



# NEXT-GENERATION LUBRICATION SOLUTIONS FOR PHARMACEUTICAL PACKAGING

In this article, appearing for the first time in ONdrugDelivery Magazine, we're pleased to introduce Jackson D Thornton, PhD, Senior Research Scientist; Daniel E Jonsen, PhD, Principal Scientist; and Vinay Sakhrani, Vice-President, Technology, all of TriboFilm Research Inc. Here, they discuss the importance of lubrication in prefilled syringes, especially in auto injector applications, outline some of the drawbacks of traditional silicone oil-based lubrication, and describe a novel Atmospheric Plasma Technology, which immobilises lubricants (including silicone and TriboFilm's own PFPE-based next generation lubrication system) onto glass and polymer primary container surfaces.

A prefilled syringe offers several advantages in pharmaceutical packaging and delivery over the conventional combination of a vial and a disposable syringe. These advantages, which have driven the growth of the prefilled syringe industry at an astonishing rate in recent years, include:

- Accurate drug dosing
- No overfill requirement – the US FDA requires up to 25% overfill for vials
- No preservatives required in the formulation
- Increased assurance of sterility
- Ease of use
- Patient comfort and compliance
- Time savings in emergency situations
- Reduced materials cost
- Less waste and lower environmental impact

A prefilled syringe is traditionally defined as a three-part device with the following components:

- (1) the syringe barrel, made of either glass or plastic, which can be formatted with a staked needle or a luer fitting;
- (2) a rubber plunger that provides container closure integrity; and
- (3) a plastic plunger rod used to advance the plunger.

However, all syringes also contain an invisible fourth component, the lubricant, which is often overlooked and can have a major impact on the syringe function and drug stability. Figure 1 depicts the four components in a typical prefilled syringe.

“Ideally, the industry would like a universal immobilised-lubricant syringe system applicable to glass and plastic syringes of all formats, which has consistent plunger forces and adds no particles to the drug medium”



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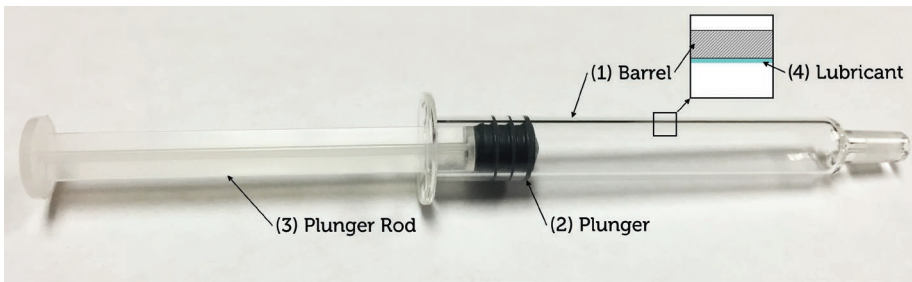


Figure 1: Anatomy of a four-part syringe.

### SILICONE OIL: THE INVISIBLE RISK IN PREFILLED SYRINGES

A prefilled syringe requires a lubricant to enable the plunger to move properly through the barrel. The traditional industry standard lubricant for prefilled syringes is silicone oil. However, silicone oil tends to migrate and is easily displaced from its original application area. Silicone oil migration can affect the mechanical function of a syringe in two significant ways. First, as the oil migrates off of the syringe barrel and into the product, some areas of the barrel may become lubricant-depleted. This will significantly increase the glide force required to move the plunger over these regions. Second, the plunger must exert compressive forces against the barrel surface in order to seal properly. Since the plunger remains stationary during storage, the long-term compressive forces exerted at its storage position cause the silicone oil in this region to be displaced, i.e. “squeezed out” over time. This increases the break-loose force required to overcome the static friction of the plunger and start moving it from its storage position.

