WHITE PAPER

Solving the Silicone Challenge in Pre-fillable Syringes

How Stevanato Group's breakthrough Alba® platform ensures stability for sensitive drugs

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Converging trends in the prefilled syringes market

Growth on all fronts

The pre-filled syringes market has grown rapidly in recent years as a result of converging factors: the vast biologics market, a growing number of biosimilar entrants, the ongoing rise of self-administration, and rising chronic illness due to ageing populations. Healthcare spending for drugs delivered through a pre-filled syringe is expected to break the $300 billion threshold by 2027, versus $200 billion in 2022[1]. Half of this value is delivered through auto-injector drug delivery systems[2], with growing demand for integrated solutions that encompass drug containment and patient self-administration. Additionally, more than 75% of the total market value comes from biologics and biosimilars, with double-digit growth forecast to 2027[3]

Biologic drug formulation & containers: moving in tandem

Biologics drugs differ significantly from conventional drugs, making their development alone a challenging endeavor. Creating safe and effective formulations, particularly those designed for injection, demands time and effort. This complexity can occasionally lead to setbacks during testing, resulting in financial losses and project delays. And the pharmaceutical industry is continuing to build on the challenge, modifying formulations to reduce dosing frequency, for example. In some cases, this means increasing drug concentration or using larger injection volumes of more than 1 mL. This in turn has created a need for high-performance containers that can accommodate these higher concentrations and injection volumes, as well as the resulting high viscosities[4].

The challenges of silicone use in prefilled syringes

Silicone & subvisible particle release

In high-dose formulations of biologic drugs, excipients and stabilizers may be added to counteract the effects of increased viscosity, minimize protein-protein interactions and ensure stability. However, the presence of these chemicals can potentially harm the silicone components used in pre-fillable syringes, inducing the release of subvisible particles. Specifically, silicone oil is commonly used as a lubricant in prefilled syringes to ensure smooth plunger action with minimal injection force. As well as chemically induced release, degradation of silicone over time also generates subvisible particles, and silicone migration can be further aggravated by agitation (i.e., flicking or dropping the syringe)[5] . The degree to which silicone migration occurs depends on a number of factors, including syringe age on filling, siliconization process and surfactant[6].

Risks related to silicon oil droplets

If silicone detaches from the glass, as described above, it can cause injection irregularities and compromise the syringe's ability to deliver the full dose. Potential interaction between silicone oil droplets and protein molecules could induce the formation of protein aggregates, which in turn reduce the concentration of the drug available for injection – a phenomenon that has been observed and investigated by multiple researchers[7]. Choosing appropriate drug delivery devices is therefore critical from a drug safety, regulatory and commercial perspective – and all the more so for ophthalmic applications, where the US Pharmacopeia (USP) standards on subvisible particles are even stricter.

References

1 IQVIA, 2022-23, analyzed by Stevanato Group

2 ibid

3 ibid

4 Badkar, Advait & Gandhi, Rajesh & Davis, Shawn & LaBarre, Michael. (2021). Subcutaneous Delivery of High-Dose/Volume Biologics: Current Status and Prospect for Future Advancements. Drug Design, Development and Therapy. Volume 15. 159-170. 10.2147/DDDT.S287323.

5 L.L.d.M. Agra, N.F.S.d. Cruz, V. Linkuviene, J.F. Carpenter, M.E. Farah, G.B. Melo, M. Maia, Quantitative assessment of silicone oil release with siliconized and silicone oil-free syringes by microflow imaging microscopy, Arq. Bras. Oftalmol. (2022), https://doi.org/10.5935/0004-2749.2021-0320.

6 Gentile K, Huang C, Liu X, et al. Variables Impacting Silicone Oil Migration and Biologics in Prefilled Syringes. J Pharm Sci. 2023;112(8):2203-2211. doi:10.1016/j.xphs.2023.05.017

7 See, for instance: Valet, O. (2015). Formation of inherent protein aggregates in the visible and sub-visible size range by excessive and inhomogeneous lubrication in syringes and cartridges. J Pharm Drug Deliv Res 2015, 3:3 https://www.scitechnol.com/2325-9604/2325-9604.S1.005-008.pdf

Industry solutions to the silicone issue

In light of the issues outlined above, manufacturers have envisaged a number of potential solutions to minimize interactions, which either reduce, modify or completely avoid silicone oil in primary packaging. Some have developed lubricant-free plastic or glass syringes by incorporating stoppers that eliminate the need for silicone oil. Others opt for alternative silicone optimized processes, like baked-on technology, for example.

While baked-on silicone and silicone oil free solutions offer an alternative to using sprayed-on silicone oil as a lubricant, neither can be considered a risk-free option. Syringes with staked-in needles, widely regarded as the gold standard for injectable biopharmaceuticals, are largely incompatible with baked-on silicone technology. This is because the adhesive used to attach the needle cannot withstand the temperature needed to bake the silicone. Furthermore, although silicone migration is greatly reduced with baked-on coating technology, with numbers much lower than for sprayed-on siliconized containers, it is not completely mitigated[8]. Finally, the use of silicone-free prefilled syringe technology for injectable biopharmaceuticals comes with a limited track record and introduces a new set of challenges and risks, including manufacturability and compatibility, which the pharmaceutical industry must take into account.

8 Funke S, Matilainen J, Nalenz H, Bechtold-Peters K, Mahler HC, Friess W. Silicone Migration From Baked-on Silicone Layers. Particle Characterization in Placebo and Protein Solutions. J Pharm Sci. 2016 Dec;105(12):3520-3531. doi: 10.1016/j.xphs.2016.08.031. Epub 2016 Oct 20. PMID: 27773525.

