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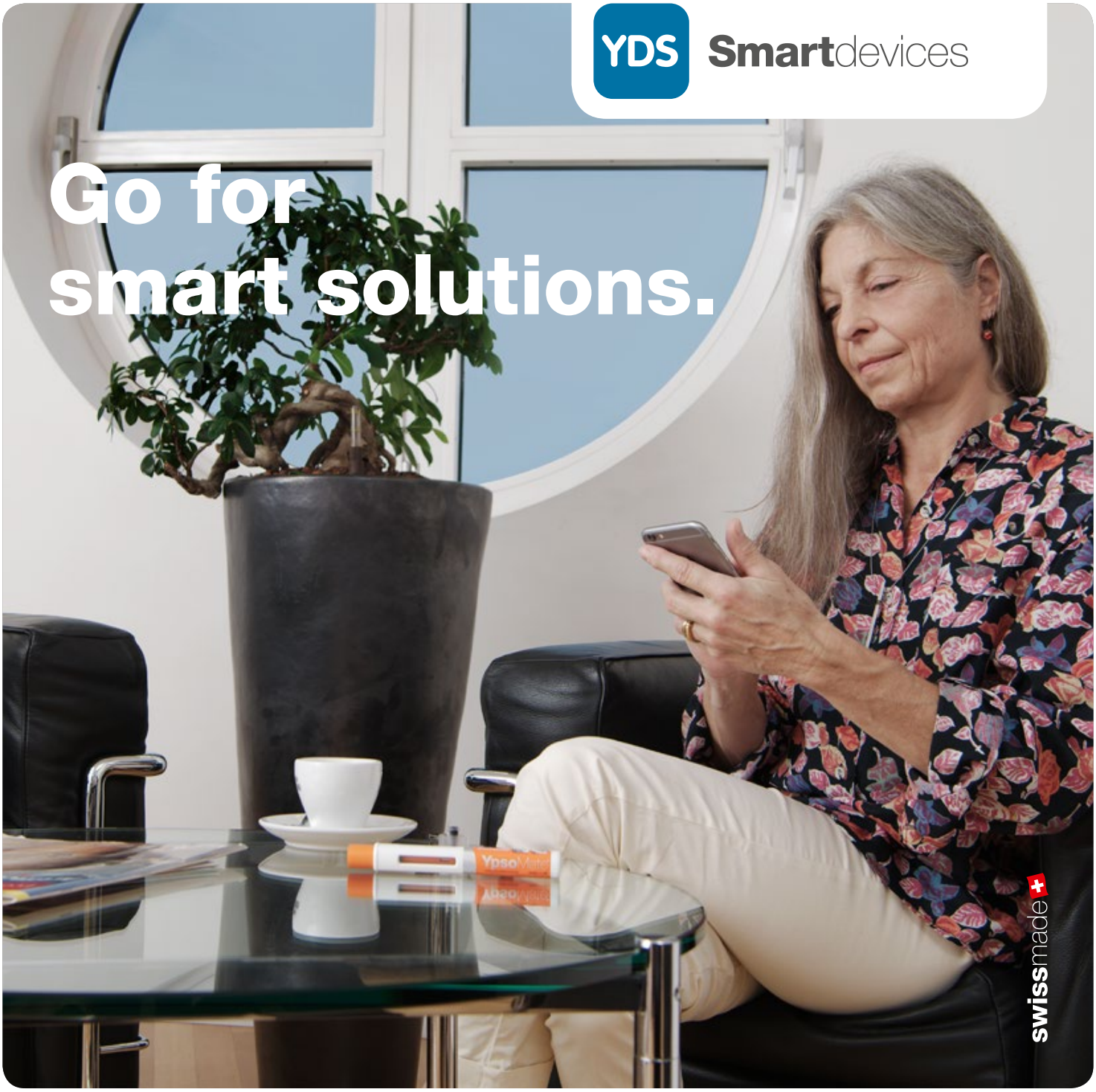

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DEVELOPMENT OF SMART INJECTION DEVICES: INSIGHTS FROM THE YPSOMATE SMART CASE STUDY

Here, Andreas Schneider, PhD, Business Development Manager, Ypsomed, provides insights into recent development activities at Ypsomed in the area of smart self-injection systems, reflecting on the case study of YpsoMate Smart, a two-step auto injector with built-in connectivity and status sensor. YpsoMate Smart is one example of how Ypsomed has taken up the emerging market needs for injection devices with built-in intelligent functions requiring electronics and software. The article first looks at the aspects driving innovation around smart devices. It then focuses on how integrating information technology and cloud connectivity into smart injection devices necessitates opening up internal R&D engines and adopting open innovation methodologies. Finally, the article describes how development activities around smart devices have triggered Ypsomed's shift from traditional routines of problem solving toward broad and flexible technology assessments beyond industry boundaries.

Improvement in therapy outcomes is increasing the need for injection devices that support the administration of medicine with intelligent built-in electronics and software, so-called smart devices. In particular, four major forces are driving innovation around smart devices:

1. Recently developed formulations of new-generation biologics, necessitate only weekly, every- two-weeks, or even monthly, subcutaneous injections. Less frequent dosing is of great value to patients, but the lack of routine calls for more intense patient guidance and feedback before, during, and after injection, beyond the visual and audible feedbacks that current injection devices offer.
2. Health insurers – particularly in US and Europe – are moving away from unit priced payment toward outcome-based compensation models for therapies that generate superior clinical results, particularly for chronic illnesses where self-administration devices are most popular. This, again, increases the need for technical solutions that accurately record whether and how the patient follows the therapy guidelines in addition to providing patient education and coaching. Indeed, improving adherence holds enormous potential. Recent figures, from the US market only, estimate costs of some US$290 billion (£200 billion) – or approximately 8% of total healthcare cost – that result from lack of adherence on the part of the patient.
3. Healthcare stakeholders are starting to accumulate vast amounts of data around therapies from clinical trials as well as "real-world" environments. However, one piece in the jigsaw largely missing so far is whether patients in selfcare environments have correctly administered their medicine.

"Less frequent dosing is of great value to patients, but the lack of routine calls for more intense patient guidance and feedback before, during, and after injection, beyond the visual and audible feedbacks that current injection devices offer."

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4. The responsibility for treatment outcomes is moving from physicians to patients and health insurers. As mobile devices, social networks and internet forums become an integral part of everyday activities, patients' awareness for their therapy is increasing significantly.

Together, these four factors accelerate the development of smart injection devices that support the administration of medicine with supplementary intelligent, built-in functionalities. Specifically, information technology, cloud connectivity, and smart phone access are penetrating the fields of drug delivery devices. Such development opens up a new phase of device innovation that looks at interfaces beyond the device.

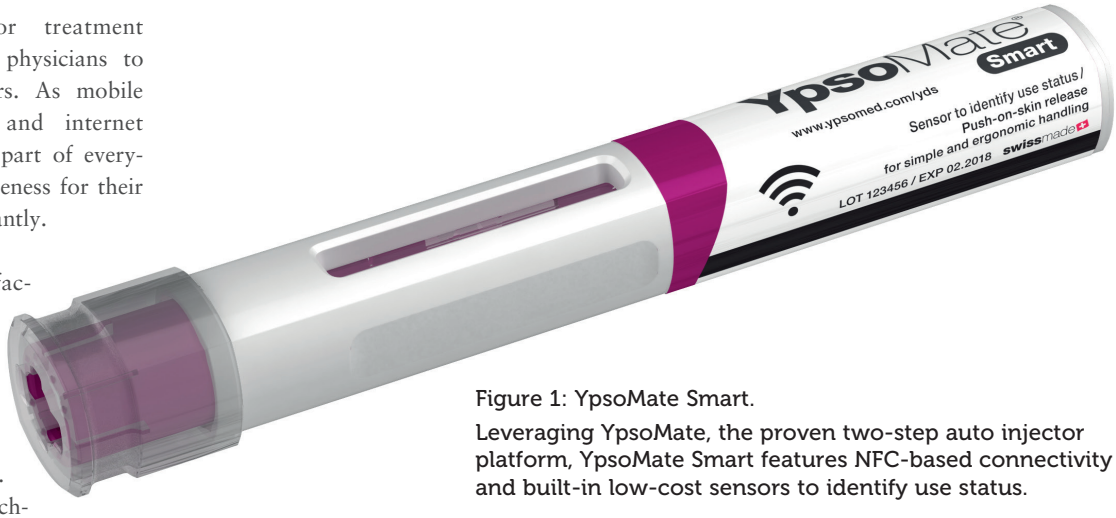

Figure 1: YpsoMate Smart.

Leveraging YpsoMate, the proven two-step auto injector platform, YpsoMate Smart features NFC-based connectivity and built-in low-cost sensors to identify use status.

It requires the opening up of internal R&D competencies to encompass sensor technologies, big data analytics, and management of cloud data services. Inter-organisational collaborations – within and beyond industry boundaries – are necessary for the successful development of smart devices. As Henry Chesbrough, Adjunct Professor and Faculty Director of the Center for Open Innovation (Haas School of Business, University of California, Berkley, CA, US) stated on open innovation in 2003: "Not all the smart people work for us. We need to work with smart people inside and outside our company".

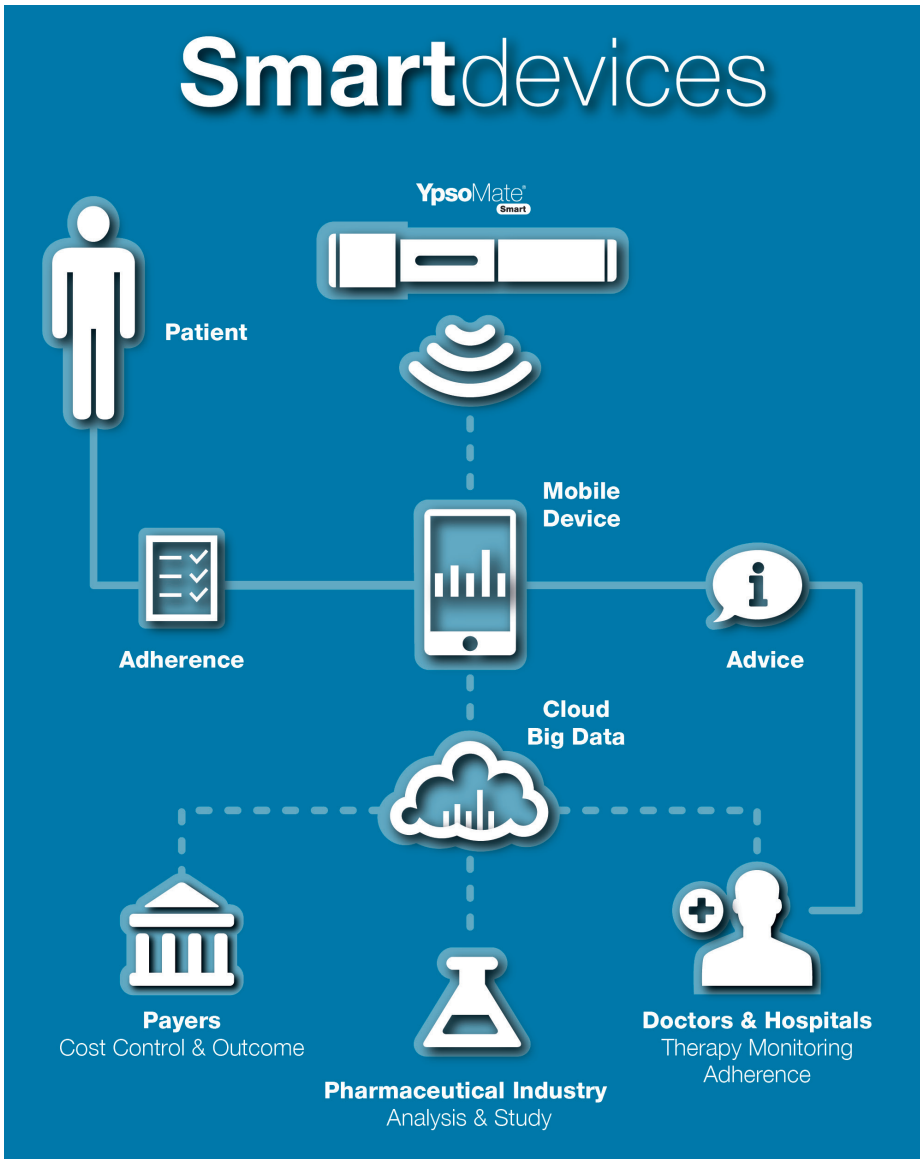

Figure 2: Visualisation of how smart devices integrate into the complex healthcare environment.

The combination of previously unrelated technologies means that this guiding principle for innovation has become more important than ever. This principle is well illustrated by the case of a recent innovation announced by Ypsomed, that is, the development of YpsoMate Smart (see Figure 1).

YpsoMate Smart leverages the proven two-step auto injector platform, YpsoMate, and enhances this popular auto injector platform with electronics and built-in connectivity. Starting from the fully industrialised YpsoMate platform, this enables customers to upgrade their customised YpsoMate device flexibly to YpsoMate Smart as part of lifecycle management.

Specifically, YpsoMate Smart introduces low-cost integrated sensor technology to detect the use status of the auto injector which is wirelessly transmitted to a smartphone using Near Field Communication (NFC). YpsoMate Smart is a first outcome of Ypsomed's strategic initiative that embraces a portfolio of innovation projects supporting the seamless provision of information to patients, physicians and pharmaceutical companies with smart self-injection devices (see Figure 2).

YpsoMate Smart supports all stakeholders in a number of ways. For instance, novel medicines that require infrequent dosing prevent patients from developing an injection routine. It is therefore beneficial to guide patients through the injection process

closely as well as supporting them by recording therapy events. By scanning YpsoMate Smart with a smartphone, the patient calls up video-enhanced operating instructions before using the device. Once the medicine is administered and the patient scans the device again with his smartphone the patient receives conclusive confirmation that the injection has been successfully administered – including an automatically generated entry in the injection diary and a reminder for the next injection (see Figure 3 for an illustration of YpsoMate Smart's handling concept).

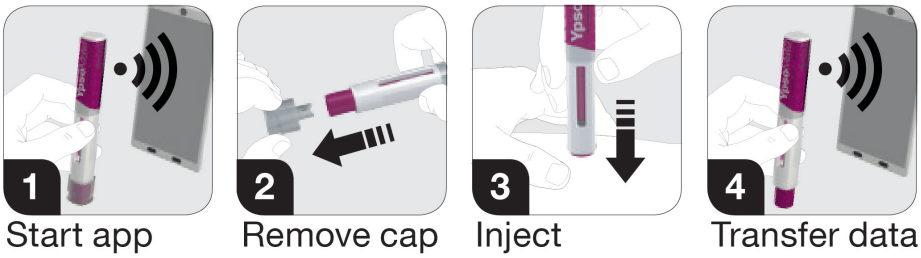

Figure 3: Illustration of YpsoMate Smart handling concept. Before injection, the patient scans YpsoMate Smart with their smartphone to, for example, read video-enhanced instructions for use or check authenticity, perform the injection, and reconnect YpsoMate with the smartphone in order to transfer relevant data.

> "Such development opens up a new phase of device innovation that looks at interfaces beyond the device. It requires the opening up of internal R&D competencies to encompass sensor technologies, big data analytics, and management of cloud data services."

YpsoMate Smart is also of great interest to pharmaceutical companies, allowing devices to be tracked individually on their journey from end-assembly to their use by the patient. Uniquely identifiable NFC tags provide new possibilities for supply chain management. Tracing patient behaviour, it similarly unlocks new dimensions of data collection and analysis during clinical trials as well as in the real world environment. YpsoMate Smart also allows medical practitioners to monitor patient adherence and tailor their patient guidance and advice accordingly. For instance, patients may be asked to self-assess their perceived wellbeing after each injection. Physicians are provided with more information regarding the therapy and have the opportunity to interact with patients between consultations.

The YpsoMate Smart case study reveals how opening up internal R&D processes has become more important than ever to meet emerging market requirements for smart devices. In order to access the cutting-edge technology for development of YpsoMate Smart, Ypsomed collaborates with Thinfilm Electronics (Oslo, Norway).

Thinfilm is a market leader in the area of "printed electronics", that is, electronic circuits manufactured at low cost that can be flexibly scaled up for commercial production. Interestingly, Thinfilm's unique NFC-based tags have initially been used for consumer goods, to fight counterfeits or unauthorised refills, rather than self-injection devices (see Figure 4 for an illustration). As such, Thinfilm's sensor tag has already provided fast-track development of a "smart whiskey bottle", smart enough to detect – by help of a smartphone – whether a given bottle has already been opened or not. The consumer then receives relevant messages guiding his future behaviour.

The big question in forming the collaboration between Ypsomed and Thinfilm was: how exactly to link Thinfilm tags with delivery systems? Systematic external technology assessment concluded that the NFC tag's capabilities add value to auto injectors. The case study thus re-emphasises the importance of broadly scanning seemingly unrelated external technologies and knowledge sources beyond industry boundaries.

YpsoMate Smart is the result of Ypsomed's strategic initiative to broaden the scope of technology and knowledge search activities – with a particular emphasis on the consumer electronics industry, in order to minimise costs and speed up time to market. This enables Ypsomed to meet requirements such as connectivity and data handling via the readily available capabilities of external partners.

Entering strategic collaborations allows Ypsomed to focus on its core competences – the design and development of the interface between device and electronic components.

There's yet another lesson to be learnt from the YpsoMate Smart case study. It shows how the need to integrate information technology or cloud connectivity with injection systems has altered innovation routines at Ypsomed. In particular, the case study highlights how Ypsomed is rethinking how it engages in technology problem solving. Ypsomed broadly scans its environment for technologies that possibly fits the context of injection devices. Ypsomed does not depart from a problem statement narrowly defined before scanning its environment. In addition, it has increased its efforts in technology screening and aims at broadly assessing technologies that offer potential utility to the development of innovative injection devices.

Opening up our internal R&D processes and shifting toward broad technology search patterns reflects two key drivers of innovation around smart devices at Ypsomed. These innovation routines complement other success factors for the development of intelligent injection systems. For instance, consider Ypsomed's unparalleled 30-year experience in design and development of insulin pumps, pens and auto injectors, its ability to anticipate customer needs and translate these into flexible platform products, with a clear focus on fully automated high-volume manufacturing processes. This unique set of capabilities puts Ypsomed in a favourable position to develop exciting novel smart product platforms beyond YpsoMate Smart, the final result being smart functionalities, which can be reliably integrated into disposable pens, auto injectors and wearable injectors.

ABOUT YPSOMED

Ypsomed is a leading developer and manufacturer of innovative auto injector and pen injector systems for self-administration of injectable drugs. The customisable product platforms cover auto injectors for prefilled syringes in 1 mL and 2.25 mL formats, disposable pens for 3 mL and 1.5 mL cartridges, reusable pens that include automated injection mechanisms, and easy-to-use injection devices for drugs in dual-chamber cartridges such as lyophilised drugs.

Our modular and proven custom product technologies guarantee that Ypsomed injection systems are rapidly available for clinical studies and market introduction. Innovative and patented technologies offer our customers user-friendly injection systems with which they stand out successfully in the market. All our products are characterised by reliable and well-thought-out technical concepts, which are optimised for automated manufacturing. Unique click-on needles and infusion sets complement the broad self-injection systems product portfolio. Ypsomed provides its partners excellent technological expertise and full regulatory support for the device relevant aspects of the registration process.

Ypsomed's injection systems are developed and manufactured in Switzerland with strong in-house competencies covering concept and product development, tool-making, injection moulding and automated assembly. Ypsomed is ISO 13485 certified and all processes are run according to design control and cGMP guidelines with operational QA/QC experts on-site at each location. Ypsomed's US FDA-registered manufacturing facilities are regularly inspected by both pharma customers and regulatory agencies and supply devices for global markets including US, Europe, Japan, China and India. Ypsomed has more than 30 years of experience and well-established relationships with numerous leading pharma and biotech companies.

Figure 4: Thinfilm's sensor technology used in combination with YpsoMate Smart. The sensor is a printed integrated circuit for use in electronic read-only transponders (passive sensor). The tag transmits data (128 bits) at a frequency of 13.56MHz used by HF RFID and NFC (operating in a Tag-Talks-First manner). The code of the NFC signal changes as the linker of its antenna is physically disrupted. As such, the change in the NFC signal corresponds to the actual use status of YpsoMate Smart.

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ASSESSING THE IMPACT ON DRUG DOSE DELIVERY OF PASSIVE SAFETY DEVICES

In this article, Adrien Tisserand, Category Manager, Parenteral, at Nemera, reports findings from a comparative study on drug dose delivery of the company's passive needle-safety platform, Safe'n'Sound® and describes how the device's performance in terms of variability of residual volume, together with various other factors, differentiate it from other needle-safety devices.

Historically, injectable drugs were contained in vials and administered in healthcare facilities by professionals. But with an increasing trend towards self-administration and at-home administration, prefilled syringes (PFS) emerged in the early 2000s. The growing popularity of the PFS is due to its ease of use, facilitating the injection process and reducing the total injection steps, but also the improved user safety and the reduction of dosage errors. It is also linked to their cost efficiency, not requiring drug as much drug overfilling as vials, which require overfill of up to 25%.