Both increased glide forces and increased break-loose forces can cause significant problems when a prefilled syringe is used in the increasingly popular auto injector format. The increased glide force required at lubricant-depleted points along the barrel can significantly slow the motion of the plunger, often to the point that the overall injection time becomes unacceptably long. In more severe cases, where the force of the advancing spring is lower than the required travel force, the plunger will stop entirely, resulting in incomplete injection. Furthermore, if the force of the spring on the plunger exceeds the strength of the syringe flange, the flange will break, resulting in device failure and a potentially serious safety issue. All of these issues associated with lubrication problems have resulted in numerous recalls for auto injector devices.

The migration of silicone oil into the drug product can also generate unwanted sub-

visible particles. Agitation during shipping, formulation excipients, and plunger movement during injection can all exacerbate this problem. Recently, a number of publications have shown that suspended silicone oil particles may cause protein-based pharmaceutical molecules to aggregate.<sup>1-3</sup> These particles introduce several product quality concerns, such as exceedance of USP limits for particulates in parenteral containers,<sup>4</sup> structural instabilities in proteins caused by adsorption,<sup>5</sup> and/or immunogenic responses caused by injection of silicone oil induced protein aggregates or silicone oil/protein complexes.<sup>5-6</sup> The latter two of these problems can result in significantly reduced drug efficacy and/or potentially dangerous reactions in the patient, making the product unfit for use. In fact, several biopharmaceutical drugs carry a strict warning to avoid using a siliconised syringe to deliver the drug, as doing so would render the drug ineffective and dangerous<sup>7-9</sup>.

#### PRODUCT QUALITY PROBLEMS ASSOCIATED WITH SILICONE OIL MIGRATION

- Higher, more erratic plunger forces
- Sub-visible silicone oil particles in the product
- Protein aggregation and immunogenic responses

The pharmaceutical industry has actively sought solutions to the shortcomings of silicone oil, and a few alternatives are available. Several manufacturers promote a “baked-on” silicone lubricant for glass prefilled containers where the siliconised glass barrel is heated to a high temperature. Reduction of the extractable silicone oil is attributed to the vaporisation of the lower-molecular-weight silicone molecules during the baking process. However, because the temperatures used are too high for both plastic syringes and staked-needle glass syringes, the silicone baking process is only applicable to glass luer cone syringes and cartridges. Another alternative is

to reduce the amount of silicone in the syringe system, with the resulting compromise of higher plunger forces. Additionally, some companies are exploring the use of laminated plungers that do not require a lubricant on the syringe barrel. However, these plungers will not work with the industry standard glass containers as they are compatible only with plastic syringes. Ideally, the industry would like a universal immobilised-lubricant syringe system applicable to glass and plastic syringes of all formats, which has consistent plunger forces and adds no particles to the drug medium. An immobilised lubricant would give the pharmaceutical industry another option for their delivery systems and would allow silicone-sensitive formulations to be provided in a prefilled format.

### TRIBOFILM'S ADVANCED LUBRICATION SOLUTIONS

TriboFilm Research has developed Atmospheric Plasma Technology that can immobilise a lubricant onto a pharmaceutical container surface. TriboFilm's advanced lubrication technologies include TriboLink-Si™, a superior silicone oil based lubrication technology; and TriboGlide-DS™, a high-performance next-generation lubricant system based on perfluoropolyether (PFPE) chemistry. Both TriboLink-Si™ and TriboGlide-DS™ use a Downstream Atmospheric Pressure Plasma process to crosslink the lubricant onto the container as seen in Figure 2.

