BRIEFING

⟨1382⟩ Assessment of Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems. This proposed new general chapter contains information and guidance to assist users in the functionality assessment of elastomeric closures as part of packaging/delivery systems intended for injectable dosage forms described in *Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems* ⟨382⟩. Such closures include primary packaging components that are partially or completely made of elastomeric material. Proper selection and design of functionality assessment studies is based on sound scientific principles that are consistent with 1) the nature of the packaging system and packaged drug product; 2) the clinical use of the packaged drug product; and 3) the perceived safety risk associated with the packaging system and drug product. Alternative testing strategies for functionality assessment may be appropriate in certain circumstances with proper justification.

A workshop, *Modernization of USP Packaging Standards for Glass and Elastomeric Components*, will take place June 19–20, 2017 at the USP Meetings Center in Rockville, Maryland, to discuss the proposals for three new chapters including this one, ⟨382⟩, and *Elastomeric Evaluation of Elastomeric Components Used in Pharmaceutical Packaging/Delivery Systems* ⟨1381⟩, as well as the revision proposals to *Elastomeric Closures for Injections* ⟨381⟩. All four chapters appear in this issue of *PF*. See http://www.usp.org/meetings-courses/workshops/modernization-usp-packaging-standards-glass-and-elastomeric-components for more information about the workshop.

(GCPD: D. Hunt.)
Correspondence Number—C185736

Add the following:

⟨1382⟩ ASSESSMENT OF ELASTOMERIC CLOSURE FUNCTIONALITY IN INJECTABLE

PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS

1. INTRODUCTION

This chapter contains information and guidance to assist in the functionality assessment of elastomeric closures as part of packaging/delivery systems intended for injectable dosage forms outlined in *Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems* ⟨382⟩. Such closures include primary packaging components that are partially or completely made of elastomeric material. Proper selection and design of functionality assessment studies is based on sound and justifiable scientific principles that are consistent with 1) the nature of the packaging system and packaged drug product; 2) the clinical use of the packaged drug product; and 3) the perceived safety risk associated with the packaging system and drug product. Alternative testing strategies for functionality assessment may be appropriate in justified circumstances.

2. EARLY PACKAGE DEVELOPMENT: CLOSURE FUNCTIONALITY ASSESSMENT

Early in the package selection and development process, the final packaging system with its closures may not be fully defined; functionality requirements may not be established. This is especially true if the packaging system or the drug product is novel to the drug product manufacturer. At this phase of the product life cycle, functionality assessments are performed to better understand packaging system performance and/or to screen potential closure and container candidates. To that end, *Table 1* lists closure functionality tests for packaging systems intended to contain dosage forms for injection 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.

Although not mandated, testing components and/or closed packaging systems according to such standards may provide useful information,

especially during early product–package development. Other relevant internationally recognized standards deemed scientifically appropriate may be used instead of, or in addition to, those listed in *Table 1*.

Table 1. ISO Standards: Functionality Tests for Elastomeric Closures

ISO Standard		Elastomeric Closure Functionality Tests
Sterile hypodermic syringes for single use	7886-1	**Syringes for manual use** Fit of piston in barrel Freedom from air and liquid leakage past piston
	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
Infusion equipment for medical use	8536-2	**Closures for infusion bottles** Fragmentation Spike penetration force Spike retention/sealability
	8536-6	**Freeze drying closures for infusion bottles** Fragmentation Spike penetration force Spike penetration/sealability Self-sealing Container-closure seal integrity
Sterile single-use syringes, with or without needle, for insulin	8537	Fit of plunger stopper in barrel (forces to operate piston)

ISO Standard		Elastomeric Closure Functionality Tests
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	Freedom from leakage at needle Freedom from leakage past plunger stopper **Functional requirements and testing** Penetrability Fragmentation Self-sealing and container–closure seal integrity Aqueous solution tightness
Prefilled syringes	11040-3	**Seals for dental local anaesthetic cartridges** Fragmentation Freedom from leakage
	11040-4	**Glass barrels for injectables and sterilized subassembled syringes ready for filling** Closure system allowance for sterilization Glide force Closure system liquid leakage (past needle shield or tip cap) Pull-off force of tip cap or needle shield Closure system barrel integrity (dye solution tightness test)
Needle-based injection systems for medical use – Requirements and test methods	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 force and extrusion force)

