BRIEFING

⟨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. 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 add a modern method for extractable element determination.
5. Omit functionality tests and assessment from the chapter and move them to new chapters appearing in this issue of *PF*.
    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 is meant to support the current chapter revision 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

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 these revision proposals and proposals for three new chapters including ⟨382⟩, ⟨1381⟩, and ⟨1382⟩. 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.

Additionally, minor editorial changes have been made to update the chapter to current *USP* style.

(GCPD: D. Hunt.)
Correspondence Number—C162377

Change to read:

⟨381⟩ ELASTOMERIC ~~CLOSURES FOR INJECTIONS~~ COMPONENTS USED IN INJECTABLE PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS.1S

(*USP41*)

Add the following:

4.9 Ammonium
4.10 Extractable Elements

▪1S (*USP41*)

Change to read:

~~INTRODUCTION~~

~~Elastomeric closures for containers used in the types of preparations defined in the general test chapter *Injections and Implanted Drug Products* ⟨1⟩ are made of materials obtained by vulcanization (cross-linking) polymerization, polyaddition, or polycondensation of macromolecular organic substances (elastomers). Closure formulations contain natural or synthetic elastomers and inorganic and organic additives to aid or control vulcanization, impart physical and chemical properties or color, or stabilize the closure formulation.~~

~~This chapter applies to closures used for long-term storage of preparations defined in the general test chapter *Packaging and Storage Requirements* ⟨659⟩*, Injection Packaging*. Such closures are typically used as part of a vial, bottle, or pre-fill syringe package system.~~

~~This chapter applies to closures formulated with natural or synthetic elastomeric substances. This chapter does not apply to closures made from silicone elastomer; however, it does apply to closures treated with silicone (e.g., Dimethicone, *NF*). When performing the tests in this chapter, it is not required that closures be treated with silicone, although there is no restriction prohibiting the use of siliconized closures.~~

~~This chapter also applies to closures coated with other lubricious materials (e.g., materials chemically or mechanically bonded to the closure) that are not intended to, and in fact do not provide, a barrier to the base elastomer. When performing the tests, closures with lubricious nonbarrier coatings are to be tested in their coated state.~~

~~The following comments relate solely to closures laminated or coated with materials intended to provide, or in fact function as, a barrier to the base elastomer (e.g., PTFE or lacquer coatings). It is not permissible to use a barrier material in an attempt to change a closure that does not meet compendial requirements to one that does conform. Therefore, all *Physicochemical Tests* apply to the base formula of such closures, as well as to the coated or laminated closure. To obtain *Physicochemical Tests* results, the tests are to be performed on uncoated or nonlaminated closures of the same elastomeric compound, as well as to the laminated or coated closure. The *Functionality Tests* apply to and are to be performed using the laminated or coated elastomeric closure. *Biological Tests* apply to the~~

lamination or coating material, as well as to the base formula. *Biological Tests* may be performed on the laminated or coated closure, or they may be performed on the laminate/coating material and the uncoated or nonlaminated closures of the same elastomeric compound. In the latter case, the results are to be reported separately. The base formula used for physicochemical or biological tests intended to support the compendial compliance of a barrier-coated closure should be similar to the corresponding coated closure in configuration and size.

For all *Nephelometry, Turbidimetry, and Visual Comparison* ⟨855⟩ tests performed on any closure type, it is important to document the closure being tested, including a full description of the elastomer, and any lubrication, coating, laminations, or treatments applied.

This chapter states test limits for Type I and Type II elastomeric closures. Type I closures are typically used for aqueous preparations. Type II closures are typically intended for nonaqueous 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. If a closure fails to meet one or more of the Type I test requirements, but still meets the Type II requirements for the test(s), the closure is assigned a final classification of Type II. 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.

It is appropriate to use this chapter when identifying elastomeric closures that might be acceptable for use with injectable preparations on the basis of their biological reactivity, their aqueous extract physicochemical properties, and their functionality.

The following closure evaluation requirements are beyond the scope of this chapter:

- The establishment of closure identification tests and specifications
- The verification of closure–product physicochemical compatibility
- The identification and safety determination of closure leachables found in the packaged product
- The verification of packaged product closure functionality under actual storage and use conditions

The manufacturer of the injectable product (the end user) must obtain from the closure supplier an assurance that the composition of the closure does not vary and that it is the same as that of the closure used during compatibility testing. When the supplier informs the end user of changes in the composition, compatibility testing must be repeated, totally or partly,

depending on the nature of the changes. Closures must be properly stored, cleaned for removal of environmental contaminants and endotoxins, and, for aseptic processes, sterilized prior to use in packaging injectable products.

