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General ChaptersGeneral Tests & Assays⟨382⟩ Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems — PF 48(3)

Reference Standards

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BRIEFING

⟨382⟩ Elastomeric Component Functional Suitability In Parenteral Product Packaging/Delivery Systems. This proposal is based on the version of the chapter to be official on December 1, 2025. Due to stakeholder comments, a revision is being proposed to Table 1 to clarify the applicability of the spike retention and sealability capacity test as it relates to certain size vials. Depending on vial size, neck finish, and product volume, a spiking device is not used or does not fit.

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

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Add the following:

▲⟨382⟩ ELASTOMERIC COMPONENT FUNCTIONAL SUITABILITY IN PARENTERAL PRODUCT PACKAGING/DELIVERY SYSTEMS

(*USP is proposing a delayed implementation date of December 1, 2025 for this revision. The date of December 1, 2023 for the current revision reflects the targeted official date for all proposals in this issue of PF. However, the dates in this chapter will be updated to reflect the delayed implementation date upon official publication.*)

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 ⟨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 Extrusion 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. 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; and
- 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. All elastomeric components in direct or indirect contact with the pharmaceutical product are within scope. 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. Excluded from this chapter are products and their packaging that are regulated as medical devices (e.g., unfilled syringes, infusion administration sets, delivery systems for drug-eluting stents).

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 ⟨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 ferrule). The closure is intended to permit product access via penetration by a hypodermic needle (for single or multiple penetrations), or by a spike piercing device (for a single penetration). 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 penetration 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. 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

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. Other relevant details may include the component and the relevant interfacing component's age, design, and material.

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, with input from a risk assessment, 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.

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 and method of choice), test sample quantity (with justification), 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.

Change to read:

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	▲If applicable▲ (USP 1-Dec-2023)
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 product-access piercing devices.
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 not less than 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 or coating film 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. 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 ⟨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 ⟨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 not less than 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 ⟨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 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 ⟨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. Select 10 samples for test. 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 with a sampling rate of at least 100 Hz. 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 with a sampling rate of at least 100 Hz.

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 with a sampling rate of at least 100 Hz.
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 with a sampling rate of at least 100 Hz.

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 ⟨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 a 21-gauge hypodermic injection needle (0.8-mm outer diameter). Penetrate each closure 3 times in 3 different locations. Use a new needle for each closure.
BFS systems:
The following procedure applies to large volume parenteral BFS systems. For dosage form preparation penetrations (addition of drug product), if no needle is designated, use a 21-gauge hypodermic injection needle (0.8-mm outer diameter) with a medium bevel angle. Penetrate the closure in its part intended for product addition 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:
For dental cartridge systems, use a 27-gauge needle (0.41-mm outer diameter). For other cartridge systems, use a 29-gauge hypodermic needle (0.34-mm outer diameter) or the needle designated for product access. 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 large volume parenteral 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 with a sampling rate of at least 100 Hz 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 with an appropriate pressure gauge attached to the container such that the internal pressure can be properly measured without potential for leakage from the test measurement system. (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 with a sampling rate of at least 100 Hz 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 extrusion 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 Extrusion Forces

Some of the numerous variables that impact plunger break-loose and extrusion 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 extrusion 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 not more than 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 extrusion forces while allowing sufficient time to complete the test. An elution speed of 3–4 mm/s 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 extrusion 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 extrusion force.

When testing dual-chamber syringes and cartridges containing 2 plungers (one that separates the 2 chambers and another that seals the syringe barrel) 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 extrusion forces measured. Include justification for the quantitative acceptance criteria chosen for break-loose and plunger extrusion 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. Any degree of stick-slip behavior should be investigated, and the acceptability must be justified by the manufacturer.
3. The minimum and maximum plunger extrusion forces allow for ease of plunger movement propagation.
4. The maximum plunger extrusion force allows for ease of complete product elution.
5. Dual-chamber syringes and cartridges: Measure and report the break-loose force and the minimum and maximum extrusion forces for each of the 2 plungers. To achieve acceptable performance, each plunger must meet the functional acceptance criteria. The difference between the maximum and minimum plunger extrusion forces is indicative of barrel lubrication consistency. Other phenomena, such as dimensional variations, may also affect 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 extrusion 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 first rib of 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 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 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:

Force = $p \times d^2$

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 adapter 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.▲

(Official 1-Dec-2025)

Auxiliary Information-

Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
<382> ELASTOMERIC COMPONENT FUNCTIONAL SUITABILITY IN PARENTERAL PRODUCT PACKAGING/DELIVERY SYSTEMS	Desmond G. Hunt Principal Scientific Liaison	GCPD2020 General Chapters - Packaging and Distribution

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Commenting open for 49 more days

General ChaptersGeneral Tests & Assays⟨383⟩ Cured Silocone Elastomers for Pharmaceutical Packaging and Manufacturing Components — PF 48(3)

Reference Standards
Notice:Documents in PF Online are not official and not suitable to demonstrate compliance. They may never become official.
BRIEFING
⟨383⟩ Cured Silicone Elastomers for Pharmaceutical Packaging and Manufacturing Components. The General Chapters—Packaging and Distribution Expert Committee is proposing this new chapter, based on comments received from the *PF* 45(2) [March–Apr 2019] publication of Plastic Materials, Components, and Systems Used in the Manufacturing of Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products ⟨665⟩ and the *USP General Chapter Prospectus* (https://www.uspnf.com/notices/gc-prospectus-688-cured-silicone-elastomers-for-pharm-manufacturing-and-packaging-components).
This chapter would apply to cured silicone components such as tubing, gaskets, and O-rings that are used in manufacturing operations for drug substances and drug products, as well as silicone components for pharmaceutical packaging systems.
Due to the scope of the proposed new chapter, the Packaging and Distribution Expert Committee is proposing a 5-year delayed implementation to allow industry adequate time to implement.
(GCPD: D. Hunt)
Correspondence Number—C266457

Add the following:
▲⟨383⟩ CURED SILICONE ELASTOMERS FOR PHARMACEUTICAL PACKAGING AND MANUFACTURING COMPONENTS
(*USP is proposing a delayed implementation date of December 1, 2028 for this revision. The date of December 1, 2023 reflects the targeted official date for all proposals in this issue of PF. However, the dates in this chapter will be updated to reflect the delayed implementation date.*)
INTRODUCTION
Cured silicone components are used as elastomeric closures for pharmaceutical packaging and also as components in manufacturing operations for drug substances and drug products, such as tubing,

gaskets, and O-rings. Silicone elastomers are obtained by cross-linking (curing) a linear polysiloxane constructed mainly of dimethylsiloxy units with small quantities of methylvinylsiloxy groups, where the chain ends are blocked by trimethylsiloxy or dimethylvinylsiloxy groups.

The cross-linking is carried out via high-temperature vulcanization, either by a free-radical reaction using organic peroxides, or by an addition reaction using platinum as a catalyst. The free-radical reaction uses 2,4-dichlorobenzoyl peroxide or a lower amount of peroxide together with alkyl or alkaryl peroxides such as di-t-butyl peroxide or dicumyl peroxide. The addition reaction is a hydrosilylation of polysiloxane with –SiH groups using a platinum catalyst and has the advantages that no by-products are formed, and only very small amounts of catalysts (ppm range) are required.

In all cases, appropriate additives such as silica are used. Organosilicon additives such as α,ω- dihdroxy polydimethylsiloxane can also be used in small quantities.

SCOPE

The scope of the chapter includes elastomeric closures for pharmaceutical packaging and manufacturing components such as tubing, gaskets, and O-rings.

TEST METHODS

•Biological Reactivity

Perform biological reactivity tests for systemic injection and intracutaneous injection according to Biological Reactivity Tests, In Vivo ⟨88⟩ to obtain classification of sample according to Class VI. [Note—The implantation test in Class VI is not required for manufacturing and packaging components.]

Biological reactivity testing is not required for elastomeric closures used to package oral or topical dosage forms, or for manufacturing components, but may be performed if a Plastic Classification is desired.