> "The comparative residual volumes study highlights how Safe'n'Sound® optimises drug dose delivery, minimising the non-injected volume compared with other commercially available passive safety devices."

In the parenteral industry, needlestick injuries remain a global concern. According to the WHO, more than three million exposures to blood occur every year, resulting in health, psychological and cost issues. Safety devices for PFS have been developed to aid in the protection of users from needlestick injuries. Safety devices are classified in two categories: "passive" if the safety feature automatically activates at the end of the injection without any additional gesture from the user; or "active" if the user needs to perform an additional gesture to trigger the safety feature once the injection completed.

Nemera has developed Safe'n'Sound® (see Figure 1), a passive safety device platform for PFS, which not only responds to the recommendations of the EU Council Directive 2010/32/EU and US Federal Needle stick Prevention Act, 2000 and aids in the protection from accidental needlestick injuries, but has also been designed to optimise drug dose delivery (consistency of drug dosing) thanks to a patented mechanism. Design optimisation of these output parameters is key for pharmaceutcal companies as they could impact treatment efficiency and drug overfilling.

Safe'n'Sound® is an open platform of passive safety devices for prefilled syringes. It is an add-on to the PFS whereby the PFS is snapped in to the safety device. Assembly with the PFS is carried out at the pharma company or CMO facility and, thus, end-users (patients and healthcare professionals) always receive the product assembled.

Safe'n'Sound® 1 mL is on the market in both staked and Luer versions. Nemera has industrial capacity of more than 25 million units per year. Nemera has also developed a version compatible with 2.25 mL staked syringes.

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Figure 1: The Safe'n'Sound® platform, for 1 mL and 2.25 mL prefillable syringes.

Figure 2: In the study, each user performed six injections on a silicone pad. (Safe'n'Sound® device shown here post-injection, i.e. in the safety-activated state).

DRUG-DOSE DELIVERY STUDY

Marketed passive safety devices have based their safety feature mechanism on the same kind of concept: when the head of the plunger rod reaches the position corresponding to the theoretical end of the injection, a spring is released covering the needle with a sheath. In reality, safety feature activation is designed to be triggered just before the theoretical end of the injection to ensure activation. The main advantage of passive safety devices is the limited control the user has on the activation. However, if the activation trigger is not well adjusted, a limited volume of drug may not be injected.

Nemera conducted a study to compare the non-injected volume between three marketed passive safety devices for 1 mL PFS after simulated injection performed by non-healthcare and healthcare professionals.

MATERIALS & METHOD

Three registered nurses and seven non-healthcare professionals were involved in the study. Each user performed six injections on a silicone pad (Figure 2) with each of the three passive safety devices. Safety devices were equipped with 1 mL PFS and stopper from the same batch, and filled with 0.5 mL of distilled water. To reach those conditions, marketed safety devices were disassembled from the syringes containing the marketed drug, and mounted with the new syringe and stopper mentioned previously. The specific plunger rod of each device was screwed back in the new stopper. As a result, the only difference between the three systems including the syringe, the stopper, the distilled water and the safety device was the safety device. As syringes, stopper and liquid used were the same, injection force was similar between the systems. Safe'n'Sound® device is referenced as Safe'n'Sound® System. The two other marketed devices A and B are respectively referenced as System A and System B.

The tests were performed according to Nemera internal protocol P084-02.[1] The main steps were:

1. Assembly of the empty syringe with the device
2. Stopper screwing on the device specific plunger rod
3. Plunger rod insertion (syringe temporarily uncapped)
4. System weighting without syringe needle shield (mass1)
5. Syringe filling with 0.5ml of distilled water by suction
6. System weighting (mass2).

The non-injected volume was defined as the difference between the weight after injection and the weight of the empty system (mass2 - mass1).

As shown in Figure 3, average and variability of the non-injected volume

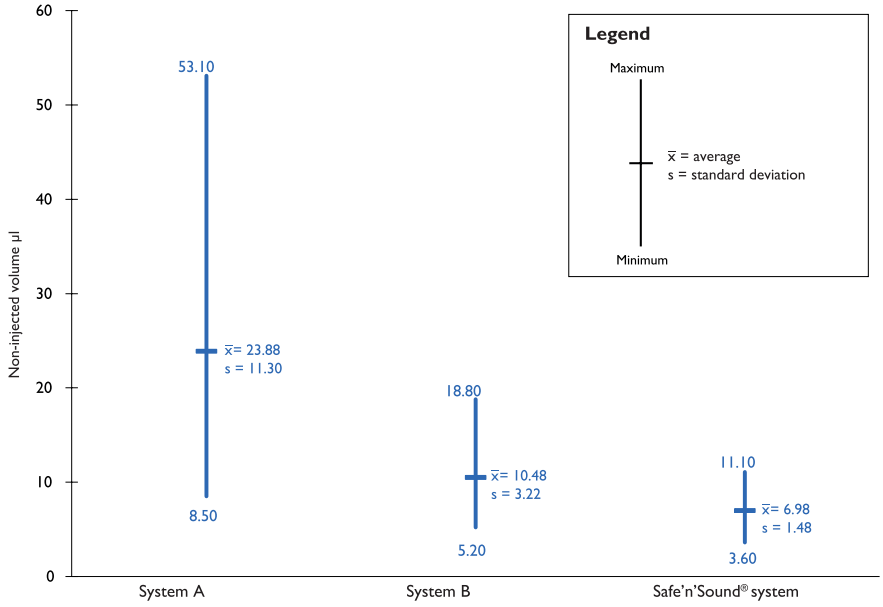

Figure 3: Results showing the measured non-injected volume with three different needle-safety systems.

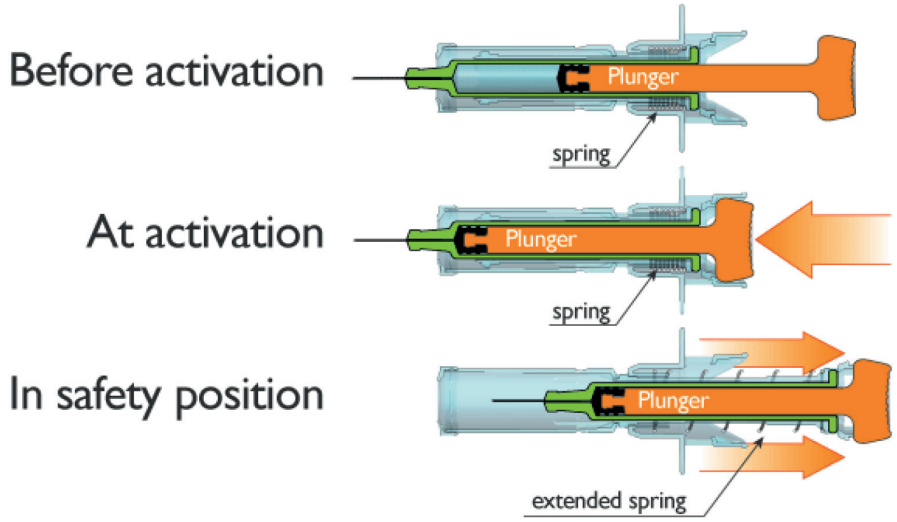

Figure 4: The Safe'n'Sound® mechanism helps syringe emptying, thanks to the two opposites forces applied by the user and the spring during injection.

were very different between the systems. Safe'n'Sound® demonstrated better results than the two comparators, with significantly lower values for both parameters. The average non-injected volume of system A and B were respectively 3 and 1.5 times higher than the non-injected volume from Safe'n'Sound®. Moreover, three residual volume values out of the 60 for System A were larger than 50 µL, representing 10% of the filled volume.

DISCUSSION

The study highlights how safety device design impacts non-injected volume. Improved performances of Safe'n'Sound® system can be explained for the following reasons:

1. Just before the end of injection, an extra force is applied by the user which activates the safety feature. As Safe'n'Sound® is a passive safety device, this extra force is not felt by the user who continues to push on the plunger rod to complete the injection. A spring is then released pulling the syringe back, while the user thumb is still pushing on the plunger rod. These two opposites forces applied by the user and the spring during the injection process help emptying the syringe (Figure 4).

This patented mechanism compensates the advanced release of the safety feature which happens on the three marketed passive safety device. It is critical not to have an additional force too high (the user must not feel it) as it could give him the false perception that the injection is completed. If so, the user could stop pushing on the plunger, resulting in higher non-injected volume and device non-activation. The adjustment of this additional force being critical for safety devices, it has been validated through simulated user studies for Safe'n'Sound®.[2]

2. In addition to its mechanism, Safe'n'Sound® has also been designed for ease of use. Through several design features, Safe'n'Sound® improves the ergonomics for the user, allowing them to push smoothly and continuously on the plunger rod until the end of the injection. It results in an improved precision of injection. With Safe'n'Sound®, users can activate the device in a very convenient and repeatable way, making it less user dependent than other marketed safety device. This advantage is even more critical for non-professional users.

3. Moreover, contrary to other passive safety device, Safe'n'Sound® spring is located at the syringe flange allowing clear visibility of the tip and inspection of the drug prior during and after injection. As a result, if necessary, the user can check that all the drug has been delivered prior removing the pressure on its thumb.

4. Nurses agree that Safe'n'Sound® doesn't modify the standard injection process.[2]

CONCLUSION

The comparative drug-dose delivery study highlights how Safe'n'Sound® optimises drug dose delivery, minimising the non-injected volume (lower average and variability) compared with other commercially available passive safety devices. This promotes increased treatment compliance and results in cost savings for pharmaceutical companies, reducing the need for overfilling. Other tests [3] have further highlighted how Safe'n'Sound® guarantees a non-injected volume comparable with a naked syringe. The performance of Safe'n'Sound® is linked with its function, which reduces human error.

Design optimisation of these output parameters is key for pharmaceutical companies as they have an impact on treatment efficiency and drug overfilling.

In addition to lower variability of residual volume highlighted in the study, Safe'n'Sound® differentiates from other passive safety devices on numerous other points. For example, the platform integrates numerous ergonomic features to facilitate the handling, gripping and comfort for the user: a large thumb pad surface to smooth the injection; large built-in finger flange to facilitate handling; a round shape for easy and comfortable handling; a spring located

Figure 5: An optional ergonomic extended finger flange (available in a variety of colours) overcomes the problematic of dexterity issues and drug viscosity.

at the syringe flange position to provide good visibility of the syringe tip and able inspection of the drug; an optional ergonomic extended finger flange (available in a variety of colours) to overcome the problematic of dexterity issues and drug viscosity (see Figure 5).

Results from Safe'n'Sound® simulated clinical user study performed with device-naïve patients and healthcare professionals from US and Europe showed how these design features translate into real clinical benefit.

There are numerous advantages for pharma companies too, in addition to those arising from clear clinical and patient benefits. For example, thanks to its specific patented clips design, Safe'n'Sound® requires low force to snap the syringe into the safety device while high force is required to unload the syringe. As a result, the risk of syringe breakage during insertion is reduced and the syringe is hold firmly once inserted into Safe'n'Sound®.

Finally, the device is robust against shocks and vibrations allowing safe handling during transport and on assembly lines. Consequently, Safe'n'Sound® can be delivered in trays or bulk, making it a cost-effective solution for pharmaceutical partners.

SAFE'N'SOUND® KEY FEATURES

- Single-use device
- Designed for patients and healthcare professionals
- Suitable for a wide range of patients including children and adults
- Compatible with subcutaneous and intramuscular injections
- Easy to use, convenient and ergonomic system
- Robust, reliable device ensuring safer injection
- Patented product/ 510(k) cleared
- On the market for both staked and Luer versions
- Open platform of add-on safety devices
- Compatible with 1ml & 2.25ml syringes of different:
  - o filling volume
  - o flange type (e.g. cut, round, small round, extra small round etc)
  - o suppliers (ISO standard marketed syringes including from BD, Gerresheimer, Nipro Glass, Ompi, Schott etc)
- Available in bulk or tray
- Optional ergonomic extended finger flange.

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PREFILLED SYRINGE DEVICE TRAINING: NOVEL APPROACHES & TECHNOLOGIES TO INCREASE PATIENT CONFIDENCE & DECREASE ANXIETY

In this article, Joe Reynolds, Research Manager, Noble, outlines some of the fundamental principles and benefits of training devices in the context of prefilled syringes, and highlights some specific training device technologies including novel needle simulators and angle aids.

As one of the oldest forms of drug delivery, the first medical application of syringes can be traced back to the 9th century where early embodiments were used as surgical instruments by Egyptian surgeons. For hundreds of years following their advent, syringes were largely viewed as surgical instruments until the nineteenth century and the discovery of early injectable compounds, including morphine and other analgesics. During the 20th century the commercial use and application of syringes as drug delivery devices grew exponentially.

Today, more than 50 biologic medications and vaccines are marketed and supplied in prefilled syringes.[1] Globally, more than 3.5 billion prefilled syringes are produced annually and used by patients and healthcare providers to treat a broad spectrum of conditions. In addition to currently marketed products, PhRMA estimates that more than 907 biologic medications and vaccines are currently in clinical development (Phase I-III) across more than 100 disease states, many of which will leverage prefilled syringes as the preferred delivery systems and primary containers.[2] As these products continue to augment and launch into new therapeutic sectors, training and education will remain a critical success factor that will determine a patient's ability to safely and effectively use prefilled syringes and adhere to therapy.

According to the World Health Organization (WHO), 50% of patients diagnosed with chronic conditions do not take their medications as prescribed.[3] While a number of factors contribute to patient adherence and therapy acceptance, confidence and anxiety are key external variables that influence patients' perceptions and attitudes toward medications and drug delivery devices.

These attitudes are largely established as patients onboard to therapy (i.e. their first 30, 60 or 90 days of treatments) and are key indicators of future behaviours and outcomes. During onboarding, research suggests that 45% of patients skip or avoid injections due to anxiety or fear.[4] Due to these avoidance behaviours, many patients fail to realise the full therapeutic benefits of medications and ultimately discontinue treatment.

Over the past decade, advancements in science and technology have greatly improved our understanding of patient adherence and the value of training and education in relation to health outcomes. Historically, training and educational initiatives were largely supported by Instructions for Use (IFU), package inserts and other content-based collateral. While these materials are effective for select populations, it is estimated that only 12% of patients have proficient health literacy and the ability to manage their health and wellness with these materials, resulting in significant training gaps and treatment barriers for prefilled syringe users.[5]

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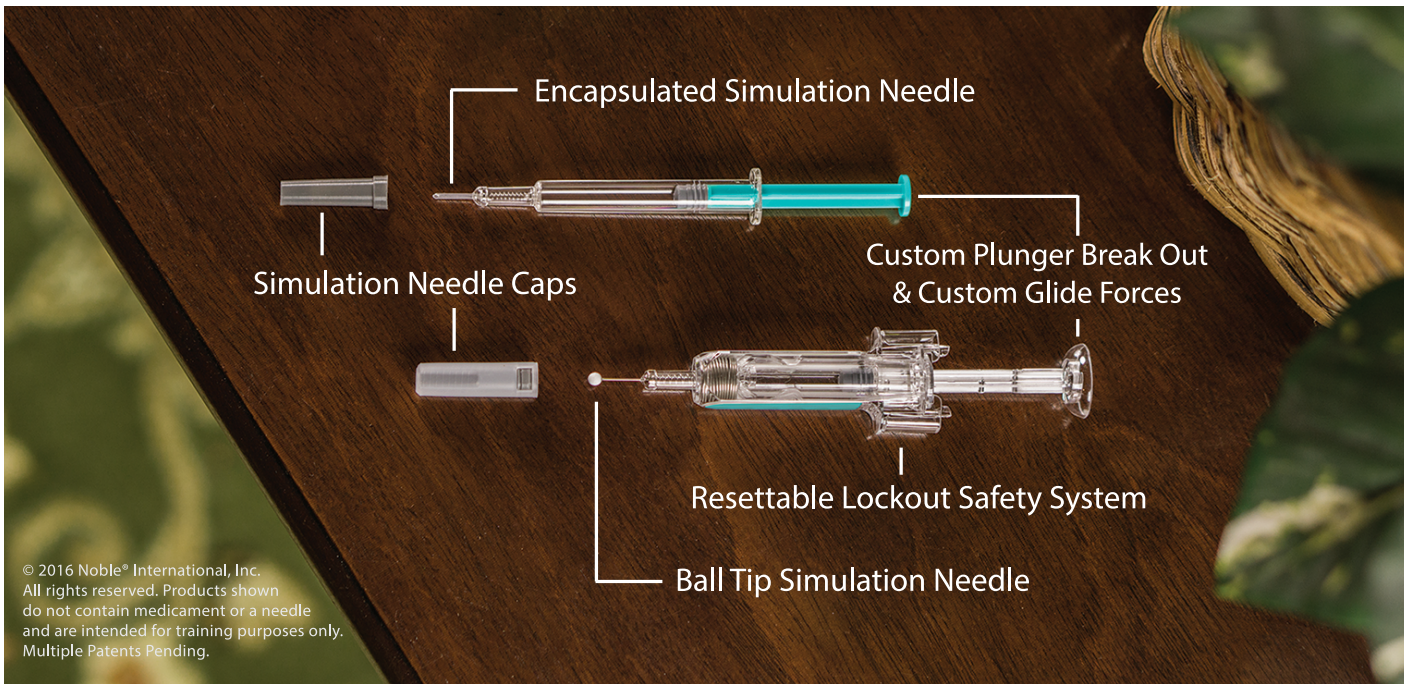

Figure 1: Training syringes simulate attributes of real syringes including: plunger break-out, glide forces for varying viscosities, volumes, resettable safety systems and other product-specific features to build confidence and proper administration behaviours.

In recent years, novel training strategies have emerged and greatly improved the patient onboarding experience through the use of training devices, multisensory packaging, angle aids and other ancillary support tools. By many industry standards, training devices have become the cornerstones of effective onboarding strategies by allowing patients and healthcare providers to learn safely how to use prefilled syringes and other forms of drug delivery device. Based on the findings of a recent user study, training devices can increase patient confidence indicators by 86% and decrease anxiety by 15%; two variables research suggests are closely related to adherence and outcomes.[6]

ESTABLISH MUSCLE MEMORY & ADHERENT BEHAVIOURS TO BUILD CONFIDENCE

As drug delivery devices, prefilled syringes have specific handling and operational requirements to support their intended use by patients and healthcare providers. In order to train and onboard users to prefilled syringes successfully, training devices must fully mimic the handling and operational requirements of commercial syringe experiences, which commonly include the following tasks:

1. Visually inspecting the syringe for damage, clarity and expiration
2. Selecting and cleaning an approved injection site (typically the thigh, abdomen and/or the back of the upper arm for caregivers)
3. Preparing the prefilled syringe by removing the needle shield and priming and/or re-constituting/suspending, as needed
4. Inserting the needle at the proper angle (typically 90 or 45 degrees) and depth into a pinched or stretched injection site, as required
5. Fully depressing the plunger to deliver the prescribed dose of medication
6. Removing and properly disposing of the used syringe.

To maximise the value and consistency of training, training syringes (see Figure 1) can be further supported by multisensory or ancillary support tools to improve the perception, retention and recall of key usage behaviours. Such capabilities allow patients to establish the muscle memory and motor skills required to build confidence and effectively use prefilled syringes.

NOVEL NEEDLE SIMULATORS REDUCE NEEDLE ANXIETY

Needle anxiety is a significant adherence barrier for patients using prefilled syringes and other forms of injectable drug delivery. Many of these associations are related to patients' negative perceptions of needles and past experiences with injections. This anxiety is often magnified when needles are visible, lengthy, or are of larger gauge.

To help reduce this anxiety and overcome the emotional barriers of self-injecting, novel needle simulation technologies have been developed to fully mimic the deformation, puncture and insertion force characteristics of various needle gauges, bevel geometries and other key attributes (see Figure 2). When applied to prefilled syringe training, these proprietary technologies allow patients to safely learn the force and technique required to insert needles into the skin.

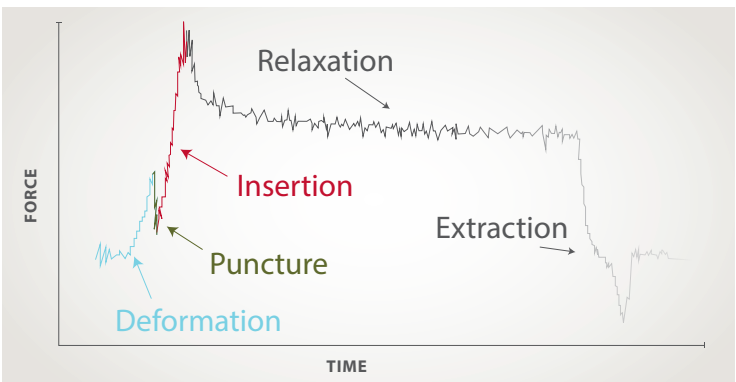

Figure 2: Needle insertion force graph depicting an injection from beginning to completion.

Key insertion behaviours captured in needle simulators include the following:

- Deformation: induced when the needle tip is in contact with the injection site. The force continues until a deflection at which the deformation force is maximised.
- Puncture: force related to the needle tip puncturing and entering the skin.
- Insertion: insertion force continues to increase in relation to the insertion depth and injection site characteristics.

