

BRIEFING

⟨382⟩ Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems, *PF* 43(3) [May–June 2017]. The previous proposal for this chapter, published in *PF* 43(3) under a different title, *Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems*, was canceled and an updated version is being proposed. This new general chapter addresses the fitness-for-use functional suitability requirements for packaging/delivery systems that are intended for parenteral dosage forms and that include primary packaging components partially or completely made of elastomeric material. Elastomeric components, when properly fitted with dimensionally compatible packaging/delivery systems, are intended to protect and contain the package contents while enabling safe and effective product access at the time of use. The function being performed by any single elastomeric component type is dependent on the packaging/delivery system and may cover more than one functional parameter. A more complete discussion of fitness-for-intended-use testing, as compared to component functional suitability assessment in early package development, is presented in *Assessment of Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems* ⟨1382⟩, which is also being proposed in this issue of *PF*. Also refer to ⟨1382⟩ for guidance on test samples and their preparation, test sample population size, test procedures, test acceptance criteria, and test outcome reporting. Due to the scope of the proposed new chapter and the industry impact, the Packaging and Distribution Expert Committee is proposing a 5-year delayed implementation to allow industry adequate time to implement. Until this chapter becomes fully implemented, the functionality test in ⟨381⟩ will remain.

(GCPD: D. Hunt.)

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1 **Add the following:**

2 **^⟨382⟩ Elastomeric Component Functional Suitability in**
3 **Parenteral Product Packaging/Delivery Systems**

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21 **1. INTRODUCTION**

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

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

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

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

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

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

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

82 **2. SCOPE**

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

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

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

96 **2.1 Packaging/Delivery Systems**

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

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

117 **Vial and bottle systems:**

118 Vial and bottle packaging/delivery systems have elastomeric closures fitted
119 and compressed onto the container flange opening, mechanically held in
120 place by a seal component (also called a cap). The closure is intended to
121 permit product access via penetration by a hypodermic needle (for single-
122 dose or multiple-dose product access), or by a spike piercing device (single-
123 dose access). Applicable closures include those designed to accommodate
124 either liquid-fill, lyophilization, or powder-fill production processes. Chapter
125 tests were informed by ISO 8362-2 and -5, ISO 8536-2 and -6, and ISO
126 8871-5.

127 **BFS systems:**

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

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

133 **Plastic systems:**

134 Plastic packaging/delivery systems refer to plastic containers for parenteral
135 dosage forms having one or more chambers with a total nominal capacity of
136 50–5000 mL. Examples include film bags or containers formed by blow-
137 molding processes that are intended for direct administration of liquids by
138 infusion or injection. Elastomeric septum closures are sealed onto the
139 container access port by mechanical means, welding, or other means. The
140 access point consists of the insertion point (point that accepts the insertion
141 part of the infusion device) and the injection point (point for injecting
142 pharmaceuticals), if applicable. The injection and insertion points can be
143 identical in some cases. Product injection through the injection point is
144 performed using a narrow-gauge cannula. Product access for patient
145 administration is through the insertion point via an infusion device with a
146 spike piercing device. Chapter tests were informed by ISO 15747.

147 **Cartridge systems:**

148 Cartridge systems are sealed with two elastomeric components. One is a
149 septum compressed onto the cartridge flange opening, mechanically held in
150 place by a seal (also called a cap). The septum is intended to permit product
151 access via penetration by a double-sided hypodermic needle. The other
152 elastomeric component is a plunger fitted inside the cartridge barrel that
153 expels the contents of the cartridge. Cartridge systems are found in two
154 main application areas: dental local anesthesia product cartridge
155 packaging/delivery systems and cartridges intended for pen-injector
156 packaging/delivery systems for treatment of conditions such as diabetes or
157 growth disease. Chapter tests were informed by ISO 11040-2 and -3, ISO
158 13926-2 and -3, and ISO 11608-3.