CHARACTERISTICS

Elastomeric closures are translucent or opaque and have no characteristic color, the latter depending on the additives used. They are homogeneous and practically free from flash and adventitious materials (e.g., fibers, foreign particles, and waste rubber.)

IDENTIFICATION

Closures are made of a wide variety of elastomeric materials and optional polymeric coatings. For this reason, it is beyond the scope of this chapter 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 elastomeric formulation and any coating or laminate materials 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, FTIR-ATR test, thin-layer chromatography of an extract, UV absorption spectrophotometry of an extract, or IR absorption spectrophotometry of a pyrolysate.

TEST PROCEDURES

Elastomeric closures shall conform to biological, physicochemical, and functionality requirements both as they are shipped by the closure supplier to the injectable product manufacturer (the end user), and in their final ready-to-use state by the end user.

For those elastomeric closures processed by the supplier prior to distribution to the end user, the supplier shall 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 closures to compendial requirements subsequent to such processing and/or sterilization conditions (i.e., in their ready-to-use state). This is especially important if closures shall be exposed to processes or conditions that ma/y significantly impact the biological, physicochemical, or functionality characteristics of the closure (e.g., gamma irradiation).

For closures that are normally lubricated with silicone prior to use, it is permissible to perform physicochemical testing on nonlubricated closures, in

order to avoid potential method interference and/or difficulties in interpreting test results. For closures supplied with other lubricious nonbarrier 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 prior to 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 appropriate to document all conditions of closure processing, pretreatment, sterilization, or lubrication when reporting test results.

Table 1 summarizes the testing requirements of closures, and the responsibilities of the supplier and the end user.

Table 1

Closure Types (As Supplied or Used)	**Test Requirements**		
	Physicochemical Tests	**Functionality Tests**	**Biological Tests**
Closure with or without Silicone Coating	• Tests are to be performed.	• Tests are to be performed.	• Tests are to be performed.
	• Silicone use is optional.	• Silicone use is optional.	• Silicone use is optional.
	• Responsibility: supplier and end user	• Responsibility: supplier and end user	• Responsibility: supplier and end user
Closures with Lubricious Coating (Nonbarrier Material; Not	• Tests are to be performed on coated closures.	• Tests are to be performed on coated closures.	• Tests are to be performed on coated closures.
	• Responsibility: supplier and end user	• Responsibility: supplier and end user	• Responsibility: supplier and end user

Closure Types (As Supplied or Used)	Test Requirements		
	Physicochemical Tests	Functionality Tests	Biological Tests
Silicone)			
Closures with Barrier Coating	• Tests are to be performed on coated closures.	• Tests are to be performed on coated closures.	• Tests are to be performed on coated closures.
	• Responsibility: supplier and end user	• Responsibility: supplier and end user	OR:
	AND:		• Tests are to be performed on uncoated closures (base formula) and the laminate/coating material (report results separately).
	• Tests are to be performed on uncoated closures (base formula).		
	• Responsibility: supplier		• Responsibility: supplier and end user

BIOLOGICAL TESTS

Two stages of testing are indicated. The first stage is the performance of an in vitro test procedure as described in general test chapter *Biological Reactivity Tests, In Vitro* ⟨87⟩. Materials that do not meet the requirements of the in vitro test are subjected to the second stage of testing, which is the performance of the in vivo tests, *Systemic Injection Test and Intracutaneous Test*, according to the procedures set forth in the general test chapter *Biological Reactivity Tests, In Vivo* ⟨88⟩. Materials that meet the requirements of the in vitro test are not required to undergo in vivo testing.

Type I and Type II closures must both conform to the requirements of either the in vitro or the in vivo biological reactivity tests. [NOTE—Also see the general information chapter *The Biocompatibility of Material Used in Drug Containers, Medical Devices, and Implants* ⟨1031⟩.]

PHYSICOCHEMICAL TESTS

Preparation of Solution S

Place whole, uncut closures corresponding to a surface area of 100 ± 10 cm^2 into a suitable glass container. Cover the closures with 200 mL of Purified Water or Water for Injection. If it is not possible to achieve the prescribed closure surface area (100 ± 10 cm^2) using uncut closures, select the number of closures that will most closely approximate 100 cm^2, and adjust the volume of water used to the equivalent of 2 mL per each 1 cm^2 of actual closure surface area used. Boil for 5 minutes, and rinse five times with cold Purified Water or Water for Injection.