What is atmospheric pressure plasma? Physicists define plasma as the fourth state of matter, which can be described in simple terms as an ionised gas. It is composed

of ions, electrons, photons, and excited neutral atoms or molecules. Examples of plasma from common experience include flames, lightning, and the glowing medium inside a neon lamp. While most plasmas used in industrial processes must be generated under vacuum, which greatly increases costs and severely limits their applications, TriboFilm has developed

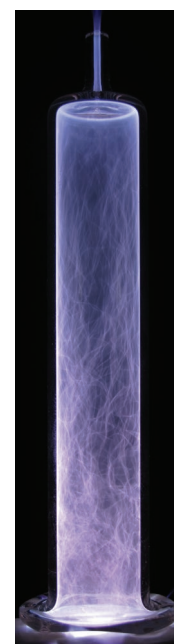


Figure 2: Syringe filled with downstream atmospheric pressure plasma during crosslinking treatment.

a unique low-cost atmospheric pressure plasma process that requires no vacuum and can operate in open air. Therefore this low-cost system can easily be integrated inline into a continuous process for syringe manufacturing. TriboFilm's atmospheric plasma process uses only inert gas, which eliminates any risk of exposing the syringe contents to unwanted reaction by-products that are typical of other crosslinking techniques. Further, this process uses a patented downstream plasma configuration, where the plasma is generated in one location, then flows "downstream" to a second location where the part is processed. This is beneficial in that the resulting treatment is gentler on the lubricant and syringe, and since no electrodes or other foreign objects enter into or come in contact with the syringe, contamination with foreign material becomes much less likely.

The crosslinking of the lubricant onto the syringe barrel greatly reduces its mobility, which has two important benefits. First, the rate of displacement of the lubricant by the syringe plunger during storage is significantly reduced, thereby reducing the break-loose force. Second, the tendency of the lubricant to migrate off of the syringe barrel and into the drug product is also reduced, resulting in fewer sub-visible particles and less potential for aggregation of protein-based pharmaceuticals.

Both TriboLink-Si™ and TriboGlide-DS™ are applied by the following steps (Figure 3):

1. The syringe surface is pre-treated with downstream atmospheric plasma to prepare the surface and enhance its wettability by the lubricant precursor.

2. The appropriate high-purity lubricant precursor is sprayed onto the syringe surface using a diving nozzle to ensure uniform application.
3. The sprayed-on lubricant precursor on the syringe surface is exposed to a second downstream atmospheric plasma treatment, which crosslinks it into an immobilised gel with superior lubricating properties.

#### BENEFITS OF TRIBOFILM'S LUBRICATION PROCESSES

- Downstream Atmospheric Plasma crosslinks the lubricant onto the device surface
  - Reduced lubricant migration
  - Fewer sub-visible particles than free oil
  - Lower plunger forces with no stick-slip behaviour during movement
- Scalable process compatible with inline, continuous manufacturing
- Applicable on glass, plastic (e.g. COP, COC, PP), and metals (e.g. needles)
- Compatible with staked-needle and luer syringe formats
- Both silicone and silicone-free options available

#### LUBRICANT PERFORMANCE STUDIES

As established above, low break-loose forces and consistent, low glide forces can be critical factors in the reliability, dosing accuracy, and ease of use of a prefilled syringe,

"Standard plunger designs are compatible with both TriboLink-Si™ and TriboGlide-DS™, with no changes in material or design required to maintain container closure integrity. Both of these lubricants are compatible with glass and plastic pharmaceutical containers"

especially when used in an auto injector. In addition, sub-visible lubricant particles can also play a major role in the shelf life, efficacy, and safety of the product in a prefilled syringe. The superiority of the TriboLink-Si™ and TriboGlide-DS™ lubrication systems over traditional silicone oil and baked-on silicone lubricants was demonstrated on glass syringes by evaluating the corresponding syringe force profiles and particulate loads.

#### Syringe Force Testing

Syringe force testing was performed on 1 mL long glass syringes with 0.5 inch long 27 gauge needles. Syringes lubricated with silicone oil, TriboLink-Si™, and TriboGlide-DS™ were filled with a solution of 0.05% Polysorbate 80 in sterile filtered water. The polysorbate surfactant is commonly used with protein-based pharmaceuticals and provides a challenging test case for syringe performance measurements. Groups of samples were aged for 2, 4, and 12 weeks at 40°C. Plunger force measurements were performed using a Zwick/Roell Z0.5 force tester at 100 mm/min. Ten samples were prepared for each of the nine experimental conditions.