•Identification

Apparatus:

Use an infrared spectrophotometer capable of measuring in transmission mode or reflectance mode (equipped with an internal reflectance accessory). See Mid-Infrared Spectroscopy ⟨854⟩.

Sample Preparations

Transmission mode:

Prepare a specimen of appropriate thickness without visible defects (cracks or holes) and mount it onto an appropriate sample holder. The specimens can be produced using a microtome or by compression to form a thin, uniform film by exposure to elevated temperatures and pressures (2000 psi or more). The temperatures at which the thin

films are generated represent a trade-off between producing a melt (which dictates the lowest temperature necessary) and degrading the sample (which dictates the highest temperature allowed). Ultimately, the temperatures that are used are appropriate if the film produced is conducive to the IR analysis.

Attenuated total reflection (ATR) mode:

Prepare a flat section and trim it as necessary to obtain a segment that is convenient for mounting in the ATR accessory. Taking care to avoid scratching the surfaces, wipe the specimen with dry paper or a soft cloth dampened with methanol, if necessary, and allow the surfaces to dry. Ensure close and uniform contact between the specimen and the entire internal reflection element (IRE) crystal surface by applying pressure.

Procedure:

Place the mounted specimen in the sample compartment of the infrared spectrophotometer or ensure that the ATR accessory is placed in the sample beam of the infrared spectrophotometer. Determine the infrared spectrum from 3800 to 650 cm (2.6 – 15 μm).

Acceptance criteria:

The specimen exhibits an absorption spectrum that is substantially equivalent to that of USP Silicone Elastomer RS. Substantial, as opposed to exact, equivalence allows for minor spectral differences arising from the natural compositional and/or physical variation among polymers of this class. Substantial equivalence is achieved when all differences between the sample and Reference Standard spectra can be explained in the context of such natural compositional and/or physical variations.

•Physicochemical Tests

Appearance of Solution S1

If necessary, cut the material into pieces of maximum dimension of not more than 1 cm in length.

Extraction Solution S1 (water extraction):

Place 25 g of the test material in a borosilicate glass flask with a ground-glass neck. Add 500 mL of *Purified Water*, and boil under reflux conditions for 5 h. Allow to cool and decant the solution.

Procedure:

Determine the turbidity of *Extraction Solution S1* according to *Appearance of Solution (Turbidity/Opalescence and Color)* in Elastomeric Closures for Injections ⟨381⟩ using reference suspensions described in Table 1.

Acceptance criteria:

Extraction Solution S1 is not more opalescent than *Reference Suspension A* (3 NTU).

Acidity or alkalinity

Bromothymol blue solution:
Dissolve 100 mg of bromothymol blue in 100 mL of diluted alcohol and filter if necessary.
Procedure:
To 100 mL of *Extraction Solution S1* add 0.15 mL of *Bromothymol blue solution*. Determine the titration volume of 0.01 N sodium hydroxide required to change the color of the indicator to blue.
Acceptance criteria:
NMT 2.5 mL of 0.01 N sodium hydroxide is required to change the color of the *Bromothymol blue solution* indicator to blue.
Methyl orange solution:
Dissolve 100 mg of methyl orange in 80 mL of *Purified Water* and dilute with alcohol to 100 mL. Test for sensitivity by adding 0.1 mL of *Methyl orange solution* to 100 mL of carbon dioxide-free *Purified Water*. NMT 0.1 mL of 1 M hydrochloric acid is required to change the color from yellow to red.
Procedure:
To a separate 100-mL portion of *Extraction Solution S1* add 0.2 mL of *Methyl orange solution*. Determine the titration volume of 0.01 N hydrochloric acid required to reach the beginning of the color change of the indicator from yellow to orange.
Acceptance criteria:
NMT 1.0 mL of 0.01 M hydrochloric acid is required to reach the beginning of the color change of the *Methyl orange solution* indicator from yellow to orange.
Reducing substances
Dilute sulfuric acid:
Add 5.5 mL of sulfuric acid to 60 mL of *Purified Water*, allow to cool and dilute with *Purified Water* to 100 mL.
Starch solution:
Triturate 1.0 g of soluble starch with 5 mL of *Purified Water* and while stirring, pour the mixture into 100 mL of boiling *Purified Water* containing 10 mg of mercuric iodide. [Note—Commercially available reagents may be used, including mercury-free solutions or those containing alternative preservatives.]
Carry out the test for sensitivity each time the reagent is used.
Test for sensitivity:
To a mixture of 1 mL of the *Starch solution* and 20 mL of *Purified Water* add about 50 mg of potassium iodide and 0.05 mL of *Iodine solution*.
Acceptance criteria:
The solution is blue.
Iodine solution:

To 10.0 mL of 0.05 M iodine add 0.6 g of potassium iodide and dilute with *Purified Water* to 100.0 mL.
Procedure:
To 20 mL of *Extraction Solution S1* add 1 mL of dilute sulfuric acid and 20 mL of 0.002 M potassium permanganate. Allow to stand for 15 min. Add 1 g of potassium iodide and titrate immediately with 0.01 M sodium thiosulfate using 0.25 mL of *Starch TS* as indicator. Carry out a blank titration using 20 mL of *Purified Water* instead of *Extraction Solution S1*.
Acceptance criteria:
The difference between the titration volumes is NMT 1.0 mL.
Use an infrared spectrophotometer capable of measuring in transmission mode or reflectance mode (equipped with an internal reflectance accessory). See Mid-Infrared Spectroscopy ⟨854⟩.
Substances soluble in hexane
Extraction Solution S2 (hexane extraction):
Place 2.0 g of the test material in a borosilicate glass flask with a ground-glass neck. Add 100 mL of hexane, and boil under reflux conditions for 4 h. Allow to cool, and rapidly filter the extraction solution through a sintered-glass filter (10 – 16 µm pore size). Collect the filtrate and close the container immediately to avoid evaporation.
Procedure:
Evaporate 25 mL of *Extraction Solution S2* in a weighed glass evaporating dish on a water bath and dry in an oven at 100° – 105° for 1 h. Allow to cool and weigh the dish.
Acceptance criteria:
The difference in weight of the glass evaporating dish, before and after drying of the residue, is NMT 15 mg (3% by weight).
Phenylated compounds
Procedure:
Measure the UV absorbance of *Extraction Solution S2* between the wavelengths of 250 – 340 nm.
Acceptance criteria:
The absorbance is NMT 0.4.
Mineral oils
Procedure:
Place 2 g of the test material in a 100-mL conical flask containing 30 mL of a mixture of 5 volumes of *ammonia TS* and 95 volumes of pyridine. Allow to stand for 2 h shaking frequently. Decant the pyridine solution and examine in ultraviolet light at 365 nm.
Acceptance criteria:

The fluorescence is not greater than that of a solution containing 1 ppm of quinine sulfate in 0.005 M sulfuric acid examined under the same conditions.

Volatile matter

Procedure:

Dry 10.0 g of the test material by placing it in a desiccator over anhydrous calcium chloride for 48 h. Weigh 10.0 g of the dried test material and heat it in an oven at 200° for 4 h. Allow to cool in a desiccator and weigh again. Volatile matter is calculated as.

Acceptance criteria:

Dry 10.0 g of the test material by placing it in a desiccator over anhydrous calcium chloride for 48 h. Weigh 10.0 g of the dried test material and heat it in an oven at 200° for 4 h. Allow to cool in a desiccator and weigh again. Volatile matter is calculated as.

Residual peroxides

Starch solution:

Triturate 1.0 g of soluble starch with 5 mL of *Purified Water* and while stirring, pour the mixture into 100 mL of boiling *Purified Water* containing 10 mg of mercuric iodide. [Note—Commercially available reagents may be used, including mercury-free solutions or those containing alternative preservatives.]

Carry out the test for sensitivity each time the reagent is used.

Test for sensitivity:

To a mixture of 1 mL of the *Starch solution* and 20 mL of *Purified Water* add about 50 mg of potassium iodide and 0.05 mL of *Iodine solution*.

Acceptance criteria:

The solution is blue.

Iodine solution:

To 10.0 mL of 0.05 M iodine add 0.6 g of potassium iodide and dilute with *Purified Water* to 100.0 mL.

