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REPORT ON NEW SOLUTIONS FOR PHARMACEUTICAL PACKAGING

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A CASE STUDY BY
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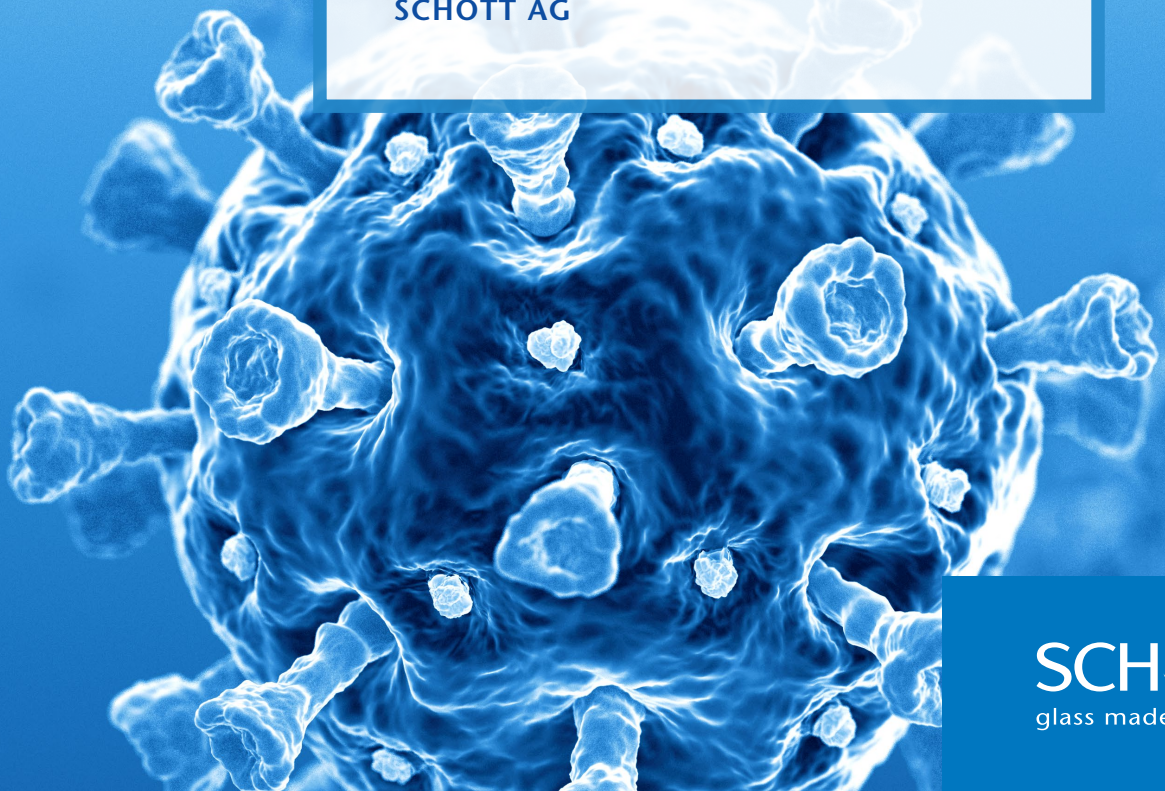

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glass made of ideas

KEY CONSIDERATIONS IN SELECTING A POLYMER PRE-FILLED SYRINGE FOR LOW-TEMPERATURE mRNA VACCINES

A case study by Tom van Ginneken, Head of Global Product Management – Polymer Solutions, SCHOTT AG

The COVID-19 pandemic has taught us that a fast and efficient vaccination rollout is paramount to fighting the spread of a virus. Quickly established vaccination centers around the world relied on the fast delivery of the vaccines, which were available in multi-dose vials to serve as many people as possible in the shortest amount of time.

Although the high vaccination rates have demonstrated very good levels of protection against symptomatic infection, public health experts agree that the COVID-19 virus, like the flu virus, is here to stay. The shift from a pandemic state to an endemic one means that a periodic re-vaccination, such as a yearly booster shot for high-risk patients, is likely to come into effect.

This will necessitate a few changes to the vaccination approach. First, vaccinations probably will be administered at a general practitioner or local pharmacy instead of at vaccination centers. Most developed countries have a vaccination rate of 50-80% of their population with some countries reaching a level as high as 90% for adults. Vaccination centers are therefore likely to disappear because of the declining need for mass vaccination.

