BRIEFING

⟨382⟩ Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems, *PF* 43(3) [May–June 2017]. The previous proposal for this chapter, published in *PF* 43(3) under a different title, *Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems,* was canceled and an updated version is being proposed. This new general chapter addresses the fitness-for-use functional suitability requirements for packaging/delivery systems that are intended for parenteral dosage forms and that include primary packaging components partially or completely made of elastomeric material. Elastomeric components, when properly fitted with dimensionally compatible packaging/delivery systems, are intended to protect and contain the package contents while enabling safe and effective product access at the time of use. The function being performed by any single elastomeric component type is dependent on the packaging/delivery system and may cover more than one functional parameter. A more complete discussion of fitness-for-intended-use testing, as compared to component functional suitability assessment in early package development, is presented in *Assessment of Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems* ⟨1382⟩, which is also being proposed in this issue of *PF*. Also refer to ⟨1382⟩ for guidance on test samples and their preparation, test sample population size, test procedures, test acceptance criteria, and test outcome reporting. 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. Until this chapter becomes fully implemented, the functionality test in ⟨381⟩ will remain.

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Add the following:

▲⟨382⟩ Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems

1. INTRODUCTION

This chapter addresses the fitness-for-intended-use functional suitability requirements of packaging/delivery systems that are intended for parenteral dosage forms as defined in *Injections and Implanted Drug Products (Parenterals)* ⟨1⟩ and that include primary packaging components partially or completely made of elastomeric material. Elastomeric components, when properly fitted with dimensionally compatible packaging/delivery systems, are intended to protect and contain the system's contents while enabling safe and effective product access at the time of use.

The function being performed by any single elastomeric component type is dependent on the packaging/delivery system and may cover more than one functional parameter. In all cases, the elastomeric component acts as a seal, protecting the drug product from product loss and from contamination by microorganisms and other environmental contaminants that pose a risk to product quality (e.g., chemically reactive gases). In the case of dual-chamber packaging/delivery systems, an elastomeric component keeps drug product components separate and limits excessive migration of solvents or gases between chambers.

Additional functional requirements depend on the intended use of the individual packaging/delivery system. In all plunger-based packaging/delivery systems (cartridge systems and syringe systems), the elastomeric component (i.e., the plunger) needs to move in order to empty the container upon demand. The *6.1 Plunger Break-Loose and Glide Forces* and *6.2 Plunger Seal Integrity*tests are provided to help evaluate these systems. Some elastomeric components are intended to be singly pierced by a spike, or by a needle, sometimes repeatedly. In this scenario, determinations of penetrability, fragmentation, and self-sealing capacity are relevant.

The tests for functional suitability described in this chapter are intended to evaluate the fitness of an elastomeric component as part of a specific, final, parenteral product packaging/delivery system. These system-specific tests are designed to supplement an overall drug product packaging/delivery system development program. The tests provided in this chapter are not exhaustive. Additional tests may be required to adequately assess the functional suitability of a given packaging/delivery system for a particular product. The tests in this chapter are not intended for routine product or component lot release. However, reevaluation of the functional suitability of a commercialized product's packaging/delivery system may be required over the product's life cycle when changes in components, processes, or the product itself occur. A more complete discussion of fitness-for-intended-use testing, as compared to component functional suitability assessment in early packaging/delivery system development, is presented in *Assessment of Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems* ⟨1382⟩.

The proper selection and design of functional suitability assessment studies is based on sound scientific principles that are consistent with the following:

- The packaging/delivery system design and mechanics
- The nature of the pharmaceutical dosage form contained and delivered by the packaging/delivery system
- The physical environment to which the finished drug product will be exposed during the product life cycle
- The clinical setting and the manner in which the product dosage form is to be administered
- The assessed safety risks to those using and/or exposed to the contents of the packaging/delivery system during patient administration

Alternative testing strategies for functional suitability assessment may be appropriate in certain circumstances with justification. In all cases, when reporting functional suitability assessment findings, the drug product applicant is advised to offer justification for the testing program chosen.

2. SCOPE

Packaging/delivery systems that have elastomeric components and are within this chapter's scope include vials and bottles with elastomeric stoppers; syringes with elastomeric plungers that have needle shields or tip caps; cartridges with elastomeric plungers and lined seals; pen, jet, and related injectors with elastomeric components; blow-fill-seal (BFS) plastic

containers with elastomeric lined caps; and infusion product containers such as plastic bags or blow-molded containers that have elastomeric access ports. Packaging/delivery systems for inhalation and nasal drug products are not in this chapter's scope.

Packaging/delivery systems intended for transient product transfer and/or product delivery are within this chapter's scope when they are co-packaged or linked by way of labeling for use with a specific pharmaceutical product. An example is a single-use syringe contained in a combination product kit.

2.1 Packaging/Delivery Systems

The various types of packaging/delivery systems that are within the scope of this chapter are described below. These system types represent broadly grouped categories with generic descriptors such as "vial and bottle systems." This same category nomenclature is used throughout the chapter. Although category titles are similar to those employed in the International Organization for Standardization (ISO) standards referenced, the use of this terminology is not intended to suggest that the systems' designs, dimensions, or materials of construction must conform to any ISO standard. The tests in this chapter apply irrespective of any elastomeric component's design or dimension and irrespective of any non-elastomeric components' design, dimension, or materials of construction.

Each system category description below includes the listing of standards published by ISO that served as the basis for elastomeric component functional suitability tests in this chapter. These references are included for information only. A listing of these standards and relevant tests is also provided in *Assessment of Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems* ⟨1382⟩*, Table 1*. In most cases, chapter tests can be performed without using these resources; exceptions are noted. When consulting referenced standards, the reader is advised to consult the most recent revision.

Vial and bottle systems:

Vial and bottle packaging/delivery systems have elastomeric closures fitted and compressed onto the container flange opening, mechanically held in place by a seal component (also called a cap). The closure is intended to permit product access via penetration by a hypodermic needle (for single-dose or multiple-dose product access), or by a spike piercing device (single-dose access). Applicable closures include those designed to accommodate either liquid-fill, lyophilization, or powder-fill production processes. Chapter tests were informed by ISO 8362-2 and -5, ISO 8536-2 and -6, and ISO 8871-5.

BFS systems:

BFS packaging/delivery systems have plastic caps with inserted elastomeric liners; the caps are attached to containers by welding or by collar technique.

The capped containers are intended to contain liquid parenteral dosage forms and to allow for product access (single-use only) via a spike piercing device. Chapter tests were informed by ISO 15759.