Procedure:

Place 5 g of the test material in a borosilicate glass flask and add 150 mL of methylene chloride, then close the flask. Stir with a mechanical stirrer for 16 h. Filter rapidly, collecting the filtrate in a flask with a ground glass neck. Replace the air in the flask with oxygen-free nitrogen, add 1 mL of a 200-g/L solution of sodium iodide in anhydrous acetic acid, then close the flask and shake thoroughly. Allow to stand for 30 min protected from light. Add 50 mL of *Purified Water* and titrate immediately with 0.01 M sodium thiosulfate, using 0.25 mL of *Starch TS* solution as indicator. Carry out a blank titration. The difference between the titration volumes is not greater than 2.0 mL.

Acceptance criteria:

NMT 0.08% calculated as dichlorobenzoyl peroxide.
Silicone elastomer prepared using platinum complies with the following additional test.
Platinum
Procedure:
Place 1.0 g in a quartz crucible and raise the temperature gradually until a white residue is obtained. Transfer the residue to a graphite crucible. To the quartz crucible add 10 mL of a freshly prepared mixture of 1 volume of nitric acid and 3 volumes of hydrochloric acid, heat on a water bath for 1 – 2 min, and then transfer to the graphite crucible. Add 5 mg of potassium chloride and 5 mL of hydrofluoric acid, then evaporate to dryness again. Repeat this operation twice. Dissolve the residue in 5 mL of hydrofluoric acid, warming on a water bath. Allow to cool and add the solution to 1 mL of 250 g/L of stannous chloride in 1 M hydrochloric acid. Rinse the graphite crucible with a few milliliters of 1 M hydrofluoric acid and dilute with 1 M hydrochloric acid to 10.0 mL.
Simultaneously prepare the reference solution by adding 1.0 mL of platinum standard solution containing 30 ppm platinum to 1.0 mL of 250 g/L of stannous chloride in 1 M hydrochloric acid and dilute with 1 M hydrochloric acid to 10.0 mL. The color of the test solution is not more intense than that of the standard.
Acceptance criteria:
NMT 30 ppm
ADDITIONAL REQUIREMENTS
•USP Reference Standards ⟨11⟩
USP Silicone Elastomer RS▲ (USP 1-Dec-2023)

Auxiliary Information–

Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
<383> CURED SILICONE ELASTOMERS FOR PHARMACEUTICAL PACKAGING AND MANUFACTURING COMPONENTS	Desmond G. Hunt Principal Scientific Liaison	GCPD2020 General Chapters - Packaging and Distribution

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Reference Standards
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BRIEFING
⟨1079⟩ Risks and Mitigation Strategies for the Storage and Transportation of Finished Drug Products. This proposal is based on the version of the chapter official as of February 1, 2021. The General Chapters—Packaging and Distribution Expert Committee is proposing this minor revision to remove the inappropriate General Notice reference. This chapter includes the following change:

1. Delete the reference to General Notices, 10.20. Labeling in section 4.1.3 Labels.

Additionally, minor editorial changes have been made to update this chapter to current *USP* style.
(GCPD: D. Hunt)
Correspondence Number—C308978
Current DocID: GUID-5EE764A5-0531-405E-9475-5D0D11E0921C_5_en-US

⟨1079⟩ RISKS AND MITIGATION STRATEGIES FOR THE STORAGE AND TRANSPORTATION OF FINISHED DRUG PRODUCTS

1. INTRODUCTION

Proper storage and transportation of finished drug products are critical activities in an integrated supply chain. These finished drug products include but are not limited to temperature-sensitive small molecules, vaccines, biologics, biotechnological products, radiopharmaceuticals, and combination products. With the globalization of the pharmaceutical industry, various individuals and organizations from locations around the world can come into contact with the finished drug product. The storage and transportation processes for a drug product may involve complex movements with differences in documentation, handling requirements, and communication between the various entities throughout the supply chain.

Environmental controls play a key role in maintaining drug safety, quality, and efficacy. Temperature is one of the most important parameters to control. Drugs must be stored and transported according to predetermined conditions (e.g., temperature) as supported by stability data. Temperature excursions outside of their respective labeled storage conditions, for brief periods, may be acceptable provided that stability data and scientific/technical justification exist, demonstrating that product safety, quality, and efficacy is not affected.

To maintain the original quality, every party involved in the storage and transportation of a finished product should have an in-depth understanding of the storage and transportation risks and have the appropriate mitigation strategies in place to control these risks. The intent of this chapter is to identify common risks in the storage and transportation of drug products and to recommend mitigation strategies. The chapter is not meant to prescribe specific approaches or discuss regulatory frameworks currently in place, but rather to focus on risks and mitigation strategies for quality processes to maintain product and supply chain integrity. The principles of this chapter can be used to facilitate the storage and transportation of drug products throughout a supply chain that is controlled, measured, and analyzed for continuous improvements while also maintaining the integrity of the drug product in its packaging during distribution.

2. SCOPE

This chapter applies to organizations and individuals involved in the storage and transportation of drug products, including but not limited to the following:

- Manufacturers of drug products, radiopharmaceuticals, biological products, and biotechnological products
- Repackaging operations in which the product may be owned by a company other than the primary manufacturer
- Healthcare providers and institutions such as hospitals; outpatient, ambulatory, and urgent care centers; home health providers; vaccine clinics; emergency departments; and medical, dental, and veterinary offices
- Pharmacies, including but not limited to retail, compounding (sterile and nonsterile), specialty, mail order, hospital, nursing home, and hospice
- Importers and exporters
- Wholesale distributors
- Third-party logistics providers, brokers, freight forwarders, consolidators, and other organizations involved in storage; road, rail, sea, and/or air transport services, or mail

distributors that offer expedited or controlled-temperature shipping services

Manufacturers of active pharmaceutical ingredients, excipients, packaging materials, medical devices, and dietary supplements are not within the scope of this chapter. However, the concepts, risks, and mitigation strategies discussed in this chapter may be useful and can be applied in these cases, if desired.

3. RISK-BASED APPROACH TO THE STORAGE AND TRANSPORTATION OF FINISHED DRUG PRODUCTS

Figure 1 illustrates the risk-based approach of a quality management system (QMS). It represents how product knowledge and process knowledge facilitate the identification of risk. The figure also illustrates how mitigation strategies that are planned to reduce the identified risks, categorized in clusters, form the pillars of a QMS.

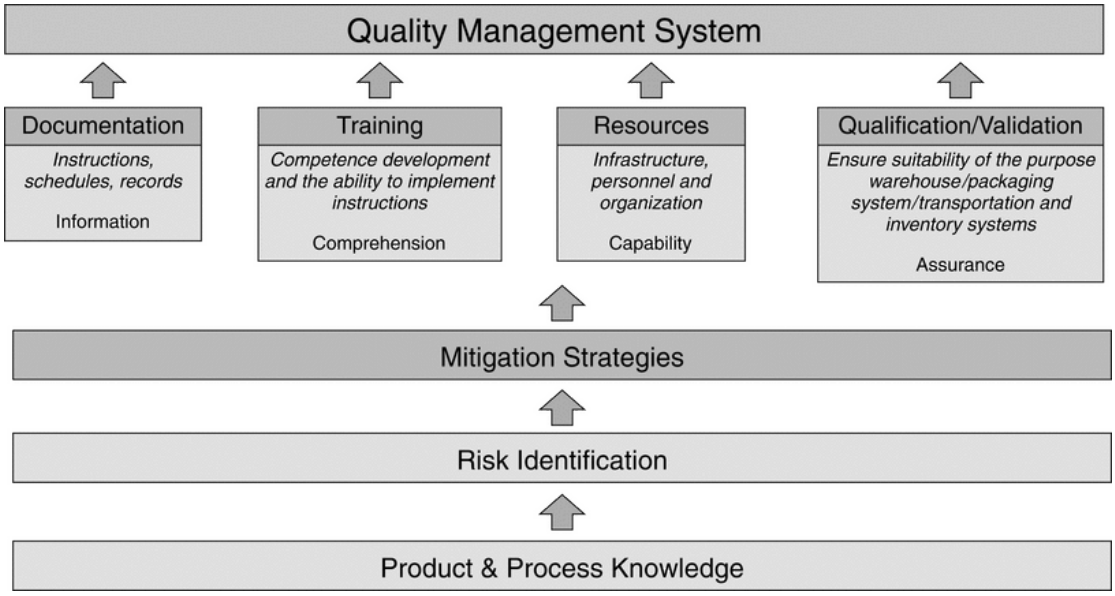

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Figure 1. Risk-based approach for a QMS.

