

DELIVERY SYSTEM DEVELOPMENT

Supporting Earlier Delivery-System Decisions in Injectable Drug Development Through a USP <382>-Aligned System-Level Approach

By: Sara Masucci and Crystal Salvans

INTRODUCTION

Injectable therapy development is increasingly shaped by the need for patient-centric delivery, reduced administration burden, and flexibility across clinical and commercial programs. As biologics and sensitive vaccine formulations become more complex, the packaging and delivery system play an important role in protecting product quality throughout the product lifecycle. In prefilled syringe (PFS) applications, the glass syringe, elastomeric plunger, rigid needle shield (RNS), and related interfaces must work together as an integrated container closure system.

This system-level perspective is aligned with USP <382>, Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems, which addresses functional suitability of parenteral packaging and delivery systems that include elastomeric components. Rather than focusing only on individual component properties, USP <382> supports evaluation of how component interfaces contribute to functional performance, container closure integrity, and intended use.

To support this evolving approach, the Aptar Pharma Injectables division and Stevanato Group developed a pre-evaluated package aligned with USP <382> for PFS configurations, combining glass syringes, elastomeric plungers and RNS as an assembled container closure system.

The objective is to assess how the assembled system performs and provide data that pharmaceutical developers can use

during early-stage feasibility, component screening, and risk assessment activities.

A dedicated technical Data Package supports the summarized findings presented in this article and is available at both Aptar Pharma and Stevanato Group. This article provides a high-level overview of the pre-evaluated package, with the Data Package serving as the detailed evidence base for technical review.

FIGURE 1



Glass syringes from Stevanato Group (EZ-fill® Nexa® and Alba® platforms)

Plungers including PremiumCoat® options and RNS for autoinjectors from Aptar Pharma

TABLE 1	
Components Role in System Integrity	
Component	Role in System Integrity
Glass syringe barrel	Provides the primary containment structure and internal surface interfacing with the fill medium; defines the dimensional environment for the elastomeric plunger seal and contributes to overall container closure integrity.
Elastomeric plunger	Establishes the primary dynamic seal within the syringe barrel, supporting maintenance of container closure integrity during storage and simulated use while enabling controlled dose delivery.
RNS	Provides closure at the syringe tip, protecting the needle and contributing to system level container closure integrity by maintaining a sealed barrier.

A COLLABORATIVE SYSTEM-LEVEL APPROACH BUILT AROUND PRACTICAL DEVELOPMENT QUESTIONS

System Overview

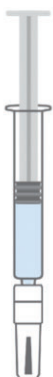
The evaluated container closure system represents a PFS primary container configuration consisting of the elements in Table 1 and Figure 1. These components are assembled to evaluate functional performance and container closure integrity independently of any specific drug product.

To evaluate component interactions

without making claims for a specific drug product or commercial lifecycle conditions, testing was performed with a placebo medium. This enabled the assessment of critical functional interactions and integrity-related behavior at system level, as a first step in the evaluation of USP <382> principles. The studies compiled in the data package characterize the baseline functional and integrity performance of the evaluated configurations detailed in Table 2 and provide early-phase, non-product-specific information to support development and de-risking activities.

The evaluated configurations are based on commercially available syringe, plunger, and RNS platforms already used in pharmaceutical development and commercial applications, including both 1mL long and 2.25mL syringe formats, allowing assessment across multiple system configurations within a common pre-verified package approach.

Because the final drug product, formulation, and processing conditions were not known at this stage, Water for Injection (WFI) was used as a neutral medium. The testing program includes:

TABLE 2						
Aptar – Stevanato Group Configurations Tested in the Data Package						
		Syringe size	1 mL		2.25 mL	
		Syringe size	Nexa®	Alba®	Nexa®	Alba®
		Needle size	Gauge: 27G and 29G, Thin Wall Length: ½"	Gauge: 27G,Special Thin Wall* Length: ½"	Gauge: 25G and 27G, Special Thin Wall Length: ½" & 8mm	Gauge: 25G and 27G, Special Thin Wall Length: ½" & 8mm
	Plunger	Coated	1mL long PremiumCoat® RTU		1-3mL PremiumCoat® RTU	
		Uncoated	1mL long RTU		1-3mL RTU	
		For Auto-Injector	½" 4900GS		1/2" & 8mm 4900GS	
	RNS	Standard	½" 4800GS		½" 4800GS	

*Stevanato Group’s Special Thin-Wall (sTW) needles feature an enlarged internal diameter to optimize the delivery of highly viscous drug formulations without the need for larger needle gauge.
The component references listed above correspond to representative platforms evaluated as part of this data package. Evaluation focused on functional interactions and system level integrity performance; no proprietary design dimensions or tolerances are disclosed.

