Elastomer Plungers with FluroTec® Film: The Right Choice for COVID-19 Vaccines

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Abstract

The unprecedented need for COVID-19 vaccines demands accelerated drug development processes and the potential use of new vaccine platform technologies; both are risks. If a vaccine is stored or delivered in a prefilled syringe, use of an elastomer plunger laminated with FluroTec® film can help to minimize these risks. FluroTec film, which is based upon poly(ethylene tetrafluoroethylene), has chemical properties that reduce migration of leachables into the vaccine, and reduce interaction with the vaccine. Plungers with FluroTec film enable consistent delivery volume and break-loose and glide-force performance over a range of viscosities. They are globally available, approved with a variety of molecule types by multiple agencies, and available in 1 mL long and 1-3 mL sizes. Discussed is how these features mitigate risks for a COVID-19 vaccine in a prefilled syringe.

Background

Development and manufacture of COVID-19 vaccines have presented challenges that are unprecedented. As of July 2021, four platforms have reached Phase-4 clinical trials (Table 1) according to the World Health Organization (WHO). (1) Note that two relatively new technologies, viral vector and mRNA-LNP, comprise a significant fraction of the vaccine pipeline, 15% and 17% respectively.

Table 1. Vaccines for COVID-19 per World Health Organization. (1) Note that other outlets also report vaccine status, e.g., The New York Times.

Platform	Candidates at Phase-3	% Candidates at All Phases (*)	Candidates at Phase-4
Inactivated Virus	7	15	2 (Sinovac, Sinopharm)
Viral Vector	1	15	3 (AstraZeneca + U. of Oxford, Janssen, CanSino)
mRNA-LNP	2	17	3 (Pfizer + BioNTech, Moderna mRNA-1273 and mRNA-1273.351)
Protein Subunit	8	33	---
DNA	1	9	---
Other	---	11	---

* prevalence of vaccine platform as a percentage of all vaccine candidates, regardless of clinical or approval status

Another challenge is storage/distribution. Whether in a vial/stopper package system or a prefilled syringe (PFS), quality and safety must be maintained up to administration. The prevalence of new technologies, and the greatly accelerated timelines for approval, place an even higher emphasis on the need to minimize risk. Selection of compatible vial/stopper components to minimize risk has been discussed previously. (2) Discussed presently is selection of compatible plungers to minimize risk for PFS.

Two technologies that back COVID-19 vaccines, mRNA-LNP (lipid nanoparticles) and viral vectors, have been granted emergency approval by the FDA, even though their use in vaccines is relatively new. Both mRNA-LNP and viral vector technologies deliver the antigen as a nucleotide, which allows alterations to the antigen with less impact on the manufacturing process. This is critical. With the rise of variants in several countries, it is likely that vaccines for said variants will need to be developed/manufactured rapidly. (3) Simultaneously, manufacturers will seek ways to both extend the stability of vaccines in countries with adequate supply and reduce the cold chain storage requirements (a challenge for distribution) for vaccines in countries with inadequate supply.

There are other challenges to consider with storage/delivery of a COVID-19 vaccine in a PFS, amplified since vaccine contact time may be longer with a plunger than a stopper.

- Interaction of Vaccine with Components. The interaction of the vaccine with the container/delivery system must be addressed. Most vaccines are based on proteins, including recombinant proteins, inactivated or attenuated viruses, and novel viral vectors. Interaction of proteins with system components has been shown to occur, resulting in reduction of protein recovery and increase in the level of particles. (4) And even though the novel mRNA-LNP vaccine contains no protein, it utilizes a complex, cationic and zwitterionic lipid formulation to encapsulate, deliver, and protect the mRNA. Interaction with system components is a risk; mRNA can hydrolyze spontaneously, and the hydrophobic/hydrophilic balance of the lipid formulation can be upset.
- Interaction of Vaccine with Leachables. Protein-leachable interaction risk has long been discussed in the literature. In fact, clinical adverse events have been reported that resulted from interaction of drug product, surfactant, and leachable from a non-laminated elastomer stopper. (5) For an mRNA-LNP vaccine, a hydrophobic leachable is likely to prefer interaction with the LNP, which may impact the stability of the vaccine, or reduce the efficiency of mRNA delivery to cells for translation into antigen.