159 **Syringe systems**

160 **Prefilled syringe systems:**

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

169 **Single-use syringe systems:**

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

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

178 **3. GENERAL TEST REQUIREMENTS**

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

184 **3.1 Test Samples**

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

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

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

206 **3.2 Test Sample Population Size**

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

214 **3.3 Acceptance Criteria**

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

222 **4. PACKAGING/DELIVERY SYSTEM INTEGRITY TESTS**

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

233 The following terms and definitions apply:

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

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

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

245 **Procedure:**

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

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

259 **Acceptance criteria:**

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

265 **5. NEEDLE AND SPIKE ACCESS FUNCTIONAL SUITABILITY TESTS**

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

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

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

277
 278 The following terms and definitions apply:

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

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

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

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

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

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

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

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

313 **5.1 Fragmentation**

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

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

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

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

327 The following term and definition applies:

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

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

337 **Vial and bottle systems**

338 **Procedure A:**

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

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

354 For all packaging/delivery systems, after performing an initial dosage form
355 preparation puncture (if applicable), proceed as follows. Use the designated
356 product-access penetration needle or piercing device fitted to a clean syringe
357 filled with *particle-free water*. If a needle is not designated, use a 21-gauge
358 hypodermic injection needle (0.8-mm outer diameter) with a bevel angle of
359 $11 \pm 2^\circ$. Pierce the closure with the needle perpendicular to the surface.
360 After each puncture, inject a volume of *particle-free water* into the vial or
361 bottle through the inserted needle while removing an equal volume of air.
362 The volume chosen should adequately purge the insertion needle of
363 elastomeric fragments. Repeat piercings for each closure, piercing each time

364 at a different location, simulating typical product-access piercing practices
365 for this packaging/delivery system type. Match the total number of product-
366 access piercings per closure to that of the intended product, but perform NLT
367 4 piercings per closure. Use a fresh needle for each closure. For closures to
368 be pierced more than 4 times each, the needle may be replaced more
369 frequently. Check that the needle penetration tip is not blunted during the
370 test.

371 Remove the tested closures from the containers. Pour container contents
372 through the particulate examination filter, taking care that no visible
373 particles remain in the container. Perform the water rinsings and particle
374 count procedure according to *Particulate Matter in Injections* (788), *Method 2*
375 *Microscopic Particle Count Test*. Adjust the magnification from 40× to 100 ±
376 10× as needed. Determine the longest linear dimensions of the elastomeric
377 particles using the linear scale on the graticule in [\(788\), Figure 1](#).

378 **Procedure B:**

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

383 For those systems requiring an initial closure penetration for dosage form
384 final preparation, pierce each test sample closure using the designated
385 dosage form preparation piercing device fitted to a clean syringe filled
386 with *particle-free water*. If a piercing device is not designated, use an 18-
387 gauge hypodermic needle (1.27-mm outer diameter) with a bevel angle of
388 $11 \pm 2^\circ$. Perform one piercing per closure with the needle or device
389 perpendicular to the surface. Use a fresh needle or device per closure. After
390 each puncture, inject a volume of *particle-free water* into the vial or bottle
391 through the inserted needle or device while removing an equal volume of air.
392 The volume chosen should adequately purge the insertion needle of
393 elastomeric fragments.

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

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

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

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

411 Perform the water rinsings and particle-count procedure according
412 to *Particulate Matter in Injections* (788), *Method 2 Microscopic Particle Count*
413 *Test*. Adjust the magnification from 40× to 100 ± 10× as needed. Determine
414 the longest linear dimensions of the elastomeric particles using the linear
415 scale on the graticule in [\(788\), Figure 1](#).

416 **Acceptance criteria**

417 **Procedure A:**

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

420 **Procedure B:**

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

423 **BFS systems**

424 **Procedure:**

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

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

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

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

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

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

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

453 Perform the water rinsings and particle count procedure according
454 to *Particulate Matter in Injections (788), Method 2 Microscopic Particle Count*
455 *Test*. Adjust the magnification from 40× to 100 ± 10× as needed. Determine
456 the longest linear dimensions of the elastomeric particles using the linear
457 scale on the graticule in [\(788\), Figure 1](#).

458 **Acceptance criteria:**

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

461 **Cartridge systems**

462 **Procedure A:**

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

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

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

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

485 the longest linear dimensions of the elastomeric particles using the linear
486 scale on the graticule in [\(788\), Figure 1](#).

487 **Procedure B:**

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

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

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

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

505 Perform the water rinsings and particle count procedure according
506 to *Particulate Matter in Injections (788), Method 2 Microscopic Particle Count*
507 *Test*. Adjust the magnification from 40× to 100 ± 10× as needed. Determine
508 the longest linear dimensions of the elastomeric particles using the linear
509 scale on the graticule in [\(788\), Figure 1](#).