Second, the current multi-dose vial format requires multiple drug preparation steps, and once opened, the shelf life of the contents inside the vial is limited to a couple of hours. If the physician doesn't have enough patients to vaccinate within this time slot, the remaining drug inside the vial has to be discarded. Therefore, a shift toward a single-dose device such as a pre-filled syringe (PFS) will offer economic advantages.

Switching the filling process from a vial to a PFS poses some technical considerations and challenges. This is especially true in the case of mRNA-based vaccines, which seem to be the preferred technology in the race to commercialize COVID-19 vaccines. mRNA vaccines are highly sensitive and must be maintained at low temperatures, thereby posing a greater challenge than traditional vaccines in terms of storage in a PFS.

This article addresses how to overcome these technical challenges and provides scientific data about how to successfully transition from a vial to a PFS for vaccines. The data show:

1. The sterility barrier can be controlled with the right PFS components and fill/finish parameters.
2. Container/closure integrity (CCI) is maintained even at -80°C.
3. Potential drug interaction can be reduced with a cross-linked siliconization.
4. Syringe functionality is not impacted by low-temperature storage.

THE STERILITY BARRIER CAN BE CONTROLLED

Before arriving at the doctor's office, an mRNA vaccine in a PFS is frozen and undergoes one or more air transport cycles. These two steps can influence plunger movement due to freeze and underpressure. Once the plunger movement exceeds the distance between the first and the last sealing lip, it is defined as breaching the sterility barrier. It is therefore extremely important to understand this phenomenon and the factors that affect plunger movement.

SCHOTT performed a range of experiments with different plunger materials, filling volumes, headspace, filling medium, and freezing temperatures on SCHOTT TOPPAC® 1ml lg Cyclic Olefin Copolymer (COC) syringes to evaluate the impact of these variables. The maximal plunger movement was determined for filled syringes that were frozen for 12 hours with one or multiple freezing cycles and at underpressure simulating worst-case air transport in an unpressurized aircraft.

Chart 1 shows that three factors have significant influence on plunger movement:

– **Filling volume:** The bigger the filling volume is, the more plunger movement. More filling volume will expand more during freezing and cause the plunger to move more.

– **Headspace:** The bigger the headspace is, the more plunger movement. Two factors are in play here: First, during freezing, the air will contract in volume and, therefore, force the plunger to move toward the cone. The other force in play is the underpressure of the air transport simulation. This force will push the plunger toward the flange. Overall, the resulting force is pushing the plunger toward the flange.

– **Plunger type and material:** The lower the plunger break-loose and gliding properties are, the more the plunger will move. There are multiple plunger factors that could influence the gliding properties, including geometry, compression set, overlap with barrel, low friction coatings, and sterilization mode. It is important to understand each parameter in order to select the right plunger and material for the application.

Another critical point is that the design of the plunger has an impact on the sterile barrier. The distance between the first and last sealing lip is not identical for all plungers and also might affect the choice of plunger.

Chart 2 shows the statistical significance of all parameters that were tested in the design of experiments. All parameters with a P-value less than 0.05 are deemed to have a significant influence on the plunger movement. The smaller the P-value, the bigger the influence of this parameter on plunger movement.

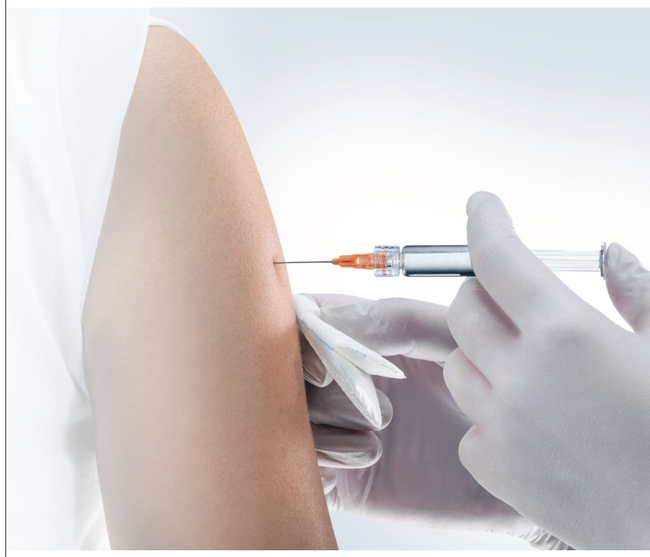


CHART 1:
Maximal plunger movement (in mm) during -20°C and at an underpressure of 430 mBar