Plastic systems:

Plastic packaging/delivery systems refer to plastic containers for parenteral dosage forms having one or more chambers with a total nominal capacity of 50–5000 mL. Examples include film bags or containers formed by blow-molding processes that are intended for direct administration of liquids by infusion or injection. Elastomeric septum closures are sealed onto the container access port by mechanical means, welding, or other means. The access point consists of the insertion point (point that accepts the insertion part of the infusion device) and the injection point (point for injecting pharmaceuticals), if applicable. The injection and insertion points can be identical in some cases. Product injection through the injection point is performed using a narrow-gauge cannula. Product access for patient administration is through the insertion point via an infusion device with a spike piercing device. Chapter tests were informed by ISO 15747.

Cartridge systems:

Cartridge systems are sealed with two elastomeric components. One is a septum compressed onto the cartridge flange opening, mechanically held in place by a seal (also called a cap). The septum is intended to permit product access via penetration by a double-sided hypodermic needle. The other elastomeric component is a plunger fitted inside the cartridge barrel that expels the contents of the cartridge. Cartridge systems are found in two main application areas: dental local anesthesia product cartridge packaging/delivery systems and cartridges intended for pen-injector packaging/delivery systems for treatment of conditions such as diabetes or growth disease. Chapter tests were informed by ISO 11040-2 and -3, ISO 13926-2 and -3, and ISO 11608-3.

Syringe systems

Prefilled syringe systems:

A prefilled syringe is a packaging/delivery system provided by the drug product applicant to the end user prefilled and ready for dosage form administration. A prefilled syringe is sealed with two elastomeric components. One is a plunger positioned inside the syringe barrel that expels the contents of the syringe. The other is a needle shield that seals on the fixed needle tip and on the syringe barrel nozzle. Alternatively, a tip cap is used that seals on the barrel nozzle of the syringe, which has no needle. Chapter tests were informed by ISO 11040-4 and -8.

Single-use syringe systems:

This category includes syringes for single use intended for transfer/delivery of specific pharmaceutical products. They are not provided by the drug product applicant in prefilled condition, and therefore, must be filled prior to administration with a drug product from another packaging/delivery system.

A single-use syringe is sealed with an elastomeric plunger designed to fit inside the syringe barrel. The plunger acts to first draw product into the empty syringe and then to expel and administer the contents of the syringe. Chapter tests were informed by ISO 7886-1 to -4 and ISO 8537.

3. GENERAL TEST REQUIREMENTS

Refer to *Assessment of Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems* ⟨1382⟩*, 4. General Chapter* ⟨382⟩ *Background and Guidance* for general guidance and clarification regarding test samples and their preparation, test sample population size, test procedures, and test acceptance criteria.

3.1 Test Samples

Test samples used for each functional suitability test are to mirror as closely as possible the packaging/delivery system of the intended product. Components are to be prepared, processed, and assembled as defined for the final product packaging/delivery system. Some tests require that test samples be filled with a specified liquid, such as water. However, in such cases where the system's contents can influence the test outcome, it is recommended that test samples be filled instead with product or a product proxy so that the test outcome better reflects the system's intended use.

Some flexibility in test sample preparation and content is permitted if the variation is judged to have little or no impact on test outcome. Bracketing may be employed to allow a functional suitability assessment program that addresses a wider spectrum of packaging/delivery systems and/or products.

When reporting functional suitability test results, provide a full description of the test samples used, including all relevant components of the primary packaging/delivery system. These parts may include closures, containers, and, in some cases, additional essential components (e.g., vial or bottle caps). Other relevant details may include component age, design, material content, material or batch lot identification, system contents, methods of component and/or packaging/delivery system processing, and packaging/delivery system assembly methods. Finally, justify and document any deviations from the test samples described in the test method.

3.2 Test Sample Population Size

Test sample population sizes cited in the methods represent minimal test sample population size requirements. Inclusion of larger quantities than those specified in test procedures is encouraged to provide greater assurance of packaging/delivery system performance and to minimize the risk of product failure during commercial use. Report test sample population sizes employed with the test results, noting deviations from quantities specified in the method.

3.3 Acceptance Criteria

The majority of tests include definitive acceptance criteria. Some tests do not include definitive acceptance criteria due to the wide range of packaging/delivery systems and their functional performance demands. In these cases, the user is responsible for selecting pass/fail criteria that best represent the demands of the finished product packaging/delivery system. Include justification for the acceptance criteria chosen when reporting the test results.

4. PACKAGING/DELIVERY SYSTEM INTEGRITY TESTS

This section applies to the fit of an intact closure (meaning any component intended to seal or effect container closure) that is in contact with a container. Packaging/delivery system integrity refers to the ability of a packaging/delivery system to keep product contents in and keep detrimental environmental contaminants out. All closures must ensure adequate system integrity, as defined by the level of protection necessary for product quality maintenance. Therefore, all systems within the scope of this chapter are to pass an appropriate functional suitability assessment of packaging/delivery system integrity. This section does not apply to systems with closures after they have been breached by a needle, spike, or other access device.

The following terms and definitions apply:

Maximum allowable leakage limit: The greatest leakage rate (or leak size) tolerable for a given product packaging/delivery system that poses no risk to product safety and has no impact, or inconsequential impact, on product quality.

Inherent integrity: The leakage rate (or leak size) of a well-assembled packaging/delivery system with no system defect; it is a measure of packaging/delivery system leak tightness.

See *Package Integrity Evaluation—Sterile Products* ⟨1207⟩, as well as its subchapters, for further guidance on the concepts of inherent integrity and maximum allowable leakage limit, and for guidance on the proper selection, development, validation, and use of appropriate leak test methods.

Procedure:

Select 30 samples per test. Test each sample for integrity according to the leak test method of choice. No one specific integrity test method is applicable to all packaging/delivery systems. For systems with multiple closures (e.g., syringes with a plunger and a needle shield), separate and perhaps different types of leak tests may be required to effectively evaluate the system’s inherent integrity, given all the various closure seal types. The leak test(s) chosen are to be capable of verifying that the system’s inherent integrity meets the maximum allowable leakage limit for the intended product packaging/delivery system.

When reporting test results, include a full description of the integrity test method, including critical attributes and settings, test acceptance criteria (with justification for such criteria), test sample quantity, and the test sample quantity that passed/failed as per acceptance criteria.

Acceptance criteria:
The packaging/delivery system is acceptable if the inherent integrity results for all test samples conform to the maximum allowable leakage limit demanded of the product to ensure that there is no risk to product microbiological quality and no impact, or inconsequential impact, on product physicochemical quality attributes.