ANGLE AID TRAINING SOLUTIONS TO IMPROVING DEPOSITION & INJECTION TECHNIQUE

Subcutaneous tissue is the lowermost layer of the integumentary system, consisting of connective and vascular tissues that support the absorption and systemic uptake of injectable medications. Clinical guidelines recommend that prefilled syringes be administered at 45° or 90° to achieve the optimal deposition for subcutaneous injections (Figure 3). Failure to achieve the proper injection depth can result in injection site pain and adversely affect the bioavailability and other pharmacokinetic properties of medications that reduce their overall efficacy or tolerability. To mitigate these risks, angle aids were developed to demonstrate proper needle insertion angles and techniques required to administer medications successfully. The geometry, form, angle, skin-pinch and features of these products are customisable based on the unique needs of patients and prefilled syringe platforms. To enhance the training experience further, feedback loops, spoken instruction, sensors and wireless technologies can be incorporated into angle aids to provide active learning experiences and collect data related to prefilled syringe training.

As noted by Tim McLeroy, Senior Manager at AbbVie (North Chicago, IL, US): "The goal of training is to decrease patient anxiety and increase confidence through hands-on experience." From his industry experience, Mr McLeroy has found that "the patient's first experiences with drug delivery devices can largely determine their outcome to therapy". He said, "Self-injection is a lot like dating, if you have a bad first date, it's difficult to want to go on the second one."

Novel training technologies like simulation needles, angle aid tools, auditory packaging and other multisensory solutions help promote positive onboarding experiences and empower patients to lead healthier lives. In the modern era of patient-centric care, products that are able to provide superior onboarding and patient experiences will be well positioned and benefit by reducing patient errors, while improving patient satisfaction and outcomes.

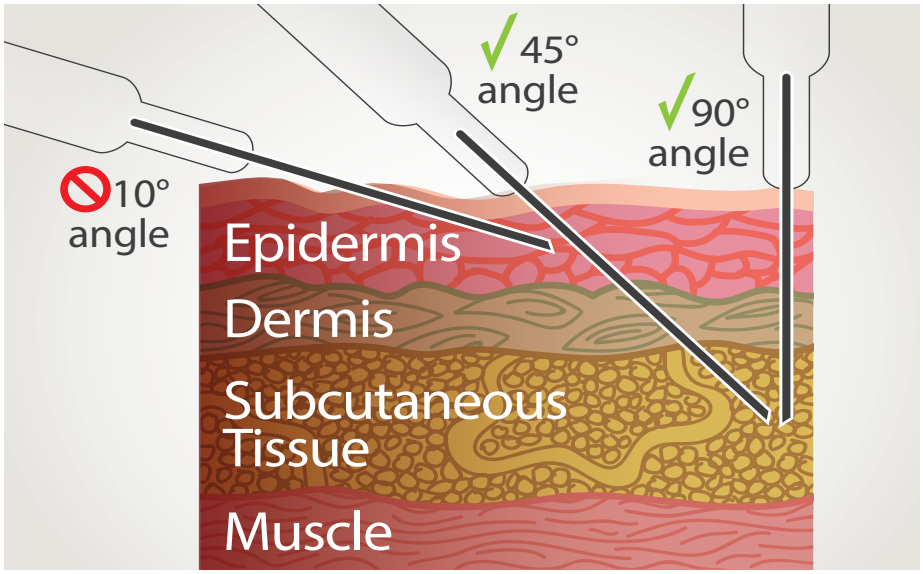

Figure 3: Recommended subcutaneous injection angles.

ABOUT NOBLE®

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Joe Reynolds is Research Manager at Noble, where he leverages his knowledge and experience to develop and implement strategies that improve the patient experience and maximise value for stakeholders. His experiences include commercial, managed care and product development initiatives with leading medical device, pharmaceutical and biopharmaceutical brands. Mr Reynolds holds a Bachelor of Science in Business Administration from the University of Central Florida, a Master of Science in Marketing from the University of South Florida and a Master of Science in Pharmacy and Master Certificate in Drug Regulatory Affairs from the University of Florida.

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AN INNOVATIVE SOLUTION TO ADDRESS SILICONE-RELATED CONCERNS

In this piece, Christian Herget, Worldwide Strategic Marketing Leader Biotech, BD Medical – Pharmaceutical Systems, explores the potential impacts of silicone coatings on prefilled syringe-based injectable biopharmaceutical combination products and recent advances at BD to reduce these impacts.

Injectable biopharmaceuticals are a pivotal element in the arsenal of treatments for chronic diseases like multiple sclerosis and rheumatoid arthritis [1] and, as with all therapeutics administered regularly over long periods of time, efficacy and safety are particularly critical to ensuring consistent quality of care. However, biopharmaceuticals are highly complex and, consequently, vulnerable to several forms of degradation [2] that can have an impact on their efficacy and safety.

> "SbVP detection is constantly improving, thanks to new analytical techniques.[5] Particles smaller than 10 µm – and potentially into the submicron range – are now detectable. We can now also determine the types of these tiny particles."

Because of their protein structure,[2] biopharmaceutical formulations must be parenterally administered; many are injected. With prefilled syringes – the packaging of choice for many biopharmaceuticals – pharma companies must grapple with new challenges like interactions between the container (i.e. the syringes) and drug [1] that could affect drug efficacy and safety and, in the event of undesirable reactions, lengthen time to market or compromise safety and efficacy of the drug.

For biopharmaceuticals packaged in prefilled syringes, this adds a new challenge: the syringe, now part of the product,[3] has the potential to compromise the drug inside. A number of syringe attributes must be carefully assessed to ensure that the drug will not interact in any unexpected ways with its primary container. Therefore, choosing the right syringe is now one of the key factors to consider in order to avoid costly development delays or, worse, potential product recalls.[1]

The prefillable syringes available on the market are not always completely suitable for biopharmaceuticals and several of their common components – like the silicone oil used as a lubricant to ensure smooth plunger action with lower injection force [4] – have been evaluated and deemed potentially incompatible with biopharmaceuticals.

BD draws upon decades of collaboration with pharma industry leaders and understands the importance of satisfying the most

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stringent efficacy, safety and quality criteria to provide patients with innovative injectable therapies while helping pharmaceutical companies mitigate product development and commercialisation risks.

SILICONE & BIOPHARMACEUTICALS: WHAT YOU SHOULD KNOW

A number of concerns have been raised about silicone, used as a prefilled syringe lubricant and possible interactions with biopharmaceutical drugs:[1,5]

- Cosmetic: sub-visible (SbVPs) and visible particles may compromise drug purity verification, resulting in increased false rejects and higher total cost of ownership
- Pharmaceutical: potential loss of therapeutic response and changes in activity that could affect drug safety, efficacy and quality
- Technical: aggressive formulations can affect the syringe's gliding properties, leading to incomplete injection with auto injectors and, in some cases, product recalls
- Clinical: according to some research, and under specific experimental conditions, silicone SbVPs could promote aggregation or co-aggregation of biopharmaceuticals. Such aggregates are suspected potentially to play a role in unwanted immune responses leading to the production of anti-drug antibodies (ADAs). ADAs may bind to therapeutic proteins molecules reducing their therapeutic efficacy by neutralising their activity and/or increasing their rates of clearance.[6]

Some manufacturers have introduced syringes equipped with baked silicone and non-siliconised plastic syringes as a potential solution to these challenges.[7,8,9] However, baked silicone technology is generally not compatible with staked needle design, the gold standard for injectable biopharmaceuticals. Furthermore, baked silicone only partially reduces silicone-induced SbVPs.

Plastic prefilled syringe technology has a limited track record for injectable biopharmaceuticals and introduces a whole new set of inherent challenges and risks – such as drug compatibility and manufacturability – that pharmaceutical companies need to control. BD is addressing silicone-related issues with innovative technologies to reduce silicone-induced SbVPs to their lowest ever levels, based on well characterised chemistry of silicone lubricant and therefore supplementary challenges and risks, while retaining the time and force required for injection, known as syringeability [4] – a key factor in patient compliance with auto injected drug regimens – and auto-injector functionality, as well as managing change control risk.

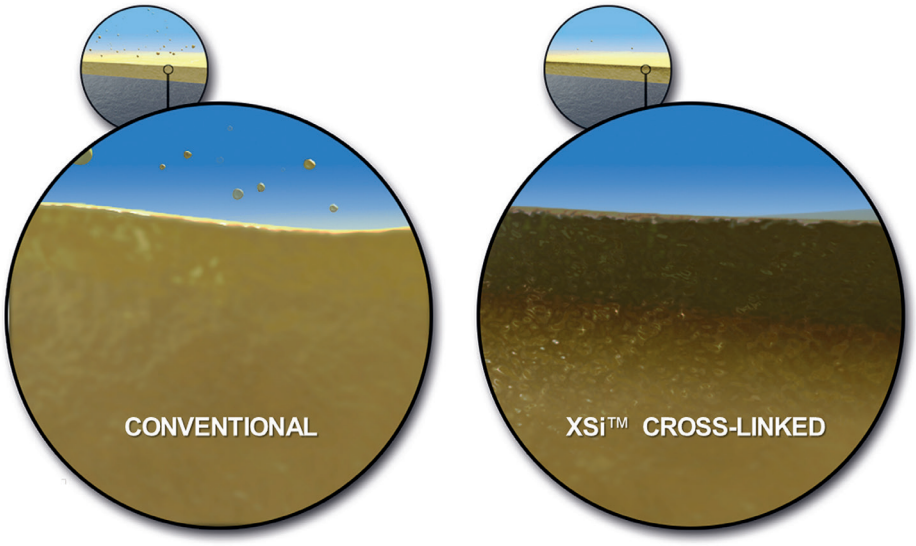

Figure 1: Conventional versus BD XSi™ cross-linked silicone chain networking. The modified lubricant layer acts as a barrier to silicone emulsification, reducing the migration of silicone oil from the barrel and maintaining the lubricity required for the syringe to perform as intended.

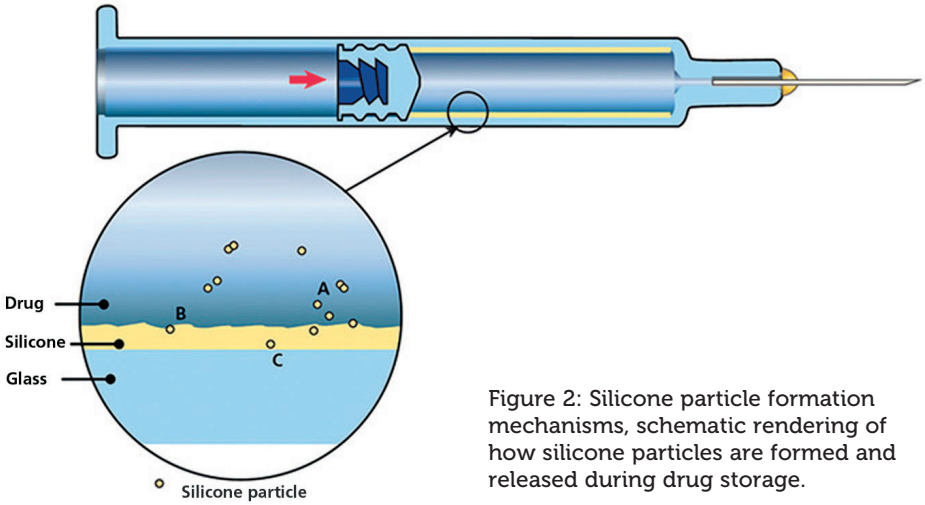

Figure 2: Silicone particle formation mechanisms, schematic rendering of how silicone particles are formed and released during drug storage.

REDUCING SbVPs WITHOUT COMPROMISING PERFORMANCE

The emergence of biopharmaceuticals and the associated combination product development challenges [3] have made silicone a topic of discussion in the prefilled syringe market. BD responded with the BD XSi™ research programme to develop a staked needle prefillable syringe that ensures full auto injector compatibility and that significantly reduces potential risks associated with sub-visible silicone particles.

The programme resulted in an innovative immobilised silicone coating: cross-linked silicone BD XSi™, shown in Figure 1. This coating reduces the risks associated with sub-visible silicone particles while retaining lubrication performance; in addition, BD XSi™ is based on established chemistry of silicone lubricant, for rapid implementation of the prefilled syringe format for both legacy and pipeline drugs.[1]

BD XSi™ technology ensures container and lubricant layer inertness, resistance to degradation by drug product, biological drug stability, full gliding performance and the low silicone-derived SbVPs comparable with levels of non-siliconised prefilled syringes and better than baked silicone. A more robust lubricant layer also offers added benefits for innovative, more aggressive, drug

formulations aiming to increase payload.

BD XSi™ technology is ready for adoption with no alteration to existing prefillable syringe manufacturing or filling processes. In addition to its strategic benefits, BD XSi™ exhibits overall container performance that is equal or superior to conventional delivery systems.[1] Designed for staked needle syringes and used with conventional stoppers, the BD XSi™ proprietary coating employs an advanced, well-characterised and unique silicone based technology that minimises the risks and facilitates adoption.

PARTICLE FORMATION MECHANISMS & DETECTION

Gathering data is a fundamental prerequisite to assessing the performance of any new technology, and silicone prefillable syringe coatings are no exception. But first we must understand the mechanisms that cause the formation of silicone-induced SbVPs.

As their name indicates, silicone-induced SbVPs in prefilled syringes originate from the silicone lubricant applied to the inner syringe surface. There are three SbVP groups, each with its own formation mechanisms and potential impacts. The three significant populations of silicone-induced SbVPs present in a prefilled syringe format are:

Type A: silicone droplets released (or emulsified) into the drug solution soon after filling and therefore in contact with the drug solution throughout the entire product shelf-life; could potentially form silicone-protein complexes.

Type B: Silicone particles from the silicone surface that remains in contact with the drug solution throughout the product shelf-life and that could move into solution at some point in time.

Type C: Silicone particles from the bulk silicone layer sloughed off the wall during injection. In contact with the drug for a much shorter time than the other particle types, these nevertheless represent a significant portion of the particles measured using current compendial methods.

SbVP detection is constantly improving, thanks to new analytical techniques.[5] Particles smaller than 10 µm – and potentially into the submicron range – are now detectable. We can now also determine the types of these tiny particles. This more detailed data will greatly enhance SbVP monitoring and, ultimately, provide a deeper understanding of the contribution of silicone oil to the overall pool of detected SbVPs. This will contribute to accelerating the industry's discussion of silicone oil and PFSs and drive the emergence of solutions to reduce SbVP formation and impacts.

MEASURING SbVP REDUCTION

Our study [1] looked at commercially available prefillable glass syringes with no silicone coating, a conventional sprayed-on silicone coating, baked silicone coating and the BD XSi™ cross-linked silicone coating. We used reflectometry, optical microscopy, and time-of-flight secondary ion mass spectrometry to measure particle content in a model buffer system (polysorbate 80/phosphate-buffered saline: PS80/PBS).

Our findings show that the syringes with the BD XSi™ cross-linked silicone coating outperformed syringes with a conventional sprayed-on silicone coating, and baked silicon coating (see Figure 3). Enhanced integrity of the lubricant coating led to significantly fewer SbVPs in the liquid formulations, particularly after agitation stresses introduced by shipping of the syringes. The BD XSi™ coating also maintained the syringes' intended functional properties as determined by high-performance size-exclusion chromatography.

ASSESSING PRODUCT PERFORMANCE OVER TIME

Our BD XSi™ study also assessed two critical syringe properties that indicate product performance over time: the integrity of the BD XSi™ coating layer after incubation with the drug and syringeability, manifested by the time and force required for injection.

Coating integrity over time and syringeability [4] are increasingly important in the development of innovative biopharmaceuticals packaged in prefilled syringes. The formulations of these drugs are enhanced to increase the dose of active pharmaceutical ingredient (API) to achieve better patient outcomes and/or extend injection intervals. These enhancements may cause degradation of the lubricant layer during drug storage. This degradation can lead to SbVP release, of course. However, it can also compromise drug syringeability and thus jeopardise the flawless drug delivery of the combination

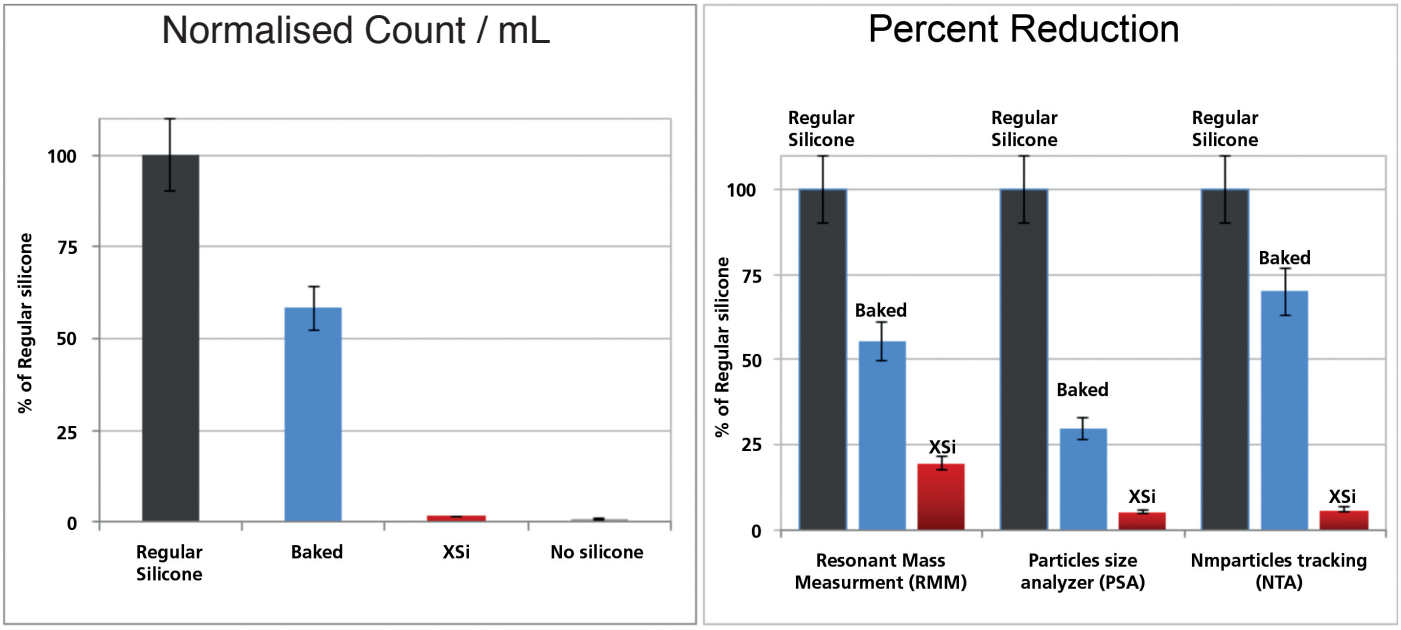

Figure 3: Silicone SbVPs released after agitation of PS80 solutions in PBS from various PFS.

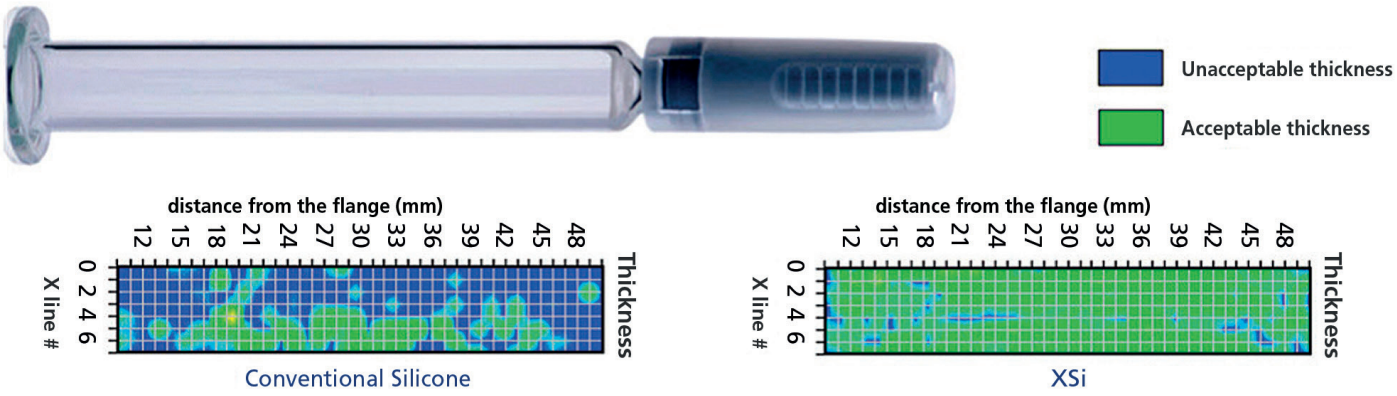

Figure 4: Layer integrity after drug contact. Thickness of coating measured in distance from flange using reflectometry.

product. If identified during product development, these types of issues can lengthen time to market. BD XSi TM reduces degradation and therefore can help minimise the risk of development delays due to undesired drug-container interactions.

For auto injectors and attached needles, BD XSi™ provided the expected lubricious behaviour with a similar level of functional gliding performance as conventional siliconised syringes. This syringeability is widely accepted as a factor in patient compliance with auto-injected drug regimens.