510 **Acceptance criteria**

511 **Procedure A:**

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

514 **Procedure B:**

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

517 **5.2 Penetration Force**

518 The following practices are recommended when performing penetration
519 force tests.

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

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

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

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

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

538 **Vial and bottle systems:**

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

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

546 **Procedure A:**

547 This procedure is a dosage form preparation simulation applicable to
548 systems requiring initial closure penetration for dosage form final
549 preparation using a hypodermic needle. If a needle is not designated, use an
550 18-gauge hypodermic needle (1.27-mm outer diameter) with a bevel angle
551 of $11 \pm 2^\circ$.

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

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

559 **Procedure B:**

560 This procedure is a product-access simulation applicable to systems intended
561 for product access via a hypodermic injection needle. Select 10 samples for
562 test. Perform tests using the designated penetration needle. If a needle for
563 product access is not designated, use a 21-gauge hypodermic needle (0.8-
564 mm outer diameter) with a bevel angle of $11 \pm 2^\circ$.

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

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

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

573 **Procedure C:**

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

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

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

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

590 **Acceptance criteria**

591 **Procedure A:**

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

600 **Procedure B:**

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

608 **Procedure C:**

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

617 **BFS systems**

618 **Procedure:**

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

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

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

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

633 **Acceptance criteria:**

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

640 **Plastic systems**

641 **Procedure:**

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

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

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

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

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

656 **Acceptance criteria:**

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

663 **5.3 Needle Self-Sealing Capacity**

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

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

674 The following terms and definitions apply:

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

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

682 **Procedure:**

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

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

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

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

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

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

709 **Vial and bottle systems:**

710 For dosage form preparation penetrations, use an 18-gauge hypodermic
711 injection needle (1.27-mm outer diameter) with a bevel angle of $11 \pm 2^\circ$.
712 Penetrate each closure one time, piercing within the closure target area. Use
713 a new needle for each closure.

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

717 **BFS systems:**

718 For dosage form preparation penetrations, use an 18-gauge hypodermic
719 injection needle (1.27-mm outer diameter) with a bevel angle of $11 \pm 2^\circ$.
720 Penetrate each closure one time, piercing within the target area. Use a new
721 needle for each closure.

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

725 **Plastic systems:**

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

729 **Cartridge systems:**

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

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

739 **Acceptance criteria:**

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

745 **5.4 Spike Retention and Sealability Capacity**

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

750 Perform all piercings using the designated device intended for finished
751 product access. If the device is neither specified nor provided, use the
752 recommended piercing device cited in the test protocols that follow.

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

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

759 **Vial and bottle systems**

760 **Procedure:**

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

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

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

775 **Acceptance criteria:**

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

780 **BFS systems:**

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

785 **Procedure A:**

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

791 **Procedure B:**

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

798 **Acceptance criteria**

799 **Procedure A:**

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

802 **Procedure B:**

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

806 **Plastic systems**

807 **Procedure:**

808 Select 10 samples for test, nominally filled with liquid product or product
809 proxy. Use the designated spike for product access for all penetrations. If a
810 spike is not designated, use a closure-piercing device as described in ISO
811 8536-4 and referenced in ISO 15747. Use a fresh spike for each test sample.
812 Place the spike perpendicular to the center of the insertion point closure
813 target area. Force the spike through the closure until complete penetration is
814 achieved. Allow the spike to remain in the insertion point for 5 h. Then place
815 the infusion containers between 2 parallel plates and compress to achieve an
816 internal pressure of 20 kPa for 15 s. (If the infusion container is intended to
817 be used with a pressure cuff, perform the test with an internal pressure of
818 50 kPa for 15 min). Inspect for liquid leakage between the closure and spike.

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

822 **Acceptance criteria:**

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

826 **6. PLUNGER FUNCTIONAL SUITABILITY TESTS**

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

830 The following terms and definitions apply:

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

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

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

837 **6.1 Plunger Break-Loose and Glide Forces**

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

847 **Procedure:**

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

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

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

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

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

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

885 **Acceptance criteria:**

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

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

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

902 **6.2 Plunger Seal Integrity**

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

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

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

920 **Procedure A:**

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

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

931 **Procedure B:**

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

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

944 **Procedure C:**

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

951 **Procedure D:**

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

958
$$\text{Result} = p \times d^2$$

$p = 0.64 \text{ N/mm}^2$

$d = \text{nominal inner diameter of the container barrel (mm)}$

959 Release the pressure and visually examine the plunger and septum.

960 **Acceptance criteria**

961 **Procedure A:**

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

964 **Procedure B:**

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

967 **Procedure C:**

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

972 **Procedure D:**

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

977 **7. TIP CAP AND NEEDLE SHIELD FUNCTIONAL SUITABILITY TESTS**

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

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

990 The following terms and definitions apply:

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

996 **Tip cap:** An elastomeric component that seals the nozzle end of a syringe
997 barrel. The tip cap is intended to physically protect the nozzle or Luer end of
998 the syringe, to permit sterilization of the nozzle, and to maintain sterility of
999 the syringe contents and of the nozzle up to the time a needle is affixed and
1000 the dosage form is administered. Tip caps are removed by axial pull-off
1001 force.