5. NEEDLE AND SPIKE ACCESS FUNCTIONAL SUITABILITY TESTS

Needle and spike access functional suitability tests (*5.1 Fragmentation*, *5.2 Penetration Force*, *5.3 Needle Self-Sealing Capacity*, and *5.4 Spike Retention and Sealability Capacity*) apply to packaging/delivery systems with closures that allow for drug product access by a hypodermic needle, spike, or other closure penetration device. For systems that also require an initial closure penetration for final dosage form preparation (e.g., reconstitution, constitution, admixture, or dilution), test conditions are intended to simulate such challenges. The tests described in this section that apply to individual packaging/delivery systems are shown in *Table 1*.

Table 1. Needle and Spike Access Functional Suitability Tests Applied to Individual Packaging/Delivery Systems

Packaging/Delivery Systems	5.1 Fragmentation	5.2 Penetration Force	5.3 Needle Self-Sealing Capacity	5.4 Spike Retention and Sealability Capacity
Vials, bottles	X	X	If applicable	X
BFS	X	X	If applicable	X
Plastic		X	If applicable	X
Cartridges	X		If applicable	

The following terms and definitions apply:

Dosage form preparation piercing device: Any piercing device used to penetrate the closure to allow the addition of a diluent or other liquid for final dosage form preparation prior to patient administration. For example, a

hypodermic needle or other closure penetration tool used to introduce a diluent for powdered product constitution, lyophilized product reconstitution, product admixture, or dilution.

Product-access piercing device: Any device used to penetrate the closure and access the product for dosage administration, such as a hypodermic needle, a spike, or other closure penetration tool.

The following piercing instructions apply to all tests in this category. If the product packaging/delivery system closure must be penetrated to permit dosage form administration and/or final preparation prior to patient administration, perform such piercings using the designated dosage form preparation piercing device intended or recommended. For example, if the intent is to provide or to specify a needle or other piercing device with the marketed product for this purpose, then use this same item or a facsimile. If a piercing device will be neither specified nor provided (i.e., not designated), use the recommended dosage form preparation needle cited in the test procedure.

Degrease all metal device facsimiles prior to use. Degreasing is not required for lubricated hypodermic needles.

Perform all test piercings in the same manner recommended or anticipated for the marketed product. For example, if product-use directions recommend pushing the needle or screwing the spike through the packaging/delivery system closure, then perform the test penetrations accordingly. If directions require vertical insertion of the needle or spike, perform the piercings in the same manner.

The number of piercings is meant to simulate the most challenging product use conditions, but should be no fewer than the number specified in the tests.

In cases where multiple piercing devices, multiple piercing conditions, and/or multiple access equipment exist, tests may be designed to examine worst-case (i.e., most challenging) conditions, or to bracket such conditions, as appropriate.

5.1 Fragmentation

The following practices are relevant to the performance of all fragmentation tests described in this section. Use *particle-free water* to fill the test sample containers. Alternatively, if the product dosage form can influence test results, filtered product or a filtered product proxy may be substituted with justification. Liquids that bracket multiple products are another option.

Adjustments to the test procedure container-filling volume and the volume withdrawn and injected into the test sample may be necessary to accommodate the wide range of packaging/delivery system types and sizes

tested. Report all modifications to the test sample preparation and test procedures with the test results.

Additional test procedure information and the acceptance criteria specific to various packaging/delivery systems are provided in the following sections.

The following term and definition applies:

***Particle-free water*:** Purified water filtered to remove particles that could interfere with the analysis (e.g., filtered through a membrane with a nominal pore size of 0.22 µm).

When reporting test results, include a description of the piercing device(s) used and the manner in which the penetrations are performed (e.g., manually or via pen injector). Include the number of piercings performed per piercing device used, per closure tested. Also include the number of closure particles observed (within the specification size range) per number of samples tested that support the final pass/fail findings.

Vial and bottle systems

Procedure A:

This procedure is applicable to systems intended for product access for patient administration via a hypodermic injection needle. Select 12 samples for test. Fill each container to 80% nominal capacity with *particle-free water* prior to closure.

For those systems requiring an initial closure penetration for dosage form final preparation, first pierce each test sample closure using the designated piercing device fitted to a clean syringe filled with *particle-free water*. If such a device is not designated, use an 18-gauge hypodermic needle (approximately 1.27-mm outer diameter) with a bevel angle of 11 ± 2°. Perform one piercing per closure with the needle or piercing device perpendicular to the surface. Use a fresh needle or piercing device per closure. After this initial puncture, inject a volume of *particle-free water* into the vial or bottle through the inserted needle while removing an equal volume of air. The volume chosen should adequately purge the insertion needle of elastomeric fragments.

For all packaging/delivery systems, after performing an initial dosage form preparation puncture (if applicable), proceed as follows. Use the designated product-access penetration needle or piercing device fitted to a clean syringe filled with *particle-free water*. If a needle is not designated, use a 21-gauge hypodermic injection needle (0.8-mm outer diameter) with a bevel angle of 11 ± 2°. Pierce the closure with the needle perpendicular to the surface. After each puncture, inject a volume of *particle-free water* into the vial or bottle through the inserted needle while removing an equal volume of air. The volume chosen should adequately purge the insertion needle of elastomeric fragments. Repeat piercings for each closure, piercing each time

at a different location, simulating typical product-access piercing practices for this packaging/delivery system type. Match the total number of product-access piercings per closure to that of the intended product, but perform NLT 4 piercings per closure. Use a fresh needle for each closure. For closures to be pierced more than 4 times each, the needle may be replaced more frequently. Check that the needle penetration tip is not blunted during the test.

Remove the tested closures from the containers. Pour container contents through the particulate examination filter, taking care that no visible particles remain in the container. Perform the water rinsings and particle count procedure according to *Particulate Matter in Injections* ⟨788⟩*, Method 2 Microscopic Particle Count Test*. Adjust the magnification from 40× to 100 ± 10× as needed. Determine the longest linear dimensions of the elastomeric particles using the linear scale on the graticule in ⟨788⟩*, Figure 1*.

Procedure B:

This procedure is applicable to systems intended for product access for patient administration via a spike or other closure-piercing device. Select 10 samples for test. Fill each container to 50% nominal capacity with *particle-free water* prior to closure.

For those systems requiring an initial closure penetration for dosage form final preparation, pierce each test sample closure using the designated dosage form preparation piercing device fitted to a clean syringe filled with *particle-free water*. If a piercing device is not designated, use an 18-gauge hypodermic needle (1.27-mm outer diameter) with a bevel angle of 11 ± 2°. Perform one piercing per closure with the needle or device perpendicular to the surface. Use a fresh needle or device per closure. After each puncture, inject a volume of *particle-free water* into the vial or bottle through the inserted needle or device while removing an equal volume of air. The volume chosen should adequately purge the insertion needle of elastomeric fragments.

