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Prefilled Syringes

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INTRODUCTION
LEVERAGING NEEDS-CHARACTERISATION TO FUEL SMARTER DESIGN

By Mark Tunkel and Craig Scherer

In today's increasingly competitive pharmaceutical marketplace, combination product speed to market is no doubt uppermost in the thoughts of biologics manufacturers. However, today's market dynamic begs for a more strategic approach to innovation based on the sheer number of available options for pharma industry developers to choose from. Companies that make patient needs-characterisation the launching point for development efforts will quickly discover this approach can be vital to navigating these development decisions successfully, and driving patient adoption and healthcare provider prescription rates.

> "Companies that make patient needs-characterisation the launching point for development efforts will quickly discover this approach can be vital to navigating these development decisions successfully, and driving patient adoption and healthcare provider prescription rates"

QUESTIONS OF SPEED & ACCURACY

Being the first to hit the ground running in delivery device development doesn't ensure success. Making development decisions based on timeline alone may get a product to market faster but deliver a sub-par user experience with low adoption. At the same time, layering in too much technology and complexity to compete with competitor product features alone may actually make it more difficult for users to stay on regimen.

At its core, needs-characterisation is designed to help companies strategically define device development plans with the best chance for market success. Beyond the drug, needs-characterisation gives pharmaceutical companies a broader context for not only patient device use and lifestyle, but also that of caregivers and healthcare professionals – all of which contribute to the success or failure of an injectable device.

Needs-characterisation primarily leverages ethnographic research (Figure 1), a qualitative method in which in-context observations are supported by in-depth interviews with both patients and relevant healthcare professional stakeholders such as physicians or nurse educators as part of due diligence to help define the requirements of a device. The deeper level of patient understanding that needs-characterisation offers helps developers understand and define where it is appropriate to integrate technology such as data management and, equally importantly, where it is not (Figure 2). By virtue of its focus and timing, it can lead to demonstrably differentiated devices that are not only safe and effective, but also capable of simplifying what is difficult for patients to manage, destigmatising a disease state, and helping navigate feature trade-offs that drive key patient population demand.

Perhaps the most substantial risk today in delivery device development is not giving equal weight to needs-characterisation from a user perspective as the weight given to a drug, primary packaging, regulatory, or a technical perspective for the sake of making it first to market.

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Figure 1: Applied ethnography to evaluate lifestyle influences impacting medication administration.

Figure 2: In-context research to understand the influence of technology on medication administration and larger health management issues.

CURRENT TRENDS FUELLING THE MARKET

There's certainly no shortage of challenges today for pharmaceutical manufacturers. Current trends driving accelerated competition include the sheer volume of biologics expected in the market, evolving perceptions among payers and physicians surrounding combination product efficacy, and the consumerisation of healthcare driving new expectations.

Let's consider the value of leveraging needs-characterisation in response to just a few of these market dynamics in play today:

THE PROLIFERATION OF BIOLOGICS

While growth forecasts vary, there's no question that biologics will at least double their share of the drug market by 2020. Given the promise this drug category holds for myriad treatment indications across disease states, this market trajectory is expected to continue well into the future.

Multiple disease states often represent unique patient attributes and drug delivery challenges. By virtue of their multi-indication nature, the proliferation of biologics also signals the need for a more strategic approach to delivery systems development with user needs-characterisation at its core.

Take for instance a biologic indicated for multiple disease states. Patient needs across each of these distinct disease states might necessitate entirely different proprietary delivery systems to serve each patient group effectively, given their unique physical capabilities and limitations (Figure 3). Conversely, closely examined user needs might dictate the development of a single device that accommodates both patient populations. Decision-making challenges in either instance are further compounded by the large number of commercially available devices from auto-injectors to patch-pumps that claim to work across an array of different parameters.

Of course, companies equipped to develop their own custom delivery devices must also factor in patient complexity when making their selections from the same vast array of delivery options – beyond overcoming the inherent challenges of large molecule drug delivery. In every scenario, a developer must also consider the follow-on biosimilars for these biologics that will also require delivery systems. This final consideration poses unique challenges for incumbent manufacturers, as interchangeability applies to the drug alone – not delivery systems as with other combination products.

THE CONSUMERISATION OF HEALTHCARE

The trend towards large tech manufacturers entering the healthcare space is having substantial influence on consumer expectations for technology's role in helping them manage things beyond a therapy regimen. With both Apple and Samsung now in the market with their Health Kit and Gear Fit consumer health devices and apps, pharmaceutical companies are also tasked with delivering user interfaces and experiences on a par with what people expect from the large tech companies. Needs-characterisation can serve as a launching point for developers to identify meaningful ways to leverage current trends in the consumer space strategically – from the "gameification" of healthcare that utilises incentive-based regimen adherence, to the personalisation of mobile phone health applications – and migrate them to drug delivery.

PHYSICIAN AND PAYER PERCEPTION

Perception is truly reality in matters of therapy decision-making among physicians and healthcare payers. With more than one biologic therapy available for individual disease states, physicians are far less inclined to prescribe those they've received direct or indirect negative patient feedback to. Cumbersome regimens and overly complex feature sets are likely to deter treatment adherence and contribute to unfavourable physician perception and lower prescription rates. Lack of patient

> "Across physician and payer audiences, an injectable product's fate in the market is increasingly based directly on user needs, and the delivery device's efficacy in meeting those needs – both real and perceived"

Figure 3: Observing the impact of physical and cognitive challenges and the limitations for certain disease states.

Figure 4: Examining the impact of patient environment on adherence and disease-state management through patient interviews and observations.

therapy adherence represents a substantial business risk, as an individual patient's treatment regimen can cost tens of thousands of dollars. For payers it's critically important that an injectable delivery device not only performs but also drives patient adherence (Figure 4), thus delivery systems that integrate technology in an effective way toward this end are viewed increasingly favourably.

While direct patient feedback is one source fuelling physician and payer perception, lack of awareness is another. Proactive physician and payer education by drug delivery manufacturers that supports the performance and efficacy claims of new therapies not yet widely adopted is paramount to competing. Across physician and payer audiences, an injectable product's fate in the market is increasingly based directly on user needs, and the delivery device's efficacy in meeting those needs – both real and perceived.

NEEDS-CHARACTERISATION SUCCESSES

Prime examples of effectively leveraging needs-characterisation at the offset of a device development programme come from the start-up world. Both Sanofi's Auvi-Q, an auto-injector for epinephrine, which talks the user through the injection process, and Insulet's advanced miniature insulin pump, OmniPod, demonstrate how a clear understanding of user needs and tailoring the features of a therapy device to serve targeted patient groups can drive market success.

Epinephrine pens were widespread in the market with the same form factor dominated by the same pharmaceutical players for years. The developers of the Auvi-Q epinephrine delivery system – twins Evan and Eric Edwards, were inspired by their own personal experience surrounding epipen usage, and the critical situation that could ensue if one of them were to go into anaphylactic shock in the presence of those that have never administered epinephrine. In response to this critical need, their company developed a portable delivery system the size of a credit card that provides audio feedback to guide epinephrine novices effectively through the process of drug delivery.

Similarly, having experienced the limitations that insulin delivery regimens represent to the highly active segment of the diabetes population first-hand, the developer of OmniPod delivered a paradigm-changing delivery alternative. The system's subcutaneous patch delivery allows patients to manage their insulin therapy through a personal digital assistant (PDA) at a pre-set dosage and delivery rate without worry or involved attendance in effect to eliminate lifestyle interruptions inherent to traditional regimens. By recognising the lifestyle needs of this patient group and understanding the limitations that traditional insulin pumps and injectors imposed on them, the company was well positioned to respond directly with an adherence-driving solution.

Each of these market successes were primarily driven by the key user insights of each developer, underscoring the tremendous value of needs-characterisation in strategic device development.

Making applied ethnography primary to a development program can serve as the baseline for understanding user needs and context that can be synthesised with technology, establish clear options for device delivery and derivations of options, translate those options to functional requirements for robust, producible devices, and ultimately create a roadmap for innovation across entire device portfolios positioned for market success.

Mark Tunkel is a Partner and Director of Business Development at Insight Product Development. With more than 20 years of global business development experience and a deep understanding of the marketplace challenges and trends impacting the pharmaceutical industry, Mark has advised many of the world's leading companies on their product development and innovation strategies with an emphasis on driving realisation and the most favorable business outcomes. Mark holds a BA in Political Science from Indiana University.

Craig Scherer is Senior Partner and Co-Founder of Insight Product Development. Since 1988, he has helped Insight grow into a leading design firm that serves companies globally in a variety of health care spaces. He plays an active role in project management, working with start-ups to the Fortune 50, and has been central to the company's innovations for clients, which have garnered numerous industry accolades. Craig holds a BFA in industrial design from the University of Illinois at Urbana-Champaign, and an MBA from the University of Illinois at Chicago.

Insight Product Development is a design innovation consultancy in Chicago that leverages more than 25 years of professional insights to create strategy that's actionable, technology that's scalable, and design and development that translates into marketable success for its clients in the pharmaceutcial delivery device space.

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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

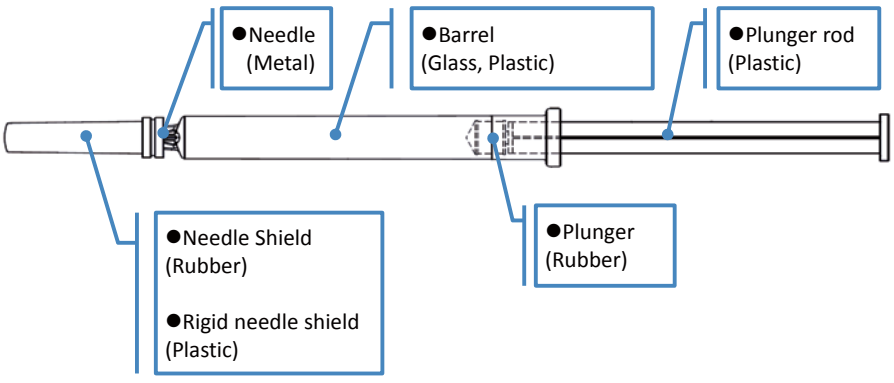

Figure 1: The components of a standard prefillable syringe.

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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.

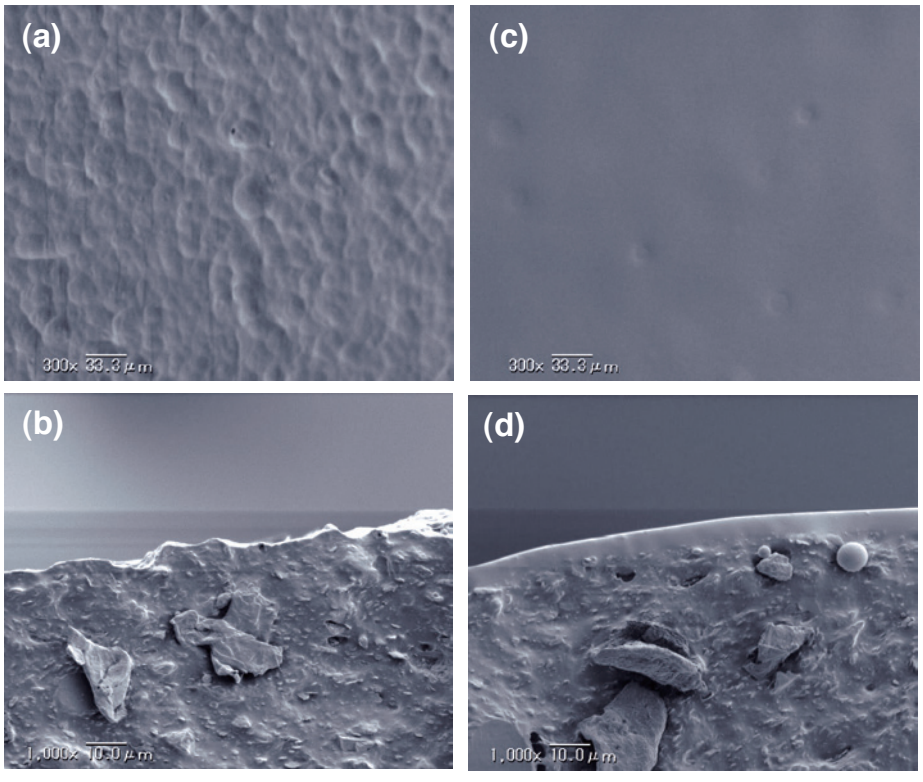

Figure 2: SEM micrographs of surface and cross-section of the plunger stoppers. (a) top surface of an uncoated plunger stopper (x300), (b) cross-section of an uncoated plunger stopper (x1000), (c) top surface of an i-coating™ coated plunger stopper (x300), and (d) cross-section of an i-coating™ coated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

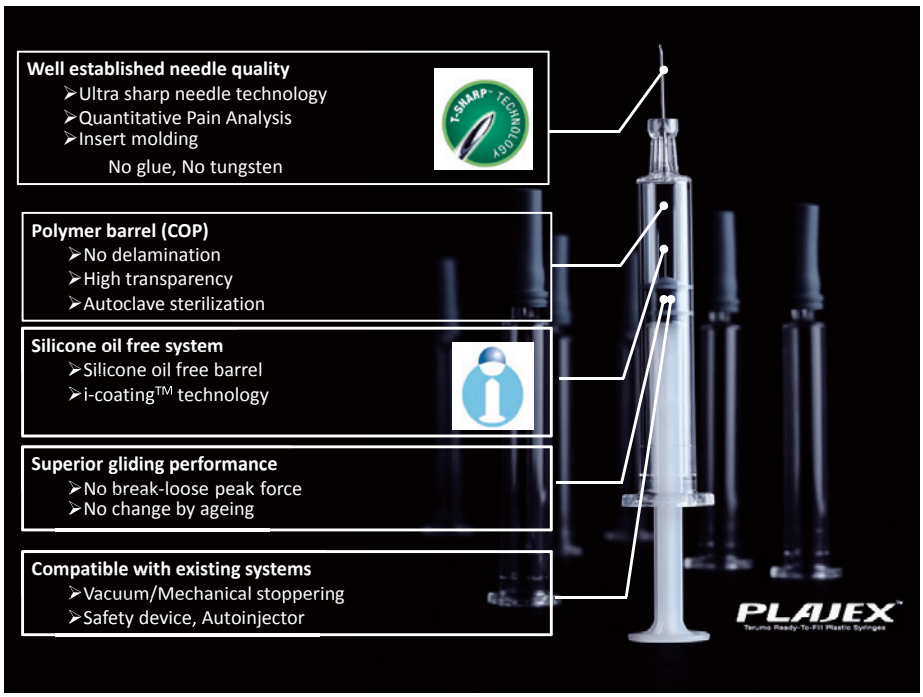

Figure 3: The components of a PLAJEX™ plastic prefillable syringe.

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]

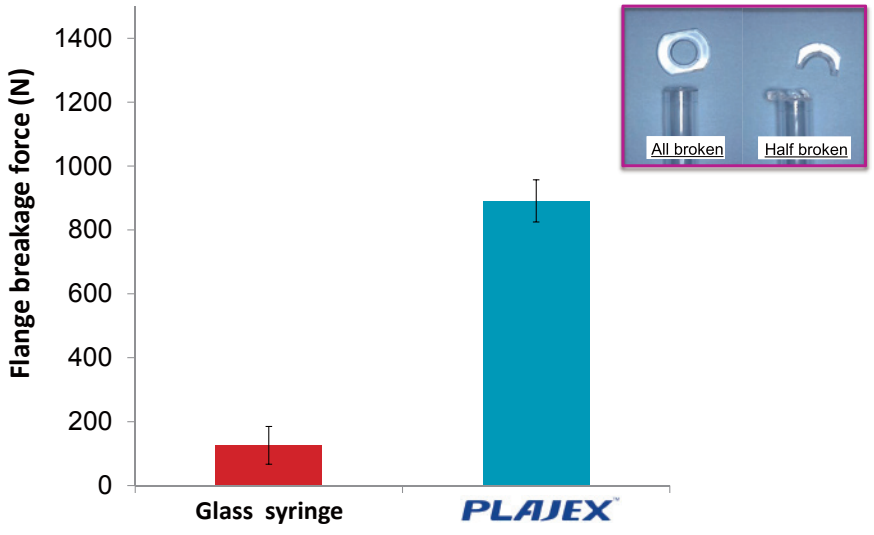

Figure 4: Flange breakage force (all flange) measured by universal tensile tester at a stroke rate of 50 mm/min. The value represents the mean ± SD (n=10).

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.

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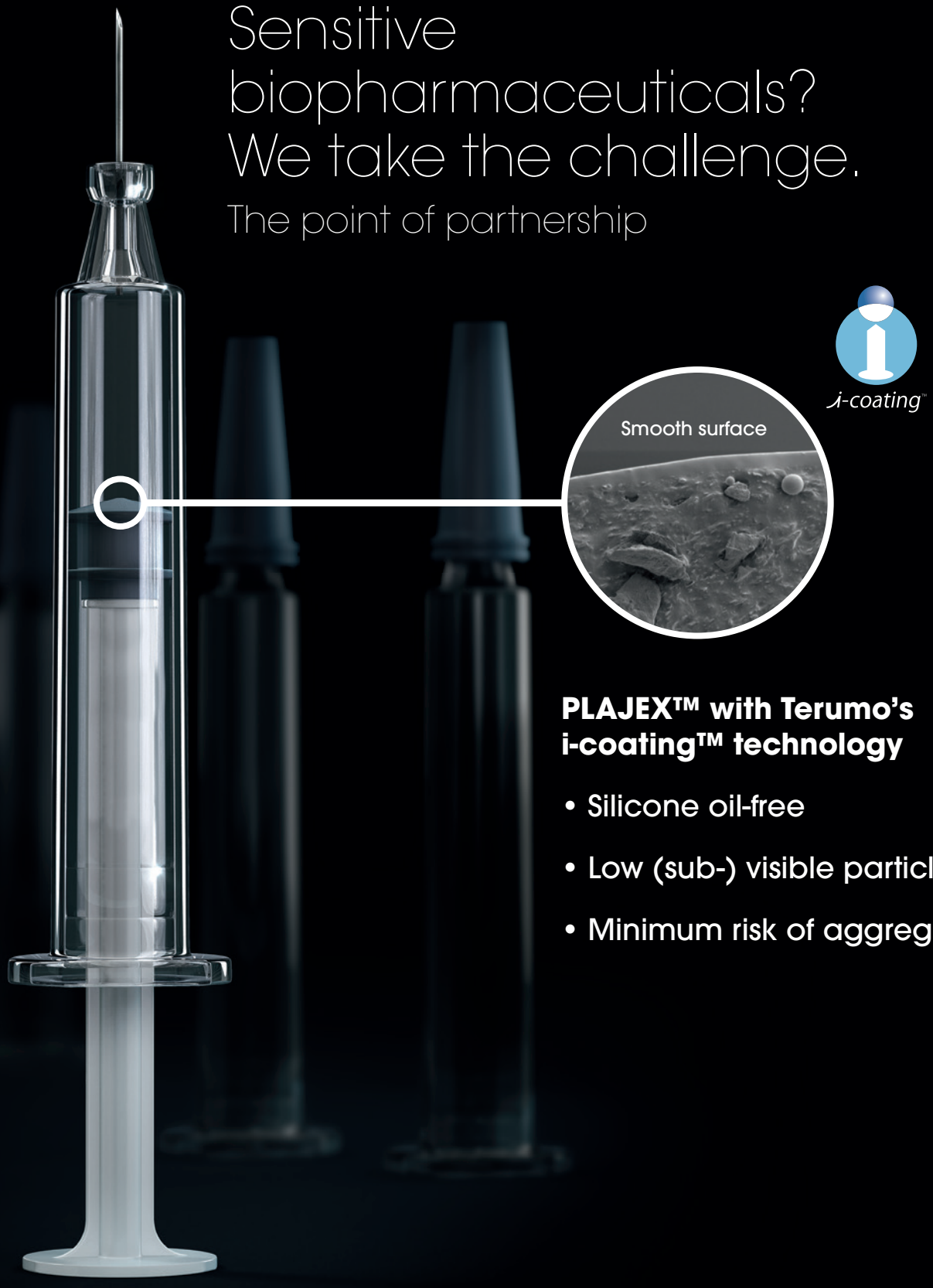

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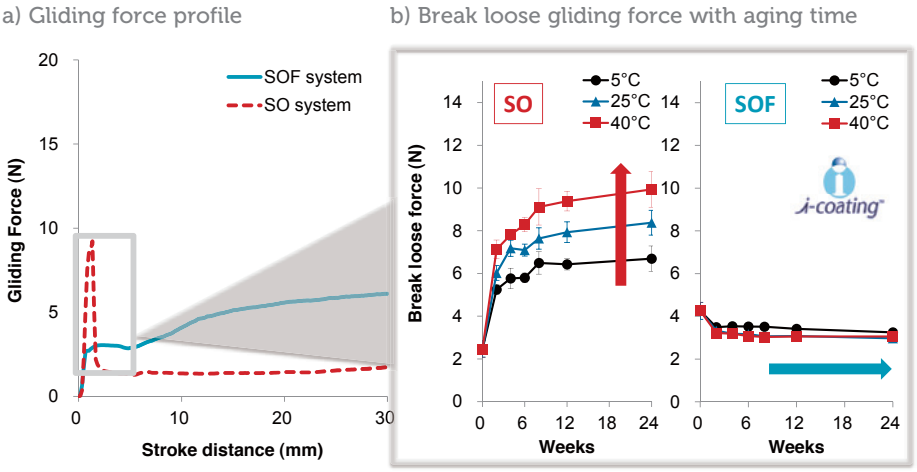

Figure 5: (a) Glide force profile of silicone oil system (SO) and silicone oil-free system (SOF) stored for 12 weeks at 40°C. The data was obtained at a stroke of 200 mm/min. Glide forces were measured with a universal tensile meter. (b) Break-loose glide force change with aging time and temperature 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.