We also looked at the integrity of the BD XSi™ coating after drug contact. We used shelf-life testing designed to mimic realistic but extremely stringent conditions on placebo-filled prefilled syringes with the BD XSi™ coating. BD XSi™ demonstrated exceptional stability over time, retaining its critical quality attributes of density, chemical composition and dimension even after storage in contact with a drug.

CONCLUSION

Biopharmaceuticals are revolutionising care. However, innovations are needed to make sure the promise of biopharmaceuticals is fulfilled, especially for patients with chronic diseases where drug safety and efficacy are particularly crucial. Prefilled syringes have emerged as the delivery system of choice for biopharmaceuticals, but several challenges must be overcome to ensure the ultimate safety and efficacy of syringe-based combination products.

Container-drug interactions are one such challenge, and silicone syringe linings are facing particular scrutiny. BD has made silicone a priority R&D topic, and is making advances in product engineering materials and characterisation tools that show positive results in meeting and overcoming these challenges.

Innovative products like BD XSi™ have been shown to reduce silicone-induced SbVPs to the lowest extent ever, minimising the risk of undesired drug-container interactions with optimised drug delivery performance. And, because BD XSi™ is based on conventional chemistry of silicone lubricant, it delivers the full spectrum of benefits of high-end staked needle prefillable syringes, while minimising the complexity, risks and costs of the development and commercialisation of innovative combination products.

BD XSi™ is just one product in BD's range of solutions for biotech. BD draws on a long track-record of customer-centric innovation and real-world problem solving to develop innovative products and services to support pharmaceutical companies' product development and lifecycle management strategies. From the BD Neopak™ top-of-the-line glass PFS system to BD VisioGuard™ inspected stoppers, BD is a trusted partner for biopharmaceuticals, helping pharmaceutical companies reduce time to market, improve in operational efficiency and create competitive advantage by gaining the preference of patients and prescribers.

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Here, SHL Group first explores the importance of fundamental design principles in injector design, as exemplified by the Molly® auto injector, and then goes on to introduce connectivity and describe how SHL is incorporating connectivity into its devices, via dedicated connectivity innovation program called Alubena®, and the significant benefits this brings.

Pharmaceutical companies and product manufacturers must be acutely aware of trending needs of existing and potential patients, prescribers, payers, and patient-care providers, to be able to provide products that resonate well with these different groups of customers. The relationship between pharma and product makers should also be successful, in terms of launching a successful product that is well received by these customer groups. Thus, it is crucial for manufacturers to produce innovative products and services that help pharma companies differentiate their products and services.

To achieve this, device manufacturers must understand what "innovation" means and how it is measured. In terms of devices, if we look at auto injectors and pen injectors, what makes a good injector? What is needed and what is currently missing in our existing product that has unmet user needs? What is the next step? What can make this product more useful and convenient for the user? Further, how do we stay a step ahead of our customers and predict their needs and preferences? These questions and more should be addressed purposefully as the process is a critical step towards meeting healthcare needs. Often, the best way to approach these questions is to go back to the basics, rediscover the fundamentals, and start over from there.

THE FUNDAMENTALS OF A WELL-DESIGNED AUTO INJECTOR

In the competitive auto injector market, a design and manufacturing company that is able to stand out with a long-lasting product in terms of its presence in the market will be an invaluable partner for a pharmaceutical company.

A successful and sustainable device manufacturer should follow the celebrated ten principles for good design of German industrial designer Dieter Rams. First and foremost, a good design is innovative, which is a principle device manufacturers must adhere to. A good design must be innovative in terms of function, use, and appearance. This is clearly the case for the Molly® auto injector,

> "Following the "less but better" concept, SHL eliminates any unnecessary design without sacrificing safety and aesthetics. A good design is always the simplest possible working solution, unburdened with non-essentials and rid of unnecessary waste during the manufacturing process."

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with its revolutionary two-step injection process, making it easy for patients and caregivers to administer a shot comfortably in their own homes. Apart from its essential functions, it is also aesthetically pleasing and extremely portable. According to Dieter Rams, "Only well-executed objects can be beautiful. The aesthetic quality of a product is integral to its usefulness because products used every day have an effect on people and their well-being." This is especially true in the medical and healthcare industry as the products will indeed affect patients' everyday lives.

A good design is also self-explanatory. Much like the Molly® 1.0, the Molly® 2.25 (Figure 1) is designed to be intuitive and self-instructing. Intuitive design is essentially human factors engineering or ergonomics, and clarifies the product's structure. Care and accuracy in the design process involve various case studies to understand user preferences and previously unmet needs. User-oriented design adds both intellectual and material value to a product and in turn increases satisfaction and the life situation of its user. Ergonomically designed products are generally self-explanatory and will be extremely simple to use, which should be the case for patients who use auto injectors or pen injectors on a daily basis. Following the "less but better" concept, SHL eliminates any unnecessary design without sacrificing safety and aesthetics. A good design is always the simplest possible working solution, unburdened with non-essentials and rid of unnecessary waste during the manufacturing process.

LARGE-VOLUME AUTO INJECTORS

Aside from the steadily increasing demands of auto injectors, the market for single-use technology and auto injectors for higher volume and more viscous drugs is increasing. The Molly® 2.25 has a larger capacity than its predecessor, with the same two-step simple operation. The cap is an ergonomic pull- or twist-off design with improved features to prevent unwanted rolling for safety. The ready-made platform Molly® 1.0 was given a new form to become the Molly® 2.25, which is able to effectively deliver more viscous drugs at a higher volume.

Mats Persson, Executive Vice-President of SHL, explains, "The 1 mL Molly® device has attracted a lot of success and interest since being launched, but increasingly we are seeing new biologics being unable to be formulated into a single 1 mL dose. To meet this need for simple delivery of larger doses, SHL has developed a larger version of Molly® to accommodate a 2.25 mL prefilled syringe, enabling delivery of larger volumes with the same simple, easy, and proven two-step operation."

Figure 1: The Molly® 2.25 auto injector, with its revolutionary two-step injection process, makes it easy to administer a shot comfortably at home. It is also aesthetically pleasing and extremely portable.

As a pre-configured device, the development timelines, business model, and cost will be similarly attractive for the 1 mL Molly® to drug companies looking for the right device for their product.

> "There is no doubt that connectivity will improve patient (and healthcare provider) compliance, but whether the data and information can be handled in a secure and robust system will be the next challenge."

As previously stated, the Molly® 2.25 is designed to be as intuitive and self-instructing as its predecessor. However, unlike the Molly® 1.0, the larger version has a new back end, which is covered by a double curved cap; this gives the device a more natural and ergonomic feel and look. The needle shield remover cap is attached to the outer body to improve assembly. Furthermore the cap, which can be pulled or twisted off, is enlarged with two flanges intended for firm grasp (particularly for rheumatoid arthritis patients) and prevention of unwanted rolling of the product. The cap also comes with arrow-shaped cut-outs to further clarify handling directions (Figure 2). The result is a robust device that is easy to handle and improves user experience. Even if the original model is a success, that does not mean it can never be improved. A product can be reinvented again and again, equipped with new or improved forms and uses.

Figure 2: Molly® 2.25 has a much better grip with improved cap design.

CONNECTIVITY FOR ADVANCED DRUG DELIVERY SYSTEMS

Anything innovative these days may involve connectivity. Connectivity is obviously a widespread trend, one we see not only in healthcare, but with the Internet of Things assuming a greater role in our everyday lives, in lighting and home security as well, and so much more. Connectivity has now become a viable means to satisfy a need to communicate, as well as to store and transfer information, for example, through wearable sensors. For a healthcare industry facing many challenges, this can bring value from several different perspectives.

"Connectivity has now become a viable means to satisfy a need to communicate, as well as to store and transfer information, for example, through wearable sensors. For a healthcare industry facing many challenges, this can bring value from several different perspectives."

One of the biggest challenges in the healthcare industry is poor patient compliance. Low adherence to medication is important in many respects. First of all, it contributes to unnecessary suffering for both patients and their families, and also results in large but avoidable healthcare expenses, as well as significant financial loss for the pharmaceutical industry. A connected drug delivery device enables patient support programs by providing real usage data to analyse and personalise the patient's support and experience (Figure 3). The intention is to increase adherence to the prescribed therapy and increase patients' quality of life. Increased adherence will contribute to a healthy outcome, which will benefit all parties involved.

The pioneering devices on the market are stepping away from the traditional mechanical auto injector. With improving technical sophistication, and with decreasing costs, there is more flexibility to develop injection devices further in terms of functionality, usability, and aesthetics.

Figure 3: Summary of connectivity concept which enables a connected drug delivery device to enhance patient support programs by providing real usage data.

There would be no fundamental changes to the core function, but only in whether the drug is delivered efficiently and effectively. Additional functions should and would only be added to target different patient groups with specific needs.

SHL has developed a connected auto injector concept, the disposable Molly® C auto injector with a reusable recording unit, which enables data recording and transmission to a smartphone via Bluetooth (Figure 4). This is the first initiative by Alubena®, SHL's connectivity innovation program for drug delivery systems.

However, connectivity inevitably raises issues such as protection of patient information, which has long been a focus for healthcare and its relative, regulatory affairs. With technology infiltrating deeper and deeper into our everyday lives, there is no doubt that connectivity will improve patient (and healthcare provider) compliance, but whether the data and information can be handled in a secure and robust system will be the next challenge.

As a current leader in design, development, and manufacturing of auto injectors and other delivery devices, SHL will have an advantage in developing connectivity capabilities, as it has extensive experience developing injection devices and possesses the core knowledge for tailor-made, user-friendly, and safe devices. SHL also has more leverage when it comes to in-house

manufacturing capabilities, exploration of new technologies, and keen market awareness. However, it is still imperative that the manufacturer approach the subject carefully and focus on providing unmet needs, rather than getting carried away with the numerous possibilities for connectivity, some of which the market is not yet ready for. First and foremost, the product must bring real value to both customers and users. Therefore, technology development is significant to a company's growth, but equally important is the ability and capability to develop solutions at different stages throughout the entire product chain.

Today's healthcare organisations need partners who can help design and introduce solutions that deliver care effectively and efficiently amidst evolving reimbursement structures. SHL has worked with many types of organisations, including worldwide international pharma companies as well as smaller organisations with less experience in developing a product from scratch. It is paramount for a device manufacturer such as SHL to learn and progress along with the industry, and develop innovative and good products that ultimately meet the fundamental needs of both customers and patients.

Figure 4: The connected, disposable Molly® C auto injector (a) with re-usable data recording and transmission device (b) which enables transmission to a smartphone via Bluetooth (c).

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Molly®

The ideal safety solution 2.25 mL

- ✓ Easy to Use 2-step Operation
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PRODUCT PROFILE: **PREMIUMCOAT™**

Aptar Stelmi

Figure 1: PremiumCoat™: the alternative coated stoppers for sensitive drugs. (Image courtesy of Aptar Stelmi.)

APTAR STELMI, A TRUSTED GLOBAL PARTNER FOR PREMIUM ELASTOMERIC CLOSURES

Driven by quality, service and innovation for more than 50 years, Aptar Stelmi is a trusted partner of leading pharmaceutical and biopharmaceutical companies throughout the world. We design and manufacture elastomeric closures: stoppers for vials, and prefilled syringe and cartridge components such as plungers, needle shields and tip caps for all parenteral applications.

Whether for vaccines, existing or new drugs, applications or delivery systems, our committed teams of experts work closely with our customers around the world to deliver fully compliant premium quality products.

> "Biopharmaceuticals are very sensitive in nature and prone to interaction with the rubber of the stopper. The challenge, therefore, is to maintain the integrity of the container closure while minimising interaction between the formulation and the components of the elastomeric closure system."

OUR SHARED GOAL: PRODUCT PROTECTION, EFFICACY & SAFETY

We strive to provide the highest quality packaging components for injectable drugs. Our consistent quality, innovation and customer service are the cornerstone of the trusted partnerships we build with our customers.

QUALITY SOLUTION PROVIDER

Our elastomeric closure solutions comply with the highest industry and regulatory standards. Our state-of-the-art cGMP-compliant manufacturing processes include automation, camera inspection and classified cleanrooms. In addition, our team of experts, quality system and procedures support these production processes up to and including sterilisation - a premium quality environment for your drug products.

PREMIUMCOAT™: ALTERNATIVE COATED STOPPER FOR SENSITIVE DRUGS

Biopharmaceuticals are very sensitive in nature and prone to interaction with the rubber of the stopper. The challenge, therefore, is to maintain the integrity of the container closure while minimising interaction between the formulation and the compo-

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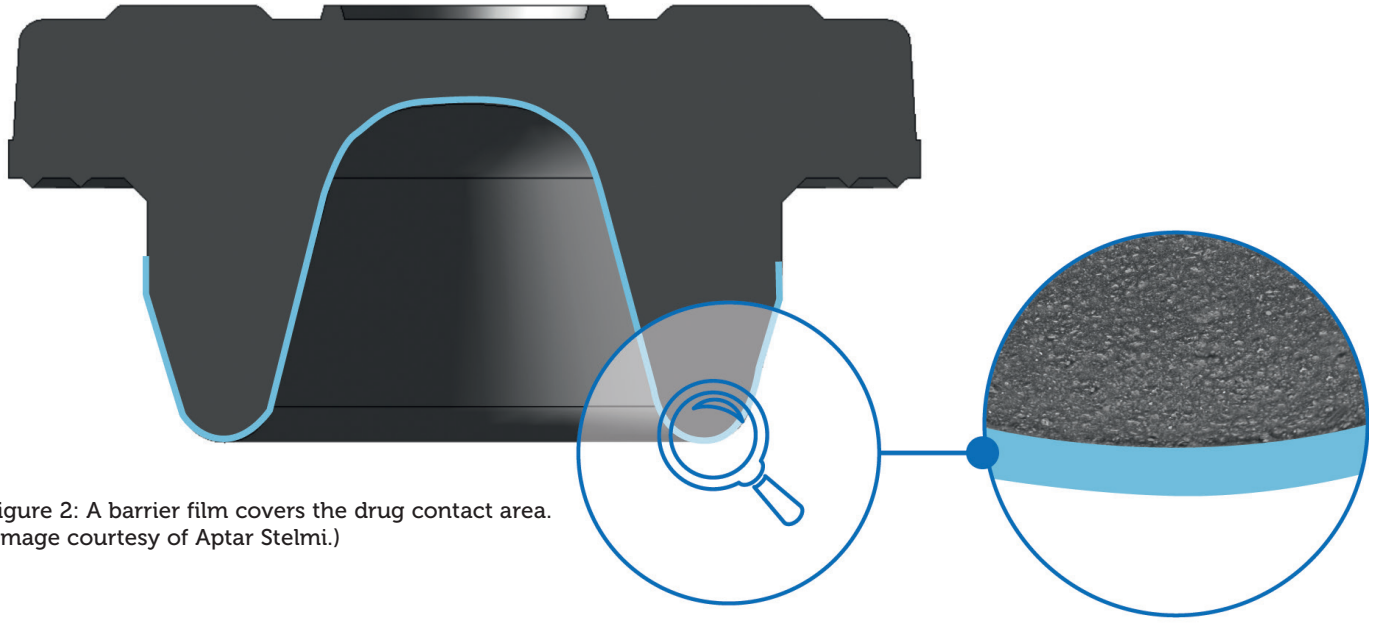

Figure 2: A barrier film covers the drug contact area. (Image courtesy of Aptar Stelmi.)

nents of the elastomeric closure system. To meet this demand, Aptar Stelmi developed the PremiumCoat™ range of elastomeric stoppers (Figure 1).

PremiumCoat™ is a novel range of elastomeric stoppers developed by Aptar Stelmi, launched in 2015 and designed for the protection of sensitive and high-value drugs, including biopharmaceuticals. Based on an approved, pure, state-of-the-art formulation, the surface of the elastomer is coated during manufacturing with a thin fluoropolymer film. This coating acts as an effective barrier to many of the extractables and leachables that can be released from the elastomer and contaminate the drug (Figure 2). As a result, compatibility of the drug and the closure is significantly superior with PremiumCoat™ stoppers.

The first design to be released in 2015 was a 20mm coated stopper. We are widening our PremiumCoat™ range, introducing a 13mm coated stopper at Pharmapack Europe 2016, and will soon extend our offer with other products.

PROVEN INNOVATOR

Our experience in elastomeric closures and container closure systems is supported by the capabilities of our International Technical Center based in our headquarters in Villepinte (France). This state-of-the-art facility has been specifically designed and equipped for mechanical, functional, chemical, container closure integrity and microbiology/particle testing. A pioneer in proprietary designs and finishing processes which have now become industry standards, our team of technical and scientific specialists pursues the development of tomorrow's products and processes.

A member of the AptarGroup, we benefit from the global market presence, innovation and technical capabilities of an industry leader.

ABOUT APTAR STELMI

Part of the Pharma division of AptarGroup, Aptar Stelmi is a trusted partner of leading pharmaceutical companies in the design and manufacturing of elastomeric closures for parenteral applications.

Driven by quality, service, and innovation for more than 50 years, Aptar Stelmi products meet the evolving drug industry demands for cleanliness, efficiency and compliance. Our prefilled syringe components and stoppers for vials are used to multiple applications in more than 70 countries worldwide.

AptarGroup, Inc, (NYSE: ATR) is a leading global supplier of a broad range of innovative dispensing systems for the beauty, personal care, home care, prescription drug, consumer health care, injectables, food and beverage markets. AptarGroup is headquartered in Crystal Lake, IL, US, with manufacturing facilities in North America, Europe, Asia and Latin America.

Meet Aptar Stelmi at Pharmapack Europe (Paris, France) – February 10-11, 2016 – Booth N° 614!

COMPANY PROFILE: CREDENCE MEDSYSTEMS

Credence MedSystems is a drug delivery company focused on delivering medications safely for the benefit of patients, caregivers and partners. The Companion Safety Syringe System was born from Credence's philosophy of *Innovation Without Change*. The Companion offers our pharmaceutical and biotech partners a simplified path to commercialisation of a best-in-class drug delivery system by providing superior safety and usability while using existing primary package components.

INNOVATION WITHOUT CHANGE - THE CREDENCE COMPANION SAFETY SYRINGE SYSTEM

Innovation Without Change simplifies the commercialisation path for drug manufacturers while introducing critical innovation in the end device. The modular approach gives drug manufacturers the freedom to select existing syringe barrel, stopper and tip cap/needle shield primary package components from preferred vendors, mitigating much of the development, regulatory and supply chain risk associated with combination product development.

The Companion needle and plunger rod are incorporated with the syringe barrel, yielding an end device that features passive needlestick safety and syringe disabling technology. Upon completion of the injection, the user receives audible, visual and tactile cues that the dose has been delivered and then the needle automatically retracts into the barrel of the syringe, rendering the syringe needle-free and preventing reuse (see Figure 1).

> "Credence shifts the paradigm for conventional drug-delivery device development, allowing drug manufacturers to provide their end-users the best safety and usability features that have traditionally been abandoned due to the time, cost and risk conventionally associated with implementing innovation."

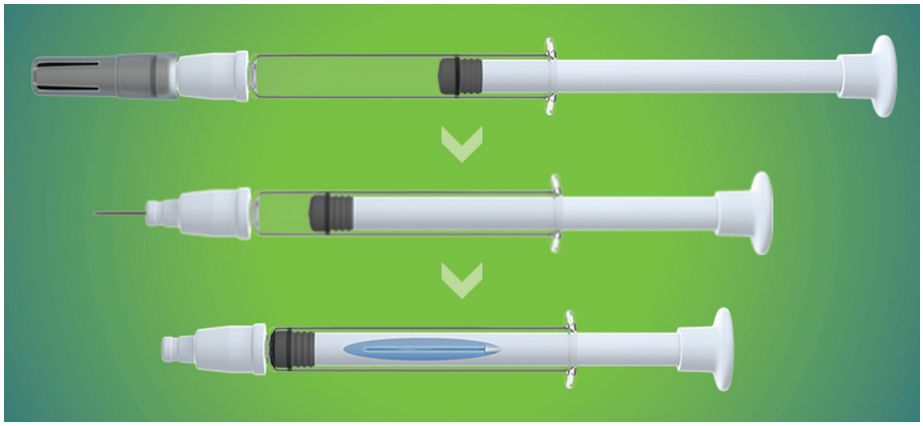

Figure 1: Upon completion of the injection the needle automatically retracts into the barrel of the syringe, rendering it needle-free and preventing re-use.

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A SIMPLIFIED PATH TO BEST-IN-CLASS DRUG DELIVERY

Benefits for the **Drug Manufacturer**	Benefits for the **End-User**
Marketable Differentiation	Passive Integrated Needlestick Safety
Uses Existing Syringe Components	Smart Syringe Reuse Prevention
Simplified Commercialization Path	End-of-Dose Cues
Reduced Supply Chain Risk	Glue-Free Staked & Luer Needles
Standard Filling & Assembly	Allows Standard Syringe Procedures
Glue-Free Design	User Friendly Design

Figure 2: Credence shifts the paradigm for drug-delivery device development, allowing drug manufacturers to provide end-users the best safety and usability.

Credence shifts the paradigm for conventional drug-delivery device development (Figure 2), allowing drug manufacturers to provide their end-users the best safety and usability features that have traditionally been abandoned due to the time, cost and risk conventionally associated with implementing innovation.