For all packaging/delivery systems, after performing an initial dosage form preparation puncture (if applicable), proceed as follows. Perform product-access penetrations using the designated spike or piercing device. If no spike or piercing device is designated, use a stainless steel closure-piercing device such as that described in ISO 8536-2 (closures for infusion bottles) or ISO 8536-6 (freeze-drying closures for infusion bottles), as appropriate.

Manually pierce each test sample closure one time within the closure target area with the spike or piercing device positioned perpendicular to the surface. Holding the test sample with spike or device vertically, shake for a few seconds and then withdraw the spike or device.

Use a fresh spike or piercing device for each closure unless product usage directions differ. If a stainless steel piercing device is used, the same device may be used for each closure. Exercise care to avoid blunting or otherwise damaging the device tip.

Remove the tested closures from the test sample. Pour all container water contents through the particulate examination filter, taking care that no visible particles remain in the containers.

Perform the water rinsings and particle-count procedure according to *Particulate Matter in Injections* ⟨788⟩*, Method 2 Microscopic Particle Count Test*. Adjust the magnification from 40× to 100 ± 10× as needed. Determine the longest linear dimensions of the elastomeric particles using the linear scale on the graticule in ⟨788⟩*, Figure 1*.

Acceptance criteria

Procedure A:

The packaging/delivery system is acceptable if NMT 5 elastomeric closure particles ≥150 µm in any dimension are observed, per 12 samples tested.

Procedure B:

The packaging/delivery system is acceptable if NMT 20 elastomeric closure particles ≥150 µm in any dimension are observed, per 10 samples tested.

BFS systems

Procedure:

Select 10 samples for test. Nominally fill each container with *particle-free water* prior to closure.

For systems requiring an initial closure penetration for dosage form final preparation, manually pierce each test sample closure one time with the designated piercing device fitted to a clean syringe filled with *particle-free water*. If a piercing device is not designated, use an 18-gauge hypodermic needle (1.27-mm outer diameter) with a bevel angle of 11 ± 2°. Perform one piercing per closure with the needle or device perpendicular to the surface. Use a fresh needle or device per closure. After each puncture, inject a volume of *particle-free water* into the vial or bottle through the inserted needle or device while removing an equal volume of air. The volume chosen should adequately purge the insertion needle of elastomeric fragments.

For all packaging/delivery systems, after performing an initial dosage form preparation puncture (if applicable), proceed as follows. Perform product-access penetrations using the designated spike or piercing device. If no spike or piercing device is designated, use a stainless steel closure-piercing device such as that described in ISO 15759.

Manually pierce each test sample closure one time within the closure target area with the spike or piercing device positioned perpendicular to the

surface. Holding the test sample with spike vertically, shake the test sample for a few seconds and then withdraw the spike or device.

Use a fresh spike or piercing device for each closure unless product usage directions differ. If a stainless steel piercing device is used, the same device may be used for each closure. Exercise care to avoid blunting or otherwise damaging the device tip.

Remove the tested closures from the containers. Pour all container water contents through the particulate examination filter, taking care that no visible particles remain in the containers.

Perform the water rinsings and particle count procedure according to *Particulate Matter in Injections* ⟨788⟩*, Method 2 Microscopic Particle Count Test*. Adjust the magnification from 40× to 100 ± 10× as needed. Determine the longest linear dimensions of the elastomeric particles using the linear scale on the graticule in ⟨788⟩*, Figure 1*.

Acceptance criteria:

The packaging/delivery system is acceptable if NMT 7 elastomeric closure particles ≥150 µm in any dimension are observed, per 10 piercings.

Cartridge systems

Procedure A:

This procedure is applicable to cartridge systems such as those used for dental local anesthesia product applications. Select 12 samples for test. Fill each container with an appropriate volume of *particle-free water*. Perform penetrations using the designated needle or piercing device. If no needle is designated, use a 27-gauge hypodermic injection needle (0.4-mm outer diameter) that conforms to the butt-end requirements in ISO 7885. Pierce the closure with the needle or piercing device perpendicular to the surface. After each puncture, purge the lumen of the needle or piercing device using *particle-free water*, allowing the water to pass through the particulate examination filter. Perform replicate penetrations for each test sample at the same site of insertion. The total number of piercings per closure should match that of the intended product, but should be NLT 4 per closure.

Use a fresh needle or piercing device for each closure unless product usage directions differ. For closures intended to have more than 4 piercings each, the needle or device may be replaced more frequently. Check that the penetration tip is not blunted during the test.

After the requisite number of piercings, empty the cartridge contents onto the same or a separate filter, taking care that no visible particles remain in the cartridge.

Perform the water rinsings and particle count procedure according to *Particulate Matter in Injections* ⟨788⟩*, Method 2 Microscopic Particle Count Test*. Adjust the magnification from 40× to 100 ± 10× as needed. Determine

the longest linear dimensions of the elastomeric particles using the linear scale on the graticlule in ⟨788⟩, *Figure 1*.

Procedure B:

This procedure is applicable to cartridges such as those used in pen injectors. Select the systems for test. The number of test samples selected should permit a minimum of 100 punctures to be performed. For example, if each closure is to be punctured 10 times, select at minimum 10 test samples; if each closure is to be punctured 20 times, select at minimum 5 test samples. The cartridge system is to be tested in the manner in which it will be used. In other words, if the cartridge is to be pierced after, or while it is inserted in a pen-injector system, then it should be tested in that manner.

Perform penetrations using the designated needle or piercing device. Match the number of penetrations performed on each system's closure to product-use recommendations.

Use a new needle or piercing device per penetration, unless otherwise indicated in product-use directions. After each puncture, purge the lumen of the needle or device using *particle-free water*, passing the water through the particulate examination filter.

After the requisite number of piercings, empty the cartridge contents onto the same or a separate filter.

Perform the water rinsings and particle count procedure according to *Particulate Matter in Injections* ⟨788⟩*, Method 2 Microscopic Particle Count Test*. Adjust the magnification from 40× to 100 ± 10× as needed. Determine the longest linear dimensions of the elastomeric particles using the linear scale on the graticule in ⟨788⟩, *Figure 1*.

Acceptance criteria

Procedure A:

The packaging/delivery system is acceptable if NMT 5 elastomeric closure particles ≥150 µm in diameter are observed, per 12 samples tested.

Procedure B:

The packaging/delivery system is acceptable if NMT 6 elastomeric closure particles ≥150 µm in any dimension are observed, per 100 punctures.

5.2 Penetration Force

The following practices are recommended when performing penetration force tests.

Consider the possible impact of liquid in the test sample on penetration force test results. For example, liquid in the package may afford some force resistance to the penetration device. If so, fill test samples with product or an appropriate product proxy. If not, empty test samples may be tested.