Figure 4 shows a series of force-displacement curves for silicone, TriboLink-Si™, and TriboGlide-DS™ lubricated syringes after 12 weeks of storage at 40°C. As shown in the figure, the break-loose force ( $F_B$ ) is defined as the peak force required to overcome static friction, and the glide force ( $F_G$ ) is defined as the force required to maintain gliding motion after breaking the plunger loose. Note the relatively high  $F_B$  and  $F_G$  values for silicone oil compared to both TriboLink-Si™ and TriboGlide-DS™. In addition, a high degree of inconsistency is seen among the samples with silicone oil lubrication compared to those with TriboLink-Si™ or

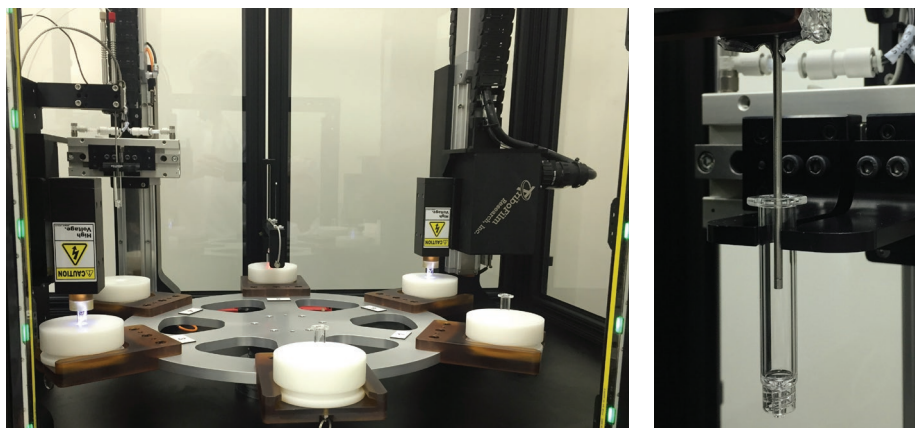


Figure 3: Left, Syringes receiving TriboGlide-DS™ treatment on TriboFilm's automated processing system. Note the live pre-spray surface activation plasma and post-spray crosslinking plasma at 8 o'clock and 2 o'clock positions, respectively. Right, Close-up of syringe receiving dynamic PFPE spray (the station at 10 o'clock position in left-hand image) during TriboGlide-DS™ application process.