Place the washed closures into a Type I glass wide-necked flask (see *Containers—Glass* ⟨660⟩), add the same quantity of Purified Water or Water for Injection initially added to the closures, and weigh. Cover the mouth of the flask with a Type I glass beaker. Heat in an autoclave so that a temperature of 121 ± 2° is reached within 20 to 30 minutes, and maintain this temperature for 30 minutes. Cool to room temperature over a period of about 30 minutes. Add Purified Water or Water for Injection to bring it up to the original mass. Shake, and immediately decant and collect the solution. [NOTE—This solution must be shaken before being used in each of the tests.]

Preparation of Blank

Prepare a blank solution similarly, using 200 mL of Purified Water or Water for Injection omitting the closures.

APPEARANCE OF SOLUTION (TURBIDITY/OPALESCENCE AND COLOR)

Determination of Turbidity (Opalescence)

[NOTE—The determination of turbidity may be performed by visual comparison (*Procedure A*), or instrumentally using a suitable ratio turbidimeter (*Procedure B*). For a discussion of turbidimetry, see *Nephelometry, Turbidimetry, and Visual Comparison* ⟨855⟩. Instrumental assessment of clarity provides a more discriminatory test that does not depend on the visual acuity of the analyst.]

Hydrazine Sulfate Solution—Dissolve 1.0 g of hydrazine sulfate in water and dilute with water to 100.0 mL. Allow to stand for 4 to 6 hours.

Hexamethylenetetramine Solution—Dissolve 2.5 g of hexamethylenetetramine in 25.0 mL of water in a 100-mL glass-stoppered flask.

Opalescence Stock Suspension—Add 25.0 mL of *Hydrazine Sulfate Solution* to the *Hexamethylenetetramine Solution* in the flask. Mix, and allow to stand for 24 hours. This suspension is stable for 2 months, provided it is stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before use.

Opalescence Standard Suspension—Prepare a suspension by diluting 15.0 mL of the *Opalescence Stock Suspension* with water to 1000.0 mL. *Opalescence Standard Suspension* is stable for about 24 hours after preparation.

Reference Suspensions—Prepare according to *Table 2*. Mix and shake before use. [NOTE—Stabilized formazin suspensions that can be used to prepare stable, diluted turbidity standards are available commercially and may be used after comparison with the standards prepared as described.]

Table 2

	Reference Suspension A	**Reference Suspension B**	**Reference Suspension C**	**Reference Suspension D**
Standard of Opalescence	5.0 mL	10.0 mL	30.0 mL	50.0 mL
Water	95.0 mL	90.0 mL	70.0 mL	50.0 mL
Nephelometric Turbidity Units	3 NTU	6 NTU	18 NTU	30 NTU

Procedure A: Visual Comparison—Use identical test tubes made of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 25 mm. Fill one tube to a depth of 40 mm with *Solution S,* one tube to the same depth with water, and four others to the same depth with *Reference Suspensions A, B, C,* and *D*. Compare the solutions in diffuse daylight 5 minutes after preparation of the *Reference Suspensions,* viewing vertically against a black background. The light conditions shall be such that *Reference Suspension A* can be readily distinguished from water and that *Reference Suspension B* can be readily distinguished from *Reference Suspension A*.

REQUIREMENT—*Solution S* is not more opalescent than *Reference Suspension B* for Type I closures, and not more opalescent than *Reference Suspension C* for Type II closures. *Solution S* is considered clear if its clarity is the same as that of water when examined as described above, or if its opalescence is not more pronounced than that of *Reference Suspension A* (refer to *Table 3*).

Procedure B: Instrumental Comparison—Measure the turbidity of the *Reference Suspensions* in a suitable calibrated turbidimeter (see ⟨855⟩). The blank should be run and the results corrected for the blank. *Reference Suspensions A, B, C,* and *D* represent 3, 6, 18, and 30 Nephelometric Turbidity Units (NTU), respectively. Measure the turbidity of *Solution S* using the calibrated turbidimeter.

REQUIREMENT—The turbidity of *Solution S* is not greater than that for *Reference Suspension B* (6 NTU FTU) for Type I closures, and is not greater than that for *Reference Suspension C* (18 NTU FTU) for Type II closures (refer to *Table 3*).

