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▲⟨1382⟩ ASSESSMENT OF ELASTOMERIC COMPONENT FUNCTIONAL SUITABILITY IN PARENTERAL PRODUCT PACKAGING/DELIVERY SYSTEMS

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1. INTRODUCTION

This chapter contains information and guidance to assist in the functional suitability assessment of elastomeric components as part of packaging/delivery systems intended for parenteral dosage forms contained in *Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems* ⟨382⟩. Such components include primary packaging/delivery system components that are partially or completely made of elastomeric material. 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). The proper selection and design of functional suitability assessment studies is based on sound and justifiable scientific principles provided in ⟨382⟩, *1. Introduction*.

2. EARLY PACKAGING/DELIVERY SYSTEM SELECTION AND DEVELOPMENT: FUNCTIONAL SUITABILITY ASSESSMENT CONSIDERATIONS

Early in the packaging/delivery system selection and development process, the final packaging/delivery system and its components may not be fully defined and functional suitability requirements may not be established. This is especially true if the packaging/delivery system or the drug product is novel to the drug product applicant. At this phase of the product life cycle, functional suitability assessments are performed to better understand packaging/delivery system performance and/or to screen potential elastomeric component and container candidates. To that end, *Table 1* lists elastomeric component functional suitability tests in standards published by the International Organization for Standardization (ISO). The list should not be considered all-inclusive. The most recent standards should be referenced.

The terms "standards" and "recognized standards" used throughout this chapter and ⟨382⟩ refer to those published by ISO.

Although not mandated, testing components and/or closure packaging/delivery systems according to such standards may provide useful information, especially during early product packaging/delivery system development. Other relevant internationally recognized standards deemed scientifically appropriate may be used instead of, or in addition to, those listed in *Table 1*. Standard test data may be made available by elastomeric component or packaging/delivery system suppliers.

Table 1. ISO Standards: Functional Suitability Tests for Elastomeric Components

ISO Standard (listed in numeric order)		Functional Suitability Tests
Sterile hypodermic syringes for single use[a]	7886-1	**Syringes for manual use** • Freedom from air and liquid leakage past plunger stopper • Force to operate the plunger (also called the piston) • Fit of plunger stopper/plunger in barrel
	7886-2	**Syringes for use with power-driven syringe pumps** • Freedom from air and liquid leakage past piston • Flow characteristics • Plunger movement forces
	7886-3	**Auto-disable syringes for fixed-dose immunization** • Freedom from air and liquid leakage past piston • Auto-disable feature • Performance after shipping
	7886-4	**Syringes with re-use prevention feature** • Freedom from air and liquid leakage past piston • Re-use prevention feature • Performance after shipping
Injection containers and accessories	8362-2	**Closures for injection vials** • Penetrability • Fragmentation • Self-sealing and aqueous solution tightness test • Dye solution tightness test
	8362-5	**Freeze-drying closures for injection vials** • Penetrability • Fragmentation • Self-sealing and aqueous solution tightness test • Aqueous solution tightness test • Moisture barrier
Infusion equipment for medical use (closures used in combination with bottles and intended to be pierced with an injection needle or spike)	8536-2	**Closures for infusion (glass) bottles** • Fragmentation • Spike penetration force • Spike retention/sealability
	8536-6	**Freeze-drying closures for infusion bottles** • Fragmentation • Spike penetration force • Spike penetration/sealability
Sterile single-use syringes, with or without needle, for insulin	8537	• Fit of plunger stopper in barrel (forces to operate piston) • Freedom from leakage at needle • Freedom from leakage past plunger stopper
Elastomeric parts for parenterals and for devices for pharmaceutical use (used in combination with vials and intended to be pierced with an injection needle)	8871-5	**Functional requirements and testing** • Penetrability • Fragmentation • Self-sealing and aqueous solution tightness • Aqueous solution tightness

Table 1. ISO Standards: Functional Suitability Tests for Elastomeric Components *(continued)*