- 1. Pull-Off Force (PoF)
- 2. Break-loose and Extrusion Force (BLEF)
- 3. Container Closure Integrity Testing (CCIT)
- 4. Seal Integrity

1. Pull-off Force (PoF)

In staked-needle PFS, the RNS must protect the needle, support closure of the syringe tip during storage, transportation and handling, and remain removable in a controlled, predictable way. This is especially important for self-administration or autoinjector integration. Pull-off force is a critical functional attribute for PFS systems equipped with RNS, reflecting the force required to remove the RNS prior to injection. If the pull-off force is too high, the user or device may struggle to remove the RNS; if too low, retention during handling, transport, or device assembly may be affected.

Test method

Aptar Pharma RNS were assembled onto Stevanato Group PFS and sterilized using Ethylene oxide (EtO). The pull-off

force was measured using a dynamometer in which the syringe was fixed while an axial displacement was applied to the RNS at a constant speed of 500 mm/min (Figure 2A). Force is continuously recorded, and the maximum value is reported as the PoF. The method is performed according to an internally validated procedure aligned with USP <382>, Section 7 (Tip Cap and Needle Shield Functional Suitability Tests), Procedure A.

Results

Within the evaluated configurations, pull-off force testing demonstrated consistent performance across EZ-fill® syringe platforms with Aptar Pharma RNS 4800GS. The graph (Figure 2B) presents one representative example from the broader testing program and illustrates observed system-level performance trends. Pull-off force values are reported as normalized values relative to the median of the tested population (median = 1.0).

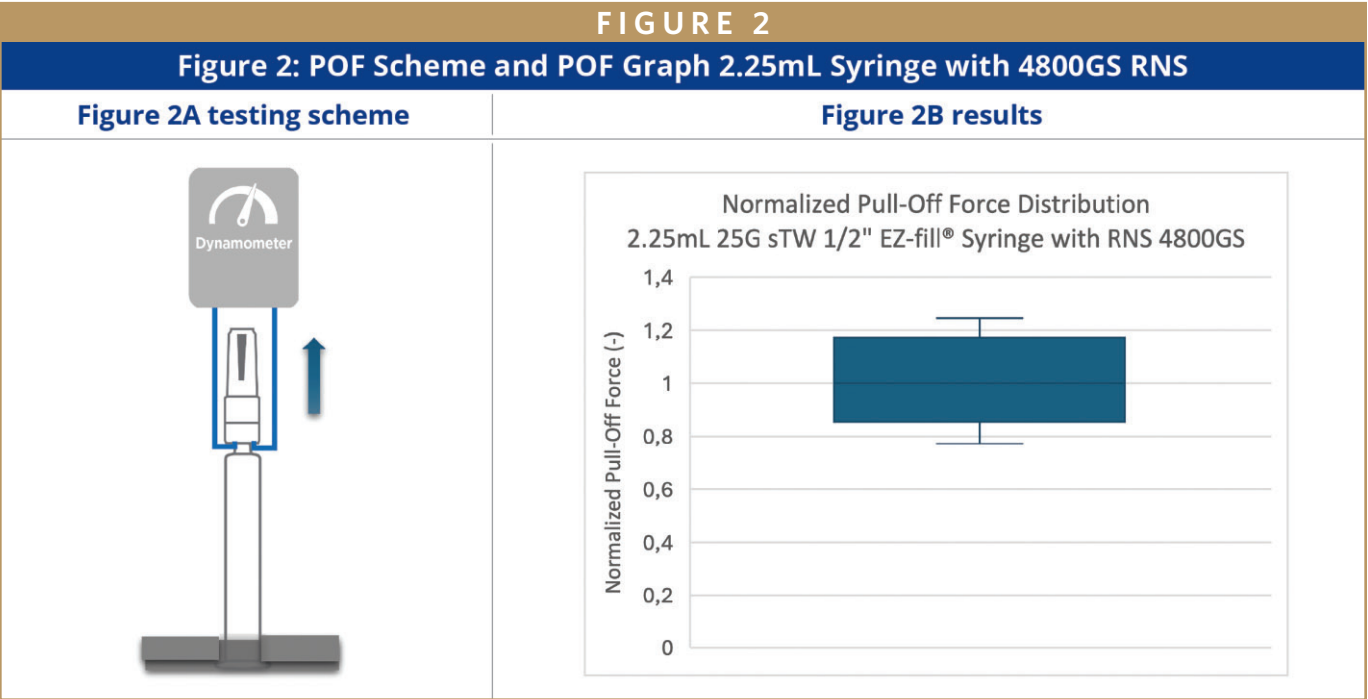
The results indicate robust compatibility between the tested Stevanato Group syringe platforms and Aptar Pharma RNS

configurations, supporting reliable shield retention without introducing excessive removal forces. Because pull-off force reflects the combined interaction between syringe, needle and RNS system-level testing provides a more realistic indication of functionality under intended-use conditions than isolated component testing separately.