1002 **Luer lock rigid tip cap (LLR tip cap):** An elastomeric component designed
1003 with a plastic Luer lock adaptor collar system that seals the nozzle end of a
1004 syringe barrel. The LLR tip cap is intended to physically protect the nozzle or
1005 Luer end of the syringe, to permit sterilization of the nozzle, and to maintain
1006 sterility of the syringe contents and of the nozzle up to the time a needle is
1007 affixed and the dosage form is administered. LLR tip caps are removed by
1008 torque force.

1009 **Procedure A:**

1010 This procedure applies when testing a needle shield or tip cap removed by
1011 axial pull-off force. Select 10 samples for test; test samples may be tested
1012 empty or filled with product or a product proxy.

1013 Tests are performed using a universal tensile and compression testing
1014 machine appropriately equipped with a load cell (e.g., 50–100 N) linked to a
1015 data gathering system (typically NLT 40 Hz sampling rate). The machine
1016 should be capable of applying an axial force at the desired test speed
1017 (typically 100–1000 mm/min).

1018 Position and secure the test sample in the holder of the test instrument in
1019 a vertical position with the needle shield or tip cap oriented upwards. Secure
1020 the tip cap or needle shield in a manner that does not deform/distort or slide
1021 against the component. Apply an axial tensile force at a minimum data
1022 sampling rate of 40 Hz until the tip cap or needle shield is completely
1023 removed from the syringe tip. Record the maximum force required to
1024 remove the closure in Newtons.

1025 When reporting test results, include test speed, sampling rate, load cell
1026 used, maximum load recorded in the force versus displacement curve, test
1027 sample quantity, and the number that passed/failed according to the
1028 acceptance criteria.

1029 **Procedure B:**

1030 This procedure applies when testing an LLR tip cap removed by torque force.
1031 Select 10 samples for test; test samples may be tested empty or filled with
1032 product or a product proxy.

1033 Tests are performed using a torque tester combined with a rotation device
1034 appropriately equipped with a torque cell with 35 Newton centimeters (Ncm)
1035 capacity and 0.05 Ncm resolution (or as appropriate to the torque to be
1036 measured) and linked to a data gathering system (typically NLT 65 Hz
1037 sampling rate). The machine should be capable of applying a torque force at
1038 the desired test speed (typically 20 rpm). For this test, either the syringe or
1039 the LLR tip cap can be rotated.

1040 Position and secure the test sample in the holder of the test instrument in
1041 a vertical position with the LLR tip cap oriented upwards. Secure the LLR tip
1042 cap in a manner that does not deform/distort or slide against the
1043 component. Ensure that the torque cell is set to 0 prior to test start (no pre-
1044 torque should be applied). Rotate the tip cap (or the syringe) at a rotation
1045 speed of 20 rpm, or as appropriate, until the LLR tip cap is completely
1046 removed from the syringe tip. Record the peak load of the applied torque.

1047 When reporting test results, include rotation speed, sampling rate,
1048 maximum torque, test sample quantity, and the number that passed/failed
1049 according to the acceptance criteria.

1050 **Acceptance criteria**

1051 **Procedure A:**

1052 The quantitative acceptance limit established by the end user may vary with
1053 the product-specific packaging/delivery system. The packaging/delivery
1054 system is acceptable if, for all test samples, the maximum observed removal
1055 pull-off force does not exceed the maximum force that allows for ease of
1056 access and if the minimum observed force is sufficient to ensure that the
1057 closure remains in place during the product life cycle, preserving product
1058 sterility.

1059 **Procedure B:**

1060 The quantitative acceptance limit established by the end user may vary with
1061 the product-specific packaging/delivery system. The packaging/delivery
1062 system is acceptable if, for all test samples, the maximum observed removal
1063 torque force does not exceed the maximum force that allows for ease of
1064 access and if the minimum observed force is sufficient to ensure that the
1065 closure remains in place during the product life cycle, preserving product
1066 sterility.▲ (USP 1-Dec-2020)

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