Introducing Alba®: a breakthrough solution for biologics

Platform featuring a novel, inert coating technology for sensitive drugs.
To address the challenges presented by silicone use in prefilled syringes, Stevanato Group has developed Alba®, a novel syringe platform employing a plasma treatment on silicone coating, creating a barrier that ensures exceptional stability and resistance to breakdown.

This coating significantly reduces the potential interaction between a drug product and the container surface, making Alba® product well-suited for supporting drug formulations highly sensitive to silicone oil droplets released in solution, drug and surface interaction, extractables, and pH shifts. Using this technology reduces the risk of setbacks during the complex biologics development process, facilitating compliance with the latest regulatory guidance, including USP <787>: Subvisible Particulate Matter in Therapeutic Protein Injections, and USP <789>: Particulate Matter in Ophthalmic Solutions.

Designing a stability study for Alba®

Stevanato Group carried out in-depth stability testing of this innovative technology at EMEA Technology Excellence Center, to determine its functional performance. Firstly, empty samples of Alba® were monitored for any variation in thickness and distribution of the coating over a six-month period. Secondly, Alba® and a silicone oil syringe were both submitted to subvisible particle analysis and extrusion force testing over twelve months.

Alba®-coated syringes and the silicone oil syringe were placed in static storage at different temperatures with two different filling solutions to assess container performance across a broad spectrum of conditions. The study utilized a placebo solution mimicking a pharmaceutical solution available in the market. This placebo solution aimed to evaluate the impact of certain excipients on the stability of the coating over time, in particular polysorbate, a surfactant known to interfere with the stability of the silicone oil coating due to its amphoteric nature.

For each solution, the samples were stored for twelve months in different storage conditions (following the ICH Q1A guidelines) to evaluate thermal stability and sensitivity to solution. This included conditions of -40°C to assess the product's performance under stress, simulating temperatures commonly encountered in deep cold storage for potential mRNA applications. The testing conditions included the temperatures and relative humidity (RH) specified below:

- 5±3°C (real time)
- 25°C/60% RH (accelerated)
- -40°C.

This study used a 0.5 mL Luer Lock Cone syringe, for both Alba®-coated syringes and the silicone oil syringes. For the stoppering process of each filled syringe, West Flurotec® plunger stoppers were used. Filling and stoppering operations were performed through an automatic fill and finish machine, while plunger positioning was performed through the vacuum technique, leaving a headspace between the plunger and the filling solution.

Extrusion force testing & subvisible particle analysis

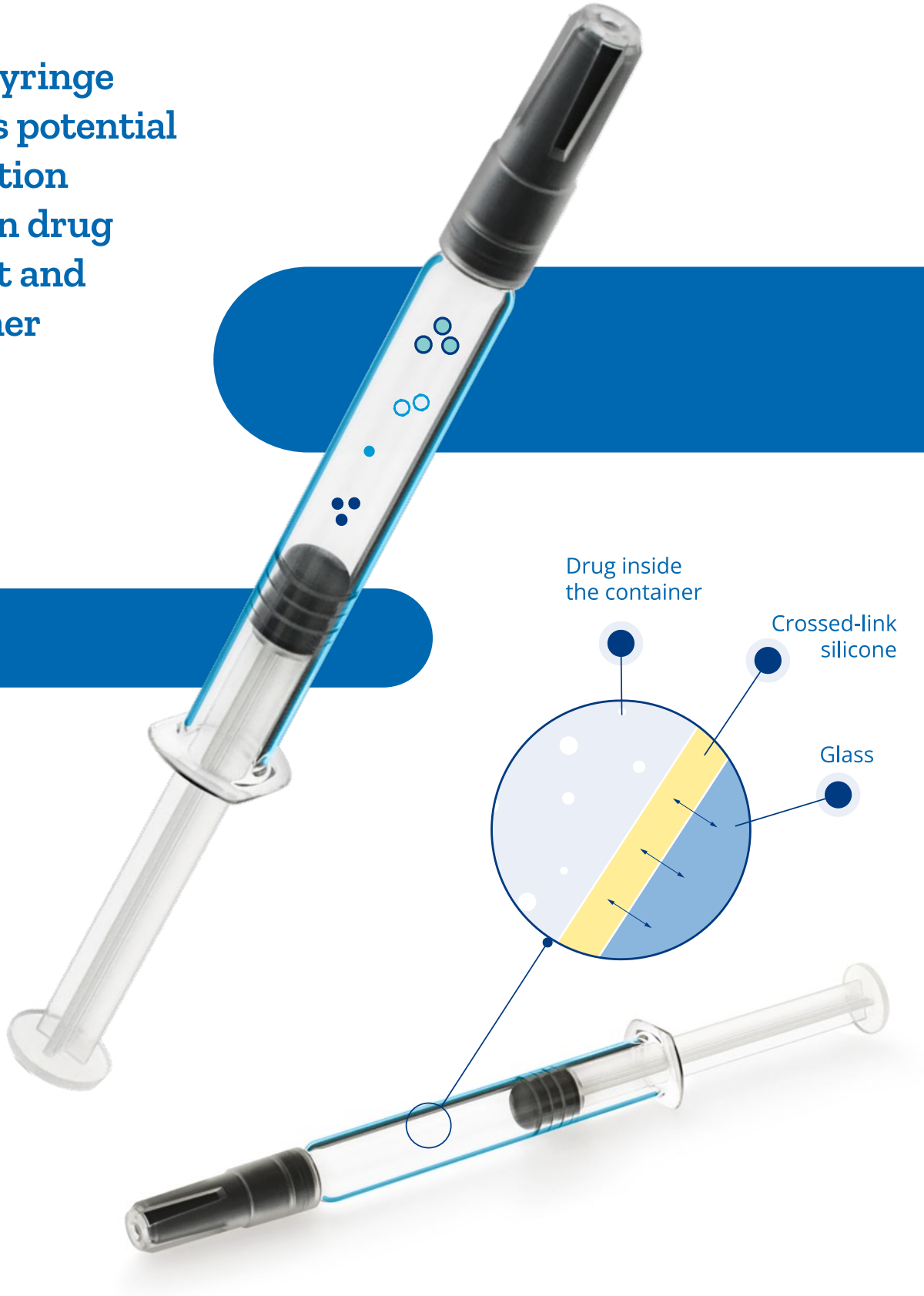
Mechanical performance was assessed through extrusion force testing of the syringes, as per ISO 11040-8:2016 (Prefilled syringes). Both break-loose force, i.e., the static friction of the plunger, and extrusion force, i.e., the dynamic force of the plunger needed to move it along the syringe barrel, were measured at a speed of 100 mm/min, to simulate a manual extrusion. For each syringe submitted to extrusion force testing, a 30 G needle was attached to the syringe using the Luer Lock Adaptor system.