ISO Standard (listed in numeric order)		Functional Suitability Tests
Prefilled syringes	11040-2	**Plunger stoppers for dental local anesthetic cartridges** • Freedom from leakage • Sliding characteristics
	11040-3	**Seals for dental local anesthetic cartridges** • Fragmentation • Freedom from leakage
	11040-4	**Glass barrels for injectables and sterilized subassembled syringes ready for filling** • Closure system allowance for sterilization • Extrusion force • Closure system liquid leakage past needle shield or tip cap • Luer lock rigid tip cap unscrewing torque • Pull-off force of tip cap or needle shield • Closure system barrel integrity (dye solution tightness test)
	11040-6	**Plastic barrels for injectables and sterilized subassembled syringes ready for filling** • Closure system allowance for sterilization • Extrusion force • Closure system liquid leakage past needle shield or tip cap • Luer lock rigid tip cap unscrewing torque • Pull-off force of tip cap or needle shield • Closure system barrel integrity (dye solution tightness test)
	11040-8	**Requirements and test methods for finished prefilled syringes** • Break-loose and extrusion forces • Liquid leakage beyond plunger • Pull-off force of tip cap or needle shield • Luer lock rigid tip cap unscrewing torque • Container closure integrity
Needle-based injection systems for medical use (cartridges for dental use not included)	11608-3	**Finished containers** • Plunger force • Freedom from leakage • Resealability • Coring
Pen systems	13926-2	**Plunger stoppers for pen injectors for medical use** • Freedom from leakage past plunger stopper under axial pressure • Initiating and sustaining forces (break-loose and extrusion forces)
	13926-3	**Seals for pen injectors for medical use** • Fragmentation • Freedom from leakage past seals under axial pressure • Resealability
Plastic containers for intravenous injections (blow-molded bottles, film bags)	15747	• Resistance to temperature stability, pressure, and leakage • Penetration ability • Adhesion strength of the infusion device and impermeability of the insertion point • Tightness of the injection point
Medical infusion equipment—Plastic caps with inserted elastomeric liners for containers manufactured by the blow-fill-seal (BFS) process	15759	**Physical requirements and testing for liners** • Fragmentation • Penetration force • Dynamic spike-retention capability • Static spike-retention capability of the liner and leak resistance of the piercing area • Resealability

[a] Single-use device: A single-use device, also referred to as a disposable device, is intended to be used on one patient during a single procedure. It is not intended to be reprocessed (cleaned, disinfected/sterilized) and used on another patient.

3. FINAL PRODUCT PACKAGING/DELIVERY SYSTEM FITNESS-FOR-INTENDED-USE SUITABILITY ASSESSMENT

Evidence of the elastomeric component's ability to satisfactorily function as part of the final packaging/delivery system according to its intended product use is required to support commercial market approval of a finished drug product. Internationally recognized standards, such as those listed in *Table 1*, can provide a useful benchmark when designing appropriate elastomeric component functional suitability assessment studies. However, the drug product applicant is advised to exercise caution before prescriptively adopting standardized tests. Such tests may not provide a complete or adequate assessment of the elastomeric component's ability to meet the final packaging/delivery system's product-specific functional demands and instead should be considered a precursor to design verification and validation of the final finished combination product. Standardized tests may not be adequate or appropriate in specific situations for many reasons, for example:

- The final packaging/delivery system components may differ in design or dimension from the description in the standard.
- The manner in which the final packaging/delivery system's components are processed, reprocessed, and/or assembled may differ from the description in the standard.
- The manner in which a liquid, such as a diluent, must be added to the packaging/delivery system for final dosage form preparation (such as for lyophilized product reconstitution, powdered product constitution, product dilution, or admixture) may differ from the description in the standard.
- The manner in which the packaged product is to be accessed at the time of use may differ from the description in the standard. Differences may include needle or spike design, material, or lubricity; needle puncture speed; and the number of penetrations per closure.
- The standard's test procedure or analysis method may provide an inadequate measure of packaging/delivery system functional suitability given the specific rigorous demands placed on the final packaging system. For instance, bench test conditions may not sufficiently mirror the rigors imposed on the marketed product during actual storage, distribution, and usage conditions.
- The test method may lack sufficient sensitivity or precision to provide an adequate measure of packaging/delivery system functional suitability. For example, a container-closure seal integrity test that relies on dye ingress observation may be too insensitive to provide an accurate picture of a lyophilized dosage form package's ability to meet the maximum allowable leakage limit demanded by the finished product packaging/delivery system.
- The standard test's acceptance criterion may not reflect the functional performance demanded of the final packaging/delivery system for the particular intended use. For example, the maximum allowable needle penetration force for a closure dictated by a standard may result in damage to the penetration needle supplied with the intended delivery device.
- The standard test's sample size may not reflect the reliability demanded of the final packaging/delivery system. A larger sample size will be expected in design verification and validation of the final packaging/delivery system.

