Prefillable Syringes

Critical Features for Ophthalmological Applications

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Prefilled syringes (PFS) have proven themselves very well as a primary packaging and at the same time as a medical device allowing safe administration of drugs for ophthalmo-logical applications, such as cataract surgery and treatment of pathological blood vessel growth in the inner eye. The market for antineovascular agents for ophthalmology has grown steadily over the years, making PFS increasingly popular. This article provides an overview of critical features for PFS for ophthal-mological application and discusses the safety and functionality of silicone-free PFS that could certainly be considered as an alternative for siliconized PFS for ophthalmological injections already existing on the market.

Drugs for ophthalmical applications

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Drugs for ophthalmological applications
Alongside many primary packaging components, Gerresheimer manufactures prefillable syringes. After filling, a prefillable syringe becomes a prefilled syringe (PFS). For oph-thalmological applications, the syringes are frequently filled with drugs to treat different eye diseases. There are 2 major eye therapy areas: cataract surgery, performed in the anterior eye segment, and treatment of pathological blood vessel growth in the inner eye. During cataract surgery, viscoelastics (table 1) such as hyaluronic acid are injected with a syringe into the anterior chamber and lens cavities of the eye. On the one hand this ensures that the anterior chamber of the eye remains stable, on the other hand the substances help to enhance the visibility of ophthalmic tissues (fig. 1a). Injection of re-combinant monoclonal antibodies (mAbs) – antivascular endothelial growth factor (an-ti-VEGF) proteins (table 1) into the inner eye prevents the growth of pathological blood vessels. This relatively novel therapy option enables non-surgical treatment of such diseases as wet macular degeneration, diabetic macular edema, and retinal vein occlusion (fig. 1b).

There are two large eye therapy areas: cataract surgery, performed in the anterior eye segment and treatment of the pathological blood vessel growth in the inner eye.

Table 1

Examples of drugs for ophthalmic applications.

	Active Pharmaceutical Ingredient (API)	Commercial Name	Ophthalmic Indication	Principle of Action
Anterior Eye and Lens Injection	sodium hyaluronate	Healon [1]	Cataract extraction, intra-ocular lens (IOL) implantation, corneal transplant, glaucoma filtration and retinal attachment surgery	Ensures the stability of the anterior eye chamber, enhances visibility of the ophthalmic tissue and preserves corneal endothelium and other surrounding tissues during surgery
	sodium chondroitin sulfate and sodium hyaluronate	Viscoat [2]	Cataract extraction IOL implantation	
	sodium hyaluronate	Provisc [3]	Cataract extraction IOL implantation	
Vitreous body injection	Ranibizumab	Lucentis [4]	Neovascular (wet) age-related macular degeneration (wAMD), macular edema following retinal vein occlusion (RVO), diabetic macular edema (DME), diabetic retinopathy (DR) myopic choroidal neovascularization (mCNV)	Anti-VEFG agents. Prevention of pathological vessel growth by inhibition of cognate VEGF receptors activation.
	Aflibercept	Eylea [5]	wAMD, RVO, DME, DR	
	Brolucizumab	Beovu [6]	RVO, DME	
	Pegaptanib	Macugen [7]	wAMD	

Cataract surgery

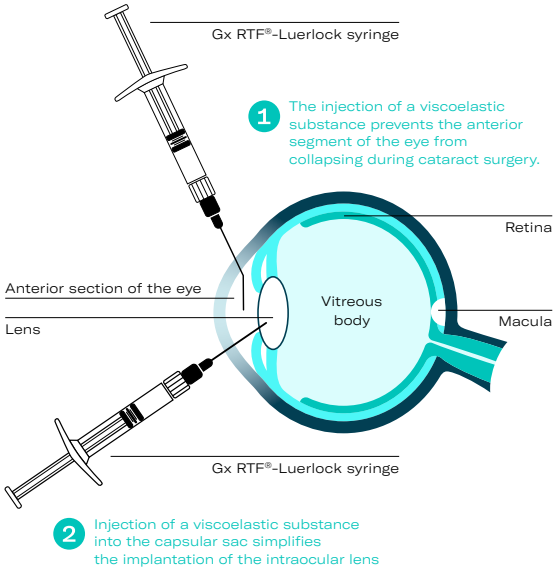


Figure 1a

Injection into the anterior section of the eye.