Perform these automated penetration tests using a mechanical testing machine that can be mounted with the designated penetration needle, spike,

or other piercing device and can then move perpendicularly at the required constant rate of strain. The force exerted backward on the piercing device at the time of penetration is to be indicated or registered in such a way that it can be read with the stated accuracy required of the test analysis.

Additional test protocol information and acceptance criteria are provided in the following sections, specific for each packaging/delivery system.

When reporting test results, document test measurement accuracy, test sample content, and the piercing devices used. Report the number of penetrations performed per device used, per container tested. Include the penetration force findings that support the final pass/fail conclusion. For tests without defined quantitative acceptance limits, include justification for the limit chosen.

Vial and bottle systems:

Dosage form preparation *Procedure A* applies to systems that require an initial piercing for dosage form final preparation using a needle. Product-access *Procedure B*and *Procedure C* apply to systems that require closure piercing by a needle (*Procedure B*) or by a spike or similar device (*Procedure C*) to allow for product access for patient administration.

A packaging/delivery system may require testing by more than one procedure to address all intended use conditions.

Procedure A:

This procedure is a dosage form preparation simulation applicable to systems requiring initial closure penetration for dosage form final preparation using a hypodermic needle. If a needle is not designated, use an 18-gauge hypodermic needle (1.27-mm outer diameter) with a bevel angle of 11 ± 2°.

Use a mechanical testing machine capable of accommodating the test sample fixture while monitoring the axial force required to penetrate the closure [load cell tolerance ±0.25 Newtons (N)] at a constant insertion rate of 200 mm/min.

Pierce each test sample closure one time within the closure target area with the needle positioned perpendicular to the surface. Use a fresh needle for each closure.

Procedure B:

This procedure is a product-access simulation applicable to systems intended for product access via a hypodermic injection needle. Select 10 samples for test. Perform tests using the designated penetration needle. If a needle for product access is not designated, use a 21-gauge hypodermic needle (0.8-mm outer diameter) with a bevel angle of 11 ± 2º.

Use a mechanical testing machine capable of accommodating the test sample fixture while monitoring the axial force required to penetrate the

closure (load cell tolerance ±0.25 N) at a constant insertion rate of 200 mm/min.

Pierce each test sample closure one time within the closure target area with the needle positioned perpendicular to the surface. Unless product usage recommendations differ, use a fresh needle for each closure. Exercise care to avoid blunting or otherwise damaging the needle tip.

Procedure C:

This procedure is a product-access simulation applicable to systems intended for product access for patient administration via a spike or other closure-piercing device. Select 10 samples for test. Use the designated spike or piercing device for all penetrations. If a spike or device is not designated, a stainless steel closure-piercing device such as that described in ISO 8536-2 (closures for infusion bottles) or ISO 8536-6 (freeze-drying closures for infusion bottles) may be used, as appropriate.

Use a mechanical testing machine capable of accommodating the test sample fixture while monitoring the axial force required to penetrate the closure (load tolerance ±2 N) at a constant insertion rate of 200 mm/min.

Pierce each test sample closure one time within the closure target area with the spike or device positioned perpendicular to the surface.

Use a fresh spike or piercing device for each closure unless product usage directions differ. If a stainless steel piercing device is used, the same spike may be used for each closure. Exercise care to avoid blunting or otherwise damaging the device tip.

Acceptance criteria

Procedure A:

The packaging/delivery system is acceptable if the penetration force for all test samples, measured from the moment the dosage form preparation hypodermic needle first pierces the closure, does not exceed the maximum force that allows for ease of access and does not cause the closure to be pushed into the container. The packaging/delivery system is acceptable if the penetration force for all test samples does not exceed the quantitative acceptance limit established by the end user. Penetration force readings should be accurate to within 0.25 N.

Procedure B:

The packaging/delivery system is acceptable if the penetration force for all test samples, measured from the moment the product-access hypodermic needle first pierces the closure, does not exceed the maximum force that allows for ease of access and does not cause the closure to be pushed into the container. The packaging/delivery system is acceptable if the penetration force for all test samples does not exceed 10 N. Penetration force readings should be accurate to within 0.25 N.

Procedure C:

The packaging/delivery system is acceptable if the penetration force for all test samples, measured from the moment the spike or piercing device first pierces the closure, does not exceed the maximum force that allows for ease of access and does not cause the closure to be pushed into the bottle. For systems intended for manual spike insertion, the packaging/delivery system is acceptable if the penetration force for all test samples does not exceed 80 N and the average of all test samples is less than 75 N. Penetration force readings should be accurate to within 2 N.

BFS systems

Procedure:

Select 10 samples for test. Use the designated spike for product access for all penetrations. If a spike is not designated, a stainless steel closure-piercing device may be used (ISO 15759).

Position the test sample in a test fixture with the insertion point of the infusion device/spike aligned to permit vertical penetration of the closure.

Use a mechanical testing machine capable of accommodating the test sample fixture while monitoring the axial force required to penetrate the closure (load cell tolerance ±2 N) at a constant insertion rate of 200 mm/min.

Pierce each test sample closure one time within the closure target area with a spike positioned perpendicular to the surface. Use a fresh spike for each closure. If a stainless steel piercing device is used, the same spike may be used for each closure. Exercise care to avoid blunting or otherwise damaging the device tip.

Acceptance criteria:

The packaging/delivery system is acceptable if the penetration force for all test samples, measured from the moment the spike first pierces the closure, does not exceed the maximum force that allows for ease of access. The packaging/delivery system is acceptable if the penetration force for all test samples does not exceed the quantitative acceptance limit established by the end user. Penetration force readings should be accurate to within 2 N.

Plastic systems

Procedure:

Select 10 samples for test. Use the designated spike, infusion device, or other piercing device intended for product access for all penetrations. If a spike, infusion device, or other piercing device is not designated, a closure-piercing device may be used (ISO 8536-4).

Position the test sample in a test fixture with the insertion point of the piercing device positioned perpendicular to the closure surface.

Pierce each test sample closure one time at the insertion point. Use a fresh piercing device for each closure. If a stainless steel piercing device is used,

the same spike may be used for each closure. Exercise care to avoid blunting or otherwise damaging the device tip.

Use a mechanical testing machine capable of accommodating the test sample fixture while monitoring the axial force required to penetrate the closure (load cell tolerance ±2 N) at a constant insertion rate of 500 mm/min.

Acceptance criteria:

The packaging/delivery system is acceptable if the penetration force for all test samples, measured from the moment the piercing device first pierces the closure, does not exceed the maximum force that allows for ease of access. The packaging/delivery system is acceptable if the force to fully penetrate each test sample closure does not exceed 200 N. Penetration force readings should be accurate to within 2 N.