Both challenges can be mitigated by a risk-based approach to compatible storage/distribution system component selection – in particular, use of PFS elastomer plungers laminated with FluroTec® films. This use will address both interaction and leachables, and is consistent with the FDA consideration of risk-based approaches to facilitate implementation chemistry, manufacturing, and control changes to closure systems. (6)

FluroTec® Film

Based upon West Pharmaceutical Services, Inc. ("West") analyses, elastomer components with FluroTec® film are used on over 131 approved drug products, 32 of which are novel drugs, and at least three of which are vaccines (Table 2). These comprise vial/stopper, syringe, and cartridge systems. Concentrations of active pharmaceutical ingredients range approximately from 0.1 mg/mL to 600 mg/mL.

Novel drugs, as defined by the FDA, are those that are not yet approved, but serve unmet needs or advance patient treatments; they are either new molecular entities or new therapeutic biologics. (7) Novel drugs typically are classified as first-in-class, or treat rare diseases, or receive expedited development and review pathways. The expedited designation they receive includes fast track, breakthrough therapy, priority review, and accelerated approval. *Where novel drugs are concerned (i.e., new molecules are involved or rapid decisions are needed), components with FluroTec film are a frequent choice*.

Table 2. Drug Products Packaged 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
Viral Vector	0	2	1	3
Oligonucleotide	---	3	---	3
Carbohydrate	1	---	---	1
Total	66	59	6	**131**

Chemistry

Because of the electronegativity of fluorine and the strength of carbon-fluorine bonds, fluoropolymers are largely chemically inactive. This feature has resulted in vast applications – one of which is films for elastomer stoppers and plungers in drug product package/delivery systems. Among the many fluoropolymers known, West principally uses 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 processing or gamma irradiation

The structure of ETFE is depicted in Figure 1.

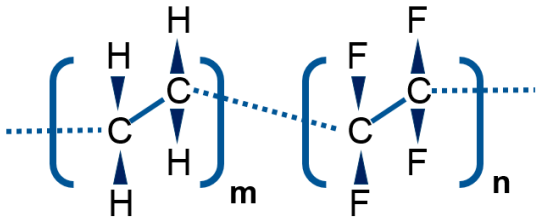

Figure 1. Structure of Poly(ethylene tetrafluoroethylene) (ETFE)

Interaction

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. (8) Interaction was evaluated at West. This was done by measurement of particles, turbidity, and recovery of drug products (simulated/commercial) under agitated/stressed conditions. (4) The results, as shown in Table 3, demonstrated that stoppers with FluroTec® film resulted in lower levels of particle formation, lower turbidity, and higher protein recovery.

For protein-based vaccines, including recombinant proteins, inactivated or attenuated viruses, and viral vectors, the benefit of reduced interaction with FluroTec film is expected to be similar. Moreover, based on its general low level of interaction, FluroTec film is expected to interact less with vaccines across the board, including negatively charged nucleotides, cationic/zwitterionic compounds, and hydrophobic lipids.

Table 3. Levels of Particles, Turbidity, and Recovery Resultant for Protein-Based Products, with and without FluroTec® Film. Values for particles are in thousands. (4)

	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 inactivity, 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 the ETFE acting as a barrier that reduces the occurrence of transport in two directions: (a) movement of leachables from elastomer into drug product; and (b) movement of drug product into elastomer, which may promote solubilization of leachables.

Leachables migration was evaluated at West. 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. (9) Headspace gas chromatography / mass spectrometry was performed to analyze for organic volatile compounds (Figure 2).