Table 3

Comparison Method		
Opalescence Requirements	**Procedure A (Visual)**	**Procedure B (Instrumental)**
Type I closures	No more opalescent than Suspension B	No more than 6 NTU
Type II closures	No more opalescent than Suspension C	No more than 18 NTU

Determination of Color

Color Standard—Prepare a solution by diluting 3.0 mL of *Matching Fluid O* (see *Color and Achromicity* ⟨631⟩) with 97.0 mL of diluted hydrochloric acid.

Procedure—Use identical tubes made of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 25 mm. Fill one tube to a depth of 40 mm with *Solution S,* and the second with the *Color Standard*. Compare the liquids in diffuse daylight, viewing vertically against a white background.

Requirement—*Solution S* is not more intensely colored than the *Color Standard*.

Acidity or Alkalinity

Bromothymol Blue Solution—Dissolve 50 mg of bromothymol blue in a mixture of 4 mL of 0.02 M sodium hydroxide and 20 mL of alcohol. Dilute with water to 100 mL.

Procedure—To 20 mL of *Solution S* add 0.1 mL of *Bromothymol Blue Solution*. If the solution is yellow, titrate with 0.01 N sodium hydroxide until a blue endpoint is reached. If the solution is blue, titrate with 0.01 N hydrochloric acid until a yellow endpoint is reached. If the solution is green, it is neutral and no titration is required.

Blank Correction—Test 20 mL of *Blank* similarly. Correct the results obtained for *Solution S* by subtracting or adding the volume of titrant required for the *Blank,* as appropriate. (*Reference Titrimetry* ⟨541⟩.)

Requirement—Not more than 0.3 mL of 0.01 N sodium hydroxide produces a blue color, or not more than 0.8 mL of 0.01 N hydrochloric acid produces a yellow color, or no titration is required.

Absorbance

Procedure—[NOTE—Perform this test within 5 hours of preparing *Solution S*.] Pass *Solution S* through a 0.45-µm pore size filter, discarding the first few mL of filtrate. Measure the absorbance of the filtrate at wavelengths between 220 and 360 nm in a 1-cm cell using the blank in a matched cell in the reference beam. If dilution of the filtrate is required before measurement of the absorbance, correct the test results for the dilution.

Requirement—The absorbances at these wavelengths do not exceed 0.2 for Type I closures or 4.0 for Type II closures.

Reducing Substances

Procedure—[NOTE—Perform this test within 4 hours of preparing *Solution S*.] To 20.0 mL of *Solution S* add 1 mL of diluted sulfuric acid and 20.0 mL of 0.002 M potassium permanganate. Boil for 3 minutes. Cool, add 1 g of potassium iodide, and titrate immediately with 0.01 M sodium thiosulfate, using 0.25 mL of starch solution TS as the indicator. Perform a titration using 20.0 mL of blank and note the difference in volume of 0.01 M sodium thiosulfate required.

Requirement—The difference between the titration volumes is not greater than 3.0 mL for Type I closures and not greater than 7.0 mL for Type II closures.

Heavy Metals

Procedure—Proceed as directed for *Method I* under *Heavy Metals* ⟨231⟩. Prepare the *Test Preparation* using 10.0 mL of *Solution S*.

Requirement—*Solution S* contains not more than 2 ppm of heavy metals as lead.

Extractable Zinc

Test Solution—Prepare a *Test Solution* by diluting 10.0 mL of *Solution S* to 100 mL with 0.1 N hydrochloric acid. Prepare a test blank similarly, using the *Blank* for *Solution S*.

Zinc Standard Solution—Prepare a solution (10 ppm Zn) by dissolving zinc sulfate in 0.1 N hydrochloric acid.

Reference Solutions—Prepare not fewer than three *Reference Solutions* by diluting the *Zinc Standard Solution* with 0.1 N hydrochloric acid. The

concentrations of zinc in these *Reference Solutions* are to span the expected limit of the *Test Solution*.

Procedure—Use a suitable atomic absorption spectrophotometer (see *Atomic Absorption Spectroscopy* ⟨852⟩) equipped with a zinc hollow-cathode lamp and an air–acetylene flame. An alternative procedure such as an appropriately validated inductively coupled plasma analysis (ICP) may be used.