Therefore, the drug product applicant is tasked with developing a body of elastomeric component functional suitability assessment tests that logically and most appropriately assess the final packaging/delivery system. Challenges placed on the final product's packaging/delivery system during testing should mimic challenges the product is likely to encounter through storage/distribution, product expiry, and clinical in-use condition. These testing challenges should provide clear and definitive measures of packaging/delivery system performance.

4. GENERAL CHAPTER ⟨382⟩ BACKGROUND AND GUIDANCE

Chapter ⟨382⟩ offers drug product packaging/delivery system fitness-for-intended-use functional suitability assessment procedures and acceptance criteria that are reflective of current best practices. These best practices take into consideration all the recognized ISO standards in *Table 1* as well as USP tests and guidances (e.g., *Biological Reactivity Tests, In Vitro* ⟨87⟩ and *Biological Reactivity Tests, In Vivo* ⟨88⟩). Specific sources for the various tests are detailed in the following sections. These tests are not intended to be exhaustive. The drug product applicant may require additional tests to adequately assess the component's functional suitability as part of a particular packaging/delivery system.

Re-evaluation of functional suitability may be required when changes occur in components, processes, or even the commercialized product itself during its life cycle. The functional suitability of a drug product packaging/delivery system is the responsibility of the drug product applicant.

The following sections contain guidance and background information relevant to tests in ⟨382⟩.

4.1 Test Samples

The following relates to ⟨382⟩*, 3. General Test Requirements, 3.1 Test Samples*. Functional suitability of elastomeric components cannot be tested for in isolation from the intended packaging/delivery system. Furthermore, a component's functional performance assessment outcome can be affected by the design, mating interfaces, processing, and assembly of that packaging/delivery system. For example, closure processing parameters and vial package sealing forces directly impact parenteral vial packaging integrity results. Plunger break-loose and extrusion forces are directly related to the design, material of construction, and lubricity of the syringe barrel.

Test samples employed for each functional suitability test are to mirror the components and packaging/delivery system of the intended product as closely as possible, because component functionality is connected to the packaging/delivery system. Components are to be prepared, processed, and assembled as defined for the final product packaging/delivery system, especially if such steps are believed to have a potential impact on component functionality.

The following examples are offered as illustration:

- Components are to be washed, lubricated, and sterilized according to intended product protocol.
- Components are to be laminated or coated according to the requirements of the intended product packaging/delivery system.
- Vial and bottle closures are to be optimally capped onto vials in a manner reflective of the intended finished product packaging/delivery system.
- Syringe/cartridge barrels are to be prepared and lubricated according to the requirements of the intended pharmaceutical product.
- Syringe/cartridge plungers are to be inserted into syringe barrels according to production practices (e.g., by use of a vent tube or vacuum insertion). Manual placement can be utilized for feasibility assessment.
- Cartridge line seal crimping pressure is to be reflective of the intended finished product packaging/delivery system.

Some tests, such as ⟨382⟩*, 5. Needle and Spike Access Functional Suitability Tests, 5.1 Fragmentation*, state that the test samples are to be filled with water. However, in cases where package contents can influence test outcome, such as ⟨382⟩*, 6. Plunger*

Functional Suitability Tests, 6.1 Plunger Break-Loose and Extrusion Forces tests, it is recommended that test samples be filled with product or a product proxy so that the test outcome better reflects packaging/delivery system intended use. Alternatively, content material that brackets the characteristics of multiple products may be chosen.

Some flexibility in test sample preparation and content is permitted if the variation is judged to have little or no impact on test outcome. With appropriate justification, test samples may bracket relevant parameters of packaging/delivery system design, intended interfaces, dimensional analysis, component processing, package assembly, and product contents. Bracketing may be employed to allow a functional suitability assessment program that addresses a wider spectrum of packaging/delivery systems and/or products.

The selection, design, preparation, assembly, and contents of test samples should follow sound scientific principles so that the final product packaging/delivery system can be comprehensively evaluated for functional suitability.