The release of subvisible particles in solution was also analyzed, after filling and after mechanical stress of the samples. The samples were agitated end-over-end, allowing the solution to move around the syringe barrel and thus inducing a mechanical stress to the coating. The presence of the headspace and consequently of an air bubble allows higher stress of the coating on the surface; thanks to the end-over-end agitation, the air bubble can move along the barrel, thus inducing a higher release of silicone oil droplets release in solution compared to a static sample[9].

Two orthogonal analytical techniques were applied to assess the subvisible particles release in solution: Light Obscuration and Micro Flow Imaging, which enabled the collection of both particle count and particle morphology data.

9 Gerhardt A, Mcgraw NR, Schwartz DK, Bee JS, Carpenter JF, Randolph TW. Protein aggregation and particle formation in prefilled glass syringes. J Pharm Sci. 2014 Jun;103(6):1601-12. doi: 10.1002/jps.23973. Epub 2014 Apr 11. PMID: 24729310.

Alba® syringe reduces potential interaction between drug product and container surface



Results: thickness, extrusion & sub-visible particle testing

Silicone thickness in Alba® samples over time

The coating thickness and distribution along the syringe is evaluated through an optical technique: white light interferometry and laser interferometry are analytical techniques designed to accurately measure the silicone layer thickness over a glass cylindrical surface. Comparing silicone oil profile at 0, 3 and 6 months in empty samples of Alba® showed no significant variation in silicone thickness over time [See Figure 1].

The profiles showed a typical hill & dip morphology, resulting in a silicone oil coating with a flat distribution along the barrel.

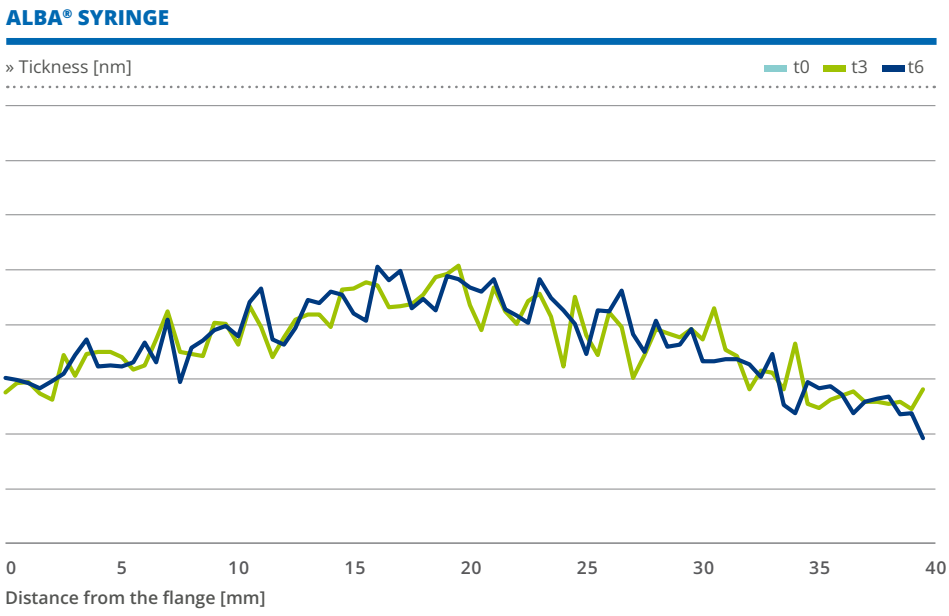


Figure 1: Comparison of Alba® coating profile at 0, 3 and 6 months

Alba® vs. silicone oil syringe

Subvisible particle testing with placebo solution

With regard to subvisible particle (SbVP) release in solution, Alba® syringes outperformed silicone oil syringes in all storage conditions [See Figures 2-7]. Slightly higher levels of SbVP in solution were observed at -40°C versus real-time conditions (5±3°C), due to the impacts of refrigerated storage and freezing. Nevertheless, SbVP concentrations remained compliant with the requirements of USP <787> for deep-freezing conditions, and USP <789> for real time and accelerated storage conditions.

Moreover, there was no significant increase in SbVP release over time thanks to the stability of the plasma-treated coating (already assessed through silicone oil thickness and distribution analysis). In addition, Alba® syringes treated with the new coating technology also presented lower sample-to-sample variability and thus greater reliability than silicone oil optimized syringes for prolonged use. Sample-to-sample variability is also one of the factors contributing to the non-linear, reducing trend of SbVP release in the silicone oil optimized product over time.