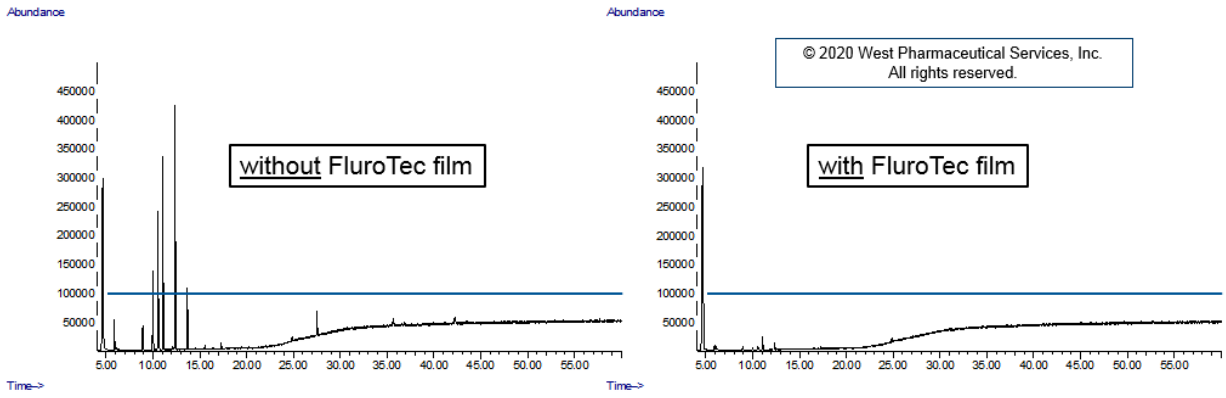

Figure 2. Headspace Gas Chromatography / Mass Spectrometry of Lined Seals, with and without FluroTec® Film. Data are at six months. Blue line indicates an estimated identification threshold of 0.5 µg/unit.

A large number of compounds were observed for the system without film. The system with film was able to significantly diminish the level and the number of compounds observed. The drawn blue line indicates an estimated identification threshold of 0.5 µg/unit, which is below the Product Quality Research Institute recommended safety concern threshold for parenteral drug products. (10) Note that stoppers with FluroTec film have been used successfully to address leachable-excipient-protein interactions. (5) For protein-based vaccines, mitigation of leachables must be considered. This is likewise true for mRNA-LNP vaccines. Note that risk of leachable migration is likely to increase when higher storage temperatures are employed.

PFS Performance

For COVID-19 vaccines stored/delivered in a PFS, a plunger with a FluroTec® film provides all the benefits just enumerated. Such plungers are offered by West in 1 mL Long (Article 2340) and 1-3 mL (Article 2345) configurations. See Figure 3.

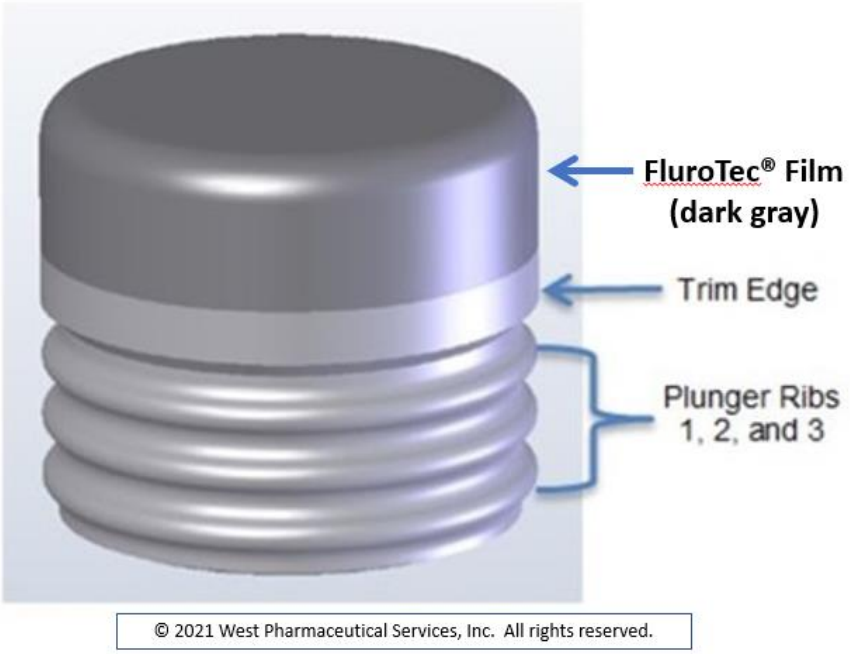

Figure 3. Design of Article plungers. FluroTec® film faces drug product.