Injection into the vitreous body

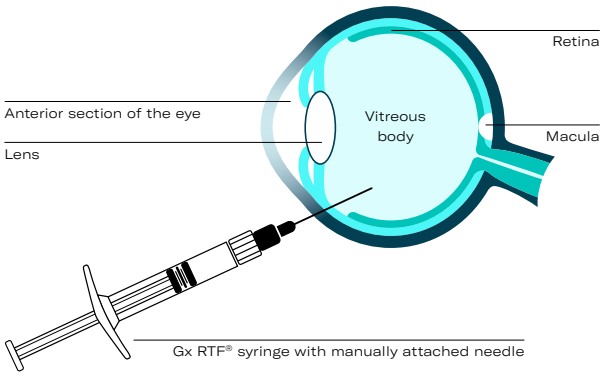


Figure 1b

Injection into the vitreous body

Market for ophthalmological drugs

During recent years, the market for anti-neovascularization agents for phthalmological applications has grown steadily, while the market for surgical aids has stayed the same or even declined. This reflects well the aging population, the growing number of indications for anti-VEGF therapy and repeated application of the products (fig. 2). And although the development of anti-VEGF products will progress toward prolongation of their therapeutical effect, to reduce the number of intravitreal injections, their growth tendency is expected to continue.

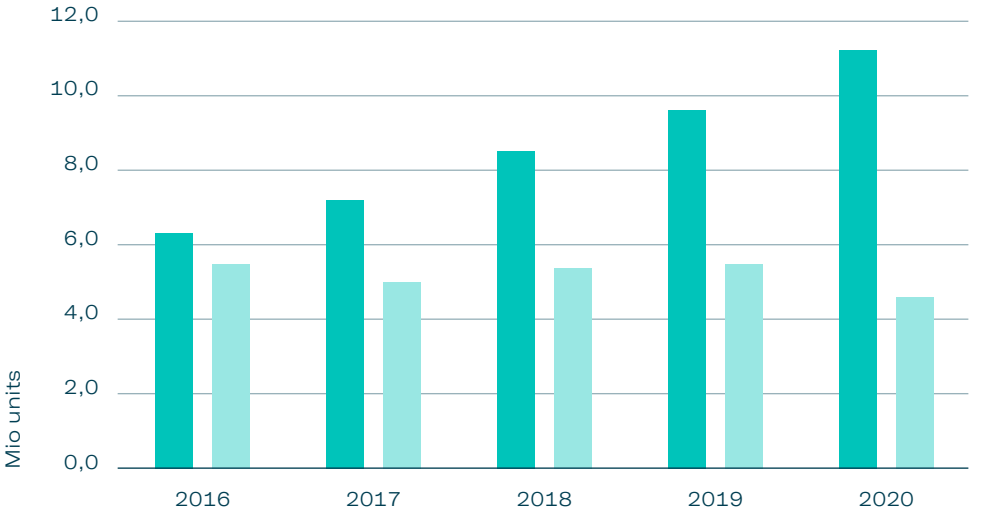


Figure 2

Markets of ophthalmological aids: antineovascularisation products vs medicaments for surgical application, million units sold in 2016-2020 (IQVIA).

Advantages of PFS over repackaging systems

There are different scenarios of preparing anti-VEGF drugs for intravitreal injection:

- The drug can be stored in a vial and then subsequently transferred into syringe for injection by
  - the physician
  - or repackaged by 503A pharmacies that prepare compounds n accordance with patient-specific prescriptions for home use only, or by 503B outsourcing facilities producing large batches with or without prescriptions to be sold for office use only.1) Both pharmacies repack the drug into a polypropylene or polycarbonate transfer syringe, which is siliconized or lubricated with oleamide.
- Alternatively, the anti-VEGF drug can be stored in a PFS that is used directly for the ophthalmic injection. This can be a glass syringe with bakedon silicone (BOS). Newly developed silicone-free glass or Cyclo-Olefin-Polymer (COP) syringes must be further tested for ophthalmological applications.

The advantage of using a PFS over vial-and-syringe combinations is that it eliminates a number of preparation steps and minimizes dose error, as PFS already contains the drug in the required injection volume of the right concentration (fig. 3).

This advantage is reflected by the increasing sales of anti-VEGF products packed in PFS over the last 4 years in comparison to vial-packed products (fig. 4).

Apart from that, it was shown by S.M. Dounce et al. [8] that glass PFS with BOS and silicone-free COP syringes both show a lower particle level than syringes commonly used for repack-aging.

