Impart flexibility, fatigue resistance, mold flow
Antioxidants/antiozonants	Provide stabilization, i.e., protection against UV, oxygen, ozone
Plasticizers	Aid processing by providing flexibility, hardness
Dyes/coloring materials	Impart color

4.1.2 POLYMER TYPES AND ATTRIBUTES

Typical polymers used in elastomeric components for packaging/delivery systems for injections, along with characteristic physical attributes and component examples, are shown in *Table 2*.

Table 2. Typical Elastomers for Thermoset Elastomeric Components

Elastomer	Physical Attributes	Typical Components
Isobutylene/isoprene copolymer (butyl) (IIR); Brominated isobutylene isoprene (BIIR); Chlorinated isobutylene isoprene (CIIR); Brominated isobutylene para methylstyrene terpolymer (BIMS)	Gas barrier; Aging resistance	Stoppers, plungers, lined seals
Natural polyisoprene (NR);[a] Synthetic polyisoprene (IR)	Good coring and reseal behavior; Abrasion resistance; Higher gas permeability	Stoppers, plungers for single-use syringes, septa, needle shields, tip caps
Styrene butadiene rubber (SBR)	Higher gas permeability	Needle shields, tip caps
Ethylene propylene diene monomer rubber (EPDM)	Chemical resistance; Aging resistance	O-rings
Acrylonitrile butadiene rubber (nitrile) (NBR)	Chemical resistance (e.g., mineral oils)	Stoppers, plungers, gaskets, O-rings
Polychloroprene (neoprene) (CR); Epichlorohydrin (ECO/CO)	Chemical resistance	O-rings, gaskets
Polysiloxane (VMQ,PMQ,PVMQ)	Heat resistance	Stoppers, plungers, tubing, gaskets, O-rings

[a] NR must be labeled appropriately per CFR 21:*www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070929.pdf*

4.2 Thermoplastic Composition (Typical)

A thermoplastic elastomer (TPE) is a polymer system with a different nature. Elasticity is incorporated in a different way (see below), and, more importantly, thermoplastic elastomers have a thermal behavior that is comparable to plastics. Thermoplastic elastomers when heated lose their elasticity and become deformable like a plastic. Cooled down again, they regain their elasticity. This cycle can be repeated. Unlike thermoset elastomers, the elastic behavior of thermoplastic elastomers is reversible.

TPEs, like thermoset elastomers, owe their elasticity to a polymer network that has a certain degree of structure. However, for thermoset elastomers, the structure occurs through chemical cross-linking with covalent bonding, whereas TPEs use a different mechanism. For example, in styrenic block copolymers, hard polystyrene blocks serve as physical cross-links in a three-dimensional network of softer chains of a different polymer such as polyisoprene or ethylene/butylene copolymer.

In a different class of thermoplastic rubber named thermoplastic vulcanizates, a hard plastic phase and a soft elastomeric phase are present. The hard phase can use material such as polyolefin, while the soft phase is a thermoset rubber phase with a high degree of chemical cross-linking. The curing of the rubber phase is done in a process known as "dynamic vulcanization". During this process, chemical cross-linking takes place during the mixing of the elastomer with the vulcanization system and other ingredients, such as polyolefin. Additional ingredients that may be present in TPEs are fillers, antioxidants, antiozonants, and plasticizers.

4.3 Surface Coatings and Treatments

After manufacturing, elastomeric components may not fulfill all the properties that are required for their application. An additional coating or surface treatment may be necessary. The most common surface treatment is siliconization, which is used to overcome the inherent tackiness of components and to provide lubricity. Tackiness will negatively impact component processing (e.g., sterilization, machinability at filling) and may introduce permanent component deformation. Chlorination is a less frequently used surface treatment. In this treatment, the component surface is exposed to chlorine, resulting in non-tacky and somewhat lubricious parts. In order to provide non-tackiness and lubricity, but at the same time reduce extractable levels (i.e., barrier effect), components may be covered, on part of their surface or on their entire surface, with lubricious barrier materials that are applied either by coating or by film lamination. Polymeric coatings and surface treatments are shown in *Table 3*.