5.3 Needle Self-Sealing Capacity

This section applies to product packaging/delivery systems with closures required to ensure adequate packaging/delivery system integrity during in-use conditions of multiple breaches by a needle. Such systems include 1) multiple-dose product packaging/delivery systems and 2) systems with closures that must be penetrated more than once during the course of dosage form preparation and/or prior to final penetration for product access for patient administration.

Whether a particular system is subject to this functional suitability requirement is based on the intended product and its preparation and administration parameters.

The following terms and definitions apply:

In-use system integrity: The ability of the punctured closure to prevent microbial ingress and product loss between and during periods of dosage form preparation and/or product access.

In-use maximum allowable leakage limit: The level of protection required that ensures maintenance of product physicochemical and microbiological quality attributes between and during periods of dosage form preparation and/or product access.

Procedure:

Select 30 samples per test. For packaging/delivery systems requiring an initial closure penetration for final dosage form preparation, perform a single closure puncture on each test sample using the designated dosage form preparation needle. Following the initial dosage form preparation for penetration (if applicable), perform multiple closure punctures on each test sample using the designated product-access needle. The needle(s) chosen and the number of penetrations should simulate the most challenging intended use directions. Automated equipment may be used if appropriate to ensure consistency in penetration force and method. If a dosage form

preparation needle or a product-access needle is not designated, or if intended-use directions are absent, the directions below for systems apply.

Test each punctured closure packaging/delivery system for integrity according to the leak test method of choice.

No one specific method for in-use system integrity testing is applicable to all parenteral product packaging/delivery systems. The leak test method chosen must be capable of verifying that the system's in-use integrity meets the in-use maximum allowable leakage limit for the intended product.

The user is referred to *Package Integrity Evaluation—Sterile Products* ⟨1207⟩ and its subchapters for further guidance on 1) the concepts of in-use integrity and in-use maximum allowable leakage limit, and 2) the proper selection, development, validation, and utilization of appropriate leak test methods.

When reporting test results, include a description of the piercing device(s) and the closure penetration method(s) used. Also, describe the integrity test method employed with acceptance criteria, along with proper justification. Include the integrity test findings that support the final pass/fail conclusion.

Vial and bottle systems:

For dosage form preparation penetrations, use an 18-gauge hypodermic injection needle (1.27-mm outer diameter) with a bevel angle of 11 ± 2°. Penetrate each closure one time, piercing within the closure target area. Use a new needle for each closure.

For product-access penetrations, use an 18-gauge hypodermic injection needle (1.2-mm outer diameter) with a medium bevel angle. Penetrate each closure 3 times in 3 different locations. Use a new needle for each closure.

BFS systems:

For dosage form preparation penetrations, use an 18-gauge hypodermic injection needle (1.27-mm outer diameter) with a bevel angle of 11 ± 2°. Penetrate each closure one time, piercing within the target area. Use a new needle for each closure.

For product-access penetrations, use an 18-gauge hypodermic injection needle (1.2-mm outer diameter) with a medium bevel angle. Penetrate each closure 3 times in 3 different locations. Use a new needle for each closure.

Plastic systems:

Use a 23-gauge (0.6-mm outer diameter) needle. Penetrate each injection point closure one time. Keep the needle in position for 15 s before removing the needle and testing for leakage. Use a new needle for each closure.

Cartridge systems:

Use a 29-gauge hypodermic needle (0.34-mm outer diameter). Penetrate each closure 1.5 times, the maximum number of possible penetrations. Use a new needle for each puncture. Perform the penetrations in a manner consistent with product intended-use directions. For example, a pen

cartridge should be punctured while held in the cartridge holder, or fully assembled into the packaging/delivery system if provided prefilled and loaded or required to be loaded into the packaging/delivery system before puncturing. Puncture the membrane by screwing or pushing on the needle or as defined in the intended product-use instructions.

Acceptance criteria:

The packaging/delivery system is acceptable if the in-use system integrity results for all test samples conform to the in-use maximum allowable leakage limit demanded of the product to ensure that there is no risk or inconsequential risk to product microbiological and physicochemical quality attributes.

5.4 Spike Retention and Sealability Capacity

This test applies to packaging/delivery systems intended to permit product access for patient administration via a spike piercing device. The test evaluates the ability of a closure to be penetrated by a spike and to seal properly around it.

Perform all piercings using the designated device intended for finished product access. If the device is neither specified nor provided, use the recommended piercing device cited in the test protocols that follow. Additional test protocol information and acceptance criteria are provided in the following sections, specific to various packaging/delivery systems.

When reporting test results, include a description of the piercing device(s) used. As applicable, include the spike removal force findings, spike retention findings, and visible leakage findings for all test samples that support the final pass/fail conclusion.

Vial and bottle systems

Procedure:

Select 10 samples for test, filled to at least 50% nominal capacity with liquid product or a liquid product proxy. Use the designated spike for product access for all penetrations. For bottle systems, if a spike is not designated, a stainless steel closure-piercing device such as that described in ISO 8536-2 (closures for infusion bottles) or ISO 8536-6 (freeze-drying closures for infusion bottles) may be used, as appropriate.

Place the spike perpendicular to the center of the closure target area. Manually force the spike through the closure until complete penetration is achieved or until efforts to achieve penetration become too difficult.

For test samples in which complete penetration is achieved, position the bottle with the bottom end up and attach a total mass of 0.5 ± 0.025 kg to the spike. Leave undisturbed for 4 h. Inspect the sample for the presence of liquid between the closure and spike or on spike surfaces, as well as for changes in the spike position.

Acceptance criteria:

The packaging/delivery system is acceptable if, for all test samples, 1) closures are able to be penetrated fully without pushing the closure into the bottle; 2) spikes are retained in the closures for the test time period; and 3) no liquid leakage is observed.

BFS systems:

The following two procedures apply to all BFS systems. For both procedures below, use the designated spike for product access for all penetrations. If a spike is not designated, a stainless steel closure-piercing device described in ISO 15759 may be used.

Procedure A:

Select 10 samples for test. Place the spike perpendicular to the center of the closure target area. Manually force the spike through the closure until complete penetration is achieved. Immediately following insertion, measure the force needed to withdraw the spike at a speed of 200 mm/min using a tensile testing machine (load cell accuracy ±2 N).

Procedure B:

Select 10 samples for test, nominally filled with product or product proxy. Place the spike perpendicular to the center of the closure target area. Manually force the spike through the closure until complete penetration is achieved. Position the test sample with the closure end down. Hang a 1-kg weight from the device for 4 h. Inspect for signs of liquid between the spike and closure or on spike surfaces, as well as changes to the spike position.

Acceptance criteria

Procedure A:

The packaging/delivery system is acceptable if spike removal force for all test samples is NLT 15 N (±2 N).

Procedure B:

The packaging/delivery system is acceptable if all test samples are observed to have no leakage at the insertion point and no insertion spike slides out from the insertion point.