Preparation for ophthalmical injection

Using vial and PP syringe

1	Prepare: sterile filter needle (19-gauge x 1-1/2 inch), sterile Luer lock syringe (with appropriate marking), sterile injection needle (30-31-gauge x 1/2-inch)
2	Disinfect the outer part of the rubber stopper of the vial
3	Place a filter needle onto a Luer lock syringe used for ophthalmological injection using aseptic technique
4	Push the filter needle into the center of the vial stopper until the needle touches the bottom edge of the vial
5	Withdraw all the liquid from the vial, keeping the vial in an upright position, slightly inclined to ease complete withdrawal
6	Draw the plunger back sufficiently to be able completely empty the filter needle
7	Discard the filter needle
8	– Attach a sterile injection needle firmly onto the syringe by screwing it tightly onto the Luer lock. – Carefully remove the needle cap by pulling it straight off.
9	Hold the syringe with the needle pointing up. Gently tap the syringe with your finger if there are any bubbles until they rise to the top.
10	Carefully push the plunger rod until the plunger tip is aligned with the dose mark on the syringe.

Using PFS

1	Using aseptic technique, remove syringe from package tray.
2	Remove syringe cap.
3	Attach a 30-31G x ½ inch sterile injection needle firmly onto the syringe by screwing it tightly onto the Luer lock.
4	Carefully remove the needle cap.
5	If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top
6	Carefully push the plunger rod until the edge below the dome of the rubber stopper is aligned with a dose mark.

Figure 3

The steps that are required for ophthalmological injection preparation using vials and syringe combination vs using PFS. This advantage is reflected by the increasing sales of anti-VEGF products packed in PFS over the last 4 years in comparison to the vial-packed products (Fig.5).

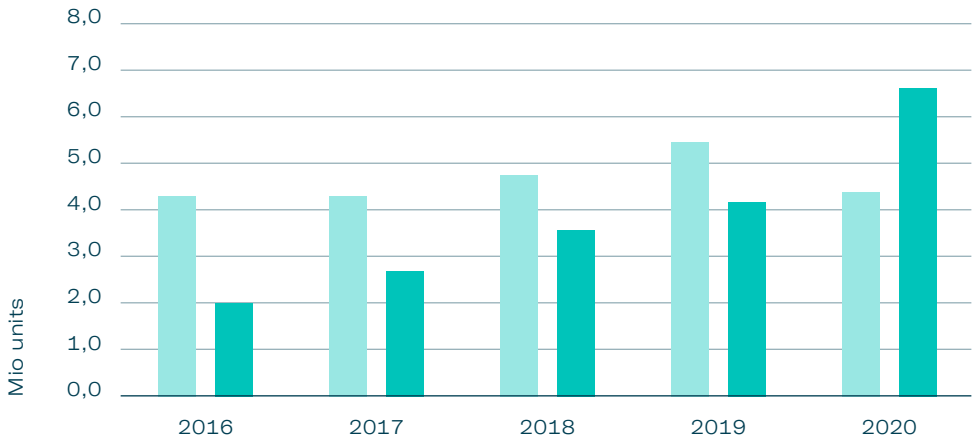


Figure 4

Sales of ophthalmological drugs in vials vs in PFS million units sold in 2016-2020 (IQVIA).

Critical features of ophthalmological syringes

Syringes that are used for ophthalmological injections must comply with the following requirements: They must be able to deliver the low volumes of drugs precisely and reproducibly, have good functionality and low particles load as well as be compatible with the intended drug formulation (fig. 5). Here is a review of all these features in more details.