Two essential performance requirements of PFS are consistency of: (a) delivered volume versus time, and (b) force needed to initiate and sustain plunger movement (usually called break-loose and glide-force, i.e., BLG force) versus time. The plunger must enable both. Both aspects were evaluated at West.

Delivered Volume

For 1 mL Long plungers and 1-3 mL plungers, delivered volume performance versus time is shown in Tables 4 and 5 respectively. Note both consistency of delivered volume independent of solution viscosity, and consistency versus time.

Table 4. Delivered Volume for 1 mL Long PFS. Components are: (a) ISO standard 1 mL long glass syringe (siliconized) with 27 gauge staked needle, and (b) Article 2340 plunger with FluroTec® film, elastomer formulation is 4023/50 gray. Fill volume is nominally 1.0 mL. Data are averages of 30. Parenthetical numbers are standard deviation.

Solution Viscosity (cP)	**Average Delivered Volume** (ml)	
	Initial	**12 Months**
1.0	1.00 (±0.01)	1.00 (±0.01)
8.0	1.01 (± < 0.01)	1.01 (± < 0.01)
15	1.01 (± < 0.01)	1.02 (±0.05)

Table 5. Delivered Volume for 1-3 mL PFS. Components are: (a) ISO standard 1-3 mL glass syringe (siliconized) with 27 gauge staked needle, and (b) Article 2345 plunger with FluroTec® film, elastomer formulation is 4023/50 gray. Fill volume is nominally 2.0 mL. Data are averages of 30. Parenthetical numbers are standard deviation.

Solution Viscosity (cP)	**Average Delivered Volume** (mL)	
	Initial	**14 Months**
1.0	2.08 (±0.01)	2.07 (±0.04)
8.0	2.06 (±0.01)	2.08 (±0.01)
15	2.05 (±0.01)	2.06 (±0.01)

BLG Force

For 1 mL Long plungers and 1-3 mL plungers, BLG force versus time is presented in Figures 4 and 5 respectively. As expected, higher viscosity solutions require higher BLG force. BLG force does not vary appreciably with time.

