Primary Packaging Systems to De-Risk Bringing a Sensitive Biologic to Market

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Abstract

As companies develop complex and life-changing sensitive biologic treatments, it is critical to evaluate packaging decisions early in development. Drug development timelines are accelerating, challenging companies to bring their drugs to market as quickly as possible. Selecting an inadequate packaging solution could pose risks to patient safety and delays to timelines, potentially jeopardizing a successful commercialization. West's Ready Pack® system addresses these challenges by providing the highest quality integrated containment system that has demonstrated excellent performance over time, is available in various configurations (serum/lyo, 13/20 mm, 2R/6R/10R), and is readily available for quick delivery. The Ready Pack system comprises the highest-performing components, developed for use with sensitive biologics: NovaPure® stoppers, Flip-Off® CCS (clean, certified, sterilized) seals, and Schott adaptiQ® glass vials. Together these components mitigate potential interactions with drug product and provide container closure integrity over time. Ready Pack components are delivered ready-to-use in small quantity packs which are ideal for development work.

Background

When deciding on a primary packaging system for a sensitive biologic, there are challenges that should be considered early in the development timeline, namely avoiding the risk of selecting a system that is not suitable for the drug product, and minimizing potential risks that could jeopardize the development timeline, thus delaying the time it takes to get to market. With selection of the Ready Pack® system, these challenges can be overcome. Ready Pack components comprise a system with proven performance and container closure integrity. They are available in a wide range of possible formats, and perform at temperatures, that sensitive biologics may require for storage and delivery:

- form: serum or lyophilized
- delivery: multi- or single-dose
- temperature: room (25°C) through ultra-low (-80°C)

The Ready Pack system is available from stock for quick delivery, allowing for adherence to key milestones in the development timeline, and for easy scale up from clinical to commercial volumes.

West's Ready Pack® System

The Ready Pack system includes the highest-performing stopper and seal components that West offers, paired with glass vials from Schott. Together they are demonstrated to fit together to provide an integrated system with container closure integrity over time. Components are West's NovaPure® elastomer stoppers, West's Flip-Off® CCS (clean, certified, sterilized) seals, and

Schott's adaptiQ® glass vials. All are offered read-to-use (i.e., sterilized) and meet USP, EP, and JP pharmacopeia requirements.

West's NovaPure® Elastomer Stoppers

NovaPure 4023/50 gray elastomer stoppers (bromobutyl-based) are West's premium offering. See Table 1. Each lot is tested for extractables profile, and each component is visually verified (with the ENVISION™ process) for absence of defects and visible particles. NovaPure stoppers, through high-level particle control, decrease risk of drug recalls due to contamination.

Table 1. NovaPure 4023/50 Gray Elastomer Stopper Configurations

	13mm	20mm
Serum	Article 1358	Article 1343
Lyophilization	Article 1356	Article 1346

All NovaPure stoppers have a FluroTec® barrier film. FluroTec film, which is based on poly(ethylene tetrafluoroethylene), has been demonstrated to provide enhanced performance, in particular reduction of migration of leachables from the stopper and reduction of interaction of drug product with the stopper. See Figure 1. Elastomer components with FluroTec film have gained global acceptance and are used on over 125 approved drug products. The use of FluroTec film in the biologics market is highly valued because of its exceptional barrier properties. Over 65 approved biologics and biosimilars, such as monoclonal antibodies and proteins, use a FluroTec stopper. (1) See Table 2.

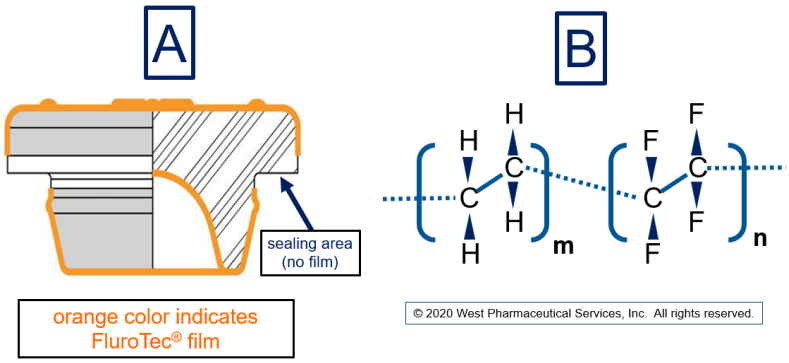

Figure 1. A. Schematic of FluroTec Film on an Elastomer Stopper. Lyophilization stoppers have film on top surface. B. Structure of poly(ethylene tetrafluoroethylene).