Test each of the *Reference Solutions* at the zinc emission line of 213.9 nm at least three times. Record the steady readings. Rinse the apparatus with the test blank solution each time, to ensure that the reading returns to initial blank value. Prepare a calibration curve from the mean of the readings obtained for each *Reference Solution*. Record the absorbance of the *Test Solution*. Determine the ppm zinc concentration of the *Test Solution* using the calibration curve.

Requirement—*Solution S* contains not more than 5 ppm of extractable zinc.

Ammonium

Alkaline Potassium Tetraiodomercurate Solution—Prepare a 100 mL solution containing 11 g of potassium iodide and 15 g of mercuric iodide in water. Immediately before use, mix 1 volume of this solution with an equal volume of a 250 g per L solution of sodium hydroxide.

Test Solution—Dilute 5 mL of *Solution S* to 14 mL with water. Make alkaline if necessary by adding 1 N sodium hydroxide, and dilute with water to 15 mL. Add 0.3 mL of *Alkaline Potassium Tetraiodomercurate Solution,* and close the container.

Ammonium Standard Solution—Prepare a solution of ammonium chloride in water (1 ppm NH_4). Mix 10 mL of the 1 ppm ammonium chloride solution with 5 mL water and 0.3 mL of *Alkaline Potassium Tetraiodomercurate Solution.* Close the container.

Requirement—After 5 minutes, any yellow color in the *Test Solution* is no darker than the *Ammonium Standard Solution* (no more than 2 ppm of NH_4 in *Solution S*).

Volatile Sulfides

Procedure—Place closures, cut if necessary, with a total surface area of 20 ± 2 cm^2 in a 100-mL flask, and add 50 mL of a 20 g per L citric acid solution. In the same manner and at the same time, prepare a control solution in a separate 100-mL flask by dissolving 0.154 mg of sodium sulfide in 50 mL of a 20 g per L citric acid solution. Place a piece of lead acetate paper over the mouth of each flask, and hold the paper in position by placing

over it an inverted weighing bottle. Heat the flasks in an autoclave at 121 ± 2° for 30 minutes.

Requirement— Any black stain on the paper produced by the test solution is not more intense than that produced by the control substance.

FUNCTIONALITY TESTS

[NOTE—Samples treated as described for preparation of *Solution S* and air dried should be used for Functionality Tests of *Penetrability, Fragmentation,* and *Self-Sealing Capacity. Functionality Tests* are performed on closures intended to be pierced by a hypodermic needle. The *Self-Sealing Capacity* test is required only for closures intended for multiple-dose containers. The needle specified for each test is a lubricated long bevel (bevel angle 12 ± 2°) hypodermic needle[1].]

Penetrability

Procedure— Fill 10 suitable vials to the nominal volume with water, fit the closures to be examined, and secure with a cap. Using a new hypodermic needle as described above for each closure, pierce the closure with the needle perpendicular to the surface.

Requirement— The force for piercing is no greater than 10 N (1 kgf) for each closure, determined with an accuracy of ±0.25 N (25 gf).

Fragmentation

Closures for Liquid Preparations—Fill 12 clean vials with water to 4 mL less than the nominal capacity. Fit the closures to be examined, secure with a cap, and allow to stand for 16 hours.

Closures for Dry Preparations— Fit closures to be examined into 12 clean vials, and secure each with a cap.

Procedure— Using a hypodermic needle as described above fitted to a clean syringe, inject into each vial 1 mL of water while removing 1 mL of air. Repeat this procedure four times for each closure, piercing each time at a different site. Use a new needle for each closure, checking that it is not blunted during the test. Filter the total volume of liquid in all the vials through a single filter with a nominal pore size no greater than 0.5 µm. Count the rubber fragments on the surface of the filter visible to the naked eye.

Requirement— There are no more than five fragments visible. This limit is based on the assumption that fragments with a diameter >50 µm are visible

~~to the naked eye. In case of doubt or dispute, the particles are examined microscopically to verify their nature and size.~~

~~Self-Sealing Capacity~~

~~*Procedure*—Fill 10 suitable vials with water to the nominal volume. Fit the closures that are to be examined, and cap. Using a new hypodermic needle as described above for each closure, pierce each closure 10 times, piercing each time at a different site. Immerse the 10 vials in a solution of 0.1% (1 g per L) methylene blue, and reduce the external pressure by 27 kPa for 10 minutes. Restore to atmospheric pressure, and leave the vials immersed for 30 minutes. Rinse the outside of the vials.~~

~~*Requirement*—None of the vials contain any trace of blue solution.~~

1. INTRODUCTION

Every elastomeric component used in a pharmaceutical packaging/delivery system should be proven safe and compatible for its intended use. The purpose of this chapter is to provide baseline requirements for the selection of elastomeric components to be further qualified for use in a given system. These same principles can be applied to elastomeric components used in medical devices and combination products, with consideration of the appropriate guidances and regulations.