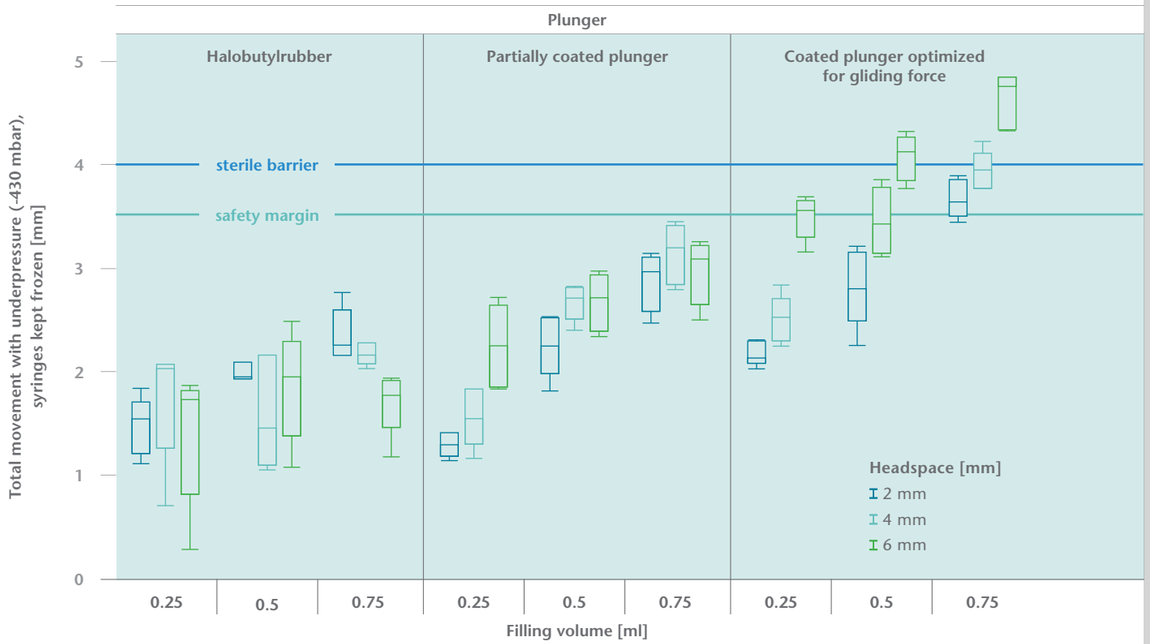


CHART 2:
Statistical analysis on impact plunger movement (for frozen syringes and at underpressure)

SOURE	LOG WORTH	P VALUE
Plunger	42.398	0.00000
Filling volume [ml]	28.099	0.00000
Headspace [mm]*Plunger	11.749	0.00000
Headspace [mm]	8.350	0.00000
Filling volume [ml]*Plunger	5.056	0.00000
Filling volume [ml]* Headspace [mm]	2.017	0.00961
Filling volume [ml]* Headspace [mm]*Plunger	1.057	0.08777

CHART 3:
Maximum plunger movement for different drug solutions.
Comparison between Placebo and WFI