2. Break-Loose and Extrusion Force (BLEF)

In PFS, the plunger must close the barrel and protect the drug during storage, transportation and handling, while delivered the dose upon activation. Break-loose force represents the force required to initiate plunger movement, while extrusion force reflects the force needed to maintain plunger travel during injection. Together, these parameters influence both functionality of the delivery system and user experience.

Aptar Pharma offers a broad range of plungers designed for compatibility with syringes and devices using ultrapure formulations. For sensitive drug products, PremiumCoat® plungers combine a fluo-



For this evaluation, Stevanato Group's Nexa® and Alba® PFS platforms were considered. In combination with these syringe platforms, Aptar Pharma's PremiumCoat® plunger was selected as a representative solution for biologic applications due to its

Representative examples from the broader testing program included coated and uncoated plunger variants to assess break-loose and extrusion force performance across system configurations.

Break-loose and extrusion force performance was evaluated on fully assembled syringes filled with Water for Injection (WFI) as medium. Syringes were mounted in a dynamometer while controlled axial displacement was applied to the plunger at 240 mm/min, as defined by the USP <382> (Figure 3A). Force was continuously monitored throughout medium ex-

Figure 3: Break-Loose and Extrusion Forces

Figure 3B standard curves

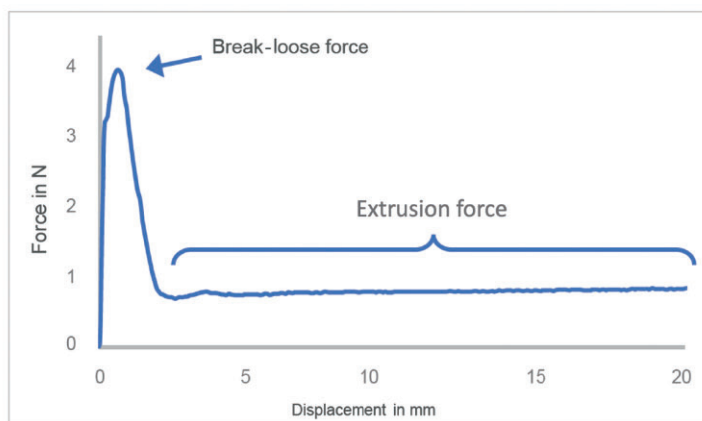
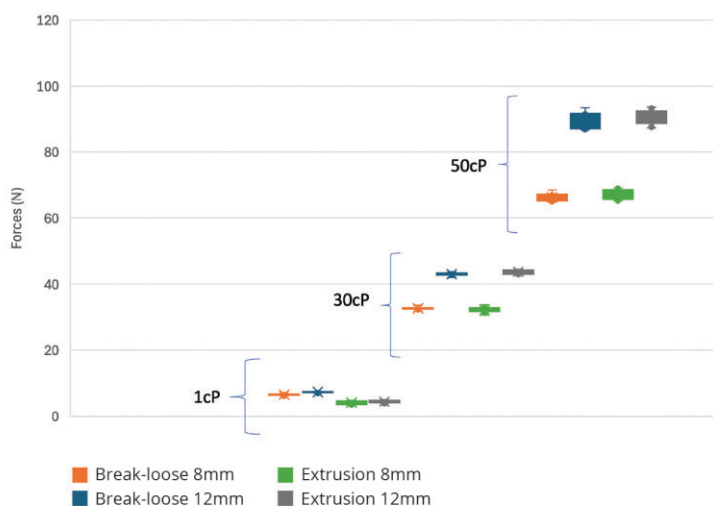


Figure 3D results on 2.25mL syringes filled with different viscosities

Comparison of BLEF depending on needle size (Nexa® syringe with PremiumCoat® 1-3mL Plunger)



trusion to determine break-loose force, average extrusion force, and potential stick-slip behavior (Figure 3B).

The method was executed using an internally validated procedure aligned with USP <382>, Section 6.1, Plunger break-loose and extrusion force performance.