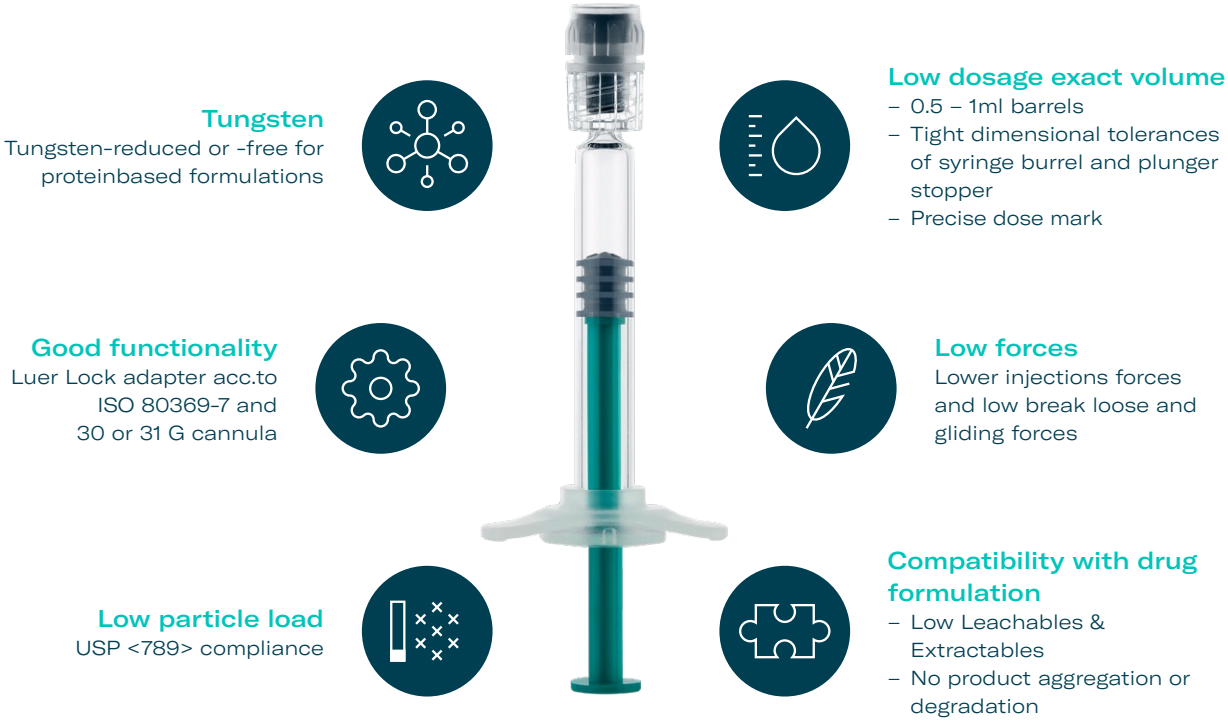


Figure 5

Critical features of ophthalmological syringes.

Low dosage, exact volume

Exact volumes must be repeatedly introduced during ongoing ophthalmological treatment. This is critical for the efficacy of an administrated drug and for patient safety. Many drugs for ophthalmological applications have a high viscosity and are injected in low volumes, most commonly 50–100 µl. For the correct administration of such volumes the best suited are 0.5 and 1 ml PFS with a rather small internal diameter that allows good injectability, tight dimensional tolerances and very precise graduation to measure the administered dose.

Dimensional tolerances and accurate dose marks or graduation printing is usually controlled during the manufacturing processes. At Gerresheimer, the dimensions and accuracy of printing (distance from the syringe tip to the

dose mark) is checked by a proprietary camera system, ensuring 100 % control. The tolerances for the internal diameter of PFS made of glass can be set to ±0.05 or ±0.1 mm and the best automated printing process usually results in a dose mark position tolerance of ±0.25 mm. Additional variation of ±0.5 mm usually comes from the shoulder shape. Considering all the parameters, this results in a worst-case variation in expelled volumes of ±22.4 µl [9]. Basically, this variability is lower for 0.5 ml PFS and even lower for COP syringes which have much tighter tolerances of the dimensional parameters due to the peculiarities of their manufacturing process based on molding.

It should be noted that plunger stopper design as well as the naked eye and thumb also add variability to the dose accuracy for intraocular injection. Therefore, the use of a dosing device, for example Congruence MDS, can be recommended [10].

Biotechnological drugs used for anti-VEGF therapy are usually very expensive, so the residual volume in the PFS which comprises the hold-up volume of the cannula, conus and shoulder is of additional importance and must be optimized to avoid undesired wastage of the drug. The use of special cannulas with low dead volume (LDV) is also recommended (fig. 6).