Product and process knowledge is the starting point in identifying risks related to the storage and transportation of drug products. Product knowledge includes but is not limited to the following: intended use; storage conditions; potential hazards to environment and personnel (e.g., hormones, cytotoxic drug products, and radiopharmaceuticals); and inherent vulnerability (e.g., high potential for abuse, high-value drugs, attractiveness of freight to criminals, counterfeiting, and diversion). Process knowledge includes but is not limited to the following: knowledge of supply chain partners; physical modes of transportation (air, sea, rail, road, or a combination of modes); transportation routes; and national and

international regulation. Understanding these factors helps an organization identify their associated risks. Process mapping is a useful tool for organizations to gain further understanding of a particular process and/or operation (e.g., transport lane selection or loading/unloading patterns of warehouses and vehicles).

Risk identification is the systematic use of information to identify potential sources of harm (hazards). Information can include historical data, theoretical analysis, informed opinions, product and process knowledge, and the concerns of stakeholders. Risk identification addresses the question: “What might go wrong?”

Mitigation strategies are part of the risk control process, specifically risk reduction. Risk reduction addresses the question: “What can be done to reduce or eliminate risks?” In this way, risk reduction can include actions taken to mitigate the severity or probability of harm. Processes that improve the detectability of hazards and quality risks can also be used as part of a risk control strategy.

Different stakeholders perceive risks differently; for example, they may assign different levels of risk based on their experience and knowledge or they may estimate the probability of risk to product differently. Regardless of where your organization fits into the supply chain, consideration of risks and mitigation actions taken should consider potential impact throughout the supply chain. The mitigation strategies can be divided into four categories that are fundamentals (or pillars) of a QMS (see Figure 1). These strategies, when implemented, give an organization the autonomy to plan, implement, measure, and improve their processes according to current regulations and associated risks. Generally, mitigation strategies fall within four categories related to: 1) documentation, i.e., providing instructions for a specific operation or process to standardize it and establish consistency; 2) training, i.e., ensuring competence; 3) resources, i.e., providing capability through infrastructure and human resources; and 4) qualification and validation, i.e., assurance that the resources and processes are reliable, reproducible, and robust.

Several informal and formal tools can be used to conduct risk assessments and control risk. Examples of tools used to perform risk identification include (but are not limited to): flow charts, process mapping, trends, historical data records (such as temperature records over a particular route), and observations. Other tools—such as failure mode effects analysis (FMEA), fault tree analysis (FTA), hazard analysis and critical control points (HACCP), hazard operability analysis (HAZOP), and preliminary hazard analysis (PHA)—can also be used for conducting risk management [Note— See

International Council for Harmonisation (ICH) in *Additional Sources of Information*].

Table 1 contains illustrative examples of the risks related to drug product storage and transportation, along with their mitigation strategies. The list presented below is not exhaustive and is meant to stimulate discussion and provide examples.

Table 1. Storage and Transportation Risks and Mitigation Strategies

Hazard	Effect	Mitigation Strategy	Mitigation Category
General Risk			
Human error due to excessive duties or lack of training or competence	Mishandling along the supply chain, which can affect product quality and integrity and patient safety	• Evaluate training effectiveness [are trainees competent in key aspects of the standard operating procedures (SOPs)?] • Assign appropriate number of personnel to avoid excessive duties placed on one individual • Assign employees to duties that they are qualified for based on education, experience, and competence	Training and Resources
Procurement and Sales			
Buy from or sell to unlicensed trading partners	Legal sanctions; patient safety	• Supplier qualification • Customer qualification • Checks to ensure license is current and appropriate • Quality agreements between supplier	Documentation and Resources

Hazard	Effect	Mitigation Strategy	Mitigation Category
	General Risk		
		and trading partners	
	Receiving and Shipping		
Receive adulterated, falsified, or recalled product	Patient safety; introduction into legitimate supply chain of a product that is potentially substandard, illegal, or counterfeited	• Quarantine • Quality control test • Packaging identification fingerprints • Recall awareness • Notify regulatory authorities or trading partners • Qualification of supply chain partners and on-going performance qualifications	Documentation and Training
Receive product that was not ordered	Unmatched transaction (e.g., wrong paperwork or transaction data sent); introduction into legitimate supply chain of a product that is potentially substandard, illegal, or counterfeited	• Adhere to receiving SOP	Documentation and Training
Mix products with different status (rejected,	Patient safety; shipping or selling of	• Product segregation, physical in the	Storage, Documentation, and Resources

Hazard	Effect	Mitigation Strategy	Mitigation Category
		General Risk	
recalled, or returned)	inappropriate product	location and/or system • Warehouse layout (logical flow and holding areas in order to avoid mix-ups) • Adhere to receiving SOP	
Shipping and receiving delays due to inclement weather, natural disasters, traffic disruption	Patient safety; arrival delays; temperature out of specification (temperature excursions, e.g., product freezes accidentally)	• Reschedule the delivery • Temporary parking (waiting for opportunity to unload) or off-loading to a temperature-controlled facility or vehicle • Recondition materials to ensure temperature maintenance during delay • Rescue services • Monitoring to demonstrate that the product integrity was not compromised; in cases when monitoring was not implemented due to qualifications and risk assessments, these delays might be out of scope due to the	Documentation, Training, and Resources

Hazard	Effect	Mitigation Strategy	Mitigation Category
		General Risk	
		qualification parameters	
		Storage	
Improper entry into a materials management system: wrong batch number, wrong expiration date, wrong status (e.g., product was approved but should be quarantined), or wrong amount	Inaccurate stock; picking and/or shipping product that should have been quarantined but was marked approved	• Adhere to stocking SOP • Software validation	Documentation and Validation
	Patient safety because of picking error (software shows location, but staff can pick the wrong product if there is no check of the physical location)	• Adhere to stocking SOP • Automated checking system	Documentation, Training, and Validation
Product stored in wrong physical location	Product exposed to temperature excursions Legal sanctions for controlled	• Refer to SOP showing list of products and their temperature specifications • Refer to SOP showing list of products and their	Documentation Documentation

Hazard	Effect	Mitigation Strategy	Mitigation Category
		General Risk	
	substance; risk of diversion for controlled substance	license category (e.g., controlled, radiopharmaceutical)	
Environmental conditions out of specification	Affects product quality, product integrity, and patient safety (e.g., freezing of vaccine or biologic product); product loss causing financial loss Out-of-range cold or hot areas; product storage temperature excursion product loss; financial loss; patient product availability	• Warehouse, packaging, and transportation qualification (temperature mapping) • Product storage identification • Qualification (temperature mapping) • Storage temperature monitoring program • Homogenous airflow • Monitoring and alarms • Adhere to excursion-handling SOP	Qualification and Validation, Training, and Documentation Documentation, Resources, and Qualification and Validation
Temperature monitoring device failure	Out-of-range cold or hot areas; product storage temperature	• Backup monitoring devices with independent power source	Documentation and Resources

Hazard	Effect	Mitigation Strategy	Mitigation Category
		General Risk	
	excursion; product loss	• Adhere to excursion-handling SOP	
Storage or temperature system failure due to: • Loss of electrical power • Failure of temperature control or air circulation systems • Unusual weather event	Out-of-range cold, warm, or hot areas; product storage temperature excursion; product loss	• Temperature and power alarms • Backup power and coolant systems (redundant) and/or contingency storage • Adhere to excursion-handling SOP	Documentation and Resources
Fear of reporting nonconformance and exception conditions	Affects product integrity and patient safety due to serious conditions not communicated	• Independent quality reporting structure • Education on product integrity and impact on patients and the supply chain	Training and Resources
		Picking	
Picking (human) error	Patient safety; wrong item shipped (product availability); product returns	• Automated checking system or second-person verification	Documentation, Training, and Qualification and Validation

[Note—The effect of a hazard, if not mitigated, could impact product integrity and ultimately patient safety.]

