Elastomer Stoppers with FluroTec® Film: The Right Choice for SARS-CoV-2 Vaccines

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Abstract

For primary package systems for SARS-CoV-2 vaccines, elastomer stoppers with FluroTec® film enable the lowest risk. Employing the chemical properties of poly(ethylene tetrafluoroethylene), FluroTec film: (1) reduces migration of leachables into drug product, (2) reduces interaction of drug product with stopper, and (3) enables excellent container closure integrity down to low temperatures. This article discusses how these features mitigate package system risks with the six platforms of SARS-CoV-2 vaccines in development – especially important in view of greatly accelerated timelines that do not permit standard evaluations. Components with FluroTec film are globally available and market accepted – over 125 drugs, including three vaccines and 30 novel drugs, are FDA/EMA approved.

Background

Development and distribution of a vaccine for SARS-CoV-2 presents challenges that are, without hint of exaggeration, unprecedented. One of these challenges concerns storage, namely selection of vial/stopper primary package systems that guarantee quality and safety of the vaccine from manufacture through delivery. This selection is complicated greatly by the accelerated timelines for vaccine approval.

Two aspects comprise the challenge in package system selection:

1. The first concerns the vaccine platform. Six platforms are now considered; they are listed with their proposed vehicles in Table 1. (1) Noteworthy is that two of them (RNA, DNA) are new. Ordinarily, there would be no difficulty in selecting a package system for any of the platforms, since ample time would be available for evaluation of compatibility with both the vaccine and the vehicle. But, for a SARS-CoV-2 vaccine, this is not the case, since approval timelines are accelerated. So, whether the vaccine platform is extant or new, selection of the package system must be made quickly. This creates a risk.
2. The second concerns stability during storage and distribution. A vaccine platform and package system may be identified, but other factors must be considered, such as:
   - form: serum or lyophilized
   - delivery: multi- or single-dose
   - temperature: room (25°C), refrigerated (2-8°C), or low (-80°C)
   - availability of package system components

Lack of certainty regarding whether a package system is available, and can accommodate the format needed, creates a risk.

Table 1. Potential Vaccines for SARS-CoV-2 (1)

Vaccine Platform	Chemical Composition	Vehicle	Existing, Licensed Human Vaccine
RNA	nucleotides (ribose groups, amino/amide groups, charged phosphate groups)	encapsulated in lipid in non-polar liquid	No
DNA	nucleotides (ribose groups, amino/amide groups, charged phosphate groups)	aqueous (saline) solution, encapsulated in lipid in non-polar liquid	No
Recombinant Protein	polypeptides (amino acid groups)	aqueous	Yes (baculovirus and yeast expression)
Viral Vector Based	virus shell comprises proteins (i.e., polypeptide: amino acid groups)	aqueous	Yes (vesicular stomatitis virus)
Live Attenuated	virus shell comprises proteins (i.e., polypeptide: amino acid groups)	aqueous	Yes
Inactivated	virus shell comprises proteins (i.e., polypeptide: amino acid groups)	aqueous	Yes

An approach that addresses the risks of both aspects is use of the highest performing elastomer stopper platform, namely elastomer stoppers with FluroTec® film. See Figure 1.

1. FluroTec film has been demonstrated to reduce migration of leachables from the stopper, reduce interaction of proteins with the stopper, and as part of vial systems, enable excellent container closure integrity down to -80°C. These features indicate enhanced preservation of drug product quality and safety, as compared to stoppers without film.
2. Elastomer stoppers with FluroTec film are available worldwide, in serum and lyophilized configurations, in 13 mm and 20 mm sizes, and are compatible with vial systems down to -80°C.

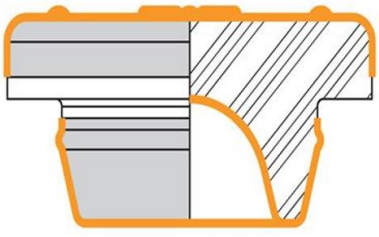

Figure 1. Schematic of FluroTec Film on an Elastomer Stopper

Timelines for SARS-CoV-2 vaccines are accelerated; ordinary evaluations cannot be performed. The package systems must be selected quickly, and this creates risks. These risks can be addressed by selection of the highest performing elastomer stoppers, namely those with FluroTec film. They have been shown to have lowest potential interaction with drug product, and

hence are the best option to maintain quality and safety. This article discusses FluroTec film in detail: market presence, chemistry, and the experimental work that demonstrates performance.

