BRIEFING

⟨382⟩ Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems. This proposed new general chapter addresses the fitness-for-intended-use functionality requirements of packaging/delivery systems that are intended for injectable dosage forms and that include primary packaging components partially or completely made of elastomeric material. Elastomeric closures, 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 closure 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 closure functionality assessment in early package development, is presented in *Assessment of Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems* ⟨1382⟩ that is 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 (data interpretation), and test outcome reporting.

A workshop, *Modernization of USP Packaging Standards for Glass and Elastomeric Components*, will take place June 19–20, 2017 at the USP Meetings Center in Rockville, Maryland, to discuss the proposals for three new chapters including this one, *Elastomeric Evaluation of Elastomeric Components Used in Pharmaceutical Packaging/Delivery Systems* ⟨1381⟩, and ⟨1382⟩, as well as the revision proposals to *Elastomeric Closures for Injections* ⟨381⟩. All four chapters appear in this issue of *PF*. See http://www.usp.org/meetings-courses/workshops/modernization-usp-packaging-standards-glass-and-elastomeric-components for more information about the workshop.

(GCPD: D. Hunt.)
Correspondence Number—C185735

Add the following:

⟨382⟩ ELASTOMERIC CLOSURE FUNCTIONALITY IN INJECTABLE

PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS

5.4.3 PLASTIC CONTAINERS FOR INTRAVENOUS INJECTIONS

1. INTRODUCTION

This chapter addresses the fitness-for-intended-use functionality requirements of packaging/delivery systems that are intended for injectable dosage forms and that include primary packaging components partially or completely made of elastomeric material. Elastomeric closures, 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 closure type is dependent on the packaging/delivery system and may cover more than one functional parameter. In all cases, the elastomeric closure 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 systems, the elastomeric closure 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 prefilled syringes and cartridges, and in pen, jet, and related injectors, the elastomeric closure (i.e., the plunger) needs to move in order to empty the container upon demand. Some elastomeric closures are intended to be singly pierced by a spike, or by a needle, sometimes repeatedly. In this scenario, determinations of *5.1 Fragmentation*, *5.2 Penetration Force*, and *5.3 Self-Sealing Capacity* are relevant.

The tests for functionality that are described in this chapter are intended to evaluate the fitness of a closure as part of its specific, final product-packaging system. A more complete discussion of fitness-for-intended-use testing, as compared to closure functionality assessment in early package development, is presented in *Assessment of Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems* ⟨1382⟩. The proper selection and design of functionality assessment studies is based on sound scientific principles that are consistent with 1) the nature

of the packaging system and packaged drug product; 2) the clinical use of the packaged drug product; and 3) the perceived safety risk associated with the packaging system and drug product. Alternative testing strategies for functionality assessment may be appropriate in certain circumstances with justification.

2. SCOPE

Packaging/delivery systems with elastomeric components include bottle and vial stoppers intended to be accessed with a needle or spike; plungers, needle shields, and tip caps for prefilled syringes or cartridges; components for pen, jet, and related injectors; lined caps for blow-fill-seal (BFS) plastic containers; and access ports to plastic bags or blow-molded infusion containers.

2.1 Package/Delivery Systems

The specific types of package/delivery systems within the scope of the chapter are listed below.

2.1.1 VIAL PACKAGES

Vial packages are package/delivery systems with closures intended to permit either single-dose or multiple-dose product access via a hypodermic needle. The applicable closures include those designed to accommodate either lyophilization or liquid-fill production processes.[1]

2.1.2 BOTTLE PACKAGES

Bottle packages are bottles with closures intended to permit dosage form access (single use only) via a spike piercing device. Closures that are applicable include those designed to accommodate either liquid-fill or lyophilization production processes.[2,3]

2.1.3 BFS CONTAINERS WITH PLASTIC CAPS THAT HAVE INSERTED ELASTOMERIC LINERS

This type of package/delivery system refers to BFS containers with plastic caps that have inserted elastomeric liners. The caps are attached to the container by welding or by collar technique. The capped containers are intended to contain liquid parenteral dosage forms and to allow for dosage form access (single use only) via a spike piercing device. Closures that are applicable include those described in ISO 15759.[4]

2.1.4 DENTAL CARTRIDGE PACKAGES AND PEN-INJECTOR PACKAGES

This package/delivery system refers to cartridge packages with closures intended to permit product access via a hypodermic needle or other piercing device for dental anaesthetic products.[5] Additionally, cartridges with closures intended for pen-injector packages are included.[6]

2.1.5 NEEDLE-BASED INJECTION SYSTEM PACKAGES

These containers are provided prefilled or are to be filled by the user with a dosage form intended by the applicant to be used with needle-based injection systems (e.g., cartridges).[7] Note that tests identified for these packages are not intended for dental anesthetic cartridge packages.