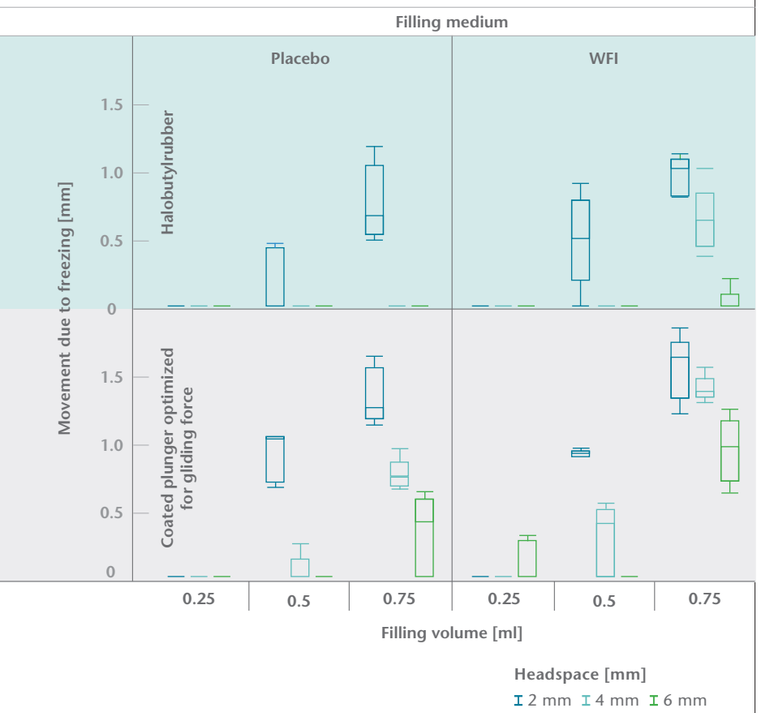
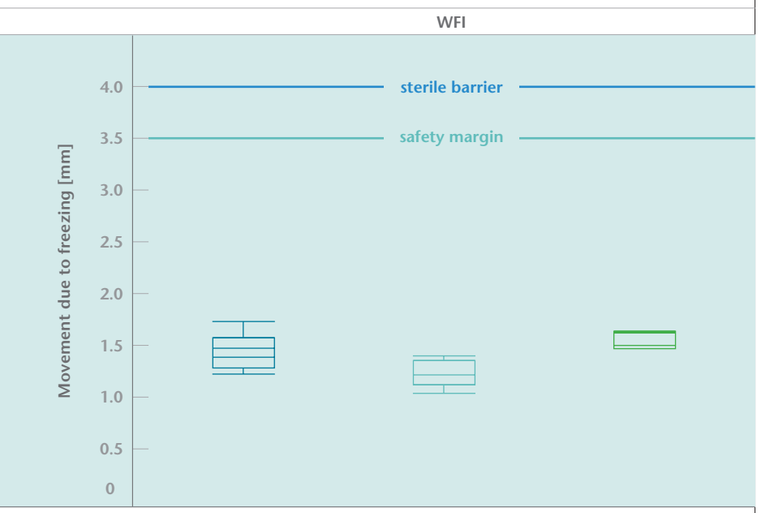


CHART 4:
Maximum plunger movement at different freezing temperatures



Two other parameters were investigated, but didn't show any significant impact on plunger movement:

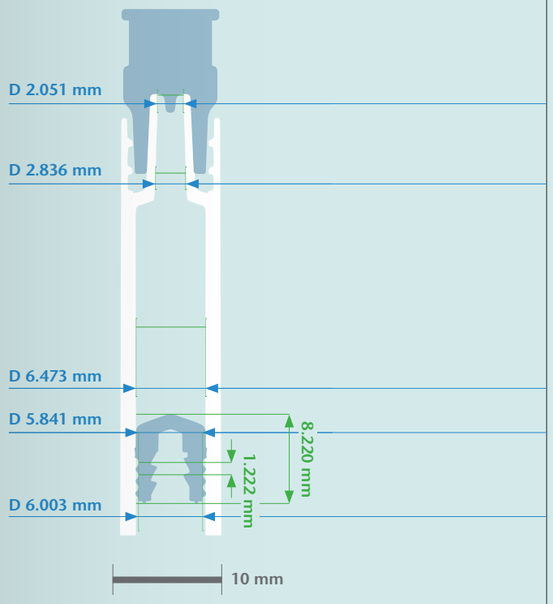
– **Drug solution:** Water for Injection (WFI) was compared with an mRNA placebo solution (8.7 % sucrose solution) with no significant impact on plunger movement. This means the results of this study executed on WFI should be comparable with drug solutions.

– **Freezing temperature:** Temperatures of -20°C, -50°C, and -80°C were compared to investigate impact on plunger movement. No significant differences were seen. The density – temperature curve of ice – shows that with decreasing temperature, the density of ice increases, indicating that the lower the temperature, the less volume the ice will have. Because filling volume is the second most significant factor to plunger movement after plunger type, we can expect no significant changes in plunger movement at different freezing temperatures.