Change to read:

4. RISK MITIGATION CATEGORIES AS QMS ELEMENTS

A QMS is necessary to implement, monitor, and maintain a robust storage and transportation process. Key elements of a QMS are management responsibility, documentation, training, resource management, complaint handling, deviation/excursion handling, returns and recalls management, qualification/validation, monitoring, audit, corrective action, preventive action, and continuous improvement. This chapter does not intend to provide a QMS framework; rather this chapter highlights how risk mitigation strategies are pillars of a QMS and how QMS elements ensure the quality and security of drug products throughout storage and transport.

The four categories of risk mitigation strategies are discussed in Table 2, with a matrix that links the mitigation strategy to the role that an organization plays within the supply chain.

Table 2. Mitigation Strategies Used by Organizations within Supply Chain

Applicable Mitigation Strategies	Role of Organization within Supply Chain					
	Manufacturer	Wholesaler and Distributor	Pharmacy or Compounding Pharmacy	Hospital and Healthcare Provider	Broker	Logistics Service Provider (LSP)
Documentation (Manuals, Procedures, Protocols, Records)						
Quality manual	Yes	Yes	Yes	Yes	Yes	Yes
Labeling	Yes	Yes	Yes	Yes	No	Yes
Procurement	Yes	Yes	Yes	Yes	Yes	Yes
Receiving	Yes	Yes	Yes	Yes	No	Yes
Picking	Yes	Yes	Yes	Yes	No	Yes
Packing	Yes	Yes	Yes	Yes	No	No
Sales	Yes	Yes	Yes	Yes	Yes	No
Storage	Yes	Yes	Yes	Yes	No	Yes
Transportation	Yes	Yes	Yes	Yes[a]	No	Yes
Supplier qualification	Yes	Yes	Yes	Yes	Yes	Yes

Applicable Mitigation Strategies	Role of Organization within Supply Chain					
	Manufacturer	Wholesaler and Distributor	Pharmacy or Compounding Pharmacy	Hospital and Healthcare Provider	Broker	Logistics Service Provider (LSP)
Documentation (Manuals, Procedures, Protocols, Records)						
Customer qualification	Yes	Yes	No	No	Yes	No
Quality agreements	Yes	Yes	Yes	Yes	Yes	Yes
Licenses and authorizations	Yes	Yes	Yes	Yes	Yes	Yes
Recall	Yes	Yes	Yes	Yes	Yes	Yes
Return	Yes	Yes	Yes	Yes	No	No
Temporary parking	Yes	No[b]	Yes	No	No	Yes
Excursion handling	Yes	Yes	Yes	Yes	No	Yes
Disposal of expired and nonconforming drug products (e.g., suspect, expired, recalled, quarantined)	Yes	Yes	Yes	Yes	Yes	No
Pest control and pallet conservation	Yes	Yes	Yes	Yes	No	Yes
Training						
Training	Yes	Yes	Yes	Yes	Yes	Yes
Resources						
Product segregation	Yes	Yes	Yes	Yes	No	Yes

Applicable Mitigation Strategies	Role of Organization within Supply Chain					
	Manufacturer	Wholesaler and Distributor	Pharmacy or Compounding Pharmacy	Hospital and Healthcare Provider	Broker	Logistics Service Provider (LSP)
Documentation (Manuals, Procedures, Protocols, Records)						
Storage area (layout/logical flow)	Yes	Yes	Yes	Yes	No	Yes[c]
Maintenance	Yes	Yes	Yes	Yes	No	Yes
Calibration	Yes	Yes	Yes	Yes	No	Yes
Monitoring systems and alarms	Yes	Yes	Yes	Yes	No	Yes
Appropriate number of personnel	Yes	Yes	Yes	Yes	Yes	Yes
Organizational chart and job descriptions	Yes	Yes	Yes	Yes	Yes	Yes
Qualification and Validation						
Temperature mapping	Yes	Yes	Yes	Yes	No	Yes
Shipping packaging qualification	Yes	Yes	Yes	No[a]	No	No
Software validation (automated checking systems, inventory management system)	Yes	Yes	Yes	Yes	Yes	Yes

[a] Unless the healthcare entity ships between owned facilities or to the patient.

[b] If the ownership of the product has already transferred to the distributors, then temporary parking could be the responsibility of the distributors/wholesaler.

[c] Applied only if the logistics service provider has a temporary storage area.

4.1 Documentation and Procedures

Documentation provides written information that allows for consistency and traceability of actions. For this reason, documentation is a fundamental part of any quality system. In a risk-based approach, documentation is a category of risk mitigation. Some examples of documentation include quality manuals; standard operating procedures (SOPs); labeling; records pertaining to procurement, receiving, storage, and transportation; supplier qualification records; quality agreements; recalls; and excursion-handling records. The sections that follow describe key types of documents that are fundamental for a QMS supply chain system. These documents can be used in a range of different organizations (see Table 2).

4.1.1 quality manual

A quality manual is a top-level quality document for all areas of the business affected by the quality system. The quality manual contains the quality policy, quality objectives, quality system structure, and information related to the management of a specific organization. The content may also include information on inspection management, customer complaints, recalls, withdrawals and holds, corrective and preventive actions, nonconformance and change control, information about regulatory issues, and performance evaluation through quality indicators.

4.1.2 standard operating procedures

SOPs are controlled documents, with document owners and approvers, effective dates, revision management, and scheduled reviews. Procedures should cover areas governed by the quality manual and should cover all aspects of the operation that may affect product quality, including handling, distribution, and all regulated activities in relation to the specific business (e.g., national and international laws). SOPs should also address actions that are performed to identify and mitigate risks.

Some key components are, but not limited to, the following:

- Corrective action/preventive action (CAPA)
- Documentation
- Record keeping
- Inventory management
- Licensing
- Management reviews

- Nonconforming product (for example, but not limited to, damaged or adulterated, expired, recall, suspect or illegitimate product, and temperature deviation)
- Order processing
- Purchasing
- Picking
- Packing and shipping
- Receiving
- Returns
- Storage
- Training

Procurement:
One of the risks in procurement is buying and selling for transport with an unlicensed trading partner, leading to legal sanctions. A procurement procedure ensures that a product is purchased according to product specifications and that purchases are made from qualified partners that are licensed as appropriate.
Receiving:
One potential risk when moving a product forward and backward along the supply chain is the introduction of substandard, illegal, or counterfeit products into the legitimate supply chain. Receiving is the operation related to the entrance of cargo into the operation's facility, starting with unloading the cargo from vehicles and then receiving, checking, and stocking the operation's facility. Each organization should have a receiving procedure that determines the appropriate checks for this operation. A checklist can be used as a reminder of what to inspect and what to record. Where appropriate, the transport vehicle can be inspected before unloading to verify that adequate protection from contamination was maintained during transit. To avoid the risk of receiving a product that was not ordered, all deliveries should be verified at the time of receipt in order to check that containers were not damaged and that the consignment corresponds to the order.
All incoming products should be segregated from salable inventory and identified. Products should be transferred to their respective storage areas according to their classification and storage specification. When products arrive at warehouse loading docks and other arrival areas, they should be transferred as quickly as possible to a designated storage area within a time period that is consistent with the organization's receiving SOP.
Inclement weather, natural disasters, and traffic disruption can cause receiving delays and potential temperature excursions. Rescheduling the delivery, temporarily parking while waiting for an

opportunity to unload, rescue services, or even reconditioning materials to ensure temperature maintenance during delays are all mitigation strategies that can be implemented. Procedures to follow for these contingencies should be written, and personnel should be trained on them.