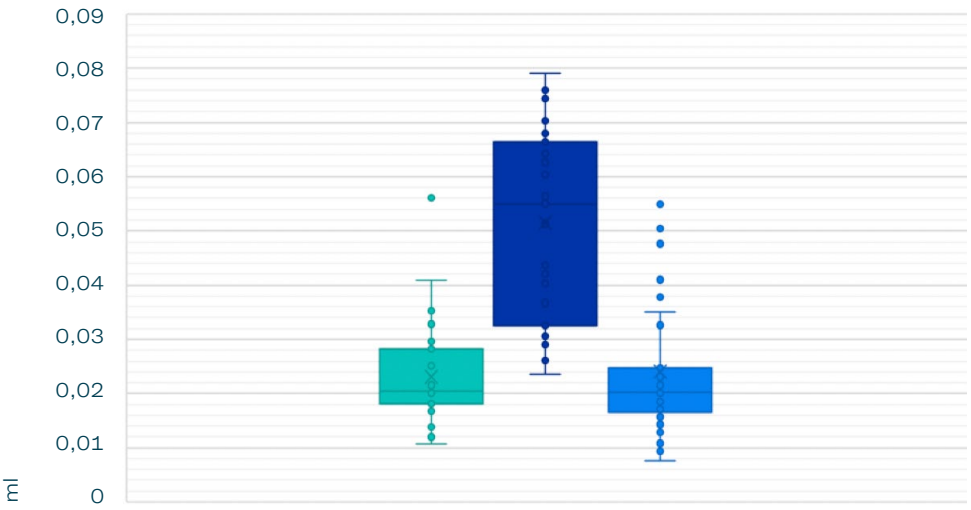


Figure 6

Comparison of residual volumes for 1 ml long TWILC glass syringe without or with 30 G regular or 30 G low dead volume (LDV) cannula.

Low particles load – USP <789> compliance

Although silicone oil is harmless to the human body, the repeated nature of intravitreal injections for the treatment of neovascular retinal diseases and the fact that the vitreous body is a small, confined space can raise the risk of such therapy complications as floating particles, endophthalmitis and high intraocular pressure [1114]. Moreover, not only silicone but also other particles detaching from the syringe body, rubber or secondary particles resulting from the interaction of the internal syringe surface with a drug, silicone, or other particles can also contribute to such safety risks.

Therefore, the PFS intended for ophthalmological application must comply with USP <789> which defines the particulate requirements for ophthalmological products. However, it should be considered that USP <789> specifies particle loads for drug/device combination products, so the particle count for the device alone should be lower.

In the study of Dounce S.M. et al, 2021 it was shown that both glass syringes with baked-on silicone and silicone-free COP syringes have significantly lower particles levels in comparison with insulin and oleamide-lubricated plastic transfer syringes [8]. The latest syringes have the particles levels (of 1–100 µm size) significantly exceeding USP <789> requirements.

In this set of experiments, the purpose was to check other silicone-free systems comprising a glass silicone-free syringe and 3 different kinds of plunger stoppers having a special design and coating to be used with silicone-free barrels (further indicated as plunger 1, 2 or 3) [15]. 2 of them have polytetrafluoroethylene (PTFE)-based coatings (plunger 1 and 2) but different rubber formulations and manufacturing processes and one is made of thermoplastic elastomers (TPE) without additional coating. The glass silicone-free system was compared with the silicone-free COP system with the same set of plungers (plungers 1, 2, 3) and glass syringes with BOS and modern coated plungers.

The syringes were filled with water for injection (WFI) and stoppered using laboratory equipment. The subvisible particles were measured according to USP <789> after 3 months of real time storage (T1) using the light obscuration method, see fig. 7, fig. 8, fig. 9. [15].

It is obvious that the particle count for silicone-free syringes is exceptionally low. There was no statistical difference determined, either between glass and COP barrels or between 3 different variants of plunger stoppers. Moreover, BOS syringes show particle loads comparable to the silicone-free option, suggesting that both are well suited for ophthalmological applications. Both silicone-free and BOS PFS comply well with USP <789> requirements, having additional buffers for particles derived from a drug.

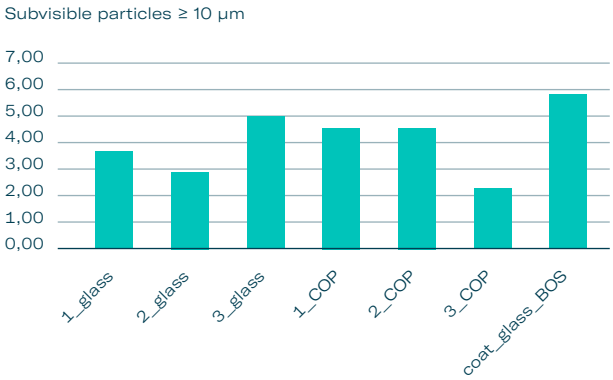


Figure 7

Number of subvisible particles ≥10 µm / 1 ml.
USP <789> requirements for drug/device combination products: max 50 µm / 1 ml.

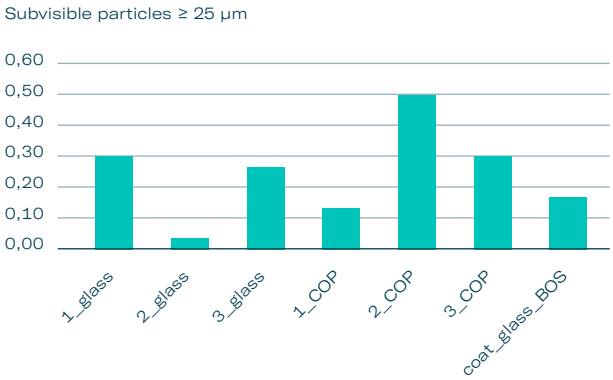


Figure 8

Number of subvisible particles ≥ 25 µm / 1 ml.
USP <789> requirements for drug/device combination products: max 5 µm/ml.