ISO Standard		Elastomeric Closure Functionality Tests
Plastic containers for intravenous injections	13926-3	**Seals for pen-injectors for medical use** Fragmentation Freedom from leakage past seals under axial pressure Resealability
	15747	Resistance to temperature stability, pressure, and leakage Resistance to dropping Penetration ability Adhesion strength of the infusion device and impermeability of the insertion point Tightness of the injection point
Medical infusion equipment – Plastics caps with inserted elastomeric liner for containers manufactured by the blow-fill-seal (BFS) process	15759	**Plastics cap tests**[a] Leak resistance test Opening force needed to expose the piercing area **Elastomeric liner tests** Fragmentation Penetration force Dynamic spike-retention capability Static spike-retention capability of the liner and leak resistance of the piercing area Resealability

[a] Plastic caps are an integral part of the elastomeric liner and are therefore included for completeness.

3. ASSESSMENT OF THE FITNESS OF FUNCTIONALITY TEST FOR ITS INTENDED USE

Evidence of the ability of the elastomeric closure to satisfactorily function as part of the final packaging system according to its intended product use is required to support market approval of a packaging system or a packaged drug product.[1] Internationally recognized standards can provide a useful benchmark when designing appropriate elastomeric closure functionality assessment studies. However, the drug manufacturer is advised to exercise

caution before prescriptively adopting standardized tests, as such tests may not provide a complete or adequate assessment of the elastomeric closure's ability to meet the final packaging system's product-specific functional demands. There are many reasons why the standardized tests may not be adequate or appropriate in specific situations, for example:

- The final packaging system components may differ in design or dimension from those described in the standard.
- The manner in which the final packaging system's components are processed, reprocessed, and/or assembled may differ from that described in the standard.
- The manner in which the packaged product is to be accessed at time of use may differ from that described in the standard. Differences may include, for example, needle or spike design, material, lubricity; needle puncture speed; and number of penetrations per closure.
- The standard's test procedure or analysis method may provide an inadequate measure of packaging system functionality given the specific rigorous demands to be placed on the final packaging system. For instance, bench test conditions may not sufficiently mirror the rigors to be 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 package functionality. To illustrate, 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–package.
- The standard test's acceptance criterion may not reflect the functional performance demanded of the final packaging system. 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.

Therefore, the drug manufacturer is tasked with developing a body of elastomeric closure functionality assessment tests that logically and most appropriately assess the final packaging system. Challenges placed on the final product–package during testing should mimic those that the product is likely to encounter through storage/distribution, product expiry, and final use. These testing challenges should provide clear and definitive measures of packaging system performance. When reporting functionality assessment findings, the drug manufacturer is advised to offer justification for the testing program chosen.

3.1 Role of ⟨382⟩

Chapter ⟨382⟩ offers fitness-for-intended-use functionality assessment procedures and acceptance criteria reflective of current best practices. Although the most commonly employed test methods are represented, the drug manufacturer may require additional tests to adequately assess the closure functionality as part of a particular packaging system. General guidance relevant to tests in ⟨382⟩ appears below.

3.1.1 TEST SAMPLES

Elastomeric closures cannot be tested for functionality in isolation from the intended packaging system. Furthermore, a closure's functional performance assessment outcome can be affected by the design, processing, and assembly of that packaging system. For example, closure processing parameters and vial package sealing forces directly impact parenteral vial packaging integrity results. Plunger break and extrusion forces are directly related to the design, material of construction, and lubricity of the syringe barrel.

Because closure functionality is connected to the packaging system, the test samples employed for each functionality test are to mirror as closely as possible the closures and packaging system of the intended product. Components are to be prepared, processed, and assembled as defined for the final product–package system, especially if such steps are believed to have a potential impact on closure functionality.

The following examples are offered as illustration:

- Closures are to be washed, lubricated, and sterilized according to intended product protocol
- Vial closures are to be optimally capped onto vials in a manner reflective of the intended finished product–packaging system
- Syringe/cartridge barrels are to be prepared and lubricated according to the requirements of the intended pharmaceutical product
- Syringe/cartridge closures are to be inserted into syringe barrels according to production practices (e.g., by use of a vent tube or vacuum insertion)

Some flexibility in test sample preparation is permitted if the variation is judged to have little or no impact on test outcome. Test samples may bracket relevant parameters of packaging system design and dimension, component processing, package assembly, and product contents given appropriate justification. Bracketing may be employed to allow a functionality assessment program to address a wider spectrum of packaging systems and/or products.