Storage and transportation:

During storage and transportation, two approaches can be used to keep the product within its required labeled specifications:

1. Controlling the environmental conditions within equipment, storage rooms, and transportation vehicles; and when applicable, using thermostatically controlled devices such as a heating, ventilation, and air conditioning (HVAC) system or refrigerators
2. Using packaging materials that allow for the control of environmental conditions (e.g., passive/thermal packaging, thermal blankets, temperature stabilizers, desiccants, and light-resistant material)

The organization should have written procedures for qualification of storage, shipping containers, and transportation (in-transit storage) of drug products, taking into account at a minimum:

- Product category (e.g., narcotics, medical devices, temperature-sensitive or hazardous products)
- Layout of the area [e.g., floor-standing pallets, pallet racking, and boxes inside refrigerators where practical and applicable (not feasible for air freight)]
- Volume of stored product (including peaks of storage)
- Air circulation and environmental conditions (e.g., temperature, relative humidity, pressure, shock, and vibration)
- Contingency plan for outages and employee breaks

The procedure should be written based on a risk assessment of factors that can impact product quality during storage and transportation. This procedure will be a measure to mitigate this risk.

If there are problems with vehicles during the transportation process (e.g., breakdowns, accidents, and loss of fuel), a product should be protected against environmental factors, theft, and diversion. The risk assessment and written procedures should take these situations into consideration. Depending on the probability of occurrence and the level of risk, an organization may consider backup systems or access to backup systems in the event of logistics disruption (e.g., severe weather).

Recalls:

All supply chain partners are responsible for maintaining the quality and integrity of products under their control. Anytime a deviation is found that likely affects the safety or efficacy of a marketed product, an appropriate action should be taken, including a potential recall. A challenge involved in recalling a product is ensuring that the amount of product that was initially distributed is returned. Thus, sharing information on product recall increases the efficacy of the recall procedure, provides transparency to supply chain partners, and mitigates the risk of reintroducing a recalled product into the supply chain. The organization should have a written procedure that establishes the steps for recalling products and the control of recalled products, such as product identification and segregation. The extent of the recall needs to correspond to the level of risk. The extent of the recall may change if the risk is re-evaluated.
Returns:
Accepting a returned product for restocking poses the risk that the product may not be authentic or its quality may have decreased. A risk-based evaluation should be performed to determine if the product will be acceptable for restocking and resale or if it needs to be destroyed. During the evaluations, returned products should be kept in a segregated area designated specifically for returns until final disposition. A written procedure for handling returns should be in place, taking into account:

- Reasons for return
- Appearance and integrity of the original packaging
- Evidence of conditions in which the cargo was transported and stored throughout the entire time span
- Duration of time between the original shipment and its return
- Authenticity of the product, to include product identifier verification covered by applicable traceability and serialization laws and evidence of proper storage while in possession of the entity returning the product (e.g., ongoing assurance)
- Representative sampling for quality control analysis (if applicable and following regulation)
- Expiry date and batch number
- Batch trace history of excursion
- Information from any track-and-trace system in place

Supplier qualification (logistics service provider, third party logistics provider, material suppliers, maintenance providers, etc.):
Supplier qualification is a process in which the organization assesses its suppliers regarding their licenses, authorizations, and

compliance with regulatory requirements for the distribution of drug products. The organization should establish a written procedure for how suppliers are selected and evaluated, including the criteria for qualification and the period for requalification on a risk-based approach.

4.1.3 labels

Labels are fundamental to material identification. For this reason, any label change should be communicated to downstream supply chain partners. Labels applied, even to small containers, should be clear, indelible, unambiguous, and permanently fixed in the format established by the manufacturer, packager, or repackager. The shipping label should include wording or icons to emphasize storage and transportation conditions, handling requirements, and hazards. The use of symbols that are recognized by international organizations is strongly recommended. See General Notices, 10.20. Labeling.▲▲ (USP 1-Dec-2023)

4.1.4 quality agreements

Written agreements (e.g., quality agreement, technical agreement, service level agreement) should be in place between applicable organizations involved in the supply chain. Each supply chain partner should ensure that its respective service level agreements and supporting documents cover delivery and receiving responsibilities. The use of written agreements ensures clarity and transparency, while delineating the responsibilities of each organization in the supply chain.

4.1.5 excursion handling

Short-term temperature excursions can occur during distribution, storage, and transportation (see Packaging and Storage Requirements ⟨659⟩). Each excursion should be documented and handled with a deviation or appropriate risk assessment. Product disposition should be established on the basis of an assessment of the excursion (i.e., the temperature to which the material or product was exposed, and for how long), the stability data obtained from traditional stability studies (under accelerated, intermediate, if appropriate, and long-term conditions and performed in accordance with ICH guidelines), and distribution stability studies (e.g., extremes of temperature, thermal cycling, and freeze–thaw studies, as appropriate). Combining stability data from long-term and accelerated studies with mean kinetic temperature (MKT), temperature-excursion, and thermal-cycling studies should provide the information necessary to evaluate the effects of excursions. Excursions out of temperature range defined by thermostability data or ⟨659⟩ should be addressed/corrected in order to prevent recurrence using a risk-based approach. Downstream handlers of finished drug products may rely on the manufacturer's

product disposition instructions. See ⟨659⟩ for excursion allowances and MKT limits and Mean Kinetic Temperature in the Evaluation of Temperature Excursions During Storage and Transportation of Drug Products ⟨1079.2⟩ for MKT. MKT should be calculated for the period of time that a drug is in residence at a warehouse and/or in transit on a truck to avoid the problem of diluting the impact of excursions by calculating annual MKT values.[1,2]

4.2 Training

Training is a teaching-learning process used in the workplace to provide knowledge and develop skills and behaviors. The objective of training is to reduce the gap between the existing competencies and those required for performing the work. Training comprises knowledge of the topic to be taught and the types of training practices such as class-like, on-the-job training, web-based, blind sample analysis, mocks, and simulations. The type of training can influence the effectiveness of that training.

A written training procedure is necessary to establish who can be the trainer, how training needs are identified, and how training effectiveness will be evaluated. Selection of trainers must adhere to applicable laws as appropriate. Training needs could be identified and linked to job descriptions, complexity of duties, types of product handled, management reviews, and any kind of human resources program for competence development.

SOPs are the foundation of a quality system, and training must be provided for each SOP to the appropriate job roles responsible for executing the processes outlined in each SOP. Frequency of training and when training or retraining should occur should also be outlined in the overarching training SOP. Training records should be maintained either as hard copies or electronically.

The effectiveness of training should be considered and evaluated to determine its impact on task execution and quality. Evaluation of training effectiveness is not necessarily a separate document, but it may include a review of written or performance tests, observation, error rates, non-conformance or CAPAs, customer complaints, and internal and external audits. Any identified training effectiveness gaps should be corrected and evaluated. This may include retraining or evaluation and modification of SOPs, training materials, training method, or the instructor.

As a risk mitigation strategy, training should be performed before the SOP becomes effective. All employees whose actions have an impact on product quality and security should have initial and ongoing training based on an approved schedule. Basic training should be provided regarding risks and mitigation for storage and transportation of drug products so that employees will better

understand how individual and collective actions impact product quality, and so they will develop awareness and a risk-based mindset.

4.3 Resources for Storage, Transportation, and Personnel

In the context of this chapter, resources are warehouses, vehicles, and organizational personnel. Facilities, equipment, and transportation vehicles are emphasized as systems that function to control environmental conditions in accordance with product specifications. Evaluation of facilities, equipment, packaging, and transportation systems should be part of the quality system of the organization. Sampling family or type of equipment/vehicles (e.g., shipping containers or trailers) should be part of the risk assessment, when evaluation of individual systems is not feasible. Additionally, trading partner facilities/vehicles can be evaluated by risk by family or type, which may include sample lane mapping to evaluate the exposure of product through the transportation system.

