USING PREFILLABLE SYRINGES FOR BIOPHARMACEUTICALS – DEVELOPMENT & CHALLENGES

In this piece, William Dierick, Senior Manager, Technology Development, Terumo Europe, and Keisuke Yoshino, PhD, Vice-President, Drug & Device Group, Terumo Corporation, describe the development of Terumo's PLAJEX™ prefillable syringe system, which combines specific features of a COP syringe with the proprietary i-coating™ technology to create a silicone oil-free system. The authors also review a series of studies demonstrating that PLAJEX™ overcomes the range of difficulties and challenges associated with designing a suitable primary drug container and parenteral delivery system for biotech products.

INTRODUCTION

The progress of genetic engineering has spurred a shift in pharmaceutical development from low-molecular drugs towards biopharmaceuticals. Looking at the top ten drug sales ranking in the world, biotherapeutics, such as Humira (adalimumab), Remicade (infliximab) and Rituxan (rituximab), have progressed substantially, in contrast to low-molecular blockbusters like Lipitor (atorvastatin calcium) or Plavix (clopidogrel), which mainly constitute the market in the last decade.[1] At the same time, the patent cliff of several biotherapeutics and thus the loss of exclusivity (LOE) is propelling the development of biosimilars and biobetters.

Many biotech drug products are lyophilised in vials due to their poor stability for parenteral administration. However, the development of liquid formulations of biotech products applying prefilled syringes has been increasing rapidly, driven also by enhanced safety in use, user convenience and ease of administration. Another important aspect is the shift from hospital treatment to homecare and patient self-injection for many chronic diseases and specific therapeutic areas.

This article addresses a technology approach to developing a prefillable syringe system as an appropriate parenteral drug container for biopharmaceuticals.

APPLICATION OF PREFILLABLE SYRINGES IN BIOPHARMACEUTICALS: ISSUES & PROVISIONS

Prefillable syringe systems have to meet various requirements and functionalities, for instance container closure integrity, heat resistance, shock resistance, plunger gliding

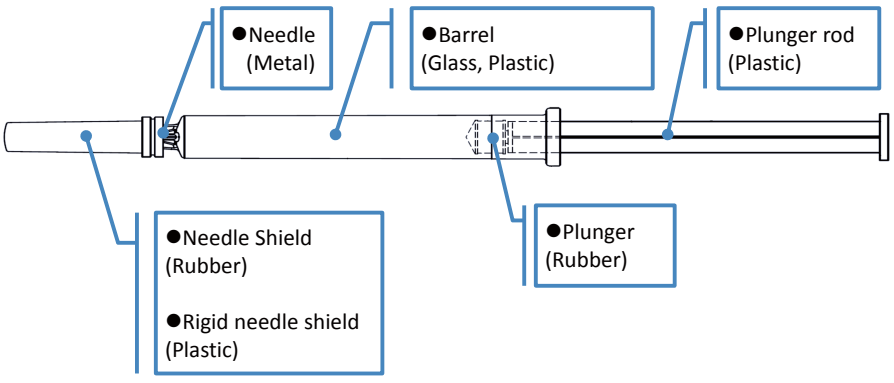

Figure 1: The components of a standard prefillable syringe.

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forces, waste disposal and so on. Prefillable syringes consist of various components and materials such as glass, polymers and elastomers, which have to be selected appropriately to ensure they meet the requirements for their intended use (Figure 1).

In developing prefillable syringe systems, various optimisations are considered, such as product design, contact surface treatment and materials to satisfy quality requirements for injection. Biotherapeutics are often sensitive and not so stable thus, for example, causing aggregation and being subject to oxidation. Several publications have reported specific quality issues with biomolecules in prefillable syringe systems. Aggregation of therapeutic proteins is one of the most critical risk factors since it may impact negatively on efficacy and safety due to the protein deactivation and immune responses in patients. For example, it has been reported that inducement of neutralised antibody of epoetin-alpha makes endogenous erythropoietin less active, resulting in an increased incidence of antibody-mediated pure red cell aplasia (PRCA).[2,3] The US FDA recently published a guidance for industry entitled "Immunogenicity Assessment for Therapeutic Protein Products" recommending minimising any aggregation risks.[4]

"PLAJEX™, in conjunction with the smooth i-coating™ layer on the plunger stopper surface, has demonstrably achieved secure closure integrity"

Quality and safety issues can be very diverse and may be material related, or related to the biomolecule itself. A non-exhaustive overview is listed in Table 1.

