BRIEFING

⟨381⟩ Elastomeric Closures for Injections, *USP 42* page 6596 and *PF* 43(3) [May–June 2017]. The previous proposal that was published in *PF* 43(3) has been canceled. The Packaging and Distribution Expert Committee is proposing a new version of the chapter that updates and expands the scope with the following key changes:

1. Emphasize baseline requirements on the selection of thermoset and thermoplastic elastomeric components.
2. Expand the scope to include all elastomeric components in injectable product packaging/delivery systems. 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 cap liners for blow-fill-seal containers. The scope is further expanded to include components used in systems intended for transient product storage and/or delivery for specific pharmaceutical products, for example, co-packaged single-use syringes and infusion set components for specific products.
3. Delete Table 1.
4. Delete the washing and boiling step prior and include a temperature monitoring probe in the autoclave cycle for preparation of *Sample solution* in 4.2 Physicochemical Tests.
5. Delete the Heavy Metals and Extractable Zinc tests. It is left up to the component user to evaluate the need for performing extractable elements testing and, if such testing is necessary, to establish and justify the means by which testing is accomplished. An example of an extractable elements testing strategy is provided in *Assessment of Elastomeric Components Used in Injectable Pharmaceutical Product Packaging/Delivery Systems* ⟨1381⟩.
6. Refer to the new informational chapter ⟨1381⟩, which is meant to support the current chapter revision by:
    - Describing elastomeric components and their materials of construction for use in pharmaceutical product packaging/delivery systems
    - Providing a high-level introduction to elastomer chemistry, manufacturing technology, and the post-processing of components
    - Discussing identification testing
    - Discussing extractable elements

7. Due to the scope of the proposed revisions, the changes outlined will become official via the normal implementation time frame, which is 6 months from publication in the *USP–NF*.
8. A new general test chapter, *Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems* ⟨382⟩, also appears in this issue of *PF*. This chapter addresses the fitness-for-use functional suitability requirements of packaging/delivery systems that are intended for parenteral dosage forms and that include primary packaging components partially or completely made of elastomeric material. Due to the scope of the proposed new chapter and the industry impact, the Packaging and Distribution Expert Committee is proposing a 5-year delayed implementation to allow industry adequate time to implement ⟨382⟩. Once ⟨382⟩ becomes fully implemented, the functionality test in ⟨381⟩ will be omitted.

The following list includes monographs and/or chapters that reference this general chapter and require revision to keep those references accurate. Other monographs and/or chapters may also be listed, even where the reference to this general chapter remains unchanged, as an additional notice to stakeholders where there is believed to be potential for the chapter revision itself to affect pass/fail determinations for particular monograph articles.

- *Injections and Implanted Drug Products* (*Parenterals*)*—Product Quality Tests* ⟨1⟩
- *Packaging and Storage Requirements* ⟨659⟩
- *Ophthalmic Products—Quality Tests* ⟨771⟩
- *The Biocompatibility of Materials Used in Drug Containers, Medical Devices, and Implants* ⟨1031⟩
- *Quality Assurance in Pharmaceutical Compounding* ⟨1163⟩
- *Package Integrity Testing in the Product Life Cycle—Test Method Selection and Validation* ⟨1207.1⟩
- *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems* ⟨1663⟩
- *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems* ⟨1664⟩
- *Mandelic Acid* monograph

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

(GCPD: D. Hunt.)

Correspondence Number—C198123

Change to read:

⟨381⟩ ELASTOMERIC ~~CLOSURES FOR INJECTIONS~~▲COMPONENTS IN INJECTABLE PHARMACEUTICAL PRODUCT PACKAGING/DELIVERY SYSTEMS▲ (USP 1-Dec-2020)

Add the following:

▲ (USP 1-Dec-2020)

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 may 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 Silicone)	• 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
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, according to the procedures set forth in the general test chapter *Biological Reactivity Tests, In Vivo* ⟨88⟩, *Systemic*

Injection Test and *Intracutaneous Test*. 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 Materials 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 *Color and Achromicity* ⟨631⟩, *Color Determination and Standards*, *Matching Fluids*, *Matching Fluid O* 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. (*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

Lead nitrate stock solution:

Dissolve 159.8 mg of lead nitrate in 100 mL of water to which has been added 1 mL of nitric acid, then dilute with water to 1000 mL. Prepare and store this solution in glass containers free from soluble lead salts.