2.1.6 PLASTIC CONTAINERS FOR INTRAVENOUS INJECTIONS

This type of package/delivery system refers to plastic containers for parenterals; these containers have one or more chambers and have a total nominal capacity of 50–5,000 mL. Examples include film bags or blow-molded bottles for direct administration of infusion (injection) liquids.[8]

3. GENERAL TEST REQUIREMENTS

Refer to ⟨1382⟩ for guidance on test samples and their preparation, test sample population size, test procedures, test acceptance criteria (data interpretation), and test outcome reporting.

4. PACKAGE INTEGRITY

This section applies to the fit of an intact closure that is in contact with a container. All closures are required to ensure adequate package integrity, therefore, all packages within chapter scope are to meet an appropriate package integrity functionality assessment. Examples of closed packages within scope include 1) a stopper mechanically sealed to a vial or bottle; 2) a plunger stopper in contact with the wall of a syringe or cartridge (under ambient pressure or positive axial pressure); 3) a lined seal fitted to a cartridge; 4) a needle shield or tip cap fitted to a prefilled syringe (under ambient pressure or positive axial pressure); 5) the covered piercing area of a BFS container; and 6) access ports to plastic bags or blow-molded infusion containers. This section does not apply to closures after they have been breached by a needle or spike.

Package integrity refers to the ability of a packaging system to keep product contents in and detrimental environmental contaminants out. All packaging systems for injectable products closed with elastomeric closure components are required to demonstrate packaging integrity, as defined by the level of protection necessary for product quality maintenance. All packages with elastomeric closures mechanically fitted to the container demonstrate gaseous leakage past the seal interface to some extent, even when optimally assembled. Leaks of concern for sterile product–packages are those that pose risk to relevant product physicochemical and microbiological quality attributes.

Specifically, all injectable product–packages must 1) prevent microbiological ingress to ensure that product sterility is met; and 2) prevent product escape or entry of external liquid or solid matter to ensure that relevant product physicochemical quality attributes are met. In addition,

some products require the maintenance of package headspace content in a manner that ensures relevant product physicochemical quality attributes are met and/or allows for ease of product access by the end-user.

The maximum leakage limit is the greatest leakage rate (or leak size) tolerable for a given product–package that poses no risk to product safety and no, or inconsequential, impact on product quality. Inherent package integrity is the leakage rate (or leak size) of a well-assembled packaging system with no package defect; it is a measure of packaging system leak tightness.

Procedure: Select 30 containers per test. Test each container for integrity according to the leak test method of choice. No specific container–closure integrity test method is applicable to all injectable product–packaging systems. For packages with multiple closures (e.g., syringes with a plunger as well as a needle shield), separate and, perhaps, different types of leak tests and/or seal quality tests may be required to effectively evaluate the inherent integrity of the various closure seal types. The leak test(s) chosen are to be capable of verifying that the package's inherent integrity meets the maximum allowable leakage limit for the intended product–package.

The user is referred to *Package Integrity Evaluation—Sterile Products* ⟨1207⟩, as well as its subchapters, for further guidance on the concepts of inherent package integrity and maximum allowable leakage limit, and for guidance on the proper selection, development, validation, and utilization of appropriate leak test and seal quality test methods.

Data interpretation: The inherent package integrity results for all test packages must conform to the maximum allowable leakage limit demanded of the product to ensure that there is no risk to product microbiological quality, and no, or inconsequential, impact on product physicochemical quality attributes.

5. NEEDLE AND SPIKE ACCESS FUNCTIONALITY TESTS

Needle and spike access functionality tests apply to packaging system closures that allow for drug product access by a hypodermic needle, spike, or other closure penetration device.

