**BRIEFING**

**⟨1381⟩ Elastomeric Evaluation of Elastomeric Components Used in Pharmaceutical Packaging/Delivery Systems.** The Packaging and Distribution Expert Committee is proposing a new general chapter meant to support the planned revisions to *Elastomeric Closures for Injections* ⟨381⟩. This 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

A workshop, *Modernization of USP Packaging Standards for Glass and Elastomeric Components*, will take place June 19–20, 2017 at the USP Meetings Center in Rockville, Maryland, to discuss the proposals for three new chapters including this one, *Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems* ⟨382⟩, and *Assessment of Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems* ⟨1382⟩, as well as the revision proposals to ⟨381⟩. All four chapters appear in this issue of *PF*. See http://www.usp.org/meetings-courses/workshops/modernization-usp-packaging-standards-glass-and-elastomeric-components for more information about the workshop.

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***Add the following:***

# ⟨1381⟩ ELASTOMERIC EVALUATION OF ELASTOMERIC COMPONENTS USED IN

# PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS



## 1. INTRODUCTION

Risk to drug product quality and/or patient safety 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, performance, and safety.

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⟩ and in *The Biocompatibility of Materials Used in Drug Containers, Medical Devices, and Implants* ⟨1031⟩. The test procedures and requirements for elastomeric components are found in *Elastomeric Closures for Injections* ⟨381⟩.

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 and patient safety. 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⟩.

## 2. SCOPE

The scope of this chapter is to 1) describe elastomeric components and their materials of construction for use in pharmaceutical packaging systems; 2) provide a high-level introduction to elastomer chemistry, manufacturing technology, and the post processing of components; 3) explain basic functional characteristics of components; 4) designate baseline requirements; and 5) discuss identification testing.

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. Because it can be difficult to assess the elastomeric formulation, guidance on the responsibilities of the supplier and applicant are provided under *Test Procedures*.

## 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 development and manufacturing 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 systems qualification:

- **Component screening:** Baseline requirements consist of characterization of the elastomer's biological reactivity, physicochemical and functional properties, and extractable metals.
- **Controlled extraction (simulation) study:** Worst-case controlled extraction (simulation) study for applicants to determine the extent to which extractables may become probable leachables. (For additional information, see ⟨1663⟩.)
- **Pharmaceutical product assessment:** Actual-case measurement of confirmed leachables in the pharmaceutical product in the pharmaceutical 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 package system. For further information, refer to *Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems* ⟨382⟩ and *Assessment of Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems* ⟨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 polymer (elastomer) when the materials are subjected to heat and pressure. 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 |
|---|---|
| Polymer (elastomer) | Elastic properties after curing |
| Curatives | Form cross-links to provide elasticity and strength |
| Filler/Extender | Hardness, modulus/deformation, strength, reinforcement |
| Processing Aids | Flexibility, fatigue resistance, mold flow |
| Antioxidants/Antiozonants | Stabilization: protection against UV, oxygen, ozone |
| Plasticizer | Processing, flexibility, hardness |

#### 4.1.2 POLYMER TYPES AND ATTRIBUTES

Typical polymers used in elastomeric components for injections packaging/delivery systems, 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); Bromo isobutylene isoprene (BIIR); Chloro isobutylene isoprene (CIIR); Brominated isobutylene para methylstyrene terpolymer (BIMSM) | 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 (ECH) | Chemical resistance | O-rings, gaskets |
| Polysiloxane (Si) | Heat resistance | Stoppers, plungers, tubing, gaskets, O-rings |

[a] NR must be labeled appropriately per Code of Federal Regulations Title 21:http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=801.437.

### 4.1.3 THERMOPLASTIC COMPOSITION (TYPICAL)

Thermoplastic elastomers (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 chemical 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 like 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 that is 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, of which polyolefin is one. Additional ingredients that may be present in TPEs are fillers, antioxidants, antiozonants, and plasticizers.