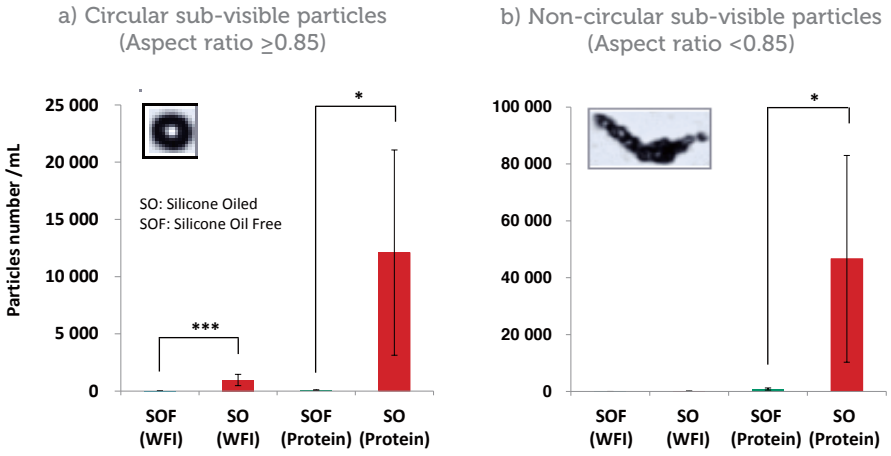

Figure 6: Comparison study between silicone oil system (SO) and silicone oil-free system (SOF) in terms of sub-visible particles using MFI analysis. (a) ECD ≥5µm, aspect ratio is more than 0.85, (b) ECD ≥5µm, aspect ratio is less than 0.85. Data are presented as mean ± standard deviation (n = 10 for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

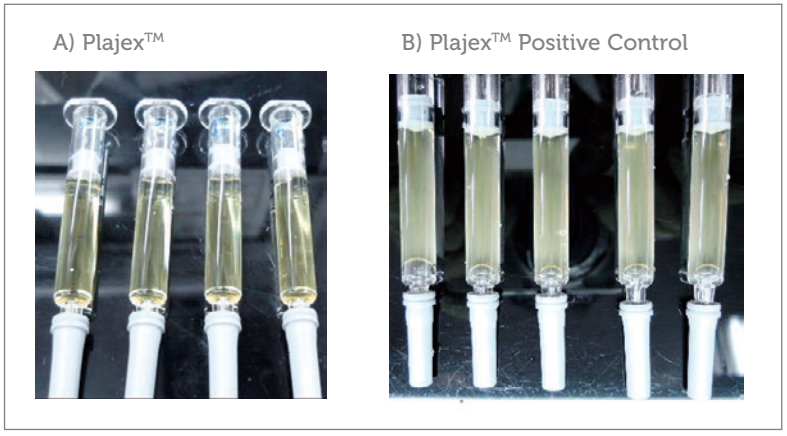

Figure 7: Micro-organism penetration study. (a) The silicone oil-free (SOF) system showing all four investigated syringes. The inner solution remained clear without any visual change. (b) Positive control (the SOF syringes with a pinhole on the barrel) of all five investigated syringes. The inner solution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

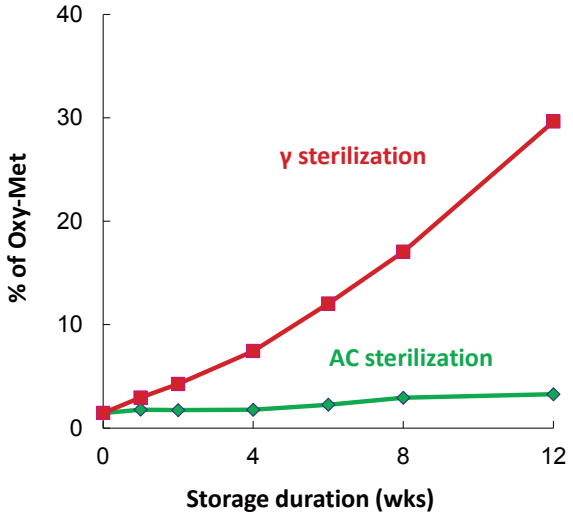

Figure 8: Profile of % oxidisation of model drug during storage at 25°C. The measurement was performed by HPLC. The value represented the mean ± SD (n=3).

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-

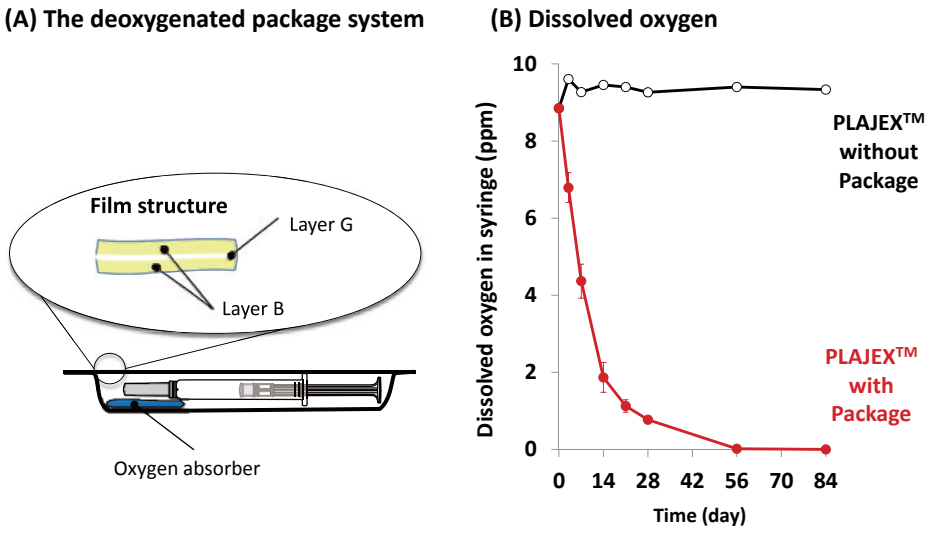

Figure 9: (a) The combination of PLAJEX™ with the deoxygenated packaging system. (b) Reduction profile of dissolved oxygen in water-filled prefilled syringes. Dissolved oxygen was measured by OXY-4 (PreSens). The value represented the mean ± SD (n=3).

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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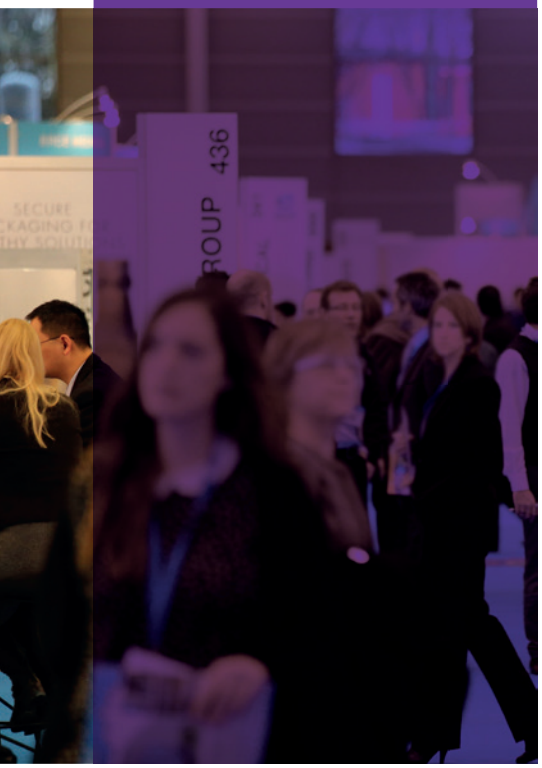

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CASE STUDY: IMPLEMENTATION OF A STATE-OF-THE-ART HIGH-VOLUME MANUFACTURING LINE FOR A DISPOSABLE PEN PLATFORM PRODUCT

In this overview, Tobias Nemeth, Business Development Manager, Ypsomed Delivery Systems, outlines the advantages of platform product development and manufacture and goes on to describe the implementation of the UnoPen™ high-volume manufacturing line, which is designed and developed to manufacture a range of customised pen versions.

INTRODUCTION

Over the last 30 years, the demand for pen injectors and more recently autoinjectors for the self-administration of therapeutic proteins and antibodies has grown significantly. This market demand has been mainly controlled and driven by global pharmaceutical companies willing to invest significant resources in the development and manufacture of new injection systems for their new biologic and chemical entities. As global demand continues to grow and pen and autoinjector technologies have matured, pharmaceutical companies at all levels are now looking to source state-of-the-art devices that are available quickly and at low risk for both clinical trials and commercial launch.

Platform products, like Ypsomed's UnoPen™ (Figure 1), disposable pen and YpsoMate® two-step autoinjector, support customers by providing fully developed state-of-the-art injection systems that are customised to fit perfectly the properties of the drug and the customer-specific trade dress.

PLATFORMS MITIGATE RISKS

The main advantage of developing a product platform is to speed up time to market and to minimise risk for the customer during product development and the commercial life of the custom product. This is achieved by developing the platform to a level, which allows customisation within defined limits as a final step before the custom product is available for clinical and ultimately commercial supply.

Self-injection platform product development is built around experienced interdisciplinary teams working in key areas:

- Broad knowledge of the patent landscape and securing IP for the new platform allowing product launches in key markets.
- Human factors studies at the platform

Figure 1: The UnoPen™ disposable pen platform accepts 3 mL or 1.5 mL cartridges and is customised for use with insulin, GLP-1, hGH, FSH and PTH.

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Figure 2: UnoPen™ is delivered for final assembly in three different subassemblies: (1) pen cap, (2) cartridge holder and (3) dose mechanism.

Figure 3: The UnoPen™ manufacturing line.

level taking into account a broad range of patient populations and disease states. This underpins design input for further human factor studies performed on the final custom product.

- Development and industrialisation specialists working hand-in-hand from concept development to the final product encompassing key aspects such as technical design, material selection, friction forces and manufacturability. In the case of UnoPen™ special attention was paid to the development of a unique "active last dose stop" and also on "sound engineering" to provide an optimal audible and tactile patient experience during dose setting and correction.
- Final assembly expertise of the UnoPen™ subassemblies (Figure 2) together with a range of specialist suppliers to fully support customers building up final assembly capacity based on manual, semi-automated and/or fully automated lines.

Ultimately, one of the most important factors is to install manufacturing capacity for the new platform to allow customers to access the platform easily at a fraction of the overall cost compared with bespoke manufacturing infrastructure. The manufacturing line must be capable of producing multiple customised design and technical versions. An individual design is important to accommodate customer requirements on human factors and trade dress. Technical modifications ensure that the injection system is compatible with the dosing requirements and the filled volume of the primary packaging container.

"The main advantage of developing a product platform is to speed up time to market and to minimise risk for the customer during product development and the commercial life of the custom product"

THE UNOPEN™ MANUFACTURING LINE

The key specification requirement for the UnoPen™ assembly line was to be able to manufacture each customised pen version with the highest accuracy and based on short changeover times between versions. New customer versions can be implemented quickly without significantly interrupting commercial manufacturing of already established products. The first installed line has an annual capacity of up to 20 million units. The overall infrastructure is available to extend this initial capacity significantly exploiting synergies between various processes.

The UnoPen™ manufacturing line (see Figure 3) not only comprises the necessary assembly steps but also the equally important inline checks and controls. The assembly stations are cam-controlled, while the work piece carrier is based on an electromagnetic system that

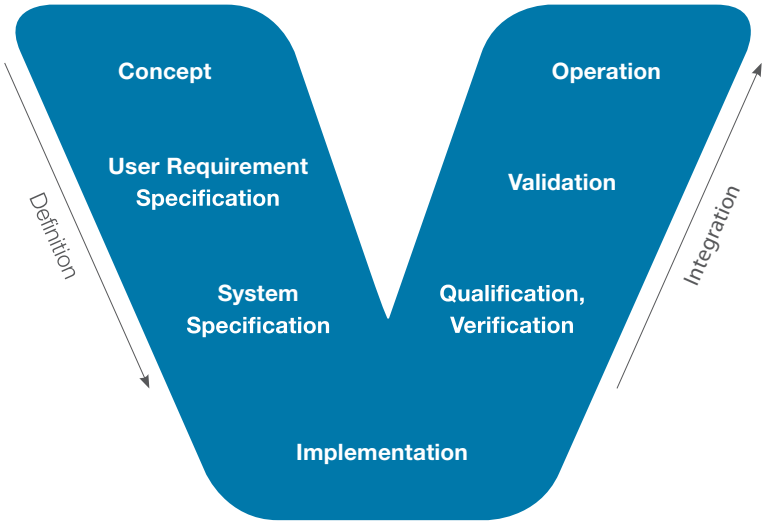

Figure 4: System engineering process V-model as used for the line set up for UnoPen™.

allows precise positioning at each work station and is almost maintenance-free. The line automatically controls the performance of each assembly station in real time. Functional checks of all assembled parts are performed in line. The line automatically withdraws parts or subassemblies for further quality checks or final customer samples. The machine is smoothly interfaced with Ypsomed's SAP system and all parts entering the machine are traceable in the finished product.

IMPLEMENTATION OF THE UNOPEN™ MANUFACTURING LINE

For line setup, Ypsomed followed a classic V-model (Figure 4). The concept phase focused on the overall manufacturing concept including injection moulding and supporting processes. For creating the User Requirement Specification it was important to consider all future technical and design variations in order to achieve the most flexible manufacturing approach. The line requires minimum human intervention during daily operation.

In addition to the technical specification and line flexibility it was also important to choose a supplier with an excellent reputation, a track record of building state-of-the-art lines with outstanding performance and reliability and which is located close to the Ypsomed manufacturing site for fast technical assistance and delivery of spare parts.

TEAMWORK

Ypsomed has been manufacturing hundreds of millions disposable pens for a number of customers since 1999 and currently has annual capacity based on customer-specific pens in excess of 90 million devices. For the UnoPen™, setting up a state-of-the-art manufacturing line with its demands in terms of quality, flexibility and reliability, requires profound know-how of all involved manufacturing processes and particularly close collaboration with the equipment supplier.

An Ypsomed industrialisation team accompanied the implementation work for the automated assembly line at the supplier's site. This not only made sure that all requirements were met, but also to train Ypsomed's engineers and operators on the new line at an early stage. After successful factory acceptance testing the line was transferred to one of Ypsomed's manufacturing sites in Switzerland.

The Swiss site was prepared by installing all necessary connections based on a "plug-and-play" approach, thus ensuring that line installation could be realised in a short time and to move quickly on to site acceptance testing. Thanks to the close collaborative efforts during implementation and qualification / validation, commercial operation could be initiated seamlessly. The overall timeline from issuing the System Specification to final operation in less than two years is remarkable. The first customer has already received commercial product from the new line and other customer products are currently being implemented and validated. With more custom products in development and commercial customers likely to increase their forecast, Ypsomed is already reviewing when to invest in a second line.

> "The key specification requirement for the UnoPen™ assembly line was to be able to manufacture each customised pen version with the highest accuracy and based on short changeover times between versions"

CONCLUSION

The development and industrialisation of a new platform product like UnoPen™ require significant knowhow, investment and resources not only to develop the basic platform, including IP and human factors, but also to industrialise the platform on a large commercial scale that allows customers to source their product reliably from a state-of-the-art line with the highest level of automation.

YDS – YPSOMED DELIVERY SYSTEMS

Ypsomed is the largest independent developer and manufacturer of injection systems for self-administration. Our pens range from simple disposable pens to reusable pens with variable dosing and spring-assisted injection. We develop and manufacture autoinjectors for use with prefilled syringes as well as innovative injection devices for use with dual-chamber cartridges. Unique click-on pen needles complete our product portfolio.

All products are developed in Switzerland, where internal capabilities include R&D, tool-making, injection moulding, clean-room production and assembly facilities. Ypsomed provides not only marketing, regulatory and technological expertise but also manufacturing expertise according to the latest quality requirements, for both low and high-volume production. Ypsomed manufactures in US FDA-registered facilities, is inspected regularly and successfully by its customers and regulatory authorities (including FDA) and supplies devices to all leading markets including US, Europe and Japan.

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team technik
PRODUCTION TECHNOLOGY

PROFITABLE ASSEMBLY AUTOMATION THROUGH USE OF STANDARDISED MACHINE PLATFORMS

Here, Reiner Zeidler, Sales Manager, Medical Systems, teamtechnik Group, describes the company's modular TEAMED production system, and how it meets the injection device industry's needs – from early development applications right through to commercial-scale manufacture.

There is increasing demand for new solutions to automate the manufacturing of injection devices from Phase I clinical trials through to a successful high-volume production program. Teamtechnik Group is a leading supplier in the development and implementation of turnkey production systems for medical devices. The company offers a wide range of machine platforms.

WHY USE MACHINE PLATFORMS?

With its TEAMED platform system (Figure 1), teamtechnik offers a scalable linear production system. It consists of proven standard modules which are then tailored specifically for each customer. With these tested modules, the engineering required is much reduced and so are, therefore, machine delivery times.

The TEAMED platform enables the integration of sophisticated assembly processes (Figure 2) with up to 100% end-of-line testing. It also facilitates production which is compliant with global standards – such as cGMP, US FDA and CE – and is certified to Class 6 Clean Room specifications. The TEAMED platform incorpo-

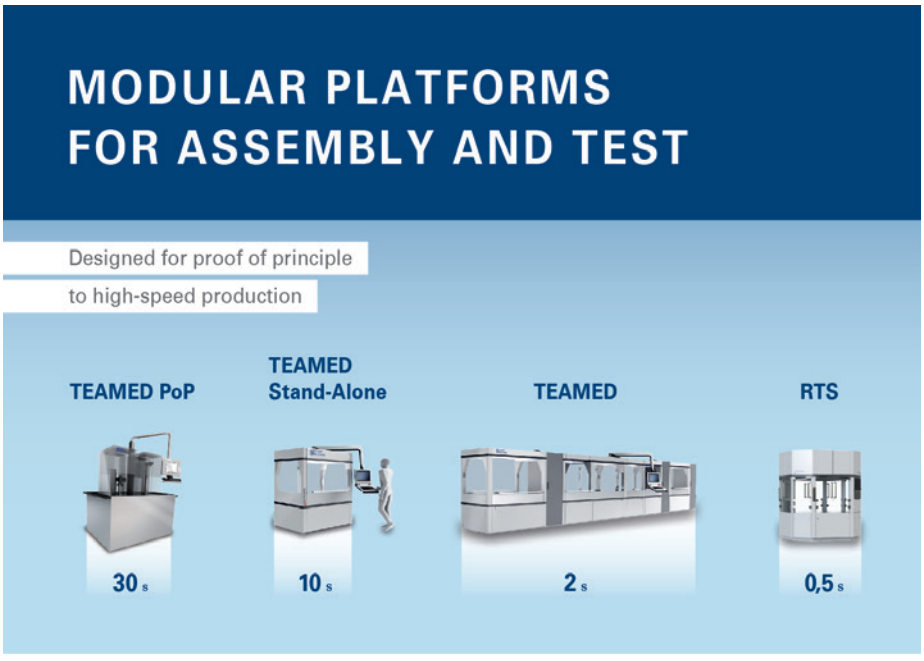

Figure 1: Modular platforms for assembly and function test.

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"The TEAMED platform incorporates processes from prototype production directly into series manufacturing, thus verifying critical process steps at the earliest possible stage"

Figure 2: Assembly system at TEAMED platform.

rates processes from prototype production directly into series manufacturing, thus verifying critical process steps at the earliest possible stage, providing reassurance for future series production from the outset.

The TEAMED platform has been developed for proof of principle applications as well as for high-speed industrialisation. Drawing upon teamtechnik's comprehensive library of processes, the TEAMED solution optimises assembly processes and reduces time to commercialisation for new products. For example, Figures 3-5 show steps in the assembly of an injection device.

A typical device project development and commercialisation cycle for a new device, utilising the TEAMED platform, is described below.

Figure 3: Testing and positioning the shell of an injector device.

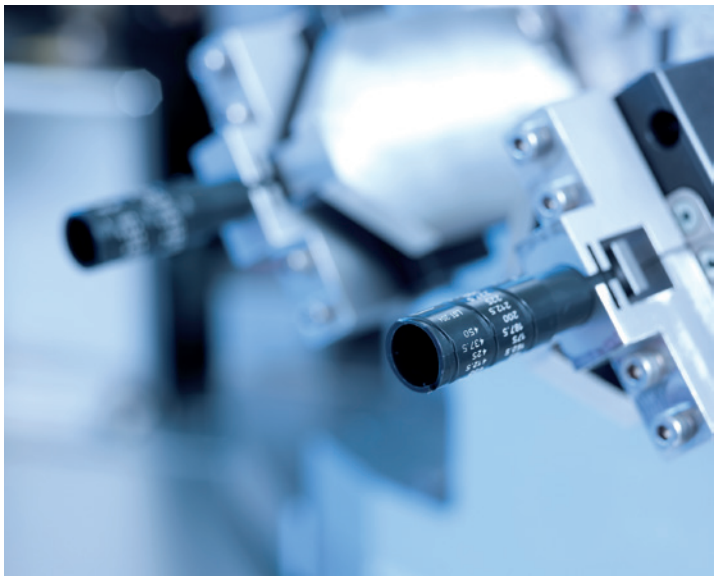

Figure 4: Laser engraving the injector's dial.

Figure 5: Testing and inserting the injector's dial.

"Incorporating both automated and manual elements, TEAMED PoP offers the ability to perform and monitor critical assembly processes with automatic solutions at a very early stage in a project, whether or not a device design has been fully defined at that point"

"TEAMED POP" FOR PROTOTYPE PRODUCTION

Phase I Clinical Trials

Assembly of injection devices involves many complicated processes, which must either be monitored in-process, or results must be verified after the process. In an ideal scenario, in order to minimise time to market, a device design and assembly process would be completely defined from the outset of Phase I. For reasons of cost, risk and design evolution, this ideal is not generally possible and teamtechnik's TEAMED PoP (proof of principle) platform provides a solution for such a challenge.

Incorporating both automated and manual elements, TEAMED PoP offers the ability to perform and monitor critical assembly processes with automatic solutions at a very early stage in a project, whether or not a device design has been fully defined at that point. Able to accommodate up to five process operators working at the machine, it is often the case that a customer will engage with teamtechnik and utilise TEAMED PoP, while a device is still under development.

"TEAMED STAND-ALONE" FOR SMALL-VOLUME PRODUCTION

Phase III Clinical Trials

Providing continuity from the Phase I experience utilising TEAMED PoP, the same process units can then be integrated into a TEAMED Stand-Alone machine for small-volume production to support Phase III trials.

TEAMED Stand-Alone is a semi-automated assembly line with process materials being fed by operators, and with process stations being linked by a carrier transport system. The carrier features have the same design as in the corresponding TEAMED PoP machine, although typically incorporating additional nests for manually pre-loaded parts. Although most of the assembly operations will be performed automatically, the refined process stations are based on similar technologies to those on the precursor TEAMED PoP system.

"TEAMED" PLATFORM FOR INDUSTRIALISATION

Commercial Scale

For high-volume, commercial scale production, teamtechnik provides a fully-automated TEAMED line with all device components being delivered by bowl feeders or palletising systems. The carrier design is ideally based on the same concept as used for the earlier TEAMED *PoP* and TEAMED *Stand-Alone* machines.

A number of critical processes, such as dosing, gluing or welding (ultrasonic or laser) – will typically have been refined and validated with the TEAMED PoP and TEAMED Stand-Alone systems, and are continued through in the design of the high volume manufacturing line. The simple replication of validated processes can significantly reduce time to market for a new device, thereby improving return on investment. This benefit can be realised by means of the modular design of the TEAMED system, using individually customised processes and a machine concept which combines the flexibility and operational efficiency of pre-validated servo-actuated motions and cam-driven units.

"RTS" CAM-DRIVEN PLATFORM FOR HIGH SPEED PRODUCTION

teamtechnik's cam driven machine RTS represents the company's high-speed automation platform. Typically operating at up to 120 cycles per minute, RTS offers a ring transfer system, providing between eight and 32 individual stations, and is designed for processes which require higher outputs.