The following tests are included in this functionality assessment category:

- *Fragmentation*. Also called coring, this is a measure of the package's tendency to fragment or core when pierced by a spike or hypodermic needle; the resulting closure fragments could be injected, risking patient harm.
- *Penetration Force*. Also called penetrability, this is the maximum force necessary to penetrate the closure using a spike or hypodermic needle. Penetration force tests also confirm the ability of the closure

to remain in place without being forced into the container during piercing.

- *Self-Sealing Capacity*. Also called reseal capacity or in-use leakage tests, this test is relevant to packaging systems that must maintain some degree of integrity during or post product access via a spike or hypodermic needle. Examples include packages intended to permit repeated dosing (e.g., a multiple-dose vial) or to permit dosing over an extended time period (e.g., a flexible intravenous infusion bag).
- *Spike Retention and Sealability Capacity*. This test is a measure of a closed package's ability to be fully penetrated by a spike (without pushing the closure into the container); to block visible evidence of liquid product leakage between the spike and the closure for the product dosing time period; and to retain the spike during this time period.

This section offers test methodology guidance for needle and spike functionality tests of various container–closure system types. Packaging systems intended for injectable products that permit dosage form access by way of needle or spike insertion are required to allow for safe and effective product access, without damaging the packaging system or the drug product, and without risking harm to either the patient receiving the medication or the individual accessing and/or administering the product.

Perform all piercings using the designated needle or device intended for finished drug product access. If the intent is to provide or to specify a needle or spiking device with the marketed product, then employ this same item or a facsimile. If the needle or device will be neither specified nor provided (i.e., not designated), employ the recommended piercing needle or device facsimile cited in the test protocols. Degrease all metal device facsimiles prior to use.

Perform all piercings in the same manner to be recommended or anticipated for the marketed product. For example, if the directions dictate that the needle or spike is to be pushed or screwed onto the package, perform the test penetrations accordingly. If the needle or spike is to be inserted vertically, perform the piercings in the same manner.

If the marketed product will include a device equipped to perform closure piercing (such as an auto-injector, pen injector, etc.), perform test piercings using this same device and in the same manner.

In cases where a notable range of access devices or conditions applies, tests may be designed to examine worst-case conditions, or to bracket such conditions, as appropriate.

5.1 Fragmentation

Practices relevant to the performance of all *Fragmentation* tests include 1) the use of *Particle-free water* to fill the test samples; and 2) adjustments to

the test procedure filling volume which may be necessary to accommodate the wide range of package types and sizes tested.

Additional test protocol information as well as the acceptance criteria are provided in the package-specific sections below.

This term and definition applies:

Particle-free water: Distilled water filtered through a membrane with a pore size of 0.22 µm.

5.1.1 VIAL PACKAGES

Procedure: Select 12 containers for test. Fill each container to 80% nominal capacity with *Particle-free water* prior to closure. Use the designated penetration needle fitted to a clean syringe filled with *Particle-free water*. In the absence of a designated needle, use a 21-gauge needle with a bevel angle of 11 ± 2° and a 0.8-mm external diameter.[9]

Pierce the closure with the needle perpendicular to the surface. After each puncture, inject 1 mL of *Particle-free water* into the vial through the inserted needle while removing 1 mL of air. Repeat piercings for each closure, piercing each time at a different location. Match the total number of 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 four times each, the needle may be replaced more frequently. Check that the needle is not blunted during the test. Perform the water rinsings and particle count procedure according to *Particulate Matter in Injections ⟨788⟩, Method 2 Microscopic Particle Count Test*.

Data interpretation: The packaging system closure is acceptable if NMT 5 elastomeric closure particles >150 µm in diameter are observed, per 12 containers tested.

5.1.2 BOTTLE PACKAGES

Procedure: Select 10 containers for test. Fill each container to 50% nominal capacity with *Particle-free water* prior to closure. Perform penetrations using the designated spike. In the absence of a designated spike, use a stainless steel closure-piercing device, such as described in ISO 8536-2[2] (closures for infusion bottles) or ISO 8536-6[3] (freeze drying closures for infusion bottles), as appropriate.