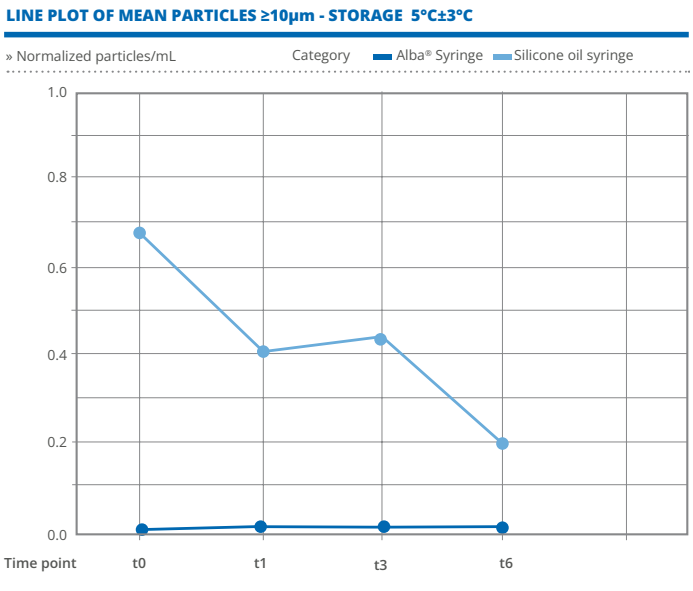


Figure 2: Results of Subvisible particle testing ≥ 10 µm at 5±3°C (real time stability) over six months
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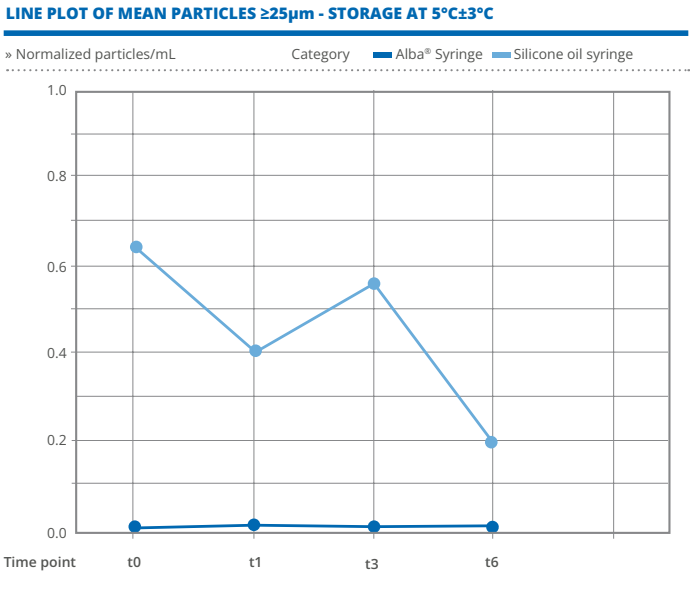

Figure 3: Results of Subvisible particle testing ≥ 25 µm at 5±3°C (real time stability) over six months
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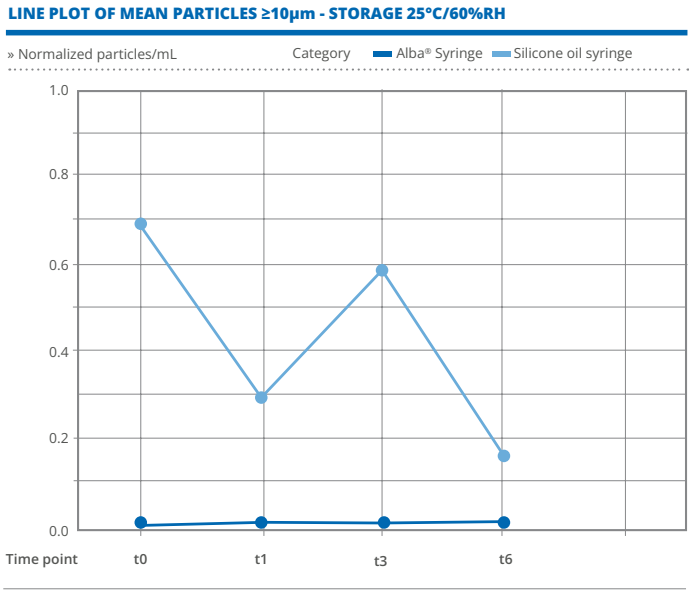

Figure 4: Results of Subvisible particle testing ≥ 10 µm at 25°C/60% RH (accelerated stability) over six months
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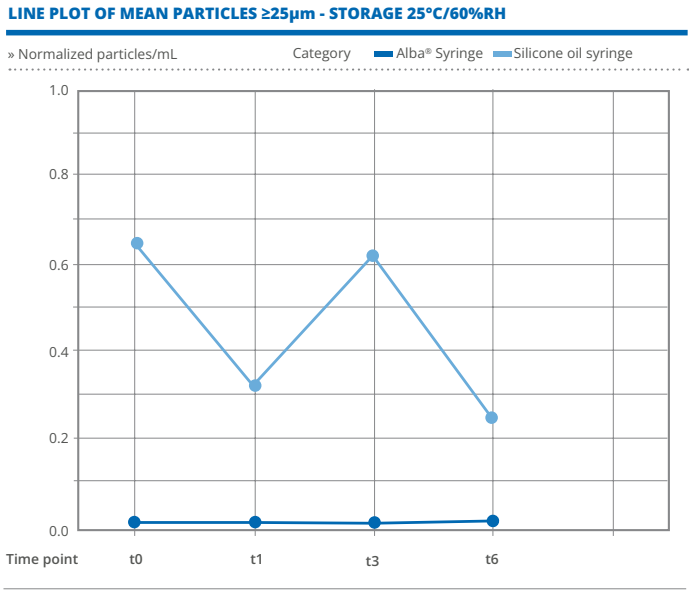

