# Prefillable Syringes in Deep Cold Storage: Is This The Way Forward for Mass Vaccinations?

**The world has just witnessed the fastest vaccine rollout in modern medical history.[1,2] This undoubtedly saved lives – but it placed intense pressure on our healthcare systems, workers, and supply chain. This begs the question: is there potential to make future vaccination programs even more efficient? The solution may lie in prefillable syringes (PFS) which have the potential to minimise the many challenges involved in vaccine production and administration.**

PFS have become an increasingly valuable option for the packaging and delivery of vaccines, as opposed to the traditional method of obtaining the contents of a vaccine from a vial via a syringe. PFS contain the vaccine which can be administered to a patient through the PFS itself, making them a 'ready-to-use' method of vaccine administration.

**Prefillable Syringes vs. Vials**

Over the years, PFS have become well-established in medicine thanks to their many benefits. Compared with vials, PFS provide benefits in terms of efficiency[3] and patient safety,[4] as they support many aspects of vaccine administration – from decreasing the time required to perform vaccinations,[3] to minimising the occurrence of handling errors[5] – and supporting dose sparing.[6]

Efficient workflows in vaccine administration are crucial. At the height of the COVID-19 pandemic, it became paramount that there was no time lost in vaccinating large numbers of society's most vulnerable people. This is where PFS would be valuable to a mass vaccination program. Efficient and simple workflows may also help integration of COVID-19 immunisation into the possible future roll out of regular immunisation programs, such as flu or pneumococcal immunisation, in the coming months.[7]

PFS are ready-to-use; they are prefilled during the fill & finish operation at pharmaceutical companies under Good Manufacturing Practices (GMPs) quality controls, with the exact dose required for a patient. Preparation steps at point of care are thus avoided, in contrast to vaccines supplied in vials, whereby the health care worker has to withdraw the proper dose from the vial with a disposable syringe. Such prefilled single dose presentation provides the potential for faster vaccine administration.[3,4] In fact, there are many evidence that support the quick administrative nature of PFS. It has been calculated that in a pandemic situation, the use of PFS to vaccinate 300 million people in the US could save over 3 million hours of HCP's time, in which more people could be vaccinated.[8]

**PFS Provide Patient Safety Benefits**

The administration process is likely to be more sterile when using PFS. Even with the most experienced HCPs, human errors can occur through the process of withdrawing a vaccine dose from a vial to a syringe. Microbial contamination during the syringe preparation process is reported to be reduced with PFS.[9]

In addition, as vaccines in PFS are predosed for a single injection, the risk of human error in dosing the vaccine is reduced.

**Reduced Wastage Through Dose-sparing**

Typically, the difficulty to extract the whole content from a vial leads to overfill of vials by the pharmaceutical manufacturers. Also, as you often need to open a 5- or 10-dose vial to immunise even one person,[10] it is common that doses are left over in multidose vials. In the absence of preservative in the solution, multi-dose vials need to be discarded a few hours after opening, even if all doses in them have not been administered. Additionally, once predawn from a vial and stored in a standard disposable plastic injection syringe, any remaining vaccine must be discarded at the end of the workday resulting in waste if more is drawn up than needed.[11] These combined issues lead to 5–25% of vaccine product being wasted, if packed in single or multidose vials.[12,13,14,15,16,17,17,18]

Some additional waste may be generated by the inability to completely empty disposable syringes used for vaccine reconstitution or administration from a vial: this is due to their "dead space", i.e., the volume between the fully pressed plunger and the end of the needle. It may reach up to 20% of a 0.5 mL standard vaccine dose. Of note, the dead space may be reduced by a factor of 10 with special syringes designed to this end.[8,9]

The dead space of the PFS and its needle may be significant but can also be reduced by the choice of the appropriate needle and the specifications of the PFS. This is an area where there is strong value for dialogue between the vaccine manufacturer and their supplier. In the glass PFS typically recommended for vaccines, the dead space is estimated to be only ~ 0.04 mL[18] i.e., less than 10% of a standard vaccine dose of 0.5 mL. Moreover, there is little overfill in PFS due to the precision of filling machinery. As a result, PFS may help reduce vaccine waste and support dose sparing.

**The Rising Demands of Deep Cold Storage**

For the past few decades, there has been increasingly innovative research into scientific vaccine technology worldwide. In what was dubbed as a 'new era in vaccinology', the development of mRNA vaccines was proof of such pioneering research. Compared to traditional protein-based vaccines, mRNA vaccines are faster and easier to create.[19] Despite these advantages, there are some challenges in the handling of mRNA vaccines. Traditional, protein-based vaccine formulations are commonly stored up to about 2°C–8°C. On the other hand, mRNA-based vaccine formulations require much colder storage temperatures. This is because these formulas are typically more unstable, and much colder storage temperatures are needed to ensure drug-product shelf-life and potency.[20] In fact, temperatures required for the storage of mRNA vaccines can go down to -40°C, and even further down to -80°C.[21]

In the case of new vaccine technologies requiring deep cold storage, the final primary packaging configuration should be carefully investigated to ensure that the container is compatible with such deep cold temperatures.