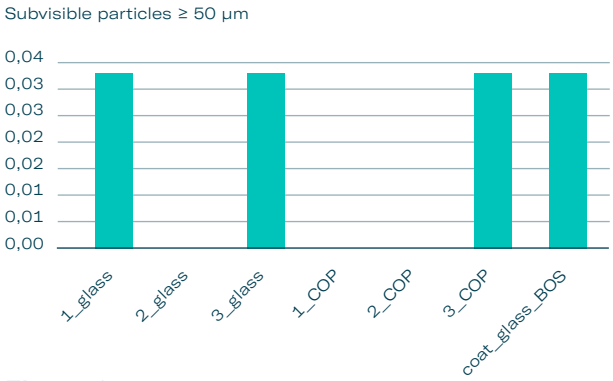


Figure 9

Number of subvisible particles ≥50 µm / 1 ml.
USP <789> requirements for drug/device combination products: max 2/ml.

Exceptionally good functionality

Although the performance of intravitreal drug administration is one of the most common procedures nowadays [16], in order to minimize the pain during the procedure and undesirable side effects, the injection itself requires well-qualified specialists on the one hand, and very good syringe functionality, leading to acceptable injection forces, on the other. Especially these factors become critical in the case of some drug formulations, most often proteinbased, being highly viscous.

The most significant performance factors in lowering injection forces are internal needle diameter and the syringe barrel itself. The use of syringe needles is more or less defined in ophthalmological practice and is limited to the use of 30 G and 31 G needles [17], which guarantee a less painful procedure for the patient. Thin-wall and micro-tapered needles are modifications that have also been shown to reduce the injection forces and make the intravitreal injection more comfortable for the patient [18]. To reduce the risk of the needle detaching and to allow the use of special ophthalmological fine needles, the use of Luer lock syringes compliant to ISO 80367–7 is mandatory.

If the ophthalmological syringe barrel is chosen, the minimal possible barrel diameter must be selected, which leaves a choice between 0.5 ml or 1 ml long syringes. On the one hand, good lubrication of the interior surface syringe barrel ensures a good break-loose and gliding force (BGLF) profile. On the other hand, silicone could be a problem in view of its interaction with a formulation and possible side effects.

In order to check the functionality of silicone-free glass and COP PFS described above, their BGLF profiles at different time points were examined: T0–3 days after stoppering; T1–3 months RT realtime aging; T1acc–3 months accelerated aging 40 °C/75 % r.F. (=1 year), T2–6 months RT realtime aging; T2acc–3 months accelerated aging 40 °C/75 % RH (=3 years).