4.3.1 storage

The facility should be designed to maintain the quality and integrity of the stored drug product. Buildings should be constructed in such a way that they are appropriate for the intended operations, taking into account:

- Security
- Product characteristics (e.g., narcotics, radiopharmaceuticals, fire/explosion risk)
- Product status (e.g., approved, recalled, returned, rejected, quarantined, falsified)
- Product required storage temperature
- Ease of cleaning and maintenance
- Logical flow of personnel and materials
- Means of preventing mix-ups and cross-contamination
- Ergonomic measures
- Product demand in order to prevent capacity constraints
- Any local, national, or international requirements
- Necessary environmental controls

Product segregation and proper identification can reduce the risk of mixing up products with different statuses, such as quarantined (rejected, expired, recalled, returned, or falsified) and released/salable. Products with special handling authorization, such as narcotics, should be segregated and locked in a secure area per applicable regulations. Radiopharmaceuticals should be contained in dedicated, locked storage areas. Hazardous products should be managed per applicable regulations for each supply chain partner. Other products that require special storage conditions such as hazardous

products (see Hazardous Drugs—Handling in Healthcare Settings ⟨800⟩) should also be segregated per applicable safety standards. Any system used to replace physical segregation should offer the same level of security and protection.

Buildings and facilities used for the warehousing, storage, and/or holding of drug products should be of adequate size for their intended use to prevent product overcrowding. The building and facility should be designed to control environmental conditions, where necessary, and should be made of materials that are readily or easily cleaned. Sanitation and pest control procedures should be written, indicating the frequency of cleaning and the materials and methods to be used. The pest control program should prevent contamination and ensure the safe use of pesticides. Records of all cleaning and pest control activities should be maintained.

Storage facilities themselves, unless thermostatically controlled, cannot be validated. However, they can be qualified via a mapping process, with appropriate attention to geography and seasons. The generator backup power supply should be qualified.

Drug product storage areas are required to maintain the product temperature between the limits defined on the product label (see ⟨659⟩). Product storage areas/units should utilize recording systems to log and track temperatures. Alarm systems should be an integral part of the monitoring system for product temperatures. Although automated systems monitor units continuously, manual checks should be performed as appropriate to ensure functionality. When automated systems are not available, manual systems may be used. A risk-based approach should be applied when using a manual system.

Controlled access to warehouses and vehicles is a measure used to prevent unauthorized personnel from coming into contact with the product. Access control can be accomplished with automated systems or by procedure. Adequate precautions should be taken to prevent theft and diversion of products.

4.3.2 transportation

All vehicles used in supply chain activities—such as trucks, vans, trains, airplanes, sea vessels, mail delivery vehicles, and emergency medical services vehicles—should be suitable for the intended purpose because they are providing in-transit storage and should prevent exposure to conditions that affect stability and package integrity. Thus, all of the precautions needed to maintain product quality, integrity, and security should be taken. Risk identification and mitigation strategies should be applied to determine whether the transportation method adequately protects the product from environmental exposures such as temperature and vibration without the

need for additional packaging, or if additional packaging is necessary to mitigate the risk.

4.3.3 personnel

Organizations should hire personnel and contractors who meet the requirements for handling drugs safely and securely per applicable laws and regulations. Job descriptions and individual profiles should be reviewed to ensure that all experience and training requirements are met and maintained.

4.4 Qualification and Validation

Qualification and validation for storage and transportation of drugs focus on the assurance that the storage and transportation methods meet predetermined criteria and that processes and procedures produce the desired outcome. Calibration is necessary for instruments used in qualification studies. Organizations need to include appropriate qualification, validation, and calibration activities in their master plan and SOPs, as well as schedules and the use of approved protocols to conduct these activities and produce final reports. The sections below provide brief explanations of calibration, qualification, and validation, focusing on storage and transportation. The scope for each stakeholder within the supply chain is described in Table 3.

4.4.1 calibration of instrument or device

Calibration ensures that measurements such as temperature and humidity meet recognized standards. Calibration frequency may be determined by the device manufacturer, device workload, operational demands, and/or damage that require repairs. Instruments or devices used for qualification or monitoring of set criteria must be calibrated to recognized standards such as those from the National Institute of Standards and Technology (NIST) and those found in Monitoring Devices—Time, Temperature, and Humidity ⟨1118⟩.

Table 3. Calibration, Qualification, and Validation Activities of Organizations

	Role of Organization within Supply Chain					
Calibration, Qualification, and Validation Activities	Manufacturer	Wholesaler and Distributor	Pharmacy and Compounding Pharmacy	Hospital and Healthcare Provider	Broker	Logistics Service Provider (LSP)
Calibration						
Temperature recording devices used for temperature	Yes	Yes	Yes	Yes	No	Yes

Calibration, Qualification, and Validation Activities	Role of Organization within Supply Chain: Manufacturer	Wholesaler and Distributor	Pharmacy and Compounding Pharmacy	Hospital and Healthcare Provider	Broker	Logistics Service Provider (LSP)
Calibration						
mapping or monitoring during storage and transportation						
Qualification						
Temperature mapping of warehouse and equipment (freezers, refrigerators)	Yes	Yes	Yes	Yes	No	Yes
Shipping packaging performance qualification	Yes	Yes	Yes	Yes	No	No
Transportation vehicle performance qualification	Yes	Yes	Yes	Yes	Yes	Yes
Validation						
Software validation for systems that make quality decisions	Yes	Yes	Yes	Yes	Yes	Yes

4.4.2 qualification

For the purposes of this chapter, performance qualification is defined as all tests designed and executed to evaluate whether the storage rooms and areas, warehouse facilities, utilities, equipment, transport vehicles, and shipping containers are suitable for their intended purpose. Qualification studies should reflect actual load configurations and environmental conditions. Testing should be performed on both active and passive thermal packaging systems. During the qualification process, temperature mapping is performed to provide information relative to temperature consistency throughout a product area. This information may confirm a uniform temperature over the mapped area or it may identify areas that need mitigation. Such mitigation may include the movement or installation of insulation, HVAC units, or fans, or the need to modify the relevant SOPs. The identification, documentation, and rationale for the mapping procedure are the foundation of temperature mapping of any temperature-controlled space (e.g., facility, vehicle, shipping containers, refrigerator, and freezer). Temperature variability in mapped locations and the level of thermal risk to the product should both be defined, unless another process to ensure environmental control has been put in place (see ⟨1118⟩).

Temperature mapping in facilities and equipment:

The following factors, which may contribute to temperature variability in a facility, should be considered during the process of temperature mapping for storage locations: 1) size of the space; 2) location of HVAC equipment, space heaters, and air conditioners; 3) sun-facing walls; 4) low ceilings or roofs; 5) geographic location of the area being mapped; 6) airflow inside the storage location; 7) temperature variability outside the storage location; 8) workflow variation and movement of equipment (weekday vs. weekend); 9) loading or storage patterns of product; 10) equipment capabilities (e.g., defrost mode, cycle mode); and 11) SOPs. The duration of temperature recordings during the thermal mapping of a warehouse or cold room should capture workflow variation that may impact airflow and the resulting temperature fluctuation; for example, this process could last from 1 day to 1 week, depending on the workflow cycle.

Temperature mapping for shipping packaging and vehicles:

Pharmaceutical manufacturers should consider primary, secondary, and tertiary packaging that best protects the drug product during storage and distribution. Shipping package performance testing should be documented as part of a QMS. Several standard test procedures are available to evaluate package performance for factors such as shock, vibration, pressure, compression, and other transit events. (See *Additional Sources of Information* for standards for test methods.)

Packaging at the tertiary level (e.g., outer, external, or shipping package) or thereafter for the distribution of the drug product should be selected and tested to ensure that product quality is maintained and to protect the contents from the rigors of distribution, including environmental or physical damage. Active, passive, or semi-active shippers and transport systems are typically subjected to operation performance qualification by the manufacturers or suppliers of such equipment.

Thermal packaging and vehicles used for transporting the drug product for pharmaceutical manufacturers, wholesalers, and pharmacies should be evaluated based on the labeled storage or transport conditions of the product as well as anticipated environmental conditions. Special consideration should be made for seasonal temperature differences, transportation between hemispheres, and the routes and modes of transport.

Identification of risks and mitigation strategies to protect the product should be based on documented studies of specific distribution environments, including domestic and international lanes (as appropriate), mode(s) of transport, duration, temperature, and other potential environmental exposures or sensitivities that may impact product quality. If risks to product integrity have been identified by using historical data, observation of current practices, or operational changes, mitigation strategies may be employed to address the identified risks. Strategies include temperature-controlled vehicles, active or passive thermal containers or packaging, or ambient conditions based upon identified risks (product storage labeling, time, temperature, and geography). Temperature monitors/indicators may include calibrated monitoring or recording devices, real-time monitors such as GPS, and chemical indicators of temperature. Monitoring devices may include an alert mechanism if the preset ranges are breached (see ⟨1118⟩).