For the establishment of the potential safety of a component, one cannot rely on a single testing strategy, because one strategy cannot cover all of the component's attributes that have a potential safety impact. The chemical testing prescribed is orthogonal in that the physicochemical tests provide a general overview of extracted chemical entities and the extractable elements test provides a quantitative assessment of extractable elements of concern. Because chemical testing alone may not be adequate to establish a component's safety and compatibility, it is augmented with the orthogonal approach of establishing biological reactivity.

In addition, evaluation of the suitability of a component to function properly requires that the complete system be considered, and testing must be designed to meet the requirements for intended use, as described in *Assessment of Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems* ⟨1382⟩. 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⟩.

Establishing the suitability of packaging systems for pharmaceutical products involves multiple tests and testing procedures including:

- **Component screening:** The baseline requirements described in this chapter comprise characterization of the elastomer's biological reactivity, physicochemical properties, and extractable elements.
- **Controlled extraction (simulation) study:** The worst-case controlled extraction (simulation) study is performed so that applicants can determine the extent to which extractables may become probable leachables. (For additional information, see ⟨1663⟩.)
- **Pharmaceutical product assessment:** This type of testing is 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⟩.)

2. SCOPE

Elastomeric packaging components are used in packaging systems for various parenteral preparations as defined in *Injections and Implanted Drug Products* ⟨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. Packaging systems, also referred to as container–closure systems, are defined in *Packaging and Storage Requirements* ⟨659⟩; these systems are the sum of packaging components that together contain, protect, and in certain cases, deliver the drug product.

Elastomeric components are formulated with elastomeric substances and can be either thermoset or thermoplastic in nature (refer to *Elastomeric Evaluation of Elastomeric Components Used in Pharmaceutical Packaging/Delivery Systems* ⟨1381⟩). Physicochemical, extractable elements, and functionality tests, along with biological reactivity, are always conducted on the components after surface modifications. This includes chlorinated surface treatments, fluoropolymer coatings and films, cross-linked polydimethylsiloxane, and polydimethylsiloxane (e.g., *Dimethicone*, *NF*) that have been applied to the component surface as a lubricant.

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

The following elastomer evaluation requirements 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. Note that elastomer components are made of a wide variety of elastomeric materials and optional polymeric coatings. For this reason, it is not possible to have identification tests that would encompass all possible component presentations. The applicant is responsible for verifying that the component's elastomeric formulation and any coating or laminate materials used are consistent with the qualified component.

In view of the considerable diversity of elastomeric components, packaging systems, and dosage forms, it is not possible to provide specific test conditions for performing all relevant functionality studies. Nevertheless, the essential principles and demonstrated best practices for functionality assessment relevant to elastomeric component for injections can be found in *Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems* ⟨382⟩ and ⟨1382⟩.

3. SPECIFICATIONS

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 or Type II, is not intended to serve as the sole evaluation criterion for the selection of the elastomeric component.

3.1 Biological Reactivity

Test selection and results are consistent with *Biological Reactivity Tests, In Vitro* ⟨87⟩ and/or *Biological Reactivity Tests, In Vivo* ⟨88⟩. Only materials that fail ⟨87⟩ are candidates for the tests described in ⟨88⟩.

3.2 Physicochemical

Appearances

For Procedure A (visual comparison): *Solution S* is not more opalescent than *Reference suspension B* for Type I closures, and not more opalescent than *Reference suspension C* for Type II closures.

For Procedure B (instrumental comparison): The turbidity of *Solution S* [in Nephelometric Turbidity Unit (NTU) or Formazin Turbidity Unit (FTU)] is NMT that for *Reference suspension B* (6 NTU/FTU) for Type I closures, and NMT that for *Reference suspension C* (18 NTU/FTU) for Type II closures.

Color: *Solution S* is not more intensely colored than the *Color standard*.