Standard lead solution:

On the day of use, dilute 10.0 mL of *Lead nitrate stock solution* with water to 100.0 mL.

pH 3.5 acetate buffer:

Dissolve 25.0 g of ammonium acetate in 25 mL of water, and add 38.0 mL of 6 N hydrochloric acid. Adjust, if necessary, with 6 N ammonium hydroxide or 6 N hydrochloric acid to a pH of 3.5, dilute with water to 100 mL, and mix.

Standard preparation:

Into a 50-mL color-comparison tube pipet 2 mL of *Standard lead solution* (20 µg of Pb) and dilute with water to 25 mL. Using a pH meter or short-range pH indicator paper as external indicator, adjust with 1 N acetic acid or 6 N ammonium hydroxide to a pH of between 3.0 and 4.0, dilute with water to 40 mL, and mix.

Test preparation:

Into a 50-mL color-comparison tube pipet 10.0 mL of *Solution S* and dilute with water to 25 mL. Using a pH meter or short-range pH indicator paper as external indicator, adjust with 1 N acetic acid or 6 N ammonium hydroxide to a pH of between 3.0 and 4.0, dilute with water to 40 mL, and mix.

Procedure:

To each of the two tubes containing the *Standard preparation* and the *Test preparation*, add 2 mL of *pH 3.5 acetate buffer*, then add 1.2 mL of thioacetamide–glycerin base TS. [NOTE—In countries or jurisdictions where thioacetamide cannot be used, add 10 mL of freshly prepared hydrogen sulfide TS to each of the tubes, mix, allow to stand for 5 minutes, and view downward over a white surface.] Dilute with water to 50 mL, mix, allow to stand for 2 minutes, and view downward over a white surface: the color of the solution from the *Test preparation* is not darker than that of the solution from the *Standard preparation*.

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

Packaging systems, also referred to as container–closure systems, are defined in *Packaging and Storage Requirements* ⟨659⟩; these systems are the sum of 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.

Every elastomeric component used in a pharmaceutical packaging/delivery system should be proven suitable for its intended use. The purpose of this chapter is to provide baseline chemical and biological reactivity requirements for the selection of injectable packaging/delivery system components.

The establishment of the potential suitability of an elastomeric component does not rely on a single testing strategy. No single strategy can cover all component attributes that have the potential to impact suitability. The chemical testing prescribed includes physicochemical tests. Extractable elements may also be relevant in the selection of an elastomeric component since they can contribute to drug product impurities. Assessments for elemental impurities should be risked based; however, a method for the potential to extract is recommended in *Assessment of Elastomeric Components Used in Injectable Pharmaceutical Product Packaging/Delivery Systems* ⟨1381⟩. Components can vary widely in terms of their intentionally and unintentionally added elements as well as the components' potential use. Because of this, it is challenging to provide universally effective and efficient test methodologies, lists of target elements, and reporting requirements. It is the component 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 extraction conditions, target elements, and reporting requirements. An example of an extractable elements testing strategy is provided in ⟨1381⟩. The physicochemical tests are also augmented with biological reactivity tests.

If components comply with the requirements outlined in this chapter, studies should follow to determine their suitability 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⟩.

In summary, establishing chemical suitability of elastomeric components for injectable product packaging/delivery systems involves multiple tests and testing procedures including:

- Component screening—baseline requirements for biological reactivity and physicochemical tests described in this chapter.
- Controlled extraction studies—studies as described in *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems* ⟨1663⟩ to create extractables profile(s) of particular pharmaceutical packaging/delivery systems and/or packaging components.
- 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 *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems* ⟨1664⟩.)