"Critical processes, such as dosing, gluing or welding (ultrasonic or laser) – will typically have been refined and validated with the TEAMED PoP and TEAMED Stand-Alone systems, and are continued through in the design of the high volume manufacturing line"

MARKET LEADERS TRUST TEAMTECHNIK

Customers rightly expect robust, reliable and cost-effective production systems for their medical device products. Providing the foundation for long-lasting customer relationships, teamtechnik's engineers are well-versed in the design and building of process technologies which offer sophisticated assembly and function testing for a wide range of production applications.

GLOBAL SERVICE CAPABILITY

Based in Freiberg, Germany, teamtechnik Group is an international leader in highly flexible automation technology – providing intelligent and reliable automation solutions for medical, pharmaceutical, diagnostic and other industries for several decades.

With 900 employees throughout the world, supporting annual revenues of over €150 million (£118 million), teamtechnik supports customers from sites in Germany, Poland, France, China, Korea and the US.

To ensure customers have access to relevant expertise during post-installation and ramp-up phase of their projects, teamtechnik also provides resident engineers - based locally and available on-site - during this critical phase of a program. Through its global service network, teamtechnik also ensures that production equipment is available around the clock, providing customers with dedicated service team contacts, each with comprehensive knowledge of a particular customer's manufacturing system.

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THE EVOLUTION OF FLUOROPOLYMER **COATINGS** FOR PARENTERAL PACKAGING

Set against a background of changing requirements and expectations of syringe components, with reference to biologic formulations, Susan M. Dounce, PhD, Senior Manager, Business Development & Innovation, Injection Systems, Datwyler Pharma Packaging, describes how plunger coating has become about more than barrier properties and, compared with siliconisation, describes how the established Omniflex fluoropolymer coating provides numerous advantages and benefits across the board in prefilled syringes from commercial, to formulation stability and quality, to the end-user experience.

In the conservative, data-driven industry of parenteral packaging, market trends indicate a growing demand for fluoropolymer coated elastomeric closures, primarily to mitigate risks related to drug stability and compatibility. To meet the evolving needs of the biologics industry, the Omniflex fluoropolymer coating is the first coating simultaneously to provide barrier properties and to eliminate the closure as a source of silicone-oil-based subvisible particles (SbVPs). As a consequence of the coating's chemical composition and method of application, Omniflex Coated Plungers (OmniflexCP®) not only have barrier properties that result in superior chemical compatibility but have the added benefits of a significant reduction in SbVP levels and highly consistent delivery forces. OmniflexCP® continues to find broad applicability to address stability, compatibility, and performance challenges, in and beyond the world of biologics.

> "Reducing rubber leachables, while critical, is no longer the sole driver for coated closure development, and it is no longer enough to meet the needs of biologic drug packaging"

THE EVOLVING NEEDS OF BIOLOGICS PACKAGING

A growing preference for fluoropolymer coated elastomers

As the scrutiny over leachables from primary packaging components continues to escalate, so will the demand for fluoropolymer coated elastomeric closures. Traditionally, the design of film-coated closures has focused only on barrier properties. The sole function of the fluoropolymer film coating is to provide an inert barrier between the rubber and the drug formulation, especially for sensitive biologic drugs. The efficacy of therapeutic proteins can depend sensitively on their exact chemical make-up and three dimensional conformation. Interactions with leachables can lead to chemical and/or conformational changes and degradation and/or aggregation, possibly rendering the protein ineffective or immunogenic. Thus, the majority of biologics manufacturers opt for fluoropolymer coated closures.

The most well-known example highlighting the value of fluoropolymer barrier coatings is that of Eprex® (recombinant human erythropoietin alpha) in prefilled syringes. In 1998, a number of

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Eprex® products were reformulated using polysorbate 80 as a stabiliser instead of human serum albumin. Not long after those changes, the incidence of antibody-mediated pure red cell aplasia increased substantially in chronic kidney disease patients treated with Eprex® subcutaneous injections.[1] The immunogenic reactions were judged to be caused by organic leachables from uncoated rubber syringe plungers whose levels were increased by the reformulation with polysorbate 80. The leachables were believed to be acting as adjuvants which increased the immunogenicity of Eprex®. As a result, currently all Eprex® prefilled syringes use fluoropolymer film-coated plungers, and the industry has a heightened awareness of the potential for leachables to modulate an immune reaction towards biologic drugs.[1]

Beyond rubber leachables: Scrutiny over particulate matter increases

The increased scrutiny over particulate matter in parenteral drugs has been fuelled in recent years by regulatory recalls. Approximately half of the US FDA's 2013 issued recalls of parenterals were due to visible particulate matter, ranging from foreign matter (i.e. glass, or metal) to drug-related particles (i.e. crystallised or aggregated protein).[2]

While larger particulates have long been a concern due to their potential for blood vessel occlusion, SbVPs in therapeutic protein formulations have more recently begun to receive increased regulatory oversight. Although much is still unknown about the link between protein aggregates and immunogenicity, there is nonetheless concern over the possible correlation.[3] New regulations will continue to intensify the scrutiny around particle detection and characterisation, and as an example, in August 2014, the FDA issued a guidance on immunogenicity assessment which states:

"It is critical for manufacturers of therapeutic protein products to minimise protein aggregation to the extent possible. This can be done by [among other things]… choosing a formulation and container closure that minimises aggregation during storage." [4]

Elastomeric closures can contribute to particle levels both directly (from silicone oil and particles from the manufacturing processes / environment) and indirectly (from silicone oil or leachables or other particulates, acting as catalysts or nucleation sites for the formation of drug-related particles). Since leachables can potentially cause protein aggregation,[5] the aforementioned guidance appears to support the use of barrier-coated elastomeric closures. However, the increased scrutiny over SbVPs has implications beyond controlling leachables.

Thus, more SbVPs in a protein formulation means more characterisation and risk assessment activities will be required.

Aside from additional characterisation work, formulation delays can occur if a protein is found to be sensitive to aggregation in the presence of silicone oil. The adsorption / desorption of biologics at aqueous-silicone interfaces can cause non-native structural conformations to arise and protein aggregates to form.[8,9] The nucleation of proteins at silicone particle interfaces is a known degradation pathway for some biologics and can result in diminished drug efficacy.[10] These phenomena are exacerbated at high silicone concentrations, when an additional aggressor like heat or agitation is involved, and as modern formulations approach the drugs' solubility limits.[11,12]

> "OmniflexCP®, since it is not siliconised, does not show a stick-slip type phenomenon normally present for siliconised plungers. The glide forces of OmniflexCP® are highly consistent down the length of the barrel"

Barrier properties alone are no longer sufficient to address the needs of biologics packaging

Reducing rubber leachables, while critical, is no longer the sole driver for coated closure development, and it is no longer enough to meet the needs of biologic drug packaging. Particularly, silicone oil, and its direct and indirect contributions to particle levels, has become both a significant nuisance and a legitimate concern.

Traditionally, prefilled syringe plungers are siliconised with a 350-1000 cSt silicone oil for three purposes:

(1) to prevent sticking between plungers during shipping / storage
(2) to enable machinability / placement of the plunger into the syringe
(3) to ensure optimal syringe delivery forces.

Even partially film-coated plungers, must be siliconised for these three reasons.

Although its toxicological profile is generally considered to be safe,[6] silicone oil is a significant contributor to SbVP levels in prefilled syringes.[7] High levels of SbVPs in biologic drugs can mean additional characterisation will be required to identify the nature of the particles. Since protein aggregates can potentially present a danger to the patient and diminished efficacy of the drug, the FDA stresses the need for characterising SbVPs in therapeutic protein formulations:

"Assessment should be made of the range and levels of subvisible particles (2-10 µm) present in therapeutic protein products initially and over the course of the shelf life… Sponsors should conduct a risk assessment of the impact of these particles on the clinical performance of the therapeutic protein product." [4]

Silicone oil can lead to delays in the time-to-market due to the potential for additional characterisation and/or formulation work. Furthermore, the interaction of proteins with silicone oil presents a risk to the safety and efficacy of therapeutic proteins. Therefore, for coated elastomeric closures, barrier properties alone are no longer sufficient to meet the needs of the biologics industry. The closures should also reduce or eliminate the levels of silicone oil which can migrate into the drug formulation.

OMNIFLEXCP®: BARRIER-COATED PLUNGERS

The Omniflex coating technology has withstood the test of time with 20 years of commercial sales and filings with every major global regulatory agency. OmniflexCP®, which was launched in 2009 and is currently used with commercial drugs, was the first coated syringe plunger to not only provide barrier properties but also eliminate the need for plunger siliconisation. Today, OmniflexCP® is the best performing fluoropolymer-coated plunger technology that addresses the compatibility and performance challenges of the biologics industry and beyond.

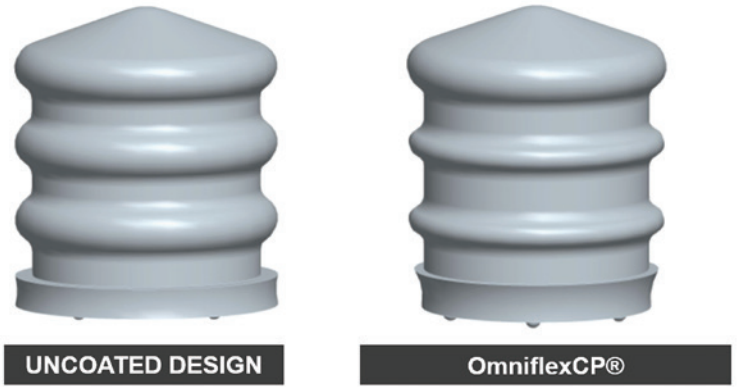

Figure 1: Three dimensional renderings of the 1 mL long uncoated (left) and OmniflexCP® (right) plunger designs.

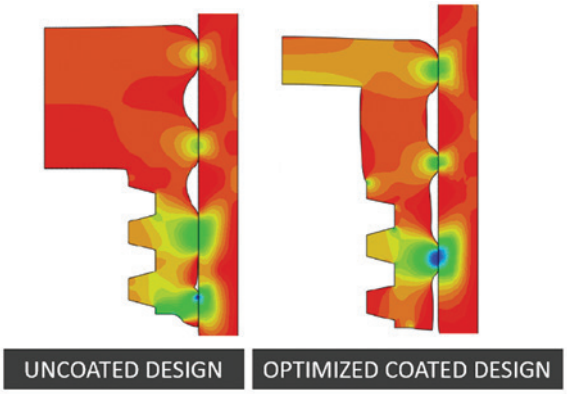

Figure 2: FEA simulations of the compressive stress profiles of the 1-3 mL uncoated (left) and OmniflexCP® (right) plunger designs.

OMNIFLEX COATING TECHNOLOGY

Omniflex (which is a general term to describe several product classes including OmniflexCP® [syringe plungers], OmniflexPlus® and Omniflex3G® [vial stoppers]) is a proprietary, flexible fluoropolymer spray coating that is applied to bromobutyl vial stoppers and syringe plungers and which is designed with two objectives: (1) to be an inert barrier to organic molecules, and metal ions and (2) to impart a low coefficient of friction and thereby eliminate siliconisation.

The OmniflexCP® coating, which is designed to be approximately 20 µm thick, is formed in a two-step process. First, the proprietary fluoropolymer film is applied by a tumble spray coating, and second, a post-treatment process provides sufficient thermal energy to bond the coating covalently to the bromobutyl substrate and to form a smooth, continuous fluoropolymer film. Due to the line-of-sight nature of the spray coating, the entire plunger surface is covered except for the interior of the plunger-rod cavity. The total coverage by the Omniflex coating is in contrast to the partial coverage of most film coatings and has the benefit of providing a complete barrier. The total coverage of the lubricious coating also eliminates the need for siliconisation of the plunger rills. Furthermore, the spray-coating process lends itself to coating custom designs easily for innovative drug delivery devices.

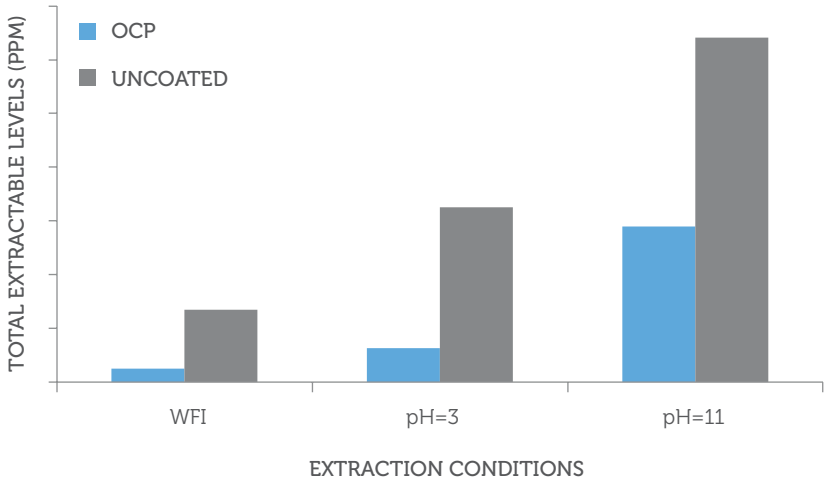

Figure 3: Relative extractable levels from an uncoated bromobutyl (gray bars) compared with OmniflexCP® (blue bars).

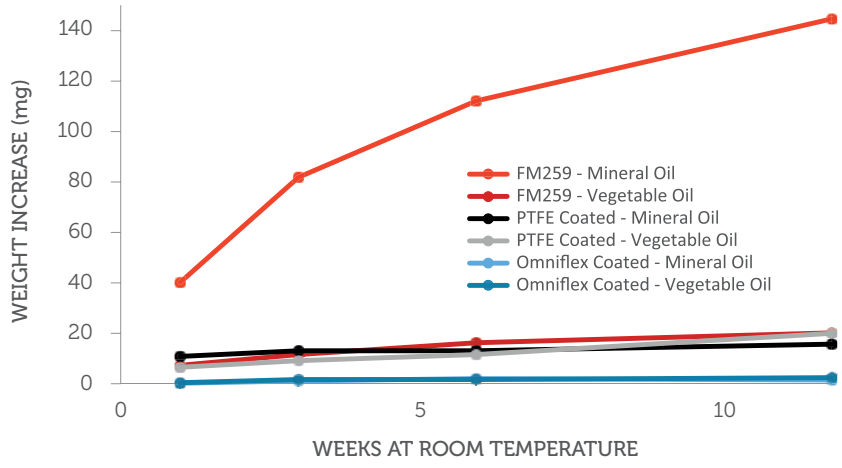

Figure 4: Weight increase as a function of time in contact with oils, for coated and uncoated bromobutyls, as specified in the legend.

All Omniflex-coated products are produced in Datwyler's state-of-the-art manufacturing facility known as FirstLine®. Today, primary packaging component manufacturing is considered to be an extension of the drug manufacturing process itself and the FirstLine® facility was designed to meet the evolving standards of the parenteral industry. The facility design, process flow, gowning protocols, personnel and material flow, and automation all result in the lowest endotoxin, bioburden, particulate, and defect levels available in the industry.

OMNIFLEXCP® PLUNGER DESIGN BY FINITE ELEMENT ANALYSIS

A unique feature of OmniflexCP® is that Finite Element Analysis (FEA) simulations were used to optimise the plunger designs. As seen in Figure 1, the designs for the ISO-standard, 1 mL long plunger (left) and for OmniflexCP® (right) have some slight, but key differences. First, the diameters of the

second and third trailing rills have been slightly decreased as compared with the ISO standard. The other main difference is that the trim edge is undercut on the OmniflexCP® design so that it is no longer in contact with the barrel.

FEA simulations, as in Figure 2, reveal that the compressive stress of the standard 1-3 mL uncoated plunger (left) is highest at the trim edge. Despite the fact that the trim edge is not intended to be a sealing rill, it is the most significant contributor to the frictional forces. In the OmniflexCP® design (right), the trim edge does not come into contact with the barrel surface. This fact, along with the reduced rill diameters in the trailing rills, lead to optimum delivery forces, as discussed below.

These design changes are achieved with no adverse impact on seal integrity. Studies scrutinising the minimum interference fit (combining the lower tolerance for the plunger diameter and the upper tolerance of the barrel inner diameter) showed zero failures of axial compression and dye ingress leak tests.

BARRIER PROPERTIES AND CHEMICAL COMPATIBILITY

Historically, the driver for the adoption of fluoropolymer coated elastomeric closures has been the need for barrier properties. An advantage of the Omniflex spray coating process is that, in contrast to most film coatings, the entire surface of the closure that is in contact with the container walls and drug product, is barrier coated. Indeed, the Omniflex coating is designed both to reduce the number and levels of extractable species from the base rubber, as evidenced in Figure 3.

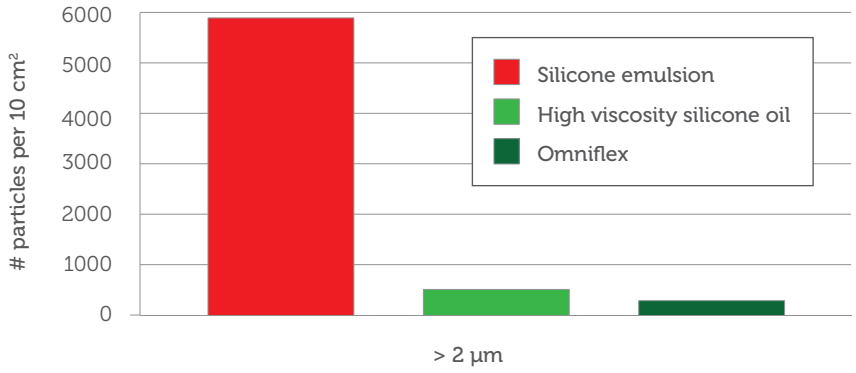

Figure 5: Number of SbVP's (>2µm) per 10 cm² measured according to ISO 8871-3 for a bromobutyl closure siliconised with 350 cSt silicone oil (red), 30,000 cSt silicone oil (light green), and Omniflex coated (dark green).

An important class of leachables that is blocked by the Omniflex barrier coating technology in Figure 3 is metal ions.

In addition to blocking rubber leachables, the Omniflex coating can also prevent the adsorption of certain formulation components and can provide an effective solution to various chemical compatibility challenges. As an example, Omniflex coatings are inherently lipophobic / oleophobic and therefore are an excellent barrier for lipid- and oil-based formulations. Figure 4 shows that uncoated bromobutyl compounds will absorb oils and increase in weight over time which can adversely affect the elastomer's functional performance. On the other hand, the Omniflex coated bromobutyl (in blue) shows close to zero weight increase as a function of contact time with oils.

REDUCED SUBVISIBLE PARTICLE LEVELS IN PRE-FILLED SYRINGES

Low viscosity silicone oils are associated with high levels of SbVPs. Figure 5 shows the number of SbVPs greater than 2 µm in size per 10 cm² of rubber with various types of lubrication including a 350 cSt silicone oil emulsion (red bar), a 30,000 cSt silicone oil (light green bar) and an Omniflex coating (dark green bar). As Figure 5 demonstrates, in terms of SbVP levels, high viscosity silicone oils have a clear advantage over low viscosity oils and the Omniflex coating provides an even further reduction in particle levels.

Figure 6 shows particle levels in three different size ranges for plungers that have been siliconised with 30,000 cSt silicone oil (red bars) *versus* plungers that have been coated with the Omniflex fluoropolymer barrier coating (blue bars). In Figure 6a, levels are expressed as the number of particles per 10 cm² of rubber while Figure 6b expresses the same as the number of particles per drug contact surface area (assumed to be 0.43 cm², or that of a typical 1 mL long plunger.) While switching from a 350 cSt silicone oil to a 30,000 cSt silicone oil results in a nearly 20-fold decrease in SbVP levels, OmniflexCP® provides a further 50% reduction over the high viscosity oil.

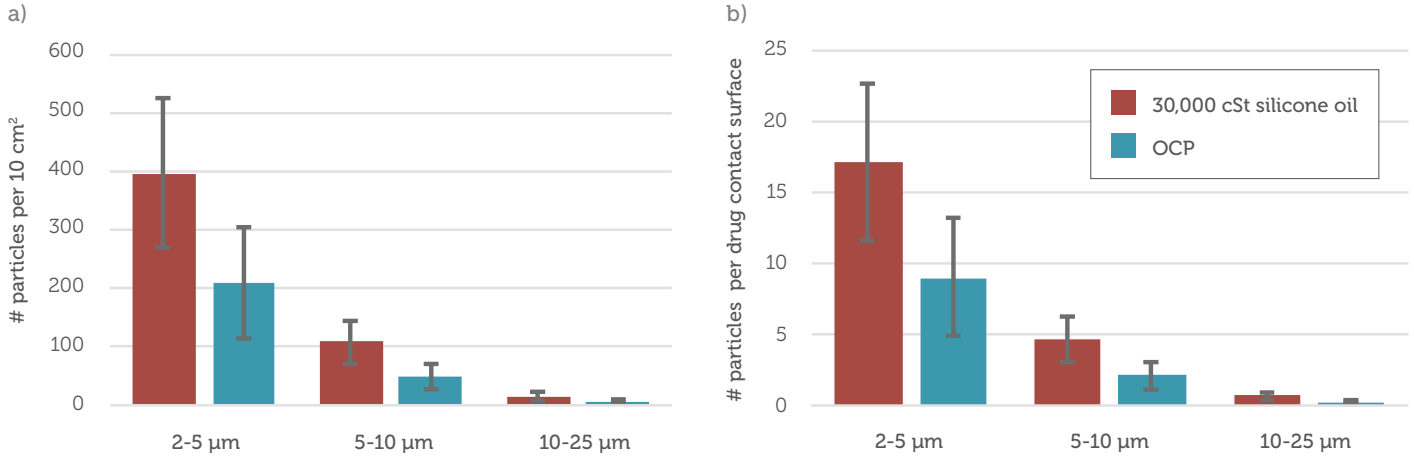

Figure 6: Subvisible particle loads for uncoated, siliconised (30,000 cSt) bromobutyl plungers (red) and OmniflexCP® (blue) (a) normalised to 10 cm² of rubber and (b) per drug contact surface area.

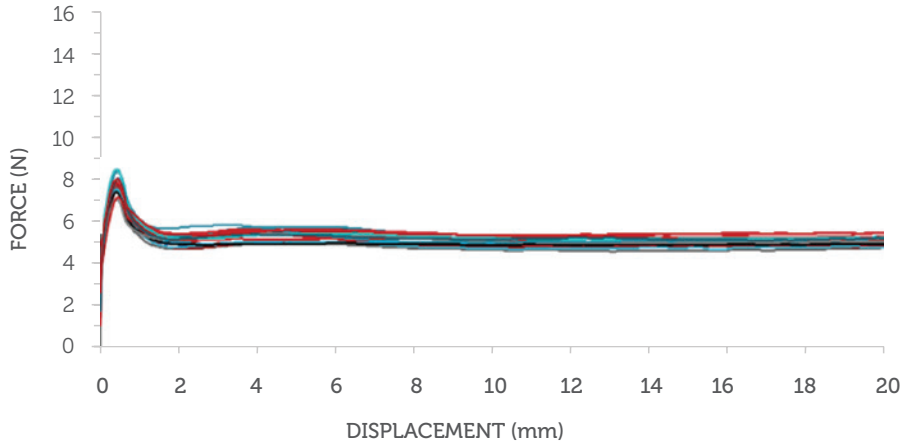

Figure 7: Delivery forces at a rate of 380 mm/min for 20 samples of 1 mL Long OmniflexCP® in WFI-filled glass barrels with baked-on silicone and 27G staked needles, after three days aging at room temperature. (Data courtesy of Gerresheimer.)