Credence has expanded the *Innovation Without Change* concept to a platform of products (see below) that includes the **Luer Companion** where the user attaches the needle, the **Staked Companion** where the needle is provided to the user pre-attached, and the **Dual Chamber Reconstitution Safety Syringe**, which vastly enhances the safety and simplicity for the user.

THE CREDENCE COMPANION
SAFETY SYRINGE SYSTEM

THE COMPANION PRODUCT FAMILY

Companion Staked Needle Syringe

When a pre-attached needle is preferred, the Companion Staked Needle Syringe allows the use of existing drug container components and provides integrated automatic needle retraction and reuse prevention.

Companion Luer Syringe

Applications that require needle-choice flexibility or reconstitution call for the user to attach the needle. The Guide-On Needle Cover promotes a proper needle attachment and the Companion Luer Syringe provides the passive safety.

Companion Dual Chamber Reconstitution Safety Syringe

The Dual Chamber Reconstitution Safety Syringe offers a pre-attached needle, the use of an existing syringe barrel and closure components, single-step reconstitution and injection, along with the Companion's passive needle safety and reuse prevention.

eleXIS Group

HEKUMA

HIGH-END PREFILLABLE SYRINGES FOR INNOVATIVE BIOPHARMACEUTICALS

In this article, HEKUMA, the German specialist for high-performance automation equipment, describes how, in developing a system for Becton Dickinson (BD) to manufacture a high-end prefillable syringe for innovative biopharmaceuticals, it exceeded BD's requirements. HEKUMA provides detailed insights into how specific process challenges arose and were met, and describes a resulting manufacturing line that excels in precision, technical reliability and cleanliness of the manufacturing environment to produce a syringe featuring highest product performance attributes.

As a worldwide leading manufacturer of medical devices, BD is the partner of choice for major biopharmaceutical companies looking for delivery solutions for injectable drugs. BD has a history of leadership in design and innovation, addressing key industry trends and customer needs with novel product and process solutions. Currently, BD is introducing a novel prefillable COP (cyclo-olefin polymer) syringe for biopharmaceuticals. The syringe has a staked needle design (with pre-attached needle) featuring ultra-low silicone, ultra-low tungsten and ultra-low particle values. In order to realise this design input, the challenge was to combine the moulding of the syringe barrel with the insertion of the needle into a single processing step.

> "The challenge was to combine the moulding of the syringe barrel with the insertion of the needle into a single processing step."

HEKUMA developed a dedicated manufacturing line with breakthrough technologies to individualise the needle cannulas, feed them to the insertion moulding stem where the syringe barrel is moulded around the needle. The syringe barrels then undergo multiple visual inspection steps and finally the needle shield is assembled. All manufacturing steps are fully integrated and conducted in a hermetically closed environment to minimise the risk of any contamination. This manufacturing process has been designed and systematically optimised for the precision, cleanliness and performance of the prefillable syringe aiming for highest patient safety and comfort and best therapeutic outcomes.

EXTENSIVE KNOWLEDGE IN SEPARATION SOLUTIONS

By teaming up with HEKUMA, BD has a strong partner company that has the capabilities to integrate the complex production requirements of these new prefillable syringes into a working equipment concept and to implement it into a practical solution. The company, located in Eching, near Munich, Germany, was the perfect match for building equipment of this kind, because of its ability to bundle a whole array of competencies, which were a sure guarantee of the equipment's quality and the parts that it produces.

HEKUMA not only has the extensive knowledge required for separation solutions for "difficult" or very small components, but also employs a highly developed gripper and robot technology for insertion and

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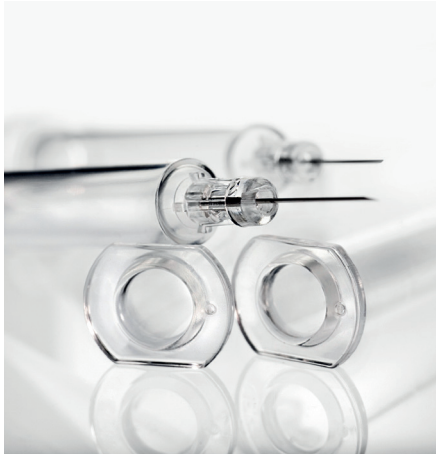

Figure 1: After the plastic body is cooled and cured, the result is the completed syringe barrel and needle.

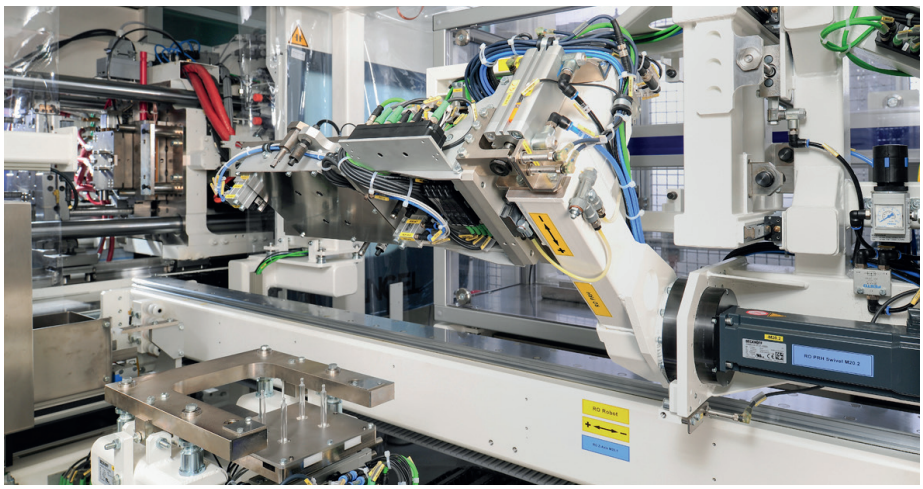

Figure 2: The take-out module includes a 4+4 insert, a take-out robot, and a shuttle system.

take-out processes that are both fast and highly precise. Moreover, HEKUMA boasts extensive experience in setting up highly sensitive quality inspections, especially in optical camera inspections.

Another important advantage is that HEKUMA already had the relevant industry-specific experience in the field of medical technology, for example when it comes to developing equipment used to manufacture disposable items such as cuvettes, Petri dishes and pipette tips. HEKUMA had already proven itself as a highly reliable partner in projects relating to developing and realising Petri dish systems for BD, amongst others. "So, we were able to rely on an existing and working platform for the collaboration," said Klaus Wanner, Director Sales and Marketing at HEKUMA, "The most important communication lines and interfaces between the two companies had already been developed."

EQUIPMENT QUALITY EQUATES TO PRODUCT PERFORMANCE

Over the last two decades an increasing number of innovative therapies have been based on biopharmaceuticals, many of which are administered via injection. Ready-to-use syringes, prefilled with the drug, have become the gold standard.

"On one hand, such prefillable syringes must perfectly protect the highly sensitive and very costly injectable biologics for up to three years. On the other hand, they must flawlessly function as a delivery device, posing high expectations regarding their precision, cleanliness and performance," commented BD Worldwide Strategic Marketing Leader Christian Herget.

High product performance requires high equipment quality: the demands that equipment operators require of the manufacturer are just as high. The quality of the equipment components must be above average, the scrap ratio during manufacturing must be extremely low. The entire system must satisfy cleanroom criteria, i.e. pursuant to GMP it must be easy to be thoroughly cleaned. Last but not least, the syringes must be produced with maximum precision in the shortest possible cycle times.

From the start, the first touchstone in realising the process sequence proved to be one of the greatest challenges: the requirement to over-mould the needles calls for an individualisation of them before a gripper takes them, each between the sizes of 27 to 29 gauges (OD of 0.360 to 0.286 mm), and insert them into the injection mould. The process was structured so it would be fast.

However, the real challenge proved to be the "momentum" of the needles, which were fed into the system in magazines in quantities of close to 100,000 units at a time. This momentum (movement or rather direction of movement in mass) had to be accounted for during the sequence of the entire separation process, and the process sequence had to be structured so that no matter what, the needles remained untouched. This was not solved until after a series of test scenarios and then in such a way that no difficult technical adjustments were needed.

STRICT PREREQUISITES FOR MEDICAL DEVICES

"As far as the actual insertion process into the injection mould is concerned, we were of course able to benefit from our wide range of processing experience from the automotive industry", says Wanner. The visible result can be easily broken down into what is most important: the needles are inserted into the movable side of the injection mould; from the solid side the liquid plastic is injected into the cavity, which completely wraps around the needle. After the plastic body is cooled and cured, the result is the already completed product (Figure 1).

After they are taken out from the mould (Figure 2), the syringe barrels are placed on a transfer shuttle and then they run through various camera inspection stations. Based on the strict specifications for medical devices, here is where the 100% quality inspection takes place, a camera inspection broken down into five single inspections. The first inspection step checks the precision of the flange; the second step is dedicated

Figure 3: Siliconisation of the needle; special attention is given to ensure that the silicone only comes into contact with the needle only, the syringe body.

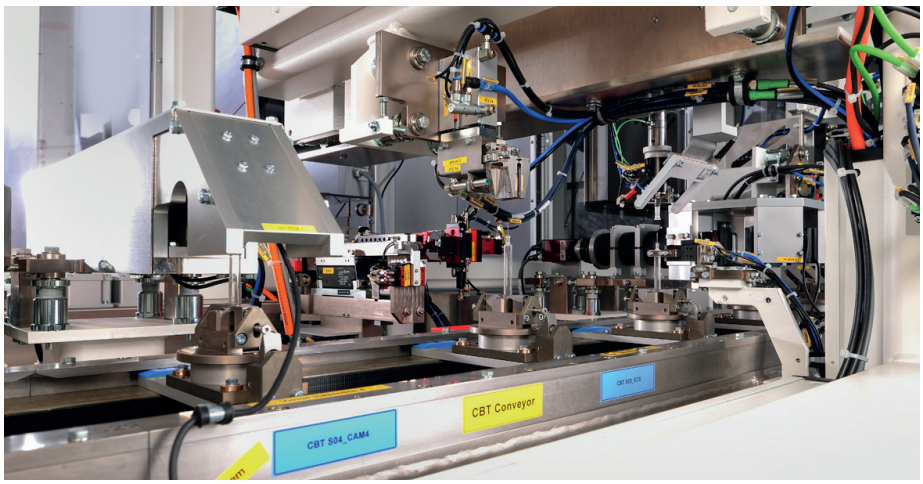

Figure 4: Visual inspection of the short neck, after needle siliconisation and the assembly of the protective cap.

Figure 5: The finished product complete with needle-caps.

to the barrel of the syringe, followed by the inspection of the tip of the syringe. The visual inspection of the main cylinder and the needle are especially thorough. Here, the entire range of the body is inspected for cosmetic defects like spots, scratches or trapped air bubbles.

At the end of the inspection process, the needle and the needlepoint are tested for possible deformations and occlusions using light rays. Once the needle has been successfully tested and proven to be intact, it is siliconised (Figure 3). Special attention is given here to ensure that the silicone only comes into contact with the needle, but not with the syringe body. The silicone ensures that the needle can be inserted into the skin smoothly, and thus without causing pain.

USING PROTECTIVE CAPS

After the siliconisation has been completed successfully, another processing step takes place. Following the various visual inspection steps, protective needle shields are mounted on each syringe, which had been fed to the system from a bowl feeder. The protective caps run through a separating and positioning process, before they are assembled onto the syringes (by way of a light clicking mechanism). Subsequently, a camera inspects to ensure that the needle shields are positioned correctly on the needle (Figure 4). Standing upright, flange showing upward, the syringes (Figure 5) are loaded into a nest in groups of 100 or 160 pieces. The nests on their part are placed into tubs and are transported from there to the packaging unit. The very compact manufacturing line, measuring approximately 4m long and 3m wide (see Figure 6), is being installed in a cleanroom in one of the seven worldwide BD manufacturing facilities for prefillable syringes.

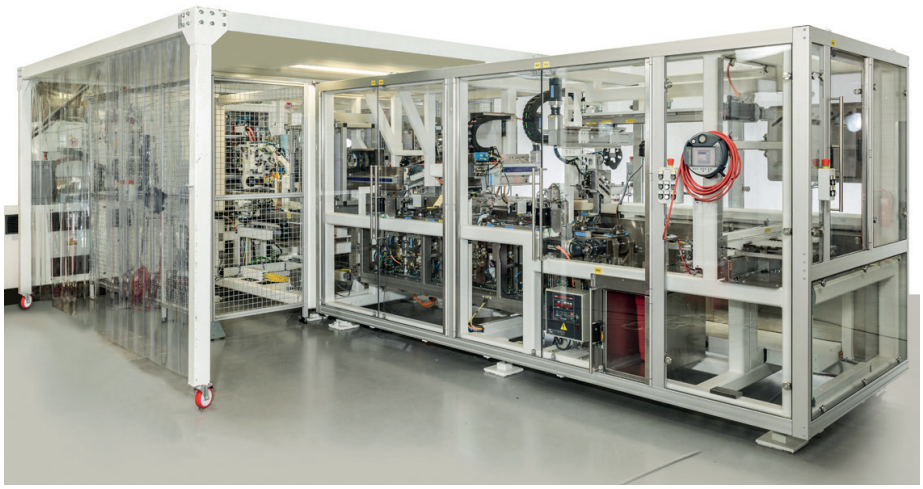

Figure 6: Overview of the whole manufacturing line.

REQUIRED CYCLE TIMES ACHIEVED

The duration of the overall process is in accordance with BD specifications, having cycle times of less than half a minute. Jakob Kammerloher, Technical Director at HEKUMA, commented: “Cycle times, precision, cleanliness standards and tight technical reliability. The requirements profile, which was placed upon us, was extraordinarily ambitious. At the end, we create a very rugged overall system were all these factors are taken into account and all requirements are fully met or even overachieved. Thanks to the intensive, extremely result-oriented collaboration, a system that is able to combine high quality with high volume arose. This way, we support our customer to manufacture a really well marketable product.”

ABOUT HEKUMA

HEKUMA (Eching, Germany) is part of the elexis Group. The company creates a sustainable competitive advantage with its innovative ideas and exciting technology in high-performance automation for customers in the plastics industry. With its dedication and ambition, HEKUMA has established itself as a competent systems manufacturer and proudly look back on more than 40 years of experience. It offers complex grippers for high-performance insert and take-out systems for injection moulding processes with upstream and downstream automation. In addition, the company considers its capability to develop turnkey solutions and production concepts, such as Sigma inside, to be one of its core competencies. HEKUMA focuses on the medical and automotive technology markets as well as the consumer goods industry.

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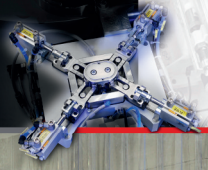

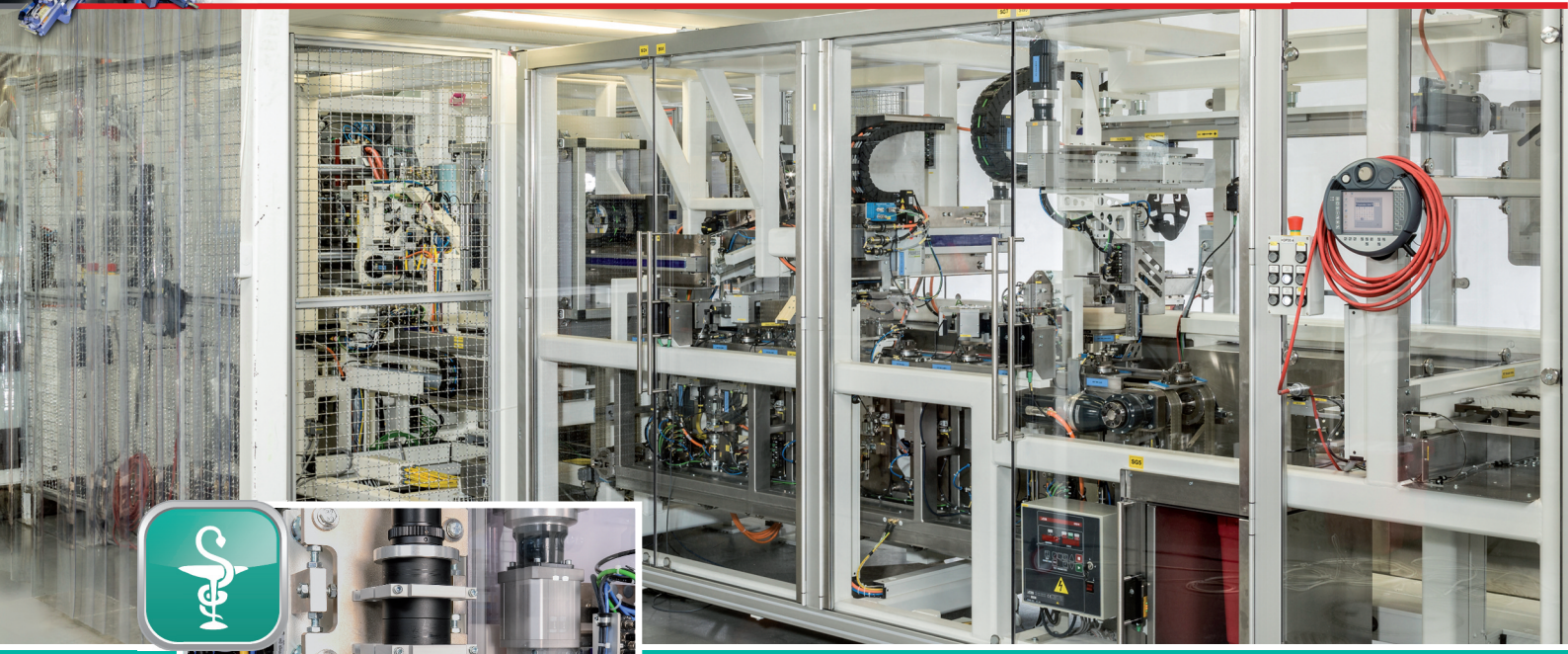

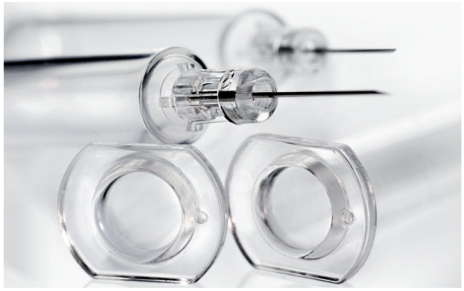

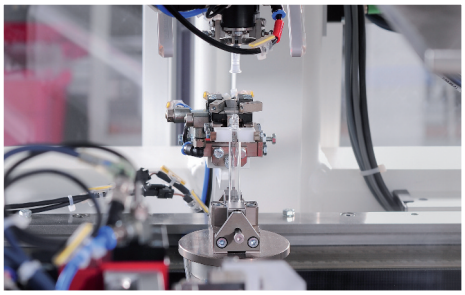

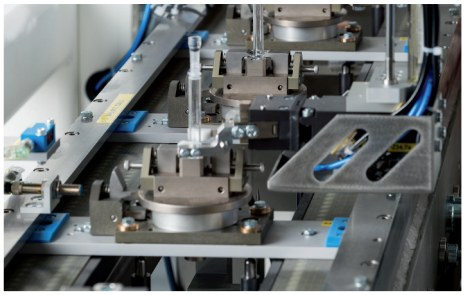

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ONdrugDELIVERY

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Publication Month	Issue Topic	Materials Deadline
March 2016	Skin Drug Delivery: Dermal, Transdermal & Microneedles	February 22nd
April 2016	Pulmonary & Nasal Drug Delivery	March 7th
May 2016	Injectable Drug Delivery: Devices Focus	April 11th
June 2016	Connected Drug Delivery Systems	May 2nd
July 2016	Novel Oral Delivery Systems	June 6th
Sepetember 2016	Wearable / High Volume Injectors	August 8th
October 2016	Prefilled Syringes	September 12th
November 2016	Pulmonary & Nasal Delivery	October 10th
December 2016	Delivering Biotherapeutics	November 14th
January 2017	Ophthalmic Drug Delivery	December 12th
February 2017	Prefilled Syringes	December 23rd

ZEON

ADDRESSING THE CONCERNS OF GLASS USAGE FOR PREFILLED DRUG DELIVERY DEVICES: INTRODUCING A NOVEL CLASS OF ENGINEERED POLYMER

In this article, Satoru Adachi, Researcher, Product Development Team, Specialty Plastics Lab, and Mark Nevitt, Market Development Specialist, New Business Division, both of ZEON, highlight some of the concerns of using conventional glass for parenteral drug storage in prefilled syringes, and provide an update on ZEONEX® cyclo-olefin polymer (COP), a novel class of transparent plastic, and describe how COP can provide solutions to some of the issues persistently encountered when using glass in prefilled drug delivery systems.

As technological advances are made at an astounding rate in the drug discovery world, new and breakthrough drug therapies using protein-based pharmaceuticals are more rapidly becoming available to the general population for treatment of genetic and infectious diseases. In fact, protein-based pharmaceuticals have been identified as one of the fastest-growing classes of biopharmaceutical drugs in recent years,[1] being used in the treatment of such common diseases as diabetes, breast cancer and arthritis.[2]

> "Not only can leachables pose a serious health risk to the patient directly, but they can also potentially cause a health risk indirectly by rendering the drug dosage less effective by initiating protein agglomeration and/or the reduction of drug shelf life. Unlike glass, ZEONEX COP has been engineered specifically as an ultra-high-purity polymer with extremely low off-gas and leachable content."