Figure 5: Results of Subvisible particle testing ≥ 25 µm at 25°C/60% RH (accelerated stability) over six months
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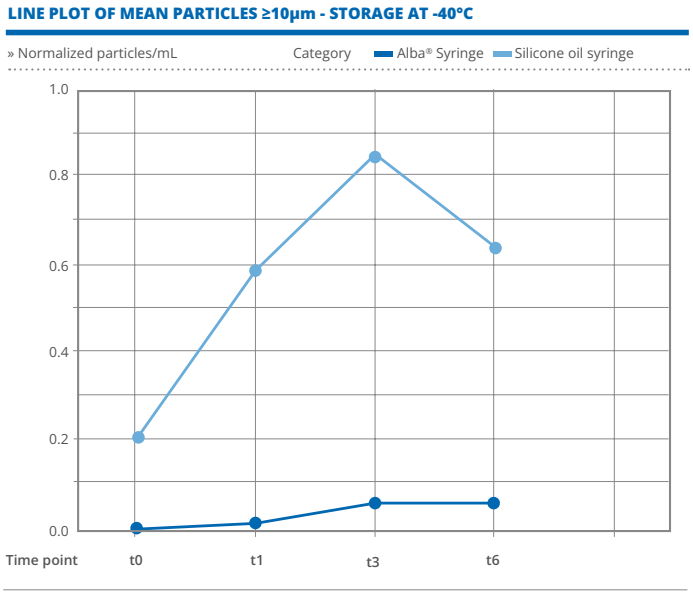

Figure 6: Results of Subvisible particle testing ≥ 10 µm at -40°C over six months
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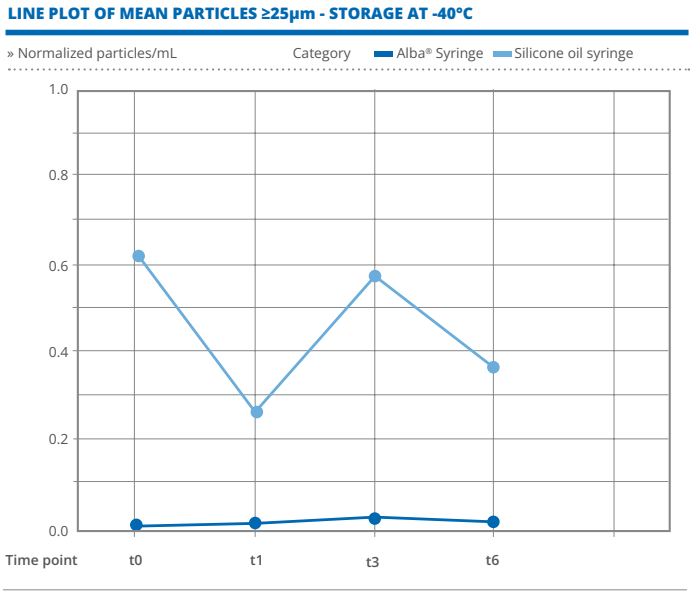

Figure 7: Results of Subvisible particle testing ≥ 25 µm at -40°C over six months
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* Alba® syringe's data at the 12-month time point are consistent with the findings from the preceding checkpoint.

The two products were tested for subvisible particle count and morphology through a micro flow imaging (MFI) technique; the morphological analysis performed by MFI allows us to discriminate between intrinsic particles, like silicone oil droplets, and extrinsic particles, like fibers or other contaminants coming from the production chain/environment.

These results are fully comparable to those obtained with light obscuration techniques, in terms of subvisible particle release trends over time, and they also show that the majority of particles are silicone oil droplets [See blue bar in Figures 8-10]. It is clear that Alba® has lower subvisible particle release in solution than the silicone oil product, and this is mainly ascribable to the coating, since the main difference between the two syringes is the silicone oil particle count.

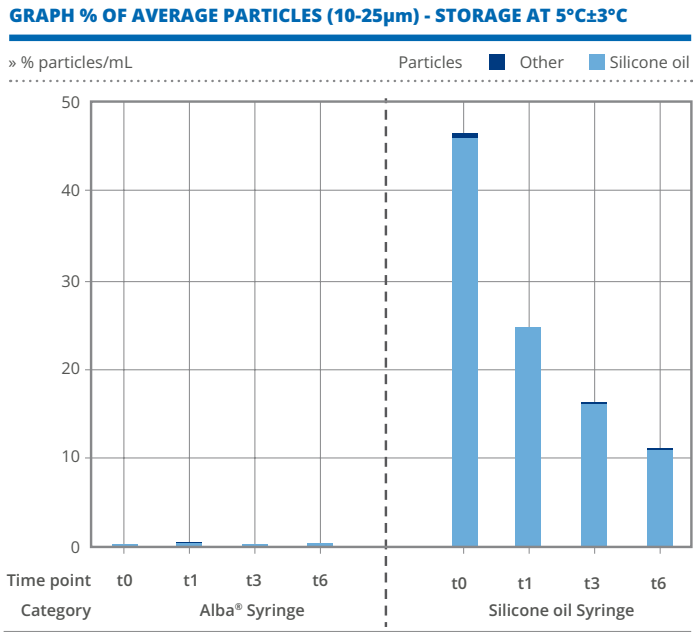

Figure 8: Results of particle concentration (10 – 25 µm) at 5±3°C (real time stability) over six months