Specific tests, such as the test for *Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems ⟨382⟩, 5. Needle and Spike Access Functionality Tests, 5.1 Fragmentation*, require that test

samples be filled with water; this allows for the capture and collection of closure shredded particles. Other tests, such as the test for *6.1 Plunger Break Force and Plunger Glide Force*, also require that the test container be filled with liquid. However, in such cases where package contents can influence the test outcome, it is recommended that test samples be filled with product or product-proxy liquid so that the test outcome better reflects package system intended use. Alternatively, content material that brackets the characteristics of multiple products may be chosen.

When reporting closure functionality test results, the test samples used are to be fully described, including all parts of the primary packaging system used in the test. These parts may include closures, containers, and in some cases, additional essential components (e.g., vial caps). Relevant details are to be documented and may include component age, design, material content, material or batch lot identification, and methods of component and/or package processing, package assembly, and package contents.

3.1.2 TEST SAMPLE POPULATION SIZE

Test sample quantity should provide a reasonable measure of confidence of the package system elastomeric closure functionality. Larger quantities than those specified in test procedures are encouraged to provide greater assurance of packaging system performance and to minimize the risk of product failure during commercial use. Test sample population sizes are to be reported with test results.

3.1.3 TEST PROCEDURES

Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems ⟨382⟩, 4. Package Integrity tests are included in ⟨382⟩ because all closures must effectively protect and contain the package contents. For closures designed to allow product access via needle or spike penetration, functionality tests of *5. Needle and Spike Access Functionality Tests, 5.1 Fragmentation*, *5.2 Penetration Force*, and *5.3 Self-Sealing Capacity* are included. Other tests are described that evaluate the functionality of plungers (or pistons) in prefilled syringes and cartridges and pen, jet, and related injectors. These tests include *6.1 Plunger Break Force and Plunger Glide Force*, *6.2 Plunger Seal Integrity*, and *7. Tip Cap and Needle Shield Functionality Tests*.

All tests described require an understanding of the product–packaging system, along with its intended function and performance requirements. This comprehensive understanding allows for selection and use of the most logical challenge to closure functionality. For example, *Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems ⟨382⟩, 4. Package Integrity* and *5. Needle and Spike Access Functionality Tests, 5.3 Self-Sealing Capacity* tests allow the user to select an appropriately sensitive, validated leak test, to be chosen based on the maximum allowable leakage limit mandated for the product. As a second example, *5. Needle and*

Spike Access Functionality Tests, 5.1 Fragmentation, *5.2 Penetration Force*, and *5.3 Self-Sealing Capacity* results require the user to use needle or spike penetration parameters that best mirror the routine or recommended final product–package access practices. This is important because outcomes may differ with penetration tool design, lubricity, and gauge along with the angle/speed of penetration.

When reporting functionality assessment test results, details about any alternative test method used, outside of methods defined in ⟨382⟩, are to be cited with justification provided.

3.1.4 DATA INTERPRETATION

Several of the tests described in ⟨382⟩ include definitive acceptance criteria. These criteria are to be applied if such requirements properly reflect the demands of the specific product–packaging system. Justification for using acceptance criteria outside those specified in ⟨382⟩ is to be provided.

Some tests described in ⟨382⟩ do not include definitive acceptance criteria due to the wide range of packaging systems and their functional performance demands. In these cases, pass/fail criteria determined to best represent the demands of the finished product–packaging system should be used, and justification for such criteria should be provided.

4. CONCLUSION

In summary, the functional performance of elastomeric closures is to be evaluated in a manner ensuring that the final packaging system is fit for its intended use of safely and effectively providing the patient with parenteral medication of the highest quality. Although this chapter's scope does not include functionality tests relevant to other components of the packaging system, or the packaging system itself, such tests are nevertheless important. Consideration should be given to the full scope of packaging 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 system guidances and standards. This process requires that the applicant employ a science- and risk-based approach to accomplish a thorough and complete functionality assessment verifying the entire packaging system's fitness for intended use.

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[1] Alternative testing strategies for functionality assessment may be appropriate in justified circumstances, subject to agreement by an appropriate regulatory authority.