While development and administration of protein- and peptide-based drugs is on the rise, there are ongoing discussions relating to the best storage and delivery systems for these often high-cost and environmentally sensitive biologics. Although the industry standard for drug storage and delivery has traditionally been glass vials and syringes, the steady increase in the number of patients who self-administer those drugs have caused the pharmaceutical industry to consider alternatives to traditional delivery methods, such as prefilled delivery systems, in an attempt to curb the risks of dosing errors and drug contamination.

In response, the prefillable syringe (PFS) is becoming one of the fastest-growing technologies in the injectable drug delivery market.[3] In the realm of PFSs, use of glass for syringes is the gold standard, for obvious reasons: a long history of use, high barrier properties and high transparency.

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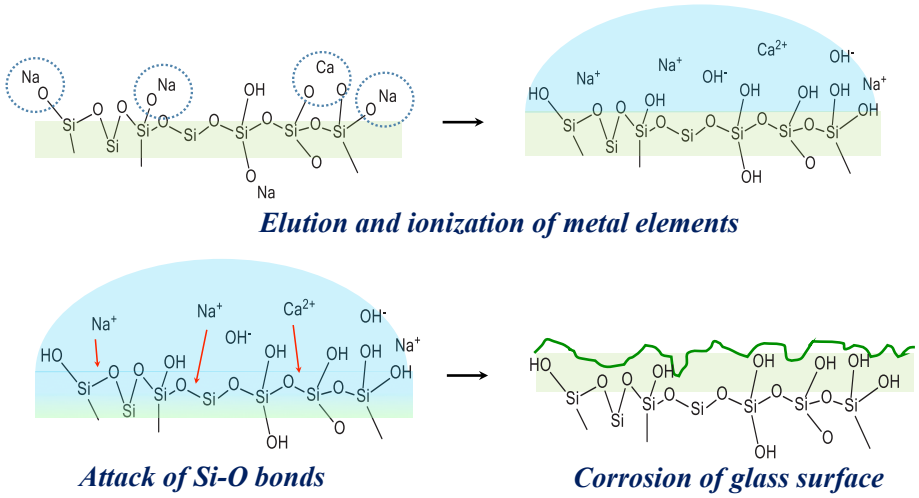


Figure 1: Mechanism of glass delamination.[6]

But as drug stability, purity and patient safety increasingly become a factor in the decision for best drug packaging and delivery solutions, syringes made of glass can potentially pose risk to the patient or compromise the high-value drug stored in the device. The solution is a novel class of engineered plastic – COP – that enables drug delivery system manufacturers to design a PFS that affords design freedom not previously obtainable with glass while promoting drug stability and patient safety on multiple levels.

Although it has been in commercial production for nearly three decades, ZEONEX COP remains a relative newcomer in the plastics industry compared with other olefins, polyamides (nylons), polystyrene and polycarbonate. However, the unique chemistry and physical properties of ZEONEX are being recognised and accepted by pharmaceutical companies as a preferable replacement to glass for a range of high-performance parenteral pre-filled drug delivery systems. The discussion that follows will serve to provide an understanding of the benefits offered by COP relative to glass.

> "When testing of ZEONEX COP resin was expanded to include a wider range of impurities, it was determined that no metals, solvents or low-molecular-weight components were detected in the stored solution. It is also notable that certain grades of ZEONEX COP have been tested to meet the requirements of USP <87> and <88> Class VI Biological Reactivity Tests."

PATIENT SAFETY, FIRST

According to the US FDA, "The administration of glass particulate, if present in a parenteral drug, can lead to sequelae of thromboembolism, some life-threatening (such as pulmonary emboli); phlebitis, mechanical block of the capillaries or arterioles; activation of platelets; and subsequent generation of microthrombi… Administration of a glass particulate can also lead to formation of granulomas, a protective local inflammatory response to the foreign material."[4]

While the cases have thus far been rare, there is increasing concern about glass and other micro-particles found in drug storage and delivery devices made of glass. In just the past few years, there have been multiple reports of product recalls by FDA relating to glass particulate caused by delamination of the glass storage devices' walls. In 2011, the recurrence of such reports prompted the FDA to issue an advisory statement to pharmaceutical companies pertaining directly to glass delamination. Some root causes were identified to be the processing method used in manufacturing the glass device, reagent pH and sterilisation methods.[5]

Taking a closer look at the mechanism that causes glass delamination, we find that metal elements are first eluted from the glass surface under certain conditions. Then, after ionisation, metal ions degrade the Si-O bond, causing erosion on the glass surface, as illustrated in Figure 1. The erosion can eventually lead to glass fragmenting and delamination (flaking). It is also important to pay attention to the first step of this process: metal elements are eluted from the glass surface. We will revisit that point later in the article.

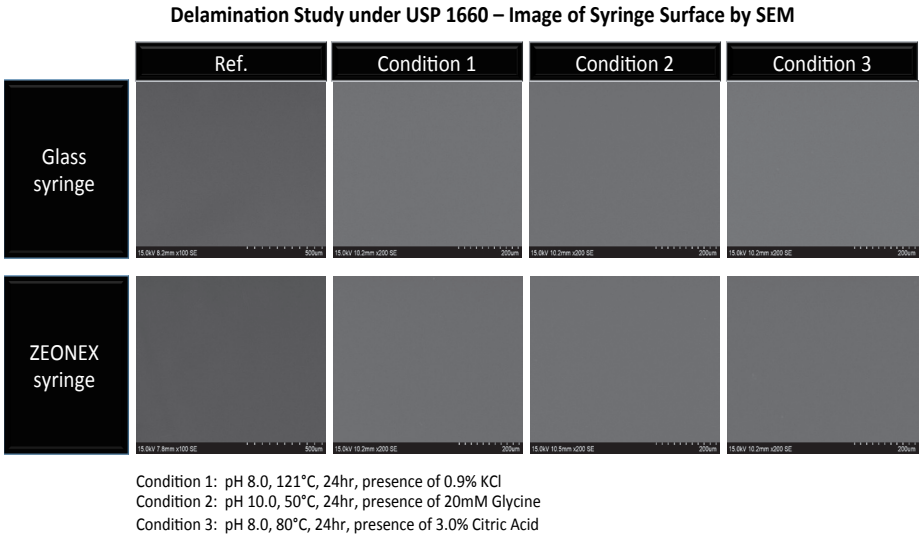
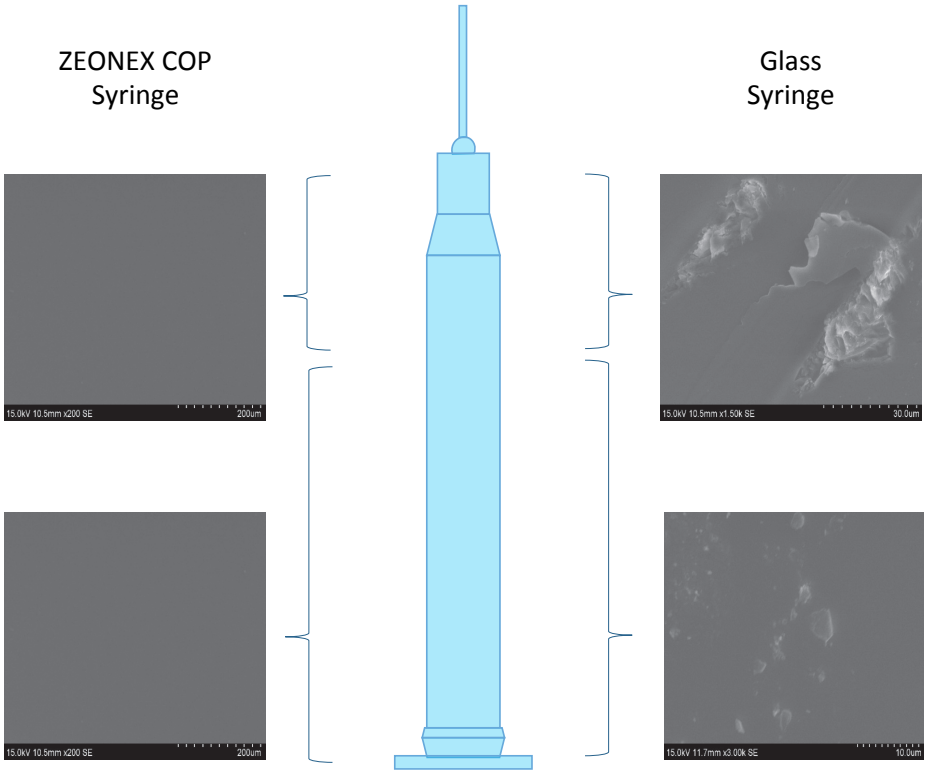


Figure 2: Result of delamination study under USP <1660>.

Zeon Corporation performed a study comparing the difference in particulate generation between syringes made of borosilicate glass – common in the manufacture of glass vials and syringes – and ZEONEX COP. The ZEONEX COP syringe was produced by conventional thermoplastic injection moulding practices, which provide for very high consistency of part dimensional and surface smoothness replication.

The test was conducted under the guidelines of United States Pharmacopeia (USP) Standard <1660> "Evaluation of the Inner Surface Durability of Glass Containers", which subsequently was created "in response to the recent product recalls that have further increased the pharmaceutical industry's heightened awareness of glass quality and glass delamination (i.e., the formation of glass flakes in a vial)".[7]



Storage condition:
pH 10.0, 80°C, 28 days, presence of 3.0% citric acid

Figure 3: Image of COP and glass syringe surface.

When storage conditions were set using the prescribed standard of 80°C at pH 8.0 for 24 hours in a 3% citric acid solution, no delamination was observed for either glass or the COP syringe (Figure 2).

However, when the same test was conducted under higher pH (pH 10.0) and extended storage conditions (28 days), the formation of microparticles was observed in the glass syringe, and was later verified as glass particulate by analytical measurement. It is interesting to note that more severe delamination was observed at the syringe tip compared with the barrel, where it is expected that the glass may have experienced a higher heat history during the manufacturing process (Figure 3). No delamination was detected in the ZEONEX COP syringe.

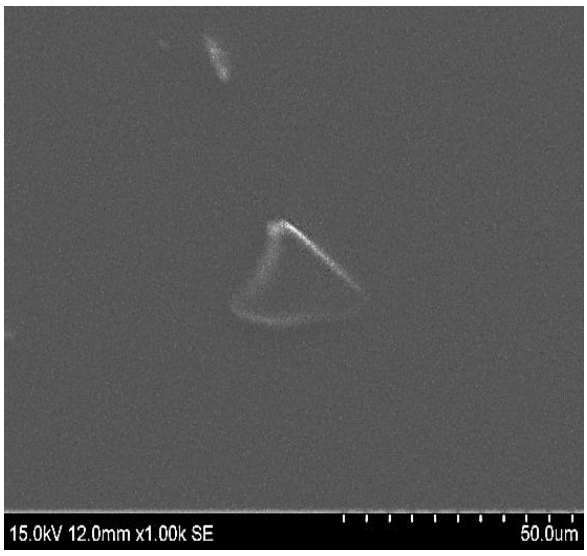
To establish additional confirmation of the delamination results, a third test was performed that more closely resembled a real-life storage scenario. That test incorporated a lower temperature (40°C), longer storage time (six months) and a pH of 8.0. Once again, glass particles were observed in the glass syringe (Figure 4), while no particulates were detected in the COP syringe.

LEACHABLE CONTENT, A SIGNIFICANT CONCERN

Earlier in this article it was discussed that the first step of glass delamination is elution of metal elements. As such, it is not surprising that leachables from the drug storage device are also a major concern to pharmaceutical companies in the long-term storage of their products. Not only can leachables pose a serious health risk to the patient directly, but they can also potentially cause a health risk indirectly by rendering the drug dosage less effective by initiating protein agglomeration and/or the reduction of drug shelf life. Unlike glass, ZEONEX COP has been engineered specifically as an ultra-high-purity polymer with extremely low off-gas and leachable content.

In a side-by-side test, glass syringes and ZEONEX COP syringes were filled with purified water and controlled at a pH of 7.0 and temperatures of 23°C and 40°C. After seven days, the water from each syringe was analysed by ICP-MS. As expected, a significant amount of tungsten was observed from the glass syringe while no tungsten was detected from the COP syringe. The tungsten found in the glass syringe is believed to have been transferred from the tungsten

Image of Glass Particulate at 'mild' condition



Storage condition:
pH 8.0, 40°C, 6 months, presence of citric acid

Figure 4: Image of glass particulate.

Result of Tungsten Elution Test by ICP-MS

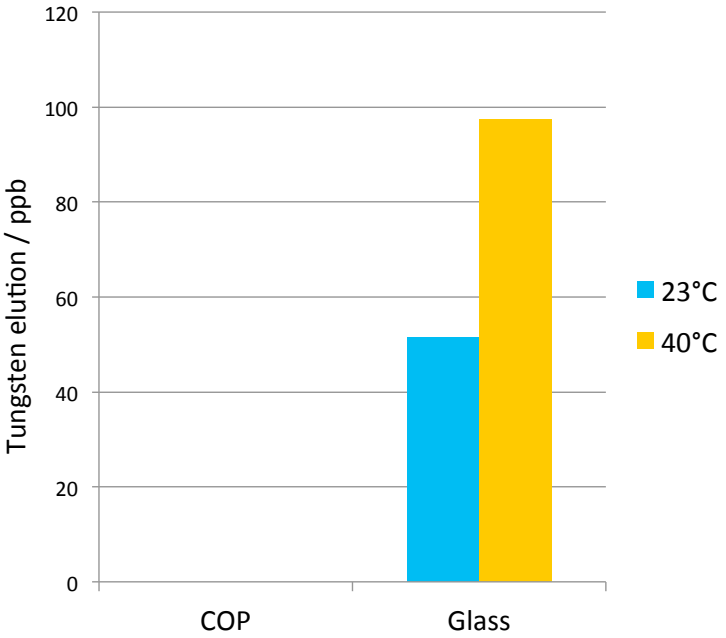


Figure 5: Measurement of tungsten concentration in water after storage in COP and glass syringe.

pin commonly used in the glass moulding process.

Although this particular study was isolated to tungsten contamination, it is well known and documented that silicon, sodium and boron are the most problematic leachables from glass. Potassium, barium, calcium and aluminium also have potential to contribute to the contamination of stored drugs.[8] Comparably, when testing of ZEONEX COP resin was expanded to include a wider range of impurities, it was determined that no metals, solvents or low-molecular-weight components were detected in the stored solution. It is also notable that certain grades of ZEONEX COP have been tested to meet the requirements of USP <87> and <88> Class VI Biological Reactivity Tests.

PROTEIN ADSORPTION, A STICKY ISSUE

We have discussed two ways in which contaminants can originate from glass (particulates and eluents). Glass can also contribute to a decrease in drug efficacy by the drug proteins migrating to the glass, commonly referred to as adsorption. Proteins exhibit a certain degree of surface activity, and tend to adsorb to glass, rubber and plastic due to their amphiphilic polyelectrolytic nature. Several factors can contribute to the amount of protein adsorption that occurs. However, the result of adsorption is always a reduction in the biological activity of the drug.[8]

While it is well documented that protein adsorption is an ongoing concern for storage of protein-based drugs in glass and conventional plastics, the unique amorphous, fully saturated chemical structure of ZEONEX COP offers a significant performance advantage over other materials by inhibiting adsorption of most proteins. To confirm that, a study was performed in which bovine serum albumin (BSA) was stored in a borosilicate glass syringe and a ZEONEX COP syringe, then measured weekly by high-performance liquid chromatography (HPLC) to determine the adsorption rate of the protein to the surface of each syringe. As illustrated in Figure 6, it is evident that COP demonstrates a very low rate of adsorption while glass exhibits a steady increase of adsorption over the same period. Testing has also been performed at varying pH levels (results not shown here) wherein COP continues to demonstrate excellent inertness to protein adsorption.

In addition to adsorption, protein aggregation (the agglomeration of the protein molecules) is also a mechanism by which drug efficacy can be diminished. One of the catalysts for protein aggregation is the presence of silicone oil, which is used to improve the sliding friction of the plunger in both glass and plastic syringes (including COP). Silicone oil can also migrate from the syringe surface, causing undesirable microparticles in the drug suspension that can be injected into the body along with the drug.

As ZEONEX COP gains recognition for its benefits in long-term parenteral drug storage, a number of drug delivery device makers have recently developed silicone oil-free syringes based specifically on COP substrate. It is expected that the new technology of silicone oil-free systems, coupled with the inherent inert nature of COP, will further contribute to the improvement of drug stability and quality afforded by ZEONEX COP over glass syringes.

ZEONEX COP, ADDRESSING THE CONCERNS OF GLASS USAGE FOR PFSS

While glass is expected to maintain a dominant position for use in PFSs due to its exceptional gas barrier properties, there will continue to be prefilled drug delivery systems for which the concern for leaching, delamination and protein adsorption must be addressed. ZEONEX COP, with its inherent qualities of high transparency, high moisture barrier, high purity, inertness, break-resistance and precision mouldability is capable of providing a superior solution that addresses the concerns of glass usage.

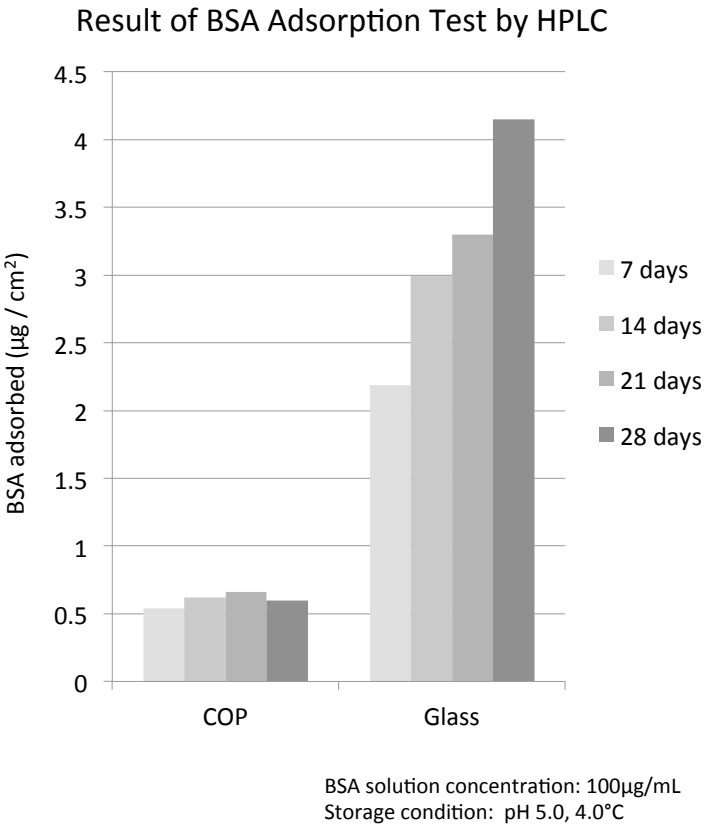


Figure 6: Result of BSA adsorption test.

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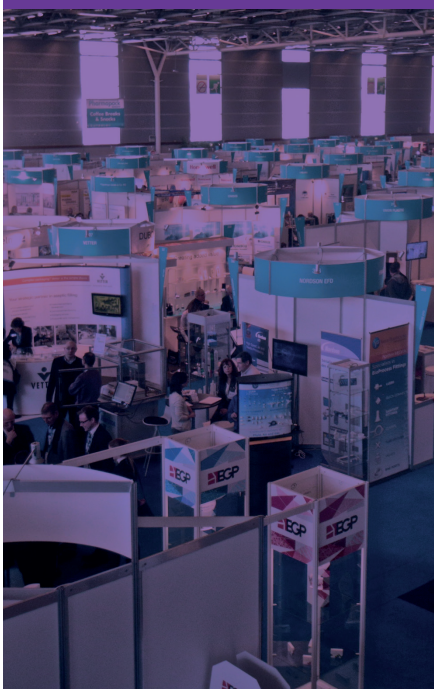

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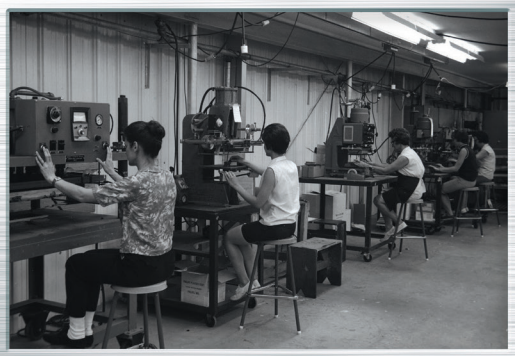

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THE POWER OF DRUG-DEVICE COMPANY COLLABORATION

During the Pharmapack Europe Conference (Paris, France) – at 4pm on Wednesday, February 10th, 2016 – Bill Welch, Chief Technology Officer, Phillips-Medisize Corporation, will give a lecture entitled "Integrated Development and Scale-Up of Combination Products". Here, he provides us with a preview of his forthcoming Pharmapack talk.