4.2 Test Sample Population Size

As described in ⟨382⟩ *3. General Test Requirements, 3.2 Test Sample Population Size*, test sample quantity should provide a reasonable measure of confidence of the packaging/delivery system elastomeric component functionality. Current recognized standards inform the test sample population sizes specified in chapter tests. For this reason, sample sizes vary across test categories and even among package types within a test category. For example, ⟨382⟩*, 5. Needle and Spike Access Functional Suitability Tests, 5.1 Fragmentation* vial system tests require 12 test samples (as per ISO 8362-2, 8362-5, and 8871-5), whereas bottle system tests require 10 test samples (as per ISO 8536-2 and -6). In the case of fragmentation tests, it was deemed important to respect the historical particulate findings generated using these varied sample population sizes. On the other hand, ⟨382⟩*, 5. Needle and Spike Access Functional Suitability Tests, 5.3 Needle Self-Sealing Capacity* tests require 30 test samples regardless of the packaging/delivery system to ensure more meaningful leakage findings even though recognized standards require fewer samples.

Test sample population sizes cited in chapter test methods represent minimal test sample population size requirements but may be inadequate depending on risk assessments and whether the data generated will be attribute or variable. Sample population sizes that are larger than those specified in test procedures are encouraged to provide greater assurance of packaging/delivery system performance and to minimize the risk of product failure during commercial use.

4.3 Packaging/Delivery System Integrity Tests

The verification of packaging/delivery system integrity is required according to ⟨382⟩*, 4. Packaging/Delivery System Integrity Tests*. All components that are intended to seal or affect container closure must adequately protect and contain the packaging/delivery system contents. In this context, all such components are termed closures. All closures are required to ensure adequate system integrity; therefore, all packaging/delivery systems within the scope of the chapter are required to meet an appropriate system integrity functional suitability assessment. This section does not apply to closures after they have been breached by a needle, spike, or other access device.

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

Specifically, all parenteral product packaging/delivery systems must: 1) prevent microbiological ingress to ensure that product sterility is met; and 2) prevent product escape or entry of external liquid or solid matter to ensure that relevant product physicochemical quality attributes are met. In addition, some products require the maintenance of package headspace content in a manner that ensures relevant product physicochemical quality attributes are met and/or allows for ease of product access by the end user. As some packaging/delivery systems employ more than one closure, and each closure may provide a different level of product protection, different integrity tests may be required to effectively evaluate the inherent integrity of the various closure types.

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

4.4 Needle and Spike Access Functionality Tests

Information in ⟨382⟩*, 5. Needle and Spike Access Functional Suitability Tests* applies to packaging/delivery system closures that allow for drug product access by hypodermic needle, spike, or other closure penetration device. Packaging/delivery systems intended for parenteral products that permit dosage form access by insertion of a closure piercing device are required to allow for safe and effective product access, without damaging the packaging/delivery system or the drug product and without risking harm to either the patient receiving the medication or the individual accessing and/or administering the product.

Traditionally, needle and spike access functionality tests have not accounted for the possibility of an additional closure penetration commonly performed to introduce liquids into the product packaging/delivery system for lyophilized product reconstitution, powdered product constitution, product admixture, or product dilution. Closure penetration practices for dosage form preparation vary widely. The piercing device employed for dosage form preparation may be very different in size or design from the needle or spike used for subsequent product access and withdrawal. There is little published information on the impact of such initial closure penetrations on closure performance or product quality. To address this gap, needle and spike

access functional suitability tests have been expanded to incorporate a first closure piercing for products requiring final dosage form preparation in addition to the closure piercing(s) for product access and withdrawal.

Tests dictate that all piercings be performed using the dosage form preparation piercing device(s) and/or the product access piercing device(s) intended or recommended by the drug product applicant. For example, if the intent is to provide or to specify a needle or other piercing device with the marketed product for a given purpose, then this same item or a facsimile is to be used. If a piercing device will neither be specified nor provided (i.e., not designated), the procedures cite dosage form preparation and drug product access devices to be used for the tests. Drug product access needles/spikes cited align with current reference standards. Dosage form preparation needles cited in the procedures are unique to USP.

The following tests are included in this functional suitability assessment category.

FRAGMENTATION

See ⟨382⟩*, 5. Needle and Spike Access Functional Suitability Tests, 5.1 Fragmentation*. Also called coring, fragmentation is a measure of the packaging/delivery system's tendency to fragment or core when penetrated by a dosage form preparation piercing device (if applicable) and by a product access piercing device. If injected, such closure fragments may pose a health risk to the patient.