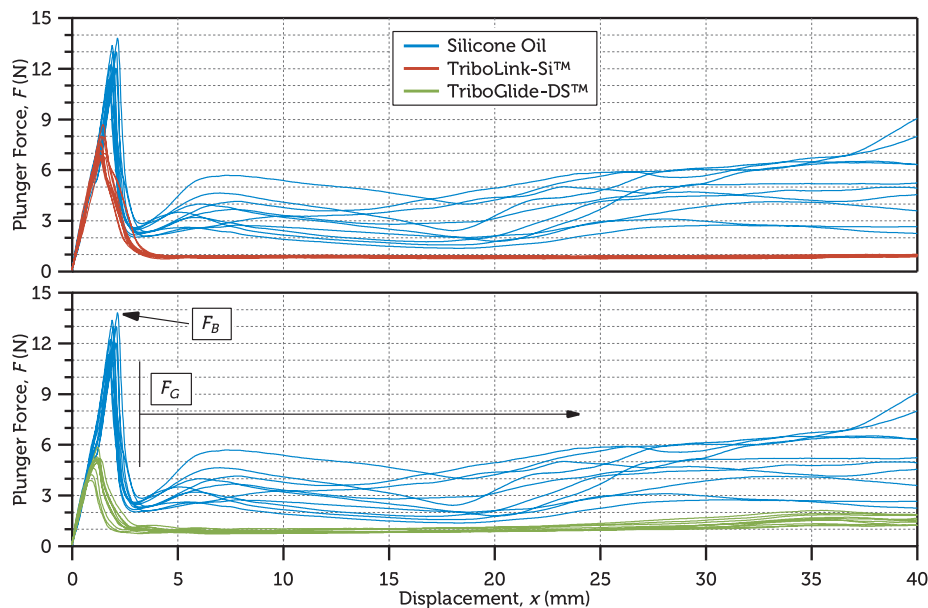


Figure 4: Force-Displacement curves for silicone oil, TriboLink-Si™ and TriboGlide-DS™ lubrication systems acquired using one of TriboFilm’s Zwick Z0.5 Force Testers (left). Break-Loose Force ( $F_B$ ) is defined as the maximum force required to break the static friction of the plunger. Glide Force ( $F_G$ ) is defined as the force required to maintain plunger movement once static friction has been overcome. All samples are 1 mL long glass syringes filled with a 0.05% Polysorbate 80 solution in sterile filtered water. All samples were stored for 12 weeks at 40°C and agitated for 24 hours just prior to characterisation.

TriboGlide-DS™ lubrication. The higher break-loose forces measured for the silicone oil lubricated syringes are caused by displacement of the silicone oil from between the plunger and barrel during storage.

The much higher glide force values and more erratic glide force profiles are attributed to migration of the silicone oil into the surfactant solution during storage.

Figure 5 shows the average break-loose and gliding force values for each of the nine experimental conditions. Note that both FB and FG increase markedly with storage time for the silicone oil lubricated syringes due to the migration of the lubricant as described above. In contrast, the forces remain much more consistent with aging for the TriboLink-Si™ and TriboGlide-DS™ lubricated syringes where the lubricant is immobilised on the syringe surface.

**Particle testing with surfactant**

A second set of experiments was performed to investigate the sub-visible particle counts found in prefilled syringes lubricated with four different lubrication systems:

1. Baked-on silicone (b-Si), vendor-purchased
2. Silicone oil (Si), vendor-purchased
3. TriboLink-Si™ (TL), plasma immobilised silicone, applied at TriboFilm
4. TriboGlide-DS™ (TG), plasma immobilised silicone-free PFPE, applied at TriboFilm.

For each lubrication system, ten 1 mL long glass syringes were filled with a 0.05% solution of Polysorbate 80 in sterile filtered water. The filled syringes were stored at 40°C for two weeks, and then agitated on a laboratory shaker for 24 hours just prior to characterisation. The particle counts were obtained by light obscuration measurements using a Particle Sizing Systems AccuSizer 780 SIS liquid particle counter. Figure 6 shows the number of particles  $\geq 2 \mu\text{m}$  in diameter for each of the four lubri-

cation systems. In all cases, note that the TriboLink-Si™ and TriboGlide-DS™ lubrication systems were consistently more stable and produced significantly fewer particles than either silicone oil or baked-on silicone.

**Particle testing with protein and shipping agitation**

A third set of experiments was performed to investigate the sub-visible particle counts found in prefilled syringes lubricated with three different lubrication systems in the