FluroTec Film

Market Acceptance

Elastomer components with FluroTec film have gained global acceptance. Based upon West analyses, they are used on over 125 approved drug products, 30 of which are novel drugs, and at least three of which are vaccines. See Table 2. Concentrations of active pharmaceutical ingredients range from approximately 0.1 mg/ml to 600 mg/ml. Packaging in vial/stopper and syringe/cartridge systems include, but are not limited to, the administration routes of intravenous, subcutaneous, and intramuscular.

Table 2. Drug Products Approved with Components Comprising FluroTec Film

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**

Novel drugs, as defined by FDA, are those that are not yet approved, but serve unmet needs or advance patient treatments, either new molecular entities or new therapeutic biologics. (2) Novel drugs typically are classified as first-in-class, rare diseases, expedited development, and review pathways. The expedited designation includes fast track, breakthrough therapy, priority review, and accelerated approval. These 30 novel drugs comprise the range of types: small molecules, proteins, peptides, monoclonal antibodies, and oligonucleotides. Since 2015, one-third of drug approvals using West and Daikyo Seiko, Ltd. components with FluroTec film were novel drugs. Where new molecules are involved and rapid decisions are needed, components with FluroTec film are a frequent choice.

Chemistry

Because of the electronegativity of fluorine and the strength of carbon-fluorine bonds, fluoropolymers are chemically inert. This feature has resulted in a vast array of applications – one of which is films for elastomer components in drug product package/systems. Among the many fluoropolymers known, West and Daikyo Seiko, Ltd. use poly(ethylene tetrafluoroethylene) (ETFE) for its FluroTec film. This is based on:

- moldability
- adhesion to elastomers (either bromo- or chloro-butyl)
- translucency
- compatibility with sterilization by either autoclave or gamma irradiation

The structure of ETFE is shown in Figure 2.

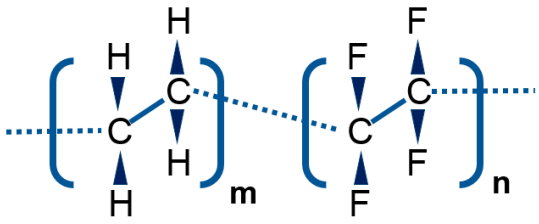

Figure 2. Structure of Poly(ethylene tetrafluoroethylene) (ETFE)

Performance of FluroTec Film

Discussed is published research at West that demonstrates the performance of FluroTec film, namely the ability to:

- reduce interaction with drug product
- reduce migration of leachables
- enable good container closure integrity of a vial/stopper package system

and explains why stoppers with FluroTec film are the lowest risk option for the six current platforms of SARS-CoV-2 vaccines. (3-6)

Interaction with Drug Product

Because of very low surface energy, fluoropolymers such as ETFE have very low levels of interactions with other compounds. Interactions of drug products with package/delivery system components may have deleterious effects, such as immunogenicity due to formation of particles. (7) Interaction was evaluated by measurement of particles, turbidity, and recovery of drug products (simulated/commercial) under agitated/stressed conditions. (3)

Four protein-based products were evaluated. This was done by placing 3 ml of aqueous solution (1 mg/ml) into 5 ml glass vials, then capping with 20 mm elastomer stoppers, with and without FluroTec film. Vials were agitated end-over-end (room temperature at 40 revolutions/minute):

- for 2 hours and 6 hours – particle level was measured by dynamic fluid imaging
- for 24 hours – protein recovery was measured by size exclusion high performance liquid chromatography; turbidity was measured by light absorbance (350 nm)

Results are shown in Table 2. For a variety of proteins, stoppers with FluroTec film resulted in lower levels of particle formation, lower turbidity, and higher protein recovery. These results demonstrate reduced interaction with drug product and mitigation of the effect of elastomer.