Results

Figure 3C provide representative break-loose and extrusion force performance results for selected 1mL long configurations with Aptar Pharma PremiumCoat® plungers.

When used with Alba® and Nexa® syringes, the PremiumCoat® 1mL plunger demonstrated improved consistency and reduced variability. These results are supported by the interaction between the syringe barrel surface and the proprietary three-rib plunger design, which maintains continuous contact with the barrel and supports smooth force profiles during injection.

As injectable therapies become more concentrated and potentially more viscous, actuation performance becomes increasingly important. Break-loose and extrusion force performance can significantly affect usability (Figure 3D). The speed was set at 300mm/min. The 8mm needle demonstrated a mechanical advantage over the 12.7mm configuration across the viscosities tested. At 50 cP, injection forces were reduced by approximately 25%, supporting the suitability of the 8mm needle for higher-viscosity drug products. While these measurements represent mechanical performance characteristics rather than clinical outcomes, they illustrate how system-level evaluation can identify configurations that support functionality and usability objectives in combination products.

3. Container Closure Integrity Testing (CCIT)

Container closure integrity remains a critical requirement for injectable packaging systems. A delivery system must maintain sterility and protect product quality throughout its lifecycle while remaining capable of delivering the drug safely and effectively. As regulatory expectations and industry focus continue to shift toward deterministic container closure integrity testing (CCIT), helium leak detection has emerged as a powerful analytical tool for investigating packaging system integrity.

Test method

Container closure integrity was evaluated using helium mass spectrometry operated in accumulation mode. Test samples were exposed to helium tracer gas, and helium transmission through potential leak pathways was measured using a calibrated high-sensitivity detector (Figure 4A). This approach enabled assessment of sealing performance at glass-elastomeric component interfaces or assembled-system levels, providing quantitative information on integrity performance across the evaluated configurations. Testing followed deterministic tracer-gas leak detection principles described in USP <382> Packaging/Delivery System Integrity Tests, with reference to USP <1207>, and was performed using an internally validated procedure.

Results

The results (Figure 4C) remained substantially below the reference limit reported within the study framework from the USP <382> guideline, supporting the assessment of container closure integrity performance for the evaluated configurations.

4. Seal Integrity

As injectable drug products become more complex and delivery systems evolve toward patient-centric designs, maintaining functional seal integrity during administration is increasingly important. USP <382> introduced dedicated functionality tests to evaluate the ability of elastomeric closure components to maintain sealing performance under conditions representative of use. Through the collaboration between Aptar Pharma and Stevanato Group, coated and uncoated plunger technologies were assessed within Nexa® and Alba® prefillable syringe platforms under challenging functional conditions. This system-level evaluation supports a broader understanding of dynamic seal integrity across representative component combinations.

Test method

Syringe systems were filled with a fluorescent tracer solution and challenged under controlled pressure conditions designed to simulate stresses experienced during drug administration. An axial force corresponding to an internal pressure of 300 kPa was applied and maintained for 30 seconds at a crosshead speed of 20 mm/min (Figure 4B). Following testing, samples were inspected under UV light for evidence of tracer migration across critical sealing interfaces. The absence of fluorescence outside the sealing area was considered evidence of maintained seal integrity. The method was executed using an internally validated procedure aligned with USP <382>, Section 6.2 (Plunger Seal Integrity), Procedure A.

Results

For all evaluated configurations, including coated and non-coated plunger variants, no infiltration events were ob-

served. All tested samples achieved 0/10 infiltration results.

Although plunger seal integrity testing is a pass/fail assessment, the results provide additional confidence in sealing performance and consistency across the evaluated component combinations.