An important issue is silicone oil-induced aggregation. Silicone oil has been used as lubrication to achieve smooth plunger gliding functionality. However, in the context of biomolecules, silicone oil became a serious issue because it can induce protein aggregation.[5-7] Furthermore, the prefillable syringe manufacturing process is considered a potential risk factor. For instance, tungsten pins are used for the glass barrel tip-forming process. Protein aggregation in the presence of tungsten has been observed.[11-14]

Historically, prefillable syringes were developed for small-molecule drugs so that many potential quality issues appeared only when introducing therapeutic proteins into prefillable syringe systems. In taking a risk-management approach, on basis of the issues shown in Table 1, it is suggested that three main attributes should be considered for a prefillable syringe system for use with biopharmaceuticals:

(1) Silicone oil-free system
(2) Polymer-based syringes
(3) Concepts to prevent protein oxidation.

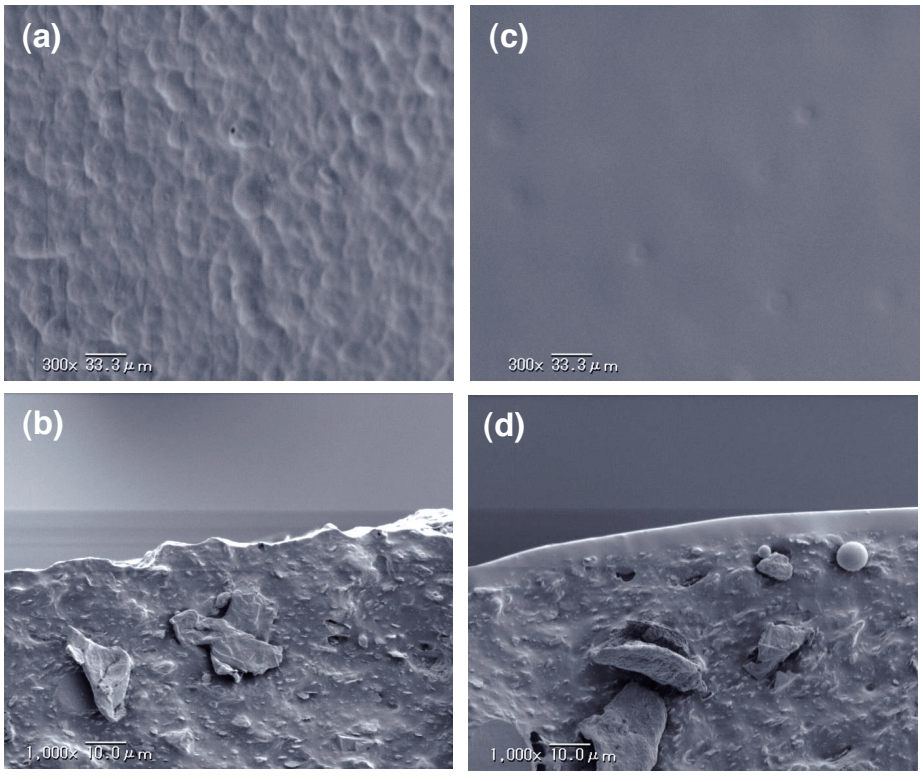

Figure 2: SEM micrographs of surface and cross-section of the plunger stoppers. (a) top surface of an uncoated plunger stopper (x300), (b) cross-section of an uncoated plunger stopper (x1000), (c) top surface of an i-coating™ coated plunger stopper (x300), and (d) cross-section of an i-coating™ coated plunger stopper (x1000).

DEVELOPMENT OF A NEW PREFILLABLE SYRINGE

Silicone oil-free system

Various publications are reporting on protein aggregation as discussed above as well as on sub-visible particles and the interactions thereof.[15-18] Therefore, the need for the development of a silicone oil-free prefillable syringe system has been established [18-22] and such quality issues became a trigger for Terumo to develop a silicone oil-free prefillable syringe system based on a plunger stopper combined with a specific coating technology. Terumo launched MINOFIT, its first silicone oil-free polymer-based prefilled syringes system in 2005.