Many biologic, biosimilar and small molecule drugs need the assistance of mechanical systems for self-administration, ranging from complex delivery devices such as metered-dose inhalers, infusion pumps, injectables and prefilled syringes, to simple delivery devices such as droppers. The trend towards growing self-administration and patient convenience increases the desire for safety mechanisms. From a pharmaceutical company's perspective, this is very important because it helps drive compliance to therapy and improves outcomes for patients. As a result, device development is increasingly focused on innovative devices, in particular smaller and smarter combination products.

> "When product launch success depends upon speed-to-market, drug and device companies benefit by joining forces. Such partnerships can free pharmaceutical and biotech companies to focus on their core competencies, while leveraging their suppliers' existing, proven, regulatory-compliant design ability and manufacturing processes and infrastructure."

A unique delivery device can also be an important differentiating factor and unique selling point, thus helping in strong brand positioning. However, there are many challenges to creating a successful combination product including regulatory, clinical, human factors and drug/device interactions. Add to these challenges the need to manage complicated supply chain logistics, from design, testing and development through low-volume clinical trial manufacturing and scale-up into higher-volume production for commercialisation. The most minor detail can derail a successful product development effort, resulting in time and resources lost and crucial deadlines missed – potentially causing the product development or regulatory submission to stall before it ever reaches the market.

When product launch success depends upon speed-to-market, drug and device companies benefit by joining forces. Such partnerships can free pharmaceutical and biotech companies to focus on their core competencies, while leveraging their suppliers' existing, proven, regulatory-compliant design ability and manufacturing processes and infrastructure. Tapping into the design expertise of device companies helps pharma companies poise their product project for

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success as early collaboration, from initial design concept phase, allows the device partner to help anticipate potentially problematic areas that can occur during pilot production, clinical trials and eventual high-volume manufacturing.

assists the customer in meeting key delivery and launch dates.

One emerging business model is in-house development of a drug delivery device by the device makers integrating human factors engineering (HFE) and design for manufacturing/design for assembly (DFM/DFA) as foundations of the combination product development process, followed by the granting of contract manufacturing licenses."

"One emerging business model is in-house development of a drug delivery device by the device makers integrating human factors engineering (HFE) and design for manufacturing/design for assembly (DFM/DFA) as foundations of the combination product development process, followed by the granting of contract manufacturing licenses."

When the pharma company engages its manufacturer early on in the development process, the need to perform knowledge and technology transfer is eliminated because the supplier is able to understand what can be achieved in, for example, the injection moulding processes and is able to optimise the design for manufacturing or assembly. Furthermore, critical tolerances are fully understood and the exchange of information and data becomes seamless. All of this

facturing/design for assembly (DFM/DFA) as foundations of the combination product development process, followed by the granting of contract manufacturing licenses. An example is the development of the SoloSTAR disposable pen by Sanofi for Lantus (insulin glargine) and Apidra (insulin glulisine). The pharmaceutical company, Sanofi, granted the contract manufacturing licenses to Phillips-Medisize for the pen and involved us in the early design phase.

Phillips-Medisize also has a history of manufacturing complex dry-powder inhalers and has been involved in the development of several different inhaler programmes, including work as the development partner of the first dry-powder inhaler.

In my Pharmapack presentation I will discuss a well-rounded approach for biopharma companies interested in developing and commercialising successful combination products, by highlighting key device development and scale-up activities and their relationship to the overall combination product development process.

Presentation Key Points:

- Smaller and smarter combination products to support the trend toward patient-administered drug delivery
- Integrating HFE and DFM/DFA as foundations of the combination product development process
- Early manufacturing involvement to speed up time-to-market and reduce risk by "getting it right the first time"
- Development of a manufacturing scale-up strategy, concurrent with the development process.

REDUCING PARTICULATES FROM METAL PRODUCTS IN MEDICAL DEVICES

Here, Graham Perkins, Medical Sales Manager, Advanex Europe, explains how, for medical device component manufactures, developing new methods to reduce particulates is becoming increasingly important.

Over the years Advanex design and engineering teams have been working in collaboration with some of the world's leading medical device manufacturers to develop techniques for reducing particulates.

> "Traditional spring coilers form springs by continuously pushing wire against an inclined tool which forces the wire to bend and form a coil. This generates high levels of friction, requires lubrication (usually in the form of soap coated wire) and greatly restricts the rate at which the coil can be formed."

Particulates are minute, separate particles of organic or inorganic matter that contaminate components. Particulates can be generated during the coiling or forming process by friction between the raw material and the tooling, and from foreign bodies such as lubricants that are picked up by contact during manufacturing.

Components can also be contaminated by airborne particulates present in the atmosphere surrounding the process and contact with operators, equipment, packaging materials etc, during manufacturing. Some coiling processes require the raw material to be coated with coiling soap to reduce the effects of friction during the coiling and forming process. Usually these contaminants are removed by secondary processes.

PROCESSES TO REMOVE PARTICULATE

Prevention by Design

In some circumstances particulates can be reduced by prevention. For some applications, bespoke processes have been designed that do not require soap-coated wire and design tooling to reduce frictional effects as far as possible.

Designing and building bespoke manufacturing equipment can provide an advantage for customers as the process can be optimised for the product.

Most spring manufacturers use "bought-off-the shelf" machinery which is very ver-

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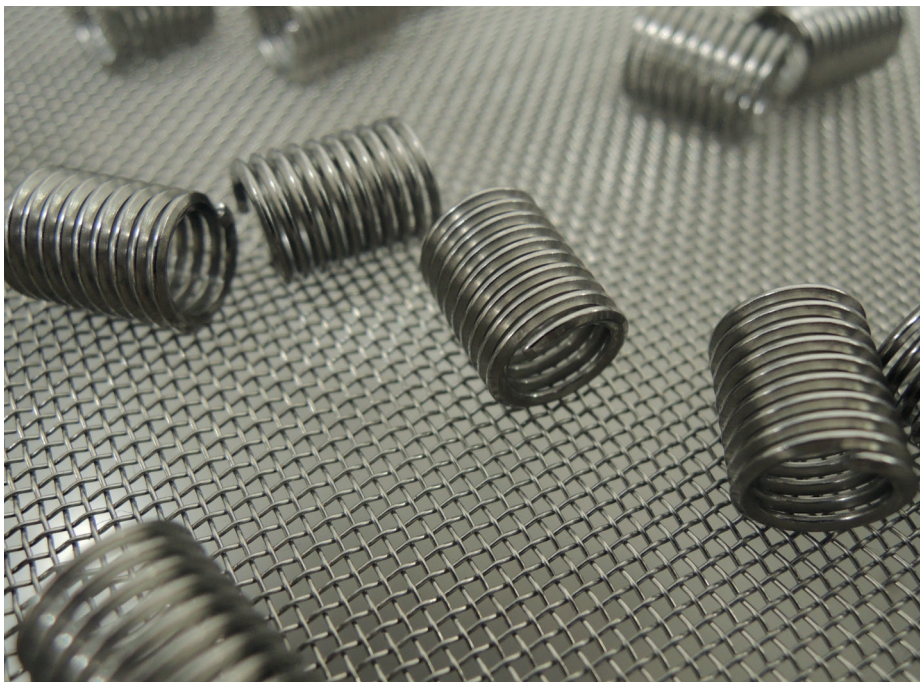

Figure 1: Sieving is a vibratory process that removes particulate by gentle abrasion while supported on a mesh or gauze.

satile and can make a huge variety of products. Traditional spring coilers form springs by continuously pushing wire against an inclined tool which forces the wire to bend and form a coil. This generates high levels of friction, requires lubrication (usually in the form of soap-coated wire) and greatly restricts the rate at which the coil can be formed.

In many cases coil springs are formed by wrapping the wire around a rotating mandrel which generates much lower levels of friction, does not require soap-coated wire and can produce springs at much higher production rates. Mandrel coiling is not as versatile as traditional coiling methods and bespoke sized tooling is required for each product. If the required quantities are high enough, this method can be very economical.

The versatility associated with general purpose spring-coiling equipment for high-volume, mass production requires a relatively large amount of equipment and tooling, some of which is redundant for manufacture of any individual product. All of the machine components provide opportunities for generation of particulates. Bespoke manufacturing equipment is better designed to fit the product so that all components used in the machine construction are critical to the manufacturing process, and there is no redundant equipment.

The design of each machine component and its potential for generating particulate matter is carefully considered. Sharp edges and situations where high levels of friction can occur are generally avoided. Using materials which reduce friction and have high wear resistance such as carbide, polished stainless steel, hard eloxated/hard anodised aluminium and other US FDA approved materials, can be employed. Opportunities for particulate to collect such as blind holes and internal corners are avoided wherever possible.

Vibratory Deburring

This is the process of removing burrs from components in order to smooth surfaces and edges. During the manufacturing process, operations such as cutting can leave raised edges or small pieces of material known as burrs that can become detached from the parent component. These can be removed by deburring using centrifugal, vibratory bowls and high density ceramic or synthetic media.

Laser Deburring

Cutting round section wire can often leave burrs where the wire has been cut. For some components, Advanex has offered laser deburring which provides a "dome" shaped end to the wire by firing a high powered laser beam directly onto the end of the wire.

Sieving

Advanex Europe can also offer in-line and off-line sieving. Sieving is a vibratory process that removes particulate by gentle abrasion while supported on a mesh or gauze. The particulate is separated from the components by dropping through the mesh. The size of the mesh is critical to the success of the sieving operation (Figure 1).

Solvent and Aqueous Cleaning

Solvent and aqueous cleaning are dedicated washing processes and are suitable for most metallic materials. These both require the component to be immersed in a heated liquid media, either solvent or water based, for a specific period. The components are usually tumbled within the media or the media agitated during the process. Particulate is washed from the components and removed by filtration of the media. Aqueous cleaning is generally more environmentally friendly than solvent-based cleaning processes.

Ultrasonic Cleaning

Ultrasonic cleaning is carried out in conjunction with either solvent or aqueous based cleaning processes. This involves using an ultrasound generating transducer immersed within the media that creates bubbles using high frequency (20-400 kHz) sound waves to agitate the media. This "cavitation" process removes contaminants that are adhered to, or embedded into the surfaces of materials such as metals, plastics and ceramics etc.

Acid Cleaning ("Pickling")

Acid cleaning, or "pickling", is usually performed in citric or hydrochloric acid solution, and removes a thin, surface layer of the material taking the embedded particulate and other contaminants with it. It is often performed as a pre-treatment prior to passivation of stainless steels.

Clean Manufacturing Areas

Some spring making processes such as traditional coiling methods that require soap-coated wire, generate large amounts of particulate. Other methods such as mandrel coiling with bright wire are inherently cleaner, but still generate particulates to a lesser degree.

The amount of residual particulate that is acceptable to the customer will largely depend upon the application of the product. Manufacturing areas that are clean and dedicated to the customer's product and isolated from other processes need to be designed to match the process and the product specification, with the aim of reducing foreign matter introduced by operators and the surrounding environment contaminating the product (Figure 2).

Depending on the process and customer requirements, some clean areas will only

require the operators to wear protective clothing, others have interlocking doors and maintain a positive air pressure etc. Manufacturing within these areas can maintain particulate to levels where the cleaning burden on the component can be dramatically reduced without the high costs and limitations imposed by clean-room manufacture.

Clean Rooms

Clean rooms are graded by the number of allowed particles per unit of volume. A Class 100,000 cleanroom, for example, can have up to 100,000 per cubic foot of air.

Where springs are ultimately to be assembled into devices within cleanrooms, customers will need the component parts to be free from biological contamination, as well as particulate matter. Class 10,000 (ISO 7) cleanrooms can be installed so that parts can be cleaned in-house. This allows the product to be passed into the cleanroom via an airlock 'pass-through', directly from the clean manufacturing area. Once inside the cleanroom, the parts are ultrasonically cleaned to remove any contamination, double-bagged within the cleanroom, and passed out through a further airlock to await despatch. The parts can then go into the customer's cleanroom, with the outer bag removed, so that no contamination is taken in via the outer packaging.

Figure 2: View of an Advanex clean manufacturing facility. Advanex Europe is approved to ISO13485.

Control of the efficacy of the cleanroom can be achieved by performing regular bioburden tests on cleaned parts. This will give assurance that the parts meet the prescribed microbial limit for the number of bacteria present.

CONCLUSION

As the medical device market evolves to become ever more sophisticated, metal part manufacturers face constant pressures in being able to reduce particulate in the production and assembly of components.

Advanex Europe is approved to ISO13485.

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QUALITY & SYSTEMS USABILITY REQUIREMENTS FOR DRUG DELIVERY DEVICES & SYSTEMS

In this article, Michael Gross, PhD, RAC, Principal Consultant, Chimera Consulting, and Adam Shames, MBA, Chief Executive Officer, Core Human Factors, discuss US FDA quality system requirements for combination products, especially Design Controls, which includes the requirement to validate the design of the medical device constituent part of a combination/borderline product. Design Validation may be accomplished through the conduct of human factors studies that demonstrate that a device can be used safely and effectively for its intended use(s), in its intended environment(s) of use, by its intended users. This is the first in a series of articles covering quality system requirements for combination products and borderline products in the US and EU. Future articles in this series will further address quality system requirements and the conduct of human factors studies intended to fulfill design validation requirements for registration of combination/borderline products and stand-alone drug delivery devices.

QUALITY SYSTEM REQUIREMENTS

In 2013, the US FDA established quality system requirements for combination products in a regulation entitled, Current Good Manufacturing Practice Requirements for Combination Products (§21CFR4).[1] The regulation applies to all medical products that combine, through either integration or co-packaging, drugs, or biological products, with a medical device constituent part, such as a syringe, auto injector, pen, nasal spray, inhaler, or other devices intended for drug delivery.

The regulation does not create new requirements for the drug (or biological product) and medical device constituent parts of a combination product. It explains how to apply existing quality system requirements for drugs, biological products and medical devices during the development and manufacture of a combination product. The regulation requires that manufacturers demonstrate that the quality system used to develop and manufacture a combination product meets the requirements of both Current Good Manufacturing Practice For Finished Pharmaceuticals [2] for drugs and biologics (§21CFR211, CGMP) and the Quality System Regulation [3] for medical devices, (§21CFR820, QSR).

§21CFR4 does not apply to stand-alone medical devices which are not intended for use with a specific drug or biological product. These requirements are covered only by the QSR.

In 2015, FDA issued, Draft Guidance: Current Good Manufacturing Practice Requirements for Combination Products [4] which is intended to expand and clarify the legalistic language of §21CFR4. The issuance of a final guidance is anticipated in the near future.

According to §21CFR4 and its companion draft guidance, a streamlined (i.e. hybrid) quality system may be structured

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that satisfies both CGMP and QSR requirements. The operating (i.e. platform) quality system for a combination product can be based on either the CGMP or QSR. Typically, a pharmaceutical company will have a CGMP-based quality system in place, so this will likely be the quality system platform used for the development and manufacture of a combination product. FDA notes that many of the requirements of the CGMP and QSR regulations are similar and are intended to achieve the same purpose. However, there are gaps between the two regulations and these must be filled to be fully compliant with §21CFR4.

In §21CFR4 FDA identifies four gaps that may exist between a compliant CGMP platform and the QSR requirements. They are, Management Responsibility (§21CFR820.20), Purchasing Controls (§21CFR820.50), Corrective and Preventive Actions (§21CFR820.100) and Design Controls (§21CFR820.30).

When FDA drafted §21CFR4 it compared the CGMP and QSR to identify gaps between the regulatory language of the two regulations but FDA did not compare current state-of-the art practices under these regulations. The ICH guideline, Pharmaceutical Quality System (ICH Q10),[5] is a pharmaceutical quality system best practices model that defines the "C" (i.e. current) in CGMP. A pharmaceutical quality system that conforms to the recommendations of ICH Q10 will substantially satisfy the Management Responsibility, Purchasing Controls, and Corrective and Preventive Actions requirements of the QSR and therefore comply with most of the requirements of §21CFR4, except for the Design Controls requirement which is unique to medical devices. Therefore, when structuring a hybrid quality system which is based on a state-of-the art CGMP platform, aside from the possibility of minor adjustments to quality system SOPs, the main gap that must be filled to fully comply with quality system requirements for combination product development and manufacture is Design Controls.

DESIGN CONTROLS

Design Controls are unique to medical device development and manufacture. They are are a set of procedures (SOPs) that serve as a framework for device development and are intended to insure that a device, or a device constituent part of a combination product, is safe and effective and meets its intended use and satisfies user needs, throughout its life cycle. The basic elements of Design Controls are:

- Design and Development Planning
- Design Input
- Design Output
- Design Review
- Design Verification
- Design Validation
- Design Transfer
- Design Changes
- Design History File
- *Risk Assessment.*

Risk Assessment is not a formal element of Design Controls. Rather, it is a tool that is used throughout the Design Control process. The use of risk assessment methodologies (e.g. ISO14971 Application of Risk Management to Medical Devices [6]) is important for identifying and mitigating

risks that will be assessed in human factors studies. By following established Design Control procedures during the device development process, design flaws and problems can be identified and mitigated before the device design is finalised.

One of the final steps in the development cycle for a device design that is intended for initial marketing is Design Validation. Validation that a device can be used safely and effectively for its intended use(s), in its intended environment(s) of use, by its intended users is typically achieved through the conduct of one or more Summative Human Factors studies.

HUMAN FACTORS STUDIES

Human factors studies should be conducted throughout the device design process. They are not clinical studies; they are engineering studies and are usually conducted under conditions that simulate actual device use. In 2011, FDA issued a draft guidance on the conduct and reporting of human factors studies.[7] The issuance of a final guidance is anticipated in the near future. Formative human factors studies are information gathering studies which are typically conducted on device prototypes or sub-assemblies as the device design process proceeds. They allow for early and iterative assessments of the device, instructions for use, packaging, and training materials (if applicable). They are intended to identify potential design flaws to be mitigated before the design of the device, instructions for use, packaging, and training program are finalised.

Summative human factors studies (a type of Design Validation) are conducted on the final (market image or equivalent) device, instructions for use, packaging, and training materials under conditions that simulate actual use, to demonstrate that the device can be used safely and effectively for its intended use(s), in its intended environment(s) of use, by its intended users.

SUMMARY & CONCLUSIONS

To be fully compliant with recently established FDA quality system requirements for the development and manufacture of a combination product, manufacturers must simultaneously comply with the requirements of both the CGMP and QSR. To meet this requirement, at a minimum, pharmaceutical manufacturers utilising a previously established CGMP-based quality system that conforms to current industry best practices, must expand their existing set of quality system SOPs to satisfy QSR Design Controls requirements. Validation that a device can be used safely and effectively for its intended use(s), in its intended environment(s) of use, by its intended users is typically achieved through the conduct of Summative Human Factors Studies.

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THE COMBINATION PRODUCT TRAINING INSTITUTE

In 2016, the Combination Product Training Institute® will conduct two identical three-day training programs that address quality system and design controls requirements for combination and borderline products in the US and EU, and the conduct of human factors studies. These programs will cover requirements for both newly developed and legacy products as well as quality system obligations of device component manufacturers. The first of the two training programs will take place on March 29-31, 2016 at the Chemical Heritage Foundation Conference Center (Philadelphia, PA, US). The second program will take place on June 14-16, 2016 at the NH Barbizon Palace (Amsterdam, The Netherlands).

Throughout the year, the Combination Product Training Institute will offer other venue-based training programs on various combination product topics. In-house training programs are also available. For additional details please visit the Combination Product Training Institute website at: CombinationProductTrainingInstitute.com

ABOUT THE AUTHORS

Michael Gross is the Principal Consultant of Chimera Consulting®, specialising in quality assurance, regulatory affairs and technical development of drugs, biologics, medical devices and combination products. He also heads the Combination Product Training Institute®, which provides professional training programs on combination product topics. Michael holds a PhD in Organic Chemistry and conducted post-doctoral research in biochemistry at the National Institutes of Health. He is a former FDA reviewer and inspector. Michael worked for 30 years in senior quality, compliance and regulatory affairs roles for a number of large and small pharmaceutical and medical device companies. Today, he provides an influential industrial perspective on the regulation of combination products and is a frequent speaker on combination products topics and has published numerous articles in regulatory and scientific publications.

Adam Shames is a recognised human factors expert and consultant and is the Founder and Chief Executive Officer of Core Human Factors, Inc, a leader in human factors and usability engineering consulting services with over 12 full-time employees. Adam holds an MBA in international business and a BS in human factors engineering and psychology. He received the De-Florez Prize in Human Engineering and holds a Certificate in Applied Ergonomics Training from the United States Army Center for Health Promotion and Preventive Medicine. Adam has over 15 years of human factors research experience and has served as the Principal Investigator on hundreds of IRB reviewed usability studies involving thousands of participants in cities around the world.