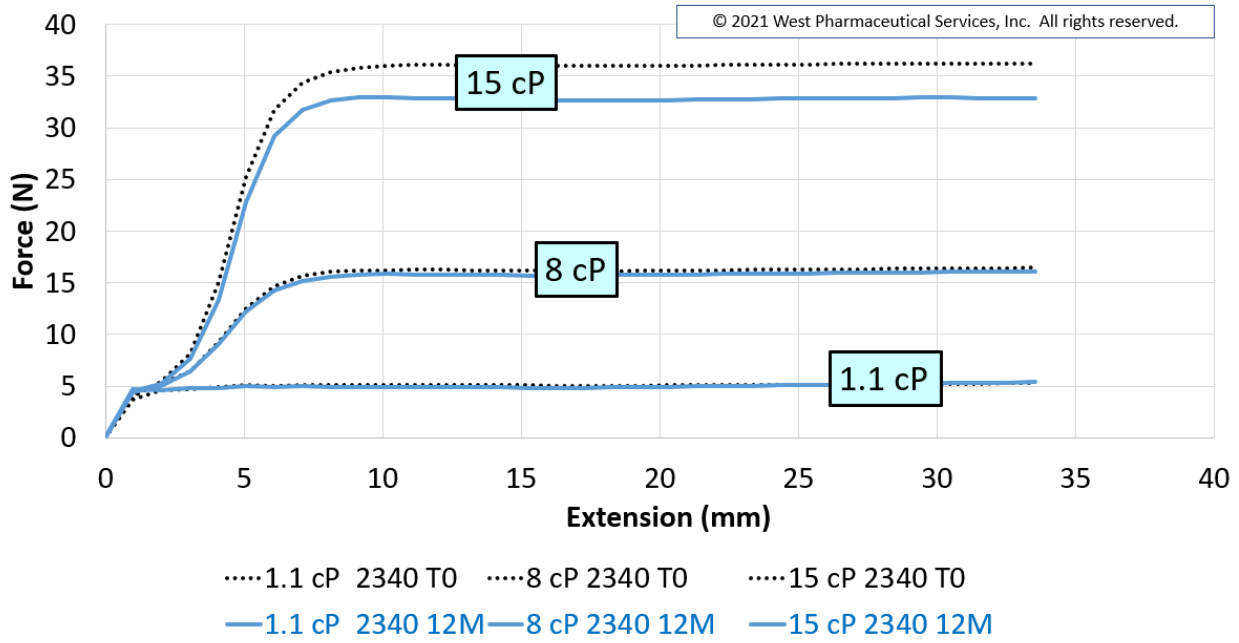

Figure 4. Break-Loose and Glide-Force for 1 mL Long PFS. Components are: (a) ISO standard 1 mL long glass syringe (siliconized) with 27 gauge staked needle, and (b) Article 2340 plunger with FluroTec® film. Elastomer formulation is 4023/50 gray. Solution viscosities are in centipoise (cP). Data are at initial time and 12 months; they are averages of 30.