Referring to Table 1, four vaccine platforms are protein-based; one is a recombinant protein, and three are virus–based (the outer shell of a virus comprises proteins). This research indicates that use of stoppers with FluroTec film would result in less interaction with these platforms, and concomitant better stability. Reduced risk comprises not only lower levels of particles, but reduced possibility of unwanted changes resultant from interaction. For the other vaccine platforms, RNA and DNA, a similar analysis applies. FluroTec film, based on chemical inertness, would be expected to interact less with these platforms that comprise not only amino/amide groups (building blocks of proteins), but ribose groups and charged phosphate groups.

Table 2. Levels of Particles, Turbidity, and Recovery Resultant for Protein-Based Products, with and without FluroTec Film. Values for particles are in thousands. Parenthetical numbers are standard deviations. (3)

	Particles per ml (1-10 µm)		Turbidity at 24 hrs (a)	Recovery at 24 hrs (%)
	at 2 hrs	at 6 hrs		
β-Lactoglobulin				
with	24.5 (6.0)	58.2 (25.3)	0.07 (0.005)	99.3 (0.13)
without	87.7 (20.7)	181.7 (29.7)	0.10 (0.006)	98.9 (0.08)
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)
Abatacept (fusion protein)				
with	12.8 (11.0)	41.0 (11.2)	0.02 (0.001)	99.1 (0.3)
without	14.3 (7.2)	64.2 (29.2)	0.03 (0.005)	97.3 (0.3)
human serum albumin – recovery at 21 days (%) (b)			with	98.6 (0.3)
			without	78.6 (0.4)

a. absorbance at 350 nm
b. not agitated, stored quiescently at room temperature

Leachables

Based upon chemical inertness, hydrophobicity, and dense packing of chains, fluoropolymers such as ETFE can mitigate 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. In other words, ETFE prevents the two processes that comprise permeability: (a) diffusion (movement of leachables from elastomer) and (b) partitioning (drug product excipient migrating into elastomer and withdrawing leachables).

In one study, bromobutyl elastomer lined seals, with and without FluroTec film, were crimped onto empty 10 ml glass vials and stored up to six months at room temperature. (4) Headspace gas chromatography and mass spectrometry were performed. See Figure 3.

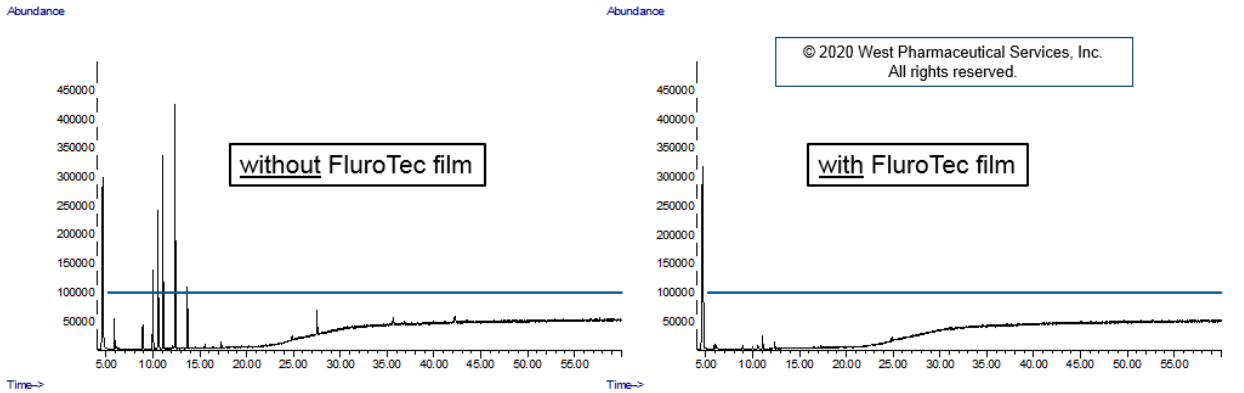

Figure 3. Headspace Gas Chromatography and Mass Spectrometry of Lined Seals, with and without FluroTec Film. Data are at six months. Blue line indicates an estimated identification threshold of 0.5 µg/unit. (4)

A large number of compounds were observed for the system without film, virtually none for the system with film. The drawn blue line indicates an estimated identification threshold of 0.5 µg/unit, which is lower than the Product Quality Research Institute recommended safety concern threshold for parenteral drug products. (8) Mitigation of leachables was achieved. Similar results were observed with chlorobutyl elastomers.