Additional information about elastomeric components, such as their composition, manufacturing processes, considerations for use, and testing procedures is found in *Assessment of Elastomeric Components Used in Injectable Pharmaceutical Product Packaging/Delivery Systems* ⟨1381⟩.

2. SCOPE

Elastomeric components within scope are those used in the packaging systems of products described in *Injections and Implanted Drug Products* ⟨1⟩.

Elastomeric components utilized for injectable products within chapter scope 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 scope are elastomeric components of systems or packages that are intended for transient product storage and/or product delivery intended for specific pharmaceutical products. For example, 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 scope. All elastomeric components in direct or indirect contact with the pharmaceutical product are within scope. An example of indirect contact is an elastomeric layer of a multilayer cap liner that does not directly contact the product but may leach into the product via migration

through the product contact layer. Another example is an elastomeric cap liner that may contact the product after being punctured to attain product access.

Elastomeric components outside of scope include those components of containers and closures that hold intermediate compounds, active pharmaceutical ingredients (APIs), and excipients. Also outside chapter scope are elastomeric components of containment and/or transport systems used in product, intermediate compound, API, or excipient manufacturing. Although outside of the chapter scope, chapter tests and requirements may be applied.

Chapter procedures and requirements are specified for physicochemical and biological reactivity tests. Component identification tests fall beyond the chapter scope. 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 encompass all possible component presentations.

Component functional suitability tests also fall outside of the chapter scope. As part of a finished product packaging system, elastomeric components must appropriately function to seal the container and, in some cases, aid in safe and effective product delivery. The essential principles and demonstrated best practices for such assessments for injectable product packaging/delivery systems can be 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⟩.

3. TEST SAMPLES

Test samples should mimic finished components after the completion of all manufacturing and processing steps (e.g., molding conditions, sterilization, etc.), and surface modifications (such as siliconization, chlorinated surface treatments, fluoropolymer coatings and films).

4. PROCEDURES

4.1 Biological Reactivity:

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

Acceptance criteria: Test selection and results are consistent with ⟨87⟩ and/or ⟨88⟩.

4.2 Physicochemical Tests

Sample solution:

Place whole, uncut components corresponding to a surface area of 100 ± 10 cm^2 into a Type I glass, wide-necked flask (see *Containers—Glass* ⟨660⟩). If it is not possible to achieve the prescribed closure surface area (100 ± 10 cm^2) using uncut components, select the number of components 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 the actual component's surface area. Add 200 mL of *Purified Water* or *Water for Injection* to the components, and weigh. Cover the mouth of the flask with a Type I glass beaker, or similar non interacting container. Immerse the temperature probe for the autoclave program control in water in a container comparable to that used for the sample. 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 components.

Elastomeric component categories, Type I and II:

Elastomeric components may be classified in two types: Type I closures meet the strictest requirements and are preferred; Type II closures have mechanical properties suitable for special uses (e.g., multiple piercing) but cannot meet the Type I acceptance criteria for *Appearance, Absorbance*, and *Reducing Substances*. For these tests, Type II closures have alternative acceptance criteria that must be met. Meeting the requirements of Type I or Type II cannot serve as the sole criterion for component selection. Furthermore, the intended final product application will determine whether a Type I or Type II component is more appropriate.

4.2.1 Appearance (Turbidity/Opalescence):

The determination of turbidity may be performed using either a visual or instrumental comparison. For a discussion of turbidimetry, see*Nephelometry and Turbidimetry* ⟨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 1.000 g of analytical grade hydrazine sulfate in *particle-free water* and dilute with *particle-free water* to 100.0 mL. Allow this solution to stand for 4–6 h.

Hexamethylenetetramine solution:

Dissolve 2.5 g of analytical grade hexamethylenetetramine in 25.0 mL of *particle-free water* in a 100-mL glass-stoppered flask.

Formazin stock suspension:
Add 25.0 mL of *Hydrazine sulfate solution* to the *Hexamethylenetetramine solution* in the 100-mL flask. Mix, and allow to stand for 48 h at 25 ± 1° before using. 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.