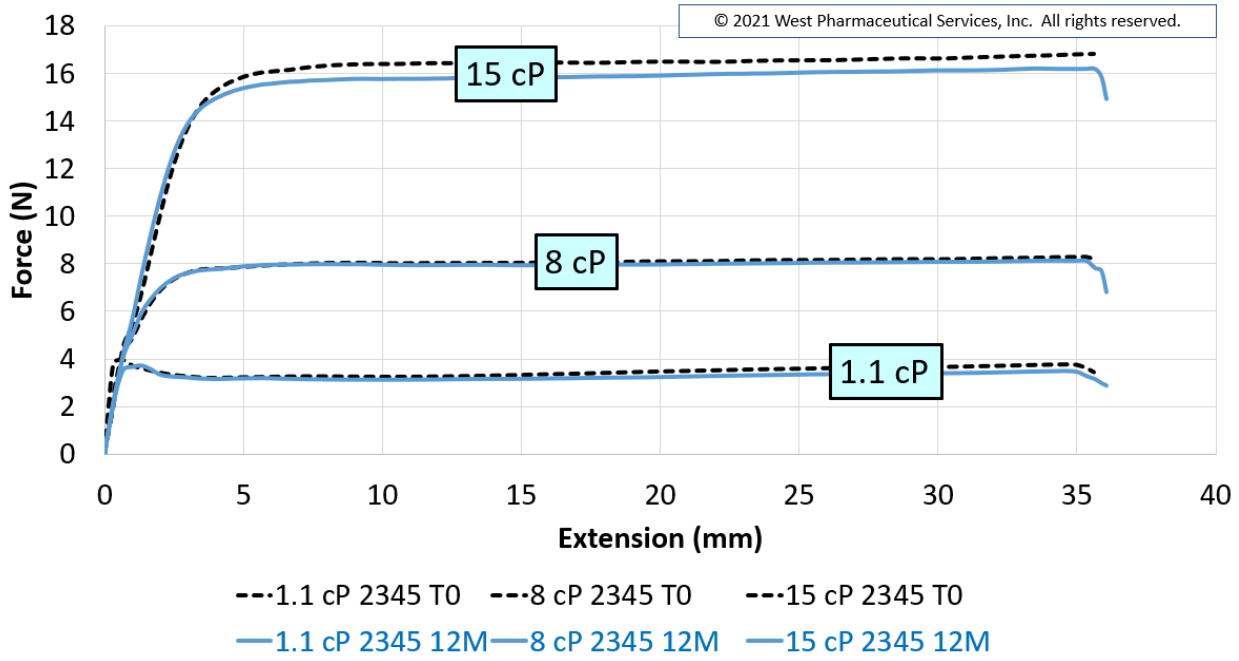

Figure 5. Break-Loose and Glide-Force for 1-3 mL PFS. Components are: (a) ISO standard 1-3mL long glass syringe (siliconized) with 27 gauge staked needle, and (b) Article 2345 plunger with FluroTec® film, elastomer formulation is 4023/50 gray. Solution viscosities are in centipoise (cP). Data are at initial time and 12 months; they are averages of 30.

NovaPure® Plungers

In addition to the Article 2340 and 2345 plungers discussed, West offers NovaPure® plungers in 1 mL long and 1-3 mL configurations, based on elastomer formulation 4023/50 gray. Comprising designs developed with Quality by Design principles, they have the exact same FluroTec® film facing drug product. See Figure 6. Extra features include:

- extractables and particles profiles for every lot
- specifications for visible and subvisible particles
- vision inspection for each component
- narrow, defined process capability index (CpK) for critical dimensions

In terms of delivery volume and BLG force, NovaPure plungers either match, or slightly exceed, Article 2340 and 2345 plungers. They may be considered the right choice for specialty applications.

Summary

Elastomer plungers with FluroTec® film have been shown to mitigate migration of leachables from elastomer into, and minimize elastomer interaction with, injectable drugs. Leading COVID-19 vaccine manufacturers have selected stoppers with FluroTec film as their packaging choice.

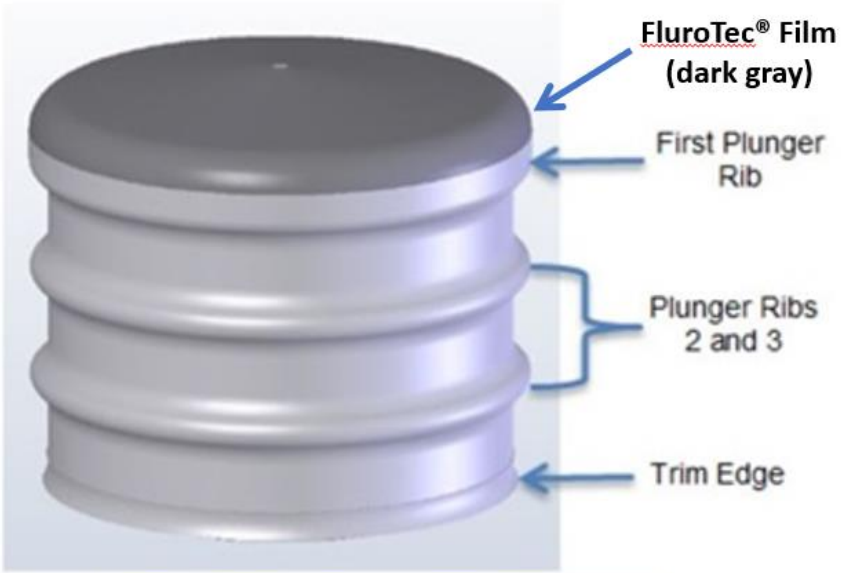

Figure 6. Design of NovaPure plungers. FluroTec® film faces drug product.

Reduced risk of drug and package interaction is essential under accelerated timelines, as delays to troubleshoot stability issues caused by choosing packaging that interacts with the drug product are unacceptable. Based on broad and extensive history of use and performance, plungers with FluroTec film are the lowest risk choice among West and Daikyo Seiko, Ltd. products for the continuing development of COVID-19 vaccines in response to variants. FluroTec plungers are exclusively offered by West and Daikyo. They are globally available, have a decades-long record of approval with a variety of molecule types by multiple agencies, and are available in 1 mL long and 1-3 mL sizes.

Acknowledgement

Thanks are given to Peggy Frandolig for her contributions.

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