Table 3. Surface Coatings, Films, and Treatments for Elastomeric Components

Coating or Treatment	Physicochemical Effect	Typical Components
Silicone: silicone oil or emulsion, cross-linked silicone oil	Non-tackiness, lubricity	All components
Chlorination	Non-tackiness	Small, thin-walled components
Parylene	Barrier, non-tackiness, lubricity	Stoppers, plungers
Fluoropolymer coating	Barrier, non-tackiness, lubricity	Stoppers, plungers
Fluoropolymer lamination [ethylene tetrafluoroethylene (ETFE), fluorinated ethylene propylene (FEP)]	Barrier, non-tackiness, lubricity	Stoppers, plungers

4.4 Compounds of Concern

Elastomeric components are made of various materials of construction. Some of these materials may raise quality or safety concerns. It is recommended that the user evaluate the presence of such materials in components, either by direct use or by use in the manufacturing processes of the materials of construction. An overview of such materials, together with the associated concerns, is shown in *Table 4*.

Table 4. Elastomeric Components: Compounds of Concern

Compound of Concern	Source	Risk
Latex	Associated with compounds containing dry natural rubber or derivatives	Associated with anaphylaxis in individuals allergic to natural rubber latex proteins
Materials of animal origin	Fatty acids and their metal salts used as processing aids or slip agents in polymers	Potential sources of transmissible spongiform encephalopathies (TSEs) in pharmaceutical products before manufacturing
2-Mercapto-benzothiazole (MBT)	Vulcanization accelerator used in the production of rubber	Potential carcinogen
N-nitrosamines	Associated with the use of certain secondary amines in the cure system	Potential carcinogens
Phthalates [e.g., orthophthalates such as bis(2-ethylhexyl) phthalate (DEHP)]	Used as a plasticizer or softener in polymers	Associated with developmental, reproductive, and endocrine health effects
Polycyclic aromatic hydrocarbons (PAHs)	Associated with carbon black (colorant or reinforcing agent)	Potential carcinogens

Latex: Contact with elastomers or packaging/delivery systems containing natural rubber latex, dry natural rubber, or synthetic derivatives of natural rubber latex has been associated with allergic reactions, including anaphylaxis, in individuals allergic to natural rubber latex proteins. There is no one threshold level of exposure that can be considered safe; factors include the exposure route and the immune status of the individual. Information regarding suitable labeling can be found in the FDA Guidance for Industry *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2, 2014).

Materials of animal origin: Pharmaceutical products having raw materials derived from animal sources have a risk of transmissible spongiform encephalopathy (TSEs). Cattle infected with bovine spongiform encephalopathy (BSE) can transmit to humans in the form of Creutzfeldt-Jakob disease (CJD) and the variant (vCJD). This disorder is caused by a prion (protein) that causes the brain to be porous or spongy. Manufacturers should use materials from “non TSE-relevant animal species” or non-animal origin where possible to minimize the risk. When tallow is derived from TSE-relevant starting material, a rigorous manufacturing process should eliminate or reduce or any TSE risk.

2-Mercapto-benzothiazole (MBT): 2-Mercapto-benzothiazole (MBT) is used as a non-volatile vulcanization accelerator in the production of rubber. MBT reacts with zinc oxide and sulfur to cross-link rubber. It can be bonded in the vulcanizate or may be present as a substance incorporated in the polymer. The amount of free MBT in the final product will be dependent on the vulcanization conditions.

***N*-nitrosamines:** *N*-nitrosamines are organic nitrogen-containing compounds that, under certain reaction conditions, are yielded as reaction products of nitrosating agents (e.g., certain oxides of nitrogen and nitrosatable secondary amines). Most secondary amines, but not all, may lead to carcinogens. There are 6 *N*-nitrosamines of concern that are listed in *Orally Inhaled and Nasal Drug Products* 〈1664.1〉.