Table 2. Drug Products Approved with Components Comprising FluroTec® Film (1)

Type	FDA Only	FDA and EMA	EMA Only	Total
Small Molecule	44	14	2	60
Monoclonal Antibody	7	19	3	29
Protein	6	17	---	23
Peptide	6	2	---	8
Protein Small Molecule	2	2	---	4
Oligonucleotide	---	2	---	2
Carbohydrate	1	---	---	1
Total	66	56	5	**127**

West's Flip-Off® CCS Seals

Flip-Off CCS (clean, certified, sterilized) seals are offered in 13 mm and 20 mm sizes, in red, white, and blue. They are certified to meet a low particle specification and a low bioburden specification prior to sterilization. They comply with the European regulatory guidelines for aseptic crimping inside Grade A environments.

Schott's adaptiQ® Glass Vials

adaptiQ vials are high-quality glass vials offered ready-to-use (i.e., sterilized) in 2R, 6R, and 10R sizes. They can be processed on a wide range of existing, and new, fill and finish equipment.

West's ReadyPack® System Performance

Leachables

The FluroTec film of NovaPure elastomer stoppers reduces leaching (migration of compounds/elements from elastomer component into drug product). This is accomplished by acting as a barrier that prevents transport of compounds/elements from the stopper. To demonstrate this, bromobutyl elastomer lined seals, with and without FluroTec film, were crimped onto empty glass vials and stored for six months at room temperature. (1,2) Headspace gas chromatography and mass spectrometry were performed. See Figure 2. A large number of compounds were observed for the system without film, virtually none for the system with film. Mitigation of leachables was achieved.

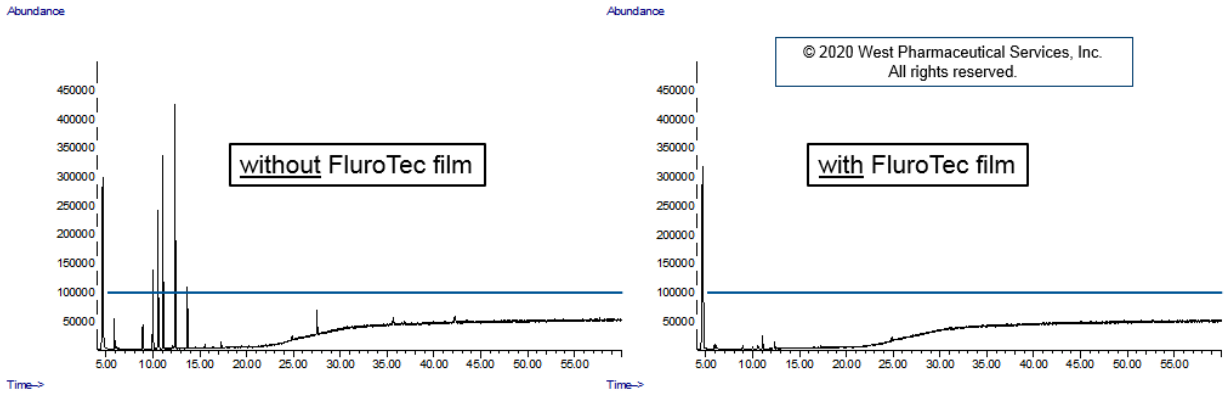

Figure 2. Headspace Gas Chromatography and Mass Spectrometry of Lined Seals, with and without FluroTec Film. Data are at six months. Blue line indicates an estimated identification threshold of 0.5 µg/unit. (1,2)

Interaction

The FluroTec film of NovaPure elastomer stoppers also reduces potential interaction with drug products. This reduces risk of deleterious effects, such as immunogenicity resultant from formation of particles. (3) To demonstrate this, interaction was evaluated for several drug products (simulated/commercial, based on proteins) by measurement of particles, turbidity, and product recovery after exposure to agitated/stressed conditions. (1,4) Results for a representative example are shown in Table 3. Stoppers with FluroTec film resulted in a lower level of particle formation, a lower level of turbidity, and higher protein recovery. These results demonstrate reduced interaction with protein and mitigation of the effect of elastomer.