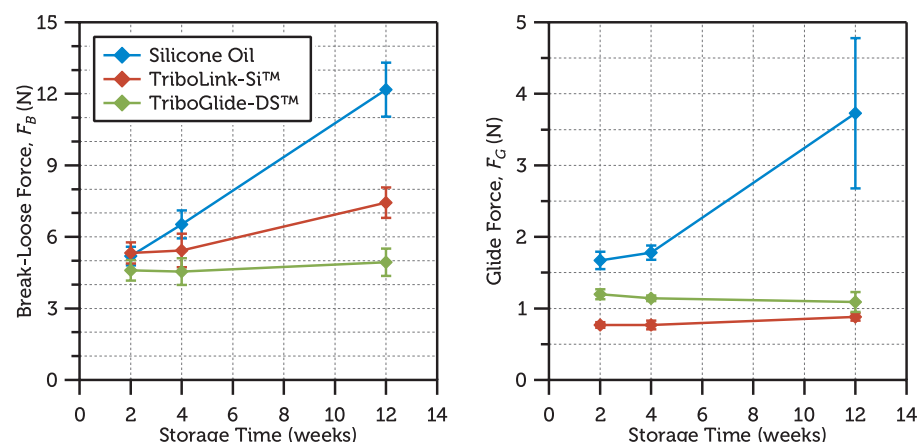


Figure 5: Average Break-Loose Force ( $F_B$ ) and average Glide Force ( $F_G$ ) for silicone oil, TriboLink-Si™ and TriboGlide-DS™ lubricated syringes. All samples are 1 mL long glass syringes filled with a 0.05% Polysorbate 80 solution in sterile filtered water. Sets of samples were aged for 2, 4, and 12 weeks at 40°C, and all were agitated for 24 hours just prior to characterisation. The error bars represent  $\pm$  one standard deviation of the values for 10 identically prepared samples averaged to obtain each point.

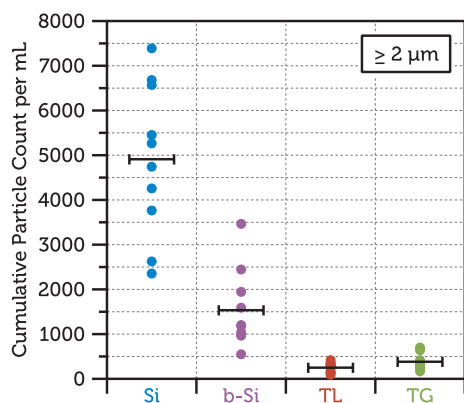


Figure 6: Particle counts for 1 mL long glass syringes lubricated with silicone oil (Si), baked-on silicone (b-Si), TriboLink-Si™ (TL), and TriboGlide-DST™ (TG). All samples were filled with a 0.05% Polysorbate 80 solution in sterile filtered water, stored for 12 weeks at 40°C, and agitated for 24 hours just prior to characterisation. The black horizontal bars represent the average value of each series.

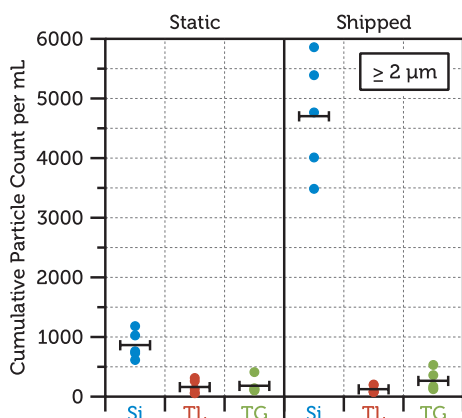


Figure 7: Particle counts for 1 mL long glass syringes lubricated with silicone oil (Si), TriboLink-Si™ (TL), and TriboGlide-DST™ (TG). All samples were filled with a 4 mg/mL solution of rHSA in pH 7.2 phosphate buffer. Half of each set of ten samples (shown on right) were overnight shipped ~2500 km. All samples were stored for four weeks at 25°C. The black horizontal bars represent the average value of each series.

presence of recombinant human serum albumin (rHSA):

1. Silicone oil (Si), vendor-purchased
2. TriboLink-Si™ (TL), applied at TriboFilm
3. TriboGlide-DST™ (TG), applied at TriboFilm.