Phthalates: Phthalates are a group of chemicals (orthophthalates and terephthalates) used in many polymer products to make plastics more flexible or as polymer-solvating agents. Phthalate esters are prepared by the esterification of phthalic anhydride with alcohols (C1/C2-C13). They are broadly divided into two distinct main groups with very different applications, toxicological properties, classification, and legal requirements. Orthophthalates used in food packaging are being reviewed by the FDA due to concerns for reproductive and endocrine health effects. More information can be found in the US *Federal Register* proposed rules (Vol. 83 No. 220, November 14, 2018).

Polycyclic aromatic hydrocarbons: Polycyclic aromatic hydrocarbons (PAHs), also known as polynuclear aromatic hydrocarbons (PNAs), are organic compounds with two or more fused aromatic (benzene) rings and are found as contaminants in oils used in elastomeric formulations and in carbon black used as a colorant or reinforcing agent. Carbon black is a material produced by the incomplete combustion of heavy petroleum products (i.e., ethylene cracking or coal tar). There are different types of carbon black and those with lower surface-area-to-volume ratios will have fewer PAHs absorb onto the surface during the manufacturing process. The PAHs are firmly bound to the carbon black surface under normal handling and use. They can only be extracted from the surface of the carbon black under rigorous laboratory conditions with strong solvents at elevated temperatures. There are 17 PAHs of concern that are listed in *Orally Inhaled and Nasal Drug Products* 〈1664.1〉.

5. ELASTOMERIC COMPONENTS—MANUFACTURING TECHNOLOGY AND STERILIZATION PROCEDURES

5.1 Generic Manufacturing

5.1.1 THERMOSET ELASTOMERS

The overall process of manufacturing thermoset elastomers consists of a rubber compound held in a heated mold under pressure. During this process, the elastomer is “cured” by undergoing a chemical reaction resulting in an elastic polymer network. The basic steps in manufacturing such components for pharmaceutical use are as follows:

- **Weighing of rubber ingredients:** Portions of the various ingredients are weighed according to instructions that reflect the rubber compound formulation.
- **Mixing:** The weighed portions of the various materials of construction are homogeneously mixed.
- **Preforming:** The mixed rubber is brought into a physical shape that allows easy handling in the subsequent step.
- **Molding:** Elasticity is introduced and the components are shaped by the curing reaction. The products are not individually shaped but are attached to a web.
- **Die-trimming:** The components are separated from the web by die-trimming.
- **Washing, lubrication, and drying:** The components are brought into their final state of microbiological and particulate cleanliness before packing. Lubrication, most often in the form of siliconization, typically is combined with washing and drying.
- **Packing:** The components are packed in suitable packaging material.

5.1.2 THERMOPLASTIC ELASTOMERS

TPEs are processed like plastic materials. They are injected, as a hot mixture, into a cooled mold. Unlike thermoset elastomers, a thermoplastic elastomer does not involve curing agents during molding. TPE components are not attached to a web, so they do not need die-trimming. Co-injection of a plastic material with a TPE is a way to create a two-material component, where the TPE part has a sealing and/or resealing function.

5.2 Sterilization Procedures

Elastomeric components for injections undergo sterilization as individual components prior to the filling process and then may be sterilized a second time as part of an assembled packaging system after filling. Sterilization of an individual component may be done using ethylene oxide, ionizing radiation, or steam; method selection is dependent on the elastomeric formulation. For example, depending on the irradiation dose, some elastomeric formulations may not withstand ionizing radiation. Sterilization of the filled packaging system is usually done using steam. The desired outcome is a sterile component with no change to its critical parameters such as material chemical profile (extractables), functional performance, or drug product compatibility. For guidance on sterilization procedures, refer to the following suite of chapters:

Sterilization of Compendial Articles 〈1229〉, *Steam Sterilization by Direct Contact* 〈1229.1〉, *Gaseous Sterilization* 〈1229.7〉, and *Radiation Sterilization* 〈1229.10〉.