The reason for the significant reduction in particle levels with OmniflexCP® is the absence of silicone oil-based SbVPs. This has been demonstrated by the investigations of Felsovalyi et al.[7] In reference 7, the silicone oil-based SbVP levels of OmniflexCP®, a siliconised plunger, and a film-coated plunger were compared. OmniflexCP® was associated with zero silicone oil-based SbVP's while the other two plungers had significant levels detected. In fact, this study showed that when it comes to silicone oil migrating into a prefilled syringe formulation, the plunger was the larger source of free silicone as compared with the barrel – even despite the fact that more silicone oil is applied to the barrel. This is not the case, however, for OmniflexCP® since it is not siliconised.

"OmniflexCP® not only has the advantage of having barrier properties and total coating coverage, it also can eliminate the plunger as a source of silicone oil which significantly reduces SbVP levels in prefilled syringes"

CONSISTENT GLIDE FORCES

Due to both the absence of silicone oil and to the optimised mould design, OmniflexCP® has extremely consistent delivery forces from three perspectives: (1) consistent forces as a function of displacement (i.e. no stick-slip behaviour), (2) consistent forces from plunger to plunger, and (3) consistent glide forces with aging.

Figure 7 shows the delivery forces for 20 samples of 1 mL long OmniflexCP®. While delivery forces for any plunger barrel combination can vary widely depending on experimental conditions, there are two important observations that can be made from Figure 7.

First, OmniflexCP®, since it is not siliconised, does not show a stick-slip type phenomenon normally present for siliconised plungers. The glide forces of OmniflexCP® are highly consistent down the length of the barrel. Second, the 20 samples, which have been treated identically in terms of sterilisation, aging, barrel lubrication, etc, yield remarkably consistent delivery forces from plunger to plunger. The standard deviations (RSD) of the break loose and glide forces are 0.4 N (5%) and 0.2 N (4%) respectively. Finally, consistent glide forces with aging of syringes are another advantage of OmniflexCP®. The effect of aging (25°C, 60% RH) on glide forces of 1 mL long plungers is shown in Figure 8 for both ISO-design siliconised plungers (red points) and for OmniflexCP® (blue points). The open squares and dotted lines represent non-sterile parts and the filled squares and solid lines represent steam sterilised plungers.

OmniflexCP® has highly consistent glide forces with aging. The temperature and humidity at which aging studies are performed (refrigerated, room temperature, accelerated aging) have a negligible influence on glide forces for OmniflexCP®.[13]

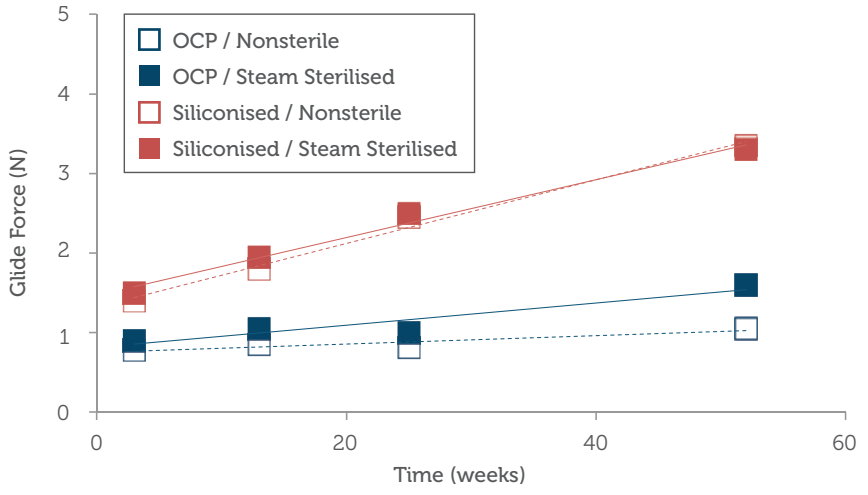

Figure 8: Glide forces for 1 mL long WFI-filled, 27G staked needle, glass syringes as a function of aging time (25°C, 60% RH) with siliconised bromobutyl plungers (red) as compared with OmniflexCP® (blue), before sterilisation (dotted lines, open squares) and after steam sterilisation (121°C / 30 minutes, solid lines, filled squares).

SUMMARY

For coated elastomeric closures, barrier properties alone are no longer enough to meet the needs of biologic drug packaging. Reducing or eliminating silicone oil is being recognised as a means to mitigate risks and reduce time-to-market. No longer is the conventional wisdom always being accepted that the syringe barrel is the predominant source of free silicone oil; instead, the plunger contribution is being more closely scrutinised. OmniflexCP® not only has the advantage of having barrier properties and total coating coverage, it also can eliminate the plunger as a source of silicone oil which significantly reduces SbVP levels in prefilled syringes. Furthermore, the Omniflex coating enables OmniflexCP® to have highly consistent delivery forces.

"No longer is the conventional wisdom always being accepted that the syringe barrel is the predominant source of free silicone oil; instead, the plunger contribution is being more closely scrutinised"

Beyond biologics, OmniflexCP® is finding broad acceptance due to its lack of free silicone oil and consistent forces. Indeed, there are numerous applications outside the scope of biologics for which OmniflexCP® may provide a unique solution including:

- Ophthalmic drugs (where silicone oil droplets must be avoided) [14,15,16]
- Lipid formulations (where oils can otherwise absorb into uncoated rubber)
- Pump delivery applications which require precise dosing (where glide forces must be highly consistent to ensure patient safety)
- Autoinjectors (which require consistent delivery forces)
- Innovative delivery devices novel plunger designs (for which the spray-coating process is well-suited).

OmniflexCP® is a mature technology designed to meet the demands of the biologics industry and beyond and provides an effective solution to a broad range of parenteral packaging needs.

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COMPANY PROFILE: PHILLIPS-MEDISIZE

Phillips Medisize

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Phillips-Medisize is a global-leader in outsource design, development and technology-driven manufacturing. With unparalleled experience in advanced moulding and assembly, Phillips-Medisize has become a dominant force in the medical device and diagnostics, drug delivery, primary pharmaceutical packaging, and commercial markets.

The company has annual sales of nearly US$600 million (£400 million) with 80% of the total revenue coming from drug delivery, medical device and diagnostic products, such as: disposable insulin pens, glucose meters, specialty inhalation drug delivery devices, single-use surgical devices and consumable diagnostic components.

Phillips-Medisize Corporation features a list of blue chip medical device, pharmaceutical and commercial customers. The company partners with its customers to provide design and development services, which accelerate speed to market of innovative products and then work with its customers to deploy advanced automated assembly and quality control technologies, which reduce manufacturing cost while improving quality.

Phillips-Medisize Corporation is headquartered in Hudson, WI and employs over 3,200 people in 14 locations throughout the United States, Europe, Mexico and China. The company also has design centres in Wisconsin and California, US, and in The Netherlands.

In a recent interview in Medical Plastics News (Issue 21, November / December 2014), company Chief Executive Officer Matt Jennings said that Phillips-Medisize was the perfect outsourcing partner because of its "ability to understand the nexus of part design, manufacturing requirements and automation capabilities. We have developed a demonstrated ability to integrate advanced moulding, automated assembly, and quality control systems into the product design and the manufacturing process, which often delivers innovative, high-quality, cost-effective solutions for our customers. We partner closely with our customers to make their innovative designs come to market with the highest regard for safety, scalability and protecting their intellectual property and designs. We believe that the integrity of our people and processes helps bring our clients' innovation, ideas, and products to market while adding to our expertise."

> "We have developed a demonstrated ability to integrate advanced moulding, automated assembly, and quality control systems into the product design and the manufacturing process"

Jennings also provided a brief history of some of the company's highlights and milestones in the interview, saying: "50 years ago the company began as the vision of its founders in northern Wisconsin. Through the years, the company expanded into the medical device space. With the expansion into medical device, we've become a true leader in drug delivery, working with the top biopharmaceutical companies in the world, manufacturing auto-injectors, pen devices and diagnostics across a variety of indications for global markets.

"In April 2014, we commenced full-scale production of the first drug delivery injector pen from our new Suzhou, China facility … We have also completed a significant plant expansions at our facilities in Finland, as well as, our metal injection moulding (MIM) facility and plan another expansion to the MIM facility next year. This is in addition to expanding our New Richmond, US, facility. These opportunities have all been made possible by new business awards from our customer base. In May we achieved the president's "E" Award for exports which is the highest recognition any US entity may receive for making a significant contribution to the expansion of US exports.

"Phillips-Medisize currently focuses on three business segments in the medical space; diagnostic devices, drug delivery systems and single-use medical devices … through innovative design and manufacturing for a variety of products that include insulin pumps, pens and auto-injectors for both branded and generic products. With the advent of new therapeutics and biosimilars we are excited about new customers and opportunities to expand our business, and our customers' success, into helping a greater number of patients who are in need."

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45°

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color of choice

Revolutionary

Auto-Injector System

45° Reusable/Disposable Auto-Injector

Don't think 45 degrees

We do it for you

Easy-To-Use-Patients controlled injection

- Controlled Delivery - Target Deposit
- Aspiration check / avoid direct deposit in veins/vessels
- Tissue depth and needle selection
- Powered by a continuing spring system
- Ergonomic Designed ON Lock System
- Ensure stability at needle penetration
- More effect / Less side effects
- Choice of needle extension depth SC Injections
- Needle shield eliminates needle exposure
- Non-slip 45 degrees pad
- Non-slip rubber grip ergonomics designed handle grip
- Controlled tissue expansion

Injector for convenience and safety

Tailor-made to fit your choice of syringe

Depot Control

Controlled Delivery

More effect / Less side effects

Specifications & Features

45° Reusable Auto-Injector

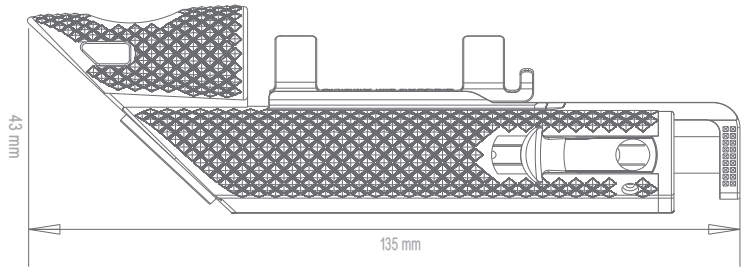
Subcutaneous

Dimensions 135 x 43 mm

Syringes range 05 – 5ml

Needle 30G and larger

Needle range 8 – 25mm



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FOUR WAYS POLYMERS TRUMP GLASS FOR CONTAINING CUTTING-EDGE INJECTABLE BIOLOGICS

In this article, using applications in West's product portfolio as examples, Nicolas Brandes, PhD, Business Development Manager, Daikyo Crystal Zenith, West Pharmaceutical Services, Inc, makes the case that polymers offer superior benefits compared with glass as a material for primary containers and delivery systems for parenteral drugs, including in particular biologics.

Glass came before plastic. Still widely used, glass became a standard for containment of injectable drugs decades ago. But that was before the rise of present-day cutting-edge biologics, such as monoclonal antibody drug products used for the treatment of cancer, and autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, Crohn's disease and psoriasis. These emerging drugs comprise nearly half of the top-20 sellers, and they continue to gain market share.

Biologics comprise genetically engineered proteins derived from living cells, and they work by targeting specific components of a disease. For example, biologics designed to treat rheumatoid arthritis may target components of the immune system that play a role in inflammation.

But biologics and glass don't always mix. This problem calls for new, custom-designed polymer containment and delivery systems. In fact, this issue has become so acute that pharmaceutical manufacturers are now making packaging systems an integral component of drug development and research, as opposed to an afterthought to be dealt with right before bringing it to market. Increasingly, they're choosing polymers, not glass, for containment. How much of a stake do these new materials claim in the industry? As demand for biologics continues to grow, the use of prefillable systems has increased with total market units of prefilled syringes estimated to reach 3.9 billion units by 2018.

There are four main reasons why biologics pair better with plastics.

PROVIDING MORE STABLE CONTAINMENT

Some biologic drug products do not react well with glass; sometimes interactions between a drug and its glass package arise, requiring new approaches to containment and delivery. For example, modern biologic formulations sensitive to silicone oil or tungsten may require alternative packaging. Other undesirable effects include breakage, delamination, particulates in the suspension, and design flexibility that do not allow for higher doses.

These problems are giving rise to new injection systems evolving to meet the needs of biologic formulations as well as alternate forms of delivery. Some new biologics in development have shown to be highly viscous. They can also require subcutaneous administration, with delivery devices designed to accommodate higher injection volumes.

Enter cyclic olefin polymers (COP), which can be moulded into a variety of shapes and designs. These unique systems with larger fill volumes and tighter dimensional control can be used, while still remaining compatible with established manufacturer filling technologies. These high-quality polymers add value to sensitive biologics through enhanced cleanliness and decreased interaction with the drug product.

Primary containers made from materials such as the Daikyo Crystal Zenith® polymer (Figure 1) can be moulded to contain higher dose volumes or provide delivery options for viscous drug products. These mouldable

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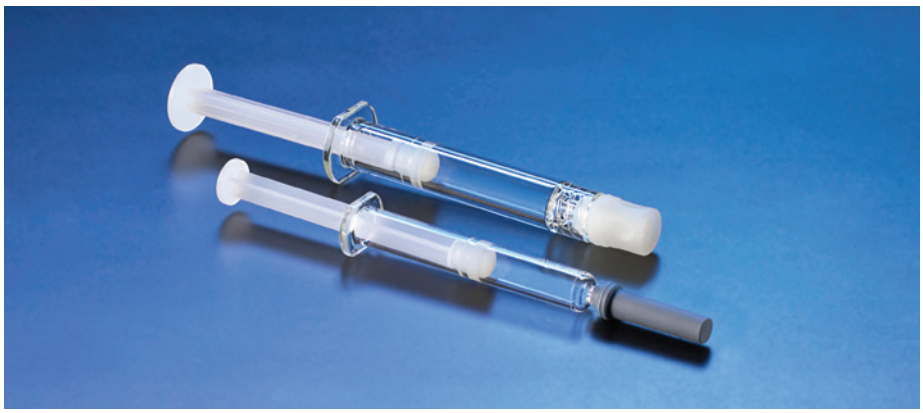

Figure 1: Daikyo Crystal Zenith® polymer syringe systems.

materials offer drug manufacturers the flexibility to create new delivery systems around customised primary containers. When combined with high-quality rubber components with barrier films, such options enable pharmaceutical companies to offer their product in combinations that clinicians and even patients may notice. The containment system could become a differentiator that helps them choose which medication among several competing choices they prefer to use.

MAKING IT EASIER ON PATIENTS

Treatments for some chronic conditions require multiple and repeated dosing at frequent intervals. Combine that with the new healthcare trend of enabling self-administration in the homecare setting, giving patients an even greater role in deciding which delivery system works best for them. As healthcare systems shift frequent treatment into the home care setting, self-injection systems must not only be designed with a patient-centric focus to improve adherence and outcomes, but also give the pharmaceutical manufacturer an edge in product differentiation.

Biologics are gaining traction in this market sector thanks to attributes that allow for self-administration. But their next-generation formulation and delivery options present multiple challenges when determining containment requirements that can accommodate dose volume, frequency of dosing, a large number of treatments and multiple delivery mechanisms.

Because patient preferences for drug administration will differ, it becomes increasingly clear that there is no "one size fits all" delivery system solution. Some people feel more confident using a prefilled syringe with a needle-safety device, while others prefer a system where the needle cannot be seen, such as a patch-injection system. All can potentially yield freedom from clinical visits and greater patient control of treatment regimens.

While patient preferences will be as varied as much as patients differ from one another, they will likely share some preferences in common. For instance, most will likely rank convenience and portability high on their list of attributes that may help them follow treatment plans more closely.

To address these issues, manufacturers of polymer primary containment and delivery systems have made strides to reduce particulates and improve the quality of materials that are in contact with the drug. They also can customize for larger doses. A typical prefilled syringe dose for a combination product is 1 mL, considered standard for subcutaneous injections by a syringe or auto-injector. Many biologics, however, require doses greater than 1.5 mL, which polymer syringes can accommodate.

ENHANCING SAFETY

The pitfalls of glass as well as a sharpened focus on safety – now that chronic disease patients are treating themselves more frequently at home – drives pharmaceutical companies' demand for increased quality from drug containment and delivery system manufacturers. While glass remains the standard for injectable drug containment for the prefilled syringe market, the material's higher dimensional variability in manufacturing could be a concern when evaluating the functionality of the syringe or cartridge in conjunction with the delivery system.

Injector systems can aid patients with self-administration while overcoming the challenges associated with biologics. New patch-injector systems can include polymer cartridges that can be designed specifically to hold high-volume doses of sensitive biologics and offer syringe-like filling on standard filling lines. Many of these systems offer subcutaneous, pre-programmable electronic injection that can deliver the drug over extended periods. They can be made more usable with human factors studies, and their electronic indicators can aid in patient medication adherence and improve caregiver monitoring. The SmartDose® system (shown in Figure 2, discussed in more detail in ONdrugDelivery, Issue 51 (July 2014), pp 26-28) strikes a balance between high-quality drug containment and user-friendly delivery.

In spite of the internal system's complexity, SmartDose has been designed for simplicity and patient comfort, while facilitating the delivery of innovative drug products. West has completed the development and validation of the SmartDose electronic wearable injector to support our customers' human clinical trials. We have also

Figure 2: SmartDose® electronic wearable injector for large-volume subcutaneous delivery.

completed our own first-in-human study successfully, which has demonstrated the performance of the system. We are working with our customers at various stages within their drug development process, including clinical studies.

Other options include designs that center on more traditional containers, such as vials, cartridges or prefillable syringes. Customised cyclic olefin polymer syringes have the potential to contain a higher volume of drug than a conventional glass syringe. Polymer options include the Daikyo Crystal Zenith® 1.5 mL insert needle and 1mL long insert needle syringe systems (Figure 3), which may help prevent breakage. The insert needle syringe may help keep medications pure by reducing exposure to extractables and significantly reducing the risk of protein aggregation caused by silicone oil or tungsten, which are not used within the syringe.

Problems with primary containment materials can result in delayed regulatory approvals, packaging variability and in the worst-case scenarios, shortages of needed drug product on the market. All three problems can significantly damage a pharma company's bottom line as well as its reputation. But quality sometimes comes with high costs, so the challenge for drug containment manufacturers becomes achieving the balance between managing the costs of providing higher quality products while staying mindful of the customer's profitability. Polymers can meet at the intersection of reasonable costs and higher quality.

MANUFACTURING WITH PRECISION

Pharmaceutical and biotech companies can design and develop an integrated system together when they partner early in the drug development process, creating appropriate delivery systems together, sooner. It's particularly effective when these partners implement Quality by Design (QbD) concepts, which are gaining acceptance within the pharmaceutical industry.

In a QbD approach, patient needs drive product specification. The process starts with examining a number of factors: intended clinical setting, dosage strength and delivery mode, sterility, particulate specifications and the container closure system itself. This data-driven component of container development helps ensure the biologic reaches the market in a delivery system that not only helps to protect the drug product's efficacy, but will also help a patient adhere to treatment during any part of the therapeutic lifecycle.

It is the convergence of the drug product itself, the drug manufacturing process and its container closure and delivery systems that establishes the quality attributes necessary for control of specifications such as subvisible particulate, extractables and other quality issues. An example of QbD-designed components includes the West NovaPure® brand of elastomeric components. These products, including vial stoppers and plungers for 1 mL long glass syringe systems were developed with a science-based approach to deliver patient-focused quality over a three-year period. The process paid off by reducing end-of-line rejections and providing high-quality and delivery performance in a variety of systems.

Figure 3: Daikyo Crystal Zenith® 1 mL Long Insert needle polymer syringe system.

Components created through QbD processes that were used in a prefillable syringe system have been shown to optimise break-loose and extrusion performance, provide low part-to-part variability and particulate specification while ensuring high cosmetic quality. When combined with a barrier film, such as West FluroTec® lamination, the components have helped to improve auto-injector performance through dimensional consistency.

SAFETY, EFFICACY BY DESIGN

From manufacturing to delivery, modern biologics require solutions for lifecycle containment. All components that come into contact with a biologic should be designed with patient safety and ease-of-use in mind, but must also suit the sensitivity of the drug product itself. In addition, regulatory agencies and pharmaceutical companies have increased quality expectations in an effort to enhance patient safety.

Glass containment, while suitable for many drug products, may present compatibility issues with biologics, resulting in safety concerns with regard to protein aggregation and glass particulate. High-quality, polymer containment components can be the foundation for effective, easy-to-use delivery systems. They provide quality containment for sensitive products while, at the same time, offering tighter dimension control, low variability and design flexibility to help create administration systems that may help with patient adherence to treatment regimens.

These options present a total lifecycle solution for injectable drug products that will continue to revolutionise packaging and delivery for biologic drug products. As these drugs gain market share, greater scrutiny is paid to the interaction between the drug product and its container closure system. Stability during shelf life, particulate burden and the ease of delivery to patients are important factors to consider.

Biologic drug products often have unique formulations that require high quality, break-resistant systems that will not react with the antibodies. Packaging systems will require flexibility in design, novel primary containment and innovative delivery systems, such as the West SmartDose electronic wearable injector, as well as a thorough understanding of how the needs of the patient, the drug product, the primary container and the delivery system must come together to drive product differentiation, patient compliance and safety.

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Daikyo Crystal Zenith® and FluroTec technologies are licensed from Daikyo Seiko, Ltd. SmartDose® is a registered trademark of Medimop Medical Projects Ltd, a subsidiary of West Pharmaceutical Services, Inc.

West seeks partners for its SmartDose® injector technology platform. This platform is intended to be used as an integrated system with drug filling and final assembly completed by the pharmaceutical / biotechnology company.

ABOUT THE AUTHOR

Dr Nicolas Brandes is responsible for business development and all project and product management activities related to Daikyo Crystal Zenith products in Europe, working hand in hand with West's strategic partner Daikyo Seiko in Japan. Dr Brandes received his PhD in Biology from the University of Wuerzburg, Germany in 2010, after performing his research studies at the University of Michigan, US.

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OMPI NEXA SYRINGES: THE IDEAL SOLUTION FOR THE MOST DEMANDING DRUGS

Here, Alessandro Morandotti, Technical & Quality Assurance Front-End Manager, and Rob Swift, Product Manager, both of Ompi, introduce the Ompi Nexa Syringe, and describe in detail how its design fulfills the challenging quality requirements for prefilled syringes used for the storage and delivery of biological molecules.

The origin of biotechnology and therapeutic biotech products can be traced to the discovery of DNA in 1953. Since that time, extensive research has explored the role of specific DNA segments or chains in biologic processes and diseases.