Table 3. Particles, Turbidity, and Recovery for a Protein-Based Product, with and without FluroTec Film. Values for particles are in thousands. Parenthetical numbers are standard deviations. (1,4)

	Particles per ml (1-10 µm)		Turbidity at 24 hrs	Recovery at 24 hrs (%)
	at 2 hrs	at 6 hrs		
Immunoglobulin				
with	23.5 (7.9)	44.0 (16.0)	0.01 (0.002)	98.2 (0.13)
without	94.6 (28.8)	289.6 (172.2)	0.04 (0.004)	95.6 (0.26)

Container Closure Integrity (CCI)

Four Ready Pack systems were evaluated for CCI over two years at room temperature. They are listed in Table 4. CCI was evaluated by tracer gas leak detection with helium (He-leak). (5) This is a deterministic method cited in United States Pharmacopeia (USP) Chapter <1207>. (6) Results are in Figures 3 and 4. As data are reported as -log (helium leak rate), higher values correspond to lower rates of He leak.

Table 4. Evaluated Ready Pack® Systems.

Combination	Stopper	Vial	Seal
1	NovaPure 13mm Serum ART 1358	Schott adaptiQ 2R (straightwall)	FOCCS 13mm 5417
2	NovaPure 13mm Lyophilization ART 1356	Schott adaptiQ 2R (straightwall)	FOCCS 13mm 5417
3	NovaPure 20mm Serum ART 1343	Schott adaptiQ 6R (straightwall)	FOCCS 20mm 5415
4	NovaPure 20mm Lyophilization ART 1346	Schott adaptiQ 6R (straightwall)	FOCCS 20mm 5415

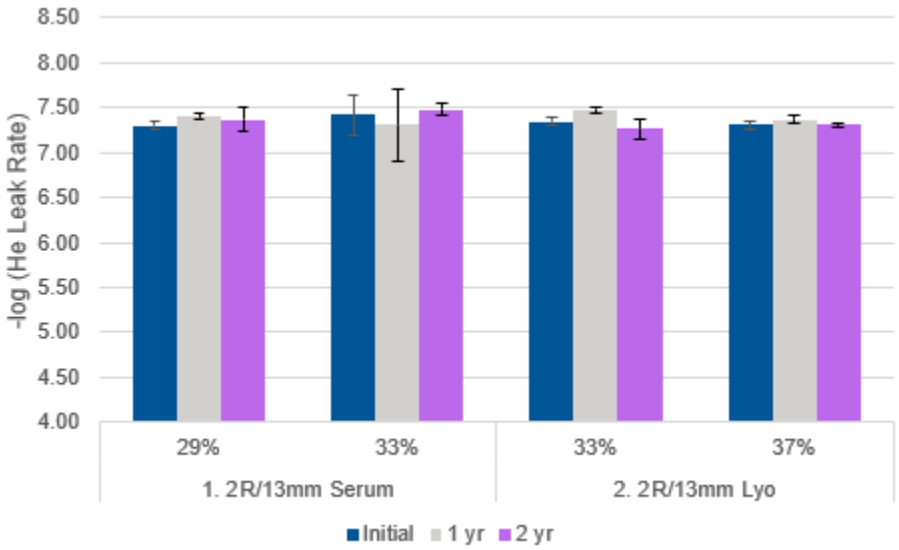

Figure 3. Container Closure Integrity at Room Temperature over Two Years for 13mm / 2R Systems as Determined by He-Leak Performance. Data are reported as [-log of helium leak rate (cm^3/s) at standard temperature and pressure]. Percentage values are stopper compression levels. Error bars are standard deviation (n = 20).