Ethylene oxide sterilization: Ethylene oxide (EtO) can be used to sterilize elastomeric components, but the method has the drawback of requiring an outgassing time period to allow the levels of residual compounds to fall below the regulatory limits. Most EtO sterilization processes involve three different stages, which are preconditioning, sterilization, and degassing. The preconditioning stage includes a dwell time, under controlled temperature and humidity,which may decrease the resistance of microorganisms to inactivation and reduce the sterilization cycle time. Sterilization is completed by the introduction of EtO gas followed by an aeration phase that removes residual EtO. The aeration phase also allows time for removal of the common EtO degradants, ethylene chlorohydrin and ethylene glycol, from the elastomer. The degassing time required depends on factors such as the composition and size of the elastomeric part.

Ionizing radiation sterilization: Ionizing radiation can use either electron beam (e-beam) or gamma radiation. Cobalt 60 is a frequently used source of gamma rays, which are very penetrating. An e-beam produces accelerated electrons, which do not have the ability to penetrate materials to the same depth achieved by gamma rays. The energy provided by these two methods is sufficient to deliver a sterilizing dose but is also capable of exciting and dissociating polymer bonds. The free radicals produced within polymer structures initiate a series of complex chemical reactions (e.g., chain scission or cross-linking) that may continue for a period of time after irradiation is completed. Inhibitors and stabilizers can be added to polymer formulations and are designed either to absorb energy or react with the free radicals. Even so, not all elastomeric formulations are deemed to be suitable for radiation sterilization.

Steam sterilization: Steam sterilization is typically performed in an autoclave under saturated steam conditions. Commonly used cycles are 121°–122° for 30–60 min. The components are dried following sterilization, not only to remove surface water but also to remove residual moisture that has entered the matrix of the elastomer. Drying procedures need to be optimized based on a number of factors including the length of the sterilization cycle, the elastomeric formulation, and the elastomer size and shape. Particular care should be taken when the elastomeric components are to be used to seal a lyophilized or powder-filled product, as residual moisture in the component can migrate into the formulation over time.

6. IDENTIFICATION TESTS

Components are made of a wide variety of elastomeric materials and optional polymeric coatings. For this reason, it is beyond the scope of 〈381〉 to specify identification tests that encompass all possible component presentations. However, it is the responsibility of the component supplier and the drug product manufacturer to verify the component’s elastomeric formulation and any coating or laminate material used according to suitable identification tests. Examples of some of the analytical test methodologies that may be used include specific gravity, percentage of ash analysis, sulfur content determination, Fourier-transform infrared spectroscopy–attenuated total reflectance (FTIR–ATR) test, chromatography of an extract, UV absorption spectrophotometry of an extract, or infrared absorption spectrophotometry of a pyrolysate.

7. TEST REQUIREMENTS AND RESPONSIBILITIES

Elastomeric closures provided by a supplier to a drug product manufacturer may demonstrate compliance with specific (e.g., biological and/or physicochemical) specifications as required by the drug product manufacturer in accordance with requirements established by the manufacturer for storage and/or delivery of a unique drug product. Processing such as sterilization may be performed on finished components by the supplier prior to delivery to the drug product manufacturer, or by the drug product manufacturer before use, as agreed upon by both the supplier and the drug product manufacturer.

For elastomeric closures that are subsequently processed or sterilized by the drug product manufacturer after receipt from a supplier, the drug product manufacturer is responsible for ensuring that the closures are compliant with appropriate specifications required for storage and/or delivery of a unique drug product after the application of such processing and/or sterilization conditions (i.e., in their ready-to-use state). This is of particular importance if closures are processed under conditions that may impact the biological, physicochemical, or functionality characteristics of the closure.

8. SUMMARY OF 〈381〉 PHYSICOCHEMICAL TESTS

8.1 Test Samples

Elastomeric components are comprised of multiple materials that have unique attributes for each configuration, application, and change resulting from any treatment that occurs after formation (post-processing). This can be a challenge for establishing elastomeric baselines due to multiple combinations of materials and post-processing treatments by the component manufacturer and the drug product manufacturer.