Referring to Table 1, vaccine vehicles can be polar (aqueous) or non-polar (lipid-based); moreover they may contain numerous ingredients (aluminum salts, oil-in-water emulsions, antibiotics, formaldehyde, sugars, amino acids, buffering agents, surfactants). (9) Leachables, whether inorganic (e.g., metal ions/salts) or organic (e.g., oligomers, antioxidants) pose a risk since interaction with vehicle or ingredient may affect quality or safety. For example, a metal salt may affect the lipid system encapsulating an RNA vaccine. Leachables also pose a risk to the vaccine itself. For example, a metal ion or organic compound could interact with DNA or a recombinant protein, alter the configuration, and render it less effective. The possibilities are numerous and very difficult to predict; use of a FluroTec film mitigates them.

Container Closure Integrity

Good container closure integrity (CCI) performance is essential; it demonstrates that a package system can meet the requirements of the maximum allowable leakage limit (MALL) of a drug product. MALL is discussed in detail in United States Pharmacopeia Chapter <1207> *Package Integrity Evaluation – Sterile Products* (2016). Stoppers were examined, with and without FluroTec film. (5, 6)

In one study, 20 mm stoppers were capped onto 6R glass vials under air at varying compression levels. Deterministic evaluation methods (endorsed by USP <1207>) were:

- tracer gas leak detection (with helium) (i.e., He-Leak): stored in air at room temperature
- frequency modulated spectroscopy headspace analysis (with oxygen) (i.e., OHS): stored in nitrogen at room temperature

Evaluation was made over two years. See Figures 4 and 5. (5)

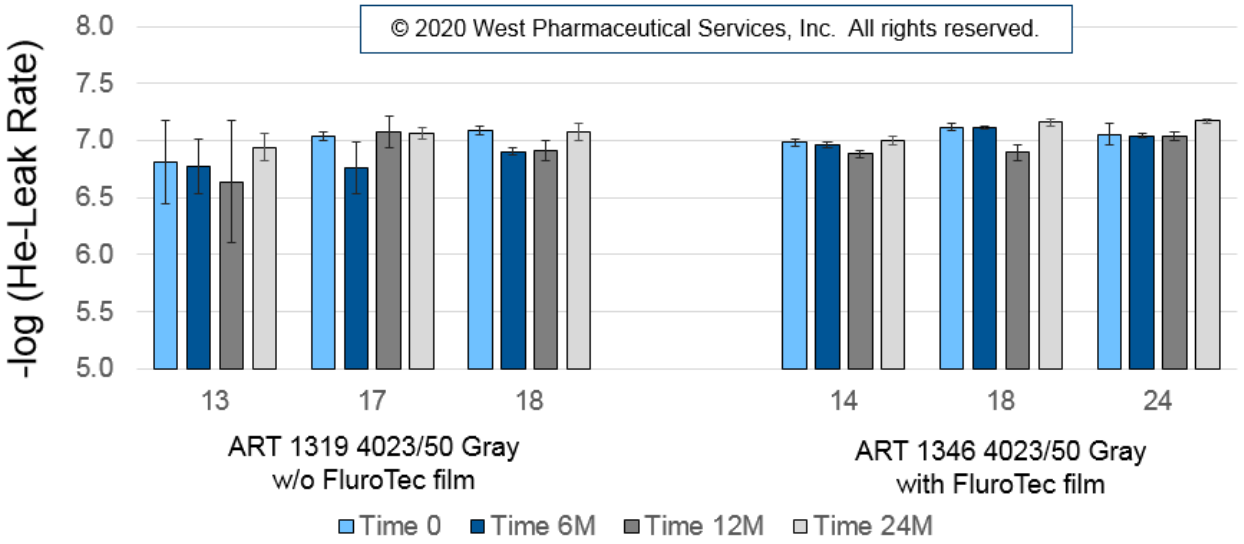

Figure 4. He-Leak Performance over Two Years. Data are reported as [-log of helium leak rate (cm^3/s)]. Initial values of compression are given (e.g., 13%). Error bars are standard deviation. (5)