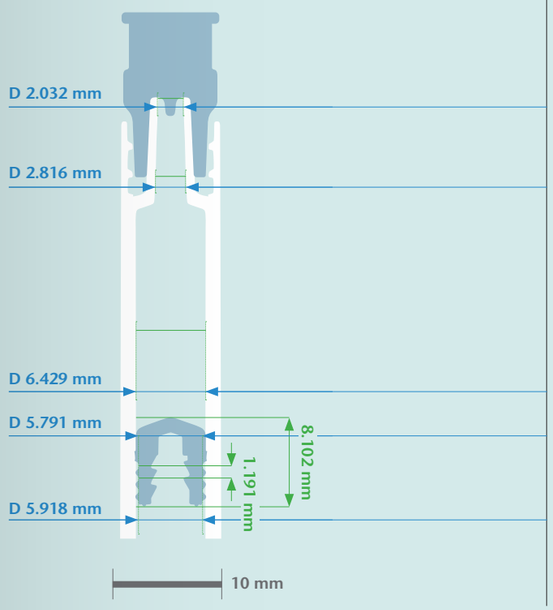
This study's recommendations are:
– Reduce headspace as much as possible (≤4mm)
– Lower fill volume (≤0.5mL)
– Choose a plunger with a higher break-loose and gliding force.

Overall, the key observation is that plunger movement can be controlled, and breaching sterility can be avoided by choosing the right primary packaging and filling parameters: filling volume, headspace size, and plunger type and material.

Before freezing without plunger rod



Frozen at -80°C without plunger rod



CCI IS MAINTAINED EVEN AT -80°C

A PFS is a complex system comprised of multiple components: a closure for the cone side; a plunger; and the syringe barrel. There is a broad range of materials for the components, chlorobutyl elastomers, bromobutyl elastomers, and various coatings used on the syringe barrel and plunger. These materials all have different thermal expansion coefficients, meaning that they will shrink at different rates when frozen. This is extremely important for CCI because reduced sealing overlap between plunger and barrel will drastically increase the risk of CCI issues.

Elaborating on the plunger as an example: The plunger has two functions – keeping the drug stable by providing a barrier against leakage and microbial ingress as well as proper functionality during drug administration. There is a certain compromise between good sealing properties and as-low-as-possible gliding forces. For mRNA-specific cold-chain conditions, the plunger and the barrel will start shrinking, each at their respective material property rates. The COC material shrinks at a similar rate as the rubber components. This can be recognized in Figure 1. The inner diameter of the COC syringe shrinks roughly 0.044mm, while the rubber plunger outer diameter shrinks with 0.050mm, 0.047mm, and 0.040mm for the three respective sealing lips (Figure 2). These absolute shrinkage values are comparable. Therefore, even at -80°C, no CCI breach is seen with a COC syringe.

This scenario looks completely different with other primary packaging materials such as glass. The thermal expansion coefficient for Type I glass is less than COC or the rubber components by at least a factor of 10. The glass container will shrink at a much lower rate than the rubber plunger, reducing the sealing overlap between the plunger and syringe barrel and, ultimately, pose a potential risk for leakage or microbial ingress.