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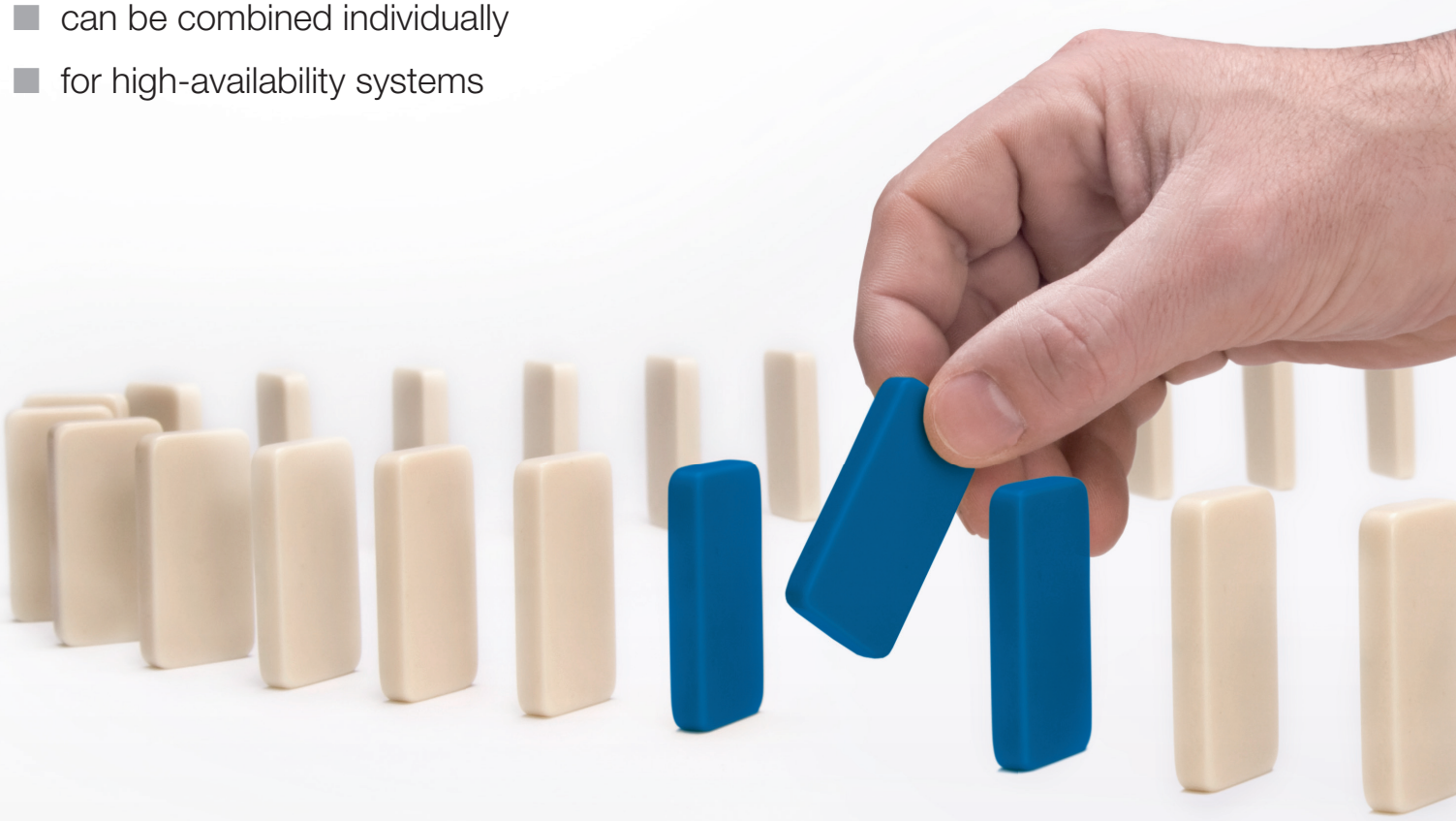

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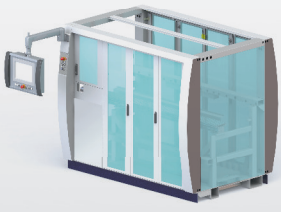

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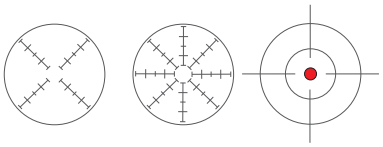

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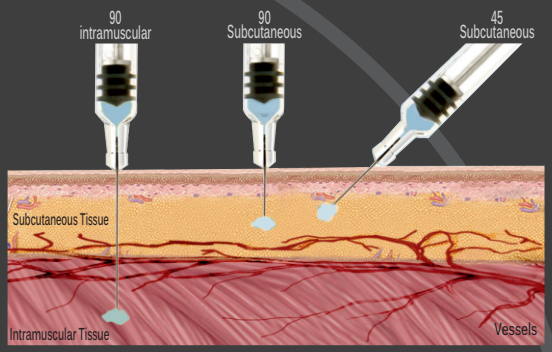

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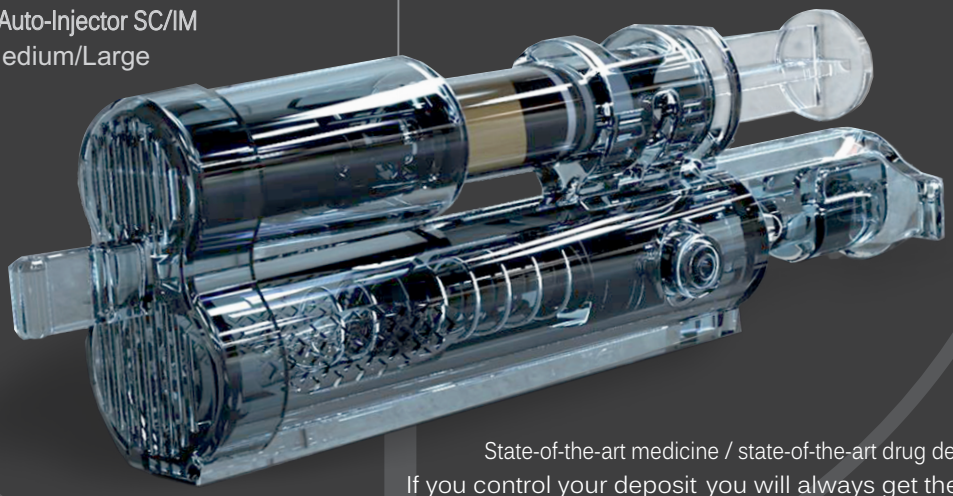

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POLYMERS, GLASS AND PARTICULATES: CHOOSING THE BEST CONTAINMENT FOR CUTTING-EDGE BIOLOGICS

In this piece, Kevin Cancelliere, Marketing Director, West Pharmaceutical Services, Inc, provides a run-down of the benefits that cyclic-olefin polymers syringes can bring compared with glass, including better dimensional tolerances and the ability to be moulded into more complex shapes for innovative delivery systems, as well as reduction of particulate contamination, in particular for biomolecular therapeutics that are not compatible with glass.

As more biologics and biosimilars come onto the market, they present unique packaging and containment challenges. Many biotech drugs are sensitive injectable drug products that can interact with containers and packaging components made from glass, potentially leading to delamination, particulates or protein aggregation. Additionally, some biopharmaceuticals have a high pH; others require storage at extremely cold temperatures. These nuances and sensitivities are putting demand on drug manufacturers and their packaging and delivery system providers to provide innovative, sophisticated solutions for securely containing and delivering advanced therapies while ensuring both drug efficacy and patient safety.

For materials that are sensitive to glass or that may require larger dose volumes or custom configurations, cyclic-olefin polymers (COPs) may offer a solution. These materials for drug container closure systems can provide a smart alternative to traditional glass containment systems for advanced therapeutics. They can also help drug manufacturers differentiate their product through container closure systems that offer more flexibility in the types of shapes and configurations used to package and deliver the next generation of injectable therapeutics.

> "Although recalls caused by glass breakage and particulate peaked in 2011, the issues persist and patient safety may be affected. In fact, in the past ten years the FDA has recalled 25 drugs for breakage, and more than 20 more for particulates. It adds up to more than 100 million drug units recalled in total.[2]"

CHALLENGES OF GLASS

The pharmaceutical industry has traditionally used glass as a primary material for containment systems due to a variety of characteristics that enable generally safe and efficient drug storage. Glass is readily available and in many cases works very well. Yet glass is not an inert material. Its chemistry can and does interact with certain medica-

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Figure 1: Daikyo Crystal Zenith® 1 mL Insert needle syringes.

Figure 2: A selection of vials made from Daikyo Crystal Zenith®.

tions in ways that can alter a drug's safety, stability, purity or effectiveness. Certain additives used in glass container closure systems, such as silicone oil applied to the inner walls of glass syringes, may also interact with sensitive injectables.

In its guidance, "Immunogenicity Assessment for Therapeutic Protein Products," the US FDA called attention to risks commonly associated with container closure systems, including denaturation and aggregation of proteins at glass-air interfaces; delamination and particulate formation in certain drug formulations; protein aggregation associated with silicone-lubricated containers; and leachables from container components. These issues may affect product quality and immunogenicity.

The recommendations come at a time when such issues have led to an increase in the number of FDA recalls. For instance, in 2011, ten drug product recalls were caused by glass particulates in injectable drug products. The pace continued in 2012 with recalls of 19 lots of four different injectable oncology products caused by the discovery of glass particles.[1,2]. The direct and indirect costs of a drug product recall may result in the loss of millions, and may also affect a company's reputation, market share and consumer trust. Although recalls caused by glass breakage and particulate peaked in 2011, the issues persist and patient safety may be affected. In fact, in the past ten years the FDA has recalled 25 drugs for breakage, and more than 20 more for particulates. It adds up to more than 100 million drug units recalled in total.[2]

GLASS ALTERNATIVES TAKE CENTRE STAGE

To help solve fundamental incompatibilities that may exist between a drug formulation and its container closure system, manufacturers are exploring and adopting alternative materials for drug packaging and containment systems – including COPs such as West's Daikyo Crystal Zenith® – that can help assure the stability of an injectable drug product.

Because COPs are more stable than glass, these polymer-based containment systems can help mitigate the risk of particulate contamination. Additionally, they can be moulded to a variety of shapes to provide customised containment solutions throughout a drug product's lifecycle. Such choices early in development may also aid decisions later in the manufacturing cycle. COPs also offer improved dimensional tolerance and design flexibility, so innovative container/device combinations can be considered to help optimise the overall system design based on the needs of the patient. In addition, COPs can be moulded to suit innovative delivery systems, offering differentiation in the market. For example, an insert needle prefillable syringe, such as the Daikyo Crystal Zenith 1 mL Insert needle syringe (Figure 1), could be utilised for a drug product with metal and silicone oil sensitivities.

ASSESSING MATERIAL COMPATIBILITY

No matter which container closure system is considered for an injectable drug, it is essential to assess the compatibility of the system's materials with the drug product in order to understand the impact on quality.

Selection of suitable container closure systems can be best judged through the performance of risk assessments based on an understanding of the physical, functional and chemical characteristics of the container closure system along with drug product. During drug development, materials that will be in contact with the drug product should be evaluated for protection, function, compatibility and safety. The drug-container interaction, adsorption, chemical resistance and the stability of packaging over time and in extreme environments are critical to the manufacturing, storage, distribution and integrity of the marketed product. By carefully assessing how the materials in a drug's container closure system interact with the drug product over time, manufacturers can best understand the potential risks to drug quality and patient safety.

"COPs can be moulded to suit innovative delivery systems, offering differentiation in the market. For example, an insert needle prefillable syringe, such as the Daikyo Crystal Zenith 1 mL Insert needle syringe, could be utilised for a drug product with metal and silicone oil sensitivities."

PARTNERING FOR QUALITY

To ensure the safety and efficacy of a drug product, pharmaceutical manufacturers should partner with drug packaging and delivery experts to properly evaluate material compatibility and select the highest-quality container closure system for a particular drug product.

Collaborating with a single partner with diverse expertise in primary packaging, delivery systems and custom design can help ensure the optimal packaging and containment solution throughout a drug product's lifecycle. Packaging manufacturers who also provide analytical laboratory services can offer product recommendations on the latest alternative technologies and provide prescreen stability work early in the process to ensure that the containment materials do not react with the drug product.

One of the most important services a packaging company can provide is material and stability testing. While it may not be possible to tell which drug product and delivery system interactions may result in delamination, several tests can help predict the possibility. Delamination can occur at any point in the drug manufacturing process, including vial manufacture and heat treatment or sterilisation processes. Container closure systems can be examined microscopically for visible indications of defects, particles, pitting or delamination before filling. For example the neck and base of a vial (see Figure 2) represent areas of high stress in the glass; microscopic evaluation of these areas after exposure to a stressed environment can detect the potential for delamination. Validating packaging and containment choices through materials testing processes can help eliminate problems that could potentially lead to costly recalls and safety issues with patients.

As the next generation of drugs become available, the limitations of glass container closure systems are becoming more pronounced. As a full product lifecycle solution, COP-based systems are quickly becoming an ideal solution for their ability to provide a high-performance, low-risk alternative. Working together, pharmaceutical and packaging and delivery systems companies can develop innovative COP containment solutions that can safely contain today's advanced biopharmaceuticals.

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ABOUT THE AUTHOR

Kevin Cancelliere joined West Pharmaceutical Services in January 2013 as Director of Marketing, Pharmaceutical Delivery Systems. Kevin brings almost thirty years of broad operational and strategic marketing and sales experience to this position. He comes to us from Vicept Therapeutics where he was Senior Director, Project Management for an investigational drug for the treatment of Rosacea. Prior to Vicept, Kevin was the Senior Director, US Marketing at Wyeth Laboratories. Kevin holds a BS in Biology from De Sales University and a Masters in Biochemistry from Thomas Jefferson University.

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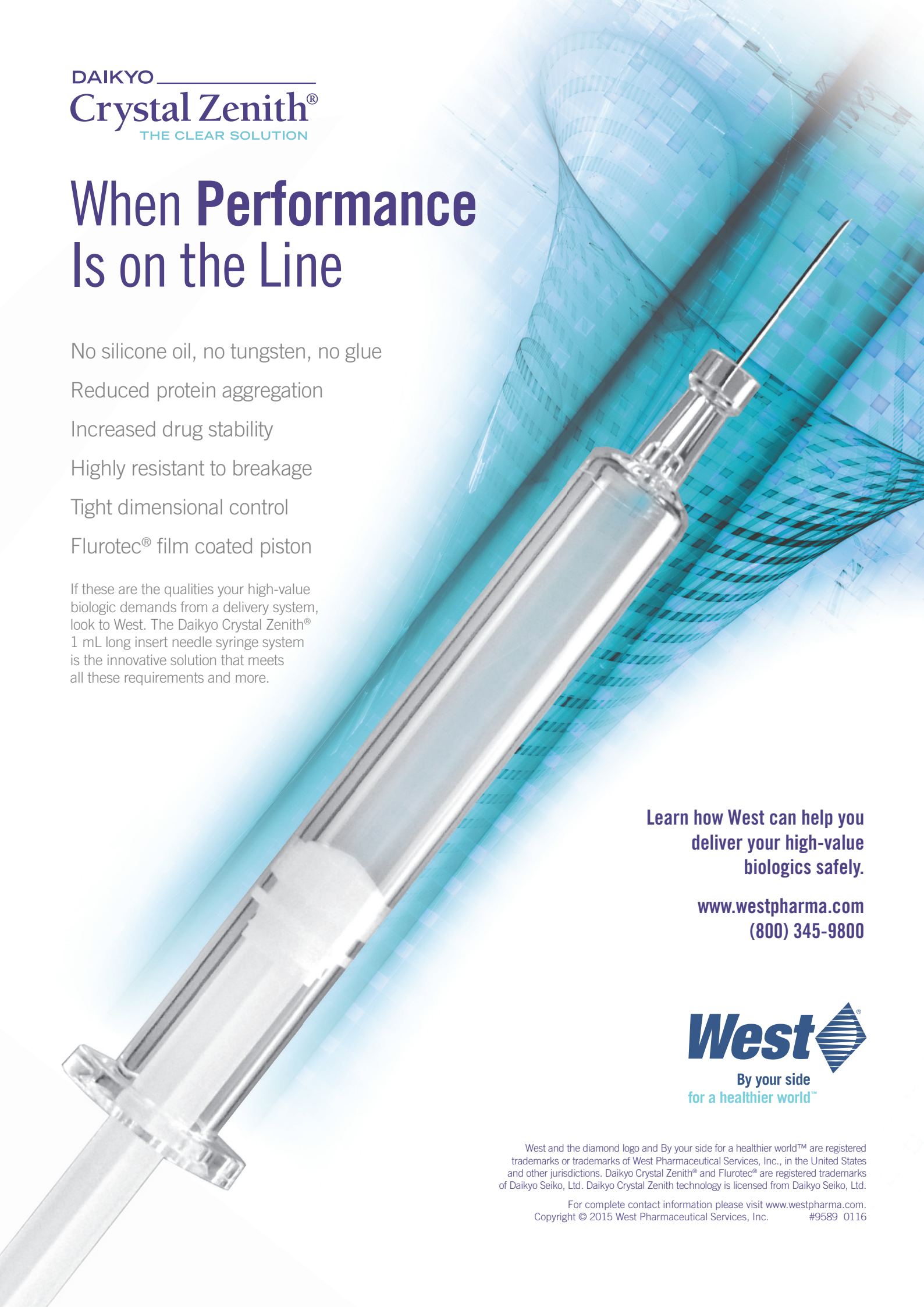

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Haselmeier offers a range of early-stage activities:

- Think-tank discussions and paper concepts
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- 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:

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- 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"

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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:

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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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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 {... CONTINUED}

"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.

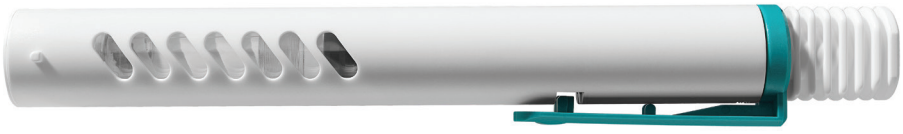

Figure 5: The Penlet is a fully automatic, fixed-dose injection device

PHARMA-
PACKAGING

PRE-FILLABLE SYRINGES

Increased filling line performance

- Optimized forming process leads to strong mechanical syringe stability
- Double stage inspection system results in less pierced needle shields
- Tight visual defect tolerances minimize cosmetic rejects

High compatibility between drug and packaging

- Optimized siliconization process decreases silicon quantity used
- Reduced risk of drug & glue interaction as a result of precise UV curing
- Low tungsten residual or tungsten free allow best choice for the drug

Reliable incorporation in injection devices

- Narrow dimensional defect tolerances support optimal fitting in devices
- Homogeneous siliconization results in smooth plunger movement

Adv-PharmaPack-Prefillable_Syringes-08.Jan.16

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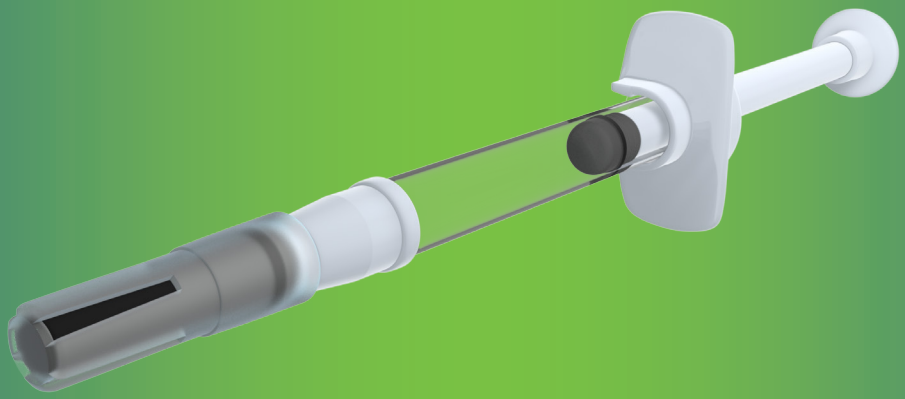
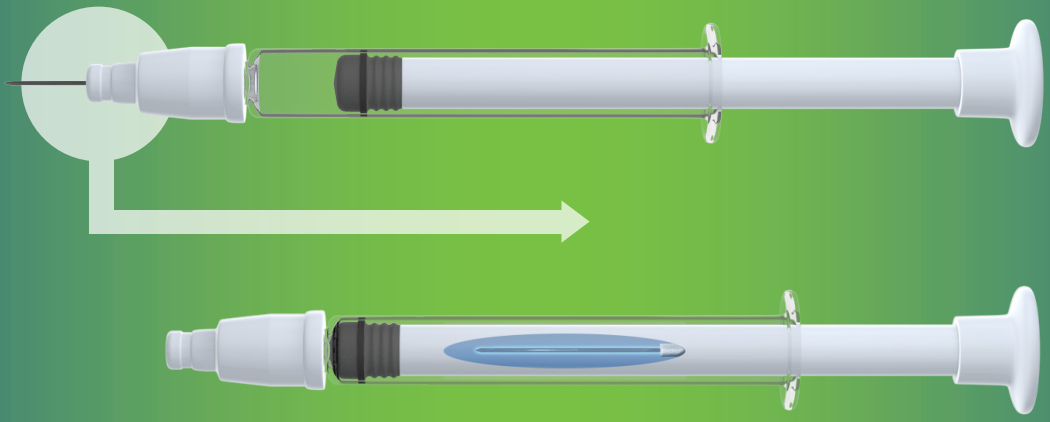
THE CREDENCE COMPANION

INNOVATION WITHOUT CHANGE



Visit Credence at Pharmapack
STAND #904 to learn more.

- Passive Needlestick Safety and Reuse Prevention
- Existing Primary Package Components
- Glue-Free Staked or Luer Needles
- Optional Finger Flange



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This product has not yet been evaluated by FDA

CREDENCE MEDSYSTEMS