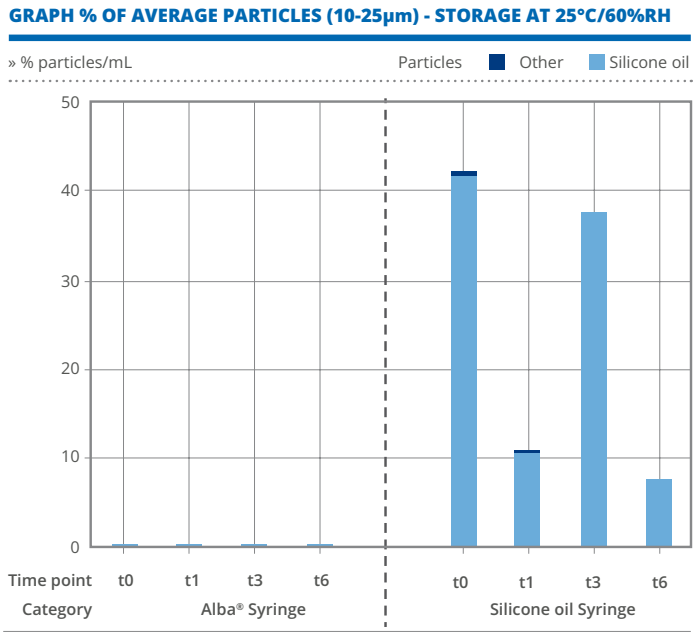

Figure 9: Results of particle concentration (10 - 25µm) at 25°C/60% RH (accelerated stability) over six months

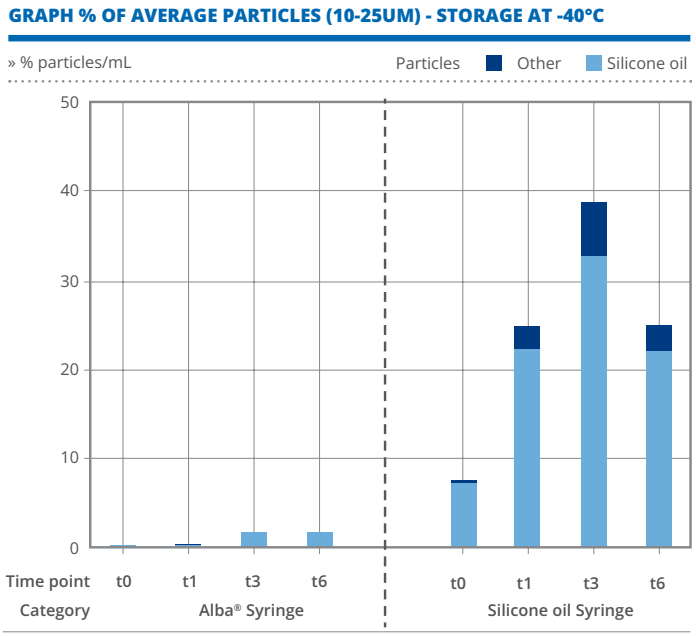

Figure 10: Results of particle concentration (10 – 25 µm) at -40°C over six months

Extrusion testing with placebo solution

In all storage conditions, Alba® syringes showed a slightly higher break-loose force (i.e., the force needed to move the plunger from its starting position) due to the increased stability of the coating enabled by the plasma treatment process [See Figures 11-16]. Break-loose force also increased over time for both products, due to the effect of the storage conditions on the rubber plunger. Break-loose force decreased after storage at -40°C for all samples due to thaw-induced plunger displacement.

Critically, extrusion force was significantly more stable over time for Alba® syringes treated with the innovative coating compared to the silicone oil syringe.

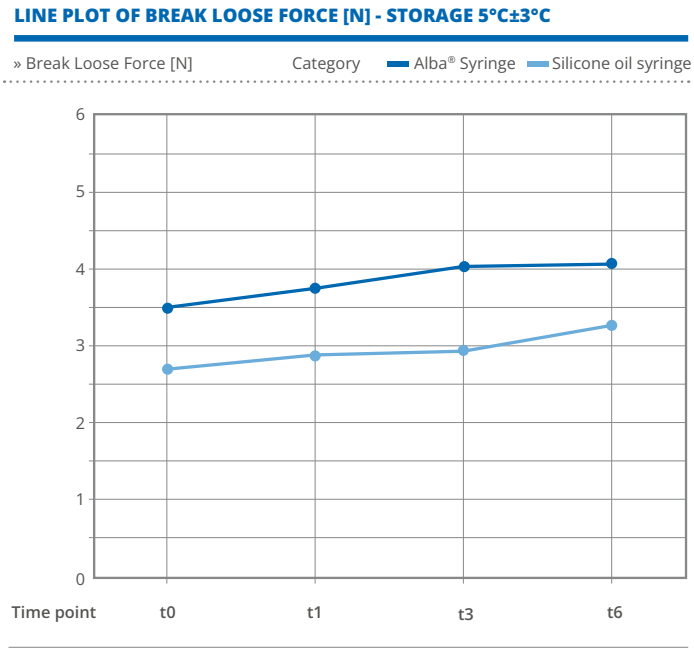

Figure 11: Results of Break loose force [N] at 5±3°C (real time stability) over six months
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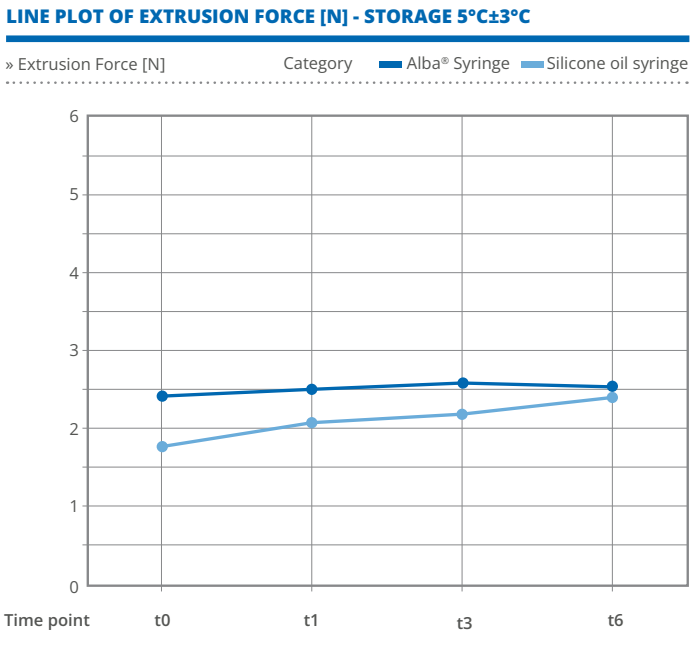

