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⟨381⟩ ELASTOMERIC ▲COMPONENTS IN INJECTABLE PHARMACEUTICAL PRODUCT PACKAGING/DELIVERY SYSTEMS

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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 and protect 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 elastomeric 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 elastomeric component attributes that have the potential to impact suitability. The chemical testing prescribed includes physicochemical tests. Extractable elements may also be relevant to the selection of a packaging system's materials of construction and therefore a relevant aspect of material characterization. Materials of construction can vary widely in terms of their intentionally and unintentionally added elements and their potential use. Because of this, it is challenging to provide universally effective and efficient test methodologies, lists of target elements, and reporting requirements. It is the material user's responsibility to evaluate the need for extractable elements testing and, if such testing is necessary, to establish and justify the means by which testing is accomplished, taking into account extraction conditions, target elements, and reporting requirement. Elastomeric 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 elastomeric 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. The physicochemical tests are also augmented with biological reactivity tests.

If elastomeric 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:

- Elastomeric component screening—baseline requirements for biological reactivity and physicochemical tests described in this chapter.
- Controlled extraction studies—studies as described in ⟨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 ⟨1664⟩.)

Additional information about elastomeric components, such as their composition, manufacturing processes, considerations for use, and testing procedures is found in ⟨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). The specified procedures and requirements outlined in this chapter are not applicable to elastomeric components used in products regulated by the Center for Devices and Radiological Health. 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.

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.

Elastomeric components outside of scope include those components of containers and closures that do not have direct or indirect contact with the pharmaceutical product or 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. Elastomeric component identification tests fall beyond the chapter scope. Elastomeric 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 elastomeric component presentations.

Elastomeric component functional suitability tests described in this chapter are within scope until *Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems* ⟨382⟩ is fully implemented. 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 ⟨382⟩ and *Assessment of Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems* ⟨1382⟩.

3. TEST SAMPLES

Test samples should mimic finished elastomeric 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: Elastomeric components (Type I and Type II) meet the requirements of *Biological Reactivity Tests, In Vitro* ⟨87⟩.[1] If components do not meet the requirements of ⟨87⟩, they can be subjected to in vivo testing set forth in *Biological Reactivity Tests, In Vivo* ⟨88⟩, *Systemic Injection Test* and ⟨88⟩, *Intracutaneous Test*. Components that meet the requirements of ⟨87⟩ are not required to undergo ⟨88⟩ 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.

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

4.2 PHYSICOCHEMICAL TESTS

Sample solution: Place whole, uncut elastomeric components corresponding to a surface area of 100 ± 10 cm^2 into a borosilicate 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 elastomeric 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 elastomeric component's surface area. Add 200 mL of *Purified Water* or *Water for Injection* to the elastomeric components, and weigh. Cover the mouth of the flask with a borosilicate 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 elastomeric components.

Elastomeric component categories, Type I and II: Elastomeric components may be classified in two types: Type I elastomeric closures meet the strictest requirements and are preferred; Type II elastomeric closures have mechanical properties suitable for special uses (e.g., multiple piercing) but cannot meet the Type I acceptance criteria for *4.2.1 Appearance, 4.2.4 Absorbance*, and *4.2.5 Reducing Substances*. For these tests, Type II elastomeric closures have alternative acceptance criteria that must be met. The intended final product application will determine whether a Type I or Type II elastomeric 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

[1] Biological reactivity testing in support of elastomeric components used for final pharmaceutical product packaging/delivery systems (drugs and drug/device combination products) provides baseline information and will often not be sufficient to assess the final suitability for use expectations of regulatory authorities. Thus, it is important to work with the appropriate regulatory authority for guidance regarding a product-specific application.

Table 1. Reference Suspensions *(continued)*

	Reference Suspension A	Reference Suspension B	Reference Suspension C	Reference Suspension D
Nephelometric turbidity units (NTU)	3 NTU	6 NTU	18 NTU	30 NTU

Procedure A (Visual Comparison ⟨630⟩): 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 *Color and Achromicity* ⟨631⟩) 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 an inert 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 elastomeric 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 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. Immerse the temperature probe for the autoclave program control in water in a container comparable to that used for the sample. 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 (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.

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 (NH_4^+) 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 *4.3.1 Penetrability, 4.3.2 Fragmentation,* and *4.3.3 Self-Sealing Capacity.* Functionality tests are performed on closures intended to be pierced by a hypodermic needle. The *4.3.3 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 with an external diameter of 0.8 mm (21 gauge).[2]]

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)

[2] Refer to ISO 7864: *Sterile Hypodermic Needles for Single Use.*