Plastic systems

Procedure:

Select 10 samples for test, nominally filled with liquid product or product proxy. Use the designated spike for product access for all penetrations. If a spike is not designated, use a closure-piercing device as described in ISO 8536-4 and referenced in ISO 15747. Use a fresh spike for each test sample. Place the spike perpendicular to the center of the insertion point closure target area. Force the spike through the closure until complete penetration is achieved. Allow the spike to remain in the insertion point for 5 h. Then place the infusion containers between 2 parallel plates and compress to achieve an internal pressure of 20 kPa for 15 s. (If the infusion container is intended to be used with a pressure cuff, perform the test with an internal pressure of 50 kPa for 15 min). Inspect for liquid leakage between the closure and spike.

Finally, measure the force needed to remove each test spike from the insertion point at a speed of 100 mm/min using a tensile testing machine (load cell accuracy ±2 N).

Acceptance criteria:

The packaging/delivery system is acceptable if, for all test samples, 1) the removal force is NLT 15 N (±2 N); 2) no leakage is observed at the insertion point; and 3) no insertion part slides out from the insertion point.

6. PLUNGER FUNCTIONAL SUITABILITY TESTS

The following sections address the functional suitability of systems having elastomeric plunger components (also called pistons), i.e., cartridge systems and syringe systems.

The following terms and definitions apply:

Plunger break-loose force: The force required to initiate the movement of the plunger of a liquid-filled syringe or cartridge.

Plunger glide force: The force required to sustain the movement of the plunger to expel the contents of the liquid-filled syringe or cartridge.

Plunger seal integrity test: Tests the ability of the plunger to maintain a fluid seal while under pressure.

6.1 Plunger Break-Loose and Glide Forces

Some of the numerous variables that impact plunger break-loose and glide forces, as well as some of the considerations for judging functional suitability, are described in ⟨1382⟩. Due to this complexity, it is not possible to provide a single test method, nor is it possible to provide specific quantitative acceptance criteria appropriate for all product packaging/delivery systems. The user is responsible for following the generic test method outlined below and for establishing meaningful quantitative acceptance criteria that best represent the demands of the finished product packaging/delivery system.

Procedure:

Select 10 samples for test, nominally filled with product or a product proxy. For test samples of syringes and cartridges that do not have a fixed (staked) needle, perform tests with the addition of "connecting devices" such as needles, needleless Luer connections, adapters, and transfer units, as per intended product-use directions.

For all test samples, perform the remaining break-loose and glide forces tests using a mechanical testing machine capable of attaching to the test sample and depressing the syringe plunger at a constant linear rate, while at the same time continuously measuring and recording the force. Force-reading accuracy is to be NMT 1% of the maximum expected force values anticipated for the test sample population.

Select an elution speed and measurement sampling rate slow enough to clearly detect and measure the break-loose force. The elution speed for large-volume syringes, e.g., >50 mL, should permit the measurement of break-loose force and glide forces while allowing sufficient time to complete the test. An elution speed of 1–2 mm/sec is generally suitable for syringes with volumes of <5 mL. When the capability of the test system allows, consider performing the test at speeds that mirror anticipated product administration flow rates and therefore demonstrate actual usage forces.

Test each sample for plunger break-loose force and glide forces, recording the forces measured in Newtons from the start of plunger movement until the plunger makes contact with the syringe barrel shoulder. Observe for plunger stick-slip behavior, also called "chattering" or "stiction" as evidenced by plunger movement hesitancy overcome by a brief increase in glide force.

When testing dual-chamber syringes and cartridges containing 2 plungers (one that separates the 2 chambers and another that seals the syringe barrel), measure and report the break-loose force and the minimum and maximum glide forces for each of the 2 plungers. Observe for plunger stick-slip behavior. To achieve acceptable performance, each plunger must meet the functional acceptance criteria.

When reporting test results, include details of the procedure(s) followed. Provide a full description of the test samples, including any connecting devices employed. Report the plunger break-loose force findings and the minimum and maximum plunger glide forces measured. Include justification for the quantitative acceptance criteria chosen for break-loose and plunger glide forces. In addition, for manual use systems, report the presence or absence of plunger stick-slip behavior.

Acceptance criteria:

For cartridge systems and syringe systems intended for manual use, the packaging/delivery system is acceptable if, for all test samples:

1. The plunger break-loose force allows for ease of plunger movement initiation.
2. The glide force does not exhibit stick-slip behavior.
3. The minimum and maximum plunger glide forces allow for ease of plunger movement propagation.
4. The maximum plunger glide force allows for ease of complete product elution.
5. The difference between the maximum and minimum plunger glide forces is indicative of barrel lubrication consistency.

For cartridge systems and syringe systems intended for power-driven (non-manual) use, the packaging/delivery system is acceptable if the plunger break-loose force and glide forces for all test samples are not greater than the capability of the spring or relevant power-driven device, allowing for complete product elution.

6.2 Plunger Seal Integrity

This test is intended to verify satisfactory plunger seal tightness for syringe systems and cartridge systems when forces simulating product delivery are applied and may induce leakage past the plunger. The test is also intended to verify satisfactory septum seal tightness for cartridge systems when the same forces are applied. *Procedure A* applies to manually operated syringe systems.*Procedure B* applies to non-manually operated prefilled syringe systems such as those in an auto-injector system. *Procedure C* applies to cartridge systems for dental local anesthesia products.*Procedure D* applies to all cartridge systems, excluding those for dental local anesthesia products.

For all procedures, use a mechanical testing machine capable of attaching to the test sample and continually applying the desired axial force (load cell accuracy NMT 1% of the applied force).

When reporting test results, include a test sample description, the test sample quantity, the axial force applied, the force application time, and visual observations supporting the final pass/fail conclusion. For *Procedure D*, include the parameters used to calculate the axial force applied.

Procedure A:

This procedure applies to manually-operated prefilled and single-use syringe systems. Select 10 samples for test, nominally filled with product or a product proxy. Coloring agent or dye may be added to the contents to improve visibility. Expel air to ensure complete product contact with the plunger. Using a suitable method and/or tool, seal the nozzle and ensure that the seal is maintained during the test. In the case of a fixed needle, ensure that the needle channel is blocked by a suitable method or tool.

Position the test sample in the sample holder. Apply an axial force to the plunger to generate a pressure of 300 kPa and maintain the pressure for 30 s. Release the pressure and visually examine the plunger.

Procedure B:

This procedure applies to prefilled syringe systems operated non-manually, as in an auto injector with a spring-driven or power-driven delivery device. Select 10 samples for test, nominally filled with product or product proxy. Coloring agent or dye may be added to the contents to improve visibility. Using a suitable method and/or tool, seal the nozzle and ensure that the seal is maintained during the test. In the case of a fixed needle, ensure that the needle channel is blocked by a suitable method or tool.