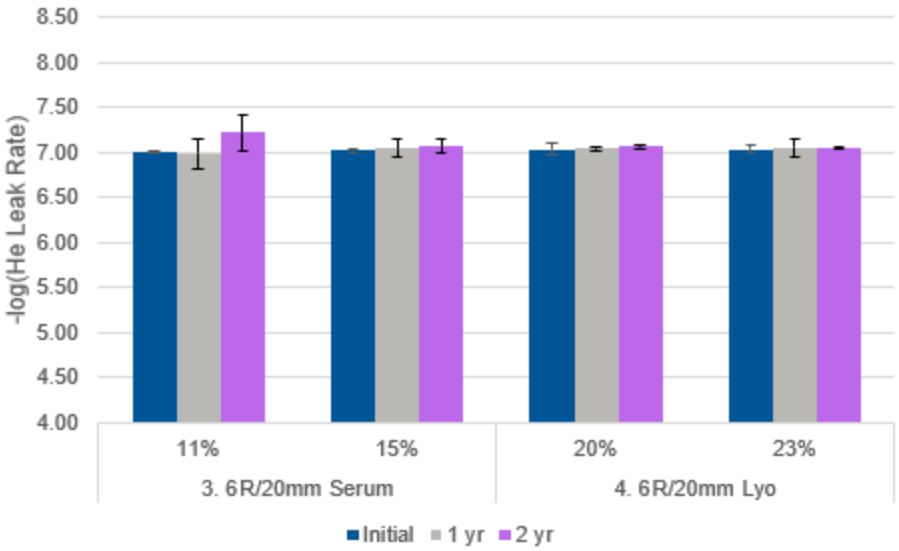

Figure 4. Container Closure Integrity at Room Temperature over Two Years for 20mm / 6R Systems as Determined by He-Leak Performance. Data are reported as [-log of helium leak rate (cm^3/s) at standard temperature and pressure]. Percentage values are stopper compression levels. Error bars are standard deviation (n = 20).

A comparative frequently used for evaluation of He-leak data is that developed by Kirsch, et al. (7). He-leak values were correlated with risk of microbial ingress for vials with holes of known diameter. Results are reproduced in Table 5.

Table 5. Correlation of He-Leak Values to Risk of Microbial Failure per Kirsch, et al. Table is a reproduction based upon data reported. (7)

Hole Diameter (µ)	**He-Leak** (cm^3/s @ STP)	**- log (He-Leak)**	**Microbial Ingress Rate** (%)
2	1.0×10^{-3}	3.0	70
0.7	2.0×10^{-4}	3.7	65
0.4	9.0×10^{-6}	5.0	11
---	6×10^{-6}	5.2	8 - 10
0.3	2.0×10^{-6}	5.7	7
0.2	2.2×10^{-7}	6.6	0
0.1	1.0×10^{-7}	7.0	0

Note that all He-leak values for Ready Pack systems are greater than -log value of 6.6. Values greater than 6.6 (i.e., measured He-leak rates below 2.2×10^{-7}) correspond to 0% chance of microbial ingress per Kirsch, et al. All systems provide CCI.

For 20mm / 6R systems, the average of all data points is approximately 7.0, whereas for 13mm / 2R systems it is approximately 7.3 – suggesting that on average slightly more helium is detected from 20 mm / 6R systems. This is probably an experimental artifact. All elastomers are known to be gas permeable. (8) The area available through which helium can diffuse through (i.e., vial opening area) is larger for a 20 mm stopper (1.2 cm^2) than for a 13 mm stopper (0.38 cm^2). A higher rate might be expected for 20mm / 6R systems.

A separate, preliminary CCI study at -80ºC was performed with 13mm NovaPure 4023/50 1358 elastomer stoppers and Schott 2R straightwall glass vials, using fequency modulated spectroscopy headspace analysis (a method cited in USP Chapter <1207>). (9) No change in oxygen headspace was observed through 60 days; CCI performance was equivalent to that

observed at room temperature. This strongly suggests suitability of Ready Pack systems for sensitive biologics stored at ultra-low temperature.

Performance Summary

For Ready Pack systems, leachables and interaction studies demonstrate reduced potential for interaction with sensitive biologics and resultant better stability. Extended CCI studies demonstrate performance over two years at room temperature, and preliminary CCI studies indicate potential performance at ultra-low temperature.

Summary

West's Ready Pack system is an ideal solution for sensitive biologics companies needing a proven containment system and a fast delivery to meet the short timelines associated with accelerated approvals. Potential interaction with drug product is mitigated and CCI over two years is provided in a variety of sizes and configurations. The Ready Pack system provides a packaging solution that, combined with the technical expertise from West, helps move a sensitive biologic quickly from small-scale development volumes through to approval and scale up.

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