On that basis, Terumo continued its development towards a proprietary commercial-scale process, in 2012 resulting in a coating method to form a strong, flexible and uniform layer of silicone resin through a chemical process including polymerisation of the layer, called i-coating™. Scanning electron microscope (SEM) images before and after the i-coating™ treatment are shown in Figure 2. Compared

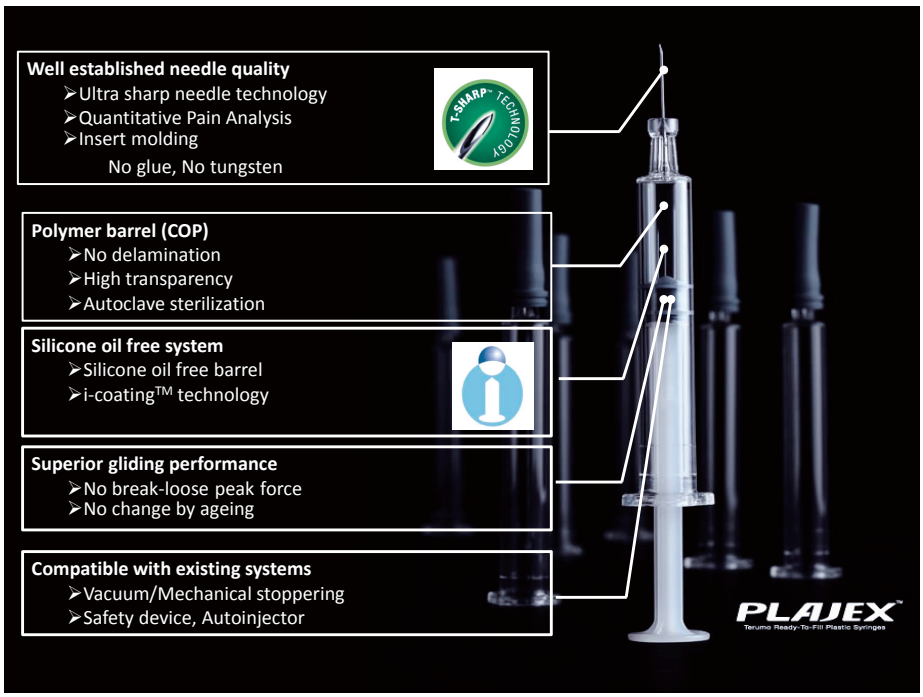

Figure 3: The components of a PLAJEX™ plastic prefillable syringe.

Phenomenon	Causing factor	Related material
Physical	Aggregation by silicone oil	Independent of material
	Aggregation by tungsten	Glass
	Interaction with glue	Dependent on manufacture
	Excessive shaking	Independent of material
Chemical	Alkali elution	Glass
	Gas permeability	Polymer
	Residual radicals	Dependent on sterilisation
Other	Container breakage	Glass
	Delamination	Glass
	Scratching of container surface	Polymer
	Silicone oil droplets	Independent of material

Table 1: Quality issues with biopharmaceuticals.[5-16]

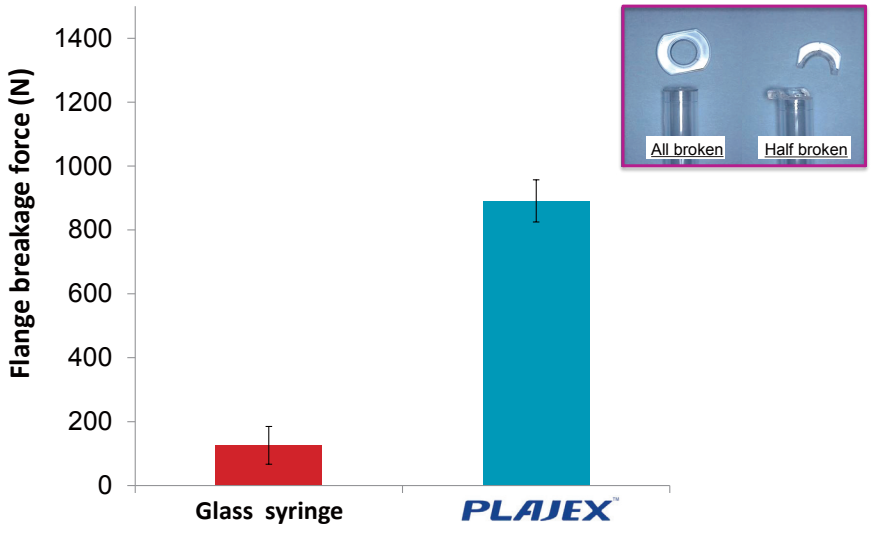

Figure 4: Flange breakage force (all flange) measured by universal tensile tester at a stroke rate of 50 mm/min. The value represents the mean ± SD (n=10).