The key dates are in 1972-1973 when scientists at Stanford University carried out the production and replication of recombinant DNA. The basis of this technology is to introduce a segment of DNA from one organism into the DNA of another host organism. One important application of this technology is to use simple organisms or cells to produce human protein that has therapeutic use as a drug. The first therapeutic product based on recombinant DNA technology was insulin, which the US FDA approved in 1982. Since then, human growth hormone and numerous additional drug products followed these new discoveries.

One of the characteristics of the biotech drugs is the size and geometric complexity of the molecules. These specific aspects have as a consequence the relative instability of the product compared with traditional small-molecule drugs. As a result, the primary packaging materials used to store and administer therapeutic protein products play an important role. Therefore, bio-pharmaceutical manufacturers may require special properties for the packaging materials and for the interactions of the container system surfaces with the drug product formulation.

In many cases, bio-pharmaceutical companies utilise lyophilisation – freeze drying – to ensure the long-term stability of protein products. However, ongoing developments in formulation science are allowing more products to be introduced as liquids for patient convenience and advantage. When this is possible, drug product presentations in prefillable syringes or auto-injectors often are the preferred marketing choice.

THE OMPI NEXA SOLUTION

Today it is common to refer to the syringes used for storing biotech drug as "Biotech Syringes". The idea of identifying these goods is to highlight that behind these syringes there are specially developed manufacturing processes based on the key requirements for the syringes dedicated to biotech drug products. Thanks to the experience from working on different development projects involving drug products, Ompi decided to put together the different identified solutions and to offer a new syringe called Ompi Nexa Syringe (see Figure 1).

This special glass primary packaging can be considered the ideal pharmaceutical packaging solution for biotech drugs. Its key elements are:

- increased compatibility between drug and container
- minimum risk of false rejects of filled syringes
- improved auto-injector compatibility
- superior gliding performance.

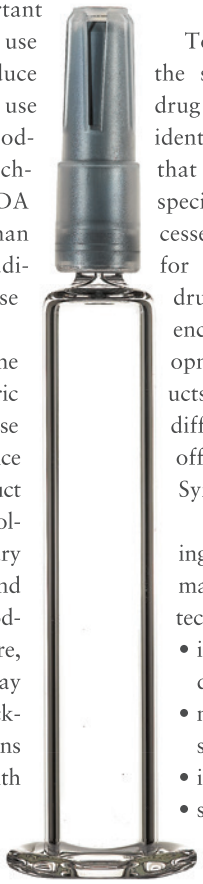

Figure 1: The Ompi Nexa Syringe.

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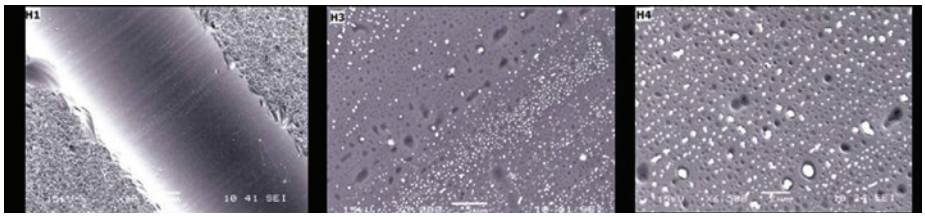

Figure 2: SEM images of showing different Tungsten residuals species.

In addition to the abovementioned features, Ompi is also able to assure regulatory support and a more proactive quality management.

INCREASED COMPATIBILITY BETWEEN DRUG & CONTAINER

In 10-15% of cases, drug formulations have a high to very high sensitivity to one or more of the components of a primary container. During shelf life, interaction between the drug product solution and silicone lubricant on the inner wall of the syringe can result in silicone droplets – typically in the 2-5 µm range. There have been some reports of protein aggregation linked with interaction with silicone.

To overcome such issues with silicone, the numerous experiments have led to an optimised siliconisation process in terms of both silicone distribution and droplet size. Each of these parameters may be factors in silicone particle generation.

Similar issues can be generated also by interactions between the drug product and with the leachable elements of the container system.

The Ompi Nexa Syringe has been developed to optimise the following attributes:

A) Low tungsten through a new specific forming process
B) Low leachables from the adhesive by using an improved needle assembling process
C) Low particles thanks to an innovative washing process of the syringe barrel.

A) Low tungsten through a new specific forming process

Tungsten is introduced into the syringe during the forming process from the pin used to create the internal channel on the barrel tip. This material is used because of the good combination between resistance to high temperatures and mechanical properties. Tungsten residuals appear in different species (Figure 2).

The tungsten metal begins to oxidise to tungsten oxide at about 400°C. Near 800°C this oxide starts to sublime and during the process these vapours are deposited to the glass surface. The contribution of the tungsten residuals is due to the mechanical contact and the high temperature of the pins.

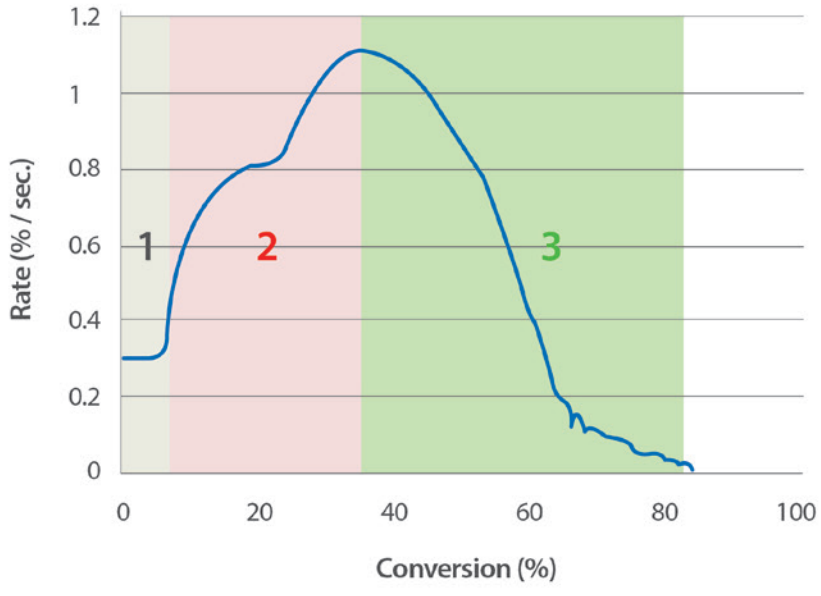

Figure 3: Graph profiling the rate of polymerisation during the UV photocuring process.

The factors influencing the tungsten residuals include temperature and mechanical contact.

Following these principles, Ompi introduced a new forming system to reduce the temperature of pins and to create a sort of protecting layer reducing the interaction as well. The Ompi Nexa Syringe with the optimised forming steps can offer an extracted residual of W mean <250 ppb (Tested according to Ompi internal method ICP-OES).

B) Low extractable from adhesive through improved needle assembling process

Originally, the process for validation of needle assembly developed at Ompi has been centered on the mechanical properties of the assembled syringes (needle pull-out force). However, thanks to a specific customer request to have ultra-low adhesive extractables, different improvements have been put in place meeting this new requirement. These improvements were achieved through a strong collaboration with the customer to develop not only a modified production process but also an adaptation of analytical methods. Up to now, there are no standardised laboratory methods for these specific tests.

The photo-polymerisation theory states that to reach the best adhesive performances (UV curing adhesive) in terms of adhesion and cohesion, the highest UV energy must be applied at the beginning of the polymerisation process. In fact, the polymerisation reaction can be divided into three steps:

1. a constant normalised rate of classical radical chain (see Figure 3, Region 1)
2. a dramatic increase in polymerisation rate (auto acceleration) due to the Trommsdorff effect (Figure 3, Region 2)
3. a rapid decrease in the polymerisation rate as a result of radical isolation: vitrification (Region 3 of Figure 3).

Significant amounts of unreacted functional groups are available in networks cured at low temperatures as a result of vitrification. For this reason, it is crucial to reach the highest possible conversion before the beginning of vitrification. Considering these principles, Ompi has redesigned the needle assembly process and developed a testing method focused on reducing the level trimethylolpropanetrimethacrylate (TMTPMA) – a specific chemical marker for incomplete polymerisation of the adhesive. With the new optimised adhesive curing process, the level of extractable of TMTPMA is typically below the detection limit (<0.05 µg per syringe).

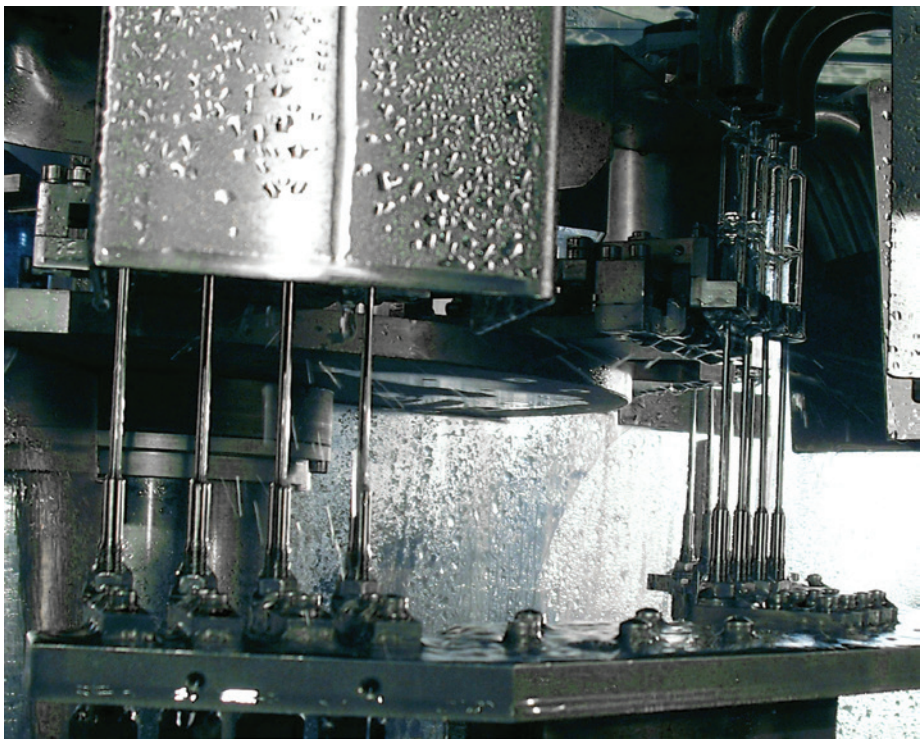

Figure 4: Ompi's high-pressure syringe barrel washing machine whose introduction means that Ompi Nexa Syringes can offer ultra-low particle levels.

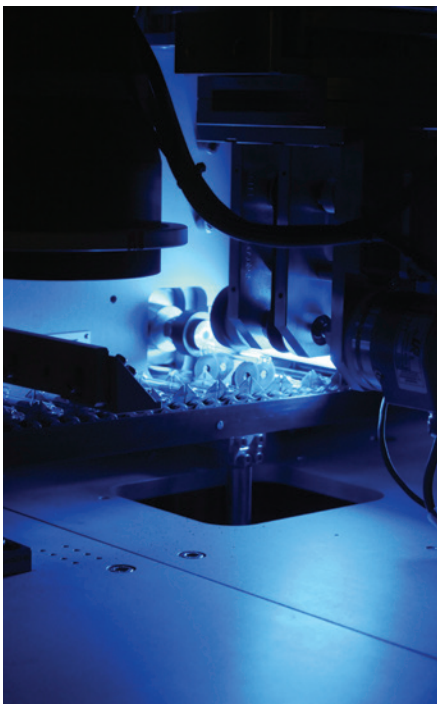

Figure 5: Automatic camera inspection systems monitor quality along the entire manufacturing process.

C) Low Particles thanks to an innovative washing process

As particulate-related issues could potentially lead to injection failure in syringe products, particulates have become an increasingly critical concern in the biopharmaceutical industry. Most of the particles are already present in the raw material (glass tubing) rather than a consequence of the converting process.

As standard practice, the glass tubes are received from the suppliers and then they are introduced into the forming process leaving them as they are. During the production of the glass cane at the supplier site the process is designed to offer raw materials respecting dimensional, chemical and quality attributes.

Specifically for particles, many efforts are put in place for minimising the issue even though the presence of particles due to the cane manufacturing process cannot be avoided. The issue is becoming even more relevant when the size limit for the particles is reduced. In this case, the raw material itself cannot meet this requirement and additional steps in the process are needed to eliminate the particles inherent in the tubing production process.

For this reason the forming process has been improved by developing a high-pressure washing machine (Figure 4) washing each single syringe barrel after forming in order to eliminate the particles already present on the raw material and also any that may be generated during syringe barrel forming.

As a result of the introduction of this process improvement, Ompi Nexa Syringes can offer very low particle levels.

MINIMISING RISK OF FALSE REJECTION OF FILLED SYRINGES

The manufacturing process for the Ompi Nexa Syringes is not only designed to have a good compatibility with the drug but also to assure the best cosmetic quality. Cosmetic quality can be considered as a secondary element. However, all the syringes must be inspected after filling and, considering that the inspection is linked to critical attributes such as small foreign particles and container closure integrity issues, inspection is based on very tight acceptance criteria. Therefore, it is possible that filled syringes may be rejected due to a cosmetic defect of the glass syringe barrel even though there is no impact on drug product quality. Such "false" rejections due to the secondary defects have a direct impact on the manufacturing costs creating losses and additional expenses and reducing the output of the manufacturing process.

The new Ompi Nexa Syringes are produced according to a specific manufacturing process in which glass-to-glass and glass-to-metal contact have been dramatically reduced. These are key factors to produce the desired Ompi Nexa quality.

In addition, to certify the quality of Ompi Nexa Syringes, specific automatic camera inspection systems monitor the quality of the product all along the manufacturing process (Figure 5). The results are stored and analysed before releasing the syringe batch. As results of the gentle handling process and the new camera inspection systems, we have been able to reduce the cosmetic defect rate significantly and offer a superior quality.

INCREASED AUTO-INJECTOR COMPATIBILITY

As a general consideration when we are speaking about drug products in prefilled syringes, we are always thinking about auto-injector devices as an option. It does not mean that all syringes are used in combination with auto-injectors but in the last years, there is an evident trend of increased demand for auto-injectors, because they:

- hide the needle from the user which can help to overcome needle phobia
- generally include safety features to prevent needle-stick injuries
- simplify the injection process which may benefit users with limited dexterity
- could enhance patient compliance through ease of use and lower perceived pain
- may offer a marketing advantage over

ompi | nexa
Syringes

For the most sensitive injectables

Increased compatibility between drug and container

Better silicone oil distribution and low level of tungsten

Superior gliding performance

Optimized silicone oil distribution inside the barrel

Improved auto-injectors compatibility

Restricted tolerances on syringe's flange and shoulders

Minimum risk of false reject of filled syringes

Advanced cosmetic inspection technology

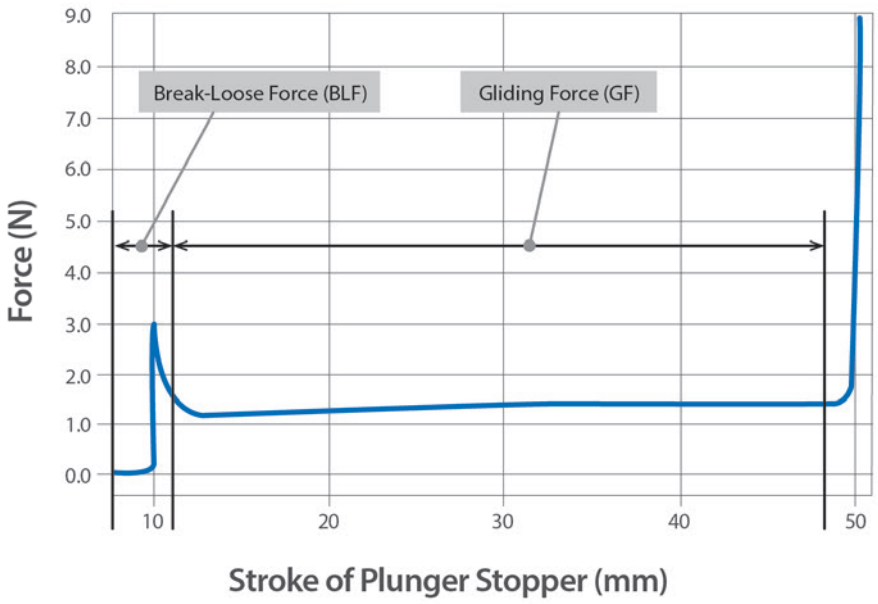

Figure 6: Graph profiling the force required to depress the plunger (break-loose, then gliding force) down the syringe barrel.

competitive products in the same therapeutic area
- can support drug product lifecycle management.

Looking at this list of benefits it seems obvious that auto-injectors are an attractive option for patients and caregivers as well as for biopharma companies. However, incorporating a prefilled syringe into an auto-injector introduces some challenging new requirements for the dimensional and functional attributes of the syringe.

Assembly and operation of the auto-injector may require tighter dimensional tolerances of the syringe flange, body and shoulder. Ompi Nexa Syringes are able to meet these new requirements thanks to manufacturing processes with minimal glass-to-glass contact, a precision forming process and sophisticated dimensional camera inspection systems.

Assembly and operation of the auto-injector may also exert new or different mechanical forces on the syringe when compared with manual injections. As such, syringes for auto-injectors may need to have greater strength. To achieve this, the prevention of surface flaws is a key factor. In Ompi Nexa Syringes, this is accomplished through the dramatic reduction of glass-to-glass contact and verified for each syringe barrel by the cosmetic camera inspection system of the Ompi Nexa production process.

SUPERIOR GLIDING PERFORMANCE

Glide force measurement of empty syringes is a way to characterise the effect of syringe and plunger friction on the overall force required to administer the dose. Typically, this requirement is defined as two distinct forces:
- Break-loose force: the initial force needed to start the injection stroke
- Gliding force: the continuous force needed to sustain motion during the injection stroke.

Figure 6 shows a series of glide force measurements where the force applied to the plunger is plotted on the vertical axis. The horizontal axis shows the distance the plunger has moved along the injection stroke. At the right side of the figure, the force rises rapidly at end of the stroke when the plunger contacts the inner surface of the syringe shoulder. A similar test procedure typically is performed using filled syringes to measure the break-loose and extrusion to deliver the drug product.

The uniform and homogenous distribution of the Ompi Nexa siliconisation process results in consistent and predictable gliding force behaviour required for demanding biotech and auto-injector applications.

CONCLUSIONS

The Ompi Nexa Syringe can be considered the optimised packaging solution designed around key attributes linked to the drug product storage and administration.

Thanks to the increased compatibility between drug and primary container and the reduced level of false rejections due to quality level, Ompi Nexa Syringes are improving the timeline for stability studies and reducing costs during the fill-finish operations. Regarding the combination with auto-injectors or safety devices, the design of the syringes has been optimised to offer improved performance and reduce risk of failure. Last but not least, the optimised siliconisation process offers a superior gliding performance that is key, especially for auto-injector platform solutions.

CREDENCE MEDSYSTEMS & THE CREDENCE COMPANION SAFETY SYRINGE SYSTEM

In this article, John A Merhige, Chief Commercial Officer, Credence MedSystems, Inc, summarises the Credence Companion Safety Syringe System, and how it fits with the company's core philosophy of Innovation Without Change for the benefit of biopharmaceutical partners.

INNOVATION WITHOUT CHANGE

The Credence Companion Safety Syringe System was born from Credence's core philosophy of *Innovation Without Change*. Traditionally, pharmaceutical companies have been forced to make an undesirable compromise between delivery system innovations and the time, cost and risk associated with implementing those innovations. The choices have been either to do nothing, to persevere along the long development path traditionally required with implementing innovations, or to seek a middle ground that checks the "needlestick safety" box but misses the opportunity to differentiate.

> "Drug companies no longer have to ask, 'What trade-offs must we make?'"

Innovation Without Change is a product design and business partnering philosophy that reframes the question. Drug companies no longer have to ask, "What trade-offs must we make?" *Innovation Without Change* enables them to ask, "How can we help the end user performing the injection and satisfy our own needs for a streamlined development path and trusted supply chain?"

INNOVATION – A BEST-IN-CLASS DRUG DELIVERY DEVICE

Safety and Compliance

The Companion Syringe is a best-in-class safety device with integrated, passive needlestick prevention features. The needle retracts automatically into the barrel of the syringe after the injection. The user is provided audible, tactile and visual cues of the safety engagement and the syringe is then automatically disabled, thereby preventing reuse. This passive safety is applicable even to deep intramuscular applications where long needles are used.

Differentiation that Goes Beyond Needlestick Prevention

The Companion allows the user to perform routine syringe procedures such as standard air bubble removal and aspiration techniques without concern for the premature activation of the safety mechanism that plagues other safety products. The Companion can even be utilised for reconstitution applications. The diluent can be injected into the vial and then the solution drawn up into the syringe without concern for premature safety engagement, all while maintaining the passive safety intact for the subsequent injection into the patient (see Figure 1, left section).

Luer or Staked: Which is best for the application?

Certain applications require a luer connection needle. For example, drugs requiring reconstitution mandate that a needle be attached after reconstitution but before patient injection to ensure a sharp needle. Intramuscular applications require needle choice flexibility at the point of injection to ensure the needle can reach the intramuscular space. However, luer needles come with a risk of a poor connection between

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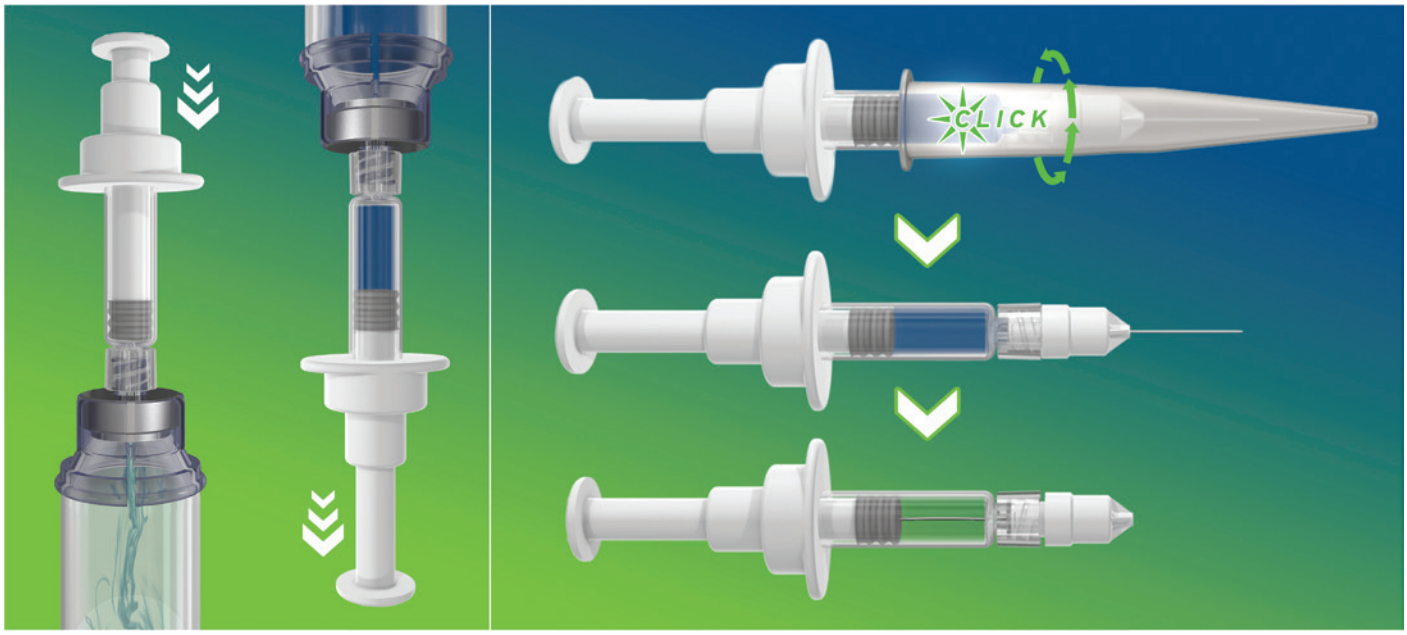

Figure 1: Best-in-Class Drug Delivery: The freedom to perform standard syringe procedures, Click Confirmation of a proper needle attachment, and passive needle-retraction safety.

the needle and the syringe. The Credence Guide-On Needle Cover addresses this risk by providing the user audible, tactile and visual feedback that the needle connection is secure. It does not expose the needle until the needle has been attached properly (see Figure 1, right section). If on the other hand a staked-in needle is preferred, the *Innovation Without Change* design philosophy has yielded a staked needle version of the Companion. The user still experiences the passive needle safety and human factors benefits seen in the luer solution, but does not have to attach a needle. Further, there are no adhesives used in the manufacture of the Companion system, removing the risk of drug substance/adhesive interaction.