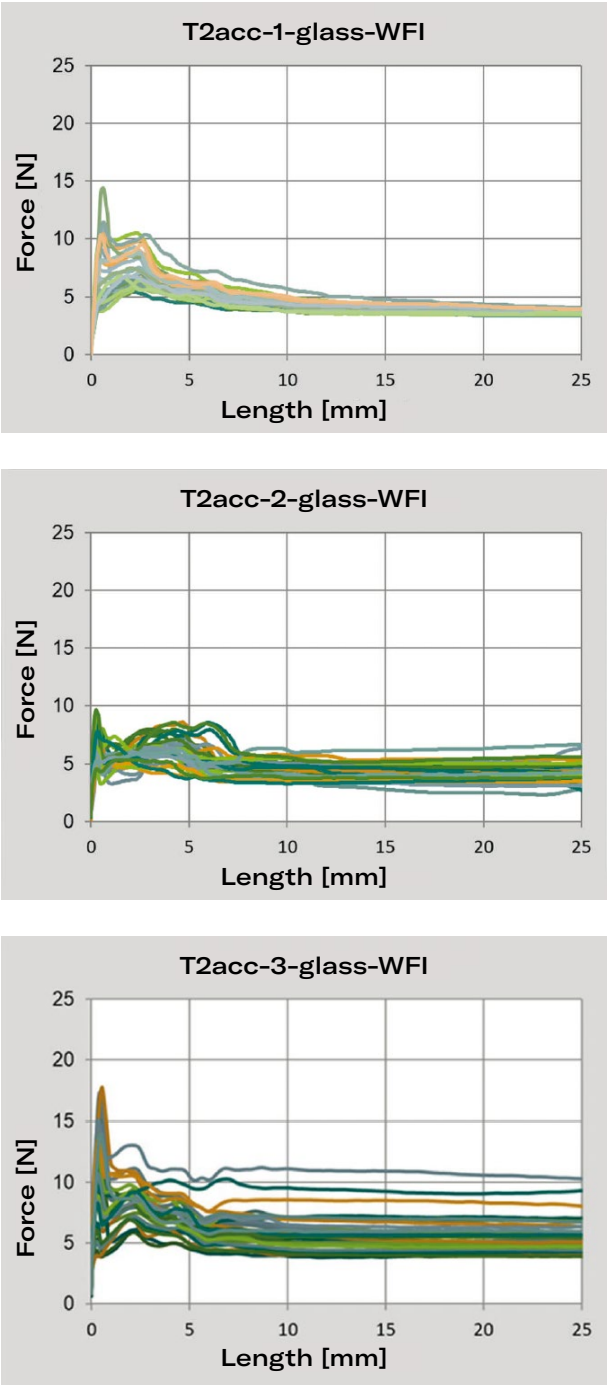


Figure 10

Break-loose and gliding forces profile for silicone free glass and COP syringes with stoppers 1,2, 3 after 3 months of accelerated storage 40°C/75 %r.F. (=3 year of real time storage).

Both glass and COP siliconefree syringes showed BLGF lower than 20 N after 3 months of accelerated aging (fig. 10, here data is only shown for glass syringes). The values and reproducibility of the results were better for plunger stopper 1. For plunger stopper 2 the results for COP barrels are not promising, because the gliding forces increased over the length of the barrel which could mean that the plungers do not fit well in the COP barrels (data not shown).

For all 3 stoppers, the variation in values seen in the first 5 mm of the syringe barrels could be explained by the transition from a dry to wet surface during this phase. The wetted surface helps the plunger stopper to glide and ensures good gliding forces. It is possible that adjustment of the stoppering process can additionally help in improving the breakloose values.

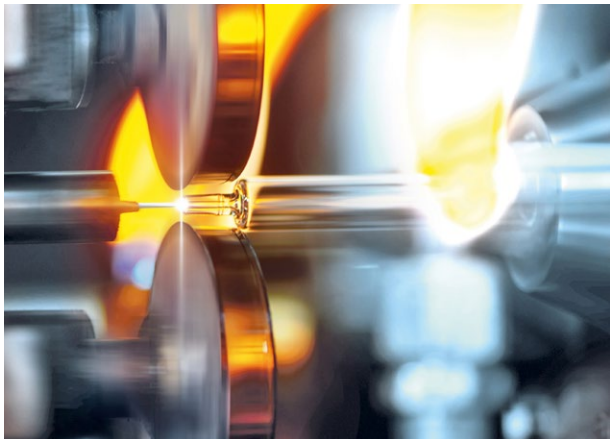
There was no aging effect or even a positive aging effect on gliding forces observed for all syringes and plunger modifications (data not shown).

All-in-all these results show that silicone-free syringes, after additional system adjustments (such as the right choice of plunger stoppers and improvement of the stoppering process) can be a viable alternative to BOS syringes in ophthalmology. Both glass and COP options can certainly be considered as having acceptable functionality and very low particle load even after long-term storage. However, it is unquestionable that such systems should be rigorously tested with a final product.

Reduced or tungsten-free

For most of the glass syringes, a tungsten pin is used during barrel forming to achieve a bore hole.Tungsten, as a trace element, is a matter of concern in PFS mainly in conjunction with protein formulations. It has been shown that tungsten-mediated unfolding and aggregation of the protein can be a cause of increased immunogenicity, although this is more likely to occur for subcutaneous administration of protein [19].

Anti-VEGF products that are broadly used in ophthalmology represent monoclonal antibodies that are proteins per se, so the tungsten issue must be accurately investigated for the PFS used in anti-VEGF storage and administration.



Different regulatory documents and methodological recommendations clearly state the following requirements for such PFS:

- The use of tungsten-reduced or ideally metal-free syringes for protein-based formulations

- Additional investigation of sensitivity of protein formulation against tungsten when syringes containing tungsten are used.

There are diverse ways to reduce or eliminate tungsten. It has been demonstrated that introduction of washing steps after standard barrel forming reduces the amount of residual tungsten significantly. Alternatively, the use of other material for the pin, e.g. ceramic pins or COP syringes (that are produced by injection molding without a tungsten pin) should be considered.