with uncoated plunger stoppers (Figure 2a and b), i-coating™ plunger stoppers, as shown in Figure 2c and 2d, provide a uniform and smooth surface layer.

Fourier transform infrared spectroscopy (FTIR) and X-ray photoelectron spectroscopy (XPS) analyses demonstrate that the surface layer material of the i-coating™ plunger stopper was identified as a silicone resin with high purity. The resulting dynamic friction force from an i-coating™ rubber sheet was about ten times lower than the same uncoated rubber, with a value similar to polytetrafluoroethylene (PTFE) sheet (data not shown). These findings have been discussed in a published article.[20]

Polymer-Based Syringes

Glass containers have been used extensively and have been substantive for the development of parenteral drugs. However, with the availability of biopharmaceuticals and the emergence of biosimilars, several aspects related to glass material are still to be resolved (Table 1).

Furthermore, considering high-value biotech products, product loss from container breakage during manufacturing and transportation becomes an issue which cannot be ignored.[23]

With a specific focus on biopharmaceuticals, Terumo has developed a polymer-based prefillable syringe (PLAJEX™) as an alternative to glass prefillable syringes to resolve problems like protein aggregation or breakage. PLAJEX™ is made of cyclo-olefin polymer (COP), having outstanding properties such as impact resistance, superior moisture-barrier, heat resistance and excellent transparency. Moreover, to eliminate the risks of protein aggregation due to interactions with the tungsten and glue, the needle is inserted directly into the barrel by insert moulding. And combined with our proprietary i-coating™ technology, PLAJEX™ provides for a silicone oil-free syringe system. In addition, Terumo adopted autoclave sterilisation for PLAJEX™ to avoid the risk of protein oxidation from radicals that form on the polymer barrel material from sterilisation by irradiation. PLAJEX™ therefore benefits from this integrated approach, having a high transparency, superior strength, and smooth and controllable plunger gliding properties, as well as minimising the risks of protein aggregation and protein oxidation. These features are summarized in Figure 3, and discussed further hereafter.

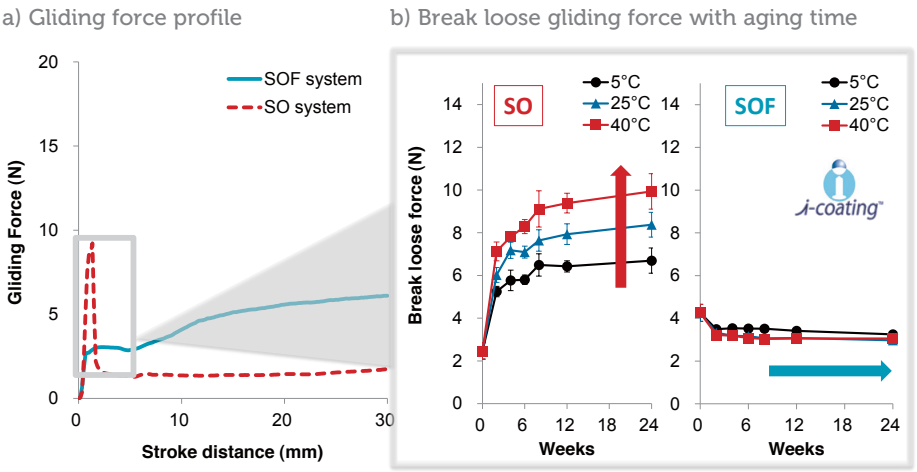

Figure 5: (a) Glide force profile of silicone oil system (SO) and silicone oil-free system (SOF) stored for 12 weeks at 40°C. The data was obtained at a stroke of 200 mm/min. Glide forces were measured with a universal tensile meter. (b) Break-loose glide force change with aging time and temperature of SO and SOF system. Break-loose glide force is the maximum glide force between 0 and 5 mm of stroke distance. Data are presented as mean ± standard deviation (n = 5).