Position the test sample in the sample holder. Apply an axial force to the plunger by the final plunger rod consistent with the maximum force generated during use. Maintain the force for a period of seconds that is at least as long as the time required during use. Release the pressure and visually examine the plunger.

Procedure C:

This procedure applies to cartridge systems for dental local anesthesia products. Select 10 samples for test, nominally filled with product or a product proxy. Coloring agent or dye may be added to the contents to improve visibility. Position the test sample in the sample holder. Apply an axial force to the plunger to generate a pressure of 30 N for 1 min. Release the pressure and visually examine the plunger and septum.

Procedure D:

This procedure applies to cartridge systems, excluding those for dental local anesthesia products. Select 10 samples for test, nominally filled with product or a product proxy. Coloring agent or dye may be added to the contents to improve visibility. Position the test sample in the sample holder. Apply an axial force to the plunger for 1 min using the following equation to calculate the force, in Newtons, to be used:

$$\text{Result} = p \times d^2$$

p = 0.64 N/mm^2

d = nominal inner diameter of the container barrel (mm)

Release the pressure and visually examine the plunger and septum.

Acceptance criteria

Procedure A:

The packaging/delivery system is acceptable if, for all test samples, no leakage past the rear rib or final seal of the plunger is visible.

Procedure B:

The packaging/delivery system is acceptable if, for all test samples, no leakage past the rear rib or final seal of the plunger is visible.

Procedure C:

The packaging/delivery system is acceptable if, for all test samples, no leakage past the rear rib or final seal of the plunger is visible. No test sample shall demonstrate visible leakage past the closure (the septum) opposite the plunger.

Procedure D:

The packaging/delivery system is acceptable if, for all test samples, no leakage past the seal closure (the septum) or past the rear rib or final seal of the plunger is visible. It is not acceptable if any test sample demonstrates visible leakage past the closure (the septum) opposite the plunger.

7. TIP CAP AND NEEDLE SHIELD FUNCTIONAL SUITABILITY TESTS

This section addresses the functional requirements of tip caps and needle shields used in syringe systems. The functional tests included examine the forces required to remove the tip cap or needle shield from the container. *Procedure A* examines the axial pull-off force for removal of needle shields and tip caps. *Procedure B* examines the torque force required to remove a Luer-lock rigid tip cap.

Tip caps and needle shields are intended to maintain the sterility of the container contents. The test is designed to demonstrate the forces required to remove the tip cap or needle shield prior to dose administration. A closure system is satisfactory if the force needed to remove the closure allows for the manual removal of the tip cap or needle shield with relative ease but prevents the accidental loss of these components during storage or transit.

The following terms and definitions apply:

Needle shield: An elastomeric cover that fits over the needle fixed to a syringe. The needle shield is intended to physically protect the fixed (staked) needle of a syringe, to allow needle sterilization, and to maintain sterility of the syringe contents and of the needle up to the time of dosage form administration. Needle shields are removed by axial pull-off force.

Tip cap: An elastomeric component that seals the nozzle end of a syringe barrel. The tip cap is intended to physically protect the nozzle or Luer end of the syringe, to permit sterilization of the nozzle, and to maintain sterility of the syringe contents and of the nozzle up to the time a needle is affixed and the dosage form is administered. Tip caps are removed by axial pull-off force.

Luer lock rigid tip cap (LLR tip cap): An elastomeric component designed with a plastic Luer lock adaptor collar system that seals the nozzle end of a syringe barrel. The LLR tip cap is intended to physically protect the nozzle or Luer end of the syringe, to permit sterilization of the nozzle, and to maintain sterility of the syringe contents and of the nozzle up to the time a needle is affixed and the dosage form is administered. LLR tip caps are removed by torque force.

Procedure A:

This procedure applies when testing a needle shield or tip cap removed by axial pull-off force. Select 10 samples for test; test samples may be tested empty or filled with product or a product proxy.

Tests are performed using a universal tensile and compression testing machine appropriately equipped with a load cell (e.g., 50–100 N) linked to a data gathering system (typically NLT 40 Hz sampling rate). The machine should be capable of applying an axial force at the desired test speed (typically 100–1000 mm/min).

Position and secure the test sample in the holder of the test instrument in a vertical position with the needle shield or tip cap oriented upwards. Secure the tip cap or needle shield in a manner that does not deform/distort or slide against the component. Apply an axial tensile force at a minimum data sampling rate of 40 Hz until the tip cap or needle shield is completely removed from the syringe tip. Record the maximum force required to remove the closure in Newtons.

When reporting test results, include test speed, sampling rate, load cell used, maximum load recorded in the force versus displacement curve, test sample quantity, and the number that passed/failed according to the acceptance criteria.

Procedure B:

This procedure applies when testing an LLR tip cap removed by torque force. Select 10 samples for test; test samples may be tested empty or filled with product or a product proxy.

Tests are performed using a torque tester combined with a rotation device appropriately equipped with a torque cell with 35 Newton centimeters (Ncm) capacity and 0.05 Ncm resolution (or as appropriate to the torque to be measured) and linked to a data gathering system (typically NLT 65 Hz sampling rate). The machine should be capable of applying a torque force at the desired test speed (typically 20 rpm). For this test, either the syringe or the LLR tip cap can be rotated.

Position and secure the test sample in the holder of the test instrument in a vertical position with the LLR tip cap oriented upwards. Secure the LLR tip cap in a manner that does not deform/distort or slide against the component. Ensure that the torque cell is set to 0 prior to test start (no pre-torque should be applied). Rotate the tip cap (or the syringe) at a rotation speed of 20 rpm, or as appropriate, until the LLR tip cap is completely removed from the syringe tip. Record the peak load of the applied torque.

When reporting test results, include rotation speed, sampling rate, maximum torque, test sample quantity, and the number that passed/failed according to the acceptance criteria.

Acceptance criteria

Procedure A:

The quantitative acceptance limit established by the end user may vary with the product-specific packaging/delivery system. The packaging/delivery system is acceptable if, for all test samples, the maximum observed removal pull-off force does not exceed the maximum force that allows for ease of access and if the minimum observed force is sufficient to ensure that the closure remains in place during the product life cycle, preserving product sterility.

Procedure B:

The quantitative acceptance limit established by the end user may vary with the product-specific packaging/delivery system. The packaging/delivery system is acceptable if, for all test samples, the maximum observed removal torque force does not exceed the maximum force that allows for ease of access and if the minimum observed force is sufficient to ensure that the closure remains in place during the product life cycle, preserving product sterility..▲ (USP 1-Dec-2020)