Summary

PFS have shown their advantages over the vial plus transfer syringe approach for ophthalmological applications, especially for ongoing treatment of pathological blood vessel growth in the inner eye. The specificity of the intraocular administration procedure and the nature of drugs used for the treatment of macular disease coincides with the critical features of PFS recommended for ophthalmic applications: dosing accuracy, good functionality, low particle load and drug compatibility. Silicone-free or BOS glass Luer lock syringes with low tungsten or without tungsten can in this case serve as a good platform for ophthalmological drugs.

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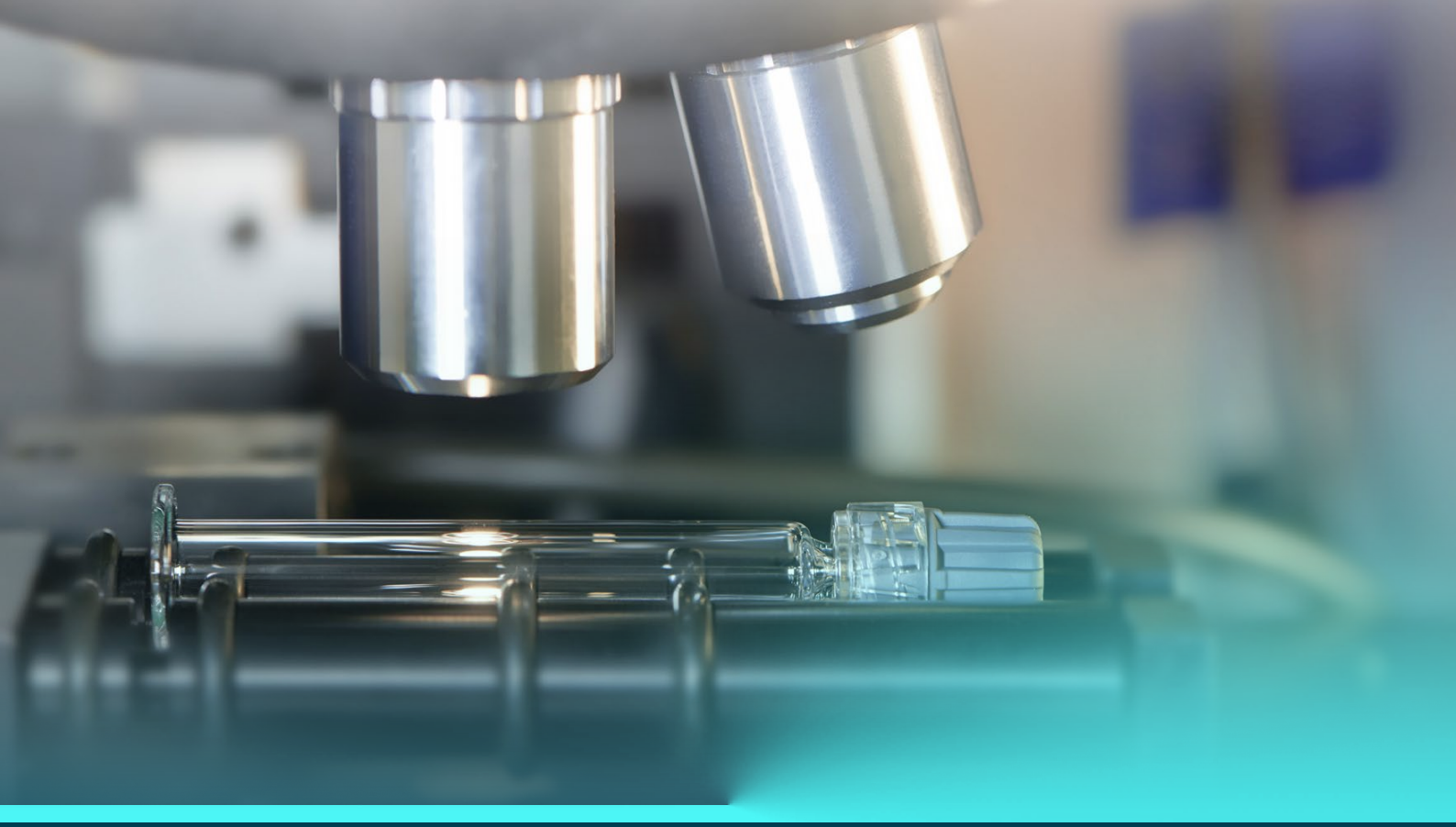

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