Mechanical Strength

A comparison of mechanical strength of the flanges of PLAJEX™ with glass syringes, measured with a universal testing machine, is shown in Figure 4, demonstrating that the flange of PLAJEX™ is nine-times stronger than that of a typical glass syringe. This is an important aspect in the context of use with auto-injector applications, in terms of functionality as well as for the detection by the user of particles or breakage inside the auto-injector.

Plunger Gliding Properties

As discussed earlier, an important feature of PLAJEX™ with Terumo's i-coating™ technology is that it is a silicone oil-free system. Figure 5a shows the comparison of gliding properties between traditional silicone oil-coated systems and PLAJEX™. In the case of the silicone oil systems, the silicone oil layer between barrel and plunger stopper may vary over time resulting in variations in initial gliding force (break-loose force), increasing over time by aging. Figure 5b, on the other hand, shows the silicone oil free system and no change is observed following aging and at various temperature conditions. The surface layer of the i-coating™-treated plunger stopper is not silicone oil but silicone resin that is bonded directly to the stopper material. The absence of break-loose peaks is very beneficial for applications with auto-injectors for consistent and trouble-free functionality.

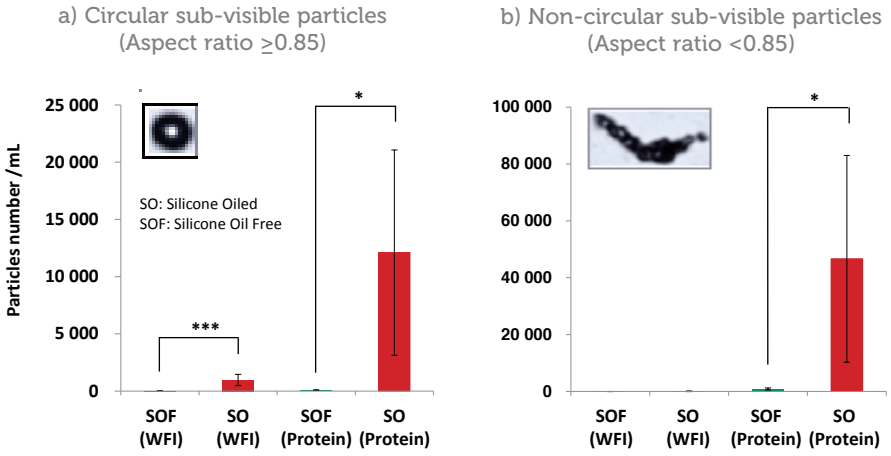

Figure 6: Comparison study between silicone oil system (SO) and silicone oil-free system (SOF) in terms of sub-visible particles using MFI analysis. (a) ECD ≥5µm, aspect ratio is more than 0.85, (b) ECD ≥5µm, aspect ratio is less than 0.85. Data are presented as mean ± standard deviation (n = 10 for water, n = 5 for samples). *: p<0.05, ***: p <0.001.

Protein Aggregation

A comparative study on protein aggregation from silicone oil interactions has been conducted. In this study, L-asparaginase is used as a protein model because of its susceptibility to aggregation from interaction with silicone oil. After the protein solution and water for injection (WFI) were filled into both silicone oil and silicone oil-free systems, each syringe was shaken gently. Protein aggregation and sub-visible particles were analysed by Micro Flow Imaging (MFI). Figure 6a shows the quantification of circular sub-visible particles representative for silicone oil and Figure 6b shows the quantification of non-circular sub-visible particles representative to protein aggregation. In the case of WFI, the number of circular sub-visible particles increased in the silicone oil system. On the other hand, this phenomenon was not observed with the silicone oil-free system, suggesting that in the silicone oil system, silicone oil from the syringe barrel wall had migrated into the WFI and formed silicone oil droplets.

With syringes filled with protein solution, a high number of circular and non-circular sub-visible particles were detected in the silicone oil system. In contrast, this was not observed in the silicone oil-free system. On the basis of these results, it can be concluded that the silicone oil-free system (the PLAJEX™ syringe incorporating Terumo's i-coating™ technology) can offer a solution for minimising both protein aggregation and sub-visible particles.