Formazin standard suspension:
Prepare a suspension by diluting 15.0 mL of the *Formazin stock suspension* with *particle-free 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
Particle-free water	95.0 mL	90.0 mL	70.0 mL	50.0 mL
Nephelometric turbidity units (NTU)	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 *Sample solution*, one tube to the same depth with water, and 4 other tubes to the same depth with *Reference suspension A, Reference suspension B, Reference suspension C*, and*Reference suspension 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*.

Acceptance criteria:
Type I—Sample solution is not more opalescent than *Reference suspension B*. *Type II—Sample solution* is not more opalescent than *Reference suspension C*.

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

Acceptance criteria:
Type I—The turbidity of *Sample solution* [in nephelometric turbidity units (NTUs) or formazin turbidity units (FTUs) corrected for the blank] is NMT that for *Reference suspension B* (6 NTU/FTU). *Type II*—The turbidity of *Sample solution* (in nephelometric turbidity units or formazin turbidity units, corrected for the blank) is NMT that for *Reference suspension C* (18 NTU/FTU).

4.2.2 Color

Color standard:
Prepare a solution by diluting 3.0 mL of *Matching Fluid O* (see *Visual Comparison* ⟨630⟩) with 97.0 mL of diluted hydrochloric acid (10 ± 0.5%).

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 *Sample solution*, and fill the second tube with the *Color standard*. Compare the liquids in diffuse daylight, viewing vertically against a white background.

Acceptance criteria:
Sample solution is not more intensely colored than the *Color standard*.

4.2.3 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 *Sample solution* 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 *Sample solution* by subtracting or adding the volume of titrant required for the *Blank*, as appropriate. (See*Titrimetry* ⟨541⟩.)

Acceptance criteria:

NMT 0.3 mL of 0.01 N sodium hydroxide produces a blue color or NMT 0.8 mL of 0.01 N hydrochloric acid produces a yellow color, or no titration is required.

4.2.4 Absorbance

[NOTE—Perform this test within 5 h of preparing *Sample solution*.]

Procedure:

Pass *Sample solution* 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.

Acceptance criteria:

Type I—NMT 0.2 *Type II*—NMT 4.0.

4.2.5 Reducing Substances

[NOTE—Perform this test within 4 h of preparing *Sample solution*.]

Procedure:

To 20.0 mL of *Sample solution* 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.

Acceptance criteria:

Type I—The difference between titration volumes is NMT 3.0 mL of 0.01 M sodium thiosulfate. *Type II*—The difference between titration volumes is NMT 7.0 mL of 0.01 M sodium thiosulfate.

4.2.6 Volatile Sulfides

Procedure:

Place components, 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 so that a temperature of 121 ± 2° is reached within 20–30 min, and then maintain this temperature for 30 min. Cool to room temperature over a period of about 30 min.

Acceptance criteria:

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

4.2.7 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 *Sample solution* 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 ($NH4^+$)]. 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.

Acceptance criteria:

After 5 min, any yellow color in the *Test solution* is no darker than the *Ammonium standard solution* [NMT 2 ppm of ammonium ($NH4^+$) in *Sample solution*].

4.3 Functionality Tests

[Note—Samples treated as described for preparation of *Sample solution* and air-dried should be used for the 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]]

4.3.1 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.

Acceptance criteria:

The force for piercing is no greater than 10 N (1 kilogram-force) for each closure, determined with an accuracy of ±0.25 N (25 gram-force).

4.3.2 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 h.

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 4 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 NMT 0.5 µm. Count the rubber fragments on the surface of the filter visible to the naked eye.

Acceptance criteria:

There are no more than 5 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.

4.3.3 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/L) methylene blue, and reduce the external pressure by 27 kPa for 10 min. Restore to atmospheric pressure, and leave the vials immersed for 30 min. Rinse the outside of the vials.

Acceptance criteria:

None of the vials contain any trace of blue solution.▲ (USP 1-Dec-2020)

~~[1] Refer to ISO 7864, Sterile hypodermic needles for single use with an external diameter of 0.8 mm (21 gauge).~~

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