FIGURE 1:
CT scan of identical COC syringe systems at different temperatures

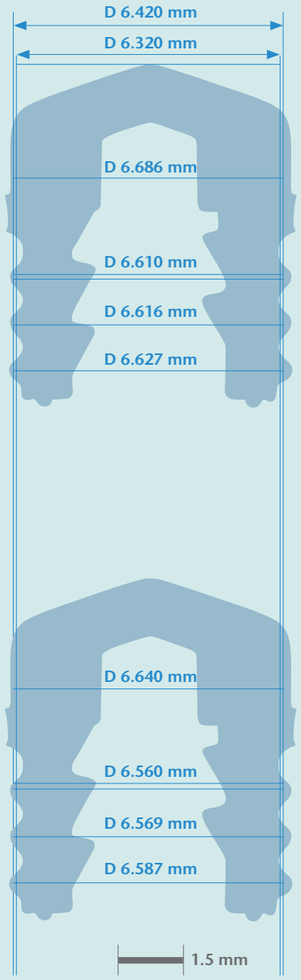
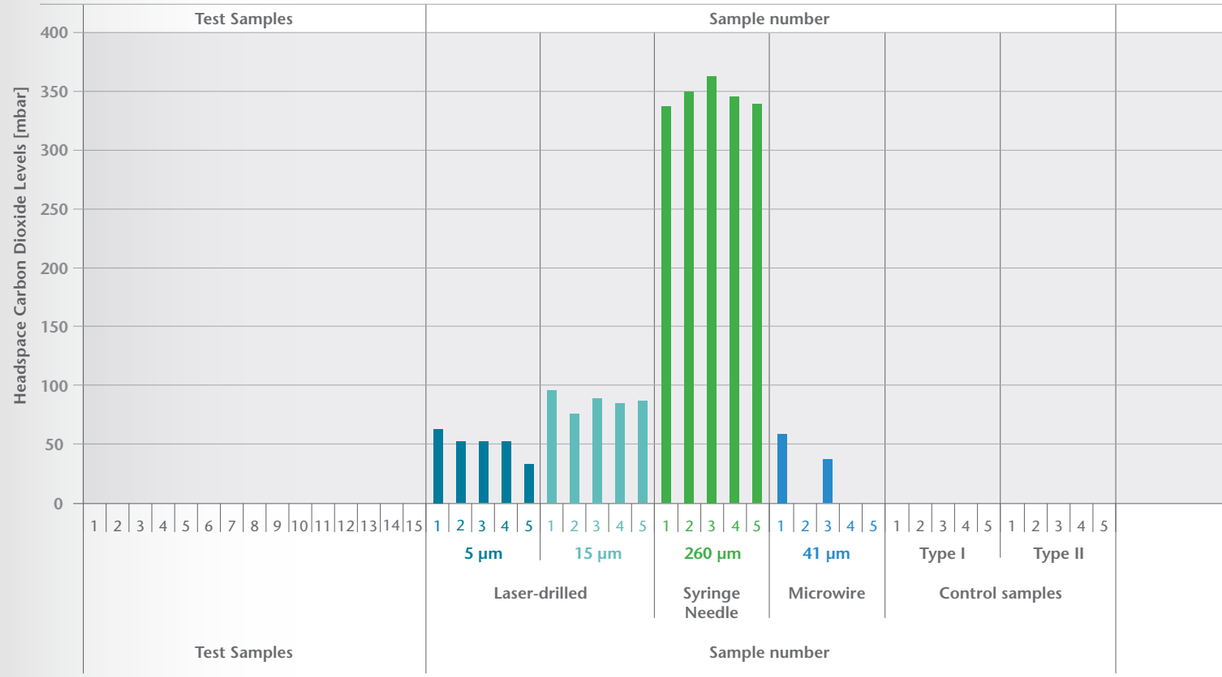


FIGURE 2:
CT scan of identical plunger in an uncompressed state (not in the syringe)

This reduced sealing overlap hypothesis was investigated further by executing an external headspace study. Fifteen empty COC syringes were stored for 24 hours on dry ice at -80°C. The syringes were tested with a qualified Lighthouse Instruments FMS-Carbon Dioxide headspace analyzer (Model FMS-CO2). Different positive control samples (laser drilled holes in plunger, a needle or a microwire bypassing the sealing lips of the plunger) were added to the test regimen to confirm the test method. The cone closure and the plunger also were tested individually to locate the source of leakage if there was one.

None of the 15 samples showed signs of carbon dioxide ingress. The data clearly indicate that even at an extremely low temperature of -80°C, the COC syringe system maintains CCI.

CHART 5:
Headspace carbon dioxide levels after 24 hours on dry ice



POTENTIAL DRUG INTERACTION CAN BE REDUCED WITH A CROSS-LINKED SILICONIZATION

A standard PFS has a lubrication layer to allow the plunger to move inside the barrel. There are many lubrication technologies, but the most common one is sprayed-on silicone oil. The silicone oil used here is normally not toxic for the human body, but an abundance of silicone oil can create sub-visible particles that could react with the drug and lower its efficacy.

One initial evaluation is the determination of leachable free silicone, which is the amount of free silicone oil that could interact with the drug substance. This value gives an indication of the potential risk of drug/lubricant interaction. Two lubrication technologies are compared: the standard silicone-oil spraying and a cross-linked technology.

For each variation, five syringes were filled with WFI and either went through three freeze/thaw cycles at -20°C or were stored at 5°C. The extract from five samples was pooled and analyzed by graphite furnace atomic absorption for free silicone oil. This test method has a detection limit of 0.2mg/L.

Table 1 shows clear differences between sprayed-on silicone oil and cross-linked silicone. Even for the reference samples which were stored at 5°C, the leachable silicone amount for sprayed-on silicone was at least five times higher. These results were even more pronounced at lower temperatures. After three cycles of freezing and thawing at -20°C, the leachable silicone quantities increase for both siliconization

	Time	Free silicone [mg/L] 3x frozen at –20°C and thawed	Free silicone compared to standard SCHOTT TOPPAC®	Free silicone [mg/L] stored at 5°C	Free silicone compared to standard SCHOTT TOPPAC®
SCHOTT TOPPAC® cross-linked siliconization Standard cross-linked silicone	0d	0.23	N/A	< 0.2	N/A
SCHOTT TOPPAC® sprayed siliconization Sprayed on DC360, 0.55 mg/barrel	0d	5.6	**24 TIMES**	1.09	5 TIMES

TABLE 1:
Leachable free silicone quantities of two siliconization technologies

technologies. But, sprayed silicone is much more affected; 24 times more free silicone oil was observed for the syringe siliconized with sprayed-on siliconization.