EVALUATION OF CONTAINER AND CLOSURE INTEGRITY

Even at the stage of the prefilled syringe design development, it is of utmost importance to ensure the container closure integrity in order to prevent leakage, microbial ingress and drug product quality deterioration. PLAJEX™, in conjunction with the smooth i-coating™ layer on the plunger stopper surface, has demonstrably achieved secure closure integrity, including in high-pressure leakage testing and microbial assessment testing.[20]

As an example, Figure 7 shows the results of micro-organism penetration assessment. Tryptic soy broth (TSB) culture medium was filled into PLAJEX™ syringes by aseptic manipulation and then immersed into a bacterial broth for a predetermined

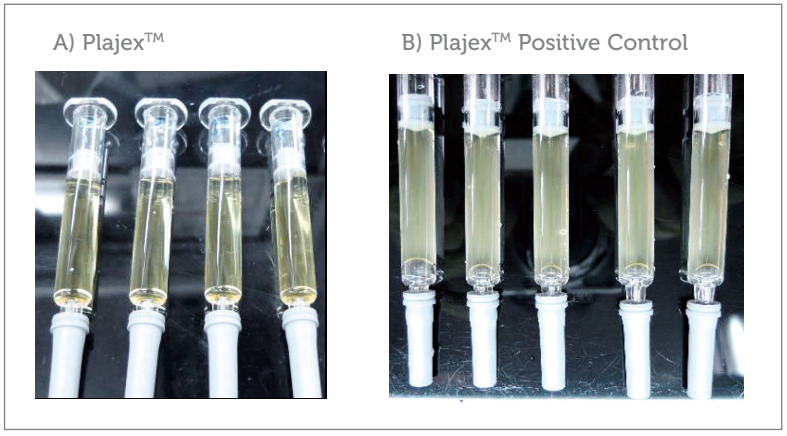

Figure 7: Micro-organism penetration study. (a) The silicone oil-free (SOF) system showing all four investigated syringes. The inner solution remained clear without any visual change. (b) Positive control (the SOF syringes with a pinhole on the barrel) of all five investigated syringes. The inner solution became considerably turbid by the invasion and growth of micro-organisms.

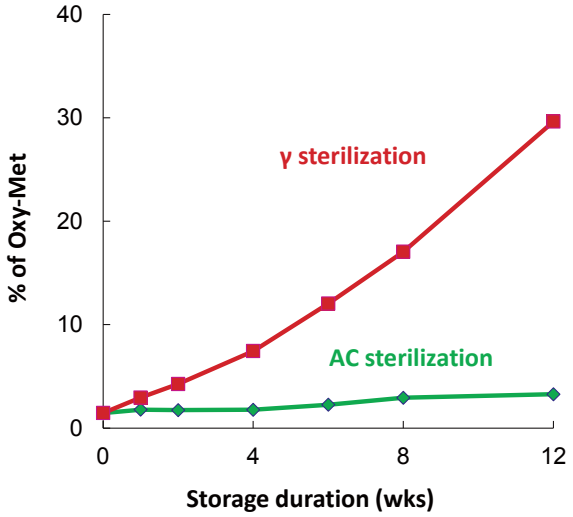

Figure 8: Profile of % oxidisation of model drug during storage at 25°C. The measurement was performed by HPLC. The value represented the mean ± SD (n=3).

time. After that, the samples were incubated at 31 ±1 °C for 14 days. PLAJEX™ demonstrated no particular changes in appearance and the culture medium inside the syringes remained clear (Figure 7a). In contrast, positive control samples showed a considerable change in that the medium became turbid (see Figure 7b).

CONCEPTS TO PREVENT PROTEIN OXIDATION

So far, we have explained on our technologies to minimize the risk of protein aggregation, minimizing sub-visible particles and other quality aspects such as container breakage. Hereafter we will address also on our applied technologies to minimize the risk of protein oxidation.

INFLUENCE OF STERILISATION METHOD

Terminal steam sterilisation is applied to prefilled syringes containing small-molecule drug products. However, since biotherapeutics are subject to denaturation by heat, aseptic filling into presterilised prefillable syringes is the norm. A consideration of the method of sterilisation and its potential impact on the drug product is of paramount importance. Figure 8 compares the degree of oxidisation of methionine during storage for gamma-sterilised polymer prefilled syringes with that in steam-sterilised PLAJEX™ products.