Acidity/alkalinity

Type I closures: NMT 0.3 mL of 0.01 N sodium hydroxide to produce a blue color

Type II closures: NMT 0.8 mL of 0.01 N sodium hydroxide to produce a blue color

Absorbances

Type I closures: NMT 0.2

Type II closures: NMT 4.0

Reducing substances (difference between the titration volumes)

Type I closures: NMT 3.0 mL

Type II closures: NMT 7.0 mL

Volatile sulfides: Any black stain on the paper produced by the *Test solution* is not more intense than that produced by the control substance.

Ammonium: After 5 min, any yellow color in the *Test solution* is no darker than the *Ammonium standard solution* [NMT 2 ppm of ammonium (NH_4) in *Solution S*].

3.3 Extractable Elements

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.

4. TEST METHODS

4.1 Biological Reactivity

In vitro and in vivo biological tests are performed on components according to test procedures described in ⟨87⟩ and ⟨88⟩.

4.2 Physicochemical

Solution S: Place whole, uncut closures corresponding to a surface area of 100 ± 10 cm^2 into a suitable glass container. Cover the closures with 200 mL of *Purified Water* or *Water for Injection*. If it is not possible to achieve the prescribed closure surface area (100 ± 10 cm^2) using uncut closures, select the number of closures that will most closely approximate 100 cm^2 and adjust the volume of water used to the equivalent of 2 mL/1 cm^2 of actual closure surface area used.

Place the washed closures into a Type I glass wide-necked flask (see *Containers—Glass* ⟨660⟩), add the same quantity of *Purified Water* or *Water*

for Injection initially added to the closures, and weigh. Cover the mouth of the flask with a Type I glass beaker. Heat in an autoclave so that a temperature of 121 ± 2° is reached within 20–30 min, and maintain this temperature for 30 min. Cool to room temperature over a period of about 30 min. Add *Purified Water* or *Water for Injection* to bring it up to the original mass. Shake, and immediately decant and collect the solution. [NOTE—This solution must be shaken before being used in each of the tests.]

Blank: Prepare a blank solution similarly, using 200 mL of *Purified Water* or *Water for Injection*, omitting the closures.

4.3 Appearance (Turbidity/Opalescence)

The determination of turbidity may be performed using either a visual or instrumental comparison. For a discussion of turbidimetry, see *Nephelometry, Turbidimetry, and Visual Comparison* ⟨855⟩. Instrumental assessment of clarity provides a more discriminatory test that does not depend on the visual acuity of the analyst.

Hydrazine sulfate solution: Dissolve 1.0 g of hydrazine sulfate in water and dilute with water to 100.0 mL. Allow to stand for 4–6 h.

Hexamethylenetetramine solution: Dissolve 2.5 g of hexamethylenetetramine in 25.0 mL of water in a 100-mL glass-stoppered flask.

Opalescence stock suspension: Add 25.0 mL of *Hydrazine sulfate solution* to the *Hexamethylenetetramine solution* in the flask. Mix, and allow to stand for 24 h. This suspension is stable for 2 months, provided it is stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before use.

Opalescence standard suspension: Prepare a suspension by diluting 15.0 mL of the *Opalescence stock suspension* with water to 1000.0 mL. It is stable for about 24 h after preparation.

Reference suspensions: Prepare according to *Table 1*. Mix and shake before use. [NOTE—Stabilized formazin suspensions that can be used to prepare stable, diluted turbidity standards are available commercially and may be used after comparison with the standards prepared as described.]

Table 1. Reference Suspensions

	Reference Suspension A	Reference Suspension B	Reference Suspension C	Reference Suspension D
Standard of opalescence	5.0 mL	10.0 mL	30.0 mL	50.0 mL
Water	95.0 mL	90.0 mL	70.0 mL	50.0 mL
Nephelometric turbidity units	3 NTU	6 NTU	18 NTU	30 NTU

Procedure A (visual comparison): Use identical test tubes made of colorless, transparent, neutral glass with a flat base and an internal diameter of 15–25 mm. Fill one tube to a depth of 40 mm with *Solution S*, one tube to the same depth with water, and four others to the same depth with *Reference suspensions A, B, C*, and *D*. Compare the solutions in diffuse daylight 5 min after preparation of the *Reference suspensions*, viewing vertically against a black background. The light conditions must be such that *Reference suspension A* can be readily distinguished from water and *Reference suspension B* can be readily distinguished from *Reference suspension A*.