The second consideration regarding siliconization is the amount of sub-visible particles, which could react with the drug and negatively impact its efficacy.

In this study, four siliconization technologies were compared to evaluate siliconization impact on sub-visible particles: cross-linked siliconization, the same siliconization mixture used for cross-linked siliconization but without the activation of the cross-linking process, and silicone oil, plus silicone-free syringes to serve as a reference.

Sub-visible particles are determined via the method described in USP <788> via light obscuration.

Syringes were filled with particle-free WFI and stored at different storage conditions: room temperature, refrigerated temperatures (2-8°C), -20°C, and also at an elevated temperature of 40°C. The syringes were stored for three time periods: 12 hours, 31 days, and 121 days.

Chart 6 presents four key messages.

1. Storage at freezing conditions are the worst case for sub-visible particles. The freezing and thawing cycle shows significantly more sub-visible particles for all siliconization technologies.

2. Longer storage conditions tend to slightly increase sub-visible particles.

3. There is a good probability that the particles observed are coming from the siliconization process because the silicone-free syringes show almost no sub-visible particles.

4. The siliconization technology has a significant impact on the sub-visible particle burden.

The tests show siliconization does affect sub-visible particle levels and could potentially impact drug stability. It is therefore important to consider the impact of siliconization technologies on a specific drug application. The results collected at -20°C are likely applicable for temperatures down to -80°C as it is the thermodynamic phase transition (crystallization) effect of the freezing process that is putting stress on the lubrication layer, not the temperature itself.

This study recommends cross-linked siliconization technology for mRNA applications as it provides superior results in leachable silicone-free quantities and sub-visible particle burden. This cross-linked siliconization process is standard for the SCHOTT TOPPAC® COC syringe portfolio. The immobilized lubrication layer not only provides great drug stability properties, but also stable gliding performance at different storage conditions, which will be discussed next.

This study recommends cross-linked siliconization technology for mRNA applications as it provides superior results in leachable silicone-free quantities and sub-visible particle burden.

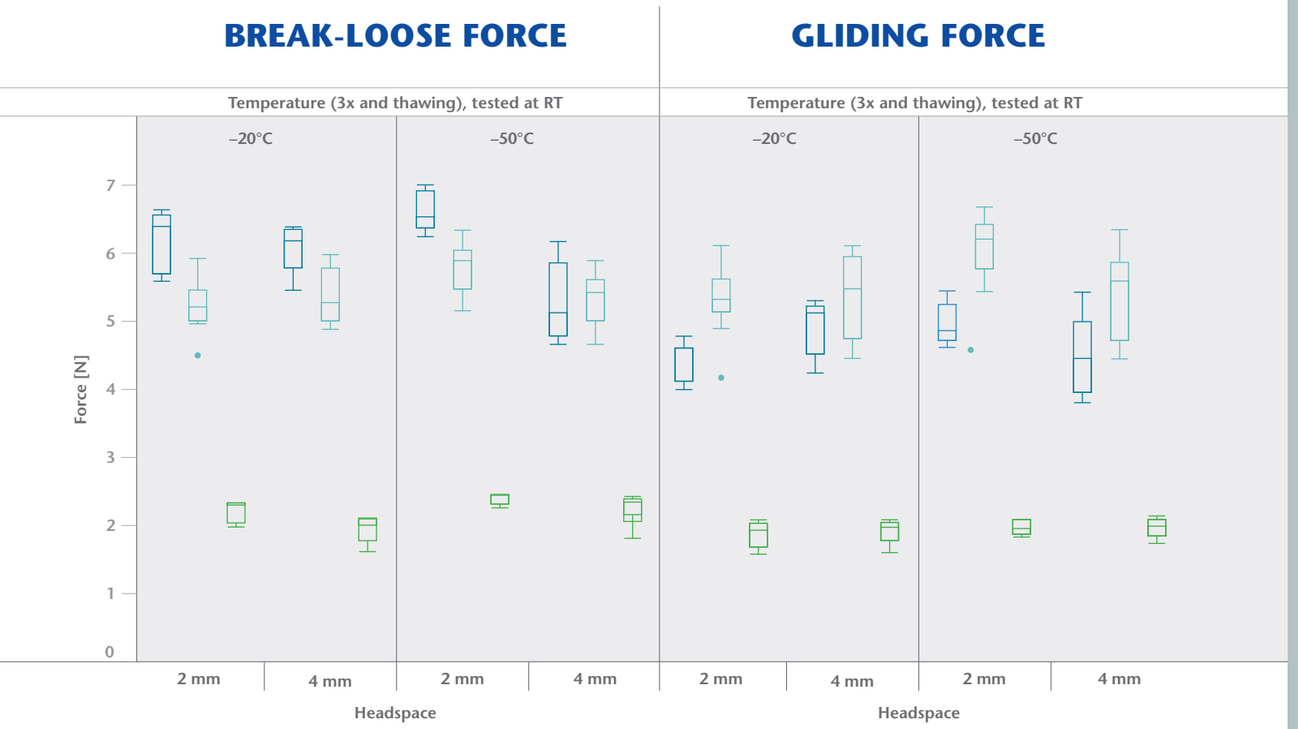
CHART 6:
Influence of storage conditions and siliconization technologies on sub-visible particle count