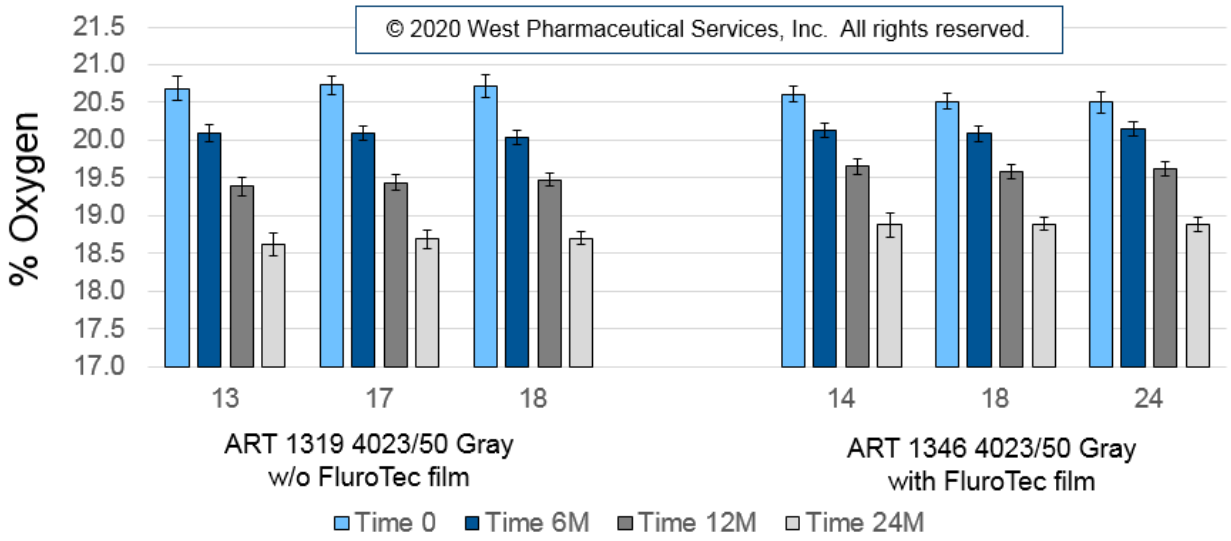

Figure 5. OHS Performance over Two Years. Initial values of compression are given (e.g., 13%). Error bars are standard deviation. (5)

For He-Leak, performance of systems with and without film was similar. Values that exceed 6.6 would correspond, per the well-known Kirsch study (10), to 0% risk of microbial ingress. For OHS, performance of systems with and without film was likewise similar. There is some egress of oxygen over time, a very small amount. This was expected; it is well known that elastomers are gas permeable. Stoppers with FluroTec film enable excellent CCI, there is no loss of performance resultant from presence of FluroTec film.

In another study, 13 mm stoppers with FluroTec film were capped onto 2R glass vials under nitrogen and stored in an air-filled freezer at -80ºC for 60 days. (6) There was essentially no ingress of oxygen observed by OHS. This indicates excellent CCI at -80ºC.

Summary

Elastomer stoppers with FluroTec film offer best performance. They mitigate migration of leachables from elastomer and minimize elastomer interaction with drug product. Moreover, they enable excellent package system container closure integrity. They are globally available, market accepted, and available in varying sizes and configurations (13 mm, 20 mm, serum, lyophilization). For these reasons, for the six platforms considered for SARS-CoV-2 vaccines, they offer the lowest risk. Reduced risk is essential since accelerated timelines do not permit standard evaluation of drug product with package system.

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