WITHOUT CHANGE – A SIMPLIFIED COMMERCIALISATION PATH

The Companion staked and luer syringes are built around the foundation of any existing prefilled syringe, plunger / stopper, and tip-cap / needle-shield primary package components. The filling process is unchanged. The Companion plunger rod and Flex Finger Flange are added to the already-filled syringe in a secondary assembly process. The Guide-On Needle is either included in the kit in the luer presentation or already affixed to the syringe in the staked presentation. Because the pharmaceutical manufacturer can choose any existing prefilled syringe from any vendor and can keep their syringe filling process unchanged, much of the development and regulatory work as well as the sourcing risk traditionally associated with delivery system advances can be avoided. This reduces the cost, time and complexity of launching drugs in a differentiated device.

INNOVATION WITHOUT CHANGE – IN THE PARTNERING MODEL

This passion for offering our partners Innovation Without Change extends to our business model and the supply chain flexibility it provides. Just as our biopharm partners have the freedom and flexibility to choose and source the critical primary package components of the syringe, they *also* have complete freedom to choose their preferred molding and assembly partners. Credence provides its expertise in technology transfer and automation to deliver a seamless integration into the assembly process.

Credence approaches every challenge with the philosophy of offering Innovation Without Change in order to improve patient care by addressing the needs of both the end-user and our pharmaceutical manufacturer partners.

ABOUT CREDENCE MEDSYSTEMS

Credence MedSystems is focused on delivering medications safely for the benefit of our patients, caregivers and pharmaceutical partners. The Credence team brings curiosity, a fresh perspective and an intense desire to understand the needs of both the end-user and pharmaceutical manufacturer to the overriding goal of improving patient care.

HOW TO CONTACT CREDENCE

Come see the Companion Safety Syringe System at **Pharmapack Europe, Stand #728**.

For more information, please visit www.CredenceMed.com or reach out to John Merhige.

Note: This product has not been evaluated by US FDA.

"There are no adhesives used in the manufacture of the Companion system, removing the risk of drug substance/adhesive interaction"

THE CREDENCE COMPANION
SAFETY SYRINGE SYSTEM

THE CREDENCE COMPANION

SAFETY SYRINGE SYSTEM

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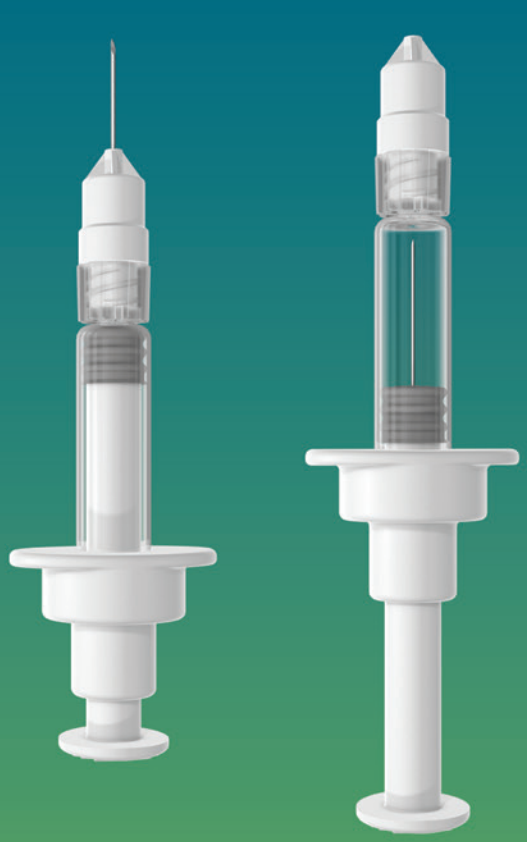

STAKED IS HERE

INNOVATION WITHOUT CHANGE

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This product has not been evaluated by FDA.

CREDENCE MEDSYSTEMS

CRACK PREVENTION & PROCESS **CONTROLS** IN PREFILLABLE SYRINGE MANUFACTURING

Here, Andrea Behrenswerth, PhD, Quality Assurance, and Marc-Oliver Luther, Method Validation & Intercalibration, both of Gerresheimer Bünde, and Bernhard Hinsch of Hinsch Consulting (Hamburg Germany), explain the most frequently encountered types of defects, their causes and specific approaches to process optimisation. The article goes on to present the process used by Gerresheimer Bünde for the identification and classification of defects in ready-to-fill syringes.

INTRODUCTION

In the production and processing of ready-to-fill syringes, a multitude of defects with varying levels of severity can occur. The spectrum extends from cracks that penetrate the glass body completely to superficial scratches. For efficient quality management it therefore makes sense to classify defects not only by patient risk but in a way that makes it possible to derive conclusions as to their cause.

The PDA Technical Report 43 defines a crack as break that penetrates the glass barrel completely.[1] However, in light of the many different types of defects that can occur, this definition leaves a number of questions unanswered. For example, it is necessary to clarify how cracks which do not penetrate the glass barrel completely and those which do not lead to breakage or permeability (non-leaking cracks) are classified.

Various approaches are feasible for such a classification. From a quality perspective, it is a good idea to take the patient-risk associated with the impaired integrity of the glass barrel as a primary criterion. This results in a three-stage classification process leading to the identification of:

- Cracks: critical defects
- Checks: major defects
- Scratches: cosmetic (minor) defects.

Cracks result in a discontinuity in the glass matrix which impairs the glass barrel's integrity. The substantial health risks to patients are potential leakage or microbiological contamination, so cracks are classified as a critical defect. If a crack is suspected, the defect must always be inspected. The methods used are described here below.

Checks are discontinuities in the glass matrix which do not impair the glass barrel's integrity, even under mechanical or thermal stress. They are classed as major defects, but they do not pose any risk to patients. Scratches are superficial defects which can mean a loss of material, but do not cause discontinuity in the glass matrix and are therefore classified as cosmetic defects.

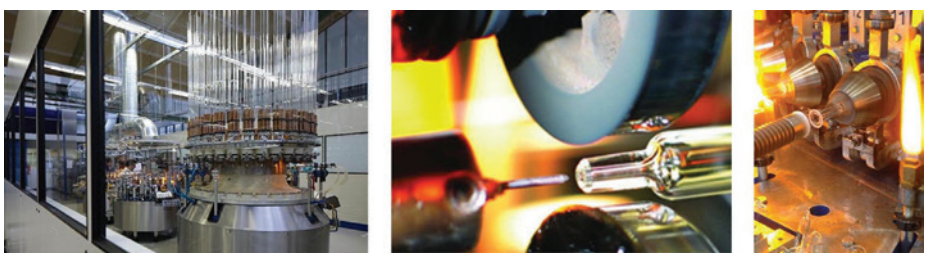

Figure 1: Syringe manufacturing: forming the cone (centre) and finger flange (right).

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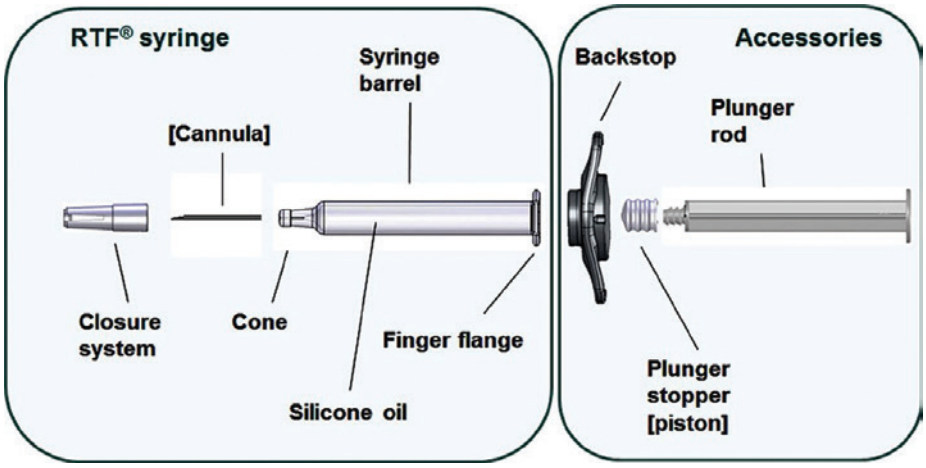

Figure 2: Components of an RTF syringe.

CLASSIFICATION OF DEFECTS BY LOCALISATION & CAUSE

If the classification of defects is to serve as the basis for the systematic optimisation of production processes, a differentiated view which is oriented on defect position and defect cause is useful. Syringe production involves a series of steps with interim quality inspections, the first of which is tube cutting.

There are two forming processes in which first the syringe shoulder and tip, and then the finger flange are created (Figure 1). Next the syringe is optionally printed, annealed and, if the customer requests it, polished. Depending on the type of syringe, a needle is sometimes also glued into the hole of the syringe tip. The production of ready-to-fill (RTF) syringes involves a number of additional process steps in which the syringe is washed, siliconised and sterilised. Some are then fitted with a tip-cap, or a rigid or flexible needle shield (see Figure 2).

The customer-side processes also have to be taken into consideration. Unpacking and packing processes, filling, labelling and transportation exert mechanical loads and therefore can potentially cause defects in syringes which are supplied intact. It therefore makes sense to ensure that customer process management is tailored to the material of glass and for the customer to take recourse to the know-how and support of the syringe manufacturer.

Defects can also be caused by factors outside the process chain. Each phase of production or processing is therefore associated with a specific range of potential defects which are typically located at a specific position on the syringe. For example, cracks typically occur on the finger flange, or on the syringe barrel originating from the finger flange or cone, and different types of cracks and damage can occur to the syringe barrel itself. Another problem is posed by so-called "cone cracks", which aren't cracks in the strictest sense, but lines or seams caused by the forming process.

Cracks on the Finger Flange

Cracks on the finger flange (Figure 3a) are classified as major defects because they do not impair the syringe's integrity. They are predominantly located on the flat sides of the finger flange and are caused when the circular glass surface is cut in the production process. These cracks can occur if the glass is too cold or due to the temperature difference between the glass and the cutting tool being too great. The cause can also be mechanical when, for example, the cutting tool is too blunt, the overcut is not large enough or when cuttings collect in the cutting area. Accordingly, the cracks can be avoided by optimising the temperature setting, improving the tools and cutting parameters and by promptly suctioning off the cuttings.

Body Cracks

A study implemented by Gerresheimer Bünde revealed that 80% of body cracks (Figure 3b) are located on the cone side and 20% on the finger flange side of the syringe barrel. This is a critical defect because it can impair the syringe's integrity, though assessments of body cracks have to be made on a case-by-case basis.

However, extensive tests have revealed that cracks of less than 1 mm in length do not cause leakage, even when the syringe is exposed to mechanical loads. Barrel cracks at the ends of the syringe are caused by tube cutting. The tubes are first scratched by a diamond blade. Afterwards the cut line is heated with a hydrogen burner and the tube is separated by application of a water nozzle. Cracks often occur when the nozzle is too wide or incorrectly positioned, so this defect rate can be considerably reduced by optimising the relevant parameters.

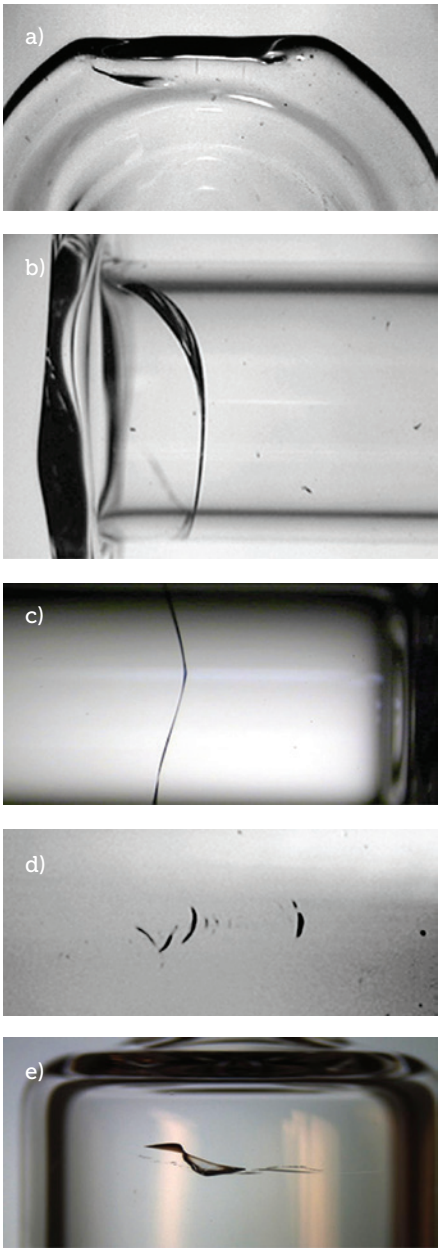

Figure 3: Examples of different types of cracks: a) on the finger flange, b) on the body, c) stress cracks, d) shell (or thermal) cracks, and e) impact cracks.

Stress Cracks

Stress cracks (Figure 3c) occur at the center of the syringe barrel. They can impair the syringe's integrity, so they are classified as critical defects. Like body cracks, these are defects that have to be assessed on a case-by-case basis. Stress cracks occur due to inadequate annealing of the glass after the moulding processes, for example, due to a defect in the annealing oven. This defect's rate of occurrence can be reduced by monitoring annealing in the production process and optimising the relevant parameters.

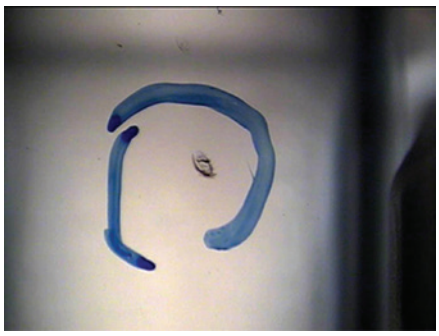

Figure 4: An example of checks on the syringe barrel.

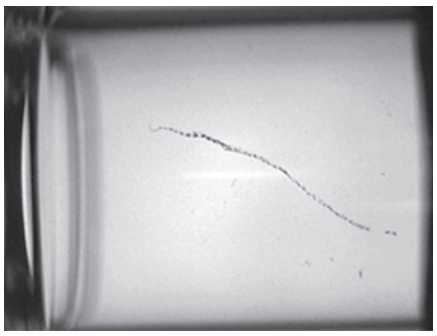

Figure 5: Scratches on the syringe barrel.

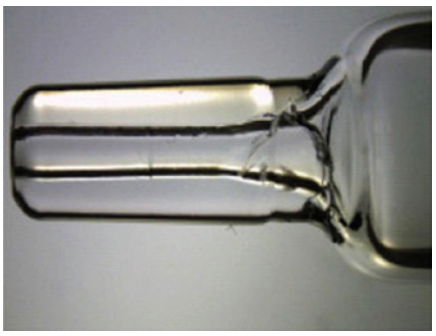

Figure 6: Spiral cracks with low fatigue strength called cone cracks can be found on the area where the cone meets the shoulder.

Shell Cracks (Thermal Cracks)

Shell cracks (Figure 3d) are also known as comma or thermal cracks. They, too, occur at the centre of the syringe barrel. Even though they are caused by thermal stress, shell cracks should not be confused with stress cracks because they are only superficial defects. They do not impair the syringe's integrity, so they are merely classified as major defects. Shell cracks are caused by the temperature difference between the syringe barrel and the lining of the metal clamp that is used to handle the syringe being too great. They can thus be avoided by reducing the temperature difference or selecting a more suitable lining material.

Impact Cracks

Most of the above-described defects are caused by thermal stress. However, mechanical stress can also cause cracks on the syringe barrel (Figure 3e). These cracks can impair the syringe's integrity, so they are classified as critical defects. Here, too, each crack has to be assessed on a case-by-case basis. They can be caused by a mechanical impact such as a knock, which can be avoided by gentle handling and transportation processes.

Checks on the Syringe Barrel

Checks on the syringe barrel (Figure 4) are caused in a similar way to impact cracks. They are a discontinuity in the glass matrix but do not impair the syringe's integrity, so they are classified as major defects. Checks can be caused by mechanical damage during transportation or hard glass-glass contact. Measures to avoid checks therefore include the optimisation of handling and transportation processes and the minimisation of contact between syringes.

Scratches on the Syringe Barrel

Scratches on the syringe barrel (Figure 5) only affect the surface and do not cause a discontinuity in the glass matrix. Therefore, they are classified as minor defects. The cause is glass-glass contact, which should be minimised in handling and transportation.

Cone Cracks

Spiral cracks with low fatigue strength called cone cracks can be found on the area where the cone meets the shoulder (Figure 6). These aren't strictly cracks, but lines or seams, created in the forming process, which do not impair the syringe's integrity. As a result, they are classified as a major defect. These cracks can be caused by an incorrect temperature profile in the forming process or if the forming roller presses the glass too hard as a result of the undercut diameter being too large, creating lines or seams. This defect can be considerably reduced by optimising the temperature profile.

AVOIDANCE OF CRACKS IN THE PRODUCTION PROCESS

By optimising the process parameters along the entire supply chain and using gentle handling technologies, glass defects in the production of ready-to-fill syringes can be systematically avoided.

Gerresheimer Bünde has implemented a pilot project and transferred the results to the other production lines. Customers in the biotech segment attach particular importance to low packaging-related reject rates because some of the pharmaceuticals they fill into the syringes are very expensive. The optimisation measures implemented by our mechanical engineering team extend from enhancing the precision of tube cutting, to optimising forming operations – particularly the cone forming process – and improved controls in the annealing process. Key overall project objectives were the reduction of temperature differences between the glass and the handling elements, and the reduction of mechanical stress during handling. Both the general avoidance of glass-glass contact and the selection of appropriate materials play an important role in this respect. For example pick-and-place technology, or the use of polyether ether ketone (PEEK) elements during syringe transportation ensure particularly gentle handling.

In-line production-quality inspections are performed with a third generation (G3) cosmetic camera system. The collaboration between the quality management and camera development teams is particularly important when selecting the defects to be identified. After forming the finger flange and before pressing, the syringe barrel is checked for cracks, checks and scratches, but also for bubbles, inclusions, airlines, glass particles and impurities. By rotating it on the vertical axis, it is possible to inspect the entire surface of the syringe barrel. Defects are identified on the basis of their specific grey scale contrast. The G3 system can theoretically detect defects as small as 0.0025 mm in length or with an area as small as 0.00625 mm^2. In practice, the system is currently used to detect defects with a length of 0.3 mm or longer or with an area of 0.1 mm^2.The shoulder, finger flange and transition areas can also be inspected for cosmetic defects.

CRACK CLASSIFICATION METHODS

Not all defects in a syringe penetrate the glass barrel leading to leakage or microbiological contamination. Thus it is necessary to differentiate between genuine cracks, which are critical defects, and checks or scratches, which are superficial and therefore only classified as major or minor defects. In this respect, the decisive issue is minimum strength under mechanical stress. Generally, all defects of less than 1 mm in length are leak-proof. There is a multi-stage inspection process for the systematic classification of defect type for syringes which are rejected in the visual inspection due to having defects of more than 1 mm in length (Figure 7).

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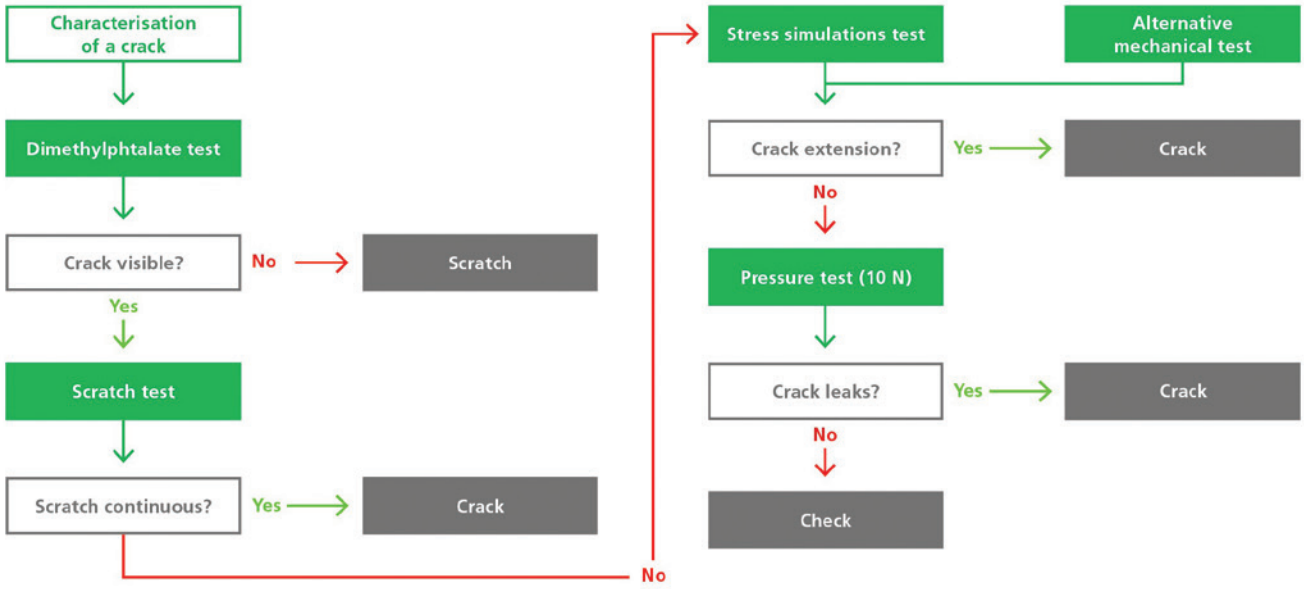

Figure 7: Crack identification procedure flowchart.