CONCLUSION

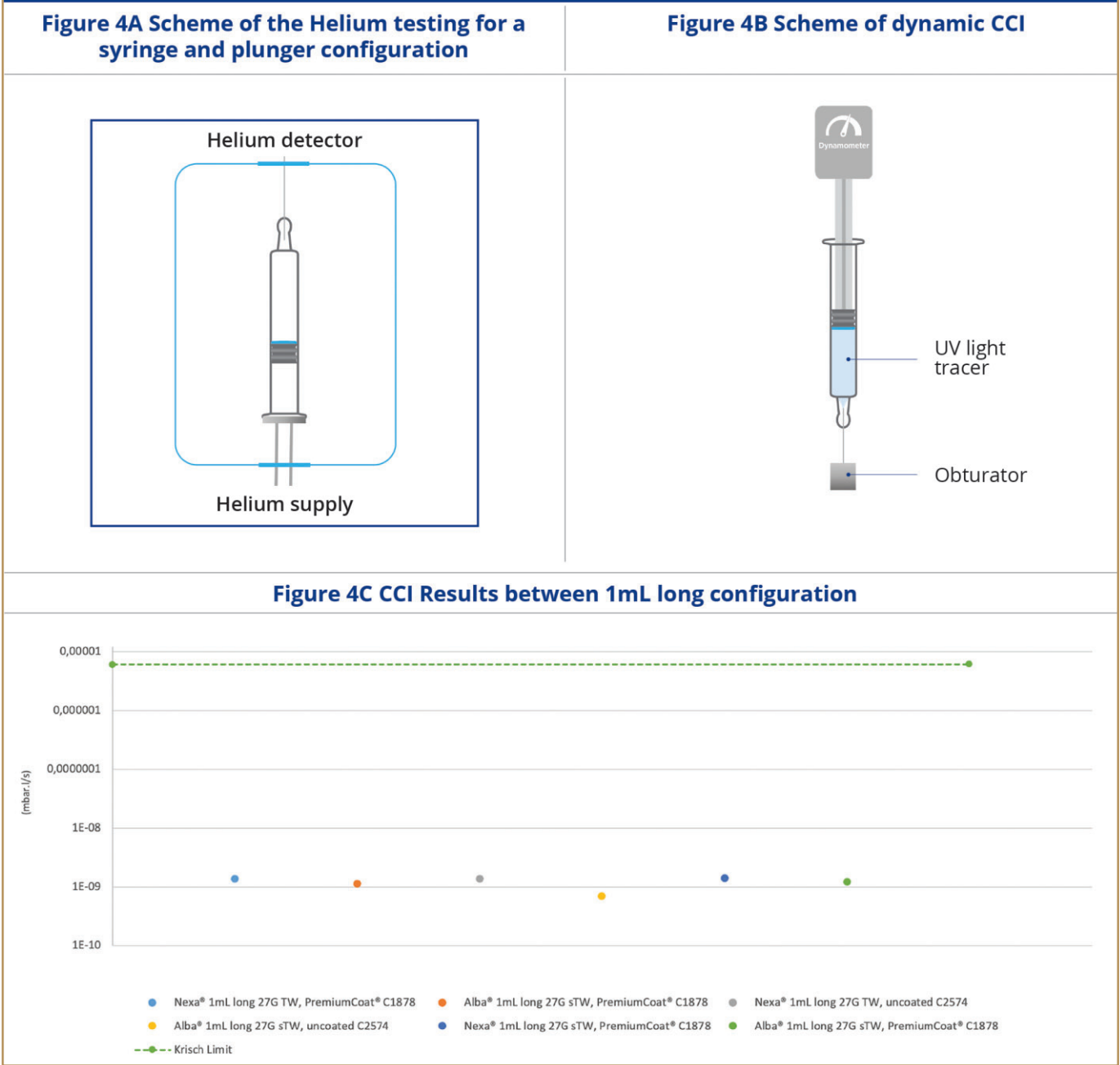
USP <382> represents an important evolution in the evaluation of injectable packaging and delivery systems. By focusing on functional suitability at system level, it reflects combination product development realities, where performance depends on the interaction of multiple

integrated components.

The collaborative study conducted by Stevanato Group and Aptar Pharma illustrates how USP <382> principles can be applied in practice. Across the evaluations, the combined prefillable syringe, plunger, and RNS generated consistent system-level performance data across the evaluated configurations.

FIGURE 4

Figure 4: Container Closure Integrity



The findings highlight the value of generating system-level data early in development to support more informed packaging decisions as formulation complexity continues to increase.

For further details, contact Aptar Pharma or Stevanato Group to access the data package summarizing the system evaluation findings. ♦

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BIOGRAPHIES



Sara Masucci is Product Manager at Stevanato Group, focusing on syringe container solutions. Sara holds a Master's degree in Business Administration from the University of Padua. She has over three years of experience in the pharmaceutical packaging and medical device industry, having built expertise in both Product Development and Product Management.



Crystal Salvans is the Product Line Manager for PFS at Aptar Pharma's Injectables division. She earned an Engineering degree in Packaging from ESIREIMS and began her career as a Packaging Engineer at Johnson & Johnson (now Kenvue), before joining Aptar Pharma Injectables in 2015. With expertise in injectables packaging, she has held roles in Technical Support, Project Management, and Sterile Gamma Irradiation, managing a Technical Product Management team. Currently, she leads a team managing the project and product life cycles for plungers, RNS, and tip cap components.

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