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

Use a fresh spike for each closure. If a stainless steel piercing device is used, the same device may be used for each closure. Care should be exercised to avoid blunting or otherwise damaging the device tip.

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

Perform the water rinsings and particle count procedure according to *Particulate Matter in Injections ⟨788⟩, Method 2 Microscopic Particle Count Test*.

Data interpretation: The packaging system closure is acceptable if NMT 20 elastomeric closure particles >150 µm in diameter are observed, per 10 containers tested.

5.1.3 BFS CONTAINERS WITH PLASTIC CAPS THAT HAVE INSERTED ELASTOMERIC LINERS

Procedure: Select 10 containers for test. Fill each container to 50% nominal capacity with *Particle-free water* prior to closure. Perform penetrations using the designated spike. In the absence of a designated spike, use a stainless steel closure piercing device.

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

Use a fresh spike for each closure. If a stainless steel piercing device is used, the same device may be used for each closure. Care should be exercised 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*.

Data interpretation: The packaging system closure is acceptable if NMT 7 elastomeric closure particles >150 µm in diameter are observed, per 10 piercings.

5.1.4 DENTAL CARTRIDGE PACKAGES AND PEN-INJECTOR PACKAGES

Procedure: Select 12 containers for test. Perform penetrations using the designated needle. In the absence of a designated needle, use a needle with a 0.4-mm outer diameter that conforms to the butt-end requirements in ISO 7885.[10]

Pierce the closure with the needle perpendicular to the surface. After each puncture, purge the lumen of the needle 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 for each closure. For closures intended to have more than four piercings each, the needle may be replaced more frequently. Check that the needle is not blunted during the test.

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*.

Data interpretation: The packaging system closure is acceptable if NMT 5 elastomeric closure particles >150 µm in diameter are observed, per 12 containers tested.

5.1.5 NEEDLE-BASED INJECTION SYSTEM PACKAGES

Procedure: Select containers for test. The number of containers selected should permit a total of 100 punctures to be performed. For example, if each container is to be punctured 10 times, select 10 containers; if each container is punctured one time, select 100 containers.

Perform penetrations using the designated needle. Match the number of penetrations performed on each container to product usage recommendations.

Use a new needle for each penetration, unless otherwise indicated in product usage directions. After each puncture, purge the lumen of the needle 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*.

Data interpretation: The packaging system closure is acceptable if NMT 6 elastomeric closure particles >150 µm in diameter are observed, per 100 punctures.

5.2 Penetration Force

The following practices are recommended when performing *Penetration Force* tests:

- Consideration should be given to the possible impact of liquid in the test package 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 the appropriate dosage form or an appropriate simulation liquid.

- Perform these automated penetration tests using an instrument or device that can be mounted with the penetration needle or spike, and which is then able to move perpendicularly at the required constant rate of strain. The force exerted backward on the spike or needle 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 as well as acceptance criteria are provided in the package-specific sections which follow.

5.2.1 VIAL PACKAGES

Procedure: Select 10 containers for test. Perform tests using the designated penetration needle. In the absence of a designated needle, use a 21-gauge needle with a bevel angle of 11 ± 2° and a 0.8-mm external diameter.[9]

Utilize a mechanical testing machine capable of accommodating the test sample fixture while monitoring the axial force required to penetrate the closure [tolerance of ±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 a needle positioned perpendicular to the surface. Unless product usage recommendations differ, use a fresh needle for each closure. Care should be exercised to avoid blunting or otherwise damaging the needle tip.

Data interpretation: The packaging system closure is acceptable if the penetration force measured from the moment the 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 vial. The quantitative acceptance limit may vary with the product–package. Otherwise, the packaging system is acceptable if the penetration force does not exceed 10 N for each closure. Penetration force readings should be accurate to within 0.25 N.

5.2.2 BOTTLE PACKAGES

Procedure: Select 10 containers for test. Use the designated spike for all penetrations. In the absence of a designated spike, a stainless steel closure piercing device such as described in ISO 8536-2[2] (closures for infusion bottles) or ISO 8536-6[3] (freeze drying closures for infusion bottles) may be used, as appropriate. Degrease all metal spikes/devices prior to use.