Dimethylphthalate Test

The first stage of the classification process is to fill the syringe with dimethylphthalate (>99%), to wet the outer surface with dimethylphthalate and to clean it with a lint-free cloth. Dimethylphthalate has the same refraction index as glass. When viewed under an overhead light, scratches lose their typical shine when they are filled with the chemical. In contrast, cracks penetrate all the way through the glass. Since the chemical cannot fill the entire crack, it remains visible. In this classification process, all syringes with scratches can be identified.

Scratch Test

In the second stage of classification, the potential crack is tested to see whether it penetrates all the way through the glass. A syringe needle (27G with V-bevel) is scratched across the defect at a right angle. This procedure is repeated on the inside and outside at least five times. Any discontinuity in the glass matrix is perceived as slight resistance, because the needle gets caught on the ridge that is created. If the same effect occurs on the inside and outside, it is established that the crack penetrates all the way through the glass.

Ph Eur & DIN EN ISO Stress Tests

In the third stage of classification, tests are performed to see whether the defect becomes larger under thermal stress. There are two official procedures for this test. In the stress test pursuant to the European Pharmacopoeia Section 3.2.1A,[2] the syringe is placed in a beaker and then put into an autoclave. The temperature is increased at a rate of 1°C/min to 121°C and maintained for 1 hr. Then it is cooled at a rate of 0.5°C/min to 100°C. In contrast, the stress test pursuant to DIN EN ISO 7459 includes temperature shocks such as occur in industrial processes.[3] The syringe is placed in a water-filled beaker and heated up to 100°C. Then it is left in there for 5 min. The syringe is then dipped into a water bath at 20°C within one second and left there for 30 seconds. If the defect becomes larger during the stress test, it is classified as a crack.

Pressure Test

In the fourth and final stage of the classification process, the defect is tested for permeability. The syringe is sealed with a tip-cap or needle protector (RNS) and filled with a coloured solution (0.5% Triton X-100, 0.05% toluidine blue in water) to a level above the defect. Then the plunger head is inserted, any air pocket is eliminated and the plunger is screwed in. Pressure of 10 N is then exerted on the plunger and maintained for more than 30 seconds. Afterwards, the outside of the syringe is wiped in the area of the defect with a white cellulose cloth. If the blue solution is visible on the cloth, the defect leaks and is therefore classified as a crack. Otherwise, the defect does not penetrate through the glass (scratch test), remains stable under stress (stress test), is impermeable (pressure test) and therefore classified as a check.

Mechanical Test

An additional mechanical test can also be performed which involves the potential crack being exposed to mechanical stress from a die. The exerted force is gradually increased until the syringe breaks or a defined value is achieved. If the syringe breaks or the defect becomes larger under the defined load, it has a critical defect.

OUTLOOK

Processes and automated quality inspections with camera systems are today so advanced that the rate of cracks and cosmetic defects in supplied products is in the low ppm range. However, there is still potential for the optimisation of post-production processes at the customer's site, particularly filling, visual inspection and packaging processes. Here, potential damage to the syringes can be avoided by reducing fall distances and shear forces. Collaboration between glass experts and the pharmaceutical industry early on in the production process and automation technology can contribute to the development of more efficient solutions. The same applies in the development of complex drug delivery devices containing syringes such as autoinjectors. Joint development operations will ensure that the syringe and injector's dimensional tolerances and functional properties (siliconisation) can be optimally matched.

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INTERVIEW: JEANNIE JOUGHIN, CSL BEHRING

Enable Injections has developed a platform technology to deliver high-viscosity / high-volume payloads up to 20cc to the subcutaneous tissue. The system, which was presented in detail in ONdrugDelivery Magazine, July 2014, Issue 51, pp 30-33, is wholly mechanical and uses standard vial, syringe or cartridge container closure, and can automatically mix lyophilised solutions. Founded in February 2010, the company has R&D and manufacturing facilities in Franklin, OH, US.

In October 2014, Enable Injections and global biotech giant CSL Behring announced a major agreement for the development of Enable's drug delivery system to improve the comfort, convenience and treatment compliance for patients with rare and serious diseases. Under the agreement, Enable will initially develop, manufacture and sell its innovative delivery device, which was specifically designed for subcutaneous dosing, to CSL Behring for use with one of CSL Behring's products on an exclusive worldwide basis. Here, Dr Jeannie Joughin, CSL Behring's Vice-President of Business Development, speaks exclusively with ONdrugDelivery Magazine about the agreement with Enable, how it came about, what it means to the two companies, and how it's going so far.

Q: Please could you give us a short overview about CSL Behring's business?

A: CSL Behring is a global biopharmaceutical company specialising in protein therapeutics also targeting products to treat patients with rare and difficult-to-treat disorders. Our products help to save lives or to improve quality of life.

In terms of our size, we have more than 13,000 employees worldwide and our market cap is close to US$40 billion. Our head office is in Australia as we are listed on the ASX. However the major operational hub is in King of Prussia, PA, US. We have major manufacturing sites in Australia, the US, Germany and Switzerland. Each site is a centre of excellence with individual specialities – not specific single protein products but specific groups of products.

As mentioned in the press release announcing the agreement with Enable Injections, this deal is with our Bern, Switzerland site, because they are responsible for certain products that we are looking to bring through development for delivery using the Enable device.

Q: Different pharma companies have different ways of looking at drug delivery and different strategies for getting their products into the right drug delivery devices. Could you give us an idea of how CSL Behring approaches drug delivery?

A: Our expertise and our heritage is in plasma therapeutics, therapeutic proteins and monoclonal antibodies, so as we develop these proteins in the key therapeutic areas that we focus on – always relating to rare and serious diseases – we now are really focusing our strategy on how we deliver those to patients. We have products approved around the world; often state-of-the-art products, leaders in their field, and first to market in some instances. For example, Hizentra®, our 20% immunoglobulin solution for subcutaneous self-administration, was the first product of its kind to reach the market.

We often lead innovation in protein therapeutics, so now we are trying to think about how we can lead innovation in delivery of our products to patients and how we can make the patient experience better. Now although we are focusing on this, our experience lies in maintaining the highest quality of our protein products and as such we know we are not a device company. Thus we're looking to form partnerships with other companies whenever it makes sense. With Enable it made sense to partner their technology with our products in certain patients with certain indications where high dose volumes and / or viscous formulations are delivered subcutaneously. However, this device is not going to be our one device applied across the board for all of our plasma protein portfolio, because there are different requirements. Some products of course are delivered only by intravenous injection, and some are only very small volume or only require very quick SC injections. Nonetheless, the Enable device is an important component of our strategy for the development of delivery devices with our products, specifically devices that meet patient needs.

Speaking generally, some of our products can be delivered both IV and SC, and the chosen route is the individual patient's choice. Some want to go to hospital and have the comfort of people who know them and nurses looking after them – some people prefer that and will go once every month or every two weeks for IV. For other people who are perhaps busier, or children, for example, SC delivery fits their lifestyle better. And within those who prefer SC delivery, there are some who want the medication administered quickly, to get it over with and get on with their day because they perhaps have work or school commitments or just don't want to be reminded about their condition. Others don't mind sitting with an SC pump for a couple of hours reading a book, and they don't mind being tethered to the pump with long tubes because they are used to that system and they trust it.

So, we see the Enable device appealing to needle-phobic patients, perhaps younger patients who are more active, patients who are working and busy and want to continue to go about their business, and various other segments that we have identified and probably others that we have not yet identified.

It offers the convenience and that's what really appeals to us and it really appeals to patients.

> "We lead innovation in protein therapeutics, so now we are trying to think about how we can lead innovation in delivery of our products to patients and how we can make the patient experience better"

We can also make the Enable technology specific to our products. Enable can make a device that delivers at a specific infusion rate, or which has a particular needle depth. It is all leading toward the end goal of delivering our products in the best possible way to our patients. That's what really drove us. And also, it's a really funky looking device, it's cool, people responded well to it, and that matters.

Q: Tell me, how are things going with Enable since partnering with them in October?
A: We have an excellent collaboration with Enable. We brought them into our company, into many of our team meetings. You can imagine – we're a really large company, we have a lot of infrastructure and many meetings, there are a lot of people involved in lots of different areas. We've invited Enable in to get to know our structure and they are adapting aspects of their structure to meet our needs. At present we are very much in the middle of the stages of planning and producing specification documents. We're also in the very early stages of running our regulatory studies. Enable is in the process of gearing up for manufacturing. So there is a lot of activity at the moment!

> "The Enable device is an important component of our strategy for the development of delivery devices with our products, specifically devices that meet patient needs"

Q: Could you give us some detail on how the agreement came into being? How did the two companies come together?
A: Sure. I've been searching for devices that could be compatible with any of our products. It has been a really thorough search in all of our different therapeutic areas. As part of that search I went to see Enable President Mike Hooven's presentation at BIO 2013 and arranged to meet with him. Immediately I could see the technology's applicability to several of our proteins.

That was the commencement of our relationship if you like – June 2013. Then, over the next year, we had several meetings discussing their technology. I introduced Enable to several members internally, and then it was a process of working through discovering whether using their technology would be feasible. So we exchanged products in effect – they sent us some of their devices and we sent them samples of our products. This was essentially to see if our products could actually be delivered using their device. This was done under a material transfer agreement. Once we'd proven it was technically feasible, that was when we moved on to discussing what a relationship between us could look like and that was when the internal presentations to CSL Behring senior management were made. We agreed in June 2014 – only one year after first meeting Enable – to offer terms. We negotiated terms and progressed to signing the agreement. So it was very fast but over that time we had interaction with Enable at all levels of our company.

Q: Whilst it's obviously a prerequisite that the technology fits with your products and other aspects of the two companies need to align for a partnership to be possible, I was wondering do you place much emphasis on the softer factors – company culture, personalities and the like – when you are looking for a partner?

A: Yes, very much! As mentioned, we started looking for device technology partners in 2010 (and I should mention that our searches in that area are still ongoing) and we have had the opportunity to review several companies, to meet with several companies, have in depth discussions. What really stood out from Enable ever since Day One – and I think everyone in our organisation who has dealt directly with them would agree with this – is that they are responsive. Incredibly responsive.

Every time we were brainstorming internally and came up with a potential roadblock I would just pick up the phone, call Mike and say, "About this aspect, we've been discussing it and we can see that we could have X issue on our side because of Y." And it would be one or two days later he would come back to us with a new prototype, a new design, completely addressing our issue. And that continued – whatever we threw at them, they would come back with a solution or an alternative, which made us really confident to go ahead in the end. You know, we didn't have the final specification nailed down when we settled the terms and signed the agreement, but we knew we were on the way and that for any issues that came up the design could be adapted. We had that much confidence in them. They are very, very attentive and customer focused I would say.

Q: This is a hugely important partnership for Enable as a relatively small company. How significant is a deal like this for a very large company such as CSL Behring?

A: It's a very important deal for us because it allows us to expand upon our patient focus. The Enable device is going to be an important offering but it is not going to be the only offering. We want to put forward a range of alternatives for our patients because we know one size does not fit all. This strategy is really going to establish us as a very customer-focused company within our sector, intent on delivering products that improve patient quality of life. The direct feedback we have had from our patient focus-groups is that the Enable design will improve their quality of life.

Q: Looking towards the future and the way things are moving in the industry with respect to parenteral drug delivery, could you speak a little on how this fits with the types of products CSL Behring develops?

A: One thing I've noticed by attending industry meetings is that interest in the area of parenteral drug delivery devices is growing, particularly for biopharmaceutical companies because in many of the therapeutic areas there is very little differentiation and companies are trying to differentiate their products for a better offering to patients. We are seeing an increasing number of "me-too" products and so the need for differentiation will likely continue.

At the moment though a lot of biopharma companies, like CSL Behring, are still very focused on the quality of our own products and so are not ready to take a leap into diversification into device development, preferring to partner. It could be that in the future larger companies will increasingly internalise device development and manufacturing but – my personal feeling is – it is probably better for pharma companies to focus on their products and look outside for devices that make the best fit. If you have invested in development of an internal device then you may be tempted to try to make that fit when in fact it doesn't quite fit. Forcing the fit with your internal device should not be the key driver – the key driver is whatever device works best for that particular product and that particular patient group.

In terms of the future of our collaboration with Enable, we signed the initial agreement with one product focus in mind. However we are working on a second product with them which we think will really benefit from the Enable Injections delivery system. So as we look to our future pipeline and the attributes line up between our products and their system, we will likely continue to expand our relationship. Naturally that will be dependent on the success of our first launch, and the continuing good collaboration and relationship between Enable and CSL Behring.

> "What really stood out from Enable ever since Day One – and I think everyone in our organisation who has dealt directly with them would agree with this – is that they are responsive. Incredibly responsive"

> "It's a really funky looking device, it's cool, people responded well to it, and that matters"

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Dr Jeannie Joughin is responsible for managing CSL Behring's current business licensing arrangements and relationships as well as building the business for tomorrow. Dr Joughin began her pharma industry career in 1992 as a Clinical Research Manager with Bristol-Myers Squibb, moving into New Product Commercialisation. From there, she worked in Brand Management. After successfully completing several marketing roles in the National Stroke Foundation, MediMark International and Mayne Pharma, Dr Joughin joined CSL Biotherapies in 2005 as Director, Pharmaceuticals Marketing and In-licensing. She has also held various scientific positions including Senior Research Scientist, Post-Doctorate and Senior Post-Doctorate positions in Australia at The Alfred Hospital, The Walter & Eliza Hall Institute, as well as internationally in Austria (University Clinic, Innsbruck) and Switzerland (Ludwig Institute for Cancer Research, Lausanne). Dr Joughin holds a Bachelor's degree (Hons) and PhD (Immunology) from Australia's Monash University and a diploma in marketing from Melbourne University.

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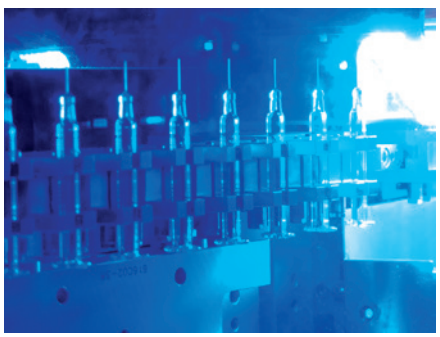

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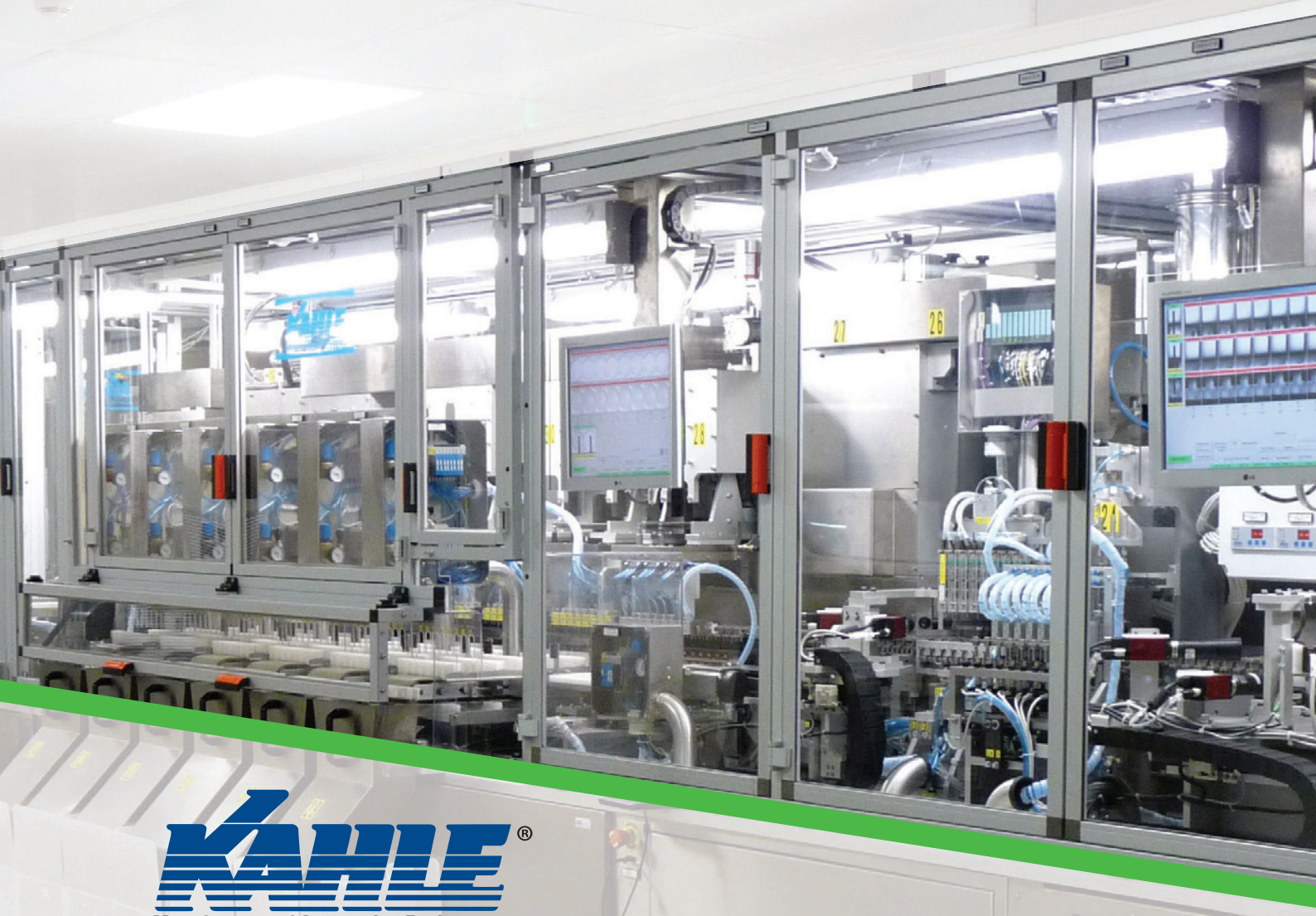

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COMPANY PROFILE: **NEMERA**

Nemera

In 2014, the healthcare business formerly known as Rexam Healthcare Devices became Nemera. This name change followed the May 2, 2014 acquisition by Montagu Private Equity. Nemera continues to operate with the same management team and its choice of name signifies a renewed commitment to its mission of providing patients with safe and accurate delivery devices.

NEMERA'S INNOVATION CENTRE

Innovating for patients is at the core of Nemera's mission. More than 50 engineers and experts work to achieve this at the Innovation Centre at La Verpillière, near Lyon, France.

The scope of the Innovation Centre includes the collection of patients' insights, market watch, concept generation, IP monitoring, regulatory expertise, detailed risk-based design, design for manufacturing and support to plants for product life-cycle management and problem solving when appropriate.

Patient Insights & Human Factors Studies
Technical expertise and patient usability always work hand-in-hand. Along with the many fields of technological expertise (like material, mechanical and manufacturing engineering, mathematical models and other), creative design and usability assessment including Human Factors (HF) studies, are central to product development. The Innovation Centre carries real-world evaluations, through impartial volunteers and collects user feedback. Sophisticated technologies, like fast-camera tracking, give engineers an inside view of the way the device is used, making it safe and accurate for the patient.

Proprietary Devices & Contract Development
We apply the same quality-oriented process to the development of proprietary devices and to customised solutions under contract with laboratories.

The development quality team guarantees full compliance not only of the final device but of all the development chain. Strong programme management ensures that the project is delivered on time and within budget.

NEMERA IN FIGURES

- 4 plants in Europe and the US
- 50 engineers and experts working at the Nemera innovation center
- >1,300 employees
- >30,000 square meters of manufacturing clean-rooms

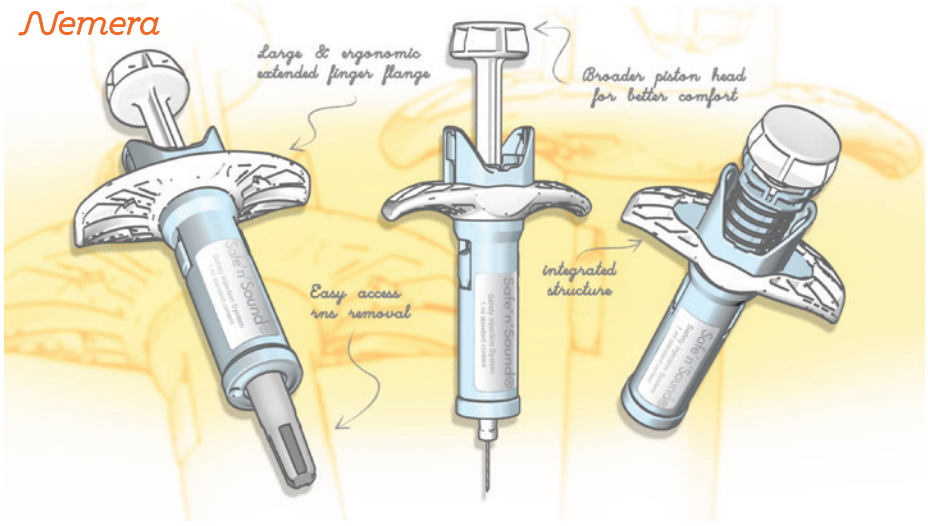

Figure 1: Concept drawings for an ergonomic Safe 'n' Sound® needle-safety device.

"More than five million diabetics and ten million asthmatics rely everyday on devices manufactured by Nemera"

A WORLD LEADER IN DRUG DELIVERY SOLUTIONS

Nemera is one of the world leaders in the design, development and manufacturing of drug delivery solutions. Nemera's expertise encompasses five modes of delivery: ophthalmic (preservative-free droppers), nasal, buccal, auricular (sprays pumps, etc); pulmonary (DPIs and standard valves for pMDIs); dermal and transdermal (dispensers); and parenteral (injectors, pens, safety devices).

More than five million diabetics and ten million asthmatics rely everyday on devices manufactured by Nemera.

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"Adding a passive automated safety feature to prefilled syringes, Safe 'n' Sound® protects patients and caregivers from contamination by blood-borne diseases."

Parenteral
Nemera's Safe 'n' Sound® device provides safety from needle-stick injuries. Adding a passive automated safety feature to prefilled syringes, Safe 'n' Sound® protects patients and caregivers from contamination by blood-borne diseases. Robust and versatile, it comes in different formats and can be combined with ergonomic accessories (Figure 1).

Pulmonary
Consistency and reliability are critical for respiratory patients. Inhalia® is a new generation of valve for pressurised metered dose inhalers (pMDI).

Nasal, Buccal, Auricular
Following the SP270, a standard spray pump for ear, nose and throat, Advancia® is a new breed of pharmaceutical pump combining user-independence and preservative-free features in one single system. Advancia® offers a new alternative to improve treatment compliance in an increasingly demanding nasal spray market.