Recombinant HSA was selected as a readily available model protein that is often used as an excipient in therapeutic protein formulations. For each lubrication system, ten 1 mL long glass syringes were filled with a

4 mg/mL solution of rHSA in a pH 7.2 phosphate buffer. Five of each set of filled syringes were shipped ~2500 km overnight by air courier, and all samples were stored at 25°C for four weeks before characterisation. The particle counts were obtained by light obscuration measurements using the same instrument described earlier. Figure 7 shows the number of particles  $\geq 2 \mu\text{m}$  in diameter for each of the lubrication systems. Air shipment provides a real-world agitation scenario after which to characterise the different lubricants. Under static conditions, the silicone oil lubricated syringes produced more particles than either the TriboLink-Si™ or TriboGlide-DST™ syringes. After air shipment, the particle counts in the silicone oil lubricated syringes greatly increased, while those in the TriboLink-Si™ and TriboGlide-DST™ lubricated syringes remained consistently low and showed relatively little change from the unshipped control samples.

### SUMMARY

Injection devices containing prefilled syringes offer many benefits for patients, while also providing product differentia-

tion to pharmaceutical companies. Many newer injectable drugs contain therapeutic proteins, which bring additional product stability challenges due to their interactions with packaging components. Therefore the design of a proper packaging strategy is now a critical part of the product development process that requires as much attention as drug formulation and should be addressed early in the development cycle.

has a tendency to migrate from the syringe surface into the drug product. The migration of silicone oil can detrimentally affect syringe function, and also produce sub-visible particles that can then impact the stability of biologics by forming protein/silicone aggregates.

An immobilised lubrication system can overcome the challenges described above. This article discussed two such advanced lubrication technologies for prefilled syringes:

1. TriboLink-Si™, an immobilised medical grade silicone lubricant, and
2. TriboGlide-DST™, a silicone-free immobilised perfluoropolyether lubricant.

As demonstrated above, both of these advanced lubricants offer superior performance over silicone oil and baked-on silicone lubricants, with lower and more consistent plunger forces and lower sub-visible particle loads. Standard plunger designs are compatible with both TriboLink-Si™ and TriboGlide-DST™, with no changes in material or design required to maintain container closure integrity. Both of these lubricants are compatible with glass and plastic pharmaceutical containers without limitations in size or format. These advanced immobilised

“Under static conditions, the silicone oil lubricated syringes produced more particles than either the TriboLink-Si™ or TriboGlide-DST™ syringes. After air shipment, the particle counts in the silicone oil lubricated syringes greatly increased, while those in the TriboLink-Si™ and TriboGlide-DST™ lubricated syringes remained consistently low and showed relatively little change from the unshipped control samples”

lubrication systems based on TriboFilm’s Atmospheric Plasma Technology effectively mitigate the risks involved with silicone oil lubrication in parenteral containers.

### ABOUT TRIBOFILM RESEARCH, INC

TriboFilm Research, Inc, based in Raleigh, NC, US, is a one-of-a-kind entrepreneurial research incubator that develops advanced technologies for pharmaceutical packaging applications. With extensive knowledge and experience in surface engineering, TriboFilm has focused its research efforts on one critical aspect of parenteral packaging: device lubrication.

With support from the US National Institutes of Health, TriboFilm has developed two advanced lubrication technologies: TriboLink-Si™ and TriboGlide-DS™. TriboFilm has established worldwide patent protection on both lubrication technologies, and licenses these patents to medical device and pharmaceutical companies in targeted fields of use. Our research facility contains state-of-the-art equipment for product development, performance testing, and small-scale manufacturing. TriboFilm has all of the tools, experience, and expertise necessary to create turnkey solutions to even the most demanding of customer challenges.

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"Syringe lubrication is often ignored during product development, which often becomes a source of significant difficulties when developing the packaging strategy for prefilled syringes"



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**POP QUIZ:**  
What is invisible  
but brings a pre-filled  
device project to a  
**screeching halt?**

**Answer:** Silicone Oil Particles

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**Risk Factors Include:**

- Large molecule biologic drugs
- Use of surfactants in the formulation
- Agitation during transportation
- High dose accuracy or consistent glide force requirement



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