The penetration tests largely align with fragmentation tests in ISO standards in the piercing devices used and the number of piercings per test sample. Specifically, *Procedure A* in ⟨382⟩*, 5. Needle and Spike Access Functional Suitability Tests, 5.1 Fragmentation, Vial and bottle systems* was informed by ISO 8362-5 and 8871-5. *Procedure B* was informed by ISO 8536-2 and -6. The ⟨382⟩*, 5. Needle and Spike Access Functional Suitability Tests, 5.1 Fragmentation, BFS systems* test method was informed by ISO 15759. *Procedure A* of ⟨382⟩*, 5. Needle and Spike Access Functional Suitability Tests, 5.1 Fragmentation, Cartridge systems* was informed by ISO 13926-3 and *Procedure B* was informed by ISO 11608-3.

Unlike ISO tests, an extra initial piercing option representing a dosage form preparation piercing is included in the vial and bottle systems as well as the BFS systems test procedures.

Also unlike ISO tests, fragmentation count analysis is to be performed according to *Particulate Matter in Injections* ⟨788⟩*, Method 2 Microscopic Particle Count Test*, with noted modifications. Modifications include allowances for microscope magnification range adjustment and the use of the linear graticule for particle sizing. Test procedures require particle sizing based on the longest linear dimension of the particle.

Acceptance criteria are defined according to the quantity of detected particles ≥150 µm in the longest linear dimension. Smaller particles are not reported. Recognized standards define fragmentation acceptance criteria according to the number of particles visibly detected, i.e., particles ≥50 µm (e.g., ISO 8871-5). ⟨382⟩*, 5. Needle and Spike Access Functional Suitability Tests, 5.1 Fragmentation* has adopted the same particle quantity limits, as per the recognized standards, but counted particles are ≥150 µm, sized microscopically, defined by the longest linear dimension. This change was based on more recent data suggesting visibly detected particles are closer to 150 µm in size, as per *Visible Particulates in Injections* ⟨790⟩.

PENETRATION FORCE

See ⟨382⟩*, 5. Needle and Spike Access Functional Suitability Tests, 5.2 Penetration Force*. Also called penetrability, penetration force is the maximum force necessary to penetrate the closure using a dosage form preparation piercing device (if applicable) and a product access piercing device. Penetration force tests also confirm the ability of the closure to remain in place without being forced into the container during piercing.

Test procedures and acceptance criteria were informed by current reference standards. In some cases details were modified so all packaging/delivery systems could be tested similarly. Details are included below.

Procedure A and *Procedure B* of ⟨382⟩*, 5. Needle and Spike Access Functional Suitability Tests, 5.2 Penetration Force, Vial and bottle systems* evaluate the penetration force required for a dosage form preparation hypodermic needle and for a dosage form access hypodermic needle, respectively. *Procedure C* evaluates the penetration force required for spike access. ISO standard vial package closure penetration tests do not specify the needle insertion rate or the use of a mechanical testing machine (ISO 8362-2, 8362-5, 8871-5). Standard bottle spike penetration force tests specify use of a mechanical testing machine, operated at an insertion rate of 200 mm/min with a load cell accuracy of ±2 Newtons (N) (ISO 8536-2 and -6). For consistency among chapter tests, the vial and bottle systems tests specify the use of a mechanical testing machine operated at the penetration rate of 200 mm/min with a data acquisition rate of NLT 100 Hz for both vials and bottles penetrated by either needles or spikes.

Procedure A and *Procedure B*, which use a needle for penetration, require a load cell accuracy of ±0.25 N in anticipation of results less than 10 N. *Procedure C*, which uses a spike, anticipates higher penetration forces, therefore, a load cell accuracy of ±2 N is specified, similar to the corresponding ISO standards.

There exists no published data or ISO standard for dosage form preparation penetration force for vial and bottle systems; therefore *Procedure A* does not include quantitative acceptance limits. The end user is responsible for establishing a limit appropriate for the system and its intended use.

The penetration force acceptance limit for BFS systems is also not specified. The penetration force limit in ISO 15759 only evaluates the penetration force through the closure, not the force required to penetrate the closure combined with the underlying plastic layer in a fully assembled BFS system. For this reason, the end user is responsible for establishing a limit that is appropriate for the system and its intended use.