Utilize a mechanical testing machine capable of accommodating the test sample fixture while monitoring the axial force required to penetrate the closure (tolerance of ±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 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. Care should be exercised to avoid blunting or otherwise damaging the device tip.

Data interpretation: The packaging system closure is acceptable if the penetration force, measured from the moment the spike 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.

The quantitative acceptance limit may vary with the product–package. Otherwise, the following criterion applies. For packages intended for manual spike insertion, the packaging system is acceptable if the penetration force does not exceed 80 N for each test sample and the average of all test samples is less than 75 N. Penetration force readings should be accurate to within 2 N.

5.2.3 BFS CONTAINERS WITH PLASTIC CAPS THAT HAVE INSERTED ELASTOMERIC LINERS

Procedure: Select 10 containers for test. Use the designated spike for all penetrations. In the absence of a designated spike, a stainless steel closure piercing device may be used.[4] Degrease all metal spikes/devices prior to use.

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.

Utilize a mechanical testing machine capable of accommodating the test sample fixture while monitoring the axial force required to penetrate the closure (tolerance of ±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. Care should be exercised to avoid blunting or otherwise damaging the device tip.

Data interpretation: The packaging system closure is acceptable if the penetration force, measured from the moment the spike 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 quantitative acceptance limit may vary with the product–package. Otherwise, the following criterion applies. The packaging system is acceptable if the penetration force does not exceed 80 N for each test sample, and the average of all test samples is less than 75 N. Penetration force readings should be accurate to within 2 N.

5.2.4 PLASTIC CONTAINERS FOR INTRAVENOUS INJECTIONS

Procedure: Select 10 containers for test. Use the designated spike or infusion device for all penetrations. In the absence of a designated spike or infusion device, a stainless steel closure piercing device may be used.[11] Degrease all metal spikes/devices prior to use.

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

Pierce each test sample closure one time at the insertion point. Use a fresh device/spike for each closure. If a stainless steel piercing device is used, the same spike may be used for each closure. Care should be exercised to avoid blunting or otherwise damaging the device tip.

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

Data interpretation: The packaging system closure is acceptable if the penetration force, measured from the moment the spike 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 quantitative acceptance limit may vary with the product–package. Otherwise, the following criterion applies. The packaging system is acceptable if the force to fully penetrate the closure does not exceed 200 N at an insertion rate of 500 mm/min, and if the device/spike penetration does not cause the closure to be pushed into the container. Penetration force readings should be accurate to within 2 N.

5.3 Self-Sealing Capacity

This section applies to multiple-dose product-package closures required to ensure adequate package integrity during in-use conditions of multiple breaches by a needle or spike. Packages intended for multiple-dose product application within chapter scope that are subject to this functionality requirement include 1) vial packages; 2) bottle packages; 3) BFS containers with plastic caps that have inserted elastomeric liners; 4) dental cartridge packages and pen-injector packages; and 5) plastic containers for intravenous injections.

In-use package integrity refers to the ability of the punctured closure to prevent microbial ingress and product loss between and during periods of dosage access. The level of protection required, also referred to as the in-use maximum allowable leakage limit, is that which ensures maintenance of product physicochemical and microbiological quality attributes.

Procedure: Select 30 containers per test. Perform multiple closure punctures on each test sample using the designated needle or spike according to the most extreme intended-use directions. Test each punctured closure package system for integrity according to the leak test method of choice.

No specific method for in-use container–closure integrity testing is applicable to all injectable product-packaging systems. The leak test chosen is to be capable of verifying that the package's in-use integrity meets the maximum allowable leakage limit for the intended product.

The user is referred to ⟨1207⟩ and its subchapters for further guidance on 1) the concepts of in-use package integrity and in-use maximum allowable leakage limit; and 2) the proper selection, development, validation, and utilization of appropriate leak test and seal quality test methods.

Data interpretation: The in-use package integrity results for all test packages are required to conform to the in-use maximum allowable leakage limit demanded of the product to ensure no, or inconsequential, risk to the product's microbiological and physicochemical quality attributes.

5.4 Spike Retention and Sealability Capacity

This test applies to packages intended to permit product access 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 dosage form access. If the applicant intends to provide or to specify a spiking device with the commercialized product, use this same device or a facsimile for the test. If the device is neither specified nor provided, use the recommended piercing device cited in the test protocols that follow. Degrease all metal device facsimiles prior to use.