Figure 12: Results of Extrusion force [N] at 5±3°C (real time stability) over six months
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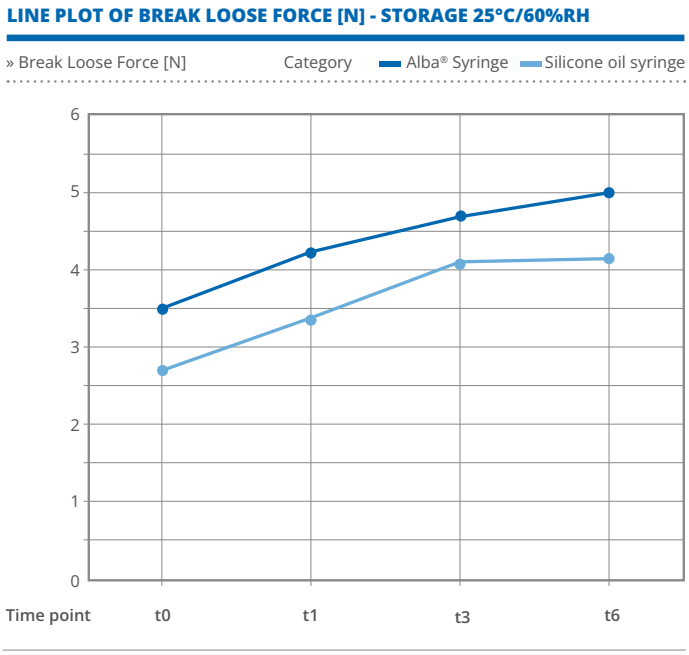

Figure 13: Results of Break loose force [N] at 25°C/60% RH (accelerated stability) over six months
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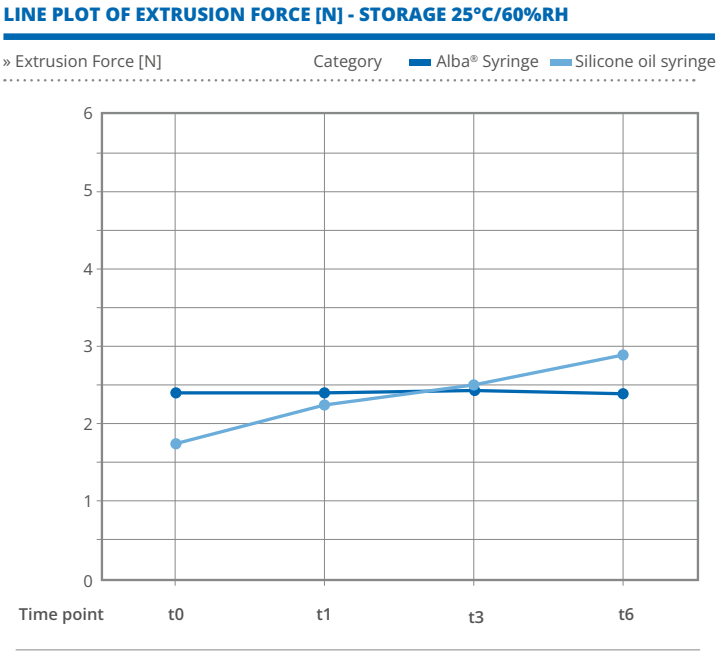

Figure 14: Results of Extrusion force [N] at 25°C/60% RH (accelerated stability) over six months
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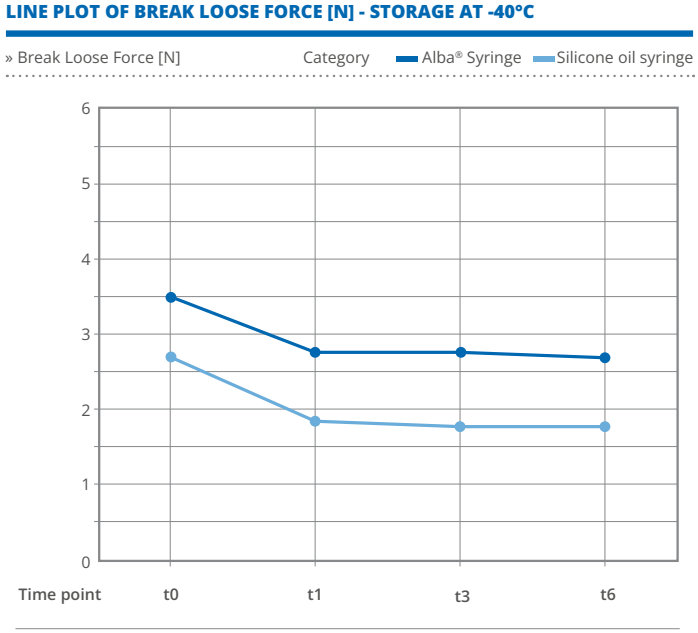