The penetration force acceptance limit for plastic systems of no more than 200 N is the highest for all package types. This high value is informed by ISO 15747 and includes the friction force between the spike and the access port tube.

NEEDLE SELF-SEALING CAPACITY

See ⟨382⟩*, 5. Needle and Spike Access Functional Suitability Tests, 5.3 Needle Self-Sealing Capacity*. Also called reseal capacity, injection port tightness, or in-use leakage tests, this term applies to product packaging/delivery system closures required to ensure adequate package integrity during in-use conditions of multiple breaches by a needle(s). Such systems include

multiple-dose product packaging/delivery systems, as well as systems with closures that must be penetrated more than once to permit dosage form preparation followed by penetration(s) for product access and administration.

Test samples are challenged prior to packaging/delivery system in-use integrity verification by exposing the closures to worst case (i.e., the most challenging) piercing conditions anticipated for the intended product. In cases where the largest gauge piercing device(s) and/or the maximum penetration quantity conditions are undefined, ⟨382⟩ lists challenge conditions to be employed, similar to self-sealing test requirements corresponding to recognized standards.

The ⟨382⟩ test requires a minimum of 30 test samples for all packaging/delivery system types. This quantity is greater than the specification in ISO's standards for resealability tests. However, the requirement for 30 test samples does align with the requirements of ⟨382⟩*, 4. Packaging/Delivery System Integrity Tests*. A smaller quantity was viewed to be less likely to yield meaningful leakage information.

No leak test procedure is mandated for self-sealing capacity. Tests described in corresponding recognized standards may be consulted. However, such tests may not accurately or appropriately measure the integrity of the compromised closure for the intended product and its use. Therefore, the reader is referred to *Package Integrity Evaluation—Sterile Products* ⟨1207⟩ and its subchapters for guidance in test method selection, development, validation, and utilization.

SPIKE RETENTION AND SEALABILITY CAPACITY

See ⟨382⟩*, 5. Needle and Spike Access Functional Suitability Tests, 5.4 Spike Retention and Sealability Capacity*. This test is a measure of a closure system's ability to be fully penetrated by a spike (without pushing the closure into the container); to block visible evidence of liquid product leakage between the spike and the closure during the product-dosing time period; and to retain the spike during this time period.

Test samples are to be challenged by exposing the closures to worst case (i.e., the most challenging) piercing conditions anticipated for the intended product. In cases where the spike piercing device is undefined, utilize the device described in the corresponding ISO standards. Note that the ⟨382⟩ test sample size and test conditions are similarly based on recognized standard procedures for the respective packaging/delivery system categories.

4.5 Plunger Functional Suitability Tests

Information in ⟨382⟩*, 6. Plunger Functional Suitability Tests* applies to packaging/delivery systems that incorporate a plunger (also called a piston), namely cartridge systems and syringe systems. This section include tests to evaluate plunger break-loose and extrusion forces as well as plunger seal integrity.

Packaging/delivery systems designed to allow for product elution via a plunger are required to allow for complete, safe, and effective product delivery without damaging the system and without risking harm to either the patient receiving the medication or the individual accessing and/or administering the product. The plunger is also required to ensure adequate product containment from the time the product is filled until product delivery to the patient is complete.

PLUNGER BREAK-LOOSE AND EXTRUSION FORCES

See ⟨382⟩*, 6. Plunger Functional Suitability Tests, 6.1 Plunger Break-Loose and Extrusion Forces*. This test evaluates plunger break-loose force (also known as the initiating force), which is the force required to initiate the movement of the plunger. It also evaluates plunger extrusion force (also known as the sustaining force), which is the force required to sustain the movement of the plunger to expel the content of the syringe or cartridge. This test allows an analysis of the ease with which product delivery may be performed.

Many variables can affect these forces. For example, product characteristics of fluid viscosity, density, and fluid surface tension can directly impact break-loose and extrusion forces. These forces are also influenced by the interference fit between the plunger and the barrel, the plunger rib design and quantity, the lubrication of the plunger and the inner surface of the barrel, the fit of the plunger rod into the threaded plunger, the needle internal diameter, the inside diameter of the syringe or cartridge, and the target injection time. The use of connecting devices with the test sample can significantly influence forces such as extrusion forces.