Additional test protocol information as well as acceptance criteria are provided in the package-specific sections that follow.

5.4.1 BOTTLE PACKAGES

Procedure: Select 10 containers for test, filled to at least 50% nominal capacity with liquid product or liquid product-proxy. Use the designated spike for all penetrations. In the absence of a designated spike, a stainless steel closure piercing device such as described in ISO 8536-2[2] (closures for infusion bottles) or ISO 8536-6[3] (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 to the spike position.

Data interpretation: The package system closure is acceptable if 1) all bottles were able to be penetrated fully without pushing the closure into the

bottle; 2) all spikes were retained in the closure for the test time period; and 3) no liquid leakage was observed.

5.4.2 BFS CONTAINERS WITH PLASTIC CAPS THAT HAVE INSERTED ELASTOMERIC LINERS

For both procedures below, use the designated spike for all penetrations. In the absence of a designated spike, a stainless steel closure-piercing device may be used, as appropriate.[4]

Procedure A: Select 10 containers for test. Place the spike perpendicular to the center of the closure target area. 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.

Procedure B: Select 10 containers for test, nominally filled with product or product-proxy. Place the spike perpendicular to the center of the closure target area. Force the spike through the closure until complete penetration is achieved. Position the test sample with the device 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.

Data interpretation (Procedure A): The package system closure is acceptable if spike removal force is NLT 15 N (±2 N).

Data interpretation (Procedure B): The package system closure is acceptable if all containers are observed to have no leakage at the insertion point, and no insertion spike slides out from the insertion point.

5.4.3 PLASTIC CONTAINERS FOR INTRAVENOUS INJECTIONS

Procedure: Select 10 containers for test, nominally filled with liquid product or product-proxy. Use the designated spike for all penetrations. In the absence of a designated spike, a stainless steel closure piercing device may be used, as appropriate.[11]

Place the spike perpendicular to the center of the 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 two plane-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.

Data interpretation: The package system closure is acceptable if 1) all containers are observed to have no leakage at the insertion point; 2) no

insertion part slides out from the insertion point; and 3) the removal force is NLT 15 N (±2 N).

6. PLUNGER FUNCTIONALITY TESTS

The following sections address the functionality of elastomeric plunger components (also called pistons) in prefilled syringes and cartridges, and in pen, jet, and related injectors.

6.1 Plunger Break Force and Plunger Glide Force

These terms and definitions apply:

Plunger break force: The force required to initiate the movement of the plunger of a prefilled syringe or cartridge.

Plunger glide force: The force required to sustain the movement of the plunger to expel the content of the syringe or cartridge.

Packaging systems designed to allow for product elution via a plunger are required to allow for complete, safe, and effective product delivery without damaging the packaging system and without risking harm to either the patient receiving the medication or the individual accessing and/or administering the product. Plunger break force and plunger glide force tests allow an analysis of the ease by which product delivery may be performed.

Product characteristics of viscosity and density can have a direct impact on break force and glide force. These forces are also influenced by the interference fit between the plunger and the barrel, and the lubrication of the plunger and the inner surface of the barrel. The use of connecting devices with the test sample (described below) also can influence the findings.

It is noteworthy that break force can increase over time to an unacceptable level at which it is very difficult to initiate plunger movement by hand. If the plunger is operated by a spring, the break force required may be greater than the capability of the spring. An irregular glide force, or one that rises significantly towards the syringe nozzle, can indicate non-homogeneous lubrication of the barrel. Given the number of variables, it is not possible to provide a single test method. Guidance for establishing an appropriate test method is offered in the procedure that follows.

Procedure: Select 10 containers for test, nominally filled with product or product-proxy. Perform tests using a mechanical testing machine capable of attaching to the test sample and of depressing the syringe piston at a constant linear rate, while at the same time continuously measuring and recording the force with an accuracy of 1% of full-scale reading.

Test samples of prefilled syringes and cartridges that do not have a fixed (staked) needle may be tested with or without the addition of "connecting

devices" such as needles, needle-less luer connections, adapters, and transfer units.