Polymer-based prefillable syringes that are gamma-sterilised, and steam-sterilised syringes, respectively were filled with erythropoietin (EPO) aqueous solution. As noted in Figure 8, prefillable syringes sterilised by gamma irradiation showed a higher degree of methionine oxidation over time. For PLAJEX™ prefillable syringes sterilised by autoclaving, methionine oxidation was not induced. Though more detailed mechanistic studies of this phenomenon are underway, we assume that radicals generated by gamma sterilisation remained inside a prefillable syringe, causing the oxidation of biopharmaceuticals.[18, 24, 25] Further studies are ongoing and planned to be published. On the basis of these results, we believe that steam sterilisation is more appropriate for polymer-based prefillable syringes for biopharmaceuticals.

PREVENTING OXIDISATION

Glass syringes, having low gas permeability, are often considered as superior to polymer-based syringes with respect to the avoidance of drug product oxidisation. Generally, for sensitive protein applications, nitrogen control and nitrogen blanketing is necessary in all processes such as drug solution preparation, filling and stoppering, to eliminate any risk of dissolved oxygen entering the filled glass syringe.

However, utilising the specific permeability characteristics of PLAJEX™, it is feasible to eliminate dissolved oxygen with a more simple and innovative method. This method consists of using an oxygen absorber inside the secondary packaging along with the filled PLAJEX™. This resulting effect is as depicted in Figure 9b.

Using oxygen absorber materials with PLAJEX™ means the concentration of dissolved oxygen decreases rapidly just after packaging and continues to decrease gradual-

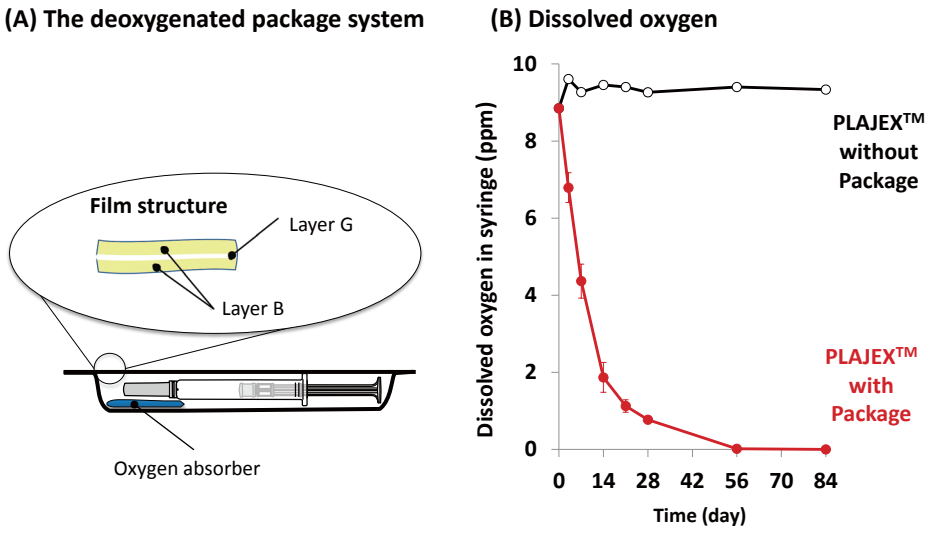

Figure 9: (a) The combination of PLAJEX™ with the deoxygenated packaging system. (b) Reduction profile of dissolved oxygen in water-filled prefilled syringes. Dissolved oxygen was measured by OXY-4 (PreSens). The value represented the mean ± SD (n=3).

ly. After eight weeks, the concentration of dissolved oxygen was close to zero. This result shows that the combination of PLAJEX™, the deoxygenated package system and oxygen absorber can prevent protein oxidisation.[24]

CONCLUSION

This article introduced specific features and functionalities of Terumo's polymer based prefillable syringe system, PLAJEX™. This system was developed by combining inherent features of a COP syringe with our proprietary i-coating™ technology to realise a silicone oil-free syringe system. Several quality issues can be addressed for applications with sensitive biopharmaceuticals. In addition, polymer-based prefillable systems offer the benefits of consistent and high dimensional reproducibility and precise processing, and allow for flexibility in design to make customised versions of design specific syringes.