### 4.1.4 SURFACE COATINGS AND TREATMENTS

After manufacturing, elastomeric components may not fulfill all 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 (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 (barrier effect), components may be provided 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 |

### 4.1.5 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 | 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 | — |
| *N*-nitrosamines | Associated with the use of certain secondary amines in the cure system | Carcinogenic | *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 carcinogenic *N*-nitrosamines. |
| Phthalates [bis(2- | Used as a | Toxicity | — |

| Compound of Concern | Source | Concern | Comment |
|---|---|---|---|
| ethylhexyl) phthalate (DEHP), diisononyl phthalate (DINP), diisodecyl phthalate (DIDP)] | plasticizer in polymers used in TPEs | | |
| PNAs (polynuclear aromatic compounds) | Associated with carbon black (colorant) | Carcinogenic | The PNA content of carbon black depends on its production process. |

## 5. ELASTOMERIC COMPONENTS—MANUFACTURING TECHNOLOGY AND STERILIZATION PROCEDURES

### 5.1 Generic Manufacturing Description

5.1.1 THERMOSET ELASTOMERS

The overall process 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 thermoset elastomeric 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, and so they do not need die-trimming. Co-injection of a plastic material with a TPE is another way to create a two-material component, where the TPE part has a sealing and/or resealing function.

### 5.1.3 STERILIZATION PROCEDURES

Elastomeric components for injections undergo sterilization as an individual component prior to the filling process and then may be sterilized a second time as an assembled packaging system, after filling. Sterilization of an individual component may be by ethylene oxide, ionizing radiation, or steam; method selection is dependent on the elastomeric formulation. For example, depending on the irradiation dose, not all elastomeric formulations can withstand ionizing radiation. Sterilization of the filled packaging system is usually by steam sterilization. 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 suite of chapters under *Sterilization of Compendial Articles* ⟨1229⟩, particularly *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, to allow microorganisms to grow. 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 lethal bioburden 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 closures 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 closures are to be used to seal a lyophilized or powdered-filled product, as residual moisture in the closure can migrate into the formulation over time.

## 6. TEST PROCEDURES

### 6.1 Test Requirements and Responsibilities

Elastomeric closures should conform to biological and physicochemical requirements, 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 those 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. Similarly, if elastomeric closures received by the end user are subsequently processed or sterilized, 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). This is especially important if closures must be exposed to processes or conditions that may significantly impact the biological, physicochemical, or functionality characteristics of the closure (e.g., sterilization procedures).

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.

For closures coated or laminated with coatings intended to provide a barrier function (e.g., PTFE or lacquer coatings), physicochemical compendial tests apply to the uncoated base elastomer, as well as to the coated closure. In this case, 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. The uncoated closure subject to physicochemical tests should be similar to the corresponding coated closure in size and configuration. 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. In all cases, it is necessary to document all conditions of closure processing, pretreatment, sterilization, or lubrication when reporting test results. The responsibility for performing the required tests is shared by the supplier and end user in all cases except for closures with a barrier coating. In this case, the physicochemical tests to be performed on uncoated closures (base formula) are the responsibility of the supplier. The testing requirements and the responsibilities of the supplier and end user are summarized in *Table 5*.

**Table 5. Testing Requirements for Closures and the Responsibilities of the Supplier and End User**

| Closure Types (as supplied or used) | Test Requirements | |
|---|---|---|
| | Physicochemical Tests | Biological Tests |
| Closure with or without silicone coating | Tests are to be performed<br>Silicone use is optional<br>Responsibility: supplier and end user | |
| Closures with lubricious coating (non-barrier material; not silicone) | Tests are to be performed on coated closures<br>Responsibility: supplier and end user | |
| | Tests are to be performed on coated closures<br>Responsibility: supplier and end user | — |
| | AND: | OR: |
| | Tests are to be performed on uncoated closures (base formula) | Tests are to be performed on uncoated closures (base formula) and the laminate/coating material (report results separately) |
| Closures with barrier coating | Responsibility: supplier | Responsibility: supplier and end user |

### 6.1.1 PHYSICOCHEMICAL TESTS

Chapter ⟨381⟩ contains test methods and specifications that 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, the 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.

### 6.1.2 IDENTIFICATION TESTS

Closures 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 closure presentations. However, 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. 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, thin-layer chromatography of an extract, UV absorption spectrophotometry of an extract, or infrared absorption spectrophotometry of a pyrolysate.

### 6.1.3 TESTS PERFORMED ON AN AQUEOUS EXTRACT

**Determination of 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.

**Acidity/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.

**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.

**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.

**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 (polymer, curing system, preservatives, antioxidants, etc.).

**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.

**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.