Furthermore, it is noteworthy that break-loose force can increase over time to an unacceptable level at which point it is difficult to initiate plunger movement by hand. If the plunger is operated by a spring, the break-loose force required may be greater than the capability of the spring. The drug product applicant is advised to consider this possibility when designing drug product shelf-life stability assessment studies. Finally, component processing can also impact plunger function. For example, an irregular extrusion force, or one that rises significantly towards the syringe nozzle, can indicate non-homogeneous lubrication of the barrel due to improper application or degradation.

The performance requirements of the packaging/delivery system should consider the intended use of the syringe or cartridge. For example, if the product is to be manually delivered, break-loose force, extrusion forces, and range of possible rates of delivery should accommodate the skill set of the population responsible for product administration. If the product is to be delivered using an automatic pen injector, forces must be appropriate for the delivery system hardware.

In conclusion, a wide number of variables can impact break-loose and extrusion force results. The many combinations of products, packaging/delivery systems, and intended uses influence acceptable functional performance criteria. Therefore, a single test method cannot be defined, nor can acceptance criteria be specified, for all relevant packaging/delivery systems, products, and intended-use applications. The user is responsible for following the generic test method outlined in ⟨382⟩ and for establishing meaningful quantitative acceptance criteria that best represent the demands of the specific product packaging/delivery system.

PLUNGER SEAL INTEGRITY

See ⟨382⟩*, 6. Plunger Functional Suitability Tests, 6.2 Plunger Seal Integrity*. This test is designed to apply a fixed force to the plunger of a sealed syringe or cartridge containing liquid product in order to detect leakage past the plunger. *Procedure A* applies to manually operated prefilled and single-use syringe systems. This procedure and acceptance criteria were informed by ISO 7886-1. *Procedure B* applies to non-manually operated prefilled syringe systems that function as part of an auto-injector system such as a spring-driven or power-driven delivery device. This procedure and acceptance criteria were informed by ISO 11040-8. *Procedure C* is specifically for cartridge systems used for dental local anesthesia products and was informed by ISO 11040-2 and -3. *Procedure D* is for all cartridge systems, excluding those for dental local anesthesia products. The procedure and acceptance criteria were informed by ISO 13926-2 and -3. For all procedures, satisfactory plunger seal tightness will not permit visible leakage of liquid product past the rear rib or final seal of the plunger when forces simulating product delivery are applied. Inspect the primary components (syringe and plunger) prior to the insertion of the plunger to avoid trapping liquid between the plunger ribs and the container. For cartridge containers that are also closed with a stopper or septum (without a needle), acceptance criteria also require the absence of visible leakage past this closure.

4.6 Tip Cap and Needle Shield Functional Suitability Tests

⟨382⟩*, 7. Tip Cap and Needle Shield Functional Suitability* tests examine the functional suitability of tip caps and needle shields. These components are intended to protect the needle or nozzle (Luer end) of the syringe, allow for nozzle/needle sterilization, and maintain the sterility of the contents of the syringe container. The functional suitability tests examine the forces required to remove the tip cap or needle shield prior to dose administration. *Procedure A* measures the axial force used to pull off needle shields and tip caps. *Procedure B* is a torque test that measures the force use to unscrew and remove the Luer lock rigid tip caps. A packaging/delivery system is satisfactory if the force needed to remove the component 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.

When selecting acceptance criteria, the user should consider the various factors that can influence removal forces. For example, processes applied to the components pre- and post-assembly, such as lubrication and sterilization, can impact test results. Other factors include elastomeric component age, age of the assembled system, and possibly finished product storage conditions.

The procedures and acceptance criteria in ⟨382⟩*, 7. Tip Cap and Needle Shield Functional Suitability* were influenced by ISO 11040-4 and -8.

5. CONCLUSION

In summary, the functional performance of elastomeric components is to be evaluated in a manner that ensures the elastomeric component is suitable. Although this chapter's scope does not include functional suitability tests relevant to other components of the packaging/delivery system, or to all aspects of the system itself, such tests are nevertheless important. Consideration should be given to the full scope of packaging/delivery system functional demands inherent in the manufacture, safety, use, and marketability of the intended product. To this end, the applicant may seek direction in other relevant packaging/delivery system guidances and standards. Determination of a suitable elastomeric component requires that the applicant employ a science- and risk-based approach to accomplish a thorough and complete functional suitability assessment verifying the entire packaging/delivery system's fitness for intended use.▲ (USP 1-Dec-2020)