Select an elution speed slow enough to clearly detect and measure the break force. The elution speed for large-volume syringes (e.g., >50 mL) should permit the measurement of break force and glide force but should not take too long a time to complete the test. An elution speed of 1–2 mm/s is generally suitable for syringes 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 force and plunger glide force, recording the forces measured in Newtons. Plunger break force is expressed as the maximum force required to initiate the movement of the plunger of the prefilled syringe or cartridge. Plunger glide force is expressed as the average, maximum, and minimum forces measured for the length of the barrel.

When testing dual-chamber prefilled syringes and cartridges containing two plungers (one that separates the two chambers and a second to seal the syringe barrel), measure and record the break force and the average and maximum glide forces for each of the two plungers. To achieve acceptable performance, each plunger must meet the functional specification limit.

Data interpretation: For injection devices intended for manual use, the packaging system closure is acceptable if the plunger break force allows for ease of plunger movement initiation. The maximum plunger glide force is acceptable if it is not greater than the plunger break force. The difference between the maximum and minimum plunger glide forces should not be indicative of barrel lubrication inconsistencies. The average plunger glide force is acceptable if the force allows for ease of complete product elution.

For injection devices intended for power-driven (non-manual) use, the packaging system closure is acceptable if the plunger break and glide forces 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 term and definition applies:

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

Packaging systems designed to allow for product elution via a plunger are required to allow for complete, safe, and effective product delivery without damaging the packaging system and without risking harm to either the patient receiving the medication or the individual accessing and/or administering the product.

The test is designed to apply a fixed force to the plunger of a sealed prefilled syringe or cartridge containing liquid product in an attempt to induce leakage past the plunger. Satisfactory plunger seal tightness will not permit visible leakage of liquid product past the plunger when forces simulating product delivery are applied.

Procedure: Select 10 containers for test, filled with product or product-proxy to nominal capacity (expel air). 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.

Utilize a mechanical testing machine capable of attaching to the test sample and continually applying the desired axial force. 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.

Data interpretation: The packaging system closure is acceptable if no leakage past the plunger is visible.

7. TIP CAP AND NEEDLE SHIELD FUNCTIONALITY TESTS

This section addresses the functional requirements of tip caps and needle shields used in prefilled syringes and cartridges, and in pen, jet, and related injectors. The functional test examines the force required to remove the tip cap or needle shield from a prefilled syringe or cartridge.

These terms and definitions apply:

Tip cap: A component that seals the nozzle end of a syringe barrel.

Needle shield: A cover intended to physically protect the fixed (staked) needle of a prefilled syringe.

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.

Procedure: Select 10 containers for test; containers may be tested empty or filled with product or 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 the test sample in a vertical position in the holder of the test instrument 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 until the tip cap or needle shield is completely removed from the syringe tip. Record the force required to remove the closure in Newtons.

Data interpretation: The quantitative acceptance limit may vary with the product–package. The packaging system closure is acceptable if the maximum observed removal 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.

SWS WORKFLOW VALIDATION

XML Attribute	XML Value	SWS Attribute	SWS Value	Notes
No validation errors found				

▪1S (*USP41*)

---

[1] ISO (2016) Elastomeric parts for parenterals and for devices for pharmaceutical use—Part 5: Functional requirements and testing.

---

[2] ISO (2010) Infusion equipment for medical use—Part 2: Closures for infusion bottles.

---

[3] ISO (2016) Infusion equipment for medical use—Part 6: Freeze drying closures for infusion bottles.

---

[4] ISO (2005) Medical infusion equipment—Plastics caps with inserted elastomeric liner for containers manufactured by the blow-fill-seal (BFS) process.

---

[5] ISO (2012) Prefilled syringes—Part 3: Seals for dental local anaesthetic cartridges.

---

[6] ISO (2012) Pen systems—Part 3: Seals for pen-injectors for medical use.

---

[7] ISO (2012) Needle-based injection systems for medical use—Requirements and test methods—Part 3: Finished containers.

[8] ISO (2010) Plastic containers for intravenous injections.

[9] ISO (2016) Sterile hypodermic needles for single use—Requirements and test methods.

[10] ISO (2010) Dentistry—Sterile injection needles for single use.

[11] ISO (2010) Infusion equipment for medical use—Part 4: Infusion sets for single use, gravity feed.