The global biopharma market is still growing apace due to the increasing prevalence of chronic diseases, an aging population and thanks to advancements in biomedical science creating more effective drugs. With the development of PLAJEX™ with i-coating™ technology, Terumo aims to ensure that biopharmaceuticals can be administered safely, reliably and uncontaminated, avoiding errors in medical practice while minimising patient trauma and discomfort.

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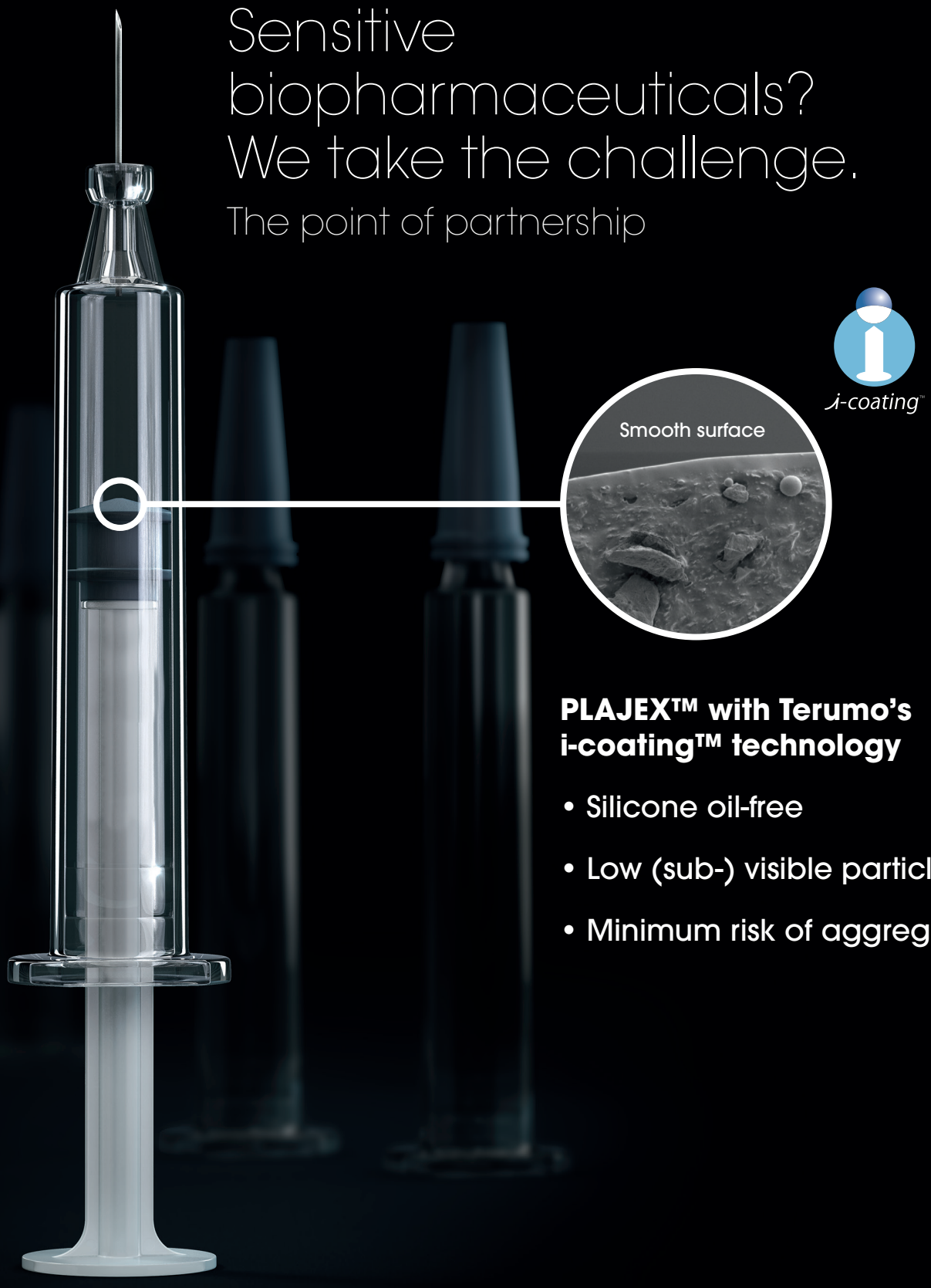

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