Figure 15: Results of Break loose force [N] at -40°C over six months
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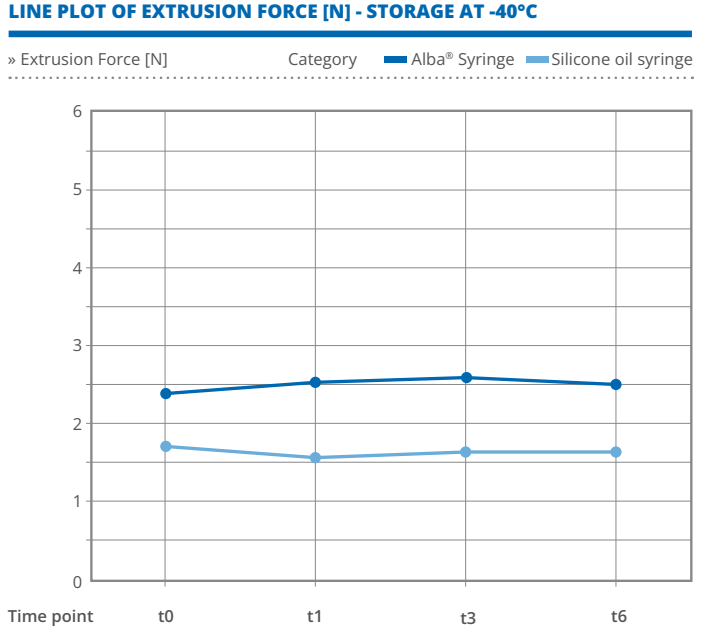

Figure 16: Results of Extrusion force [N] at -40°C over six months
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* Alba® syringe's data at the 12-month time point are consistent with the findings from the preceding checkpoint.

Summary of testing results

This comparison of the performance of a silicone oil syringe with Alba® product confirms both the superiority of Alba®'s innovative coating technology and its higher stability over time.

This unique coating is the source of the product's added value. Thanks to the siliconization technique, the final coating is less prone to variation in terms of thickness and distribution over time, as shown in white light interferometry and laser interferometry output. The coating is also less likely to release silicone oil droplets in solution – as seen in the SbVP release data – even after contact with a placebo solution for several months. Stable extrusion force data over time and also at different storage temperatures suggest that the coating is highly resistant, even when the container is exposed to harsh conditions (which is very common for specific drug products).

Overview

• Overall, the results confirmed the superiority of Alba® over traditional silicone oil syringes.
• There was no variation in silicone thickness in the Alba® syringe after six months of storage.
• The integrity of the silicone lubricant layer, which withstands challenging formulations and aggressive conditions, optimized extrusion force performance. This makes it more reliable for patient use and for safe dose delivery, especially when integrated in auto-injectors.
• Subvisible particles were significantly lower with Alba® syringes compared to a silicone oil syringe. Their release was also more stable over time. This consistency supports compliance with quality and regulatory expectations for biotech products.
• Alba® inner coating did not undergo critical variations after contact with the placebo solution. This helps to maintain optimal usability from patient perspective.

The standard for new-generation therapies

A transformative advancement in the biopharmaceutical field, Alba®'s long-lasting stability minimizes silicone degradation and ensures consistent syringe performance over time. The coating achieves comparable subvisible particle release results to silicone-free syringes, even meeting the strictest USP requirements for ophthalmic preparations, making it a superior packaging solution for sensitive molecules such as biologics.

Overall, testing results show the applicability of Alba® technology to different areas of the pharmaceutical world. It is suitable for highly sensitive drug products, thanks to low particle release and low extrusion force during both manual injections and auto-injections. It is also suitable for the large range of products stored at low temperatures, such as vaccines and mRNA-based products, thanks to the technology's outstanding performance in terms of extrusion force and particles release at deep freeze temperatures.

An ideal solution for the pharmaceutical industry, Alba® technology creates a robust barrier between drug and glass, significantly reducing drug-container stability issues while adhering to injection time specifications, thereby helping to reduce commercialization delays, regulatory issues, customer complaints, and product recalls, ultimately saving costs and expediting the delivery of novel treatments to patients.

Authors

Enrico Barichello

Product Manager, Syringe Platform – DCS Glass, Stevanato Group

With a background in Industrial Engineering and a Master's in Management at the University of Padua, Enrico Barichello acquired broad-spectrum skills in technical concepts and complex processes.

He joined Stevanato Group in 2017 as a Product Management Specialist for the Syringe platform.

He defined and coordinated all the activities required to bring the products to market, bridging gaps between different company functions and aligning the involved teams.

He has been responsible for the roadmap and execution of the innovative platform Alba®.

Since 2023 he is Product Manager for the Glass Syringe Platform.

Chiara Callegari

Research Laboratory Analyst at EMEA Tecnology Excellence Center, Stevanato Group

Chiara acquired a strong scientific background in pharmaceutical chemistry and gained in-depth knowledge of drug interaction, and patient care during her Master Degree in Chemistry and Pharmaceutical Technologies at the University of Padua, Italy.

She joined Stevanato Group in 2019 focusing on Pre Fillable Syringes and the characterization of the subvisible particles release in solution as a result of their interaction with drug formulations and surfaces.

Since 2023, Chiara has been appointed as Subject Matter Expert for the analytical development of Alba® platform.

About Stevanato Group

Founded in 1949, Stevanato Group is a leading global provider of drug containment, drug delivery and diagnostic solutions to the pharmaceutical, biotechnology and life sciences industries. The Group delivers an integrated, end-to-end portfolio of products, processes and services that address customer needs across the entire drug lifecycle at each of the development, clinical and commercial stages. Stevanato Group's core capabilities in scientific research and development, its commitment to technical innovation and its engineering excellence are central to its ability to offer value-added solutions to clients.

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Headquarters
Via Molinella, 17
35017 Piombino Dese
Padova, Italy

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