Thermal packaging and vehicles may be qualified based on historical data that are relevant to the process. If qualified thermal packaging is used without a temperature verification method (monitors or indicators), a plan should be in place to schedule transport within qualifying times and to mitigate and respond to exceptions. However, it may be acceptable to use product stability data from manufacturers and supply chain risk assessment to justify shipping without either continuous monitoring or qualification of the shipping system.

Operational and performance shipping studies should be part of a formal qualification protocol that may use controlled environments or actual field testing, depending on the projected transport channel. These studies should reflect actual load configuration conditions and

expected environmental extremes. Testing should be performed on both active and passive thermal packaging systems.
When developing a thermal package qualification protocol, the following factors and actions should be considered:

- Transportation temperature profile for the shipping lane(s)
- Delivery cycle time, accounting for reasonable delays due to weather, traffic, or customs
- Testing beyond qualification time to obtain worst-case data for excursion dispositioning
- Seasonal changes in the environment
- Use of seasonal (warm/summer and cool/winter) configurations versus universal configuration
- Testing with actual payload, worst case configuration, or a representative sample
- Variable order sizes, making it difficult to select a representative sample; testing for the minimum and maximum payload possible in each package may be necessary
- Probe placement should be inside or directly attached to the product (or representative samples) or in the most vulnerable temperature locations within the package; scientific justification should be given for the differences between monitoring for qualification and operation
- Perform at least 3 replicate tests on a representative package containing a representative thermal payload per season; tests may be performed at the same time in an environmental chamber
- Allow the product payload as well as coolant to condition before beginning testing per protocol
- Utilize a recognized standard to conduct thermal qualification (see *Additional Sources of Information*) or develop a written rationale for a qualification

4.4.3 validation of information systems
In the context of this chapter, before an information system that can impact the quality of the product in storage or in transportation is brought into use, it should be demonstrated through appropriate validation or verification studies that the system is capable of achieving the desired results accurately, consistently, and reproducibly. (See Pharmaceutical Inspection Convention in *Additional Sources of Information*). The following are considerations for using validation as a mitigation strategy. These considerations do not suggest replacing or enforcing any existing regulatory standards in place for various members of the supply chain [e.g., current good

manufacturing practices (cGMP) for manufacturers, wholesale distributors, or pharmacies].

Prior to their use, information systems should be tested according to approved protocols. The extent of the study depends on the risk or impact the software can have on product or service quality. Validation or verification is not applied to systems that have no impact on quality. An inventory of information systems should be done periodically and include at least:

- Information system identification (name, version)
- System supplier
- Processes where system is used
- Process owner
- Risk assessment
- Status (validated, not validated, validation in progress, verified, not verified, verification in progress, not applicable)

A multidisciplinary team with representatives from information technology, quality, and operations should be responsible for protocols and report approvals. Responsibilities for the tests should be assigned in the protocols. Validation or verification tests should cover the following:

- Security (e.g., access levels, profiles, responsibilities inclusion, exclusion, or changing profiles)
- Data validity (e.g., challenge the software with entries above and below specification and with entry value errors)
- Documentation (e.g., system design in accordance with user requirements and other documents)
- Functionality (e.g., calculations, operations) [Note— Most of the functionality tests for embedded software are covered during equipment qualification (installation, operation, and performance qualifications]
- Data integrity (e.g., changes, traceability, backup, recovery, and protection)

After validation or verification studies, any modification to the system should be done according to change control procedures, and records of these changes should be kept.

GLOSSARY

Calibration: A process that typically focuses on instruments or devices to provide assurance that they produce results within specified limits. Organizations need to include the appropriate qualification, validation, and calibration activities in their SOPs

and master schedules and should follow protocols to conduct these activities and final reports.

Qualification: Qualification is the assurance that systems or equipment meet predetermined acceptance criteria. This process typically focuses on equipment and utilities such as refrigerators and HVAC systems, as well as packaging. There are several different types of qualification, and an organization should determine which to use and when. Some of these include design qualification, installation qualification, operational qualification, and performance qualification.

Service level agreement (SLA): An SLA or contract is a negotiated agreement between the customer and service provider that defines the common understanding about materials or service quality specifications, responsibilities, guarantees, and communication mechanisms. It can either be a legally binding document or an information agreement. The SLA may also specify the target and minimum-level performance, operation, or other service attributes.

Temperature excursion: An event in which a pharmaceutical product is exposed to temperatures outside of the range(s) prescribed for storage and/or transport. Temperature ranges for storage and transport may be the same or different; they are determined by the product manufacturer, based on stability data.

Validation: Validation typically focuses on processes and procedures, to provide assurance that the processes or equipment produce the desired outcome.

ADDITIONAL SOURCES OF INFORMATION

American Society for Testing and Materials International. ASTM D3103-14. Standard Test Method for Thermal Insulation Performance of Distribution Packages.

American Society for Testing and Materials International. ASTM D4169-16. Standard Practice for Performance Testing of Shipping Containers and Systems.

American Society for Testing and Materials International. ASTM D4332-14. Standard Practice for Conditioning Containers, Packages, or Packaging Components for Testing.

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International Council for Harmonisation. Quality Risk Management (ICH Q9).

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International Council for Harmonisation. Good manufacturing practice guide for active pharmaceutical ingredients (ICH Q7), Chapter 10—Storage and Distribution, p 22; November 10, 2000.
International Organization for Standardization. Quality management systems—Fundamentals and vocabulary (ISO 9000:2015).
International Organization for Standardization. Risk management (ISO 31000).
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International Safe Transit Association. Testing Standard for Thermal Transport Packaging Used in Parcel Delivery System Shipment (ISTA STD-7E).
Parenteral Drug Association. Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products through the Transportation Environment (PDA Technical Report 39); 2007.
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Parenteral Drug Association. Active Temperature-Controlled Systems: Qualification Guidance (PDA Technical Report 64); 2013.
Parenteral Drug Association. Passive Thermal Protection Systems for Global Distribution: Qualification and Operational Guidance (PDA Technical Report 72); 2015.
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World Health Organization. Supplement 7—Qualification of temperature-controlled storage areas (Technical supplement to WHO Technical Report Series, No. 961, 2011); 2015.
World Health Organization. Supplement 8—Temperature mapping of storage areas (Technical supplement to WHO Technical Report Series, No. 961, 2011); 2015.
World Health Organization. Supplement 11—Qualification of refrigerated road vehicles (Technical supplement to WHO Technical Report Series, No. 961, 2011); 2015.

World Health Organization. Supplement 12—Temperature-controlled transport operations by road and by air (Technical supplement to WHO Technical Report Series, No. 961, 2011); 2015.
World Health Organization. Supplement 13—Qualification of shipping containers (Technical supplement to WHO Technical Report Series, No. 961, 2011); 2015.
World Health Organization. Supplement 14—Transport route profiling qualification (Technical supplement to WHO Technical Report Series, No. 961, 2011); 2015.
World Health Organization. WHO good distribution practices for pharmaceutical products (WHO Technical Report Series, No. 957, Annex 5); 2010.

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[1] Seevers RH, Hofer J, Harber P, Ulrich DA, Bishara R. The use of mean kinetic temperature (MKT) in the handling, storage and distribution of temperature sensitive pharmaceuticals. *Pharmaceutical Outsourcing*. May/June 2009;12 – 17.

[2] Anderson C, Seevers R, Hunt D. The use of mean kinetic temperature to aid evaluation of temperature excursions: proper and improper application. *Pharm Forum*. 2018;44(4).

Auxiliary Information–

Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
<1079> RISKS AND MITIGATION STRATEGIES FOR THE STORAGE AND TRANSPORTATION OF FINISHED DRUG PRODUCTS	Desmond G. Hunt Principal Scientific Liaison	GCPD2020 General Chapters - Packaging and Distribution

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