Test samples described in 〈381〉 are to mimic the finished, processed component intended for the final product and its packaging/delivery system. It is the drug product manufacturer who is ultimately responsible for the quality and safety of the finished pharmaceutical product. Therefore, the drug product manufacturer is responsible for ensuring component conformance to the baseline requirements of 〈381〉.

8.2 Physicochemical Tests

Appearance (turbidity/opalescence): This is 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.

Color: This is 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.

Acidity or alkalinity: This is 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.

Absorbance: This UV spectrum test 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 and curing or dying agents.

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

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

Ammonium: This test is specific 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.

8.3 Biocompatibility Tests

In vitro biocompatibility testing is performed as described in general test chapter *Biological Reactivity Tests, In Vitro* 〈87〉. Materials that do not meet the requirements of the in vitro test may require performance of appropriate in vivo tests according to the procedures set forth in the general test chapter *Biological Reactivity Tests, In Vivo* 〈88〉.

8.4 Extractable Elements Method

Knowledge of the potential extractable elements present in an elastomeric component is important in establishing the component's suitability. Knowledge of the elements that are likely to be present and the concentrations at which they may be observed provides information to determine potential product quality risk. Elastomeric components can vary widely in terms of their intentionally and unintentionally added elements and their potential use. Because of this, it is challenging to provide universally effective and efficient tests methodologies, lists of target elements, and reporting requirements. It is the material user’s responsibility to evaluate the need for extractable elements testing and, if such testing is necessary, to establish and justify the means by which testing is accomplished, taking into account target elements, extraction conditions, extract analysis, and reporting requirements.

Target elements: Relevant elements that should be tested for include those that have been intentionally added to the elastomer (e.g. zinc) and those of toxicological concern. Some of the relevant elements for elastomeric components for injections include antimony, arsenic, cadmium, cobalt, copper, lead, lithium, mercury, nickel, vanadium, and zinc.

Elastomeric components used in injectable packaging systems do not dissolve under the conditions of use. Rather, substances derived from the component accumulate in the packaged articles by the process of leaching (extraction). Thus, the appropriate and relevant sample-preparation process for assessing elements in an elastomeric component is extraction, as opposed to complete digestion. A screen for relevant extractable elements can be achieved based on a rigorous extraction method to determine the potential for elements to extract. The results of the screening study can then provide the basis for targeting elements for simulated or intended use studies. Screening is an important first step to ensure proper elements and sensitivities are realized. Trace elemental analysis can be challenging and the extraction method is critical. The following method has been verified based on recovery of critical elements related to elastomer components.

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.

Analysis: 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 to obtain a concentration of 0.05 µg/g.

Analysis and reporting threshold: Instrumentation and methods are those specified in *Elemental Impurities—Procedures* 〈233〉 and include an inductively coupled plasma–atomic emission spectrometer and an inductively coupled plasma–mass spectrometer (see *Plasma Spectrochemistry* 〈730〉), as directed. The reporting threshold is 0.05 µg/g converted to µg/component. Calculate and report results based on the original sample size. [Note—Appropriate measures must be taken to correct for matrix-induced interferences (e.g., argon chloride interference with arsenic determinations).]

Calculations:

$$\text{percent recovery} = (d \times 100)/s$$

d = amount of element detected (µg)

s = amount of element spiked (µg)

$$\text{µg/g component} = (a \times t)/w$$

a = concentration of extract (µg/mL)

t = total extract, corrected for average blank (mL)

w = sample weight (g)

$$\text{µg/component} = c \times s$$

c = element concentration in extract (µg/g)

s = total weight of component (g)

▲ (USP 1-Dec-2020)

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
<1381> ASSESSMENT OF ELASTOMERIC COMPONENT USED IN INJECTABLE PHARMACEUTICAL PRODUCT PACKAGING/DELIVERY SYSTEMS	Desmond G. Hunt Principal Scientific Liaison	GCPD2025 Packaging and Distribution
REFERENCE STANDARDS SUPPORT	RS Technical Services RSTECH@usp.org	GCPD2025 Packaging and Distribution

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