SYRINGE FUNCTIONALITY IS NOT IMPACTED BY LOW-TEMPERATURE STORAGE

Controlling the plunger movement and having a sterile syringe system that maintains CCI is necessary for a robust system, but the syringe also needs to perform well after low-temperature storage. If the low temperatures increase the probability of breakage or the likelihood that a plunger doesn't move after freezing, then the syringe system would be useless. Therefore, SCHOTT performed studies to compare polymer syringe functionality after freezing and room-temperature storage.

Syringes were filled with WFI and went through three cycles of freezing to -20°C and thawing to room temperature. The break-loose and gliding forces were tested at room temperature.

CHART 7:
Influence of temperature and plunger types on break-loose and gliding forces



	–20°C	–50°C	–80°C
Optical properties	■	■	■
Stress cracking	■	■	■
Breaking-Cracks	■	■	■
Luer Lock Adapter damage	■	■	■

■ No significant changes versus syringes stored at room temperature

TABLE 2:
Impact of temperature on syringe functionality

Chart 7 shows the results of that study:

– There is a limited difference between break-loose forces and gliding forces. Due to the stickiness effect of the rubber, break-loose forces tend to increase over time. In this application, because of the plunger movement during freezing and thawing, the thawing process already forces the plunger to move. Therefore, little increase in break-loose force is observed.

– There is no significant difference observed between storage temperatures. The -20°C and -50°C break-loose and gliding forces are comparable with syringes stored at room temperature. It seems the freezing process doesn't have a significant impact on the forces needed to perform the injection. This means that injection forces are expected to be comparable to room-temperature-stored syringes even at -80°C.

– Headspace didn't seem to have an impact on the forces.

– Significant impact of plunger type can be observed, which was expected. Different types of plungers have their own gliding profile and characteristics. It is not surprising that the plunger developed with improved gliding properties performs the best.

Another risk of extremely low storage temperatures is a change in PFS optical properties or breakage. Table 2 presents an overview of the most important functionalities tested at different temperatures compared to syringes stored at room temperature. No significant changes were observed.

In summary, the study shows that COC syringes, namely SCHOTT TOPPAC® PFSs, are ideally suited for low-temperature vaccine storage, which leads to the following major conclusions:

– Plunger movement does not breach the PFS sterile barrier, but understanding the syringe and fill/finish parameters that have an impact helps control this phenomenon.

– COC syringes can maintain container closure integrity down to -80°C because the thermal expansion coefficients of the different syringe components are similar.

– Cross-linked siliconization offers superior performance for leachable silicone oil quantities and sub-visible particles. This reduces the risk of any drug interaction and loss of efficacy.

– Normal syringe functionalities are maintained even at storage temperatures down to -80°C.

Looking forward, SCHOTT is currently preparing a container/drug interaction study to test mRNA-specific placebo solutions (including buffer solutions and lipid nano particles) with SCHOTT-specific drug containers. Results will be available in Q2 2022.

For more information, please visit:
www.schott.com/pharma

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