**The Suitability of PFS in Deep Cold Storage**

Ultralow temperatures can, however, induce changes in the container behaviour due to thermal cycle. The materials of a filled PFS system can be subject to several thermodynamic transitions and cycling mechanical stresses during the thermal cycling from room temperature to low negative temperatures. As a result, deep cold storage could compromise the functional performance of the delivery system and the vaccine contents.[22,23] Understanding the behaviour of PFS components and interfaces is crucial to assess if PFS can sustain deep cold storage temperatures.

**Glass PFS for Deep Cold Storage**

Glass PFS systems are composed of several materials and interfaces which will face various challenges. Of these key challenges, several solid materials, such as the plunger stopper, barrel and tip cap, will shrink. Elastomer components such as the plunger stopper and tip cap may cross their glass transition between -40°C and -65°C. Water and silicone components will also freeze and, in addition, the stopper may move due to the variation of the energy of the air trapped within the headspace and following the ideal gas law.[24,25,26] With these challenges, the device could be susceptible to leakage or weakness before or during injection. The integrity of the device is crucial to ensure the components with which it is filled remain stable throughout the manufacturing and handling process.

BD recently completed a preliminary study investigating the performance of glass PFS in handling the rigors of frozen chain storage. BD researchers conducted a comprehensive analysis of approximately 2,000 PFS, of several combinations of glass barrel coatings, with or without needle for injection, or nozzle for nasal administration, after deep cold storage at -20°C and -40°C.[27] Different tip and flange designs, and multiple elastomeric closures were also tested. In the study the PFS functions were unaltered when stored at these deep cold storage temperatures and then thawed. Moreover, the container closure integrity of the PFS remained unchanged compared to those stored at room temperature, indicating great potential for maintenance of sterility.

Following this study, it is anticipated that the glass barrel PFS systems tested should be suitable for use when storage temperatures of -20°C and -40°C are required.

**The Future of PFS and Deep Cold Storage**

Going back to the initial question: how can the vaccine injection system contribute to the efficiency of future vaccination programs?

PFS are known to simplify and better secure vaccine administration. The cumbersome and potentially wasting drug preparation process with vials is significantly reduced with PFS use.[28] In fact, according to recommendations from the British Royal Pharmaceutical Society guidance on the safe and secure handling of medicines, injectable medicines should be in PFS wherever possible, to minimise manipulation of medicines.[29] Furthermore, PFS avoid the need for sourcing and distributing disposable syringes, which may be a challenge for policy makers and providers in pandemic situations.[30]

Naturally, there are concerns on how PFS would perform in deep cold temperatures – including for those containing mRNA vaccines. With recent studies showing that glass PFS can be appropriate for use in such ultralow temperatures, PFS in deep cold storage may be the way forward for vaccination purposes. Take for example the Moderna and Pfizer–BioNTech mRNA-based vaccines developed for COVID-19, which are best stored in a deep freeze condition. Being able to store them in glass PFS in such conditions could significantly improve the efficiency by which they could be administered to the masses.[31] These applications for PFS in deep cold storage go beyond COVID-19. The use of mRNA

vaccines against many other viruses – for example influenza – is being investigated. Notably, following the success of Pfizer's mRNA vaccine in the fight against COVID-19, they have recently launched a mRNA influenza vaccine trial to test its potential ahead of the predicted winter flu crisis.[32]

**Collaboration is Key**

Developing vaccines for new diseases is only half the challenge – delivering them correctly is equally critical. The recent findings on glass PFS in deep cold temperatures are indeed promising. To further the significance of these findings, it is imperative that investigations on the stability of the medicines contained in glass PFS in deep cold storage continue.

Suppliers of PFS should collaborate with pharmaceutical companies. Pharmaceutical companies will be able to provide the drugs which will be contained in PFS. Such collaboration will help to better understand the interactions between the drug and the container in deep cold temperatures, ultimately enabling us to accelerate and optimise the use of glass PFS in deep cold conditions.

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**Guillaume Lehée**

Guillaume Lehée is an entrepreneur and convinced scientist, acting as Innovation Leader for BD since 2017, focusing on problem solving, need understanding and technology and solution enablement, mainly for pre-filled drug containers. Guillaume holds a MBA from Grenoble Alpes University and a PhD thesis in Micro and Nanotechnology from University Paris-Saclay. Guillaume is also co-founder of PhDTalent, a start-up facilitating collaboration between scientists and industrials to accelerate innovation.