Ophthalmic
Preservatives are harmful to patients' eyes and may jeopardise adherence to treatments, therefore Novelia® is the user friendly, preservative-free eye dropper with a precision blue tip.

Dermal/Transdermal
Sof'Bag™ is a high-performance airless dispensing device designed especially for pharmaceutical gels and creams. It brings precise dosing and protection for topical and transdermal formulations.

A NEW NAME THAT STANDS FOR LIFE & EFFICIENCY

The name Nemera comes from two sources: "Emera" from Greek meaning "day" and suggesting renewal, fresh hope and life; and "Nemer" from Hebrew and Arabic, meaning "leopard" and suggesting swiftness, efficiency and agility.

Nemera CEO Marc Haemel commented: "We work hand-in-hand with pharmaceutical companies to design, develop and manufacture the drug delivery devices that help patients every day.

"There is no limit to Nemera's ambition to serve patients. We already market devices in over 40 countries for millions of users. We'll keep investing in new products and in state of the art manufacturing equipment, to help even more patients with high quality devices all over the world."

Nemera provides solutions for the pharmaceutical industry, including standard innovative products, development of custom devices and contract manufacturing. Montagu has also bought Rexam Prescription Products, the industry leader in prescription packaging for over 100 years, which is now known as Centor.

COME AND MEET NEMERA AT PHARMAPACK EUROPE: STAND #756

COMPANY PROFILE: HASELMEIER

HASELMEIER
Drug Delivery. Tailormade.

User Focus

At Haselmeier, our mission is to create products enabling a convenient and comfortable experience. This is why patient feedback is integrated early in our device designs. Early concepts are prototyped for testing and Human Factors studies to capture the handling needs and skills of potential users. This knowledge is integrated into the device design to provide successful administration of the drug product and a positive user experience.

Haselmeier offers a range of early-stage activities:

- Think-tank discussions and paper concepts
- Detailed product concepts and industrial designs
- Detailed user handling review and risk-analysis
- Prototyping of initial concepts up to functional devices
- User focus groups and human factors studies for concept and prototype evaluations
- Detailed user requirements and product design specifications based on selected concept.

Bridge to Market

Successful development and industrialisation of drug delivery devices is dependent upon the understanding and execution of today's technical, regulatory and operational requirements. At Haselmeier we provide integrated design, development and industrialisation services to help you bridge your serial product into the market. Our qualified design control process, certified quality system, regulatory expertise, solid network of partners and strong manufacturing operations are all designed to achieve your expectations. Together we enable a smooth market introduction for your commercial drug delivery device.

Haselmeier's commercial development and industrialisation services include:

- Concept transfer into detailed User Requirements and Product Design Specifications
- A certified Design Control Process and Quality System
- Design verification, product and process validation processes
- Regulatory expertise to support your approval strategy
- Controlled design-to-manufacturing transfer, verification and validation.

> "Successful development and industrialisation of drug delivery devices is dependent upon the understanding and execution of today's technical, regulatory and operational requirements"

Manufacturing & LifeCycle Partner

We understand that each customer has individual and specific requirements for their product. Regardless of your requirements, Haselmeier applies the highest quality standard for manufacturing your drug delivery device to ensure a reliable and reproducible manufacturing and quality process. We work continuously with our customers to identify product improvements at all stages of the product's lifecycle to provide a safe and state-of-the art drug delivery device.

Haselmeier provides flexible, reliable, manufacturing and lifecycle management:

- Certified and modern production facilities and manufacturing processes
- Qualified and well trained personnel
- A strong network of sub-suppliers and manufacturing partners
- Continuous Engineering and product improvement programme
- Innovation meetings to identify next product generation.

PLATFORM & PRODUCTS

The Haselmeier Axis-D Pen System (Figure 1) is a disposable, variable-dose injection device designed for the use with a 3 mL cartridge. The elegant and compact Axis-D Pen System is available as a high quality plastic version.

- No or minimal priming
- Accurate dose reading with sliding window
- No rotating outer components
- Protected dose scale.

The Haselmeier i-pen (Figure 2) is a reusable, variable dose injection device for use with a standard 3 mL cartridge. The

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Working together to inspire your patients

At Haselmeier we work in close cooperation with our pharmaceutical partners to create and deliver the safest and easiest to use injection devices for their patients.

Our proven device platforms, world leading engineering and global manufacturing capabilities combined with an intense focus on patients provides our partners with a total product solution that helps improve patients' lives.

Experience **User Focus, Bridge to Market** and **Manufacturing & LifeCycle Partner** here:

HASELMEIER

Drug Delivery. Tailormade.

COMPANY PROFILE: **HASELMEIER**

"We understand that each customer has individual and specific requirements for their product"

i-pen features an elegant non-medical design which is the result of extensive research and patient testing.

- Dose adjustment from 0.01 mL to 0.6 mL per injection
- Compact size enables easy handling and portability
- Large, easy-to-read dose indicator
- All metal outer body.

The i-pen² (Figure 3) is a reusable, variable-dose injection device for use with a standard 3ml cartridge. The i-pen² was specifically created to provide a high-quality pen at economic cost.

- Dose adjustment from 0.01 mL to 0.6 mL per injection
- Compact size enables easy handling and portability
- Large, easy-to-read dose indicator
- All plastic components

The Softpen (Figure 4) is a fully automatic, reusable injection device featuring Haselmeier's patented hidden needle design. Upon depressing the clip on the pen, the needle automatically enters the subcutaneous tissue followed by delivery of the solution.

- Fully automatic needle insertion and injection
- Needle is hidden prior to and during injection
- Multiple injections from single 3ml cartridge.

The Haselmeier disposable Penlet (Figure 5) is a fully automatic, fixed dose injection device designed for use with a standard 3ml cartridge. Upon depressing the clip on the pen, the needle automatically enters the subcutaneous tissue, which is followed by delivery of the solution.

- Ready for use by the patient and no dose adjustment required
- Fully automatic needle insertion and injection
- Needle is hidden prior to and during injection.

Figure 1: The Axis-D Pen System – disposable, variable-dose injection device designed for the use with a 3 mL cartridge.

Figure 2: The i-pen – reusable, variable-dose injection device for use with a standard 3 mL cartridge.

Figure 3: The i-pen² is a reusable, variable-dose injection device for use with a standard 3 mL cartridge.

Figure 4: The Softpen – a fully automatic, reusable injection device featuring Haselmeier's patented hidden needle design.

Figure 5: The Penlet is a fully automatic, fixed-dose injection device

Helping all people
live healthy lives

ADDRESSING HUMAN FACTORS **ENGINEERING** AND COMBINATION PRODUCT REGULATIONS THROUGH INNOVATIVE SAFETY SYSTEM SOLUTIONS

In this piece, Sarah Malka, Commercial Integration Project Manager, and Anastasie Formey de Saint Louvent, Europe Product Manager, both of BD Medical – Pharmaceutical Systems, describe how BD integrates human factors engineering and patient-centric design into an innovative partnering model for the development of new products, such as the BD UltraSafe Plus™ Passive Needle Guard.

GLOBAL NEED FOR INJECTION SAFETY

Today's pharmaceutical landscape is deeply evolving. More than 35 million global healthcare workers face the risk of sustaining a percutaneous injury with a contaminated sharp instrument every year. This results in one million sharps injuries a year, from which 60-80% go unreported. Self-injecting patients are also concerned by the risk of needle-sticks during at-home use resulting in an increased preference for safety features.

Anti-needle-stick legislation is becoming more stringent as regulations are tightening and expanding globally, most recently with the 2013 adoption of the 2010/32/EU Sharps Injury Prevention legislation in Europe. As a result, companies have to adapt quickly to this legislation and provide hospitals and end users with drugs that can be easily and safely used.

EVOLVING PHARMACEUTICAL LANDSCAPE

Several additional key elements impact today's injectable pharmaceutical market. Amongst them, increased sensitivity and viscosity of parenteral drugs, incorporation of end user experience and needs into product development, and tighter control of healthcare expenses from governments are playing a major role. Moreover, differentiation and lifecycle management are crucial for pharmaceutical companies to overcome competitive pressure.

This leads to more advanced delivery solutions and sophisticated combination products which are being rigorously regulated.

In the US, combination products are defined as a single entity (combined into one), co-packaged (sold together) and cross labelled (dependent) [1] product.

With the growing implementation of the combination product regulations in the US and all over the world, not only should all the players work together, but excellence in regulatory support and knowledge of the paradigm change driven by combination products are critical to the success of a product launch. Selecting the best partner to supply container closure systems components or devices is vital as time, data sharing, and human factors engineering (HFE) are the essence of the future for pharmaceutical products.

Pharmaceutical companies need to partner with manufacturers of components of container closure systems or devices that are able to provide cross-functional expertise on the impact of the new combination product regulations through documentation sharing with relevant data to support product development.

HOW HFE CAN LEAD TO DIFFERENTIATED PRODUCT DESIGNS

Importance of Patient input from Conception to Launch

HFE inputs have become central in product development, particularly for combination

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products. This iterative design approach is a body of knowledge about human abilities, human limitations, and other human characteristics that are relevant to design. As described in Figure 1, the integration of HFE in the product design is a result of several steps of concept generation and experimental investigations based on requirement definition and design verifications. This puts the patient at the center of combination products development considerations.

As a result, pharmaceutical companies can improve and prove product usability. It has been established that patient-centric designs can improve patient acceptance of the treatment and thus improve effectiveness.

BD Medical – Pharmaceutical Systems has been an early innovator in developing safety engineered solutions for the market, partnering with numerous customers to ensure their commercial success. HFE has been in the center of these developments from a very early stage. With the creation of BD's Human Factors Institute in 2013, BD offers structured expertise in concept development and patient-centric design to its customers, guiding them through every step of the HFE process.

HFE & DEVELOPMENT PARTNERSHIP AS INNOVATION DRIVERS

BD product developments are made with input including end-users' needs and preference evaluation. The BD UltraSafe Plus™ Passive Needle Guard (Figure 2) is an ideal example of product development adapted to new market requirements. As patients tend to self-inject more, there is a need for ergonomic and easy-to-use devices. In addition to an innovative passive safety technology preventing any risk of needlestick injury at the time of needle withdrawal, the wider finger flange and unique ergonomic plunger rod were the results of patient centric studies,[2] ensuring successful use for self-injected viscous drugs.

The BD Ultrasafe Plus™ Passive Needle Guard includes enlarged finger flanges in order to facilitate self-injection. In light of end-user feedback, BD also developed an add-on finger flange to be used as an accessory to this device. This add-on enables dexterity-impaired patients to inject themselves comfortably. The selection of the shape for the add-on finger flange of BD Ultrasafe Plus™ Passive Needle Guard was the result of an HFE-based development, centred on the needs of this specific target population.

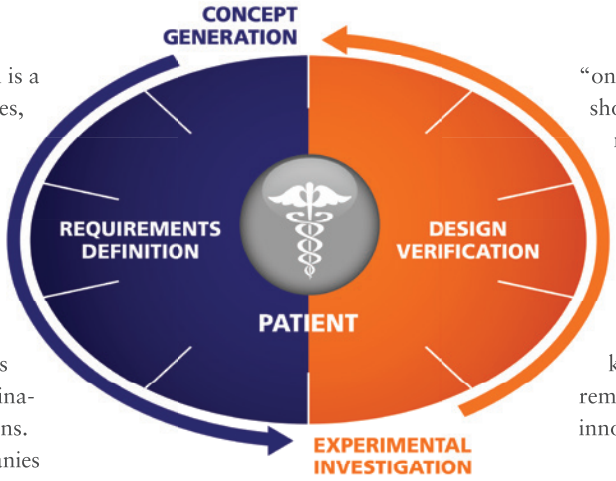

Figure 1: Integration of human factors engineering in the product design.

The first step in defining the appropriate product was to select the overall shape. An exhaustive analysis of targeted patients' preferences has been performed. Pre-selected add-on finger flange shapes were tested on patients with reduced manual dexterity, including patients with rheumatoid arthritis and multiple sclerosis.[3] After several iterations of usability studies, results indicated that downward-pointing designs and concave shape to support grasp are preferred by these patients.

In addition to this initial design evaluation, another series of usability studies has been conducted to evaluate the patient preference on texture. Patient focus groups were conducted and resulted in a better understanding of the impact of texture on patient perceived injection comfort for an add-on finger flange. As expected, data suggests that adding specific textures leads to preference of specific end-users. There is no "one fits all" solution. For example, results show that grooves in addition to texture may be perceived as uncomfortable for MS patients.[4] This evaluation led to the design of the BD Ultrasafe Plus™ add-on finger flanges.

Figure 2: The BD UltraSafe Plus™ Passive Needle Guard – an ideal example of product development adapted to new market requirements.

As the next generation of drugs is being developed, BD is evaluating new technologies to meet unique market needs. Patient acceptance and safety remain some of the key drivers to BD's innovative solutions.

SUMMARY

Changing landscapes require pharmaceutical companies and their partners to adapt and develop more ergonomic products, ensuring patient acceptance. To demonstrate ease of use and reliability of the developed products, additional studies are requested by the regulatory agencies. HFE, based on end-user needs, should be in the center of these studies to ensure their acceptance. Choosing a device and container closure system partner with expertise in product design and combination product regulations is imperative to ensure a successful product launch.

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1. *21 CFR 3.2(e), US FDA, April 2014*
2. *Data on File*
3. *Data on File*
4. *Data on File*

ABOUT BD

BD is a leading global medical technology company that develops, manufactures and sells medical devices, instruments and reagents. The company is dedicated to improving people's health through the world. BD is focused on improving drug delivery, enhancing the quality and speed of diagnosing infectious diseases and cancers, and advancing research, discovery and productions of new drugs and vaccines. BD's capabilities are instrumental in combating most of the world's most pressing diseases.

Founded in 1897 and headquartered in Franklin Lakes, NJ, US, BD employs nearly 30,000 associates in more than 50 countries throughout the world. The company serves healthcare institutions, lifescience researchers, clinical laboratories, the pharmaceutical industry and the general public.

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WEIBEL CDS AG
Container Closure Device System Solutions

RECONSTYRINGE®: FULL INTEGRATION OF ALL FUNCTIONS & PARTS, FULLY AUTOMATED RECONSTITUTION

Featuring for the first time in ONdrugDelivery Magazine, Ludwig Weibel, Chief Executive Officer, and Hans Peter Manser, Business Director, both of Weibel CDS AG, introduce the Reconstyringe® system, which offers a fully automated reconstitution of lyophilised drugs.

Safer, easier and faster drug delivery – Weibel CDS AG, Switzerland, develops and produces innovative, user-friendly, application-oriented primary packaging and devices.

The SuperCapSyringe® product family upgrades your vial practically to a prefilled syringe. Based on a modular design, the syringe is fully adaptable to your application needs. It is supplied in different sizes and, as a new offering, with staked needles including a passive safety device.

Following our mission to support safer, easier and faster preparation and administration of injections, all functions and parts needed for a specific drug application are integrated into one product. The user only opens one package and the complete handling is done in a closed system in order to reduce contamination, handling errors and needle-stick injuries, whilst also saving time.

Drug Delivery Systems of Weibel CDS AG are ready to use, no longer requiring the patient to transfer the drug into the system. Based on the MiniBagSystems concept, a unique pump system as well as needle insertion, the device is available for SC and IV injections making the life of patients as well as healthcare professionals much safer and easier. Thanks to a disposable and a re-usable unit the economic footprint is much smaller as the drive unit, controller and batteries are re-used and not discarded once the injection is completed. The final design is according to your specific needs from a functional as well as design perspective.

THE RECONSTYRINGE® CONCEPT

Our **Reconstyringe®** product family is first in offering a fully automated reconstitution of lyophilised drugs. This product line is presented in detail in this article.

TODAY'S SITUATION

One-third of parenteral drugs sold in vials are lyophilised. Especially for cytostatic drugs, the procedure the healthcare professional is required to go through can be not only cumbersome but also requires special attention as often the reconstitution needs to take place under laminar flow. Today, conventional reconstitution and administration of lyophilised drugs requires as many as 22 individual steps (see Figure 1). Not only are these 22 steps and associated handling time inconvenient, but there is also substantial potential for contaminations as well as handling errors including needle-stick injuries, as single-use syringes are not commonly available with a passive safety system.

Despite numerous solutions available to facilitate reconstitution, none of these concepts is significantly changing the process itself. In contrast, we believe in full integration of all functions and parts, plus full automation of the reconstitution process.

RECONSTITUTION – LISTENING TO THE MARKET

Market feedback is suggesting that a new approach is required and is asking for a "Swiss watch" approach. In response to numerous experts in the industry as well as hospitals, Weibel CDS AG has developed an innovative reconstitution system including the features of the SuperCapSyringe®, combined with the MiniBagSystem (described

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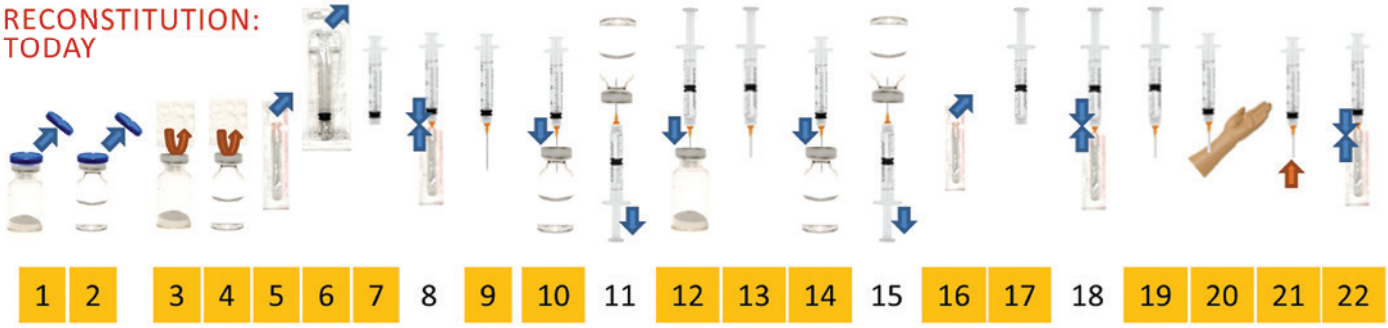

Figure 1: Conventional reconstitution and administration of lyophilised drugs requires as many as 22 individual steps.

Figure 2: Diagram showing the internal mechanism of the Reconstyringe® including the holding plates and spring.

below) to hold the solvent, and an innovative technique to automate the reconstitution procedure. The design is such that no batteries or drives are required and the complexity is reduced to a minimum thus reducing the risk of malfunction. Most importantly, no change is required with regards to the formulation of the drug.

MINIBAGSYSTEMS

Weibel's MiniBagSystem represents a revolutionary concept providing a platform for various drug delivery systems. MiniBagSystems are designed with a unique port to enable filling and discharging limiting overfill to an absolute minimum. Multilayer foils have been chosen as base material to provide lowest levels of gas and water vapour permeability close to glass. Inside the Reconstyringe®, the MiniBagSystem holds the solvent.

AUTOMATED RECONSTITUTION: ONLY EIGHT INTUITIVE STEPS

The drug is contained in its original vial, the solvent in our MiniBagSystem. Using a spring mechanism and holder plates (visible in Figure 2) the content of the MiniBagSystem is emptied into the vial. With the precision of a Swiss watch, the system runs through the full reconstitution cycle. Finally, the drug is drawn into a SuperCapSyringe® for injection (see Figure 3).

After withdrawal of the syringe, a passive safety system slides over the needle, providing the highest levels of protection against needle-stick injuries.

Reconstyringe® is available in 1 mL, 3 mL, 5 mL and 10 mL versions, all remaining in a very compact format of single-use syringes including the one-piece safety device.

Reconstyringe® offers full integration of all functions and parts plus full automation of the reconstitution process. The advantages for the end user are:

- Reduction in contamination
- Reduction in handling errors
- reduction in needle-stick injuries
- and a gain of time.

Reconstyringe® allows pharma companies both to pass on these benefits to the end user and differentiate themselves from competition.

Weibel CDS has several international patents pending for Reconstyringe®.

SuperCapSyringe® and Reconstyringe® are registered trademarks of Weibel CDS AG, Switzerland.

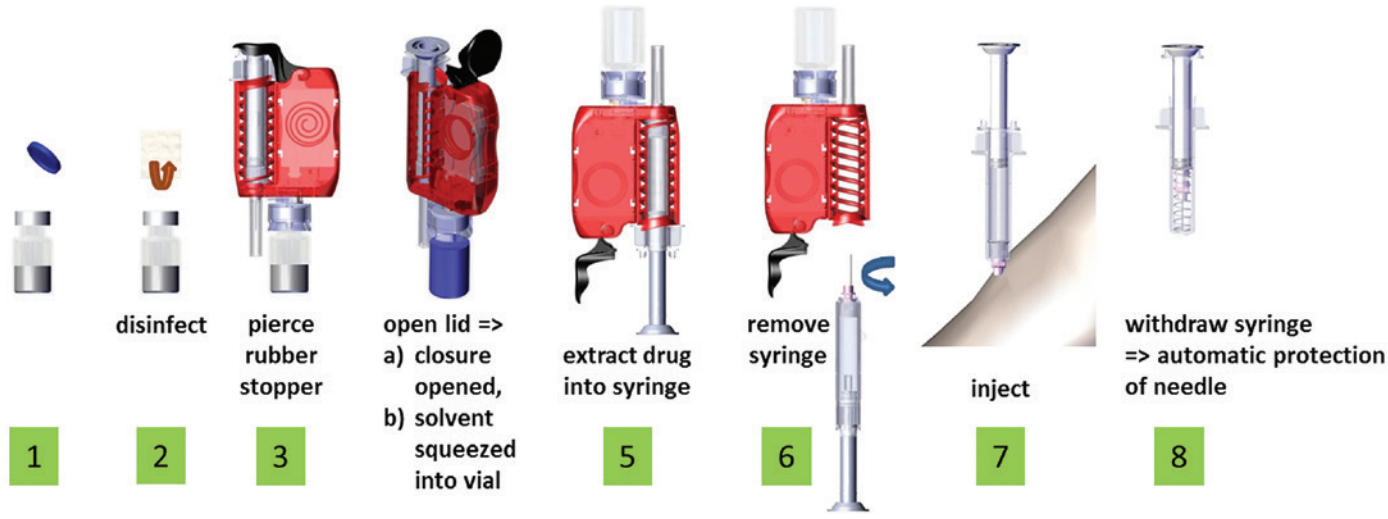

Figure 3: The Reconstyringe® runs through the entire reconstitution cycle, reducing the injection procedure down from as many as 22 steps to just eight intuitive steps.

RECONSTYRINGE®

Our **Reconstyringe®** product family is first in offering a fully automated reconstitution of lyophilised drugs. The drug is contained in the original vial, the solvent in our MiniBag. Like a Swiss watch, it runs through the full reconstitution cycle. Finally, the drug is drawn into a **SuperCapSyringe®** for injection.

safer, easier and faster drug delivery

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Container Closure Device System Solutions

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