Procedure B (instrumental comparison): Measure the turbidity of the *Reference suspensions* in a suitable calibrated turbidimeter (see ⟨855⟩). The *Blank* should be run and the results corrected for the *Blank*. *Reference suspensions A, B, C*, and *D* represent 3, 6, 18, and 30 NTUs, respectively. Measure the turbidity of *Solution S* using the calibrated turbidimeter.

4.4 Color

Color standard: Prepare a solution by diluting 3.0 mL of Matching Fluid O (see *Color and Achromicity* ⟨631⟩) with 97.0 mL of diluted hydrochloric acid.

Procedure: Use identical tubes made of colorless, transparent, neutral glass with a flat base and an internal diameter of 15–25 mm. Fill one tube to a depth of 40 mm with *Solution S*, and the second with the *Color standard*. Compare the liquids in diffuse daylight, viewing vertically against a white background.

4.5 Acidity or Alkalinity

Bromothymol blue solution: Dissolve 50 mg of bromothymol blue in a mixture of 4 mL of 0.02 M sodium hydroxide and 20 mL of alcohol. Dilute with water to 100 mL.

Test solution: To 20 mL of *Solution S*, add 0.1 mL of *Bromothymol blue solution*.

Procedure: If the solution is yellow, titrate with 0.01 N sodium hydroxide until a blue endpoint is reached. If the solution is blue, titrate with 0.01 N hydrochloric acid until a yellow endpoint is reached. If the solution is green, it is neutral and no titration is required.

Blank correction: Test 20 mL of *Blank* similarly. Correct the results obtained for *Solution S* by subtracting or adding the volume of titrant required for the *Blank*, as appropriate. (See *Titrimetry* ⟨541⟩.)

4.6 Absorbance

[NOTE—Perform this test within 5 h of preparing *Solution S*.]

Procedure: Pass *Solution S* through a filter of 0.45-µm pore size, discarding the first few milliliters of filtrate. Measure the absorbance of the filtrate at wavelengths between 220 and 360 nm in a 1-cm cell using the

Blank in a matched cell in the reference beam. If dilution of the filtrate is required before measurement of the absorbance, correct the test results for the dilution.

4.7 Reducing Substances

[NOTE—Perform this test within 4 h of preparing *Solution S*.]

Procedure: To 20.0 mL of *Solution S* add 1 mL of diluted sulfuric acid and 20.0 mL of 0.002 M potassium permanganate. Boil for 3 min. Cool, add 1 g of potassium iodide, and titrate immediately with 0.01 M sodium thiosulfate using 0.25 mL of starch solution TS as the indicator. Perform a titration using 20.0 mL of *Blank* and note the difference in volume of 0.01 M sodium thiosulfate required.

4.8 Volatile Sulfides

Procedure: Place closures, cut if necessary, with a total surface area of 20 ± 2 cm^2 in a 100-mL flask and add 50 mL of a 20-g/L citric acid solution. In the same manner and at the same time, prepare a control solution in a separate 100-mL flask by dissolving 0.154 mg of sodium sulfide in 50 mL of a 20-g/L citric acid solution. Place a piece of lead acetate paper over the mouth of each flask, and hold the paper in position by placing an inverted weighing bottle over it. Heat the flasks in an autoclave at 121 ± 2° for 30 min.

4.9 Ammonium

Alkaline potassium tetraiodomercurate solution: Prepare a 100-mL solution containing 11 g of potassium iodide and 15 g of mercuric iodide in water. Immediately before use, mix one volume of this solution with an equal volume of a 250-g/L solution of sodium hydroxide.

Test solution: Dilute 5 mL of *Solution S* with water to 14 mL. Make alkaline, if necessary, by adding 1 N sodium hydroxide, and dilute with water to 15 mL. Add 0.3 mL of *Alkaline potassium tetraiodomercurate solution* and close the container.

Ammonium standard solution: Prepare a solution of ammonium chloride in water [1 ppm of ammonium (NH_4)]. Mix 10 mL of the 1 ppm ammonium chloride solution with 5 mL of water and 0.3 mL of *Alkaline potassium tetraiodomercurate solution*. Close the container.

4.10 Extractable Elements

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.

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. 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, resulting in a concentration of 0.05 µg/g.

Calculations:

Analysis: 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).] **.**1S (*USP41*)

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‡ ~~Refer to ISO 7864, Sterile hypodermic needles for single use with an external diameter of 0.8 mm (21 Gauge).~~ **.**1S (*USP41*)